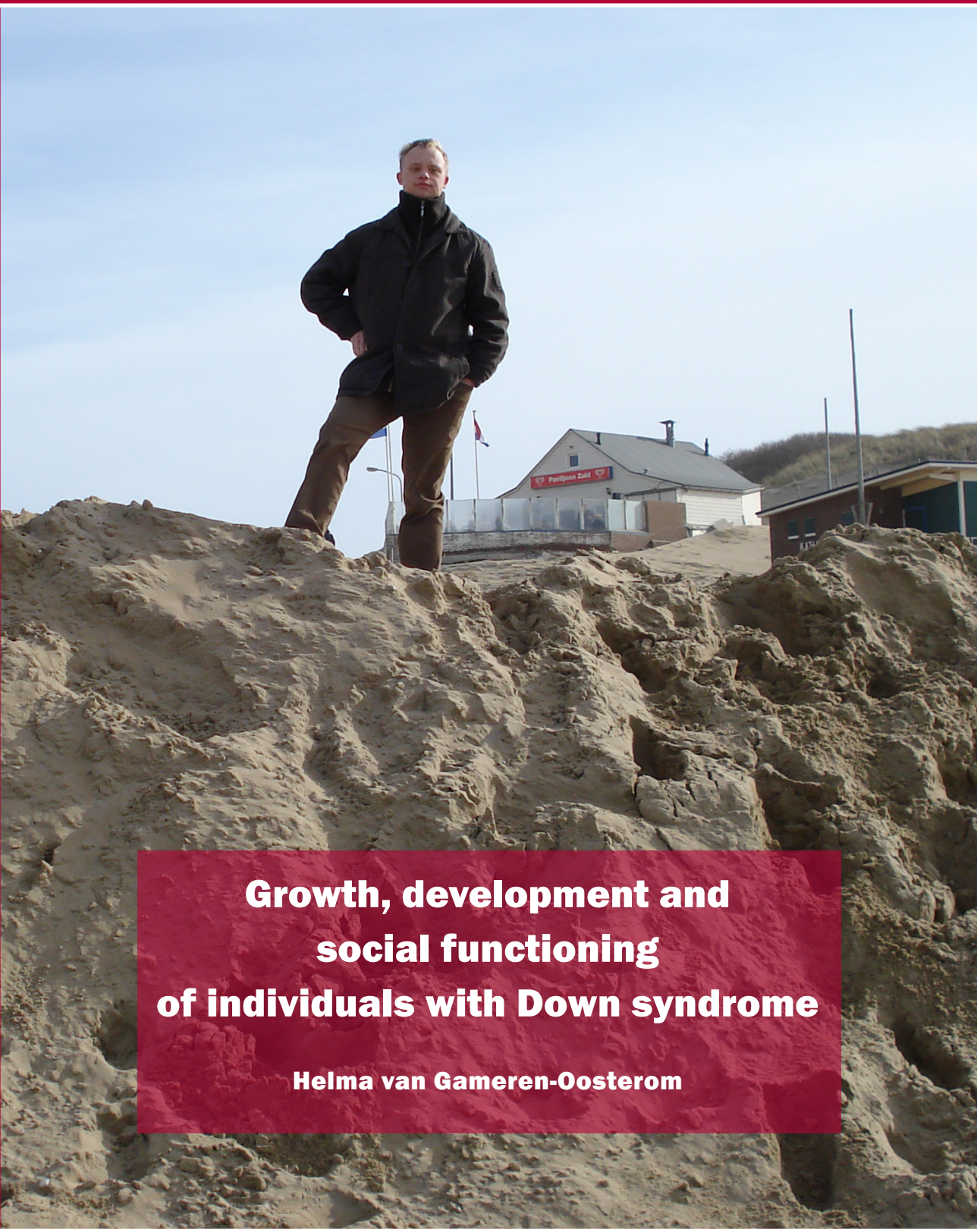

Growth, development and social functioning of individuals with Down syndrome

Helma van Gameren-Oosterom

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Growth, development and social functioning of individuals with Down syndrome

Groei, ontwikkeling en sociaal functioneren van kinderen en jongeren met Downsyndroom

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Prof. dr. F.J. Walther *(Leids Universitair Medisch Centrum)*

Contents

Part 1

Introduction

Chapter 1

General introduction

Down syndrome

Trisomy of chromosome 21, as discovered by Lejeune in 1959, is the cause of Down syndrome.[1] Little is known about the causes of non-disjunction that lead to the trisomy. However, its consequences are well known: delayed cognitive and motor development and physical disorders. Children and adults with Down syndrome are easily recognized by their external features, which were first described by the British medical doctor John Langdon Down, to whom the syndrome owes its name.[2]

Medical care

Children with Down syndrome need special medical care. Guidelines for this specific care have been developed, in the Netherlands as well as in other countries.[3-7] In 2011 a completely revised version of the Dutch guideline for medical care of children with Down syndrome was released by the Pediatric Association of the Netherlands.[3] This guideline aims to offer directions for optimal medical care by pediatricians, who work together with other (medical) specialists, e.g. youth health care physicians, physicians for the intellectually disabled, social workers and parent organizations. Early detection and treatment of concomitant disorders, facilitating best possible cognitive and motor development and support to achieve active participation in society, are important aspects of this guideline.

One of the major focuses in the medical care for neonates with Down syndrome is on cardiology, as 43-58% of children with Down syndrome are born with a congenital heart defect.[8] The most common are atrioventricular septum defects and ventricle septum defects. In the Netherlands, each neonate with Down syndrome receives a cardiac ultrasonography investigation within the first four weeks of life, in order to detect a congenital heart defect early. As a result of this early detection, improved surgical possibilities and clinical care, mortality in the first year of life (which is mainly influenced by congenital heart defects) has declined to 4% in the Netherlands in 2003.[9-11] Congenital gastrointestinal tract malformations are also frequently seen in children with Down syndrome (prevalence of 4-10%).[12]

During childhood, children with Down syndrome are at an increased risk for developing hypothyroidism. At adolescence the prevalence of hypothyroidism is 2-5%.[13] Because of the approximately 50 times higher prevalence of acquired hypothyroidism in childhood and the signs and symptoms which overlap with the Down syndrome phenotype, it is advised to screen for hypothyroidism actively by checking thyroid function annually. A coeliac disease screening program is also in place for children with Down syndrome in the Netherlands.

Prenatal screening

In the Netherlands, in 2002 screening using the first-trimester 'combined test' was introduced in a nonsystematic manner and only at the pregnant women's request.[14,15]

The test includes an assay of the serum concentrations of pregnancy-associated plasma protein A (PAPP-A) and the free ß subunit of human chorion gonadotrophin (fß-hCG) between 9-14 weeks of pregnancy and an ultrasound measurement of nuchal translucency between 11-13^{+6} weeks of pregnancy. The risk of Down syndrome is calculated based on a combination of the results of these tests, maternal age and pregnancy duration. Fetal karyotyping is offered if the risk is ≥1 in 200.
Up to 2002, only women aged 36 years or older and those with a family history of chromosomal abnormalities were offered prenatal screening for Down syndrome, using chorion villous sampling or amniocentesis.

Growth

Optimal physical growth is a reflection of good health. In the Netherlands, physical growth is being monitored during childhood and is evaluated to signal deviation of growth and allow optimal health care. To monitor growth it is necessary to have access to appropriate and up-to-date growth charts.[16] It is well known that children with Down syndrome have growth retardation and a specific growth pattern. Since growth assessment depends on the growth pattern characteristic for a specific syndrome, disorder specific charts are desirable to monitor growth.[17]
These specific charts need to reflect optimal growth. Therefore, in establishing growth charts, it is important to be aware that children with Down syndrome have a high risk of developing many disorders known to influence growth. Only those children with Down syndrome who are otherwise healthy can achieve optimal growth. References for optimal 'healthy' growth can allow health care professionals to monitor the growth of individual children with Down syndrome and identify relative growth retarding comorbidities at an early stage.

Development to independent social functioning

An important feature of children with Down syndrome is their intellectual impairment with delayed cognitive and motor development.[18] The level of functioning determines how the child functions in everyday life and the extent of support needed. The development of children with Down syndrome will also be influenced by behavioral problems. Children with Trisomy 21 are prone to psychopathology, although the risk is lower than in children who have other syndromes causing intellectual disability or children with nonspecific intellectual disability.[19,20]
A policy of stimulating children with Down syndrome from a young age has been introduced during the last decennia. Development of children with Down syndrome is often stimulated by using early intervention programs, rearing at home instead of in an institution and integration in mainstream schools. It is generally believed that increased stimulation and acceptance creates opportunities for people with Down syndrome to participate in society.

Various small studies on the short-term effects of early stimulation in Down syndrome have been published; some showing positive short-term effects on specific areas and some showing no effects of stimulation.[21-23] There is no evidence that these programs provide long-term benefits.[23] It is reasonable to expect that stimulation will have specific short term direct effect on what children learn, but these effects cannot be extrapolated to all areas of learning and to long-term effects. Furthermore, it is questionable if it can be realistically expected that stimulation can lead to a sufficiently increased developmental level to enable children with Down syndrome to function independently as (young) adults.

When a child with Down syndrome is born, parents want to be reliably informed about the expected development and predicted quality of life of their child. Most of the currently available information focuses on the medical aspects and physical disorders. It is extremely important that appropriate information on expected mental and social development is also available.

Knowledge gap

It is problematic that realistic and actual information on growth, development and social functioning in children, adolescents and young adults with Down syndrome is lacking.

Up to 2010, the available growth charts for Dutch children with Down syndrome were based on the growth of children who attended special schools and who were measured in 1989. In order to take the secular trend and the influence of co-morbidity on growth into account, new up-to-date growth references are needed. In addition, the increasing prevalence of overweight and obesity worldwide in children is alarming and needs attention, also in children with Down syndrome.

Development and behavioral problems in Down syndrome have been studied frequently during the past 50 years. However, the majority of these studies are not population-based, included fewer than 50 children with Down syndrome, or date back to the 1970s and 1980s, when the children grew up under different circumstances. Care for individuals with Down syndrome has improved during the past two decades and, consequently, life expectancy is considerably improved. However, the potential effect of these improvements on development, behavior and social functioning is less clear than the effect on life expectancy. Scarce any population based information is available on the actual expected development and level of social functioning and on the ‘dual diagnosis’ of intellectual disability and psychopathology.

Aims of the thesis

We aim (A) to evaluate trends in the prevalence of Down syndrome in the Netherlands; (B) to explore growth of children with Down syndrome and provide updated growth references for height, head circumference and weight and (C) to investigate levels of development, social

functioning and behavior in children and adolescents with Down syndrome. In this thesis we provide insight into the impact of Down syndrome on growth and development, from conception to adulthood.

These aims have been translated into the following five research questions:

1. What is the trend in the prevalence of Down syndrome in the Netherlands in the period 1997-2007?
2. What is the growth pattern of otherwise healthy children with Down syndrome in the age range of 0-18 years?
3. What are the prevalence rates of overweight and obesity in Dutch children with Down syndrome and are these influenced by concomitant disorders?
4. How is the general level of development, behavior and health-related quality of life of 8-year-old children with Down syndrome?
5. What degree of independent social functioning do adolescents with Down syndrome actually reach?

Outline of the thesis

In the first part of this thesis, **chapter 2** provides an evaluation of the trends in the prevalence of children with Down syndrome in the Netherlands, based on an eleven year birth cohort (1997-2007). In the second part of the thesis several aspects of growth in children with Down syndrome are presented. In **chapter 3** height and head circumference are described, including references for healthy Dutch children with Down syndrome and comparisons with height and head circumference references from the general population. In **chapter 4** weight is addressed, including the prevalence of overweight and obesity in children with Down syndrome.

The third part of this thesis includes a description of the level of functioning of children with Down syndrome, assessed at 8 years of age. This starts with an overview of the level of development, problem behavior and quality of life in **chapter 5**. In addition, in **chapter 6** the association between concomitant recurrent respiratory tract infections and level of development in eight-year-olds with Down syndrome is presented.

In the fourth part of this thesis the level of functioning at adolescence is being presented. For these studies, our cohort is assessed at the age of 16-19 years. In **chapter 7** the degree of independent social functioning at adolescence is described. **Chapter 8** describes the observed behavioral problems. Finally, the main findings are summarized in the fifth part. The results are discussed and implications for professional practice and further research are presented in **chapter 9. Chapter 10** contains a summary of the results. Table 1.1 shows all studies presented in these chapters.

Table 1.1: *Studies presented in this thesis*

	Study population	Data source	N	Focus of the study
Part 1 Introduction	Nationwide birth cohort (1997-2007)	National register	3169	- Prevalence of Down syndrome
Part 2 Growth	Dutch children aged 0-26 years	Retrospective from medical records	1596	- Growth of height and head circumference - Prevalence of overweight
Part 3 Development and behavior in childhood	Nationwide cohort of children born in 1992-1994, assessed at 8 year	Home visits and parent questionnaires	337	- Development, problem behavior and quality of life - Impact of recurrent respiratory tract infections on development
Part 4 Social functioning and behavior at adolescence	Nationwide cohort of children born in 1992-1994, assessed at 16-19 year	Parent questionnaires	322	- Social and practical skills - Problem behavior

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Chapter 2

Unchanged prevalence of Down syndrome in the Netherlands: results from an eleven year nationwide birth cohort

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Journal

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Abstract

Objective: This study aims to evaluate trends in prevalence of Down syndrome (DS) births in the Netherlands over an 11-year period, and how they have been affected by maternal age and introduction of prenatal screening.

Method: Nationwide data of an eleven year birth cohort (1997-2007) from the Netherlands Perinatal Registry were analyzed. First trimester combined screening was introduced in 2002, free of charge only for women 36 years of age or older and only on patients' request. Changes in maternal age, prevalence of DS births, and rates of births at <24 weeks (legal limit for termination of pregnancy in the Netherlands) during the study period were evaluated using logistic and linear regression analyses.

Results: In total 1,972,058 births were registered (91% of the births in 1997-2007). Mean prevalence of DS was 14.57 per 10,000 births (95% CI 14.43;14.73); 85% of DS were live births. No significant trend in overall prevalence of DS births was observed (p=0.385), in spite of a significant increase of mean maternal age during the same period (p<0.001). The increased prevalence of DS births at ≥24 weeks among women ≥36 years of age (p=0.011) was offset by a significant increase in the proportion of DS births at <24 weeks among women aged <36 years (p=0.013).

Conclusion: The proportion of DS births in the Netherlands has not changed during the period 1997-2007.

What's already known on this subject

— In the Netherlands, the live birth-prevalence of DS is an estimated 11-16 per 10,000.
— The overall prevalence of DS is positively correlated to increasing maternal age.
— A new screening policy for DS was introduced in 2002 in the Netherlands.

What does this study add

— Maternal age has increased progressively during the study period, with related increase in DS births.
— During 1997-2007 the prevalence of DS showed a stable trend.
— There was a significant increase in DS births at <24 weeks (including terminations of pregnancy) only among women younger than 36 years.

Introduction

Trisomy 21 is the most common chromosomal anomaly among newborns. In the Netherlands, the live birth-prevalence of Down syndrome (DS) is estimated to be 11-16 per 10.000.[1-3] This is similar to the prevalence in the United States (12 per 10,000 live births).[4] Children with DS have a well-recognized phenotype, including external characteristics, specific health problems and intellectual impairment with delayed cognitive and motor development.[5-7]

In the Netherlands before 2007, women aged 36 years or older and those with a family history of chromosomal abnormalities were offered chorion villous sampling or amniocentesis for the diagnosis of DS. However, in 2002 screening with the first-trimester combined test was introduced in the Netherlands, in a nonsystematic way and only at patients' request.[8-10] The test includes an assay of the serum concentrations of pregnancy-associated plasma protein A (PAPP-A) and the free ß subunit of human chorion gonadotrophin (fß-hCG) between 9-14 weeks of the pregnancy, and an ultrasound measurement of the nuchal translucency (NT) between 11-13^{+6} weeks of the pregnancy.[11] The risk for DS is calculated based on the results of these tests, maternal age and pregnancy duration, and fetal karyotyping is offered if the risk is ≥1 in 200. The first-trimester combined test is covered by health insurance for women with a family history of chromosomal abnormalities and for those ≥36 years of age, whereas younger women have to pay for the test (around 150 euros).

The effect of the introduction of the screen on the prevalence of live and stillbirths with DS in the Netherlands has not been studied previously. We analyzed the trends in prevalences of DS in the Netherlands based on an eleven year birth cohort. We hypothesized that the live birth-prevalence of DS in the Netherlands would decrease as a consequence of the increased prenatal detection and subsequent termination of DS pregnancies.

Methods

Dutch data on perinatal and neonatal care are registered anonymously on a voluntary basis. Three separate national professional registers operate: the National Perinatal Registry for Primary Care (LVR-1, midwife-assisted births); the National Perinatal Registry for Secondary Care (LVR-2, obstetrician-assisted births); and the National Neonatology Registry (LNR, neonatal hospital care). These three registries are managed by the Netherlands Perinatal Registry (PRN-foundation). The registries contain records for all infants born from 16 weeks (102 days) of gestation under care of a midwife at home or in a hospital, as well as born under care of an obstetrician in a hospital, or being admitted to a neonatology department within the first 28 days of life. Attainment has increased in the study period and varies between 88% and 99%.

The LVR-1 and LVR-2 register maternal demographic characteristics, details on pregnancy and delivery, and characteristics on the newborn including congenital anomalies detected

at birth or within the first week after birth. Both live and stillbirths are registered; at <24 weeks (the legal limit for terminations of pregnancy, TOP, in the Netherlands) there is no recorded distinction between spontaneous and induced abortions. The LNR contains brief perinatal information and detailed information about the physical condition of the newborns, including congenital anomalies diagnosed before or at birth or within the first month of life.

Since 1995, the LVR-1, LVR-2 and LNR have been linked annually by a deterministic record linkage procedure based on neonatal and maternal matching variables (date of birth, gender, plurality, birth weight in grams, gestational age in completed weeks and remaining days, the four digits of the postal code).[1] Prevalences of congenital anomalies – detected before or at birth or within the first month of life – are available from an eleven year birth cohort (1997 to 2007).[2] Infants with DS (Trisomy 21) are registered in the LVR as well as in the LNR with a specific code.

Statistical analysis

For all analyses data are weighted for the proportion of infants registered. Weighing factors were defined per place of birth (i.e. at home, in a general hospital or in a university hospital), and year of registration, because there are various proportions of registration in these groups. The participation of all clinics was registered annually, so the exact proportion of registration is known for every year of registration. In 1997 for example, 91% of the home births, 88% of the births in the general hospitals and 100% of the births in the university hospitals were registered; and in 2007 these percentages were 93%, 99% and 100% respectively. Besides this, a weighing factor is added for all births assisted by general practitioners, and not by a midwife or obstetrician (so not included in above-mentioned groups of births). This small group of births was not included in the registration (only the number of births assisted by general practitioners is registered and used in the weighing factors).

General characteristics of the total cohort were determined, separately for children with and without DS. The prevalence of DS per 10,000 births was calculated by dividing the number of newborns registered with DS, by the total number of newborns registered in the LVR/LNR. The proportion of DS cases born before vs. at or after 24 weeks of gestation was determined yearly. This cut-off was based on the legal limit of 24 weeks of gestation for TOP in the Netherlands. The trend in prevalence was tested by logistic regression analyses, for total DS births, and separately using a threshold of 24 weeks of gestation. Models were adjusted for maternal age (<36 years or ≥36 years). The 95% confidence interval was calculated using a *logit* transformation and finite population correction ((1-n)/N) was applied.

To evaluate the major factors that influenced the prevalence of DS, mean maternal age was determined yearly. Linear regression analyses were performed to assess the trend in maternal age. Time trends were further evaluated within the DS sample by assessing

the proportion of DS diagnosis born before 24 weeks of gestation adjusting for maternal age (<36 years or ≥36 years). The analyses were also separately performed for mothers younger than 36 years and mothers aged 36 or older, because of the differences in prenatal screening practice between these groups. In addition, to determine whether the effects for maternal age on the outcome variables were equal for both groups, the influence of interaction terms were assessed by adding cross-products (of the outcome variable and maternal age) to the regression equation. P-values less than 0.05 were considered to be statistically significant. All analyses were performed using SPSS version 17.0 for Windows (SPSS Inc, Chicago, IL, USA).

Results

Data of 1,972,058 registered newborns were available for analysis, which accounted for approximately 91% of the births in the Netherlands during this eleven year period. After weighing, the total sample amounted to 2,174,635 births, of which 3,169 were DS. The prevalence of DS was 14.57 per 10,000 births [95% CI 14.43;14.73], equivalent to 1 per 686 births. On average, each year 288 infants with DS were born, of which 245 were live born (85.0%). General characteristics of the study population are presented in Tables 2.1 and 2.2.

Table 2.1: *General characteristics of the Down syndrome population, stratified for gestational age (GA) at delivery (<24 weeks vs. ≥24 weeks).*

	GA <24w	**GA ≥24w**	
	n=405	**n=2,764**	
General characteristics	**%**	**%**	***p***
Male gender	57.2	53.1	0.127
Dutch origin	88.1	82.1	0.003
Twins	0.7	3.3	0.004
Live births	-	97.2	-
	Mean *(SD)*	**Mean *(SD)***	***p***
Maternal age (years)	37.2 *(4.1)*	33.5 *(5.1)*	<0.001
GA (weeks)	19.5 *(1.7)*	38.1 *(2.4)*	<0.001

Abbreviations: GA – gestational age , SD – standard deviation

Table 2.2: *General characteristics of the study population according to diagnosis of Down syndrome .*

General characteristics	Down syndrome n=3,169 %	Non-Down syndrome n=2,171,466 %
GA <24 weeks	12.8	0.7
GA ≥24 weeks	87.2	99.3
Live births (GA ≥24 weeks)	85.0	98.8
Male gender	53.6	51.3
Dutch origin	82.9	82.0
Twins	3.0	3.7
	Mean *(SD)*	**Mean *(SD)***
Maternal age (years)	34.0 *(5.1)*	30.8 *(4.8)*
GA (weeks)	35.7 *(6.6)*	39.4 *(2.6)*
GA live births (weeks)	38.2 *(2.2)*	39.6 *(2.0)*

Abbreviations: GA – gestational age , SD – standard deviation

Table 2.3 shows the prevalence per year; in total as well as stratified for gestational age at delivery (<24 vs. ≥24 weeks) and for maternal age (<36 vs. ≥36 years). Trends in prevalence of DS stratified for births <24 and ≥24 weeks of gestation are presented in Figure 2.1. The proportion of births with DS ≥24 weeks of gestation varied from 11.65 to 14.24 per 10,000; the proportion of births with DS <24 weeks of gestation from 1.12 to 2.58 per 10,000. Logistic regression analyses showed no significant trend in total births with DS over the years 1997-2007 (p=0.385), as well as in DS births ≥24 weeks (p=0.146). The trend in DS births <24 weeks showed a significant increase (p=0.006); however after correcting for maternal age (<36 or ≥36 years), the trend was no longer present (p=0.332). During the study period, mean maternal age in the total Dutch population increased from 30.4 years in 1997 to 31.1 in 2007 (p<0.001) (Figure 2.2).

Within the DS population, a total of 405 infants with DS were born <24 weeks in the study period (12.8% of all DS births). This proportion increased over the years from 9.9% in 1997 to 15.8% in 2007 (p=0.011) (Table 2.4). However, after correcting for maternal age (<36 years or ≥36 years) the trend was no longer significant (p=0.103). Indeed, analyses by maternal age groups showed that the proportion of births <24 weeks showed a significant increasing trend only among women under 36 years (p=0.013), whereas the trend remained stable over the years for women 36 years and older (p=0.759). Among women younger than 36 years, on average 5.1% of DS births occurred before 24 weeks, compared to 24.3% for women 36 years and older. In comparison, in infants without DS the proportions of births <24 weeks were 0.6% and 1.2%, respectively. A nearly significant interaction was observed between maternal age and year of registration (p=0.057).

Figure 2.1: *Trends in prevalence of Down syndrome per 10,000 births, with 95%-confidence intervals (n=3,169), stratified for gestational age (GA) at birth.*

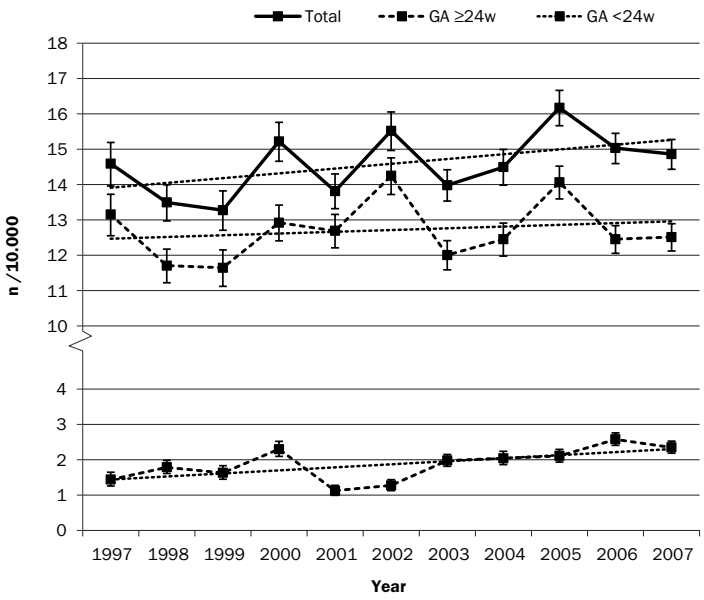
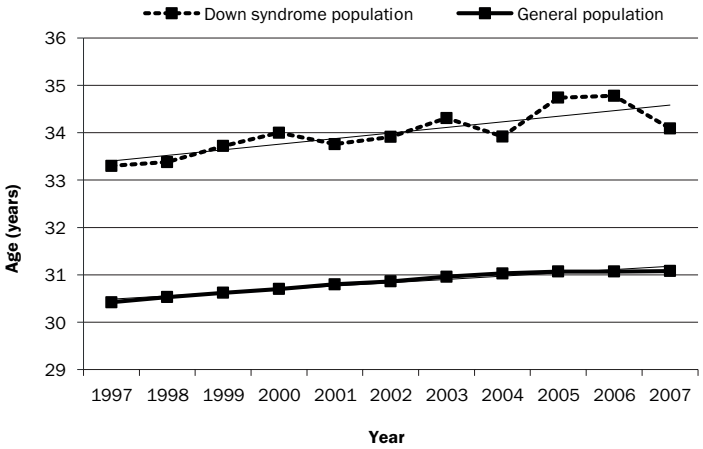


Table 2.3: *Prevalence of Down syndrome in the Netherlands during 1997-2007, born at or after 16 weeks of gestation; stratified for gestational age at delivery (<24 weeks vs. ≥24 weeks) and maternal age (<36 years vs. ≥36 years).*

	Number of births		DS prevalence per 10.000 [95% CI]	Number of DS births		Number of DS births	
Year	Total births	DS births		GA <24w	GA ≥24w	MA <36y	MA ≥36y
1997	194,663	284	14.59 [13.99;15.22]	28	256	92	192
1998	201,620	272	13.49 [12.99;14.01]	36	236	94	178
1999	202,649	269	13.27 [12.73;13.84]	33	236	99	170
2000	208,959	318	15.22 [14.68;15.78]	48	270	123	195
2001	204,880	283	13.81 [13.33;14.31]	23	260	112	171
2002	204,284	317	15.52 [14.98;16.07]	26	291	130	187
2003	202,429	283	13.98 [13.54;14.43]	40	243	113	170
2004	195,994	284	14.49 [13.99;15.00]	40	244	118	166
2005	189,837	307	16.17 [15.68;16.68]	40	267	138	169
2006	186,292	280	15.03 [14.61;15.47]	48	232	131	149
2007	183,028	272	14.86 [14.45;15.29]	43	229	107	165
Total	2,174,635	3,169	14.57 [14.43;14.73]	405	2,764	1,257	1,912

Abbreviations: GA – gestational age, MA - maternal age, DS - Down syndrome

Figure 2.2: *Mean maternal age in the Netherlands, stratified for total (n=2,174,635) and Down syndrome (n=3169) births.*



The distribution of gestational age in infants with DS, stratified for births before 24 weeks of gestation, and live and stillbirths at or after 24 weeks of gestation, is presented in Figure 2.3. Of all DS infants, 12.8% were born before 24 weeks of gestation (predominantly due to TOP, as suggested by the peak at 18-19 weeks of gestation). Mean gestational age in the total DS sample decreased from 36.2 weeks in 1997 to 35.1 in 2007 (Table 2.4).

Discussion

This nationwide eleven year birth cohort (1997-2007) shows that the prevalence of DS in the Netherlands remained stable at 14.57 per 10,000 births. Eighty-five percent of the infants were live born, resulting in on average 245 live born infants with DS annually.

Despite introduction of DS screening, there was no decrease in prevalence of DS. Prevalence of DS live births in the Netherlands was influenced by two factors. A postponement of childbearing to an older age led to an increase of DS pregnancies, also noted in other studies.[4,12,13] Such trend was offset by the effect of prenatal screening and diagnosis, which allows parents to choose whether to continue a DS pregnancy. However the counterbalancing effect of prenatal screening in the Netherlands was low. This is due to the fact that uptake of prenatal screening is rather low.[14] Towards the end of the study period only in a quarter of the pregnancies first trimester screening was carried out, resulting in a low total detection rate of DS pregnancies. Even after the official introduction of prenatal screening for all pregnant women, the uptake of first trimester screening with the combined test remained low, not surpassing 25%.[14] Factors that may influence uptake of prenatal screening may be the cost of the test (the test is free only for older women) and the attitude of parents towards DS.

Table 2.4: *Proportion of Down syndrome births according to gestational age (<24 weeks vs. ≥24 weeks).*

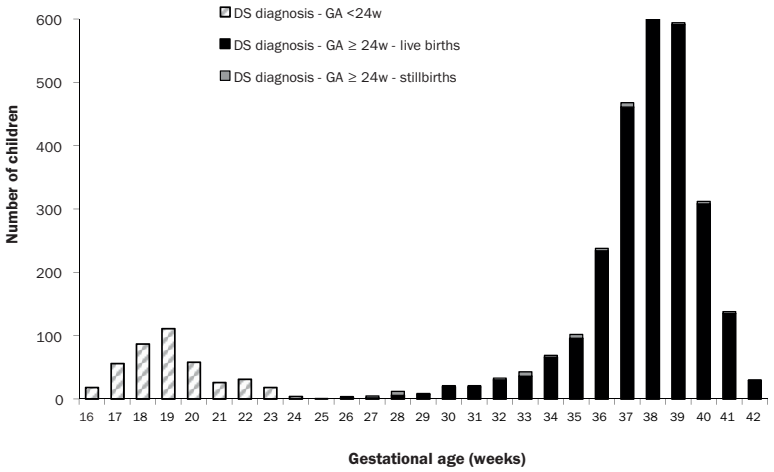
	Proportion within Down syndrome (%)					
	Total		Maternal age <36 years		Maternal age ≥36 years	
	gestational age		*gestational age*		*gestational age*	
Year	≥24w	<24w	≥24w	<24w	≥24w	<24w
1997	90.1	9.9	95.8	4.2	78.3	21.7
1998	86.8	13.2	95.5	4.5	71.3	28.7
1999	87.7	12.3	95.3	4.7	73.7	26.3
2000	84.9	15.1	95.4	4.6	68.9	31.1
2001	91.9	8.1	97.1	2.9	83.9	16.1
2002	91.8	8.2	97.9	2.1	82.9	17.1
2003	85.9	14.1	95.9	4.1	70.8	29.2
2004	85.9	14.1	91.5	8.5	78.0	22.0
2005	87.0	13.0	94.1	5.9	79.0	21.0
2006	82.9	17.1	92.6	7.4	71.8	28.2
2007	84.2	15.8	91.5	8.5	72.9	27.1
Trend		p=0.011		p=0.013		p=0.759

When interpreting the data, it should be taken into account that an underestimation of the total prevalence of DS is plausible, as a substantial number of terminations after first trimester screening will occur before 16 weeks of pregnancy, and these will therefore not be registered in the LNR/LVR. Another observation is that mean maternal age in DS births <24 weeks of gestation was much higher than in DS births ≥24 weeks (37.2 and 33.5 years, respectively). This implies that TOP was more prevalent among older women. This phenomenon could be the effect of the higher participation rate to prenatal screening in older women resulting in higher detection rates at older ages. Proportionally more older women undergo prenatal screening and diagnosis in the Netherlands, and consequently more terminations occur in this age group. The combination of the above mentioned factors resulted in a stable prevalence of DS (at or after 16 weeks of gestation) during 1997-2007. Also in other countries DS live births have not increased, despite an increasing maternal age.[15-17]

In our study TOP were not separately registered. The effect of TOP can be seen in the increase in proportion of DS births before 24 weeks of gestation. However, the increase is only significant among DS births to women younger than 36 years. This suggests that the (small) impact of first trimester screening is especially observable in younger women, while in older women participation in prenatal screening and diagnosis remained stable and low. The non-significant increase in DS births at or after 24 weeks of gestation in the study period confirms this trend indicating that the effect of increasing maternal age is not

counterbalanced by a higher participation of this age group in prenatal diagnosis.
We observed a peak in number of DS births at 18 to 19 weeks of gestation. This was most likely due to TOP. Indeed, after first trimester screening, fetal karyotyping can be performed by chorion villus sampling at 11-14 weeks with results available after 2 weeks, or by amniocentesis after 15 weeks of gestation, with results available after 3 weeks. With exclusion of early TOP, which would not be recorded in our database, the peak at 18-19 weeks account for the TOP after amniocentesis. A nationwide ultrasound screening is available in the Netherlands at 20 weeks; such screen could theoretically lead to late DS diagnoses and TOP up to the legal limit of 24 weeks, however such increase, if present, was negligible according to our analysis (see Figure 2.3). Of DS births from 16 to 23^{+6} weeks of gestation, TOP after 20 weeks accounted for a small proportion (19.3%).

