Growing up with Down syndrome
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General introduction
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DOWN SYNDROME IN THE NETHERLANDS

Each year, around 250 to 300 children with Down syndrome (DS) are born in the Netherlands [1, 2], making it the most prevalent chromosomal cause of intellectual disability. In addition to intellectual disability, other striking characteristics of DS are dysmorphic features and clearly slower physical growth [3]. Further, individuals with DS have a significantly higher risk of several health problems. These include congenital heart disease (around 40-50% of children), problems with hearing (38-78%) and vision (around 60%), thyroid disease (4-18%), leukemia (around 1%), and later in life an increased risk of Alzheimer’s disease (around 75% in those over age 60) [4, 5]. Further, psychopathology is more frequent than in the general population, around 6-8% being diagnosed with ADHD, 10-15% with oppositional or conduct disorders, while an estimated 7% meet criteria for autism spectrum disorders [6].

These specific health care requirements of children with DS have been compiled in specific DS guidelines, like the recently updated Dutch multidisciplinary guideline [7]. This guideline focuses on guidance of families around several important themes like diagnostic counseling, development, potential behavioral and psychiatric problems of the child, child abuse, and managing the care. Further, it discusses the specific medical issues by specialism (e.g. cardiology, pulmonology, endocrinology, etc.).

The increased and widespread understanding of the medical needs of individuals with DS and improvements in availability of medical and surgical interventions have led to a significant increase in life expectancy. Life expectancy has risen from around 10 years in the first half of the 20th century, to around 60 years currently [2, 8]. Further, ideas about the role of children with DS in society have changed considerably. Where children with DS were generally institutionalized in previous times, virtually all children are now raised in their own families [9]. Also, many children with DS now attend mainstream education [10].

One of the first to publish about what we now call Down syndrome was Sir John Langdon Down. Although earlier descriptions and supposed depictions of individuals with DS have been identified, Langdon Down was the first to make a clear distinction between children with hypothyroidism and children with DS [11, 12]. In his 1866 publication, Langdon Down classified several types of intellectual disability by their supposed ethnic characteristics, e.g. the Malay and the Mongolian type [13]. The chromosomal basis of DS was not discovered until 1959, when Jérôme Lejeune and colleagues identified the extra copy of chromosome 21 in individuals with DS [14]. This finding paved the way for studies on the role of this extra chromosome 21 in the expression of DS [4, 11]. Still, the genetic [12, 15] and epigenetic mechanisms that may relate to the DS phenotype are not fully known [16].

The findings of Lejeune and colleagues, somewhat ironically, also paved the way for prenatal screening, against which Lejeune strongly objected. If parents opt for prenatal screening, the current screening method in the Netherlands consists of an estimation of the chance of having a child with DS by a blood test, an ultrasound scan of the neck skin fold, together with maternal age. If this results in a chance of having a child with DS (or trisomy
13 or 18) that exceeds one in 200, follow-up testing is offered. This follow-up testing used to consist of chorionic villus testing (sampling of the placenta) or amniocentesis (sampling of amniotic fluid). These invasive tests are associated with a one in 200 chance of miscarriage [17]. Since 2014 parents can also opt for non-invasive prenatal testing (NIPT) as part of the follow-up testing. As from April 2017, NIPT will also be used as a first test, so not necessarily as a follow-up test for those with an increased chance of receiving a child with a trisomy. NIPT arguably reduces the chances of miscarriages, yet there has been considerable debate around the introduction of NIPT in the Netherlands. It has been argued that the non-invasive character of this procedure may lead more parents to opt for prenatal screening, which may have consequences for the prevalence and the societal perception of DS [18]. Further, NIPT potentially allows for the detection of other conditions, which may lead to future expansion of the prenatal screening program [19]. Currently, relatively few parents choose for prenatal screening in The Netherlands (<30%) as compared with other European countries, most notably Denmark (>90%) [20].

Paradoxically, advances in medical knowledge have vastly improved the lives of individuals with DS, while simultaneously making prenatal screening for DS increasingly reliable and accessible. Introduction of NIPT may be of influence on the number of children with DS born in the near future. Nevertheless, many children with DS are born in the Netherlands each year, whose health, development and well-being deserve our attention.

THE DEVELOPING CHILD WITH DS

As stated above, one of the key characteristics of DS is intellectual disability, although its degree varies considerably across individuals with DS [21]. The extra chromosome 21 is undeniably involved in disrupting brain development, yet the precise mechanisms by which this happens remain elusive [15]. Nevertheless, some factors that predict part of the variation in developmental outcomes in children with DS have been identified. These relate to gender of the child, parental educational level, early developmental stimulation [22-26], and comorbidity [27]. Of interest for the current thesis is a frequent health problem in DS that affects early brain development, and that has received considerable attention over the past decades: the thyroid hormone state in DS.