Figure 2.3: *Distribution of gestational age (in weeks) in Down syndrome, presented by number of children born in 1997-2007 (n=3,169), stratified for gestational age (GA) at birth and (at ≥24 weeks) for live births or stillbirths.*



In the Netherlands, the number of invasive prenatal screening tests and TOP are registered by the Working Group on Prenatal Diagnosis and Therapy, a cooperation of the Dutch Society of Obstetrics and Gynecology and the Dutch Society for Clinical Genetics. They have reported an increase in the number of TOP from 1997-2009, before the legal term of 24 weeks of gestation.[18] This is in line with our observations. Unfortunately, no direct comparison can be made between these numbers and our data, because of insoluble registration differences.
The stable trend of prevalence in DS results in a continuous population of children with DS in the Netherlands. Prenatal screening for DS is introduced in the Netherlands for all pregnant women in order to allow pregnant women and their partners either to terminate the pregnancy if DS is diagnosed, or to prepare themselves for the birth of an affected

child.[8] Given the low uptake of prenatal screening in Dutch women and the observed stable trend in prevalence of DS, it seems that the first above-mentioned aim is not fully achieved. The reasons behind the low uptake of prenatal screening should be further explored. Maybe the practice and stable trend will change by offering the test free of costs to all pregnant women (at present it is free only for older women) or by replacing screening with non-invasive diagnosis on fetal DNA during pregnancy.[19,20] For now, a substantial number of children with DS are born alive in the Netherlands. For them, medical and social facilities are still needed to properly deal with their special needs.

Conclusions

National data of an eleven year birth cohort (1997-2007) from the Netherlands Perinatal Registry showed on average a prevalence of DS of 14.57 per 10,000 births. During this period, the prevalence of DS has not decreased: an estimated 245 children with DS were live born yearly. Apparently, the increase in maternal age and the low uptake of prenatal screening were observed to be stronger determinants of the prevalence of DS births than the effect of the introduction of first trimester screening. Among mothers younger than 36 years an effect of prenatal screening is observed (observed as an increasing trend in proportion of DS births before 24 weeks of gestation). So, the overall prevalence will remain stable, until the opportunities for performing prenatal screening will change (e.g. by offering the test costless or by replacing screening by non-invasive pregnant diagnosis on fetal DNA).

Acknowledgement

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Part 2
Growth

Chapter 3

Healthy growth in children with Down syndrome

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Abstract

Objective: To provide cross-sectional height and head circumference (HC) references for healthy Dutch children with Down syndrome (DS), while considering the influence of concomitant disorders on their growth, and to compare growth between children with DS and children from the general population.

Study design: Longitudinal growth and medical data were retrospectively collected from medical records in 25 of the 30 regional hospital-based outpatient clinics for children with DS in the Netherlands. Children with Trisomy 21 karyotype of Dutch descent born after 1982 were included. The LMS method was applied to fit growth references.

Results: We enrolled 1,596 children, and collected 10,558 measurements for height and 1,778 for HC. Children with DS without concomitant disorders (otherwise healthy children) and those suffering only from mild congenital heart defects showed similar growth patterns. The established growth charts, based on all measurements of these two groups, demonstrate the three age periods when height differences between children with and without DS increase: during pregnancy, during the first three years of life, and during puberty. This growth pattern results in a mean final height of 163.4 cm in boys and 151.8 cm in girls (-2.9 standard deviation (SD) and -3.0 SD on general Dutch charts, respectively). Mean HC (0 to 15 months) was 2 SD less than in the general Dutch population. The charts are available at www.tno.nl/growth.

Conclusions: Height and HC references showed that growth retardation in otherwise healthy children with DS mainly occurs in three critical periods of growth, resulting in shorter final stature and smaller HC than the general Dutch population shows. With these references, health care professionals can optimize their preventive care: monitoring growth of individual children with DS optimal, so that growth retarding comorbidities can be identified early, and focusing on the critical age periods to establish ways to optimize growth.

Introduction

Appropriate, up-to-date growth charts are necessary for evaluation of physical growth and provision of optimal health care. The World Health Organization has produced a global standard chart describing how children, under optimal conditions, grow worldwide.[1] This is based on the idea that all humans are more or less equal. Health care workers, on the other hand, often wish to use growth charts of a well-defined reference group closely related to the subpopulation they serve, since these charts provide a more accurate evaluation for an individual child.[2] Growth charts are available for various ethnic groups at specific moments in time.[3,4] Specific growth references have also been developed for children with various disorders known to interfere with growth, such as Turner and Down syndrome (DS).[5-9] Since growth assessment depends on the growth pattern characteristic for these conditions, disorder specific charts are desirable. Growth references for American children with DS have been constructed making it possible to accurately identify concomitant disorders known to influence growth.[6] Growth charts for Dutch children with DS were first published in 1996: they are shorter than children in the general Dutch population, but taller than their US peers with DS.[8]

In order to take the secular trend into account, growth references for height and head circumference (HC) need to be updated regularly.[3] Children with DS are at high risk of many disorders known to influence growth. Such disorders are generally regarded as exclusion criteria in growth studies: all children diagnosed with growth disorders or on medication known to interfere with growth are usually excluded.[3] However, in studies on growth in children with DS such exclusion criteria are usually not applied.[5-8,10] Only two recent growth studies in children with DS (in Japan and in the UK and Ireland) excluded children with various diagnoses known to affect growth.[11,12] In addition, no previous studies have investigated in which particular age periods height growth in otherwise healthy children with DS is relatively most delayed, by comparing their growth with that of healthy controls from the general population.

Therefore, the aim of the present study is to provide updated height and new HC growth references by a large nationwide sample, reflecting healthy growth in Dutch children with DS, and to compare their growth pattern with data from a recent nationwide study among children from the general Dutch population with focus on periods during which relative height differences increases. We think it is essential to establish new growth references for children with DS in the Netherlands, whereby a strict selection on their health status will be applied. Only with such references health care professionals can monitor growth of individual children with DS optimally, and can identify growth retarding comorbidities at an early stage.

Methods

Data source

To collect representative nationwide data, all specialized regional pediatric outpatient clinics for children with DS in the Netherlands were approached (n=30). These hospital-based clinics provide standard medical care for children with DS, according to the guideline of the Pediatric Association of the Netherlands.[13] All children with DS, who live in the service area of these clinics, are eligible to participate in this standard care by specialized pediatricians that includes screening for congenital cardiac defects, thyroid dysfunction, celiac disease, hearing and visual disorders as well as motor development and growth monitoring. Youth health care physicians working in special education and looking after older children with DS were also approached. Names of all participating clinics, pediatricians and youth health care physicians are mentioned in the acknowledgement.

At the clinics all data were retrospectively collected from medical records, between July 2009 and February 2010, by the first author, who is a trained physician. The de-identification was also completed by the first author, using study numbers. Additional data from the youth health care physicians caring for older children with DS in special education were collected by completing standard forms. All measurements were carried out according to protocol.[14] Height was measured using a recumbent length device or a stadiometer and HC by using a measuring tape (fiberglass or other non-expanding material). Data concerning medical conditions and treatment of each subject, and specifically those conditions known to interfere with growth, were gathered from medical records, as well as specific background information. Children were considered to be of Dutch descent if both parents were born in the Netherlands, as reported in the medical records. If medical or background information was not available, subjects were excluded.

Inclusion/exclusion

Children with Trisomy 21 karyotype were selected, and those with DS caused by mozaïcisme or translocation were excluded (verified by karyotype). All children born after 1982 were included (aged up to 26 years). We collected semi-longitudinal data on growth over the previous 10 years, recording data from 2000 onwards. We selected only the first recorded observation per interval: from an infant (age of 0 to 1 year old) one observation in each month, from a toddler (age 1 to 3 years old) one observation in each three months period and one observation in each six months in childhood and adolescence (age up to 26 years old). Measurements of HC were selected only from full-term children (born ≥37 weeks gestation) up to the age of 5 year. If gestational age was not specifically mentioned, children were considered to be born at term.

Health status

The children were categorized according to their health status in 4 groups: healthy, with only mild CHD, with only severe CHD or with other (multiple) concomitant disorders. Table 3.1 describes the characteristics of the various health categories and details of the criteria used for these categories.

Table 3.1. *Characteristics of the various health categories in the study population of children with Down syndrome.*

Healthy
Children without concomitant disorders that could possibly interfere with growth
Children were negatively screened for CHD, celiac disease and hypothyroidism
For example: children with cataract were included and children with musculoskeletal disorders were excluded
Mild CHD
Children with CHD not needing surgical intervention or medication and without pulmonary vascular disease
For example: children with an atrial septal defect or patent foramen ovale without complaints
Severe CHD
Children with CHD needing surgical intervention, medication, or with pulmonary vascular disease
For example: children with an atrioventricular septal defect or Tetralogy of Fallot
Other disorders
Children with other disorders and treatments known to interfere with growth, and children with multiple concomitant disorders
For example: children positively screened for hypothyroidism or celiac disease, children with congenital gastrointestinal disorders, children on anti-epileptic medication or corticosteroids (including inhalation medication)

Abbreviation: CHD – congenital heart defect

Statistical Analysis

Data cleansing was performed by excluding duplicate cases and outliers. Duplicate cases have arisen when children were seen at multiple centers and were identified by comparing sex, date of birth and background information such as nationality, and medical condition. Outliers were defined using height and HC standardized by age and sex according to the reference charts of the general Dutch population, calculated in standard deviation scores (SDS).[3] Cutoff values >2 or <-6 for height SDS and HC SDS were used. If a child had one measurement outside the cutoff values, all measurements of this child were excluded. Moreover, the longitudinal growth pattern of each subject was checked by plotting them and excluding values outlying the plot. Data were analyzed separately for boys and girls.

The difference in mean height SDS and HC SDS between healthy children with DS and children with DS and a mild or severe CHD were tested by linear mixed-effects models. To correct for possible differences in the prevalence rates of sex and mean age, we adjusted

these analyses by age and sex. Furthermore, growth references for boys and girls with DS were fitted for body height by age (range 0 to 21 years) and HC by age (range 0 to 15 months) using the LMS method. Growth references were fitted in R Version 2.9.0 using Generalized Additive Models for Location Scale and Shape (GAMLSS).[15] The LMS method summarizes the distribution by three age-dependent smooth curves representing skewness (L curve), median (M curve) and coefficient of variation (S curve).[16] The LMS method is based on the principle that after a transformation the data have to follow a standard normal distribution. The following transformations of age were tested to expand the ages where growth velocity is high and compress age where growth velocity is low: the age transformation proposed by Cole, a square root transformation, a log transformation and a cube root transformation.[17] Worm plots were used as a diagnostic tool to visualize the fit to the data.[18] These plots check the residuals for different age levels and identify locations at which the fit can be improved. We fitted charts with lines of the -2.5, -2.0,-1.0, 0, 1.0, 2.0 and 2.5 SD (corresponding with 0.6, 2.3, 15.9, 50, 84.1, 97.7 and 99.4 percentile). The choice of these SD-lines is in agreement with the latest reference charts for the general Dutch population. We did not fit growth charts for the health category 'other disorders', because of the wide variety of data and medical conditions of the children in this category. Also, growth charts for subgroups in this category – like children with hypothyroidism or celiac disease – were not fitted, because of the small number of children included in our study.

In addition to the reference charts for height, formulas for Target Height (TH) for children with DS were calculated.[19] The TH was calculated by the method of Hermanussen and Cole, which takes into account two correlations (assortative mating r(P,P) and the parent-offspring correlation r(P,O)).[20] For this calculation, the data from three nationwide sources have been applied. The correlations were obtained from the latest growth study in the general Dutch population (2009) and were r(P,P)=0.19 and r(P,O)=0.58.[21] The calculation for the paternal and maternal height SD was based on the results from the previous national growth study (1997); final height of children measured in this study corresponds with final height of this generation of parents.[3] For the calculation of the TH SDS the mean and SD of final height of the children with DS observed in this study were used.

The established growth references for height and HC were compared with the most recent reference charts for the general Dutch population, by calculating SDS.[21]

Results

Pediatricians working in 25 hospital-based clinics (83% of all Dutch DS clinics) and 14 youth health care physicians caring for older children with DS in special education agreed to participate in this study. After exclusion of 7 children with a growth pattern outside the cut-off values, a total of 1,843 children with Trisomy 21 were identified. Of these, 1,596 are of Dutch origin: 891 boys (55.8%) and 705 girls (44.2%). The sample provided 10,558

measurements for height and 1,778 for HC in the age range 0 to 5 years and born at term (418 HC measurements from children born pre-term in this age range were excluded). Of all height measurements, 98% were derived from the DS clinics and 2% from the youth health care physicians in special education. The HC measurements were only derived from the DS clinics. Table 3.2 provides total number of subjects and measurements of height and HC, split according to sex and to various health categories. In our sample, 26.6% was categorized as healthy, 15.0% had only a mild CHD and 16.9% only a severe CHD. The remaining group, 41.5%, was categorized as having various other disorders; most of them (over 60%) had multiple concomitant disorders.

Table 3.2. *Number of subjects and measurements for height and head circumference of 1,596 Dutch subjects with Trisomy 21, specified by the health categories.*

	Subjects				Measurements			
	Height		HC*		Height		HC	
Health category	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
Healthy	257	167	71	57	1,378	938	202	139
Mild CHD	130	110	49	46	751	661	169	147
Severe CHD	114	155	38	50	738	997	134	187
Other disorders	390	273	140	88	2,970	2,125	443	357
Total	891	705	298	241	5,837	4,721	948	830

Abbreviations: HC – head circumference, CHD – congenital heart defect
* Only children born full-term up to the age of 5 years were included

Growth of children with DS within various health categories

Growth of healthy children with DS and those who suffer from mild CHD showed no difference in mean height SDS (p=0.832) and HC SDS (p=0.790). Both girls and boys with DS and severe CHD had significant lower mean height SDS and HC SDS compared to healthy children with DS or children with DS with mild CHD (both p-values <0.001). Mean height is observed to be 0.4 SD lower. This growth retardation arises in the first year of life; during childhood no further deflection neither catch-up growth was observed.

Growth references

Data for growth references of height and HC were derived by combining the groups of healthy children with DS and children with DS and mild CHD (664 children for height, and 223 for HC (see Table 3.2). The numbers of measurements of these selected groups, arranged by age en sex, are shown in Table 3.3. By fitting the growth references for height, the cube root transformation of age showed the best fit and was selected. Table 3.4 summarizes mean height and SD, arranged by age and sex. Mean birth length was 48.9 cm in boys and 48.4 cm in girls with DS. Mean final height was 163.4 cm in boys and 151.8 cm in girls.

Table 3.3. *Frequencies of measurements for height used for plotting the reference curves for Dutch children with Down syndrome, arranged by age and sex.*

	Height*		
Age (years)	**Male**	**Female**	**Total**
0	474	392	866
1	241	201	442
2	201	147	348
3	178	129	307
4	151	101	252
5	132	96	228
6	117	86	203
7	83	89	172
8	105	66	171
9	86	49	135
10	72	52	124
11	62	46	108
12	68	37	105
13	52	29	81
14	36	28	64
15	31	12	43
16	20	14	34
17	8	6	14
≥18	12	19	31
Total	2,129	1,599	3,728
	Head circumference^		
Age (years)	**Male**	**Female**	**Total**
0	244	199	443
1	69	50	119
2	22	18	40
3	19	10	29
4	17	9	26
Total	371	286	657

* Height measurements of the children categorized as healthy or with only mild congenital heart defect (n=664)
^ Head circumference of the children categorized as healthy or with only mild congenital heart defect, born at term (n=223)

Growth references for HC were established for up to the age of 15 months. We did not have enough measurements to construct growth references after the age of 15 months. By fitting HC references for boys no transformation of age and for girls the age transformation proposed by Cole was applied.[17] Table 3.5 summarizes the LMS-values, arranged by age and sex. At birth mean HC was 33.8 cm in boys and 32.9 cm in girls with DS; at the age of 15 months this was 45.0 cm and 43.7 cm respectively. The new reference charts are available at www.tno.nl/growth.

Target Height

The calculated formulas for TH of children with DS are:

TH boys DS (cm) = 41.8 + 0.328 x (paternal height) + 0.359 x (maternal height)

TH SDS boys DS (SD) = (TH boys DS – 163.4)/6.2

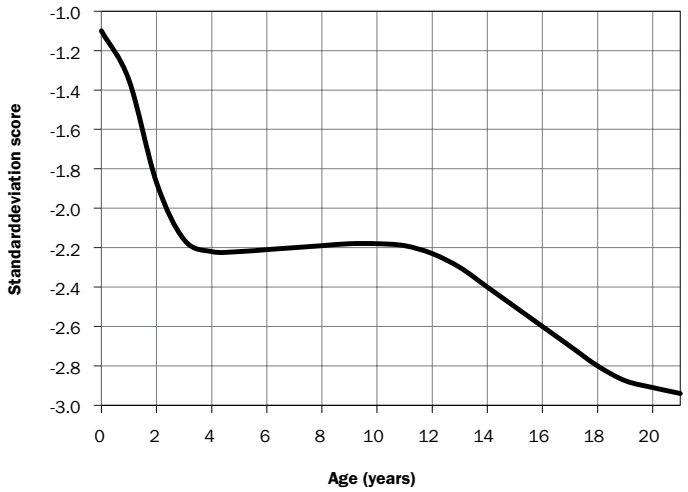
TH girls DS (cm) = 8.64 + 0.387 x (paternal height) + 0.422 x (maternal height)

TH SDS girls DS (SD) = (TH girl DS – 151.8)/7.3.

Comparison to the general Dutch population

In comparison with the currently used reference charts for the general Dutch population, a markedly shorter stature was found in children with DS.[21] Mean height revealed a deflection in the first 3 years of life from -1.1 SD at birth to -2.2 SD at 3 years, for boys as well as girls. During the age interval of 3 to 12 years average growth remained stable at -2.2 SD, and deflected again during puberty to a final height at -2.9 SD (20.4 cm shorter) for boys and -3.0 SD (18.9 cm shorter) for girls (Figure 3.1).[21] For HC, between birth and 15 months, mean values for boys and girls with DS are on average 1.8 SD lower (range -1.3 to -2.0) compared to the general Dutch population.[3]

Figure 3.1. *Mean height (SDS) of the Dutch children with Down syndrome compared to the general population*.*



* Comparison is made to the mean height of the national Dutch growth study (2009).

Table 3.4. *Mean height (cm) and standard deviation (SD) of the new references for length/height of Dutch children with Down syndrome, arranged by age and sex.*

	Boys		Girls	
Age (weeks)	**Mean**	**SD***	**Mean**	**SD***
0	48.9	2.5	48.4	2.1
2	50.4	2.6	49.8	2.2
4	51.9	2.6	51.3	2.2
6	53.4	2.6	52.6	2.2
8	54.8	2.6	54.0	2.2
10	56.2	2.6	55.3	2.2
12	57.5	2.6	56.5	2.3
16	60.0	2.6	58.7	2.3
20	62.2	2.6	60.7	2.3
24	64.1	2.7	62.6	2.4
28	65.8	2.7	64.2	2.4
32	67.3	2.7	65.7	2.4
36	68.6	2.7	67.0	2.5
40	69.8	2.7	68.2	2.5
44	70.9	2.8	69.3	2.5
48	71.9	2.8	70.3	2.6
52	73.0	2.8	71.3	2.6
Age (years)				
1.5	78.3	3.0	76.4	2.8
2.0	82.6	3.1	80.8	3.0
2.5	86.4	3.3	84.6	3.2
3.0	89.8	3.5	88.1	3.5
3.5	93.1	3.7	91.6	3.7
4.0	96.4	3.9	95.2	3.9
4.5	99.7	4.0	98.6	4.1
5.0	102.9	4.2	101.7	4.3
6.0	109.0	4.5	107.2	4.6
7.0	114.7	4.8	113.0	4.9
8.0	119.9	5.0	118.7	5.2
9.0	125.2	5.3	124.0	5.5
10.0	130.8	5.5	129.3	5.8
11.0	136.8	5.7	134.4	6.1
12.0	142.9	5.8	139.1	6.3
13.0	148.7	5.9	142.9	6.5
14.0	153.5	6.0	145.9	6.6
15.0	157.2	6.1	147.9	6.8
16.0	159.8	6.2	149.4	6.9
17.0	161.8	6.2	150.5	7.0
18.0	163.0	6.2	151.2	7.1
19.0	163.4	6.2	151.6	7.2
20.0	163.4	6.2	151.8	7.3
21.0	163.4	6.2	151.8	7.3

* Individual height SDS can be calculated by: SDS = (height (cm) – mean height (cm)) / SD (cm).
Abbreviations: SD – standard deviation, SDS – standard deviation score

Discussion

This study yields new charts of healthy growth of children with DS. Growth patterns were analyzed in 1,596 Dutch children with DS, with 10,558 height measurements and 1,778 HC measurements. All children were selected nationwide from pediatric hospital-based outpatient clinics specialized in the standard care of children with DS. Selection based on health complaints or influenced by financial restrictions was avoided, since all children with DS in the Netherlands were invited to avail of this care without financial barriers, as encouraged by the Dutch Down Syndrome Foundation (largest Dutch parent supporting organization). The result is a nationwide representative sample.

Our new reference charts for Dutch children with DS are unique. No previous studies on growth in DS made such a stringent selection of subjects with respect to their health. All children have received high quality medical care according to the guideline of the Pediatric Association of the Netherlands and underwent standard screening at regular intervals, provided by the regional hospital-based outpatient clinics for children with DS.[13] This screening program provided confidence that children categorized as healthy in fact have no undiagnosed concomitant disorders, such as hypothyroidism, mild CHD and celiac disease. To illustrate the stringent selection: children with positive screening results for hypothyroidism and celiac disease were excluded (even though appropriate treatment was started early), because there is no evidence that growth could not be affected already.

The children with severe CHD showed growth retardation during the first year of life. After this period they had growth velocities similar to the healthy children with DS. In the Netherlands the surgical correction of significant CHD takes place preferably at the age of 2-4 months.[22] This early treatment may result in normal growth after the age of 1 year without further deflection. Cronk et al. also described growth retardation caused by CHD in children with DS.[6] However, they were unable to evaluate the effects of different types of cardiac lesions (those which healed spontaneously or those treated by corrective surgery) on growth. The present study provided appropriate data to make this distinction.

When comparing mean final heights of children with DS with other countries, we should take into account the different inclusion and exclusion criteria (Table 3.6). However, it is probably reasonable to conclude that Dutch children with DS are relatively tall among children with DS. Growth charts are available for West-European children with DS in Sweden, the UK and Ireland, and Northeastern France.[5,12,23]

Our study is the first to propose formulas to estimate the expected final height in children with DS. The TH formulas were derived under the assumption that the correlation between mid parental height SD and child height SD in Dutch children with DS is identical to the general Dutch population. Further research is needed to investigate whether this assumption is justified.

Table 3.5. *New head circumference (cm) references for 0-15 months in Dutch children with Down syndrome: values of L (skewness), M (median), and S (coefficient of variation)*, categorized by age and sex.*

	Boys			Girls		
Age (weeks)	**L**	**M**	**S***	**L**	**M**	**S***
0	2.96	33.8	.0349	1	32.9	.0267
2	2.65	34.6	.0343	1	33.8	.0272
4	2.34	35.3	.0336	1	34.7	.0277
6	2.03	36.1	.0330	1	35.5	.0280
8	1.72	36.8	.0324	1	36.4	.0281
10	1.42	37.5	.0319	1	37.1	.0279
12	1.12	38.2	.0313	1	37.8	.0276
16	0.54	39.4	.0302	1	38.8	.0270
20	-0.01	40.4	.0292	1	39.7	.0265
24	-0.52	41.2	.0283	1	40.4	.0261
28	-0.99	42.0	.0274	1	41.0	.0259
32	-1.41	42.6	.0266	1	41.5	.0257
36	-1.80	43.1	.0258	1	42.0	.0255
40	-2.14	43.5	.0250	1	42.3	.0254
44	-2.45	43.9	.0243	1	42.7	.0252
48	-2.72	44.2	.0237	1	42.9	.0251
52	-2.97	44.4	.0231	1	43.2	.0249
56	-3.19	44.6	.0225	1	43.3	.0248
60	-3.40	44.8	.0221	1	43.5	.0247
65[a]	-3.64	45.0	.0216	1	43.7	.0245

a Corresponding with 15 months.
* Individual head circumference SDS can be calculated by: SDS = {(height (cm)/M)^{L} -1} / L*S, L≠0
(if L=0: SDS = ln(height (cm)/M) / S).

We compare HC in our population with values published by others. Reference charts for HC are also available for children with DS from Sweden, Northeastern France, Sicily, UK and Ireland, the USA, Egypt and Saudi Arabia, suitable for use in these countries.[5,10,12,23-26] Benefits of our study are the LMS-values presented, whereby for each individual the deviation exactly can be calculated. Comparing HC showed the Swedish children with DS have an average HC of 33 cm at birth, similar to our children with DS.[5] This mean values at birth correspond with -0.5 SD on the reference charts for the general Swedish population, however with -1.5 SD for the general Dutch population. At 15 months mean HC is also identical in Swedish and Dutch children with DS. Since the other studies do not present enough details of their observations, we were unable to make further comparisons.

Table 3.6. *Growth studies presenting mean final height (cm) of children with Down syndrome, with the applied inclusion and exclusion criteria, by country of origin.*

		Inclusion	Exclusion criteria	Boys	Girls
The Netherlands	**This study**	T21	All concomitant disorders known to interfere with growth; separate analyses of mild and severe CHD	163.4	151.8
Sweden[5]	**2002**	DS	Treatment with growth hormone	161.5	147.5
UK, Ireland[12]	**2002**	DS	Coexistent major pathology such as severe CHD or preterm birth	157	146
Japan[11]	**2003**	T21	Complications that might affect natural growth	153.2	141.9
France[23]	**1999**	T21	Severe CHD	154	140
USA[6]	**1988**	T21	Separate analyses of moderate and severe CHD (if information is available)	153	146

Abbreviations: T21 – Trisomy 21, DS – Down syndrome (including DS caused by Trisomy 21, mozaïcisme or translocation), CHD – congenital heart defect

What are the main differences in growth pattern between DS and the general population? Mean birth length in DS is 1 SD lower than in the general population, indicating that children with DS already show retarded growth during pregnancy. Also, during the first three years of life they grow slower compared to the general population; the gap stays relatively constant during the age interval 3-12 years. After the age of 12 year a further deflection in growth is observed. This pattern is observed to be the same in boys and girls with DS. The mentioned three periods are already described by Karlberg et al. in the infant-childhood-puberty (ICP) model, which described during infancy (from birth up to about 3 years of age) and during puberty higher growth velocity than during childhood.[27] So, the children with DS show growth retardation just during the critical periods of growth when the highest growth velocity occurs. This finding indicates the age periods in which further health benefit may be obtained. Health care professionals should focus on these critical periods when providing preventive care to children with DS with the aim to establish ways to optimize growth during these specific periods. Either the observed growth retardation may be due to their genetic makeup or it may be caused by physical problems they encounter, such as feeding problems. In puberty an early or short growth spurt also limits final growth. Further research is needed to explain our observations and to provide physiological clarification on the nature of this growth retardation. All in all, these effects result in a substantial difference in final height (boys: 20.4 cm; girls: 18.9 cm).

Body weight will be reported separately. Because of the current increase in the proportion of children with obesity, it is not desirable to reflect the present distribution of weight in this population. Therefore, the increase in the proportion of children with obesity and the need for normative charts for weight deserve special attention.[21,28]

A limitation of our study is that the measurements of height and HC were retrospectively collected. This methodology may lead to more variation in the measurements compared to studies that used prospectively collected data, as all general Dutch growth studies did. We were however unable to detect such increased measurement variability in the data. The S-curves (which model the coefficient of variation) were quite similar in our growth charts and the charts of the general Dutch population (established in 2009). So, we do not expect that the used methodology had an impact on the variability in the growth charts. A benefit of the applied methodology is the larger and timelier data set. Similar methods were used in other growth studies in children with DS.[5,12,23]

The longitudinal data resulted in a varied number of measurements per child. To determine the possible influence of this variation, the statistical analyses were repeated where data points were weighted – whereby a weighting factor was calculated as the inverse of the number of measurements per child – in order to prevent over-representing children with a large number of measurements. This solution was almost the same as the unweighted analysis; differences in mean height were smaller than 0.1 SD.

For the interpretation of individual growth curves plotted on a reference chart, criteria are needed to define abnormal growth. No specific criteria for the charts for children with DS have been proposed. The utility of the referral criteria for the general Dutch population as presented in the guideline 'Detection and referral criteria in short stature' has not been tested for growth in children with DS. Further research is necessary to see whether such referral criteria are equally suitable for children with DS.[29,30] For the moment, we tentatively suggest to use the criteria for the general population (which are all framed in SDS) for children with DS.

Implications

The availability of appropriate up-to-date growth charts, that reflect healthy growth of height and HC in Dutch children with DS, will potentially improve the medical care they receive. Using these charts secondary growth abnormalities may be detected more accurately. For example, limited growth of height may be a symptom of hypothyroidism and a relative large HC may be caused by hydrocephalus. The charts were based on a large sample that is stringently selected on the basis of their health status, and therefore we will encourage research to investigate the suitability of these charts for international application.

In children with DS with severe CHD growth is decelerated during the first year of life, in comparison to reference growth in the healthy infants with DS. During childhood no catch-up growth is noticed in these children with DS and severe CHD, neither does their

growth decline further. Future research should focus on the exact qualities of the observed deflections in growth of otherwise healthy children with DS: is their growth spurt restricted with a lower velocity or do other phenomena play a role. Lack of significant catch up growth in children with DS and severe CHD could be the result of similar failure to spurt. We can only hypothesis on the full nature of growth retardation in otherwise healthy children with DS: as their growth is primarily restricted by Trisomy 21 the mechanism is unknown. Is it primarily metabolic, hormonal or chondrocyte dysfunction? Or could it be explained by further advanced genome-wide analysis?

Conclusions

Growth patterns in otherwise healthy Dutch children with DS were established based on data from a large nationwide population. Growth in healthy children with DS differs from children with DS and severe CHD (0.4 SD). The established growth charts demonstrate the three age periods when height differences between children with and without DS increase: during pregnancy, during the first three years of life, and during puberty. This growth pattern results in a mean final height of 163.4 cm in healthy boys with DS and 151.8 in girls (a difference of 3 SD in comparison to the general population), and mean HC at birth of 33 cm and 44 cm at the age of 15 months (almost 2 SD less than in the general Dutch population). All in all, with these new growth charts, that reflect healthy growth in children with DS, health care professionals can monitor growth of individual children with DS optimal. In this way, early identification of growth retarding comorbidities will be enabled and ultimately the health of children with DS will be improved.