Thyroid hormones

Thyroid hormones have several important functions in the human body. They play an important role in 1) healthy pre- and postnatal brain development, 2) growth throughout childhood, and 3) metabolism throughout life [28]. In DS, congenital and acquired disorders that affect thyroid function are far more prevalent than in the general population [29]. An estimated 1.5% to 6% of children with DS suffer from congenital hypothyroidism; around 30 times more frequent than in the general population. Another 25% to 60% of children with DS qualify for subclinical hypothyroidism [29, 30]. Subclinical hypothyroidism is characterized by thyroid hormone (TH) levels within the normal range, in combination
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with an elevated thyroid stimulating hormone (TSH) level [31, 32]. TSH has the function of stimulating TH production in the thyroid gland, as presented in Figure 1. Since the hypothalamus and pituitary gland can be considered as a kind of thermostat for the circulating amount of TH, elevated TSH levels indicate that the thyroid gland (subtly) fails in providing the body with enough TH. Whether subclinical hypothyroidism has negative consequences for (brain) development, growth and healthy metabolism, and whether it should be treated, is matter of debate [31, 32]. Also among children without DS, good quality studies concerning the need for thyroid hormone treatment in subclinical hypothyroidism are lacking [33].

**Figure 1.** The thyroid and thyroid system.

Beside the thyroid disorders discussed above, Van Trotsenburg et al. [34] found that newborns with DS as a group show lower average thyroxine (T4) concentrations as compared with newborns without DS. This is shown in Figure 2. Newborns with DS also showed higher TSH concentrations than newborns without DS. These findings suggested that newborns and young children with DS are mildly hypothyroid as a group, even though most T4 and TSH concentrations are in the normal range. Mild hypothyroidism in early life could lead to suboptimal brain growth, development, and physical growth. These symptoms, however, are not easily differentiated from the general DS phenotype, with characteristic deficits in development and physical growth.

To determine whether children with DS indeed have suboptimal T4 levels that may hamper development and physical growth, Van Trotsenburg et al. [35] performed a randomized controlled trial (RCT) between 1999 and 2003. In this RCT, the effect of T4 treatment during the first two years of life on development and growth was compared with that of placebo treatment. This RCT included children with DS who had T4 and TSH
concentrations in the normal or subclinical range. Especially the children with values in the normal range would normally not be treated with T4. Yet, at the end of the trial, at age 24 months, T4 treated children showed somewhat better outcomes in motor development (0.7 months less delay) and growth (1.1 cm more gained). Although these differences were subtle, they were significant and supported the hypotheses that a) mild hypothyroidism may explain suboptimal development and growth in DS to some degree, and b) early T4 treatment might result in some improvement in development and growth.

*Figure 2.* SD scores of thyroxine concentrations in newborns with DS (minus those with abnormal neonatal screening results) versus newborns in the general population.

This RCT was unique with respect to its inclusion of very young children with DS, its methodological rigor, and its sample size. Even compared with studies concerning T4 treatment in children without DS, this RCT was unique [31]. The findings did not lead, however, to a wide introduction of T4 treatment for children with DS. First, there is the question of cost and benefit. It should be considered whether expected benefits weigh up against the burden of e.g. repeated blood sampling [36, 37]. To answer this question, it is important to determine the long-term benefits of early T4 treatment. Given the lack of trials concerning T4 treatment in children with mild hypothyroidism [38], long-term effects of early T4 treatment for this subtle condition on development and growth are hard to predict. It could be argued that optimized early brain maturation might lead to increasing benefits.
over time. On the other hand, the benefits of early T4 treatment may prove to be negligible in the long run when other, potentially more powerful, mechanisms influence development in DS.

Beside the question of cost and benefit, it was suggested that only children with DS and subclinical hypothyroidism would profit from T4 treatment [37]. Treating children whose TH and TSH levels are within the normal range, or in some children even relatively high, is controversial. Moreover, given the lack of compelling evidence that mild subclinical hypothyroidism has negative consequences, general recommendations are to only treat children with “severe” forms of subclinical hypothyroidism, i.e. TSH concentrations higher than 10 mIU/L, and children who show symptoms of hypothyroidism [38]. An important question, therefore, is whether children who showed initial signs of subclinical hypothyroidism profited more from early T4 treatment than children with normal thyroid hormone levels.

To answer the questions what the long-term effect of early T4 treatment was, and whether such effects were specific for children with initial signs of subclinical hypothyroidism, a follow-up study was needed.

**Development in children with DS**

The primary purpose of the T4 trial was to stimulate development by optimizing early brain development. Obviously, the background of this RCT is the characteristic intellectual disability in DS. Intellectual disability used to refer to an IQ under a certain threshold. IQ also used to define the severity of intellectual disability. Currently, however, IQ alone is considered inadequate to fully depict intellectual disability. Rather, (the degree of) intellectual disability is now defined by deficits in both intelligence and adaptive functioning [39]. In addition to the intellectual disability, DS is marked by particular deficits in motor functioning [40].