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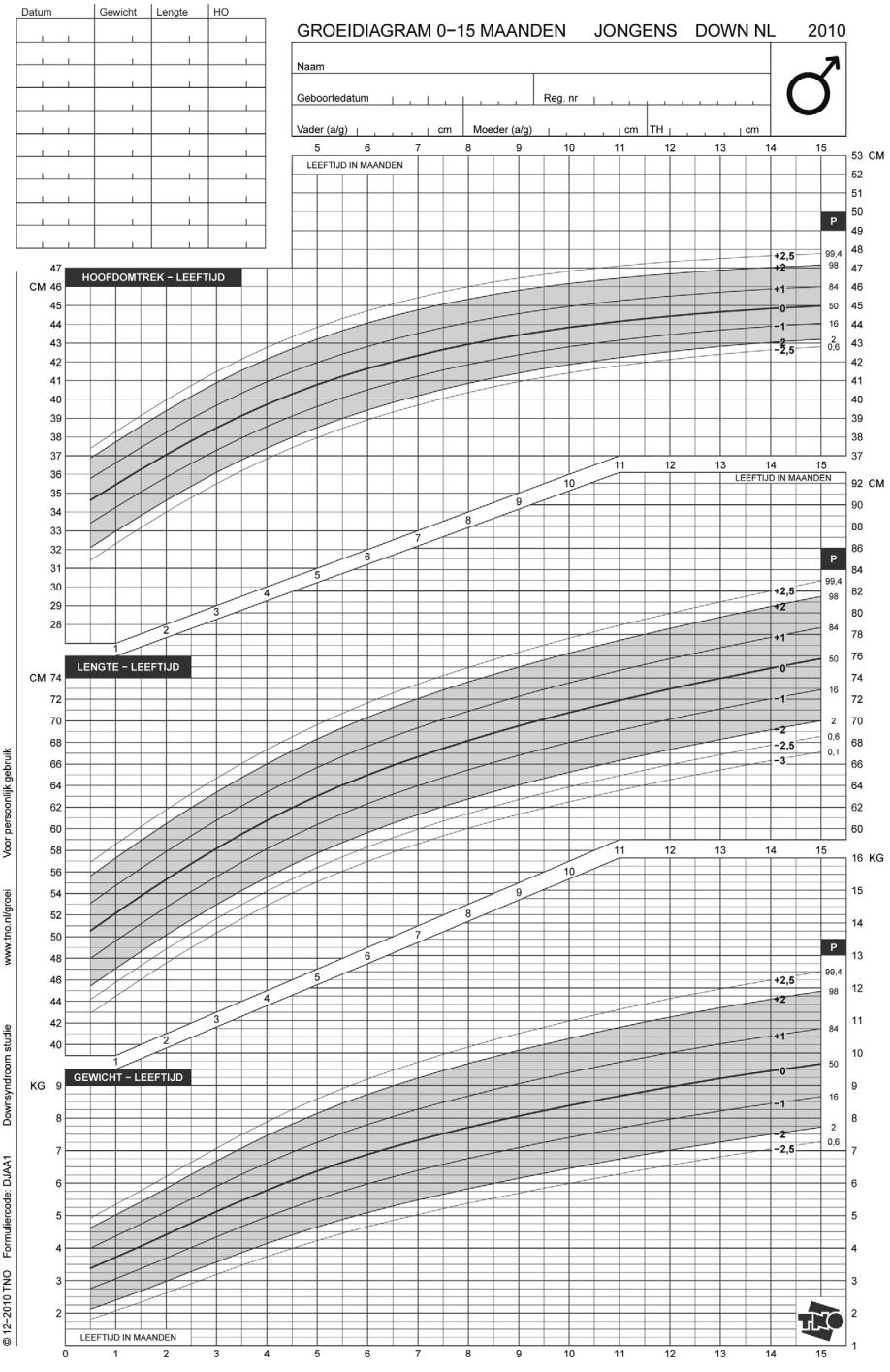
Growth charts
Groeidiagrammen

Dutch growth charts
for children with Down syndrome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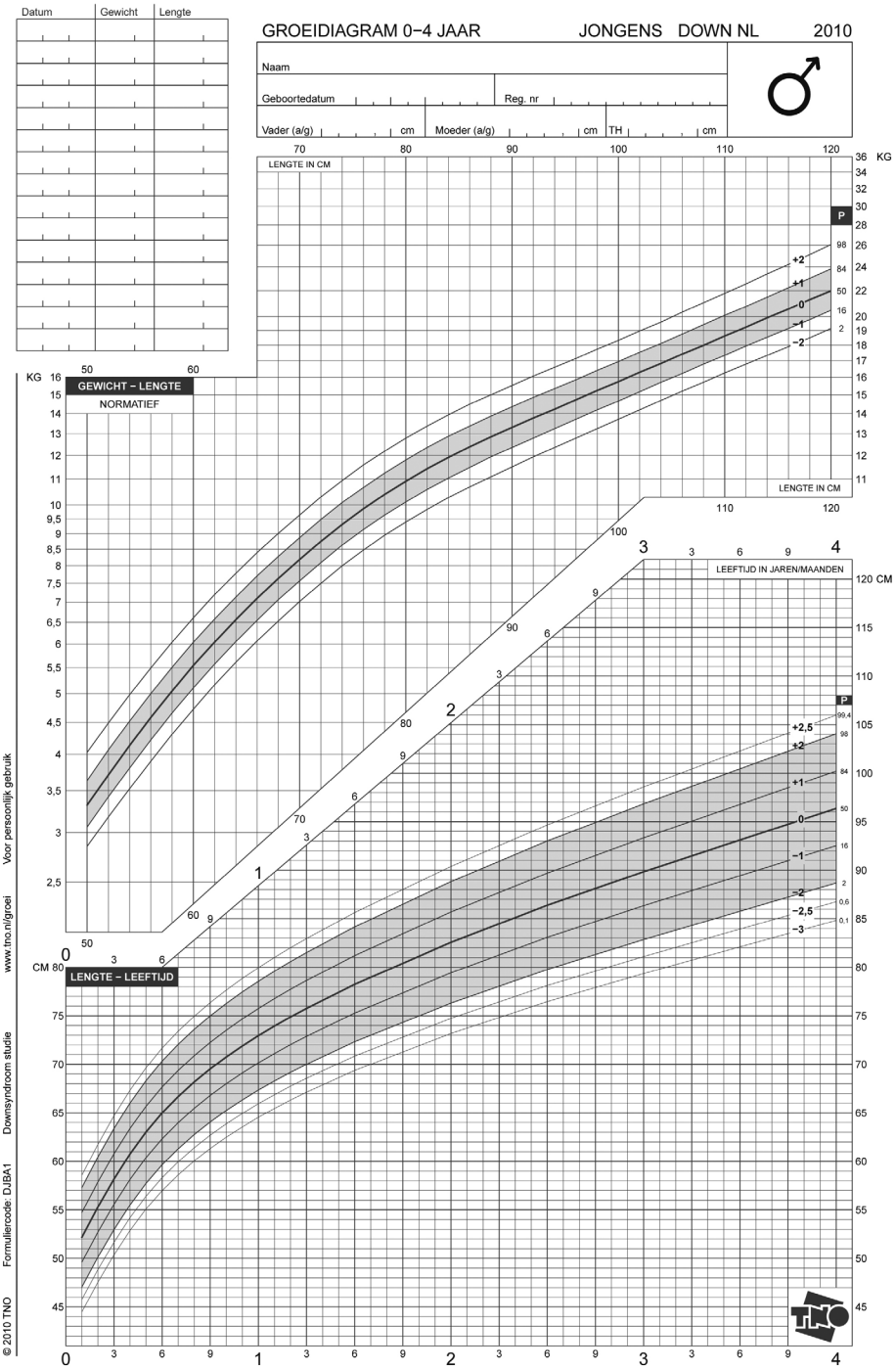
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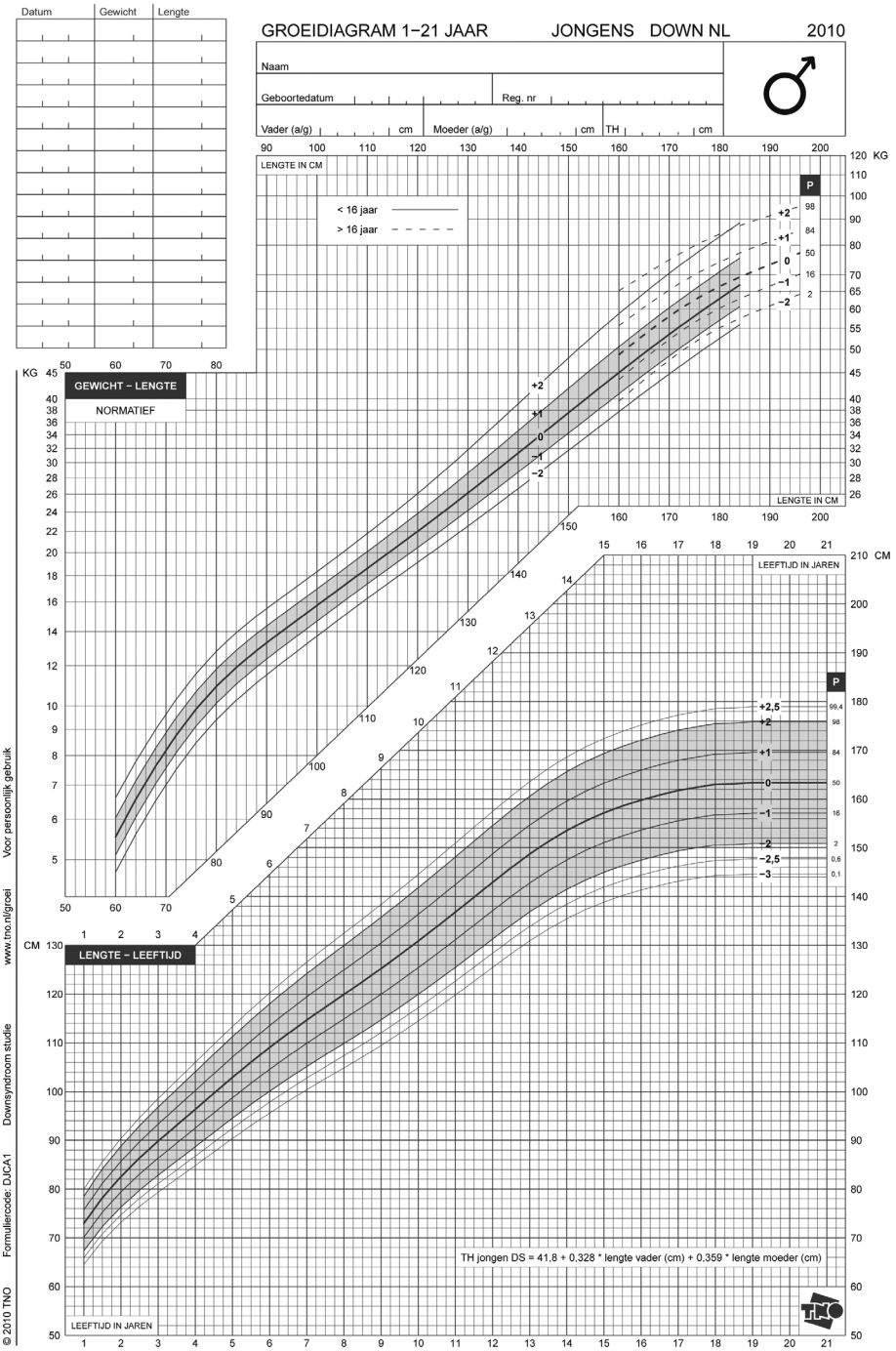
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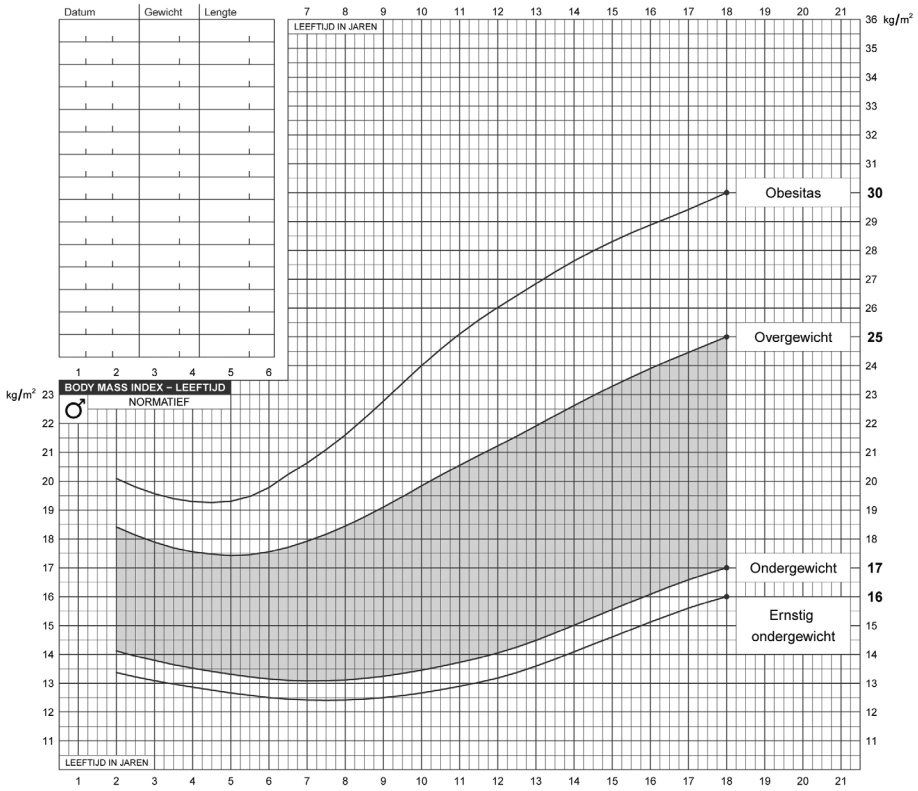
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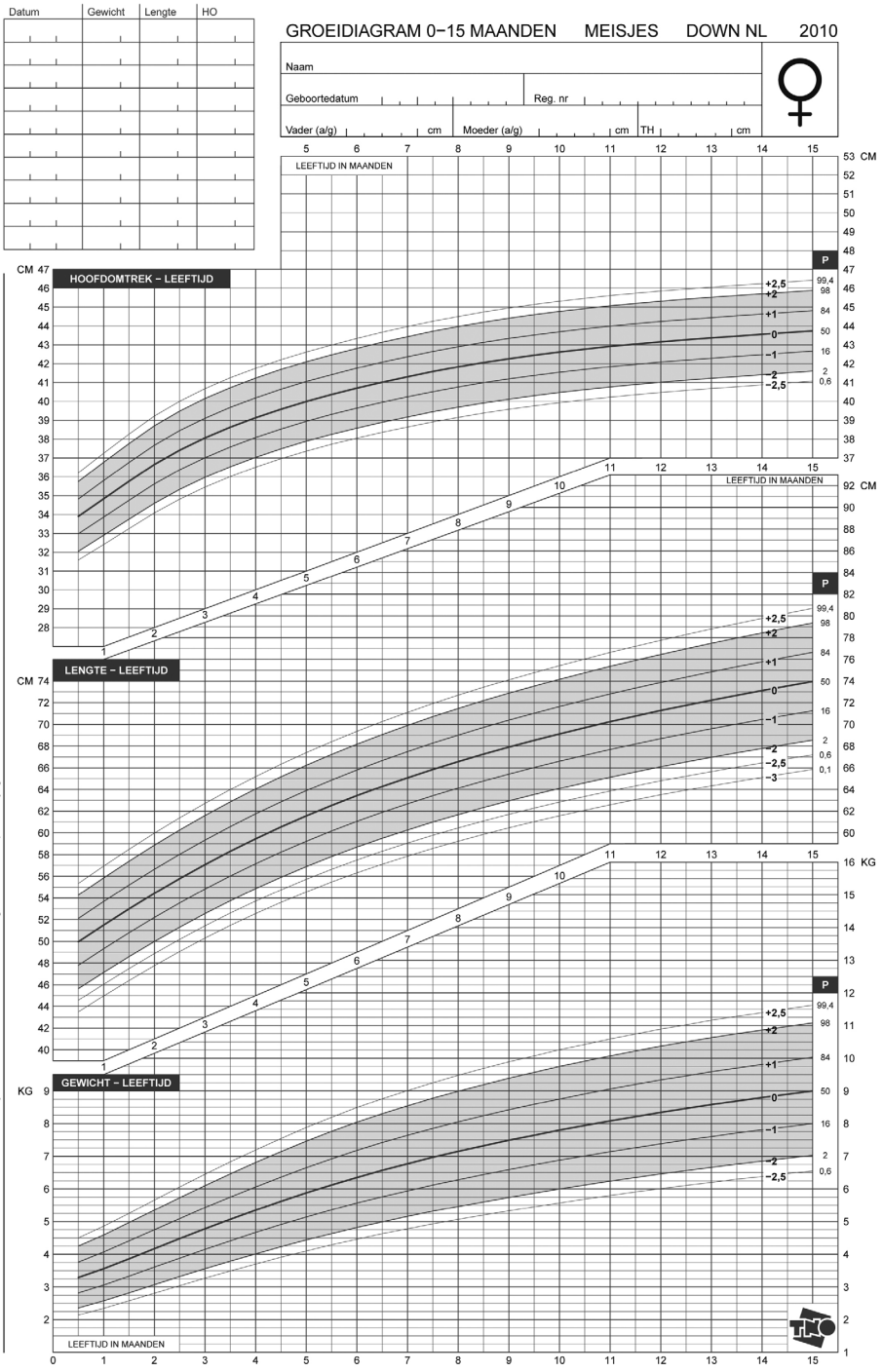
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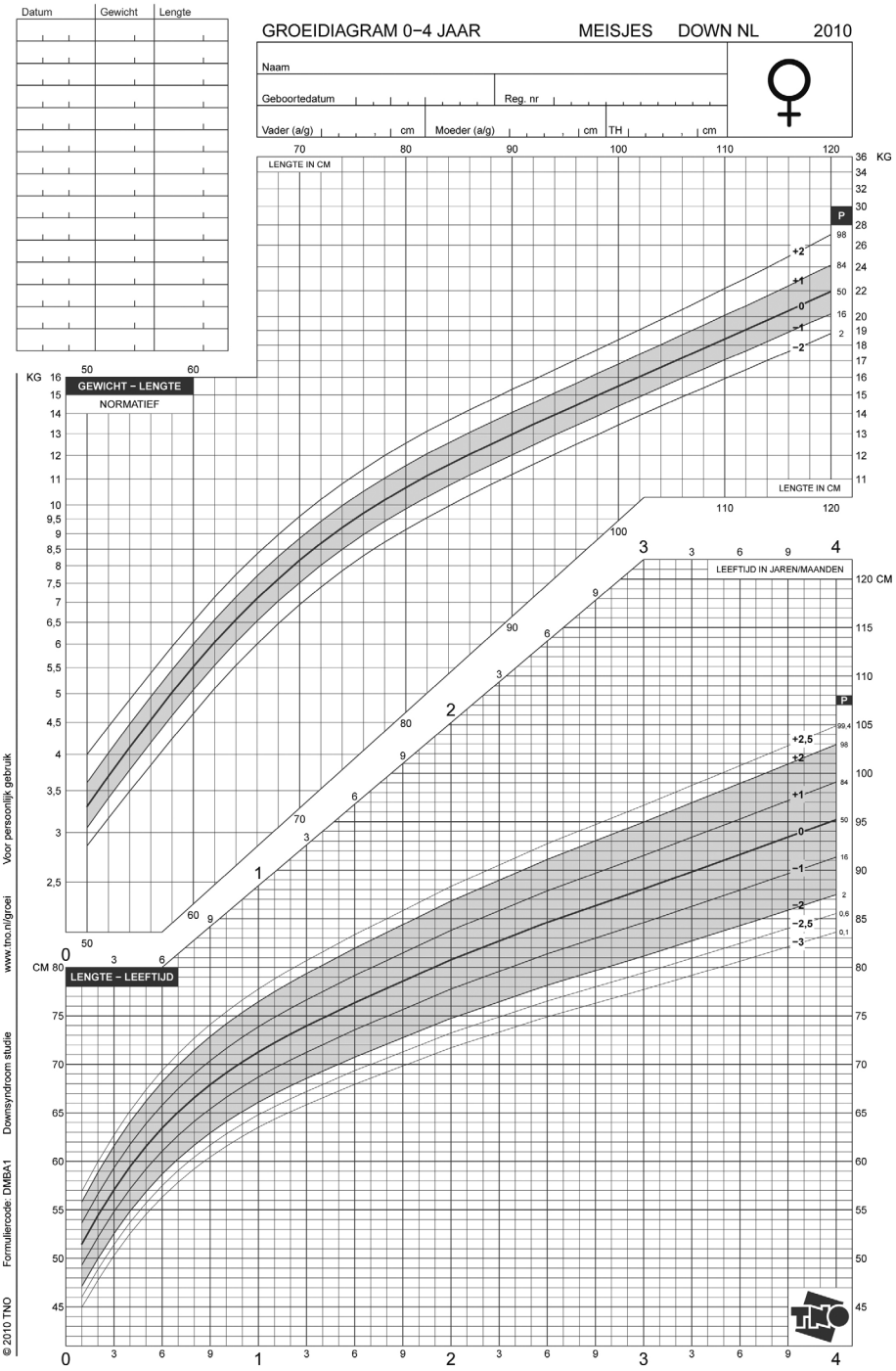
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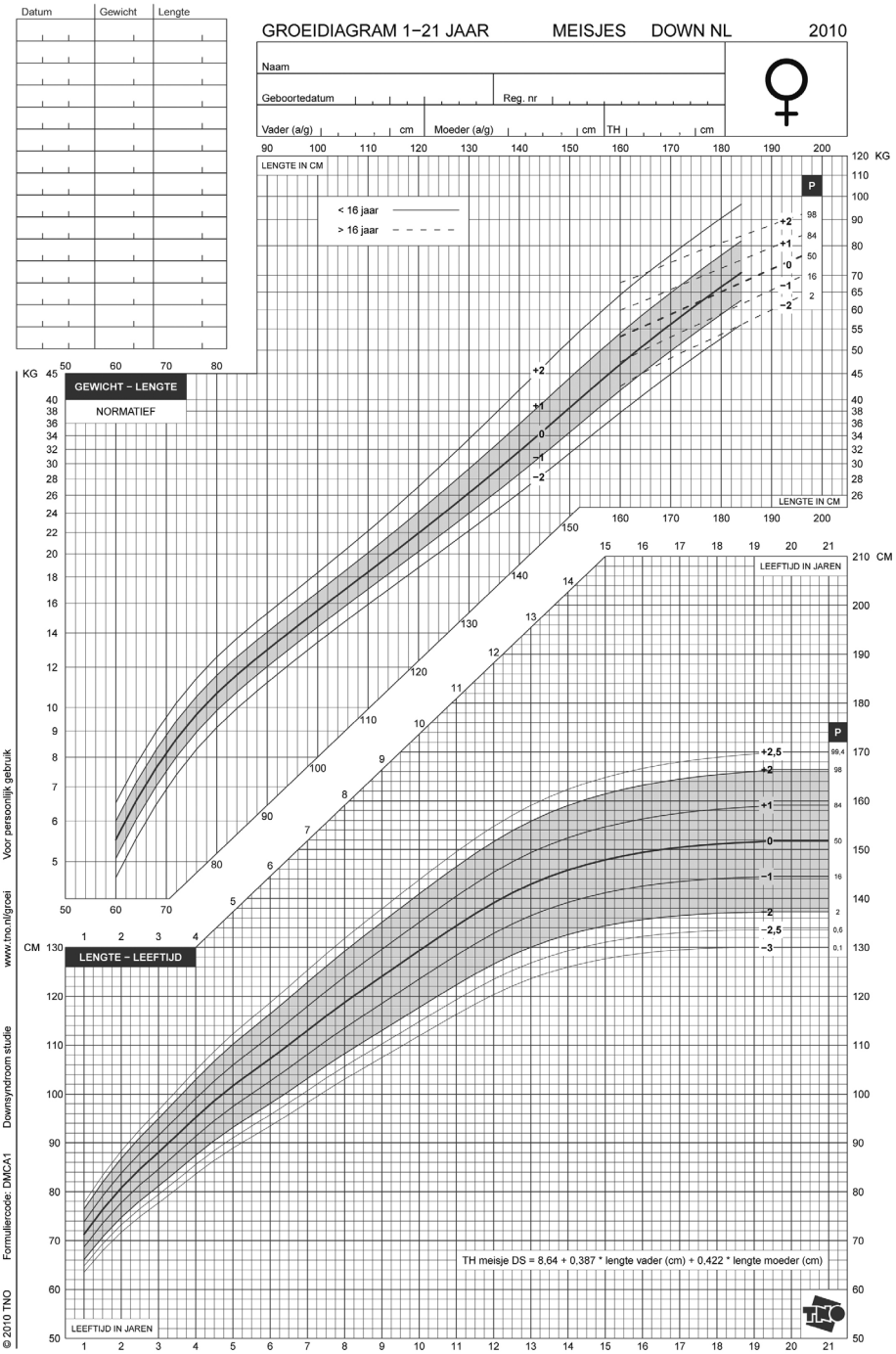
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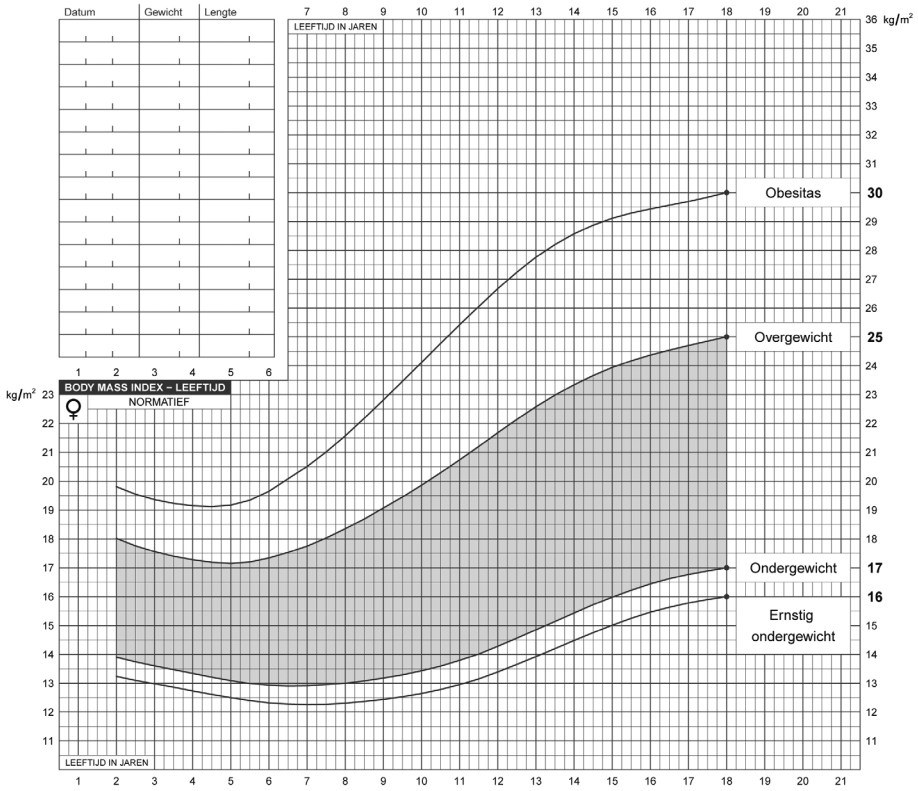
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BODY MASS INDEX – LEEFTIJD
NORMATIEF
♀
Obesitas
Overgewicht
Ondergewicht
Ernstig ondergewicht
LEEFTIJD IN JAREN

Chapter 4

Prevalence of overweight in Dutch children with Down syndrome

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Abstract

Objective: Prevalence of overweight in children is increasing, causing various health problems. This study aims to establish growth references for weight and to assess the prevalence rates of overweight and obesity in a nationwide sample of Dutch children with Down syndrome (DS), while taking into account the influence of comorbidity.

Patients and Methods: In 2009, longitudinal growth data from Dutch children with Trisomy 21 who were born after 1982 were retrospectively collected from medical records of 25 Dutch regional specialized DS centers. 'Healthy' was defined as not having concomitant disorders or having only a mild congenital heart defect. Weight and body mass index (BMI) references were calculated using the LMS method, and prevalence rates of overweight and obesity using cut-off values for BMI as defined by the International Obesity Task Force. Differences in prevalence rates were tested by multi-level logistic regression analyses to adjust for sex and age.

Results: Growth data of 1,596 children with DS were analyzed. Compared to the general Dutch population, healthy children with DS were more often overweight (25.5% vs. 13.3% in boys, and 32.0% vs. 14.9% in girls) and obese (4.2% vs. 1.8%, and 5.1% vs. 2.2%, respectively). Prevalence rates of overweight between DS children with or without concomitant disorders did not vary significantly.

Conclusions: Dutch children with DS have alarmingly high prevalence rates of overweight and obesity during childhood and adolescence. Health care professionals should be aware of the risk of overweight and obesity in children with DS, to prevent complications.

What's known on this subject

- Some groups of children are especially prone to develop overweight and obesity.
- Overweight in children affects their physical and psychological health, and shortens life expectancy.
- Overweight in children with Down syndrome is attributed to their commonly found comorbidities.

What this study adds

- Prevalence rates of overweight and obesity in a nationwide sample of otherwise healthy children with Down syndrome.
- Overweight is observed from very young ages in healthy children with Down syndrome and those with severe congenital heart defects.

Introduction

The worldwide increase in the prevalence of overweight and obesity in children is alarming.[1] Overweight and obesity are even more common in children with Down syndrome (DS). One third to one half of children with DS are overweight. These rates vary because of differences in study population, methods and cut-off values used in the studies.[2-6]

Overweight and obesity cause both psychological and physical health problems in children, such as low self-esteem, depressive symptoms, lower general physical condition, and metabolic complications. It is not known whether all these consequences of overweight and obesity in children in the general population are to be expected in children with DS, because no data have yet been published on the effect of overweight and obesity in children with DS. Another consequence of overweight and obesity in children is the increased risk of becoming obese adults, which means having an increased risk for cardiovascular diseases, musculoskeletal disorders, and metabolic disorders at an older age. Because of the shorter life expectancy, it is doubtful whether these full complications will occur among people with DS. One study of adults with DS showed that obesity appears to play an important role in the pathophysiology of obstructive sleep apnea: the apnea hypopnea index was highly correlated with the degree of obesity.[7,8] However, it is very plausible that complications such as poor general physical condition and musculoskeletal disorders will occur in children with DS.

Up to now, many explanations for the higher prevalence of overweight and obesity in DS were based on the presence of concomitant disorders. Hypothyroidism for example is more common in children with DS and predisposes to increased body weight.[9,10] Therefore, it is important to know the prevalence of overweight and obesity in children with DS, not only generally but also separately for those children with and without comorbidity. Children with DS have a high risk of concomitant disorders that are known to influence body weight both positively as well as negatively.[11-13] This study aims to establish specific growth references for weight in children with DS, and to assess the prevalence rates of overweight and obesity in a nationwide sample of Dutch children with DS, while taking into account the influence of comorbidity.

Methods

Data were collected from medical records of children attending one of the hospital-based regional outpatient clinics for children with DS in the Netherlands. All these clinics were approached for participation in order to collect representative nationwide data. Between July 2009 and February 2010 the first author visited the participating clinics and collected retrospective anonymous data on growth from 2000 onwards, medical conditions and background information. Additionally, some child health physicians involved in the care of adolescents with DS supplied data by completing standard forms. Because all children

visit one of these clinics providing standard medical care for children with DS using a well-defined screening program, their health status is accurate.[14]

Dutch children with Trisomy 21 karyotype and born after 1982 were selected. Growth data included measurements of weight, height and head circumference. In this study only weight and BMI are discussed. Full details of data collection were presented in our previous paper on healthy growth in children with DS.[15] The children were categorized into four health categories (see also Table 4.1): 1. 'healthy': no concomitant disorders and negative screening results or only mild congenital heart defect (CHD) (hemodynamic stable); 2. severe CHD (hemodynamic unstable and needing surgical intervention or medication or having pulmonary vascular disease); 3. hypothyroidism; 4. other disorders and treatments known to influence growth, and children with multiple concomitant disorders. Because our previous study demonstrated children without concomitant disorders or with only mild CHD have the same growth pattern,[15] these children are pooled to form the healthy category . The new growth references established in this study as well as the prevalence rates were based on measurements of this otherwise healthy group of children.

Table 4.1: *Characteristics of the various health categories in the study population*

Healthy	
	Children without concomitant disorders that could possibly interfere with growth or children with hemodynamic stable CHD (not needing surgical intervention or medication and without pulmonary vascular disease)
	Children with negative screens for celiac disease and hypothyroidism
	For example: children with cataract were included and children with musculoskeletal disorders were excluded; children with an atrial septal defect or patent foramen ovale without complaints were included
Severe CHD	
	Children with hemodynamic unstable CHD (needing surgical intervention, medication, or with pulmonary vascular disease)
	For example: children with an atrioventricular septal defect or Tetralogy of Fallot
Hypothyroidism	
	Children with hypothyroidism: congenital or acquired
	For example: hypothyroidism confirmed after positive screening
Other disorders	
	Children with other disorders and treatments known to interfere with growth, and children with multiple concomitant disorders
	For example: children with congenital gastrointestinal malformations, celiac disease, leukemia or diabetes, children on anti-epileptic medication or corticosteroids (including inhalation medication)

Abbreviations: CHD – congenital heart defect

Statistical Analysis

All measurements of children with one or more outlying measurements were excluded. Outliers were defined as standard deviation scores (SDS) >4 or <-6 for weight, >5 or <-7

for birth weight, and >2 or <-6 for height, using the age and sex-specific references of the general Dutch population (Fourth Dutch Growth Study, 1997).[16] BMI was calculated as weight/height^2 and expressed as kg/m^2.

Specific reference charts for weight-for-age were established for children with DS up to the age of 15 months. Reference charts reflect the range of normal growth of a healthy child. However, the present distribution of weight in the population at older ages is not something to be aimed for, because of the current increase in the proportion of children with obesity.[17-19] Therefore, references for weight-for-age are plotted in this study only for the younger ages where there still is a normal distribution of weight. References were constructed by using the LMS method, which summarizes the distribution by three age-dependent smooth curves representing the skewness (L curve), median (M curve) and coefficient of variation (S curve).[20] The references were fitted in R Version 2.9.0 using Generalized Additive Models for Location Scale and Shape (GAMLSS).[21] A log transformation of age was applied to expand the ages where growth velocity is high and compress ages where growth velocity is low. Worm plots were used as a diagnostic tool for visualizing how adequate our models fitted the data.[22]

Prevalence rates of overweight and obesity were calculated separately for boys and girls with DS within the various health categories. To obtain accurate prevalence rates, cut-off values for BMI as defined by the International Obesity Task Force were used on the LMS parameters of BMI distribution in the DS study sample.[23] All overweight rates in this paper include obesity. The prevalence rates were compared between children with DS within the various health categories, and were compared with the prevalence rates of overweight and obesity of children in the general Dutch population (Fifth Dutch Growth Study, 2009).[17] Multi-level logistic regression analyses, adjusted for sex and age, were performed to test the differences in prevalence rates of children with DS within the various health categories.

Table 4.2: *Number of children and measurements for weight of 1,596 Dutch children with Down syndrome, specified by health categories*

	Number of subjects			Number of measurements	
Health category	**n**	**Boys**	**Girls**	**Boys**	**Girls**
Healthy or only mild CHD	664	387	277	2404	1776
Severe CHD	269	114	155	864	1169
Hypothyroidism*	119	60	59	402	541
Other disorders	544	330	214	2944	1836
Total	1,596	891	705	6,614	5,322

Abbreviations: CHD – congenital heart defect
* including mild CHD

Results

Growth data of 1,596 Dutch children with Trisomy 21 were collected from medical records of 25 specialized DS clinics (83% of all DS clinics in the Netherlands) and from the participating youth health care physicians. This sample included 891 boys (55.8%) and 705 girls, with 6,614 and 5,322 measurements for weight respectively. Table 4.2 shows the number of subjects and weight measurements, specified by the various health categories. The major group is formed by the otherwise healthy children (41.6%). The children with severe CHD represent 16.9%, the children with hypothyroidism represent 7.5%, and the category with various other disorders represent 34.1%.

Table 4.3: *New weight (kg)-for-age references for 0-15 months in Dutch children with Down syndrome: values of L (skewness), M (mean), and S (coefficient of variation)*, arranged by age and sex.*

	Boys			Girls		
Age (weeks)	**L**	**M**	**S***	**L**	**M**	**S***
0	1.06	3.05	.1930	.91	3.03	.1471
2	1.05	3.36	.1848	.86	3.27	.1443
4	1.03	3.66	.1773	.82	3.51	.1418
6	1.02	3.97	.1706	.79	3.79	.1395
8	1.00	4.29	.1645	.75	4.07	.1375
10	.99	4.62	.1590	.73	4.36	.1357
12	.97	4.95	.1541	.70	4.64	.1342
16	.94	5.58	.1460	.67	5.17	.1316
20	.91	6.15	.1395	.64	5.67	.1295
24	.89	6.65	.1345	.62	6.13	.1277
28	.87	7.08	.1304	.62	6.55	.1262
32	.84	7.47	.1270	.63	6.92	.1246
36	.81	7.82	.1240	.63	7.25	.1231
40	.77	8.13	.1213	.65	7.55	.1216
44	.72	8.42	.1188	.67	7.83	.1201
48	.66	8.70	.1165	.69	8.09	.1186
52	.60	8.95	.1143	.70	8.34	.1172
56	.53	9.19	.1122	.72	8.55	.1158
60	.50	9.41	.1103	.74	8.76	.1144
65[a]	.39	9.67	.1080	.76	9.00	.1127

[a] Corresponding with 15 months.
* Individual weight SDS can be calculated by: SDS (SD) = ((weight (kg)/M)^{L} -1) / L*S.

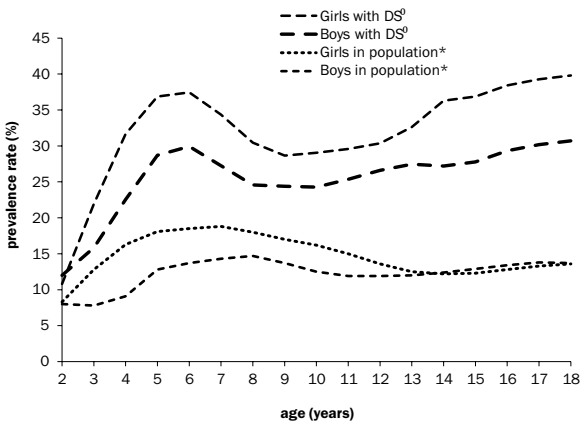
Growth references for weight-for-age were plotted for the age of 0-15 months based on 199 boys and 156 girls; yielding 959 measurements for boys and 761 for girls. Table 4.3

summarizes the LMS values, arranged by age and sex. Mean birth weight was 3.1 kg for boys and 3.0 kg for girls with DS. Compared with the general Dutch population (1997) mean birth weight of children with DS was 1.1 SD lower in boys and 0.9 SD lower in girls. At the age of 15 months, mean weight was 9.7 kg for boys and 9.0 kg for girls, respectively 1.1 SD and 1.2 SD lower than in the general population.

Prevalence rates of overweight and obesity in otherwise healthy children with DS are presented in Table 4.4. The prevalence rates of overweight are also shown in Figure 4.1. For comparison, the prevalence rates in children from the general population are also shown in this table and figure. In total, 25.5% of the boys with DS and 32.0% of the girls were overweight. Obesity was observed in 4.2% of the boys and 5.1% of the girls with DS. The prevalence rates were roughly constant over the age ranges: from the age of four years more than one quarter of the children were overweight. Compared with the general Dutch population, prevalence rates in children with DS were on average twice as high for both overweight and obesity. The rapid increase in prevalence of overweight between the age of two and six years is striking. This increase is clearer in children with DS than in children from the general population.

Prevalence rates of overweight of children with DS vary between children within the various health categories. Although children with DS and severe CHD showed almost the same prevalence rates of overweight (28.1%), the children in the category with hypothyroidism showed higher rates (35.1%). However, after correcting for sex and age, these differences were not significant.

Figure 4.1: Prevalence rates (%) of overweight in otherwise healthy children with Down syndrome (n=659), compared to children in the general population, arranged by sex and age.*



[0] DS = Down syndrome

* General population: prevalence rates of the Fifth Dutch Growth Study in 2009 [17]

Discussion

This study presents prevalence rates of overweight and obesity in a nationwide population based sample of almost 1600 Dutch children with DS. A strict selection on the basis of health status of the children resulted in data based on a group of otherwise healthy children with DS. The approach of dividing the children into various health categories based on co-morbidity that can influence their growth (height and/or weight) is an important part of this study, and provides information on the presence of overweight and obesity in children within these various health categories. It is not only healthy children with DS who have a high prevalence of overweight and obesity, but also the children with any type of co-morbidity. Prevalence rates of overweight and obesity vary between children with DS in the different health categories, but no statistically significant differences were observed.

Table 4.4: *Prevalence rates (%) of overweight and obesity in otherwise healthy children with Down syndrome (n=659), compared to children in the general population*, arranged by age and sex.*

	Overweight				Obesity			
	Boys		Girls		Boys		Girls	
Age	DS[0]	Pop.*	DS	Pop.	DS	Pop.	DS	Pop.
2.0	12.0	8.0	10.8	8.3	2.0	0.7	1.0	0.7
3.0	15.9	7.8	22.0	12.8	2.7	0.8	2.9	1.6
4.0	22.6	9.1	31.7	16.3	4.5	1.1	5.3	2.6
5.0	28.7	12.8	36.9	18.1	6.5	2.0	6.9	3.3
6.0	29.9	13.7	37.4	18.5	6.5	2.1	6.8	3.4
7.0	27.2	14.3	34.4	18.8	5.3	2.1	5.2	3.4
8.0	24.6	14.7	30.5	18.0	4.5	2.2	3.9	3.2
9.0	24.4	13.7	28.7	17.0	4.1	2.0	3.3	2.8
10.0	24.3	12.5	29.1	16.2	3.8	1.7	3.3	2.5
11.0	25.4	11.9	29.6	15.0	3.7	1.6	3.5	2.1
12.0	26.6	11.9	30.4	13.6	3.7	1.6	4.0	1.8
13.0	27.5	12.0	32.6	12.5	3.7	1.6	5.0	1.6
14.0	27.2	12.4	36.3	12.2	3.6	1.7	6.6	1.5
15.0	27.8	12.9	36.9	12.3	3.7	1.8	6.7	1.5
16.0	29.3	13.4	38.4	12.8	4.2	1.9	7.2	1.6
17.0	30.2	13.8	39.3	13.3	4.4	2.0	7.4	1.7
18.0	30.7	13.7	39.8	13.6	4.5	1.9	7.5	1.7
2.0-18.0^	25.5	12.3	32.0	14.7	4.2	1.7	5.1	2.2

[0] DS = children with Down syndrome
* Pop. = General population: prevalence rates of the Fifth Dutch Growth Study in 2009 [17]
^ Mean prevalence rate for children aged 2-18 years

From the age of four over 25% of the healthy children with DS are overweight. The rapid increase in prevalence of overweight in children with DS between two and six years of age is striking, in boys as well as in girls (presented in Figure 4.1). In view of the fact that overweight children have an increased risk of becoming obese adults, such high prevalences are alarming, since this may lead to poor general physical condition, and comorbidity such as obstructive sleep apnea, musculoskeletal disorders, and cardiovascular diseases.[7,8,24,25] This emphasizes the importance of awareness of the occurrence of overweight in children with DS at very young ages.

New reference charts are established for weight-for-age for boys and girls with DS up to the age of 15 months and will aid appropriate monitoring. After the age of 15 months no reference charts specific for DS are established, because the present distribution of weight in the population at older ages is not something to be aimed for. In the Netherlands, normative growth charts for weight-for-height and BMI-for-age are used for children in general as well as for children with DS. The normative reference charts for BMI-for-age include international cut-off values for overweight and obesity, and for thinness grades 1 and 2.[17,23,26,27] All growth charts are available at www.tno.nl/growth. Additional research is needed to determine how sensitive and specific these international cut-off values are in children with DS. Until more information is available to improve monitoring, the currently available general weight and BMI charts will be used for growth monitoring in children with DS older than 15 months, and seems to work well with the specific weight-to-age charts for the age of 0-15 months.

Another important result is that children with DS with severe CHD show nearly the same high prevalence rates. During the early years of life of these children attention is mainly concentrated on their medical heart defect condition. However, our data show that it is also necessary to be aware of the need to prevent excessive weight gain. Our data indicate a higher prevalence of overweight and obesity in children with DS and hypothyroidism. This is somewhat surprising since all children with DS were screened for hypothyroidism, as advised in the guideline of the Pediatric Association of the Netherlands.[14] This means that hypothyroidism is diagnosed and treated at an early stage before complaints arise and weight gain is caused.

For optimal prevention and intervention more should be learned about the underlying cause of excessive weight gain in children with DS. One of the theories about this cause is resistance to leptin. This is a hormone excreted by adipocytes that suppresses appetite and regulates body weight. Leptin is positively correlated with body fat, so people with obesity have a type of leptin resistance.[28,29] Magge *et al*. have observed that leptin levels and the proportion of body fat were more positively correlated in children with DS than in their brothers and sisters.[30] The cause of this phenomenon is unknown. Other studies investigated the presence of reduced resting metabolic rate. Small studies showed some

support for this theory.[31] However, Fernhall et al. demonstrated no difference in metabolic rate between individuals with DS and control individuals of similar ages.[32] Another theory is based on the influence of lifestyle. Higher rates of overweight and obesity might be attributed to lesser physical activity or higher nutrient intake.[6,33-35] Nevertheless, the few available studies on these subjects do not as yet provide convincing evidence for any specific theory.

With the knowledge we have from studies among children in the general population, we assume that physical activity and feeding patterns are likely the essential factors influencing body weight in children with DS. Additional research is needed to establish the merit of this assumption and to explore other underlying factors. As long as the underlying causes are still unknown, a specific approach to tackle the cause is not possible. However, dietary factors and insufficient physical activity are considered to be main contributors to the development of overweight. Assuming that this also applies to children with DS, we expect that they will benefit from it. Children with DS often want to keep to a strict routine to optimize their autonomy. When a healthy diet and enough physical activity is a structural part of this personal daily routine, the children will probably adhere to such a routine. Therefore, appropriate information for parents and children is essential, and must be provided by youth health care workers and pediatricians. Parents need to know what a healthy weight is for their child with DS. With this in mind they can support their child to achieve and maintain a healthy weight. These approaches to prevent excessive weight gain are an important task for the professionals involved in the care for children with DS.

Conclusions

We observed an alarming prevalence of overweight and obesity in Dutch children with DS. Overweight and obesity are observed from a young age in otherwise healthy children with DS as well as in children with DS and severe CHD. Health care professionals should be aware of the risk of overweight and obesity in children with DS and should ensure that growth is monitored regularly in all children with DS, thus enabling early detection of inappropriate weight gain and starting appropriate interventions where necessary. In this way undesirable psychological and physical health consequences may be prevented. Parents and children also need appropriate information to prevent excessive weight gain. We expect that a structured healthy life style, including eating a healthy diet and having sufficient physical activity, will be especially effective in children with DS because of their tendency to follow a strict routine. Specific prevention programs to prevent excessive weight gain that are suitable for children with DS and support their families may be valuable.

Acknowledgement

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Part 3
Development and behavior in childhood

Chapter 5

Development, problem behavior, and quality of life in a population based sample of eight-year-old children with Down syndrome

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Abstract

Objective: Children with Down syndrome (DS) have delayed psychomotor development. We investigated levels of development, problem behavior, and Health-Related Quality of Life (HRQoL) in a population sample of Dutch eight-year-old children with DS. Developmental outcomes were compared with normative data of eight-year-old children from the general population.

Method: Over a three-year-period all parents with an eight-year-old child with DS were approached by the national parent organization. Developmental skills were assessed by means of the McCarthy Scales of Children's Ability. To measure emotional and behavioral problems we used the Child Behavior Checklist. HRQoL was assessed with the TNO-AZL Children's Quality of Life questionnaire. Analyses of variance were applied to compare groups.

Results: A total of 337 children participated. Mean developmental age was substantially lower than mean calendar age (3.9 years, SD 0.87 and 8.1 years, SD 0.15 respectively). Mean developmental age was significantly lower among boys than girls (3.6 (SD 0.85) and 4.2 years (SD 0.82) respectively; $p<0.001$). Compared with the general population, children with DS had more emotional and behavioral problems ($p<0.001$). However on the anxious/depressed scale, they scored significantly more favorably ($p<0.001$). Significantly lower HRQoL scores for the scales gross motor skills, autonomy, social functioning and cognitive functioning were found (p-values <0.001). Hardly any differences were observed for the scales physical complaints, positive and negative emotions.

Conclusion: Eight-year-old children with DS have an average developmental delay of four years, more often have emotional and behavioral problems, and have a less favorable HRQoL compared with children from the general population.

Introduction

An important feature of children with Down syndrome (DS) is their delayed development. DS is known as the most prevalent cause of intellectual impairment associated with a chromosomal anomaly (Trisomy 21). In the United States prevalence of DS is estimated to be 12 per 10,000 live births; in 2002 83,400 children with DS aged 0-19 years lived in the United States.[1] In the Netherlands the prevalence of DS seems higher: 14 per 10.000 live births (approximately 270 children per year).[2-4] Children with DS have a well-recognized phenotype, including external characteristics, specific physical problems (such as congenital heart defects, gastro-intestinal disorders, thyroid dysfunction and visual impairment) and intellectual impairment with delayed cognitive and motor development.[5,6]

This delayed development has frequently been studied during the past 50 years. Results indicated that children with DS have a lower IQ and have difficulties with expressive language.[7-14] In particular, they have difficulties with verbal working memory, receptive language, reading, writing and arithmetic.[7,8,12,14,15] Studies on behavior problems indicate on average one quarter to one third of the children with DS to have significant emotional and behavior problems.[6,10,16] Most studies observe that children with DS frequently have speech problems, attention deficit and concentration problems, social withdrawal, stubbornness, as well as oppositional and disobedient behavior.[9-11,16,17] A substantial number of studies found that 8-23% of the children with DS have significant psychopathology.[10] Specifically, 7% are diagnosed with autism, 6% to 9% with attention deficit/hyperactivity disorder (ADHD), and 10% to 15% with conduct or oppositional disorders.[6,10,16-20]

The vast majority of the above-mentioned studies are not population based and included fewer than 50 children with DS. Studies that included larger numbers of children with DS date back to the 1970s and 1980s, when the children grew up under different circumstances. Improvement of medical care and general support could have enhanced overall development of children with DS or specific aspects of their development. Our sample is studied between 2000 and 2003, and since no major changes in the approach to the developmental aid, medical care and upbringing of children with DS have taken place since then, in our opinion these results are still valid.

When a child with DS is born, parents want to be informed reliably on the expected development of their child. Most of the currently available information focuses on the medical aspects like concomitant congenital anomalies and organic disorders, which children with DS are at high risk for. Hardly any information is available on the actual expected development. In this study we aimed to investigate the developmental skills, problem behavior, and Health-Related Quality of Life (HRQoL) in a large population based sample of Dutch children with DS at the age of eight years old, compared to normative data from same-age-children from the general population. Subsequently, we aimed to provide valuable information for families, health care and educational professionals all involved in the care for children with DS.

Methods

Subjects

Dutch families, who were member of the Dutch Down Syndrome Foundation and who parent a child with DS born in 1992, 1993 or 1994, were invited to participate in the study. The Dutch Down Syndrome Foundation manages a database which includes most Dutch children with DS. In the Netherlands, about 80% of all parents with a child with DS in the age up to 12 year join this organization, routinely advised by their pediatrician.[21]

The selected parents received a written request from the Dutch Down Syndrome Foundation to participate. Parents, who signed up to participate, received a set of questionnaires and an appointment for a home visit. Between June 2000 and February 2003 a professional, experienced and trained psychological assistant visited the children at home and administered the McCarthy Scales of Children's Ability (MSCA).[22] Developmental testing was conducted following their eighth birthday. If the test was not completed during one visit, the child was rescheduled for further testing within a few weeks. The set of parent questionnaires contained two formal tests: the Child Behavior Checklist (CBCL) and the TNO-AZL Children's Quality of Life (TACQOL).[23-25] Questions on background, demographic variables and medical condition of the child were included in the set of questionnaires.

Measures

The Dutch version of the MSCA developed for children aged 2.5 to 8.5 years was used.[26] The MSCA contains 18 subtests, grouped into the scales: verbal, perceptual, quantitative, memory and motor skills. The verbal, perceptual and quantitative scales are combined to form the general cognitive scale. A developmental age is calculated based on the various scale scores. To prevent an excessive influence of one of the subscales on the developmental age, the 18 subtests are each representing one competence in order to test a specific ability of the child and not a broad range of abilities, i.e. the test is developed so that level of verbal ability will minimally influence test-scores on other domains measured.

The CBCL measures emotional and behavior problems. The Dutch version of the CBCL for four to twelve years old children was used.[27] The CBCL is suitable for children with developmental delay.[28-30] It contains 118 problem behavior items rated from 0 (not true) to 2 (very true or often true), covering nine scales: withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention problems, delinquent behavior, aggressive behavior and sexual problems. These scales combined form the scales internalizing problems (containing withdrawn, somatic complaints and anxious/depressed) and externalizing problems (containing delinquent and aggressive behavior).

The TACQOL, developed in the Netherlands for children aged six to fifteen years old, was used to measure HRQoL. It assesses functional problems weighted by the degree to which a child shows negative emotions to such problems. The questionnaire contains 56 items

divided over seven scales: physical complaints, gross motor skills, autonomy, cognitive functioning, social functioning, positive emotions and negative emotions.

Statistical analysis

All questionnaires and test results were collected and merged into one dataset. The levels of developmental skills, problem behavior and HRQoL were calculated for each outcome measure, according to the accompanying (supplementary) test manuals. The test results of the DS-sample were – for each outcome measure – compared with normative data from the general population, matched on calendar age. Analyses of variance (ANOVA) were used to evaluate differences between mean values. All statistical tests were 2-tailed and statistical significance was defined at $p<0.05$. The effect sizes were estimated by dividing the differences in mean scores between the subgroups by the pooled SD. Cohen's effect sizes (d) were used for interpretation of relevant differences: $d<0.2$ is considered a negligible difference, $0.2\leq d<0.5$ a small, $0.5\leq d<0.8$ a moderate, $0.8\leq d<1.3$ a large, and $d\geq 1.3$ a very large difference.[31] Means for the total DS-sample were weighted for gender. All analyses were performed using Statistical Package for the Social Sciences, version 17.0 for Windows (SPSS Inc, Chicago, Illinois).

Analyses of the MSCA scales were carried out with raw scale scores. The norms for children of 8.25 years of age, as available in the accompanying manual and based on a nationwide sample from the United States, were used for comparison with the DS-sample.[22] In addition, developmental age was calculated and compared for boys and girls, using ANOVA.

For the CBCL, normative data were derived from a Dutch sample of 661 children aged seven to nine years (mean 7.9 years, SD 0.40).[32] In addition to the comparison of scale scores, the proportions of subjects with a scale score in the clinical area were compared between DS-sample and the normative sample, using Chi-Square test.

The TACQOL was analyzed by comparing the scale scores of the DS-sample with data from a Dutch reference population of 519 children aged eight or nine years.[25]

Results

A total of 531 parents with a child with DS born in 1992, 1993 or 1994 were approached via the Dutch Down Syndrome Foundation to participate in the present study, which holds 78% of all living children of this birth cohort in the Netherlands (based on an 84% survival rate).[33] A total of 380 parents (72%) signed up to participate; 337 parents provided actual data for the present study (response rate: 63%; equaling 50% of this birth cohort). Gender and age were known of all 337 participating children. Background characteristics were known of 325 children. The number of subjects participating in the formal tests was 325 for the TACQOL, 320 for the CBCL and 285 for the MSCA. Overall, 266 parents and their children completed all questionnaires and tests.

Background characteristics are presented in Table 5.1. Mean age was 8.1 years (SD=0.15, range 7.8-9.1); 52.0% of the subjects were boys and 94.6% of the children were of Dutch origin. A total of 156 children (48.0%) attended regular education at the age of eight years; more girls than boys (60.3% versus 36.7%; $p<.001$). Above 90% of the children with DS were diagnosed and/or treated for one or more concomitant chronic diseases, mainly visual impairment, chronic airway infection, heart defect or hearing impairment.

Table 5.1: *Characteristics of the studied population of children with Down syndrome, as reported by their parents, arranged by gender (n=325).*

	Total		**Boys**		**Girls**		
General characteristics	**n**	**%**	**n**	**%**	**n**	**%**	***p****
Number of subjects	325	*100.0*	169	*52.0*	156	*48.0*	
Education at 8 years old							
Regular primary school	156	*48.0*	62	*36.7*	94	*60.3*	.000
Special school or day-care centre	169	*52.0*	107	*63.3*	62	*39.7*	.000
Ever enrolled in regular primary school	240	*73.8*	112	*66.3*	128	*82.1*	.001
Level of regular primary school at 8 years old							
Preschool	31	*9.5*	17	*10.1*	14	*9.0*	.614
First grade	95	*29.2*	35	*20.7*	60	*38.5*	.000
Second grade	30	*9.2*	10	*5.9*	20	*12.8*	.032
Age in years (range)	7.8 – 9.1		7.9 – 9.1		7.8 – 9.0		
Age in years (mean ± SD)	8.14 ±0.15		8.15 ±0.15		8.13 ±0.15		.193
Concomitant chronic diseases							
Visual impairment	158	*48.6*	76	*45.0*	82	*52.6*	.172
Chronic Airway Infections	149	*45.8*	85	*50.3*	64	*41.0*	.094
Congenital heart defect	137	*42.2*	63	*37.3*	74	*47.4*	.064
Hearing impairment	98	*30.2*	55	*32.5*	43	*27.6*	.330
Gastrointestinal tract abnormality	45	*13.8*	27	*16.0*	18	*11.5*	.248
Thyroid dysfunction	39	*12.0*	22	*13.0*	17	*10.9*	.558
Asthma	34	*10.5*	25	*14.8*	9	*5.8*	.008
Diabetic Mellitus	3	*0.9*	2	*1.2*	1	*0.6*	.611
Other chronic disease	81	*24.9*	46	*27.2*	35	*22.4*	.758
Number of concomitant chronic diseases							
No chronic disease	26	*8.0*	18	*10.7*	8	*5.1*	.067
Only one chronic disease	81	*24.9*	39	*23.1*	42	*26.9*	.423
Two or more chronic diseases	218	*67.1*	112	*66.3*	106	*67.9*	.748

Abbreviation: SD – standard deviation
*Boys with Down syndrome compared to girls with Down syndrome

Table 5.2: *Developmental skills, measured by the McCarthy Scales of Children Abilities (MSCA) in a population of eight-year-old children with Down syndrome (DS, n=285), compared to the normative sample (NS, n=238); raw scale scores are reported; higher scores denote more favorable skills.*

	Total sample (male and female)			**DS sample**		
	DS ***(n=285)***	**NS** ***(n=106)***		**Male** ***(n=153)***	**Female** ***(n=132)***	
	Mean ± SD	**Mean ± SD**	**Effect size^**	**Mean ± SD**	**Mean ± SD**	**Effect size^**
Verbal	37.32 ± 18.11	89.00 ± 10.75	–3.15***	33.29 ± 18.73	41.36 ± 16.57	–0.46***
Perceptual-Performance	29.84 ± 15.89	76.00 ± 7.00	–3.29***	24.88 ± 15.69	34.80 ± 14.53	–0.66***
Quantitative	10.98 ± 6.78	44.00 ± 7.00	–4.84***	9.09 ± 6.71	12.86 ± 6.33	–0.58***
Memory	12.56 ± 7.81	50.00 ± 6.25	–5.06***	10.52 ± 7.30	14.60 ± 7.80	–0.54***
Motor	25.79 ± 21.42	64.00 ± 5.50	–2.07***	22.35 ± 12.49	29.23 ± 11.39	–0.58***
General Cognitive	78.15 ± 38.13	209.00 ± 20.00	–3.84***	67.26 ± 38.37	89.05 ± 34.75	–0.60***

* $p<0.05$, ** $p<0.01$, *** $p<0.001$
^ Cohen's d effect size: $d<0.2$ negligible; $0.2\leq d<0.5$ small; $0.5\leq d<0.8$ moderate; $0.8\leq d<1.3$ large; $d\geq 1.3$ very large
Abbreviations: DS – Down syndrome, NS – Normative sample, SD – standard deviation

Figure 5.1: Distribution of McCarthy Scales of Children's Abilities (MSCA) developmental age in eight-year-old children with Down syndrome, arranged by gender (n=285).

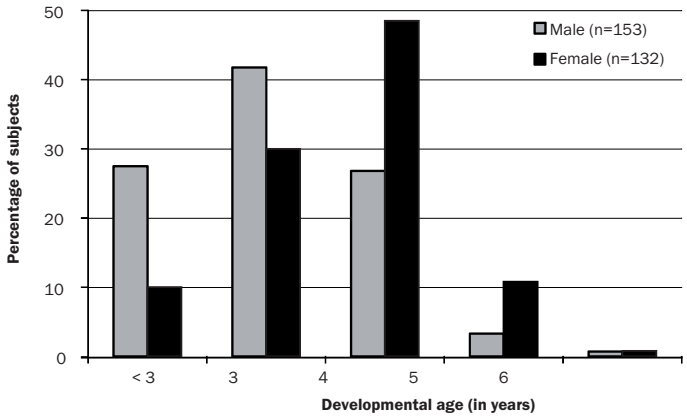

Table 5.3: *Emotional and behavioral problems, measured by the Child Behavior Checklist (CBCL), in a population of eight-year-old children with Down syndrome (DS, n=320): scale scores and proportion of children scoring in the clinical area of the scales, compared to the normative sample (NS, n=661), arranged by gender; higher scores denote more problems.*

	Total DS sample (n=320)		Male DS (*n=169*)	Male NS (*n=325*)		DS	NS
	Scale score	Clinical score	Scale score			Clinical score	
	Mean ± SD	%	Mean ± SD	Mean ± SD	Effect size^	%	%
Withdrawn	2.54 ± 2.66	5.9	2.61 ± 2.75	1.63 ± 1.85	0.45***	7.1**	1.5
Somatic complaints	1.35 ± 1.92	6.9	1.29 ± 1.85	0.77 ± 1.24	0.35***	7.7**	2.2
Anxious/Depressed	0.88 ± 1.42	0.3	0.78 ± 1.33	2.40 ± 3.20	–0.60***	0.6*	4.3
Social problems	4.38 ± 2.15	21.6	4.57 ± 2.17	1.51 ± 1.83	1.57***	18.9***	1.9
Thought problems	1.18 ± 1.66	8.8	1.30 ± 1.76	0.35 ± 0.92	0.75***	10.7***	1.9
Attention problems	6.50 ± 3.15	12.2	6.76 ± 3.19	3.22 ± 3.02	1.15***	12.4***	2.5
Delinquent behavior	1.47 ± 1.57	3.1	1.55 ± 1.60	1.11 ± 1.43	0.30**	2.4	1.5
Aggressive behavior	7.27 ± 5.69	4.4	8.13 ± 6.06	6.66 ± 6.11	0.24*	5.9	4.3
Sexual problems	0.37 ± 0.83	3.8	0.42 ± 0.89	0.15 ± 0.52	0.40***	3.6	1.2
Internalizing problems[0]	4.71 ± 4.55	10.6	4.62 ± 4.54	4.69 ± 4.96	-	11.2	11.4
Externalizing problems[x]	8.73 ± 6.84	15.3	9.68 ± 7.25	7.77 ± 7.17	0.27**	12.4	11.1
Total problems	30.08 ± 18.06	26.9	32.05 ± 18.81	19.78 ± 15.96	0.72***	27.8***	10.8

	Female DS (*n=151*)	Female NS (*n=336*)		DS	NS
	Scale score			Clinical score	
	Mean ± SD	Mean ± SD	Effect size^	%	%
Withdrawn	2.46 ± 2.55	1.65 ± 1.84	0.39***	4.6	2.1
Somatic complaints	1.42 ± 2.00	1.04 ± 1.49	0.23*	6.0*	2.1
Anxious/Depressed	0.99 ± 1.50	2.50 ± 3.26	–0.53***	0.0*	3.6
Social problems	4.17 ± 2.11	1.30 ± 1.76	1.53***	24.5***	2.7
Thought problems	1.03 ± 1.53	0.27 ± 0.67	0.75***	6.6***	0.9
Attention problems	6.22 ± 3.10	2.61 ± 2.62	1.30***	11.9***	2.1
Delinquent behavior	1.38 ± 1.53	0.78 ± 1.23	0.45***	4.0	1.5
Aggressive behavior	6.30 ± 5.11	5.07 ± 5.05	0.24*	2.6	2.4
Sexual problems	0.30 ± 0.76	0.11 ± 0.42	0.35***	4.0**	0.3
Internalizing problems[0]	4.82 ± 4.58	5.09 ± 5.32	-	9.9	11.0
Externalizing problems[x]	7.68 ± 6.21	5.85 ± 5.95	0.30**	18.5	13.4
Total problems	27.87 ± 16.97	17.98 ± 15.28	0.63***	25.8***	11.9

* $p<0.05$, ** $p<0.01$, *** $p<0.001$

^ Cohen's *d* effect size: $d<0.2$ negligible; $0.2\leq d<0.5$ small; $0.5\leq d<0.8$ moderate; $0.8\leq d<1.3$ large; $d\geq 1.3$ very large

[0] Combined from the subscales withdrawn, somatic complaints and anxious/depressed

[x] Combined from the subscales delinquent and aggressive behavior

Abbreviations: DS – Down syndrome, NS – Normative sample, SD – standard deviation

Developmental skills

The psychological assistants visited 285 children at home to administer the MSCA. Table 5.2 shows mean scores of the test scales. Higher values reflect more favorable results.

On all measures the DS-sample scored significantly lower than the normative sample, with very large effect sizes. The largest effect sizes were found for the memory scale (d=5.1) and the quantitative scale (d=4.8). Within the DS-sample, boys had significantly lower scale scores than girls; effect sizes ranged from 0.5 to 0.7, indicating a moderate effect by gender. In addition, developmental age was calculated for each child. In Figure 5.1 the developmental age of the subjects is plotted stratified for gender. In 33 children (82% boys), who had very low test scores, developmental age could not be calculated exactly, but was estimated to be at a level of under 2.5 years, according to the MSCA test manual. By calculating mean age these children were ranked as having a developmental age of 2.4 years. For the total sample, mean developmental age for boys was 3.6 years (SD=0.85) and for girls 4.2 years (SD=0.82), showing a difference of 0.53 years (p<0.001). In all children the highest developmental age scored was 6.8 years.

Emotional and behavior problems

A total of 320 questionnaires of the CBCL were completed. Mean scores are shown in Table 5.3, whereby higher values reflect more problems. On almost all subscales children in the DS-sample scored significantly more problem behavior than the normative sample. The highest effect size was found for the subscale social problems (d=1.55), followed by the subscale attention problems (d=1.15 for boys and 1.30 for girls), indicating large to very large effects. The effect size of the difference in total problem score between the children with DS and the normative sample indicated a moderate effect (d=0.72 for boys and d=0.63 for girls).

For the scale anxious/depressed an opposite score was observed: the DS-sample showed significantly fewer problems with a moderate effect size (d=0.60 for boys and d=0.53 for girls).

Additionally, scale scores were arranged in the normal or clinical area of the scale (Table 5.3). For the subscales somatic complaints, social, thought, attention and sexual problems, and the total problem scale the children with DS scored significantly more within the clinical areas. An exception again was the subscale anxious/depressed, where fewer children with DS scored within the clinical area (p<0.05).

Table 5.4: Health-related quality of life (HRQoL), measured by the TNO-AZL Children's Quality of Life questionnaire (TACOOL), in a population of eight-year-old children with Down syndrome (DS, n=325), compared to the normative sample (NS, n=519), arranged by gender; higher scores denote better HRQoL.

	Total DS sample	Male			Female		
	(n=325)	DS *(n=169)*	NS *(n=260)*		DS *(n=156)*	NS *(n=259)*	
	Mean ± SD	Mean ± SD	Mean ± SD	Effect size^	Mean ± SD	Mean ± SD	Effect size^
Physical complaints	27.26 ± 3.48	27.14 ± 3.56	27.29 ± 3.92	-	27.39 ± 3.39	26.66 ± 4.05	-
Gross motor skills	27.85 ± 3.92	27.76 ± 4.21	30.78 ± 2.50	–0.90***	27.95 ± 3.61	30.72 ± 2.85	–0.88***
Autonomy	26.28 ± 3.59	26.06 ± 3.72	31.10 ± 1.90	–1.84***	26.51 ± 3.45	31.32 ± 1.60	–1.96***
Cognitive functioning	22.76 ± 3.54	22.75 ± 3.89	28.39 ± 3.98	–1.43***	22.77 ± 3.12	28.62 ± 4.00	–1.58***
Social functioning	28.25 ± 3.54	27.95 ± 3.72	29.36 ± 2.82	–0.44***	28.57 ± 3.33	29.91 ± 2.49	–0.47***
Positive emotions	15.06 ± 1.64	15.01 ± 1.70	14.73 ± 2.01	-	15.11 ± 1.58	14.81 ± 2.05	-
Negative emotions	11.71 ± 1.99	11.70 ± 2.18	11.18 ± 2.78	0.21	11.73 ± 1.78	11.45 ± 2.30	-

* $p<0.05$, ** $p<0.01$, *** $p<0.001$
^ Cohen's d effect size: $d<0.2$ negligible; $0.2\leq d<0.5$ small; $0.5\leq d<0.8$ moderate; $0.8\leq d<1.3$ large; $d\geq 1.3$ very large
Abbreviations: DS – Down syndrome, NS – Normative sample, SD – standard deviation

Health-Related Quality of Life

Mean scores of the TACQOL – evaluating the influence of having DS in daily life – are summarized in Table 5.4, whereby higher values reflect better HRQoL. Compared with the normative population, children with DS had significantly lower scores with very large effects on autonomy (d=1.90) and cognitive functioning (d=1.51); with a large effect on the gross motor skills (d=0.89), and with a small effect on social functioning (d=0.46) scales.

For the scale negative emotions we observed a significant favorable outcome for boys, but the effect size was small (d=0.21). For the other scales – physical complaints, positive emotions and (for girls) negative emotions – there were no differences observed.

Discussion

The aim of the present study was to investigate the development of a population based sample of Dutch children with DS at the age of eight years. The study included a large nationwide cohort of children with DS born in 1992, 1993 or 1994, approximately 50% of all children with DS of this birth cohort living in the Netherlands.[2-4] We measured a wide spectrum of developmental skills, emotional and behavior problems and HRQoL. Previous studies indicated that children with DS have a delayed development.[7-12,14,15] However, detailed aspects of development and quality of life have not been quantified in a population based sample.

The large sample of our study presented an opportunity to study differences between boys and girls. Few studies addressed gender differences with regard to developmental skills

and cognition. Most observed no significant differences, probably due to their small sample size.[10]

Furthermore the present study is different from most others in defining the comparison groups. Previous studies compared their DS-sample with participants matched for mental age and gender or used siblings.[9-12,17]. We compared the selected DS-sample with randomly selected children from the general population with identical chronological age and same gender.

Our sample is born in 1992, 1993 and 1994, after the era (the 1980's) in which major changes in the care for the children with DS have taken place; i.e. medical care has been optimized; early intervention was introduced, and the majority of the children were no longer raised in institutions but at home.

Results

One of the main findings of our study is that children with DS have a substantial delay in developmental skills in comparison with the normative sample. The mean developmental age of the children with DS was 3.9 years (SD=0.87), which is four years behind their average calendar age of 8.1 years (SD=0.15). A substantial delay in development was recorded in all children. However, the range was wide, with some children indicating a developmental delay of only one or two years, and other children indicating a developmental delay of more than five years. Girls with DS scored on average more favorably on all skills and had a higher developmental age in comparison to boys with DS.

Our results further indicate that children with DS had more emotional and behavior problems in comparison to the normative sample on almost all domains measured, with the exception of the scale anxious/depressed. Some previous studies with a small number of children (less than 50) and a wide range of age, found also more behavior problems in children with DS.[11] Our finding that children with DS score significantly better on the problem scale anxious/depressed in comparison to the normative sample has not been reported in previous studies.[9,11,16] Only among adults with DS, several studies report more depression compared to the general population.[6,18,19] The internalizing problem scale score – which is composed of withdrawn, somatic complaints and anxious/depressed – did not differ significantly from the normative sample, as a result from the opposite score for the anxious/depressed scale.

The children with DS scored a lower HRQoL on the scales gross motor skills, autonomy, social and cognitive functioning in comparison with the normative sample. These domains determine the main topics in everyday life of children with DS, as reported by parents. Remarkably, HRQoL of children with DS showed no significant difference on the physical complaints scale, even though 92% of the children indicated one or more concomitant chronic conditions.

In our sample a high percentage (46%) of chronic airway infections was observed.

Prospective studies on the exact incidence of chronic airway infections are lacking. A recent national health survey showed that in children with DS in the age of 6-10 years parents reported 38% to have head or chest cold in the previous two weeks.[34] A study among Dutch children showed that 24% of the children with DS were hospitalized twice or more for pulmonary infection or use inhalation medication for more than six months.[35] In our study parents were asked "Does your child suffer from chronic airway infections (often severe common cold/bronchitis)" and "Was your child diagnosed with asthma?" to evaluate respiratory complaints. Therefore, the higher number of reported chronic airway infections in our study could be explained by the broader definition used. For other concomitant disorders, like congenital heart defects, hearing impairment and thyroid dysfunction, the incidences in our sample are in accordance with earlier studies.[6]

The data of this study were collected between 2000 and 2003. Despite this data collection occurred several years ago, these data will be valid for the current generation of children with DS, because no major changes in the approach of (medical) care for children with DS has taken place since the measurement of this study.

Of the parents with a child with DS who were approached, about 63% participated in the study. Unfortunately, we were not able to carry out a non-response analysis. It is possible that parents whose child had more serious developmental problems than most of the children with DS, more frequently refused to participate. These factors may have resulted in an underestimation of the problem behavior of these children and an overestimation of the developmental level. However, we observed a wide range in developmental level and more than 50 children to have a developmental age below three years, showing also children with more serious developmental problems are included in our study.

Implications

The results of this study provide reference information for pediatricians and other health care professionals when they inform parents of the expected development of a child with DS. They may assist parents in gaining realistic expectations about the future of their children.

Currently children with DS in the Netherlands are encouraged to attend regular education in primary school. Studies showed that attending regular education provides more positive peer relationships and can improve social skills.[36,37] However, low mean developmental age at the calendar age of eight years can be an important obstacle to enroll them in regular primary education. In order to keep them in regular education, additional support is needed to provide adequate learning conditions. If adequate support cannot be guaranteed, special education is needed.

The children with DS indicated more social, attention and thought problems than the normative sample. These problems should be recognized as they form obstacles in learning conditions. In particular the high level of social problems suggests that this is an area where

significant improvement may be made. From an early age onwards, children with DS should be stimulated to develop social skills, confirming the need for adequate support in primary school.

For the children themselves HRQoL was mainly decreased for their level of autonomy and cognitive functioning. Current medical care for children with DS focuses on the physical conditions of the children, as advised in the guidelines of the American Academy of Pediatrics, and the Pediatric Association of the Netherlands.[38,39] Medical professionals should extend their care with supportive coaching on autonomy and cognitive functioning, to improve quality of life for the children with DS.

Conclusion

Eight-year-old children with DS have an average developmental delay of four years. This finding has important implications for (parents of) children with DS and professionals. These children have more emotional and behavioral problems, and have on some domains a less favorable HRQoL compared with children from the general population.

It is recommended to investigate the factors influencing the social participation and development of children with DS, as well as the relation between developmental level and problem behavior, and its influence on quality of life. Population based longitudinal cohort studies are needed to gain insights in all aspects of functioning and social participation of children with DS.

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Chapter 6

Significant impact of recurrent respiratory tract infections in children with Down syndrome

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Abstract

Objective: Parents and health professionals believe that recurrent respiratory tract infections (RRTI) have a large impact on children with Down syndrome (DS). We studied the relation between parent reported RRTI on development, behavior, and health related quality of life (HRQoL) in 8-year-old children with DS.

Method: During a 3-year period, 325 children with DS were recruited for inclusion in this observational study. Parents were asked to fill in the Child Behavior CheckList and TNO-AZL Children's Quality of Life Parent Form. A psychological assistant administrated the McCarthy Scales of Children's Abilities. The children were divided into a group with presence of RRTI ($RRTI^+$) and a group without RRTI ($RRTI^-$), on the basis of parental report. Linear regression analyses were performed to assess the effect of RRTI, while correcting for the influence of confounders.

Results: Compared to $RRTI^-$ children (n=176), $RRTI^+$ children (n=149, 46%) showed decreased mental and motor development (mean developmental age 3.67 vs. 4.08 years), more behavioral problems and lower scores on most HRQoL scales ($p<0.05$). Moreover, school enrollment is less favorable in $RRTI^+$ children.

Conclusion: In 8-year-olds with DS, the children with parent reported RRTI show more delayed development, more behavioral problems, and lower HRQoL compared to the children without RRTI. Although this association does not prove a causal relationship, further studies should focus on this, because RRTI are potentially preventable.

Key message

- Children with Down syndrome are known to be at increased risk of recurrent respiratory tract infections.
- In 8-year-old children with Down syndrome, parental report of recurrent respiratory infections was associated with more delayed development, increased risk of behavioral problems and lower health-related quality of life.

Introduction

Down Syndrome (DS) is one of the most common genetic causes of intellectual disability in children. In the Netherlands, the prevalence is approximately 1 in 714 live born infants.[1,2] Facial dysmorphic features, hypotonia, and congenital heart defects (CHD) are variably present in newborns with DS. Also, DS is associated with celiac disease, thyroid disease, diabetes mellitus, and hematological malignancies.

Respiratory complications are common in children with DS. The risk of anatomic abnormalities, respiratory syncytial virus infection and viral induced wheezing is increased.[3-5] Recurrent lung and/or airway infections (recurrent respiratory tract infections; RRTI) are frequently encountered in children with DS.[5] Parents often report delayed development due to these RRTI. Up to now, this has been studied only once in toddlers: motor development was delayed 0.88 months in 2-year-old children with DS suffering from recurrent lung or airway disease, however mental development was not affected.[6]

In this study, we measure the association between RRTI, based on parental report, and development, behavior, and health related quality of life (HRQoL) in 8-year-old children with DS.

Methods

Study population

All members of the Dutch DS Foundation having a child with DS turning 8 years of age between January 2000 and January 2003 were invited to participate in this study. If parents agreed to participation, they returned their written informed consent to the researchers. Parents were then contacted to plan a home visit for psychological testing, and a set of questionnaires was sent to them.

Social and medical background

A questionnaire asked for information on social background and demographic variables concerning family situation, breastfeeding (>1 month after birth), and attendance to childcare and school. The level of parental education was used as indicator for socioeconomic status. The medical history of the child was evaluated by routine questions. We asked parents “Does your child suffer from chronic airway infections (i.e., often severe common cold or bronchitis)” and “Was your child diagnosed with asthma?” to evaluate respiratory complaints. Response categories for both questions were “yes” or “no”. Based on the response to the first question, children were divided into children with RRTI ($RRTI^+$) and children without RRTI ($RRTI^-$). In the same way, the presence of frequently encountered diseases in DS, such as CHD, gastrointestinal disease, thyroid dysfunction, diabetes mellitus, impaired hearing and/or eye disease was noted.

Developmental skills

The Dutch version of the McCarthy Scales of Children's Abilities (MSCA) for children aged 2.5 to 8.5 years was used to measure general developmental skills.[7] An experienced and trained psychological assistant performed this test as soon as possible after the eighth birthday of the child. The MSCA contains 18 subtests, which are grouped into verbal, perceptual, quantitative, memory, and motor skills. In addition, a general cognitive scale and the developmental age of the child can be determined as well with the MSCA.

Emotional and behavioral functioning

The presence of emotional and behavioral problems was determined by the Dutch version of the Child Behavior Checklist (CBCL).[8] This test was created for children aged 4 to 12 years and contains a total of 118 items on the following 9 scales: withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention problems, delinquent behavior, aggressive behavior and sexual problems. The scales of withdrawn, somatic complaints and anxious/depressed are combined for assessing internalizing problems as a separate score. The score for externalizing problems is comprised by the scales of delinquent and aggressive behavior.

We chose the CBCL because we wanted to compare the presence of behavioral problems in children with DS to healthy Dutch children, for which reference data is available. Besides, the manual and data on validity of the Developmental Behavior Checklist – specifically designed for children with developmental problems – were not yet available in the Netherlands at the time of writing of the study-proposal.

Health related quality of life

The TNO-AZL Children's Quality of Life Parent Form (TACQOL-PF) questionnaire for children aged 5 to 15 years was used to determine the HRQoL.[9] The 57 items are grouped in physical complaints, gross motor skills, autonomy, cognitive functioning, social functioning, positive emotions, and negative emotions. With this questionnaire parents indicated health status problems in their child and also reported negative emotions expressed by the child to these problems.

Statistical analysis

To determine differences between the group of children with parent-reported RRTI and the group without RRTI ($RRTI^+$ and $RRTI^-$, respectively), we performed chi-square tests for all variables mentioned in "Social and medical background". Age was compared between both groups by an independent *t*-test. Linear regression analyses were performed to assess the association between RRTI and each of the three outcome variables separately: MSCA, CBCL, and TACQOL-PF. Gender, level of parental education, presence of siblings, childcare attendance, being breastfed and morbidity (CHD, diagnosis of asthma, gastrointestinal

disease, eye disease, impaired hearing, and thyroid dysfunction) were used as confounders. The effect sizes were computed as Cohen's f^2, which is the effect size index for multiple regression (see for formula Cohen, 1988, p. 410).[10] If f^2 equals 0.01 for a variable, it means that this variable uniquely accounts for 1% of the variance in the outcome variable (expressed as a proportion of the unexplained variance). When comparing the effect sizes for different outcome variables, f^2 is more appropriate than R^2-change, because the latter depends on the total variance accounted for. For interpretation of relevant effect sizes we used the following reference values: small effect ($0.01 \leq f^2 < 0.10$), moderate effect ($0.10 \leq f^2 < 0.33$), and large effect ($f^2 \geq 0.33$).[11] In addition, to determine whether the effects for gender, CHD, and impaired hearing on the outcome variables were equal for both groups of RRTI, the influence of interaction terms were assessed by hierarchical regression analyses. For this purpose, cross-products were computed between RRTI (plus or minus) and, respectively, gender, CHD, and impaired hearing. These cross-products were added as an extra step to the regression equation (which included all main effects). Although asthma was significantly more reported in $RRTI^+$, this subgroup was too small for further analysis.
Power analysis showed at least 137 patients per group were needed to detect a 3-month difference in developmental delay (power 80%, alpha 0.05). All analyses were performed by SPSS for Windows 17.0; statistical significance was defined as a two-sided $p<0.05$.

Results

Patient characteristics and confounding factors

The data on patient characteristics and potential confounding factors are presented in Table 6.1. In total, 531 children with DS aged 8 years were invited to participate; which holds 78% of all estimated living 680 children of this birth cohort in the Netherlands (based on an 84% survival rate).[12] A total of 380 parents (72%) agreed to enroll and 337 children provided data for this study (response rate: 63%). Based on the estimated incidence of DS, our study group represents approximately 48% of all children with DS in this age-cohort in the Netherlands.[1,2,13] In our study, the prevalence of CHD, impaired hearing, eye disease, a diagnosis of asthma and thyroid disease is in accordance with population-based studies in DS.[1,14-16] Not all data could be collected for each patient because of practical problems to plan a home visit for psychological testing at the age of 8 years and/or incomplete returned questionnaires.
The presence or absence of RRTI is reported by parents for 325 (96% of 337) children; in 149 of these children RRTI are present ($RRTI^+$-group) and in 176 children RRTI are absent ($RRTI^-$-group). There is no difference between the $RRTI^-$ and $RRTI^+$ children in proportion of males (p=0.09) or mean age (Table 6.1). The mean age for both subgroups is 8 years and 2 months. The educational career is different between both groups: $RRTI^+$ children with DS

are less likely to primarily start with regular education. Also, the level of education of RRTI$^+$ children with DS who do attend a regular school is significantly lower. The educational level of girls is higher compared to boys, as described earlier.[17] This being the case in RRTI$^+$ as well as in RRTI$^-$ children.

The prevalence of CHD, a diagnosis of asthma, and impaired hearing are significantly increased in the RRTI$^+$ group. We found no significant differences in other potential confounding factors between RRTI$^+$ and RRTI$^-$ children (Table 6.1).

Table 6.1: *Patient characteristics and additional morbidity of 8-year-old Down syndrome population in relation to parent-reported presence of recurrent respiratory tract infections (RRTI).*

	RRTI$^+$		RRTI$^-$		Total		Chi square test
	n	(%)	n	(%)	n	(%)	*p-value*
Male	85	(57)	84	(48)	169	(51)	NS
Female	64	(43)	92	(52)	152	(49)	
Age at inclusion* (mean, range, and SD in years)	8.14 (7.8-8.8) ±0.14		8.15 (7.8-9.1) ± 0.16		8.14 (7.8-9.1) ± 0.15		
School attendance							
Ever attended regular education	99	(30)	142	(44)	241	(74)	0.003
Regular education attendance at inclusion	65	(20)	92	(28)	156	(48)	NS
Preschool *(normally age 4-5 years)*	21	(32)^	11	(12)	31	(20)	0.018
First grade *(normally age 6 years)*	33	(51)^	62	(67)	95	(61)	0.010
Second grade *(normally age 7 years)*	11	(17)^	19	(21)	30	(19)	NS
Level of parental education							
Primary or secondary education	24	(7)	31	(10)	55	(17)	NS
Higher secondary education	55	(17)	63	(19)	118	(36)	NS
University education	70	(22)	82	(25)	152	(47)	NS
Being breastfed (>1 month)	57	(18)	60	(18)	117	(36)	NS
Siblings	140	(43)	170	(52)	310	(95)	NS
Childcare (age <4 years)	142	(44)	160	(49)	302	(93)	NS
Additional morbidity^0							
Congenital heart disease	73	(49)	64	(36)	137	(42)	0.022
Diagnosis of asthma	28	(19)	6	(3)	34	(10)	<0.001
Gastrointestinal disease	26	(17)	19	(11)	45	(14)	NS
Eye disease	77	(52)	81	(46)	158	(49)	NS
Impaired hearing	66	(44)	32	(18)	98	(30)	<0.001
Thyroid dysfunction	19	(13)	20	(11)	39	(12)	NS
Diabetes mellitus	1	(<1)	2	(1)	3	(1)	NS
Other morbidity, not specified	43	(29)	38	(22)	81	(25)	NS

* There was no significant difference in age between both groups determined by a *t*-test.
^Percentage out of all children attending regular education.
^{0} Parental reported morbidity.
Abbreviations: RRTI$^+$ – children with recurrent respiratory tract infections, RRTI$^-$ – children without recurrent respiratory tract infections, NS – not significant.

Table 6.2: *Results of multiple regression analyses for scales scores of the McCarthy Scales of Children's Abilities (MSCA) of 8-year-old Down syndrome children with and without parent-reported recurrent respiratory tract infections (RRTI).*

	RRTI$^+$		RRTI$^-$			
	Total (n=130)	Male (n=75) Female (n=55)	Total (n=140)	Male (n=69) Female (n=71)		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Regression coefficient^0 (β)	Effect size$^\wedge$ (f^2)
Verbal	33.06 (19.13)†	29.64 (19.96) 37.47 (17.18)	40.68 (16.18)	37.09 (15.72) 44.11 (16.08)	-7.33**	0.04
Perceptual-Performance	26.76 (16.58)	21.80 (15.84) 33.33 (15.43)	32.34 (14.90)	28.83 (14.87) 35.93 (14.20)	-5.67**	0.03
Quantitative	9.44 (6.80)	7.86 (6.46) 11.44 (6.75)	12.22 (6.57)	10.46 (6.75) 13.93 (5.99)	-2.61**	0.04
Memory	10.74 (7.77)	9.27 (7.69) 12.64 (7.53)	13.94 (7.37)	11.77 (6.31 16.10 (7.77)	-3.12**	0.04
Motor	23.23 (12.57)	20.03 (12.64) 27.47 (11.32)	27.67 (11.78)	24.99 (11.51) 30.25 (11.62)	-4.63**	0.04
General cognitive score	69.30 (40.25)	59.36 (40.22) 82.29 (36.84)	85.24 (34.43)	76.35 (33.60) 94.00 (33.42)	-15.59**	0.04
Developmental age (SD in months)	3 y 8 m (10.91)	3 y 6 m (10.53) 3 y 11 m (10.66)	4 y 1 m (9.58)	3 y 10 m (9.08) 4 y 3 m (9.30)	-4.05**	0.04

Lower scores indicate more impaired development.
* p<0.05, ** p<0.01, *** p<0.001.
^{0} β = unstandardized regression coefficient of the effect of RRTI, correcting for the effect of socioeconomic status, childcare attendance, being breastfed (>1 month), siblings, gender, congenital heart defect, diagnosis of asthma, gastrointestinal disease, eye disease, impaired hearing, and thyroid dysfunction.
^ Effect size (f^2): small effect (0.01-0.10), moderate effect (0.10-0.33), large effect (>0.33).
† Mean scores are presented with standard deviation between brackets.
Abbreviations: RRTI$^+$ – children with recurrent respiratory tract infections, RRTI$^-$ – children without recurrent respiratory tract infections.

Developmental status, behavioral problems and HRQoL

Development of the children, measured by the MSCA was administrated in 270 children (80% of 337); the results are presented in Table 6.2. Mean scale scores on all domains of the MSCA were significantly lower in RRTI$^+$ children versus RRTI$^-$ children. Small effect sizes were found (Cohen's f^2-range: 0.03-0.04). Moreover, in RRTI$^+$ children the mean developmental age was 3 years and 8 months, compared to 4 years and 1 month in RRTI$^-$ children. Thus, the difference in mean developmental age was 5 months. Results of hierarchical regression analysis for developmental age are presented in Table 6.3. In Step 1, the effect of social economic status, childcare attendance, being breastfed and the presence of siblings was found to be negligible (all not significant), whereas male gender has significantly lower developmental age than female gender, adjusted for the effect of the other variables (Step 2). The results of Step 4 showed a significant effect of RRTI on developmental age, adjusted for the effect of all other variables in the model. Furthermore the effect of RRTI is larger than all separate forms of morbidity (Step 3). No interaction effects are present between RRTI and CHD, gender, or impaired hearing.

Table 6.3: *Hierarchical regression analysis of developmental age obtained by the McCarthy Scales of Children's Abilities (MSCA) in 8-year-old Down syndrome children (n=270).*

	ΔR^2	*p*	β step	*p*	β total	*p*
Step 1	0.006					
Socioeconomic status			0.01		0.23	
Childcare			1.16		1.51	
Being breastfed (>1 month)			1.65		1.32	
Siblings			-0.03		-2.66	
Step 2	0.084	***				
Male gender			-6.15	***	-5.90	***
Step 3	0.038					
Congenital heart disease			-2.66	*	-2.17	
Diagnosis of asthma			-2.20		-1.09	
Gastrointestinal disease			-2.73		-2.47	
Eye disease			0.27		0.41	
Impaired hearing			0.87		1.98	
Thyroid disease			-2.25		-2.61	
Step 4	0.031	**				
Presence of RRTI			-4.05	**	-4.05	**

β = unstandardized regression coefficient; β step is the beta for this variable when it was first entered into the equation; β total is the beta for the variable in the final model including all steps. Negative β means lower developmental age due to this variable.
* $p<0.05$, ** $p<0.01$, *** $p<0.001$
Abbreviations: RRTI – recurrent respiratory tract infections

In total, 317 (94%) CBCL questionnaires were completed (Table 6.4). The results showed increased behavioral problems in $RRTI^+$ children on the scales of withdrawn, somatic complaints, social problems, thought problems, and attention problems, corrected for the effect of the confounders. Effect sizes were small (Cohen's f^2-range: 0.01-0.03). Although mean scores for both internalizing and externalizing problems were significantly increased in $RRTI^+$ compared to $RRTI^-$ children, only the effect size for internalizing problems is relevant (Cohen's f^2 0.03). There was no main effect or interaction effect present for gender, CHD, and impaired hearing on any of the determined variables (data not shown).

The TACQOL-PF was completed for 323 (96%) children (Table 6.5). We found a decreased HRQoL in $RRTI^+$ children in 4 of the 7 subscales: the scores for physical wellbeing, motor skills, autonomy, and social functioning were decreased as compared to $RRTI^-$ children, corrected for the effect of the confounders ($p<0.01$). Effect sizes were small (Cohen's f^2-range 0.02-0.03). Mean scores for boys and girls were equal, and no interaction between RRTI and gender or CHD was present (data not shown). A significant interaction effect was found of impaired hearing by RRTI for the scales social problems and negative emotions (*p*-values respectively 0.05 and 0.02). This interaction effect implied that the effect of having RRTI was – for these two subscales – more pronounced in children with impaired hearing, resulting in a lower HRQoL.

Table 6.4: *Results of multiple regression analyses for the Child Behavior Checklist (CBCL) test scores of 8-year-old Down syndrome children with and without recurrent respiratory tract infections (RRTI).*

	RRTI$^+$ (n=145)		RRTI$^-$ (n=172)			
	Mean	(SD)	Mean	(SD)	Regression coefficient^0 (β)	Effect size$^\wedge$ (f^2)
Withdrawn	3.17	(2.91)†	2.02	(2.30)	1.01**	0.03
Somatic complaints	1.68	(2.20)	1.06	(1.60)	0.42	0.01
Anxious/depressed	0.93	(1.34)	0.85	(1.49)	0.06	0.00
Social problems	4.86	(2.10)	3.98	(2.11)	0.05*	0.01
Thought problems	1.48	(1.87)	0.94	(1.43)	0.58**	0.02
Attention problems	7.34	(3.08)	5.81	(3.07)	1.07**	0.03
Delinquent behavior	1.61	(1.58)	1.34	(1.53)	0.23	0.00
Aggressive behavior	8.06	(5.73)	6.62	(5.64)	1.06	0.01
Sexual problems	0.34	(0.83)	0.38	(0.84)	-0.07	0.00
Total score	34.59	(17.77)	26.25	(17.58)	6.40**	0.03
Internalizing problems§	5.72	(4.85)	3.87	(4.15)	1.49**	0.03
Externalizing problems¶	9.67	(6.84)	7.95	(6.81)	1.29	0.01

Higher scores represent increased behavioral problems.
* $p<0.05$, ** $p<0.01$, *** $p<0.001$.
^{0} β = unstandardized regression coefficient of the effect of RRTI, correcting for the effect of socioeconomic status, childcare attendance, being breastfed (>1 month), siblings, gender, congenital heart defect, diagnosis of asthma, gastrointestinal disease, eye disease, impaired hearing, and thyroid dysfunction.
^ Effect size (f^2): small effect (0.01-0.10), moderate effect (0.10-0.33), large effect (>0.33).
† Mean scores are presented with standard deviation between brackets.
§ Combined from the subscales withdrawn, somatic complaints and anxious/depressed.
¶ Combined from the subscales delinquent and aggressive behavior.
Abbreviations: RRTI$^+$ – children with recurrent respiratory tract infections, RRTI$^-$ – children without recurrent respiratory tract infections.

Discussion

We show that parent-reported RRTI is significantly associated with impaired mental and motor development, behavioral problems, and decreased HRQoL in children with DS. The mean developmental age of children with DS in the group with RRTI is 3 years and 8 months. This is 5 months lower compared to the group without RRTI. Hierarchical regression analysis shows that 3.1% of the developmental age is exclusively associated with the presence of RRTI. This is more than the association of CHD with developmental age (2.2%), only gender is more associated (5.9%). Also, behavioral problems and decreased HRQoL are more common in RRTI$^+$ children. Furthermore, school enrollment was less favorable in RRTI$^+$ children.

Table 6.5: Results of multiple regression analyses for the TNO-AZL Children's Quality of Life Parent Form (TACQOL-PF) test scores of Down syndrome children with and without parent-reported recurrent respiratory tract infections (RRTI).

	RRTI$^+$ (n=148)		RRTI$^-$ (n=175)			
	Mean	(SD)	Mean	(SD)	Regression coefficient^0 (β)	Effect size$^\wedge$ (f^2)
Physical wellbeing	26.43	(3.94)†	27.95	(2.88)	-1.02**	0.02
Motor skills	26.96	(4.40)	28.59	(3.32)	-1.35**	0.03
Autonomy	25.42	(3.99)	26.99	(3.06)	-1.33**	0.03
Cognitive functioning	22.71	(3.60)	22.80	(3.50)	0.07	0.00
Social functioning	27.43	(3.74)	28.95	(3.21)	-1.19**	0.03
Positive emotions	14.91	(1.87)	15.18	(1.42)	-0.17	0.00
Negative emotions	11.50	(1.98)	11.90	(1.99)	-0.27	0.00

Higher scores represent better health related quality of life.
* p<0.05, ** p<0.01, *** p<0.001.
^{0} β = unstandardized regression coefficient of the effect of RRTI, correcting for the effect of socioeconomic status, childcare attendance, being breastfed (>1 month), siblings, gender, congenital heart defect, diagnosis of asthma, gastrointestinal disease, eye disease, impaired hearing, and thyroid dysfunction.
^ Effect size (f^2): small effect (0.01-0.10), moderate effect (0.10-0.33), large effect (>0.33).
† Mean scores are presented with standard deviation between brackets.
Abbreviations: RRTI$^+$ – children with recurrent respiratory tract infections, RRTI$^-$ – children without recurrent respiratory tract infections.

Since RRTI are often accompanied by impaired hearing, specifically verbal skills could be more influenced compared to perceptual-performance, quantitative, memory and motor development in RRTI$^+$ children with DS. In our sample, impaired hearing was indeed more common in RRTI$^+$ compared to RRTI$^-$ children (44% vs. 18%, p<0.001). However, RRTI$^+$ children had lower scores on all developmental scales, with equal effect sizes (f^2=0.03-0.04), and no interaction between RRTI and impaired hearing was observed. So, although hearing loss is a common problem in RRTI$^+$ children with DS, other domains of development are equally decreased compared to the development of verbal skills. In other words, hearing loss does not lead to selective decrease of verbal skills nor does it enhance developmental delay of RRTI$^+$ children, and so does not seem to be a confounder that explains both RRTI and increased developmental delay.

Although RRTI$^+$ children have decreased scores on mental development in the MSCA-test, the TACQOL cognitive functioning subscore is equal in both groups. This means that decreased levels of mental development do not lead to a decreased HRQoL subscore related to cognitive functioning. An explanation for this may be that RRTI$^+$ children are, according to the results of our study, more likely to attend lower levels of education; maybe they fit in better with their classmates, resulting in a better HRQoL subscore related to cognitive functioning in these children.

The parents more often reported the diagnosis of 'asthma' in the RRTI$^+$ children. Although wheezing is a common feature in young children with DS,[4] the overall incidence of asthma

in adults and children with DS is decreased compared to the general population.[5,15,18-20] Therefore, it is doubtful whether these children really suffer from asthma. Additionally, in DS total and specific IgE-values are decreased compared to controls, and there is no increased prevalence of positive skin prick tests.[21-23] Therefore, the symptoms of wheezing and dyspnea in young children with DS are probably caused by mucosal swelling in constitutionally smaller airways during respiratory tract infections, and not attributable to asthma. Since the subgroup of children with DS with parent-reported 'asthma' was small, no separate effect sizes could be determined.

Strengths of this study include the large sample size and the consistency of the age level of all children (all studied at 8 years). Also, independent test assistants administrated the psychological tests. However, parental report is used to classify the presence or absence of recurrent airway infections, which is a methodological limitation of our study. In this way 46% of the children were classified with RRTI, which is a comparable proportion to a recent national health survey where parents reported 38% of children with DS aged 6-10 years as having had a head or chest cold in the previous two weeks.[15] Also, our data are in accordance with earlier studies regarding the overall incidence of CHD,[1,16] and the co-occurrence of hearing impairment in RRTI^{+} children with DS, which were also based on parental report in our study.

For a first exploration of the association between RRTI and development, behavioral problems and HRQoL of children with DS parent-reported RRTI may suffice to attract attention to the potential importance of this frequently encountered problem. However, further research is needed using medical records and physician-based diagnosis to determine a stricter and probably more validly defined group of children as suffering from RRTI.

Many variables that influence development, behavior, and HRQoL – like gender and CHD – cannot be changed, where RRTI potentially can. Therefore, it is important to investigate whether the observed association is based on a causal relationship. If so, better prevention of RRTI might lead to improved functioning in these children. Several causes for RRTI in DS have been proposed, such as hypotonia and (micro)aspiration. Other causes include anatomical abnormalities and different physiology of the respiratory tract including ear, nose, and throat. More frequent (chronic) ear disease, rhinorrhea, sinusitis, and obstructive sleep apnea have all been described in DS and are related to impaired hearing.[24] The co-occurrence of RRTI and impaired hearing in DS has been described before,[25] and is confirmed by our data. This study also shows that the negative effects of the association between RRTI and the HRQoL scales social problems and negative emotions is increased if these children also have impaired hearing. Probably, impaired hearing influences verbal skills, attention, and social functioning negatively. Therefore, periodic surveillance and active treatment by an ENT-specialist could be important for children with DS.

Although CHD is a potential risk factor for hospitalization during respiratory tract infections in children with DS,[26,27] it has not been described as a cause for RRTI in earlier studies. In this study, CHD is significantly more common in the RRTI^{+} children, but there is no significant effect of CHD on development, behavior, and HRQoL additional to the effect of RRTI.

Impairment of the immune system in DS has been described, and has been related to an increased infection rate.[28-30] Most studies involve development and function of T-lymphocytes.[28] B-lymphocytopenia and decreased response to unconjugated pneumococcal vaccinations are related to RRTI in non-DS patients and have been described in DS as well.[23,31] The level of impairment of the humoral immune system and its contribution to RRTI in DS has not been fully elucidated; more research on this topic is needed.

There are limited studies on pathogens of respiratory tract infections in DS. Present studies mainly report uncommon pathogens or more extreme course of disease.[3] More insight in causative pathogens may lead to specific preventive interventions, i.e. prophylactic antibiotics or additional immunizations.

Conclusion

Parent-reported recurrent respiratory tract infections (RRTI) in children with DS are associated with more impaired development, behavioral problems and HRQoL. Therefore, further studies should focus on the question whether this is a causal relationship. If so, better prevention of RRTI in children with DS might stimulate development, prevent behavioral problems, improve HRQoL and enable better school enrolment.

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Part 4
Social functioning and behavior at adolescence

Practical and social skills of 16-19-year-olds with Down syndrome: independence still far away

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Abstract

Objective: Survival of children with Down syndrome (DS) has improved considerable, but evidence lacks on their current level of daily functioning upon entering adulthood. We therefore aimed to assess the degree to which adolescents with DS master various practical and social skills.

Patients and Methods: Cross-sectional data of a Dutch nationwide cohort of DS adolescents aged 16-19 year were collected using a written questionnaire for parents. This contains the Dutch Social competence rating scale and the Children's Social Behavior Questionnaire (CSBQ), to measure practical and social skills, respectively. CSBQ outcomes were compared to norm data from adolescents without DS. Data were available from 322 adolescents (response 62.8%).

Results: Up to 60% of adolescents with DS mastered some of the skills required for independent functioning, such as maintaining adequate standards of personal hygiene, preparing breakfast and being able to spend at least 30 minutes at home alone. Less than 10% had basic skills such as some cooking and paying in a shop. No participants managed to master all the skills necessary to be able to live independently. Most adolescents with DS (90%) had more problems with social interaction than others of the same age, especially on the areas of orientation and understanding social information. Boys with DS mastered less practical and social skills than girls with DS.

Conclusions: Adolescents and young adults with DS have limited practical and social skills that are needed for independent daily functioning. They remain dependent on parents and peers and other sources of support.

Highlights

- Adolescents with Down syndrome remain largely dependent
- They have serious difficulties in practical and social functioning
- Most adolescents master skills such as personal hygiene and answering a telephone
- Only a small minority can perform relatively more complex tasks
- None master all the complex skills needed to be able to live independently

Introduction

While growing up, becoming independent is a normal prospect for every young person and it also holds true for people with Down syndrome (DS). For the latter group becoming independent does not happen as naturally as for people without DS, because of their delayed cognitive and motor development caused by Trisomy 21. Prevalence of DS is estimated to be 12 per 10,000 live births in the United States[1] and 14.6 per 10,000 live births in the Netherlands.[2] Care has improved for people with DS during the past two decades and life expectancy has increased considerably. Currently, most (>80%) people with DS reach adulthood and their median age at death has increased, e.g. in the USA from 25 years in 1983 to 49 years in 1997.[3-5]

However, evidence lacks on the effect of the improved care for people with DS on their independent practical and social functioning. Learning of skills is usually stimulated intensively in children with DS from a young age onwards, e.g. by using early intervention programs, training social skills and additional attention at school age. It remains unclear, however, to what extend young people with DS really attain the skills needed for independent living in adulthood.

Current evidence on practical and social functioning concentrates mostly on skills during infancy and childhood, showing a delay in all DS children, but with considerable variability.[6-8] Evidence on general development and social functioning in adolescence and young adulthood is limited. Carr and Melyn were among the first to describe detailed observations on general development and intelligence quotient (IQ) of adolescents and adults with DS.[9,10] They found that adults with DS have gained only a small number of basic life skills. Especially, Carr observed that mean developmental scores for the girls were significantly higher than those for the boys, and those for the home-reared children were significantly above those for the non-home-reared.[10] Some other studies provide further information on the level of functioning and cognitive development, however, all subjects in these studies were born in the 1960s, 1970s and 1980s, before improvements in family and community attitudes and in health care practices.[11-15] The children born in those periods grew up in quite different circumstances and less stimulating environments compared to the generation born after 1990, the era when interventions to stimulate development have been implemented widely. More recently, the level of functioning of adolescents or young adults with DS is not extensively studied among large cohorts. Research on adolescents with DS born after 1990 has usually included only small numbers (<50) or focus on one specific area of development and cognition, such as reading skills or working memory.[16-20] Therefore, the aim of our present study was to assess the practical and social skills that adolescents with DS currently attain, overall and by gender.

Methods

We obtained data at ages 16-19 years on a Dutch nationwide cohort of DS children born in 1992, 1993 and 1994. The families of 513 children were invited to participate by letter from the Dutch Down Syndrome Foundation (SDS, parent organization). The SDS has contact with 86% of all estimated living 595 adolescents of this birth cohort in the Netherlands, based on an 81% survival rate.[2,4] The only selection criterion for inviting parents was the year of birth of the DS child. Reminders were sent after 4 and 8 weeks. Parents were allowed up to 4 months to reply after receiving the invitation.

Participating parents filled in a paper questionnaire concerning their child with DS. This included questions on practical daily skills, social skills and background characteristics. Written informed consent was obtained from parents/next of kin of all participants.

Practical skills

Practical skills first concerned competences according to the Dutch Social competence rating scale (SRZ). The SRZ measures practical and social skills specifically in intellectually disabled children aged 4 years or older. Its validity and reliability regarding practical daily skills in children and adults with DS has been reported to be good.[21,22] The SRZ contains 31 items on the level of mastering skills at four levels (ascending from less to better mastery of a specific skill). Table 7.2 summarizes all items, whereby for each item one of the four options described on the rating scale (mostly the highest level) is presented. The items can be grouped into four subscales: Daily living skills (skills for grooming oneself), Language use (making oneself understood), Task orientation (bear some responsibility, perseverance and taking initiative) and Social orientation (interaction with others). In our sample, internal consistencies of the subscales were good; they were: α=0.96 for the total score, α=0.92 for Daily living skills, α=0.95 for Language use, α=0.84 for Task orientation and α=0.72 for Social orientation.

Additionally, practical skills were measured using a self-designed questionnaire on practical skills not covered by the SRZ. These items were selected based on semi-structured interviews with 25 parents of adolescents with DS (Table 7.3). The SRZ-items combined with these added items provide a complete view of the skills needed for independent daily functioning. The additional items could be rated as 'does not apply' (score 0), 'applies' sometimes or somewhat (score 1), or 'applies usually' (score 2).

All practical skills as measured are basic skills and adolescents (without DS) are generally considered to have all of these skills. No normative data on these items were available. However, it is possible to make an assessment because of the elementary nature of these skills.

Social skills

The mastering of social skills was investigated using the Children's Social Behavior Questionnaire (CSBQ), which measures a wide range of problems in various domains of development and social functioning.[23-25] The CSBQ has been shown to be a valid and reliable tool to assess the degree and pattern of social deficits in children with intellectual disability.[26] Normative data are available in the test manual.[25] For each of the 49 items, parents were asked to indicate whether the behavior during the preceding two months 'does not apply' for their child (score 0), 'applies sometimes or somewhat' (score 1), or 'applies clearly or often' (score 2). The items cover six subscales: Tuned (behavior/emotions not optimally tuned to the social situation), Contact (reduced contact and social interest), Understanding (difficulties in understanding social information), Orientation (orientation problems in time, place or activity), Stereotyped (stereotyped behavior and restricted activities or interests), and Changes (fear of and resistance to changes). The subscales have a good internal consistency in our sample: α=0.93 for the total score, α=0.82 for Tuned, α=0.88 for Contact, α=0.82 for Understanding, α=0.85 for Orientation, α=0.81 for Stereotyped and α=0.79 for Changes.

Statistical Analysis

General characteristics of the study population were analyzed and differences between boys and girls evaluated using *t*-tests for continuous variables and chi-square tests for categorical variables. Next, we determined the proportions of the adolescents with DS who mastered the specific skills for all items of the SRZ and self-designed questionnaire. In addition, problems in social functioning (items of CSBQ) were determined for the adolescents with DS and compared to normative data from the general population, as available in the test manual, using *t*-tests. Effect sizes were estimated by dividing the differences in mean scores between the subgroups by the pooled standard deviation (SD). Cohen's effect sizes (*d*) were used for interpretation of relevant differences: $d<0.2$ is considered a negligible difference, $0.2<d<0.5$ a small, $0.5<d<0.8$ a moderate, $0.8<d<1.3$ a large and $d>1.3$ a very large difference.[27] Furthermore, differences between boys and girls were tested using *t*-tests. For all analyses, statistical tests were 2-tailed and statistical significance was defined at $p<0.05$. The analyses were performed using Statistical Package for the Social Sciences, version 17.0 for Windows (SPSS Inc, Chicago, Illinois).

Table 7.1: *Characteristics of adolescents with Down syndrome studied (n=322), data as reported by their parents; overall and by gender*

	Total		Boys		Girls		
General characteristics	**n**	**%**	**n**	**%**	**n**	**%**	***p****
Number of subjects	322	*100.0*	170	*52.8*	152	*47.2*	.000
Dutch descent^	300	*93.2*	162	*95.3*	138	*90.8*	.110
Age in years (range)	16.8 – 19.9		16.9 – 19.9		16.8 – 19.8		
Age in years (mean ± SD)	18.32 ± 0.82		18.34 ± 0.82		18.29 ± 0.82		.553
Living at home	283	*87.9*	149	*87.6*	134	*88.2*	.888
Early stimulation program participation	265	*82.3*	143	*84.1*	122	*80.3*	.366
Education attended at 16 years (n=319)							
Mainstream secondary school	23	7,2	8	4,8	15	10,0	.075
Special school	276	86,5	142	84,5	134	88,7	.271
None	20	6,3	18	10,7	2	1,3	.001
Ever enrolled in mainstream primary school	237	73.6	108	63.5	129	84.9	.000
≥3 years enrolled in mainstream primary school	193	59.9	82	48.2	111	73.0	.000

Abbreviation: SD – standard deviation, GA – gestational age
*Boys with Down syndrome compared to girls with Down syndrome
^ Both parents born in the Netherlands

Table 7.2: *Proportion of adolescents with Down syndrome (n=321; aged 16-19 years), who have the practical skills as measured by the Dutch Social competence rating scale (SRZ).*

Subscales	% having the skill
Daily living skills	
Dresses oneself completely, including footwear	59.8
Ties shoe laces	40.2
Takes (almost) always initiative to dress	78.2
Undresses oneself and changes into night attire	81.6
Washing hands and face properly without supervision	60.0
Brushes teeth with appropriate use of toothpaste	53.6
Uses adequate toilet hygiene	61.1
Makes up the bed with new sheets and pillowcases	24.5
Uses knife and fork at lunch and dinner	81.0
Uses a knife properly at dinner, including cutting meat (without bone) by themselves	69.8
Sets the table properly (plates, cutlery, napkins, food, etc.)	61.7
Cleans up after diner, empties plates and prepares for washing up	44.2

Language use	
Is able to pick up items without list (for example at the neighbors), when one or two items are requested	57.4
Uses more compound sentences when speaking, combining more events or remarks in one sentence	29.0
Pronunciation is generally correct and clear	12.1
Speech and language can be understood by most others	44.2
Reports full name and address	63.6
Repeats full sentences expressed by others	43.6
Uses full sentences to express own wishes	53.0
When asked a question, he/she answers with complete sentences	40.2
Tells a story while being aware of a situation, e.g., in a picture (indicating what has happened, or what is going to happen)	35.6
Task orientation	
Initiates clearing up (almost) always	36.1
Finishes tasks without being reminded (almost) always	32.7
Can maintain attention at a task when it lasts for more than 15 minutes, without being encouraged in the meantime	39.3
(Almost) always tidies up toys and other things, without being told to do so	24.9
(Almost) always hangs clothes, without being told to do so	24.0
Social orientation	
Shares (almost) always toys and tools with friends or family	24.1
Asks (almost) always permission to use items belonging to others	39.9
Plays usually by himself/herself	56.4
Often, or (almost) always offers to help others, without being told to do so, if others are incapable	33.0
Walks several streets away from home without supervision	34.0

Results

A total of 322 questionnaires were filled in completely (response of 62.8%). Two cases were excluded because of severe physical handicaps, extensively limiting daily functioning, which are not typical for DS. General characteristics of our sample are presented in Table 7.1. Mean age was 18.3 years (SD=0.82, range 16.8-19.9 years). All may be classified as late-adolescents (further denoted as 'adolescents'), 52.8% were boys and 93.2% were of Dutch origin (both parents born in the Netherlands). Most adolescents lived at home (88%). The vast majority (82%) had participated in an early intervention program at home (such as the translated and adapted version of the Macquarie/Portage Programs). The majority had attended mainstream education for some years (74% had ever been enrolled in mainstream primary school). At the age of 16 years, only 7% were still enrolled in mainstream education and 87% attended special education.

Practical skills

Practical skills are presented in Table 7.2 and 7.3. Table 7.2, which shows all items of the SRZ questionnaire, and shows the proportion of adolescents who usually perform the activities in daily life. Most adolescents mastered certain skills required for independent functioning, e.g. 81% were able to use a knife and fork at lunch and dinner and 82% could undress themselves. About 60% were able to groom themselves, performing tasks such as getting dressed, and/or thoroughly washing hands and face, and/or using adequate toilet hygiene. Clear communication was difficult for most adolescents with DS and 44% can be understood by most other people, 29% only by people they know and 20% only by close caregivers. Nine per cent of adolescents were (almost) unable to speak at all.

Table 7.3 shows the additional list of practical skills. Some practical skills were mastered by most adolescents, e.g. 71% could manage to use a computer and television and 84% were able to swim. However, almost all adolescents experienced serious problems in performing practical tasks. About 55 to 60% of adolescents were able to prepare and eat breakfast and/or serve themselves a drink without assistance. Only a small proportion was able to cook a basic meal without assistance (7%) or was able to pay in a shop (12%).

Most parents could not leave their adolescent with DS at home alone for a longer period. Two thirds of adolescents with DS were able to spend at least 30 minutes alone at home, but one third of adolescents needed intensive supervision 24 hours per day. In traffic, 50% were able to cycle with supervision, but only 19% could cycle along a familiar route without supervision.

Social skills

With regard to social skills, the standard scores of the CSBQ showed that the majority (90%) of adolescents with DS experienced more problems in social functioning than adolescents without DS of the same age: 6.9% had a score just above average, 32.5% had a high score and 50.8% a very high score (the higher the score the greater the problems). A small percentage of adolescents had average (7.6%) or somewhat lower than average (2.5%) problem scores on social functioning. Scale scores of the CSBQ are presented in Table 7.4. In comparison to boys and girls without DS, total problem scores were much higher for boys and girls with DS, with very large effect sizes (1.69 and 1.50, respectively). The largest effect sizes were found in the subscales Orientation and Understanding.

Regarding interaction, 29% made little eye contact and 68% ‘lived in a world of his/her own’. Most adolescents had some trouble processing information (67%) and understanding conversations (75%). With regard to mood, 33% angered easily and 43% had mood swings without apparent reason. Problems were also noted with compliance: 33% were regularly disobedient and/or could not be corrected. Half of the adolescents found changes difficult, e.g. they panicked easily, stayed passive in new situations and/or resisted change.

Table 7.3: *Proportion of adolescents with Down syndrome (n=322; aged 16-19 years) who have (usually) the specific skills (additional list)*

	% having the skill
Able to prepare and eat breakfast independently	55.5
Serves themselves a drink (without being supervised)	59.8
Able to perform basic cooking (like preparing a simple hot meal), without supervision	6.6
Able to spend 30 minutes alone at home	63.4
Able to spend a few hours alone at home	34.3
Use a key to enter a house, when nobody else is home	37.4
Needs care 24/7	39.2
Takes care to be in time at a standard appointment (e.g. 'dinner at 6 o'clock')	12.1
Uses (without assistance) the computer and television	71.2
Answers the phone properly	54.4
Phones other people independently	32.9
Understands a simple command (e.g. 'get your coat')	95.6
Expresses personal dislikes	77.5
Speaks in full sentence	56.1
Asks for help when in a difficult situation	45.0
Speech and language is only understood by close caregivers	19,9
Communicates by sign language and use of pictograms	13.1
(Nearly) unable to speak	8.7
Able to write short memos or emails (with some words)	43.3
Able to write notes and emails with some phrases	29.0
Able to read and understand short texts in magazines or books	41.7
Able to add numbers up to 10	43.6
Realizes that 8 is higher than 4	50.9
Knows the value of money (notes and coins)	9.4
Able to pay with cash in a shop	12.1
Able to pay with a debit card in a shop	8.7
Able to swim	83.9
Able to use a normal bike	40.5
Able to walk along the street near the home without supervision	49.9
Able to cycle in traffic under supervision	50.3
Able to walk along a familiar route without supervision	38.5
Able to cycle along a familiar route without supervision	18.8
Able to find the way to a familiar address (club or friend) without supervision	18.0
Able to take a bus ride (public transport) to a familiar place such as school, independently	5.9

Table 7.4: *Social skills of adolescents with Down syndrome (n=317; aged 16-19 years), measured by the Children's Social Behavior Questionnaire; by gender and compared to the normative sample (n=400). Higher scores denote more problems in social functoning.*

	Boys			Girls		
	Down syndrome (n=165)	Norm (n=200)		Down syndrome (n=152)	Norm (n=200)	
	Scale score			Scale score		
	Mean ± SD	Mean ± SD	Effect size[1]	Mean ± SD	Mean ± SD	Effect size[1]
Tuned[a]	5.11 ± 3.67	2.70 ± 3.37	0.69***	4.63 ± 4.09	3.42 ± 3.55	0.32**
Contact[b]	6.18 ± 5.54	2.32 ± 3.16	0.88***	6.02 ± 4.68	1.60 ± 2.53	1.22***
Orientation[c]	6.48 ± 4.04	1.12 ± 1.78	1.78***	4.88 ± 3.67	0.90 ± 1.59	1.48***
Understanding[d]	6.78 ± 3.66	1.71 ± 2.06	1.75***	6.89 ± 3.12	2.06 ± 2.24	1.82***
Stereotyped[e]	3.41 ± 3.58	0.58 ± 1.06	1.12***	2.22 ± 2.88	0.48 ± 1.08	0.85***
Changes[f]	1.96 ± 1.64	0.42 ± 1.02	1.16***	1.66 ± 1.56	0.41 ± 0.90	1.02***
CSBQ total[g]	29.93 ± 15.21	8.83 ± 9.62	1.69***	26.32 ± 14.38	8.86 ± 8.99	1.50***

* $p<0.05$, ** $p<0.01$, *** $p<0.001$

[1] Cohen's d effect size: $d<0.2$ negligible; $0.2\leq d<0.5$ small; $0.5\leq d<0.8$ moderate; $0.8\leq d<1.3$ large; $d\geq 1.3$ very large

[a] Tuned = 'not optimally tuned to the social situation'
[b] Contact = 'reduced contact and social interest'
[c] Orientation = 'orientation problems in time, place or activity'
[d] Understanding = 'difficulties in understanding social information'
[e] Stereotyped = 'stereotyped behavior and restricted activities or interests'
[f] Changes = 'fear of and resistance to changes'
[g] CSBQ total = CSBQ total problem score

Abbreviation: SD – standard deviation

Gender differences

Boys with DS mastered less skills than girls with DS (mean total score of SRZ: 86.6 vs. 96.4; $p<0.001$). Also on the subscales Daily living skills, Language use and Task orientation, boys with DS scored lower than girls (p-values <0.001, <0.001 and 0.004, respectively). The subscale Social orientation was the only one in which no gender difference was observed. Boys with DS had more problems than girls with DS in social functioning on the total CSBQ score ($p=0.031$), and the subscales Orientation ($p<0.001$) and Stereotyped ($p=0.001$); effect sizes ranged from 0.2 to 0.4, indicating an additional small effect of gender.

Discussion

In the present study we measured a wide spectrum of practical and social skills in a nationwide cohort of 322 Dutch adolescent with DS in the age range of 16.8-19.9 years. This cohort includes many individuals who have participated in early intervention programs

and who often attended at least some years of mainstream education. The important issue is whether they have developed the necessary skills to be able to live independently as adults.

Our results show that most adolescents with DS master some of the skills required for independent functioning. About 60% of adolescents were able to maintain adequate personal hygiene unaided, and/or prepare and eat breakfast and serve themselves a drink without assistance, and/or spend a half hour alone at home, and/or can walk about the streets in the vicinity of the home without supervision. However, many basic practical and social skills were not mastered by them.

Carr has presented a comparable view of the level of practical and social functioning of young people with DS who were born in the 1960s, based on three cohorts.[11] She found that in general, about two-thirds of young people with DS are rated as independent in their feeding and toileting, one-third to two-thirds in dressing, about half in washing and bathing and about a quarter in hair washing. The present generation of young people with DS seems to have a roughly equal level of functioning in practical skills. However, it is difficult to compare Carr's data with our study data, because of the differences in selection of the study population and questioning. It may be that those basic life skills, measured by Carr, are the skills that parents in general try to teach their child and therefore resemble the current results of our present study. However, these days, intervention programs and care givers also try to teach children with DS basic math, reading and writing skills. It is not possible to compare specific skills, but it seems to appear that improved functioning of people with DS over the years is restricted to specific areas.

We also found that adolescents with DS had serious difficulties with social skills. Regarding the CSBQ, they scored substantially more problems on all domains of social functioning in comparison to the normative sample of peers without DS, especially on the areas of orientation and understanding social information. Studies in general samples of adolescents with intellectual disabilities reported similar findings.[28] Reports on levels of social functioning of adolescents with DS have not been previously published.

Our findings on social skills of adolescents with DS imply that they experience difficulties in dealing with others, in adapting to new situations and/or unfamiliar environments. They thus probably function better when living and working with support from familiar caregivers who know the best way to approach and stimulate them. For parents of a child with DS this has major implications. It means that the need for parental care for children with DS does not diminish when they enter adulthood. Their limited skills will hamper them from participating in activities and will limit their social engagement in activities outside the home, as shown by Wuang.[29]

Each additional specific skill that an adolescent with DS masters will have a major positive influence on daily life in their family. The extent of achieved practical and social skills affects the intensity of support needed. If an adolescent with DS is able to spend a few hours

at home alone, parents will be able to leave them without always needing to arrange a replacing caretaker. If an adolescent is able to find the way to a familiar address without supervision parents do not continuously need to accompany him or her. The ability to use the telephone independently makes it possible for the adolescent to ask for help when experiencing a problem that he or she cannot solve when alone, which in turn may prevent panicking.

Our study has considerable strengths as it measured a wide spectrum of practical and social skills in a large nationwide cohort of adolescents with DS. However, some potential limitations should be noted. Firstly, although the participants were not selected from a specific activity or school, as in other studies, selection bias can still be present.[29] Parents with a more positive attitude towards their child may be more inclined to join the parent organization, conversely it is possible that those parents with relatively more problems with their child are those who may seek support by joining a parent organization. In our sample a relatively high proportion of parents have high education (55% vs. 33% in the general population).[30] This may mean that the rather low skills of the DS children in our sample are still an underestimation of the problems all DS adolescents meet.
Secondly, all results were based on parental reports. Parents may be tempted to emphasize positive aspects of the functioning of their child, rather than the negative. For example, in our study 36% of the parents indicated that their child was able to tell the time, however, only 12% were able to be home at a standard appointment (e.g. dinner at 6 o'clock). Again this implies that our study still underestimates the problems DS adolescents meet.

Overall, this study shows that all adolescents with DS have limited skills to perform the relatively more complex tasks needed for independent practical and social functioning. This leads to dependency on others. Therefore, adolescents and young adults with DS will always need intensive supervision and support, despite of the increased stimulation of development, increased opportunities to participate and increased acceptance in society.
The findings of this study stress the importance of teaching specific practical skills to children and adolescents with DS. Improvement in social skills, which subsequently influences the intensity of care needed, is of vital importance. Moreover, it is crucial for parents as well as for care providers to have realistic expectations regarding the level of independent practical and social functioning that a child may reach. First, professionals need to have appropriate information so they are well equipped to inform parents with a (newborn) child with DS. Parents need realistic information concerning DS, including an up to date overview of the possibilities of people with DS in present day society.[31] That should include information on the extremely limited chances for people with DS to become completely independent as adults, as shown in our study.
Further research is needed to develop intervention programs to specifically improve the

skills of children with DS and to study their effectiveness. Numerous parent-directed and child-led interventions are currently available. However, it is not clear which, if any, of these approaches could be adapted for use in children with DS. The gap between our research findings and evidence-based interventions and effective educational approaches needs to be bridged. Furthermore, more insight is necessary into the social cognition of children with DS that they develop throughout childhood and on factors contributing to better daily functioning of these children.

Conclusions

We investigated a wide spectrum of practical and social skills in a unique, large nationwide cohort of Dutch adolescents with DS, assessed at 16.8-19.9 years of age. Our results show that adolescents and young adults with DS have limited practical and social skills that are needed for independent daily functioning. They remain dependent on parents and peers and other sources of support. For example fewer than 10% of the adolescents studied can cook a basic meal and pay in a shop. Only 44% can be understood by most people and one third cannot spend any time at home alone. The specific skills mastered by an adolescent with DS have effects on the degree of independence they can achieve and in turn highly affect the intensity of the support they need in later life.

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Problem behavior of individuals with Down syndrome, assessed in a nationwide cohort at late-adolescence

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Chapter 8

Abstract

Objective: To assess problem behavior in adolescents with Down syndrome (DS) and study the relation to gender and severity of intellectual disability.

Study design: Cross-sectional data of a Dutch nationwide cohort of DS children, aged 16-19 year, were collected using a written parental questionnaire. Problem behavior was measured using the Child Behavior Checklist (CBCL) and compared to normative data. The degree of intellectual disability was determined using the Dutch Social competence rating scale (SRZ). Differences were evaluated using *t*-tests and linear regression analysis.

Results: Response was 62.8% (322/513), mean age 18.3 years (SD ± 0.8). Total score of problem behavior was higher in adolescents with DS compared with adolescents without DS (26.8 vs. 16.5, $p<0.001$). Overall, 51% of adolescents with DS had problem scores within the clinical or border range on one or more CBCL subscales; more than twice as high as adolescents without DS. Adolescents with DS showed more internalizing problems (14% vs. 9% within the clinical range) and externalizing problems were almost equal (7% vs. 9% within the clinical range). Highest problem scores were observed on the subscales social problems and thought problems (with large to very large standardized differences). Male gender and/or more severe mental retarded were associated with more behavioral problems.

Conclusions: Serious problem behavior is highly prevalent in adolescents with DS. This demonstrates the need for attention for general behavior improvement as well as for detection and treatment of specific psychopathology in individuals with DS.

Introduction

Down syndrome (DS), Trisomy 21, is the most prevalent cause of intellectual impairment. In the United States the prevalence of DS is estimated to be 12 per 10,000 live births; in the Netherlands 14.6 per 10,000 live births (annually approximately 245 children with DS are live born).[1,2] Children with DS have delayed cognitive and motor development as well as specific medical problems, e.g. congenital heart defects, gastro-intestinal disorders, thyroid dysfunction and visual impairment.[3,4] Moreover, it is known that children with DS are prone to psychopathology; prevalence estimates range from 18% to 38%.[6-8] This risk is lower than in other forms of intellectual disability.[5]

The patterns of problem behavior in children change with age, especially during adolescence since this period is characterized by changes, hormonally, physically, psychologically and socially.[9] Adolescents with DS also have to deal with puberty, sexual development, (start of) emotional separation from parents and development of social autonomy.[4,10] Some studies confirmed that also among children with DS changes in behavioral pattern occur at adolescence, i.e. externalizing symptoms decreased whereas internalizing symptoms increased.[11,12]

The few studies on behavioral problems in adolescents with DS are limited as are studies on the 'dual diagnosis' of intellectual disability and psychopathology, mainly because of the small sample sizes (<60) and broad age ranges (mostly 4-19 years).[7,8,13,14] No large sample studies describing behavior in DS at a late teen age could be found. Also, gender effects in relation to behavioral problems are barely reported in DS, while these are well known in the general population.[11,15] This study aims to examine problem behavior at late adolescence in a large nationwide cohort of individuals with DS and its relation to gender and the degree of intellectual disability.

Patients and Methods

Participants

Data were collected from a nationwide Dutch cohort of parents of children with DS, assessed at the age of 16-19 years. This cohort included children with DS born in 1992, 1993 and 1994. Of all children with DS born in those 3-years period, an estimated 595 adolescents were still living in the Netherlands (based on an 81% survival rate).[2,16] The Dutch Down Syndrome Foundation (parent organization) had contact with 86% of these parents and sent them a written request. The only selection criterion for inviting parents to participate was the year of birth of the DS child. Parents could respond within 4 months after receiving the invitation. Reminders were sent after 4 and 8 weeks.

Measurements and procedure

Parents completed a written questionnaire consisting of two validated tests and additional questions on background and level of functioning. Written informed consent was obtained from parents/next of kin of all participants.

The Dutch version of the Child Behavior Checklist (CBCL) for 4-18-year-old children was used to measure problem behavior.[17,18] Although the CBCL has been developed for children with normal intelligence, it is frequently reported to be suitable for children with developmental delay.[19,20] Normative data are available in the test manual for the age group of 12-18-year-old adolescents.[17] Additionally, normative data on mean scale scores of the CBCL were available from 15-18-year-old adolescents in the general Dutch population as published by Bongers.[15] Both normative data were based on parental report. Because Bongers' sample resembles ours mostly, these normative data were used for comparing mean scale scores and normative data from the test manual for the other comparisons.

The CBCL contains 113 problem behavior items rated from 0 (not true) to 2 (very true or often true). A total problem score can be calculated using these items. The items of the CBCL can also be grouped into the following eight subscales: withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention problems, delinquent behavior and aggressive behavior. A scale of internalizing problems is constructed by combining the subscales withdrawn, somatic complaints and anxious/depressed. The scale externalizing problem is formed by combining the subscales delinquent behavior and aggressive behavior. Moreover, all scale scores can be grouped into scores within the normal, border or clinical range of the scale.

The Dutch Social competence rating scale (SRZ) was used to determine the degree of intellectual disability. This validated instrument measures social independence specifically in mentally disabled children aged 4-18 years and has already been established as a sensitive instrument to measure changes in self-help skills in adults with DS.[21,22] The SRZ was selected for its ability to measure intelligence quotient scores in the lower zones of the scale, whereas some other intelligence tests – such as the Wechsler Intelligence Scale for Children (WISC)[23] – are not. The SRZ contains 31 items that measure skills needed for independent functioning in daily life. Based on these items, the degree of intellectual disability (mild, moderate, severe or profound) can be determined. These degrees represent the following self-help skills:

— *Profound intellectual disability* means hardly able to dress oneself, wash hands and face properly and use adequate toilet hygiene, just able to eat independently (without the use of a knife) and barely able to speak.
— *Severe intellectual disability* means able to undress, wash hands and face, use a knife and fork at dinner, clear up after dinner, speak using incomplete sentences with unclear

pronunciation and can be understood only by close caregivers or familiar people.

— *Moderate intellectual disability* means the adolescent dresses himself completely, washes hands and face properly, uses adequate toilet hygiene, uses a knife and fork at dinner including cutting meat (without a bone), able to walk outside the home without supervision and his speech can mostly be understood by others.
— *Mild intellectual disability* means able to dress oneself completely including footwear, maintain complete personal hygiene, set the table properly, walk about several streets away from the home without supervision, use full or more compound sentences when speaking and speech and language can be understood by most others.

Statistical analyses

General characteristics of the study population were determined and compared between DS boys and girls using *t*-tests for continuous variables and chi-square tests for categorical variables.

Mean raw CBCL scale scores of boys and girls with DS were compared to normative data from 15-18-year-old adolescents in the general Dutch population as published by Bongers.[15] To evaluate the differences between mean values, *t*-tests were used and the standardized differences were estimated by dividing the differences in mean scores between the subgroups by the pooled standard deviation (SD). Cohen's standardized differences (*d*) were used for interpretation of relevant differences: $d<0.2$ is considered a negligible difference, $0.2\leq d<0.5$ a small, $0.5\leq d<0.8$ a moderate, $0.8\leq d<1.3$ a large and $d\geq 1.3$ a very large difference.[24]

Linear regression analysis was performed to assess the association between intellectual disability and the total CBCL problem score, adjusting for parental education and gender. In addition, to determine whether the effect of gender on the outcome variable was equal for all degrees of intellectual disability, the influence of interaction terms was assessed by linear regression analysis. For this purpose, cross products were computed between degree of intellectual disability and gender. These cross products were added as an extra step to the regression equation (which included all main effects).

For all analyses, statistical tests were 2-tailed and statistical significance was defined at $p<0.05$. The analyses were performed using Statistical Package for the Social Sciences, version 20.0 for Windows (SPSS Inc, Chicago, Illinois).

Results

In total, 322 of 513 sent questionnaires (63%) were completed. The mean age of the 322 participants was 18.3 years (SD=0.82, range 16.8-19.9 years) and 53% were boys. Ten per cent of adolescents were (very) profoundly mentally retarded, 30% severely, 43% moderately and 17% mildly. More boys with DS than girls scored a severe or profound

intellectual disability (p<0.001) and less boys than girls were mildly mentally retarded (p=0.004).Table 8.1 shows the general characteristics of our study sample.

Table 8.1: Characteristics of the study population of adolescents with Down syndrome (n=322), as reported by their parents; grouped by gender.

	Total		Boys		Girls		
General characteristics	**n**	**%**	**n**	**%**	**n**	**%**	***p****
Number of subjects	322	*100.0*	170	*52.8*	152	*47.2*	<.001
Age in years (range)	16.8 – 19.9		16.9 – 19.9		16.8 – 19.8		
Age in years (mean ± SD)	18.32 ± 0.82		18.34 ± 0.82		18.29 ± 0.82		.553
Dutch descent^	300	*93.2*	162	*95.3*	138	*90.8*	.110
Living at home	283	*87.9*	149	*87.6*	134	*88.2*	.888
Parental education							
Low	39	*12.1*	23	*13.5*	16	*10.6*	.524
Middle	105	*32.7*	58	*34.1*	47	*31.1*	
High	177	*55.1*	89	*52.4*	88	*58.3*	
Level of mental disability							
Mild	54	*16.8*	16	*9.4*	38	*25.2*	<.001
Moderate	139	*43.3*	73	*42.9*	66	*43.7*	
Severe	97	*30.2*	58	*34.1*	39	*25.8*	
Profound	31	*9.7*	23	*13.5*	8	*5.3*	

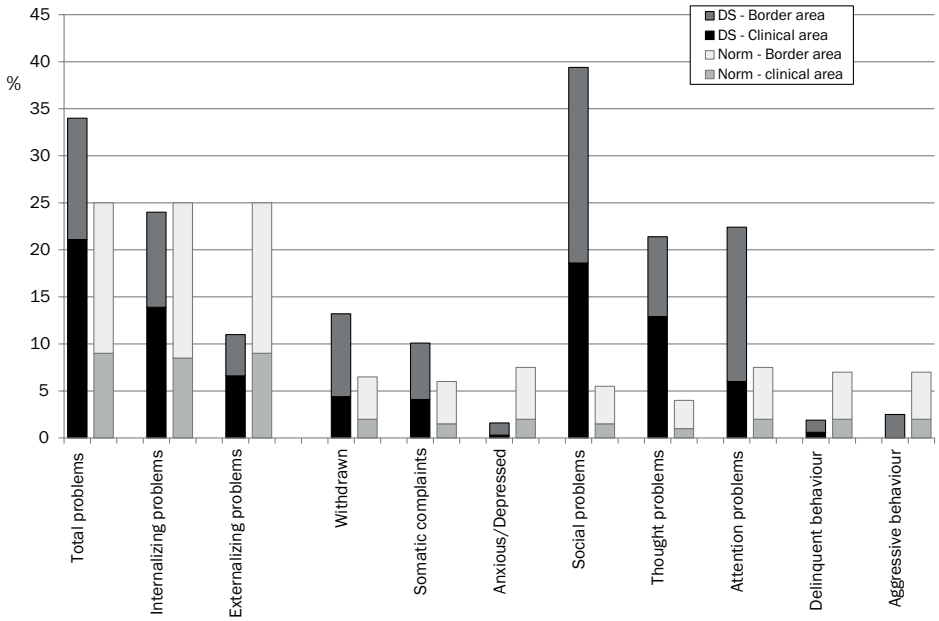
Abbreviation: SD – standard deviation,
*Boys with Down syndrome compared to girls with Down syndrome
^ Both parents born in the Netherlands

Problem behavior

The total problem score of behavior as measured by the CBCL was higher in adolescents with DS (mean score of 26.8) in comparison to the normative sample of 15-18-year-old adolescents without DS (mean score of 16.5); a moderate standardized difference was found. Table 8.2 shows all mean scores of the test scales, where higher scores denote more problems. Grouping the total problem score into the normal or clinical range of the scale showed that 21% of adolescents with DS had a total problem score within the clinical range, compared to 9% in the normative sample (12-18-year-old adolescents without DS), see Figure 8.1. Overall, 51% of adolescents with DS scored in the clinical range of one or more subscales; more than twice that for adolescents without DS.

Both boys and girls with DS showed more internalizing problems than their peers, with a small standardized difference. Fourteen percent of adolescents with DS had a score within the clinical range vs. 9% in the normative sample. This was shown by problems on the subscales withdrawn and somatic complaints, whereas less problems in the subscale

Figure 8.1: *Proportion of boys and girls with Down syndrome (aged 16-19 years; n=317) with behavioral problem scores within the clinical or border area, as measured by the Child Behavior Checklist; compared to a normative sample of 12-18-year-olds without DS hoog [0];*



[0] Norm population, as presented in the test manual by Verhulst et al, 1996 [17]
Abbrevations: DS - Down syndrome, norm - normative sample

anxious/depressed were observed in the total DS sample and in DS girls, compared to the norms. No statistically significant difference was observed on the externalizing problem scale.

The largest standardized differences were found for boys and girls with DS on the subscales social problems, thought problems and attention problems (all three not grouped within the externalizing or internalizing problems scales). Here very large standardized differences were observed on social problems in boys as well as in girls and on thought problems in boys. In detail, this concerns the following problems: the subscale social problems mainly concerns problems with age appropriate behavior, clumsy coordination and being too dependent on adults; the scale thought problems concerns problems with obsessive thoughts, repetitive acts and weird behavior; the scale attention problems involves problems with concentration, being too active, impulsiveness and nervousness. When scale scores were categorized in clinical scores, up to 40% of adolescents score within the clinical

Table 8.2: *Problem behavior of 16-19-year-old people with Down syndrome (n=317), measured by the Child Behavior Checklist; grouped by gender and compared to 15-18-year-olds without Down syndrome[0]; higher scores denote more problems.*

	Total DS sample (n=317)		Male DS (n=166)		Male Norm (n=1016)		
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Effect size[a]
Total problems	**26.76**	**(15.85)**	**28.38**	**(16.68)**	**16.52**	**(15.14)**	**0.77*** **
Internalizing problems[b]	7.09	(5.39)	6.85	(4.90)	4.78	(5.15)	0.41***
Withdrawn	3.65	(2.95)	3.52	(2.97)	2.12	(2.29)	0.58***
Somatic complaints	1.73	(1.99)	1.71	(1.81)	0.76	(1.36)	0.66***
Anxious/Depressed	1.82	(2.38)	1.73	(2.24)	1.97	(2.84)	NS
Externalizing problems[c]	5.02	(4.78)	5.81	(5.05)	5.86	(6.52)	NS
Delinquent behavior	1.20	(1.52)	1.40	(1.59)	1.34	(2.10)	NS
Aggressive behavior	3.82	(3.76)	4.41	(4.05)	4.52	(4.98)	NS
Social problems	4.07	(2.15)	4.01	(2.15)	1.04	(1.72)	1.66***
Thought problems	1.44	(1.85)	1.70	(2.05)	0.25	(0.73)	1.42***
Attention problems	5.86	(3.41)	6.53	(3.84)	3.12	(3.18)	1.04***

	Female DS (n=151)		Female Norm (n=1060)		
	Mean	(SD)	Mean	(SD)	Effect size[a]
Total problems	24.99	(14.74)	16.54	15.31	0.55***
Internalizing problems[b]	7.35	(5.90)	6.11	6.19	0.20*
Withdrawn	3.79	(2.93)	2.27	2.35	0.63***
Somatic complaints	1.76	(2.17)	1.28	1.93	0.24**
Anxious/Depressed	1.92	(2.52)	2.72	3.57	–0.23**
Externalizing problems[c]	4.14	(4.31)	4.82	5.64	NS
Delinquent behavior	0.97	(1.41)	1.01	1.72	NS
Aggressive behavior	3.17	(3.30)	3.81	4.41	NS
Social problems	4.14	(2.16)	0.99	1.67	1.81***
Thought problems	1.15	(1.56)	0.28	0.79	0.94***
Attention problems	5.12	(2.69)	2.59	2.91	0.88***

*p<0.05, ** p<0.01, *** p<0.001

[0] Norm population, published by Bongers et al, 2003[15]

[a] Cohen's *d* effect size: $d<0.2$ negligible; $0.2 \leq d < 0.5$ small; $0.5 \leq d < 0.8$ moderate; $0.8 \leq d < 1.3$ large; $d \geq 1.3$ very large

[b] Combined from the subscales withdrawn, somatic complaints and anxious/depressed

[c] Combined from the subscales delinquent and aggressive behavior

Abbreviations:DS – Down syndrome, SD – standard deviation, NS – not statistically significant

or border ranges of the subscale social problems, compared to about 6% of adolescents without DS.

Gender differences

Boys showed somewhat more problem behavior than girls within the DS sample. The difference was statistically significant for the externalizing problem scale (p=0.002) and on the subscales thought problems, attention problems, delinquent behavior and aggressive behavior (p-values 0.008, <0.001, 0.012 and 0.003, respectively). However, no overall difference is observed in the proportion of boys and girls with DS scoring in the clinical range of one or more subscales (52% and 50%, respectively).

On the subscale social problems no difference on mean scales score was observed between boys and girls DS, however more boys (24%) than girls (13%) scored within the clinical area of this subscale (p=0.019). When the proportion scoring within the border area (where the proportion of girls is larger) is added, this gender difference disappeared.

In the norm population (15-18-year-old adolescents without DS) a gender difference is also noticed. Although on the total problem score no differences were observed between boys and girls without DS, they were observed on externalizing problems and internalizing problems. Boys without DS also scored more externalizing problems than girls without DS, analogous to the observed gender difference within our DS sample. Conversely, higher problem scores were observed in girls without DS than in boys without DS on internalizing problems; this gender difference, (unfavorable for girls) was not observed among adolescents with DS.

Problem behavior and degree of intellectual disability

A statistically significant association was observed in adolescents with DS between the degree of intellectual disability and problem behavior (Table 8.3). The total problem score increased with the severity of intellectual disability. Adolescents with mild intellectual disability experienced the least problems (mean total problem score 19.7) and those with profound intellectual disability the most (mean total problem score 41.7). The interaction term on gender and degree of intellectual disability was not statistically significant (p=0.057).

Discussion

In a nationwide cohort of 322 Dutch adolescents with DS between the ages of 16-19 years, problem behavior was found to be more severe than appropriate for their age. Overall, half of the adolescents with DS had problems within the clinical or border range on one or more subscales; more than twice as high as adolescents without DS. The problems were most pronounced on the subscales social problems and thought problems. Boys with DS showed more behavioral problems than girls with DS on externalizing problems, as do boys without

Table 8.3: *Linear regression analysis of the total problem score of the Child Behavior Checklist (CBCL) in 16-19-year-olds with Down syndrome (n=317); negative β means less behavioral problems compared to adolescents with moderate intellectual disability (reference group) and positive β more.*

Degree of intellectual disability^	Unadjusted β[0]	95% CI	Adjusted β†	95% CI
Mild	- 4.67	[- 0.01; - 9.33]	- 4.92	[- 0.18; -9.67]
Moderate (reference)	0		0	
Severe	5.01	[8.89; 1.12]	4.66	[8.60; 0.72]
Profound	17.30	[23.07; 11.53]	17.13	[22.94; 11.31]

^Degree of intellectual disability is based on all items of the Dutch Social competence rating scale (SRZ)
[0] Unstandardized regression coefficient, not adjusted for parental education and gender
† Unstandardized regression coefficient, adjusted for parental education and gender

DS in comparison to girls without DS. An association between the degree of intellectual disability and behavior was observed even after adjusting for parental education and gender: adolescents with DS with more severe intellectual disability were prone to have more behavioral problems.

Our results show that internalizing problems are more severe during adolescence while externalizing problems are not prominent in individuals with DS; this is in line with other studies.[11,12] Myers and Pueschel studied a sample of 261 individuals with DS under 20 years of age (mean: 9.5, range 1-19) and observed that they often showed disruptive behavior, anxiety disorders and repetitive behavior.[7] It has to be considered that this study was performed more than 20 years ago. Compared to their results, we also found more disruptive and repetitive behavior, however, a statistical significantly lower problem score was observed on the subscale anxious/depressed of the CBCL. Contrary to our result of lower depression scores in DS, other studies among adults with DS reported prevalence rates of depression ranging from 0 to 11%.[25] Estimates rates of depression in adolescents are not available to our knowledge.
The individuals with DS in this study have previously been assessed at the age of 8 year.[26] At that age, the children also showed more problem behavior than appropriate for their age. This was most pronounced on the subscales social problems, thought problems and attention problems, identical to the findings in this study at the age of 16-19 years. They experienced fewer problems on the subscale anxious/depressed at the age of 8 as well as at 16-19 years. The proportions of children/adolescents scoring within the clinical area of the total problem scale of the CBCL were comparable in both assessments: 27% at 8 year (2.5 times more than in the normative sample) and 21% at 16-19 year (2.3 times more than in the normative sample). Also the same observed gender differences in problem behavior were found at the ages of 8 and 16-19 years.

Our results indicated that more severe intellectual disability was associated with more problem behavior. This association has not been previously described in DS populations. Bongers et al. showed that the mean score of the subscale social problems will decline with age (highest score of 1.5 at 9 years and lowest score of 0.8 at 18 years) in the general population, suggesting that the higher score in our DS sample is caused by their lower developmental age.[15] However, this does not adequately explain the observed differences, since the mean scale score was 4.1 in adolescents with DS. This means that, adolescents with DS have more social problems, regardless of age. This also applies to the subscales withdrawn, somatic complaints, thought problems and attention problems.

The present study includes a substantial part (54%) of all adolescents with DS living in the Netherlands and born in the included 3-years birth period. An additional strength is the wide spectrum of behavioral problems and background variables that were measured. This study presented the opportunity to investigate the association between problem behavior and gender and of degree of intellectual disability. However, some potential limitations should be noted. There may be selection bias in our study. The participants were invited by the parent organization. It is possible that parents with more positive attitudes may be more inclined to join such an organization and to participate in our study. However it is also possible that other parents with more concerns about their child may be more inclined to do so. Furthermore, our results are based on parental report. Parents may be tempted to emphasize positive aspects of their child's behavior. However, also the normative data were based on parental report. Despite of the potential positive information bias, the results of our study indicate that a large range of clinically important behavioral problems are present in adolescents with DS.

Implications

This study demonstrates the extent of overall problem behavior in adolescents with DS. Regrettably we found no support for the stereotypical perception of children with DS as being charming, friendly and joyful individuals. In our study we observed that adolescents with DS are happy and not anxious or worried and generally not aggressive or delinquent. At the same time, our results indicate that many adolescents with DS are withdrawn, have large social problems and thought problems. The combination of these characteristics results in a perception for others, that adolescents with DS are in general compliant with others (happy, not aggressive and not worried), but they experience many problems when they have to stand up for themselves. Therefore, the stereotypical image of individuals with DS, held by many people including professionals, fails in recognizing the great extent of problem behavior that limits adolescents with DS in their daily functioning. Professionals, parents and all others need to be informed about these characteristics of adolescents with DS, so they can socially interact in an appropriate manner and evaluate their capabilities suitably.

In consequence, special care needs to focus on general improvement of behavior in children and adolescents with DS as well as on detection and treatment of psychopathology in individuals. With regard to the first point, it may be desirable to have a structured intervention program which focusses on training social and behavioral skills. At present, early intervention programs are generally available for only young children (up to the age of 6 years). When such intervention programs for older children and adolescents are developed and evaluated, these may provide parents and professionals with essential tools for stimulating and improving behavior of individuals with DS. To be able to develop optimal tools, it is first necessary to investigate to what extent behavior can be improved and how problem behavior can be prevented. The other point of interest, the 'dual diagnosis' of intellectual disability and psychopathology, has not been studied much in adolescents with DS. Current prevalence estimates of neurobehavioral and psychiatric co-morbidity in children with DS vary from 18% to 38%.[6-8] Since limited social skills are a characteristic aspect of both intellectual disabilities and pervasive developmental disorders, definitions of 'dual diagnosis' are complex.[27] Therefore, appropriate definitions of psychopathology in DS (such as attention deficit and hyperactivity disorders and autism) are needed, as well as screening instruments to detect these. Furthermore, treatment of specific behavioral disorders in individuals with DS needs to be improved.

Conclusions

Serious problem behavior is highly prevalent in adolescents with DS. Our findings emphasize the need for prevention, detection and treatment of these behavioral problems in adolescents with DS. Professionals need to be alert to the increased risk of behavioral problems. Furthermore, (expectant) parents of a child with DS have a right to information and counseling concerning the increased chance that their child will have behavioral problems.

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Part 5
Main findings

Chapter 9

Discussion and recommendations

General discussion

The aim of this thesis is to provide an insight into the impact of Down syndrome on growth, development and social functioning.

Individuals with Down syndrome constitute a recognizable group in society. With the introduction in 2002 of prenatal screening in the Netherlands, using the first-trimester combined test, it was first believed that this population may decline and Down syndrome may become a rare condition. However, in an eleven year Dutch birth cohort (1997-2007) it was observed that the prevalence of Down syndrome has not decreased. An estimated 245 children with Down syndrome are born alive each year and Down syndrome is still the most prevalent cause of intellectual impairment. This makes it important to explore the impact of Down syndrome on fundamental aspects of health and wellbeing.

John Langdon Down not only described the external characteristics of children with Down syndrome in 1866, but also their behavior and verbal ability: 'They have considerable power of imitation, even bordering on being mimics. They are humorous and a lively sense of the ridiculous often colors their mimicry' and 'They are usually able to speak; the speech is thick and indistinct, but may be improved very greatly by a well-directed scheme of tongue gymnastics'.[1]

Although these basic aspects received attention from the first description of the syndrome, in research the main focus still is on the physical aspects of the syndrome and not on the social and emotional issues. Improvements in the medical care of concomitant disorders are crucial in preventing illness or even death and have increased life expectancy considerably in the past two decades. Survival at the age of 20 year was 77.5% in children with Down syndrome born in 1985-1990 and has increased to 90.7% in children with Down syndrome born in 1997-2003.[2] Because physical health is a basic prerequisite for daily functioning, early detection of co-morbidity is essential and needs disorder specific screening programs (such as screening for hypothyroidism) as well as growth monitoring.

Growth monitoring

The new disorder specific charts we designed reflect healthy growth with respect to height, weight and head circumference in persons with Down syndrome. By using these charts, secondary growth abnormalities may be detected more accurately. The earlier problems with weight and height are detected, the greater the health benefits can be. The established growth charts demonstrate the three age periods when height differences between children with and without Down syndrome increase: during pregnancy, during the first three years of life, and during puberty. Further research is needed to provide physiological clarification on the nature of this growth retardation.

It may also be possible to achieve some health benefits with regard to weight. Alarming prevalences of overweight and obesity from a young age are observed in Dutch children

with Down syndrome. This is the case in those who are otherwise healthy as well as in those with severe congenital heart defects. Professionals, parents and perhaps individuals with Down syndrome themselves should be aware of the risks accompanying overweight and obesity. Excessive weight gain should be prevented by using appropriate interventions. Specific programs which are suitable for children with Down syndrome need therefore to be developed.

Level of functioning

In contrast to the intensive research concerning physical disorders in Down syndrome, research on development, behavior and social functioning is less common. Our studies provide new insights into the level of functioning of children and adolescents with Down syndrome. A major developmental delay is generally observed. At the age of 8 years, children with Down syndrome show an average developmental delay of 4 years and at the age of 16-19-years the majority of adolescents with Down syndrome have limited abilities to perform complex tasks, leading to serious difficulties in social functioning. So, despite increased stimulation of development, increased opportunities to participate and increased acceptance in society, all individuals with Down syndrome remain quite dependent.

Even those adolescents with the best scores on level of functioning, who are able to cook a basic meal without assistance and to pay in a shop, for example, still have serious difficulties in general functioning. When adolescents and young adults with Down syndrome master essential life skills it may improve their capacity for independence and reduce the intensity of support needed. Therefore, when coaching children and adolescents with Down syndrome, professionals and parents need to focus on those essential basic skills that are likely to increase the degree of independence.

Consequences for society

A consequence of the lack of sufficient evidence is that, in general, incorrect assumptions are made concerning individuals with Down syndrome. It is generally believed that children with Down syndrome are charming, friendly and joyful, without scientific evidence to support this assumption. Cebula commented on this when describing social cognition in children with Down syndrome: 'In the case of Down's syndrome, an additional factor contributing to this paucity of research may be the stereotypical perception that children with Down's syndrome are highly sociable and have good 'people' skills.[1,3,4] This has led to a widely held assumption that their social understanding is relatively intact'.[5] This impression probably holds because of their high compliance: compliant children are easily accepted in society and as a result not much attention is paid to these particular aspects. However, our results show that most adolescents and young adults with Down syndrome have serious difficulties in active social functioning and experience more behavioral problems than their peers without Down syndrome. Many adolescents have problems with social interaction,

some trouble with processing information and with understanding conversations. Examples of behavioral problems are: being too dependent on adults, having obsessive thoughts, being restless and being impulsive (dealing without thinking). Many adolescents are also withdrawn and have difficulty with change.

These social and behavioral problems of individuals with Down syndrome need to be recognized as they impede optimal daily functioning and opportunities to participate in society. In particular the high levels of social problems – measured at the age of 8 years as well as at 16-19 years – have major implications. It needs to be realized that the stereotype of Down syndrome – that they are charming, friendly and joyful – fails to acknowledge the extent of behavioral problems that limit adolescents with Down syndrome in their (social) functioning. These limited abilities will hamper participation in activities and social engagement. Results suggest that this is an area where significant overall health improvement needs to be made. Medical care for children and adults with Down syndrome should focus not only on physical health, but also on what is needed for an optimal quality of life and an improved level of functioning.

Recommendations for counseling

It is important to adjust the general perceptions concerning the opportunities for children and adults with Down syndrome. This implies that (expecting) parents need to be informed and counseled concerning the extremely limited chances that their child will ever be able to live independently as an adult. Positive and negative aspects need to be balanced in the information provided for professionals and parents. Most adolescents and young adults with Down syndrome may master skills such as personal hygiene, answering a telephone or swimming. But it is also necessary to acknowledge that only one third of adolescents with Down syndrome are able to spend a few hours alone at home and/or can phone other people. This means that two thirds continuously need intensive supervision. It is important to realize that only a small minority can perform more complex tasks such as cooking, shopping and cycling in traffic. Our results indicate that most tasks can only be performed in standard and predictable situations and we found that these adolescents are generally unable to handle any changes and new or unexpected situations.

Professionals are responsible for giving appropriate information to parents and colleagues. They have to outline the full picture of the way in which individuals with Down syndrome will function. It is further essential that suitable information is available to answer parents' questions. Parents of an older child have other needs than expectant parents. Availability of appropriate information material, such as images and videos, is essential. Preferably, expectant or new parents of infants with Down syndrome should also receive information from parents of adolescents or young adults with Down syndrome who can relate their

personal experiences. In this way, they will have a better opportunity to form a correct image of the future they can expect for and with their child.

Recommendations for further research

— The stability in the prevalence of Down syndrome in the Netherlands and the fact that the population of children with Down syndrome remains constant indicate that medical and social facilities for their special needs remain necessary. Therefore, research into these needs must continue.

— Prenatal screening for Down syndrome has been introduced in the Netherlands for all pregnant women in order to allow them and their partners to either prepare themselves for the birth of an infant with Down syndrome or to terminate the pregnancy if Down syndrome is diagnosed. In view of the low uptake of prenatal screening by Dutch women and the observed stable prevalence of Down syndrome, it seems that the abovementioned second choice is not widely used. The reasons behind the low uptake of prenatal screening should be explored.

— Calculations are proposed to estimate the expected final height in children with Down syndrome. The Target Height calculations were derived under the assumption that the correlation between mid-parental height standard deviation (SD) and child height SD in Dutch children with Down syndrome is identical to the general Dutch population. Further research is needed to investigate whether this assumption is justified.

— Children with Down syndrome show growth retardation during critical periods when the highest growth velocity occurs. This finding indicates the time intervals in which further growth might possibly be achieved. Therefore, future research should focus on the exact qualities of the observed deflections in growth of otherwise healthy children with Down syndrome: is their growth spurt restricted by an inborn lower growth velocity or do other reversible phenomena play a role?

— Criteria are needed to define abnormal growth. No specific criteria have been proposed for abnormal growth on the charts for children with Down syndrome. The utility of the referral criteria for the general Dutch population as presented in the guideline 'Detection and referral criteria in short stature' has not been tested for growth in children with Down syndrome. Further research is necessary to see whether such referral criteria are equally suitable for children with Down syndrome.

— More information concerning the underlying cause of excessive weight gain in children with Down syndrome is necessary for developing strategies for prevention and intervention. From the information from studies among children in the general population, we assume that physical activity and/or eating patterns are most likely to be the important factors influencing body weight in children with Down syndrome. Further research is needed to establish the merit of this assumption and to explore other possible underlying factors.

— Excessive weight gain in children and adults with Down syndrome should be prevented. We expect that a structured healthy life style (including a healthy diet and sufficient physical activity) will be especially effective in children with Down syndrome, due to their habit of keeping to a strict routine. Specific validated prevention programs suitable for children with Down syndrome to help prevent excessive weight gain and to support their families should be tested and become widely available if proved suitable.

— Children with Down syndrome experience various behavioral problems, for example they are withdrawn, are dependent on adults, their coordination is clumsy and they have obsessive thoughts. It may be possible to significantly improve their behavior, especially the social aspects. From an early age onwards, individuals with Down syndrome should be stimulated to develop better social skills. Special programs for this should be developed and evaluated.

— Factors influencing the social participation and development of children with Down syndrome, as well as the relationship between developmental level and problem behavior, and its influence on quality of life, need to be investigated.

— Recurrent respiratory tract infections in children with Down syndrome, as reported by parents, are associated with more delayed development, more behavioral problems and a lower health-related quality of life (HRQoL). Further research is needed to investigate whether the observed association is based on a causal relationship. Many variables that influence development, behavior and HRQoL, for example gender and congenital heart defects, cannot be changed. However the problem of recurrent respiratory tract infections could potentially be influenced by improved medical care and this could possibly lead to better functioning in these children.

— The level of impairment of the humoral immune system and its contribution to recurrent respiratory tract infections in Down syndrome has not been fully elucidated; more research on this topic is needed. Also, more insight into causative pathogens may lead to specific preventive interventions, i.e. prophylactic antibiotics or additional immunizations.

— Adolescents with Down syndrome in our sample have limited abilities to perform the relatively more complex tasks needed for independent living. This leads to dependency on others and to serious difficulties in social functioning. Further research is needed to develop and study the effectiveness of intervention programs to specifically improve specific social functioning skills of children with Down syndrome.

— The gap between our research findings and evidence-based interventions and effective educational approaches needs to be bridged. Furthermore, more detailed knowledge of how social cognition of children with Down syndrome develops throughout childhood and which factors contribute to better social functioning in these children need to be studied. These results may provide additional information on the most appropriate ways to support social development in children with Down syndrome at various ages.

— Although small studies show some evidence for positive short-term effects of stimulation by early intervention programs, there is no evidence that they lead to long-term benefits. Further evidence is needed to provide knowledge about what can (or cannot) be gained by stimulation programs. The limits of these programs need to be known to prevent too high expectations beforehand and disappointment afterwards. It is essential that expectations are realistic.

— At 8 years, as well as at 16-19 years of age, individuals with Down syndrome experience more emotional and behavioral problems than other children. Further research is needed to investigate if problems at late-adolescence can be predicted by the profile of behavioral problems in childhood.

— The causes of the behavioral problems are unknown. It is obvious, that these problems are caused by the genotype of Down syndrome as well as by factors influencing the phenotype. The ‘dual diagnosis’ of intellectual disability and psychopathology needs to be studied in adolescents with Down syndrome.

— Appropriate definitions of psychopathology in Down syndrome (such as attention deficit and hyperactivity disorders (ADHD) and autism) are needed. Special screening instruments for these problems should be developed. Sufficient information concerning the clinical implications and possible treatments of these behavioral disorders is essential for provision of optimal care.

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Summary

Samenvatting

Chapter 10

Summary

For readers without a medical background

In this thesis, 4 studies on children and adolescents with Down syndrome are described. These focused on the number of births, growth, development and social functioning of these children and adolescents.
Down syndrome is a congenital defect that is caused by so-called Trisomy 21. This means that the cells in the bodies of these children contain three copies (instead of two) of chromosome 21. This results in intellectual disability and physical anomalies (such as a congenital heart defect). People with Down syndrome also have characteristic external features.
Children with Down syndrome need special medical care. In 2011, an update of the Dutch guideline for the medical care of children with Down syndrome was published by TNO in cooperation with pediatricians and other professionals. This describes the specific care needed for these children. This care aims to optimize health in children with Down syndrome and to stimulate development.

Number of births

In the first study, the number of births of children with Down syndrome in the Netherlands was determined over the period 1997-2007. Results showed that the number of live births of children with Down syndrome remained stable during this eleven-year-period. In the Netherlands, the number of births with Down syndrome (also called birth prevalence) was 14.6 per 10,000 births during the study period. Of these, 85% were live born. This meant that 245 children with Down syndrome were live born in the Netherland annually.
The number of births was influenced by two main factors. The first being maternal age. Mean maternal age increased from 30.4 years in 1997 to 31.3 years in 2007. This causes an increase in pregnancies with children with Down syndrome, because the risk for Down syndrome rises with increasing maternal age.
The second factor influencing the number of births with Down syndrome is the possibility to detect Down syndrome during pregnancy (prenatal screening) and the possibility to terminate the pregnancy. In the Netherlands, prenatal screening for Down syndrome was introduced in 2002, so from that year on it is possible, during the pregnancy, to test whether a fetus has Down syndrome. Parents may decide to terminate the pregnancy when the diagnosis of Down syndrome is made. In the Netherlands termination of pregnancy is legal until 24 weeks of pregnancy. The number of live births of children with Down syndrome will decline if more parents decide to terminate the pregnancy.
In the study, these two factors were investigated by dividing births in two groups: those in older and younger women. This showed that among women aged 36 years or older, the

number of live births with Down syndrome has increased. This is due to the increase in mean maternal age and the accompanying increased risk of Down syndrome. Furthermore, results showed that among women younger than 36 years of age, the number of fetal deaths with Down syndrome (born before 24 weeks of pregnancy) has increased. This means that in younger women more pregnancies will be ended early, by miscarriage or abortion.
In conclusion, the results showed that in younger women a small increase in still births of children with Down syndrome due to terminations seems present. This number is compensated by a small increase of live births among older women. This combination leads to a stable number of live births of children with Down syndrome in the Netherlands.

Growth

A growth study which included 1,596 Dutch children with Down syndrome was carried out. Data were collected from medical records of all children of Dutch descent with Trisomy 21, from 25 specialized regional pediatric outpatient clinics for children with Down syndrome. Measurements of height, head circumference and weight, which were recorded over the past 10 years, were collected as well as information about their health status. In total, the sample provided 10,558 measurements for height, 1,778 for head circumference and 11,936 for weight.
With these data, new reference growth charts were constructed (presented after chapter 3 and to be downloaded via www.tno.nl/growth). For the construction of these growth charts only healthy children with Down syndrome were selected and children with disorders known to interfere with growth were excluded (such as children with a severe heart defect or thyroid dysfunction). In this way, the references reflect optimal growth of a child with Down syndrome. These new specific reference charts provide physicians with an optimal tool to monitor the general health of children with Down syndrome.
Mean final height was 163.4 cm in healthy boys with Down syndrome and 151.8 in girls. This means that the final height of people with Down syndrome is, on average, 20 cm shorter than people without Down syndrome (mean final height of boys in the general Dutch population is 183.8 cm and of girls 170.7 cm). The growth retardation was most marked during the first three years of life and during puberty. Head circumference was also smaller in healthy children with Down syndrome than in children of the general population.
Boys and girls with Down syndrome with a mild or severe heart defect were studied separately. Heart defects were considered mild when no surgical corrections or medication were necessary and severe when surgical correction or medications were required. Growth in children with a mild heart defect showed the same pattern as in healthy children with Down syndrome, so they had similar mean final heights. However, growth in children with a severe heart defect decelerated in the first year of life compared to healthy children with Down syndrome. After the first year, they grew just as quickly, but they did not make up for the growth retardation and their adult height was shorter by 2-3 cm.

The weight of children with Down syndrome was also studied, with the focus on the number of children being overweight or obese (severe overweight). Also for the study of overweight and obesity only healthy children with Down syndrome were selected. The results showed that twice as many healthy children with Down syndrome were overweight when compared to children from the general population.

In total, 25.5% of the healthy boys with Down syndrome were overweight and 32.0% of the healthy girls. Obesity was present in 4.2% of the boys and 5.1% of the girls with Down syndrome. These percentages were roughly constant over the age ranges: from the age of four years more than one quarter of the boys were overweight or obese and one third of the girls.

Children with Down syndrome who had a severe heart defect or thyroid dysfunction and who were overweight or obese were studied separately. This revealed that a similar percentage of children with overweight in the group of children with a severe heart defect (28.1%) as in the healthy children with Down syndrome. In the group of children with thyroid dysfunction this percentage was higher (35.1%), but this difference may be due to a coincidence (it is not significantly different).

Fat children will suffer from serious health problems. Therefore, it is important to prevent too much weight gain and to ensure that children who are overweight or obese lose weight. This is also important for children with Down syndrome. In the growth study, a rapid increase in the number of children with overweight is observed from the age of two up to six years. This indicates that parents and physicians should attempt to prevent excessive weight gain in children with Down syndrome from a young age.

Development and behavior at childhood

In the third study, development was investigated in 337 children with Down syndrome born in 1992, 1993 or 1994. At the age of 8 years these children were tested at home and in addition their parents completed a questionnaire.

The developmental results showed that children with Down syndrome had a lower score for all areas of development compared to their peers. The children with a calendar age of 8 years and 1 month had a developmental age of, on average, 3 years and 11 months. This means that they had a developmental delay of 4 years and 2 months.

Overall, girls had a better score than boys. On average, developmental age in girls with Down syndrome was 4 years and 2 months, and in boys 3 years en 7 months. Boys had 7 months more developmental delay than girls with Down syndrome.

The 8-year-old children with Down syndrome showed much more problem behavior than their peers without Down syndrome. In total, 27% of boys and girls with Down syndrome had ‘clinical’ behavioral problems, meaning that the problems were so serious that they were not considered as ‘normal problems’ appropriate for their age. For comparison, 11% of boys and girls in the general population have ‘clinical’ behavioral problems. Children with

Down syndrome had more problems especially on the social scales. In contrary, children with Down syndrome scored fewer problems than their peers without Down syndrome in only the area of anxious/depressed signs.
In the study, the so-called health-related quality of life is also measured. This determines how children appreciate their own life with their disorder. Children with Down syndrome scored a lower quality of life than their peers without Down syndrome in the areas of *gross motor skills, autonomy, cognitive functioning* and *social functioning.* It is striking that no differences were found in the areas *physical complaints, positive emotions* and *negative emotions.*

Children with Down syndrome who suffered from recurrent respiratory tract infections were studied separately. In the sample of 8-year-old children with Down syndrome, parents of 46% of the children indicated that their child suffered from recurrent respiratory tract infections. The developmental level of these children was even lower than of children with Down syndrome without these infections. The children with recurrent infections had an additional 5 months developmental delay. In other chronic disorder, such as a congenital heart defect or thyroid dysfunctions, no extra developmental delay was found.
The children with Down syndrome and recurrent respiratory tract infections had also more behavioral problems in general and a somewhat lower quality of life.

Social functioning and behavior in adolescents
In 2011, the children with Down syndrome born in 1992, 1993 or 1994 were studied once more. These children were now 16 to 19 years old. Data were collected by using a questionnaire that was completed by their parents. This study focused on self-help skills, social functioning and behavior. From the results it can be concluded that all adolescents and (young) adults with Down syndrome remain dependent on caregivers and exhibit serious difficulties in social functioning.
The results showed that most adolescents with Down syndrome master some of the skills required for independent social functioning. Eight out of 10 adolescents were able to use a knife and fork at lunch and dinner, and 7 out of 10 adolescents were able to use (without assistance) the computer and television. Also, 8 out of 10 adolescents were able to swim and 4 out of 10 adolescents were able to use a normal bike. Furthermore, about 6 out of 10 adolescents were able to get up in the morning by themselves, including dressing, taking a shower and having breakfast. However, less than 1 out of 10 adolescents was able to perform basic cooking or pay in a shop.
In the field of cognitive skills, 4 out of 10 adolescents were able to write notes and emails with some phrases, read and understand short texts in magazines or books, and 4 out of 10 adolescents were able to add numbers up to 10.
Most parents were not able to leave their child with Down syndrome at home alone for any

length of time. Two thirds of adolescents with Down syndrome were able to spend at least 30 minutes alone at home, but one third of adolescents needed intensive supervision 24 hours per day. In traffic, 5 out of 10 adolescents were able to cycle with supervision, but only 2 out of 10 adolescents could cycle along a familiar route without supervision.

In the field of social functioning, 9 out of 10 adolescents with Down syndrome experienced more problems in social functioning than is usual for their age. Regarding interaction, for example, 3 out of 10 adolescents made little eye contact and 7 out of 10 adolescents regularly 'lived in a world of his/her own'. Most adolescents (7 out of 10) had some trouble with processing information and with understanding conversations. Concerning mood, 1 out of 3 adolescents angered easily and 4 out of 10 had mood swings without apparent reason. One out of 10 adolescents was regularly disobedient and/or could not be corrected. Half of the adolescents had difficulties with changes, e.g. they panicked easily, stayed passive in new situations and/or resisted change.

Adolescents with Down syndrome had more problem behavior than adolescents without Down syndrome, mostly social problems, thought problems and attention problems. A few examples of this problem behavior are: being too dependent on adults, having obsessive thoughts, not being able to keep their attention focused, being restless, daydreaming (absorbed in thoughts) and being impulsive (dealing without thinking). Many adolescents also were withdrawn. They preferred being alone, were closed, shy or did not make contact with others.
In these areas, adolescents with Down syndrome had also 'clinical problems'. These are problems are so serious that they cannot be classified as normal problems appropriate for their age. Almost 40% of adolescents had more social problems than appropriate for their age and about 20% had more thought and attentions problems. In comparison, about 10% of adolescents without Down syndrome have clinical problems.
Adolescents with Down syndrome had fewer problems than adolescents without Down syndrome in only the fields of anxious/depressed signs.
Within the Down syndrome sample, boys scored higher on problem behavior than girls. Furthermore, problem behavior is related to the level of intellectual disability: behavioral problems increase with the severity of intellectual disability.

Consequences for society

In general, incorrect assumptions are made concerning individuals with Down syndrome. It is generally believed that children with Down syndrome are charming, friendly and joyful, without any scientific evidence for this assumption. Our results show that most adolescents and young adults with Down syndrome have serious difficulties in active social functioning and they experience more behavioral problems than their peers without Down syndrome.

These problems need to be recognized as they impede optimal daily functioning and opportunities for these individuals to participate in society. Results suggest that this is an area where significant overall health improvement could and possibly should be made. Medical care for children and adults with Down syndrome should focus not only on physical health, but also on (what is needed for) an optimal quality of life and an improved overall level of functioning.

Recommendations for counseling

It is important to adjust the general perceptions concerning the opportunities for children and adults with Down syndrome. This implies that (expectant) parents need to be informed and counseled concerning the extremely limited chance that their child will ever be able to live independently as an adult.

Positive and negative aspects need to be balanced in the information for professionals and parents. It needs to be generally known that most adolescents and young adults with Down syndrome master skills such as personal hygiene, answering a telephone or swimming. But, it is also necessary to acknowledge that only one third of adolescents with Down syndrome are able to spend a few hours alone at home and/or can phone other people. Professionals are responsible for providing parents and other colleagues with appropriate information. They should be able to explain the full picture of the way individuals with Down syndrome function.

Samenvatting

Voor de niet medisch onderlegde lezer

In dit proefschrift zijn de resultaten beschreven van 4 onderzoeken bij kinderen en jongeren met Downsyndroom. Deze onderzoeken richtten zich op het aantal geboorten, de groei, de ontwikkeling en het functioneren van deze kinderen en jongeren.
Downsyndroom is een aangeboren aandoening die veroorzaakt wordt door een zogeheten Trisomie 21, wat betekent dat er in de lichaamscellen van het kind geen twee maar drie exemplaren van het 21^{e} chromosoom aanwezig zijn. Dit veroorzaakt een verstandelijke beperking en lichamelijke afwijkingen bij het kind (zoals een aangeboren hartafwijking). Mensen met Downsyndroom hebben specifieke uiterlijke kenmerken.
Kinderen met Downsyndroom hebben extra medische zorg nodig. In 2011 is een nieuwe versie verschenen van de Nederlandse richtlijn 'Medische begeleiding van kinderen met Downsyndroom', ontwikkeld door de werkgroep Downsyndroom onder leiding van TNO. De richtlijn beschrijft de specifieke zorg die kinderen met Downsyndroom nodig hebben. Het doel van deze zorg is dat kinderen met Downsyndroom zo gezond mogelijk zijn en zich zo optimaal mogelijk kunnen ontwikkelen.

Het aantal geboorten

In het eerste onderzoek in dit proefschrift werd het aantal geboorten van kinderen met Downsyndroom in Nederland gedurende de periode 1997-2007 bestudeerd. De resultaten lieten zien dat over deze periode van 11 jaar het aantal levendgeborenen met Downsyndroom stabiel bleef.
Het aantal geboren kinderen met Downsyndroom (ook wel de geboorteprevalentie genoemd) was in Nederland 14,6 per 10.000 geboortes tijdens de onderzoeksperiode, waarbij 85% van de kinderen levend geboren werden. Dit betekent dat er ieder jaar gemiddeld 245 kinderen met Downsyndroom levend geboren werden in Nederland.

Het aantal geboorten van kinderen met Downsyndroom werd door twee belangrijke factoren beïnvloed. Eén van de factoren was de leeftijd van de moeder. Elk jaar steeg de gemiddelde leeftijd waarop moeders een kind krijgen een beetje, van 30,4 jaar in 1997 naar 31,3 jaar in 2007. Het risico op het krijgen van een kind met Downsyndroom is hoger naarmate de moeder ouder is. Dit betekent dat door de stijging van de gemiddelde leeftijd van de moeders, het aantal moeders dat zwanger was van een kind met Downsyndroom toenam.
De tweede factor die het aantal geboorten van kinderen met Downsyndroom beïnvloedde, was de mogelijkheid om Downsyndroom tijdens de zwangerschap op te sporen (prenatale screening) en de zwangerschap af te breken. In Nederland is prenatale screening naar Downsyndroom sinds 2002 mogelijk, dus sindsdien is het mogelijk om al tijdens de

zwangerschap te onderzoeken of een kind Downsyndroom heeft. Ouders kunnen besluiten een zwangerschap af te breken als ze weten dat het kind Downsyndroom heeft. Als veel ouders dit doen, daalt het aantal levendgeborenen met Downsyndroom.
In het onderzoek zijn deze twee factoren onderzocht door oudere en jongere moeders als aparte groepen te bestuderen. Daarbij bleek dat, onder moeders die 36 jaar of ouder zijn, het aantal levendgeborenen met Downsyndroom steeg. Dit is het gevolg van het feit dat de gemiddelde leeftijd van de moeders opliep en er hierdoor het risico op Downsyndroom groter werd. Daarnaast bleek dat, in de groep moeders die jonger dan 36 jaar zijn, juist het aantal doodgeborenen met Downsyndroom (geboren voor 24 weken zwangerschap) steeg. Dat wil zeggen dat bij jonge moeders meer zwangerschappen vroegtijdig eindigden door een miskraam of een abortus.
Deze resultaten toonden dat er onder jonge moeders mogelijk een kleine toename was van abortus bij Downsyndroom, maar dat dit aantal gecompenseerd werd door een kleine toename in levendgeborenen met Downsyndroom onder oudere moeders. Hierdoor bleef het totaal aantal kinderen met Downsyndroom, die levend geboren werden, in Nederland stabiel.

Groei

Het tweede onderzoek is een groeistudie onder 1.596 Nederlandse kinderen met Downsyndroom. Uit medische dossiers van 25 Downpoli's werden van alle kinderen van Nederlandse afkomst met Trisomie 21 de metingen overgenomen van lengte, hoofdomtrek en gewicht, die in de afgelopen 10 jaar gemeten waren, evenals gegevens over hun gezondheid. In totaal werden 10.558 metingen van lengte, 1.887 van hoofdomtrek en 11.936 van gewicht verzameld.
Met deze gegevens zijn nieuwe groeidiagrammen voor kinderen met Downsyndroom gemaakt (weergegeven na hoofdstuk 3 en te downloaden via www.tno.nl/groei). Bij het samenstellen van deze groeidiagrammen werden alleen gezonde kinderen met Downsyndroom geselecteerd, dus geen kinderen met aandoeningen die de groei kunnen beïnvloeden (zoals een ernstige hartafwijking of schildklierafwijking). Hierdoor geven de groeidiagrammen weer wat de optimale groei van een kind met Downsyndroom is. Met de nieuwe groeidiagrammen voor kinderen met Downsyndroom hebben artsen een goed instrument om de algemene gezondheid van het kind te monitoren.
De gemiddelde eindlengte van gezonde jongens met Downsyndroom was 163,4 cm en van gezonde meisjes met Downsyndroom 151,8 cm. Dit betekent dat mensen met Downsyndroom, als ze uitgegroeid zijn, gemiddeld 20 cm kleiner zijn dan mensen zonder Downsyndroom (de eindlengte van jongens in de algemene bevolking is 183,8 cm en van meisjes 170,7 cm). De achterstand in groei nam vooral toe in de eerste drie levensjaren en tijdens de puberteit. Naast de lengte, was ook de hoofdomtrek van gezonde kinderen met Downsyndroom kleiner dan van kinderen in de algemene bevolking.

Jongens en meisjes met Downsyndroom die een milde of ernstige hartafwijking hadden, zijn apart bestudeerd. De hartafwijking werd als mild beschouwd als er geen operatie of medicijnen voor nodig waren en als ernstig als er wel sprake was van een operatie of medicijn gebruik. De kinderen met een milde hartafwijking bleken even goed te groeien als de gezonde kinderen met Downsyndroom en werden dus gemiddeld even lang. Echter, de kinderen met Downsyndroom en een ernstige hartafwijking groeiden in het eerste levensjaar iets minder hard dan de gezonde kinderen met Downsyndroom. Daarna groeiden ze even snel, maar haalden ze deze kleine achterstand in lengte niet meer in waardoor ze als volwassene iets kleiner waren (2-3 cm).

Het gewicht van de kinderen met Downsyndroom werd in deze groeistudie ook bestudeerd. Hierbij werd vooral gekeken naar het aantal kinderen met overgewicht of obesitas (ernstig overgewicht). Ook hier werd geselecteerd op de gegevens van gezonde kinderen met Downsyndroom. De resultaten toonden dat deze gezonde kinderen met Downsyndroom twee keer vaker overgewicht of obesitas hadden dan kinderen in de algemene Nederlandse bevolking.
In totaal had 25,5% van de gezonde jongens met Downsyndroom overgewicht en 32,0% van de gezonde meisjes. Obesitas kwam bij 4,2% van de jongens voor en bij 5,1% van de meisjes met Downsyndroom. Deze percentages bleven grofweg constant over de verschillende leeftijden. Al vanaf de leeftijd van 4 jaar had meer dan een kwart van de jongens en bijna een derde van de meisjes met Downsyndroom overgewicht of obesitas.
Het aantal kinderen met overgewicht en obesitas werd apart bestudeerd in de groep kinderen met Downsyndroom met een ernstige hartafwijking of een te traag werkende schildklier. Hierbij bleek het percentage kinderen met overgewicht in de groep met een ernstige hartafwijking (28,1%) even groot te zijn als in de groep gezonde kinderen met Downsyndroom. Bij de groep met een traag werkende schildklier was dit percentage wat hoger (35,1%), echter dit verschil kan op toeval berusten (het verschil is niet significant).
Dikke kinderen kunnen gezondheidsproblemen krijgen. Daarom is het belangrijk om te voorkómen dat kinderen (te) dik worden en ervoor te zorgen dat te dikke kinderen afvallen. Dit geldt ook voor kinderen met Downsyndroom. In de groeistudie was op de leeftijd van 2-6 jaar een duidelijke stijging zichtbaar van het aantal kinderen dat overgewicht heeft. Dat betekent dat ouders en artsen al vanaf jonge leeftijd erop moeten letten dat kinderen met Downsyndroom niet te dik worden.

Ontwikkeling en gedrag op de kinderleeftijd

In het derde onderzoek werd de ontwikkeling onderzocht van 337 kinderen met Downsyndroom die geboren zijn in 1992, 1993 of 1994. Op 8-jarige leeftijd werd thuis bij het kind een ontwikkelingstest afgenomen en vulden ouders een vragenlijst in.
De ontwikkelingstest liet zien dat de kinderen met Downsyndroom op alle

ontwikkelingsgebieden lager scoorden dan normaal voor hun leeftijd. De kinderen hadden gemiddeld een kalenderleeftijd van 8 jaar en 1 maand. Wat betreft ontwikkeling functioneerden ze gemiddeld op de leeftijd van 3 jaar en 11 maanden. Dit betekent dat ze gemiddeld een ontwikkelingsachterstand van 4 jaar en 2 maanden hadden.
Over het geheel scoorden de meisjes beter dan de jongens. Gemiddeld was de ontwikkelingsleeftijd bij meisjes met Downsyndroom 4 jaar en 2 maanden en bij jongens 3 jaar en 7 maanden. Jongens hadden dus 7 maanden extra achterstand in hun ontwikkeling in vergelijking met meisjes met Downsyndroom.
Bij 8-jarige kinderen met Downsyndroom kwamen meer gedragsproblemen voor dan bij hun leeftijdsgenoten zonder Downsyndroom. In totaal had 27% van de jongens en meisjes met Downsyndroom 'klinische' gedragsproblemen, dat wil zeggen dat de ernst van het probleem buiten het gedrag valt dat past bij hun leeftijd. Bij 8-jarige kinderen in de algemene bevolking is dit bij 11% het geval. Kinderen met Downsyndroom hadden vooral meer problemen op sociaal gebied. Alleen op het gebied van angst en depressie scoorden de kinderen met Downsyndroom minder problemen dan hun leeftijdsgenoten.
Bij de kinderen werd ook de zogenaamde gezondheidsgerelateerde kwaliteit van leven gemeten. Dit geeft weer hoe kinderen hun eigen leven waarderen mét hun ziekte. De kinderen met Downsyndroom bleken een lagere kwaliteit van leven te scoren dan hun leeftijdsgenoten zonder Downsyndroom op de gebieden grove motoriek, autonomie, cognitief functioneren en sociaal functioneren. Opvallend is dat er geen verschillen werden gevonden op de gebieden lichamelijke klachten, positieve emoties en negatieve emoties.

Kinderen met Downsyndroom die chronische luchtweginfecties hadden, werden extra bestudeerd. In het onderzoek op 8-jarige leeftijd had 46% van de kinderen met Downsyndroom chronische luchtweginfecties. Het ontwikkelingsniveau van deze kinderen lag lager dan bij de kinderen met Downsyndroom zonder chronische luchtweginfecties. De kinderen met chronische luchtweginfecties hadden 5 maanden meer ontwikkelingsachterstand. Opvallend was dat bij andere chronische ziektes, zoals een aangeboren hartafwijking of schildklierziekte, niet een zodanig verschil werd gevonden.
De kinderen met Downsyndroom en chronische luchtweginfecties hadden over het algemeen ook iets meer gedragsproblemen en een iets lagere kwaliteit van leven.

Sociaal functioneren en gedrag van jongeren
In 2011 werden de kinderen die geboren zijn in 1992, 1993 en 1994 opnieuw onderzocht. Bij dit onderzoek waren de kinderen tussen de 16 en 19 jaar oud. De gegevens werden verzameld door middel van een vragenlijst die door de ouder(s) is ingevuld. In dit onderzoek werden de zelfredzaamheid, het sociaal functioneren en het gedrag gemeten. De conclusie is dat alle jongeren en (jong)volwassenen met Downsyndroom in grote mate afhankelijk waren en grote moeite hadden om goed sociaal te functioneren.

Het onderzoek toonde dat een deel van de jongeren in bepaalde mate voor zichzelf kan zorgen. Zo konden 8 op de 10 jongeren zelf eten met mes en vork en 7 op de 10 jongeren konden zonder hulp een computer of televisie bedienen. Ook konden 8 op de 10 jongeren zwemmen en 4 op de 10 jongeren fietsen op een gewone fiets. Verder kon ongeveer 6 op de 10 jongeren 's ochtends zelf opstaan: zich zonder hulp aankleden, zich douchen en ontbijten. Echter, minder dan 1 op de 10 jongeren kon taken uitvoeren als een eenvoudige maaltijd koken of betalen in een winkel.
Wat betreft schoolse vaardigheden konden 4 op de 10 jongeren eenvoudige briefjes schrijven, een stukje uit een boek of tijdschrift lezen en begrijpen, en konden 4 op de 10 een eenvoudige som (onder de 10) maken.
De meeste ouders konden hun kind niet alleen thuis laten. Twee derde van de jongeren kon wel een half uur alleen thuis zijn, maar de andere jongeren hadden 24 uur per dag (intensieve) begeleiding nodig. In het verkeer konden de 5 op de 10 jongeren fietsen met begeleiding en 2 op de 10 ook zonder begeleiding (op een voor hen bekende route).

Op sociaal gebied hadden 9 op de 10 jongeren met Downsyndroom duidelijk meer problemen dan hun leeftijdsgenoten zonder Downsyndroom. Ze hadden bijvoorbeeld moeite met sociale interactie met anderen: 3 op de 10 jongeren maakten weinig oogcontact en 7 op de 10 jongeren bleken regelmatig in een 'eigen wereld' te leven. De meeste jongeren (7 op de 10) hadden moeite met het verwerken van informatie en het begrijpen van een gesprek. Wat betreft stemming, 1 op de 3 werd snel boos en 4 op de 10 jongeren hadden plotselinge stemmingswisselingen. Eén op de 3 jongeren was geregeld ongehoorzaam en moeilijk te corrigeren in situaties waarin hij/zij iets verkeerd deed. De helft van de jongeren blokkeerde of raakte in paniek bij nieuwe situaties of veranderingen.

Jongeren met Downsyndroom hadden meer gedragsproblemen dan jongeren zonder Downsyndroom, vooral meer sociale problemen, denkproblemen en aandachtsproblemen. Enkele voorbeelden hiervan zijn: zich te afhankelijk van volwassenen gedragen, bepaalde gedachten niet uit je hoofd kunnen zetten, niet lang de aandacht bij iets kunnen houden, onrustig zijn, dagdromen (opgaan in je gedachten) en impulsief zijn (handelen zonder na te denken). Ook kwam het vaak voor dat jongeren met Downsyndroom veel teruggetrokken zijn. Ze waren bijvoorbeeld liever alleen dan met anderen, gesloten, verlegen, of kwamen niet tot contact met anderen.
Op deze gebieden hadden veel jongeren ook 'klinische problemen'. Dit zijn problemen die zo ernstig zijn dat ze niet meer worden beschouwd als normale problemen die passen bij de leeftijd. Zo had bijna 40% van de jongeren meer sociale problemen dan passend voor hun leeftijd en ongeveer 20% had meer denk- en aandachtsproblemen. Ter vergelijking: bij jongeren zonder Downsyndroom heeft ongeveer 10% klinische problemen.

Alleen op het gebied van angst en depressie werden bij jongeren met Downsyndroom juist minder problemen gezien dan bij jongeren zonder Downsyndroom.
Gedragsproblemen kwamen meer voor bij jongens met Downsyndroom dan bij meisjes met Downsyndroom. Daarnaast hingen die problemen samen met de ernst van de verstandelijke beperking. Dat wil zeggen, des te ernstiger de verstandelijke beperking, des te meer gedragsproblemen de jongere meestal heeft.

Betekenis voor de maatschappij

In het algemeen lijkt er een onjuist beeld over kinderen met Downsyndroom te bestaan. Gedacht wordt dat alle kinderen met Downsyndroom schattig, vriendelijk en vrolijk zijn; een stereotype dat niet door onderzoek bewezen is. Sterker nog, de resultaten van de onderzoeken in dit proefschrift laten juist zien dat de meeste kinderen en volwassenen met Downsyndroom ernstige problemen hebben op sociaal gebied en meer gedragsproblemen hebben dan hun leeftijdsgenoten zonder Downsyndroom.
Deze problemen moeten worden (h)erkend, omdat ze het dagelijks leven van mensen met Downsyndroom en hun mogelijkheden om deel te nemen in de maatschappij sterk beïnvloeden. Waarschijnlijk is op dit gebied winst te behalen. Verder onderzoek moet zich richten op de manier waarop het sociaal functioneren van mensen met Downsyndroom kan worden verbeterd. Het is wenselijk dat de medische zorg voor kinderen en volwassenen met Downsyndroom zich niet alleen richt op de lichamelijke gezondheid, maar ook op een optimale kwaliteit van leven en een zo goed mogelijk functioneren in het dagelijks leven.

Aanbevelingen voor voorlichting over Downsyndroom

Het is belangrijk dat het beeld dat mensen hebben van de mogelijkheden van kinderen en volwassenen met Downsyndroom klopt. Dus moeten (toekomstige) ouders goed geïnformeerd worden over de zeer kleine kans dat hun kind met Downsyndroom zelfstandig zal worden.
Informatie over Downsyndroom voor professionals en ouders moet zowel de positieve als negatieve kanten bevatten. Het is goed te weten dat de meeste jongeren en (jong) volwassenen met Downsyndroom in staat zijn om bijvoorbeeld zichzelf te wassen en aankleden, de telefoon te beantwoorden en te zwemmen. Maar het is ook goed dat bekend is dat twee derde van de jongeren niet een paar uur alleen thuis kan zijn en/of niet zelf iemand kan opbellen. Artsen zijn verantwoordelijk voor het geven van juiste en volledige informatie aan ouders en andere professionals. Zij moeten een compleet beeld geven van wat Downsyndroom betekent voor het functioneren in dagelijks leven.

About the author

Curriculum vitae

List of publications

Curriculum vitae

Hillegonda Bertine Matthea (Helma) van Gameren-Oosterom was born on May 23th, 1985 in Bleskensgraaf, the Netherlands. She attended primary school in her domicile Broek op Langedijk and started secondary school at the CSG Jan Arentsz in Alkmaar and graduated in 2003 at the Driestar College in Gouda. In September 2003 she started studying Medicine at the Leiden University Medical Centre in Leiden, the Netherlands. During her study she was a member of the students association Navigators Studentenvereniging Leiden. She chose an internship at the Department of Pediatrics in the Rijnland Hospital in Leiderdorp and finished her study with an internship at TNO where she developed growth reference charts for children with Down syndrome.
In January 2010, she graduate from medical school and started working at the department of Child Health of TNO. Her PhD-program focused on growth and development of children and adolescents with Down syndrome. She was also involved in other research projects at TNO, such as the development of a guideline for the medical support of children with Down syndrome and guidelines for youth health care about skin disorders, asthma, excessive crying, positional preference in children, nutrition and eating behavior, referral for undescended testis and bullying.
Helma lives in Hazerswoude-Dorp with her husband Stian van Gameren.

Hillegonda Bertine Matthea (Helma) van Gameren-Oosterom werd geboren op 23 mei 1985 te Bleskensgraaf. Zij ging naar de basisschool in haar woonplaats Broek op Langedijk en daarna naar de middelbare school CSG Jan Arentsz in Alkmaar. Na verhuizing maakte zij haar middelbare school af op de Driestar College in Gouda, waar zij in 2003 eindexamen deed. In september 2003 startte zij haar studie Geneeskunde in het Leids Universitair Medisch Centrum te Leiden. Tijdens haar studie was ze lid van de Navigators Studentenvereniging Leiden. Haar coschappen sloot zij af met een semi-arts stage bij de kindergeneeskunde in het Rijnland Ziekenhuis te Leiderdorp. Hierna verrichtte zij haar wetenschapsstage bij TNO in Leiden, waarbij zij groeidiagrammen voor kinderen met Downsyndroom ontwikkelde.
In januari 2010 deed ze artsexamen en aansluitend ging zij werken bij de afdeling Child Health van TNO. Zij startte haar promotieonderzoek naar de groei en ontwikkeling van kinderen met Downsyndroom. Daarnaast werkte zij ook aan andere projecten van TNO, zoals de ontwikkeling van een richtlijn voor de medische begeleiding van kinderen met Downsyndroom en richtlijnen voor de jeugdgezondheidszorg over huidafwijkingen, astma, excessief huilen, voorkeurshouding, voeding en eetgedrag, verwijzing bij niet-scrotale testis en pesten.
Helma woont in Hazerswoude-Dorp met haar man Stian van Gameren.

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Nawoord

Epiloog

Dit proefschrift heb ik geschreven als arts

Maar ook als zus

Mijn broer heeft Downsyndroom

De kans die ik kreeg om onderzoek te doen bij kinderen met Downsyndroom heb ik daarom met beide handen aangegrepen. Ik ben er trots op dat ik mijn persoonlijke ervaring en kennis heb kunnen gebruiken om wetenschappelijke onderbouwde kennis over kinderen met Downsyndroom en hun mogelijkheden te verkrijgen.

Ik wil laten zien wat Downsyndroom voor het leven betekent voor een kind en zijn of haar ouders. Hoewel het moeilijk is in te schatten hoe kinderen het zelf beleven, zijn we in onze onderzoeken hierover veel te weten gekomen via hun ouders.

Voor ouders is het heel moeilijk, om te horen bij de geboorte van een kind, dat zijn of haar toekomst nooit zo zal zijn als elke ouder hoopt voor zijn of haar kind. Maar het is essentieel voor ouders dat zij reële informatie krijgen, omdat het vaak nog veel moeilijker is om een te positief beeld keer op keer te moeten bijstellen tijdens het opgroeien van het kind. Er voor gaan en het kind stimuleren met de juiste doelen voor ogen is van onschatbare waarde.

Leven met een familielid met Downsyndroom geeft een extra dimensie aan het leven. Het leren kijken naar alle positieve kanten van deze extra dimensie, zonder al te veel verwachtingen van te voren te hebben, is waardevoller dan menigeen beseft.

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