In the first part of the twentieth century, children with intellectual disability were described as a single group, without much attention for etiology [41]. Increasingly, however, it was appreciated that etiology related to specific developmental and behavioral outcomes, i.e. the behavioral phenotype [42]. This has resulted in a substantial body of literature describing characteristic developmental outcomes in DS [15, 21]. Typically, children with DS continue to acquire new skills for a long period throughout childhood and adolescence, yet at a much slower pace than peers without DS [43]. This increasing delay translates to a decreasing IQ during childhood, with mean IQ dropping from around 50 at the age of 4 to 5 years to around 35 at the age of 10 to 11 years [21].

Further, the behavioral phenotype of DS entails characteristic developmental deficits and relative strengths to which children with DS are predisposed. The cognitive profile has been summarized by Grieco et al. as “a consistent pattern of weaknesses in the processing of verbal information relative to visual information” [44]. Children with DS show particular deficits in expressive language, while nonverbal abilities, implicit memory and
social motivation tend to be relatively preserved as compared with other skills [44-46]. In adaptive functioning individuals with DS have been described to show marked deficits in communication skills relative to daily living skills and socialization [47-51]. Also in motor skills children with DS show characteristic outcomes, with balance, posture, strength, and motor planning being particularly weak relative to ball skills and running speed [40, 41, 52-55]. These specific outcomes in children with DS not only reflect brain development, but also the interaction of children and their environment, and the characteristics such as short fingers, loose ligaments, hypotonia and poor control of muscle tone [15, 56]. Understanding typical developmental trajectories and outcomes in DS is valuable in accommodating to the needs and possibilities of children with DS [42].

Notwithstanding the considerable body of literature on developmental outcomes in DS, as discussed above, there are important gaps that need to be addressed. First, the description of the DS behavioral phenotype implies that there is a single DS phenotype. Yet, this may be an oversimplification, as results on group level can mask the large individual variability and possible subgroups of strengths and weaknesses in DS [57]. Some studies have indeed found subgroups that show different cognitive profiles; one study statistically defined clusters of strengths and weaknesses in DS [43], while another found different profiles in readers versus non-readers [21, 58]. These are important distinctions, since knowledge about the DS phenotype(s) feeds e.g. interventional programs [42]. Incomplete knowledge about the DS phenotype can lead to faulty assumptions in designing such interventions.

Second, the DS behavioral phenotype emerges over time and changes with the child’s age [21, 40, 42, 45, 48, 59]. Descriptions of the behavioral phenotype should thus be age-specific. This may also help in identifying early precursors and predictors of later developmental outcomes [41, 42]. For that purpose, longitudinal studies that follow children from the infant years to later in life are invaluable. There have been some important longitudinal studies that started in infancy, yet these included children with DS born in the 1960s [25, 60], 1970s [23] or 1980s [61]. As pointed out earlier, circumstances in terms of health care and developmental stimulation changed considerably over the last decades [9]. Therefore, not all findings in these studies apply to children growing up today. Unfortunately though, recent longitudinal studies that started early in life are lacking.

Conclusion
In conclusion, thyroid hormones play an important role in early development, yet young children with DS appear to suffer from a mild form of congenital hypothyroidism. An RCT during the first two years of life suggested that early T4 treatment may improve development and physical growth. The long-term effects of this early T4 treatment, however, were unknown to date. Further, it should be determined whether children who showed early signs of mild hypothyroidism in particular profited from early T4 treatment. Therefore, a follow-up study was needed, assessing development and growth in children who participated in the RCT. This would result in a large dataset that would also allow
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for a detailed description of relative strengths and weaknesses in a group of children of a homogeneous age. Further, the developmental data that spanned the first decade of life would allow for analysis of early predictors for later developmental outcomes.

PARENTING A CHILD WITH DS

The unique characteristics of children with DS make parenting a child with DS a unique experience. First of all, for most parents the diagnosis DS is unexpected, leading to grief over the loss of an envisioned ‘normal’ parenthood and a redefinition of life goals [62]. Beside emotional challenges, parents face practical challenges concerning the management of the health, education, and care for their child with DS. Further, challenging behavior and frequent sleeping problems can be demanding for parents [63, 64]. On the other hand, many parents report that raising a child with DS is a rewarding experience that is associated with personal or even spiritual growth [62, 65].

The challenges of raising a child with DS are associated with consequences in everyday life, at the individual level and the level of the family. For instance, the care demands often compete with other demands and wishes in life, concerning e.g. personal, occupational, family and social activities [66, 67]. Parents of children with DS struggle with time demands, which often lead to limited participation in e.g. leisure or social activities [66]. The main focus in previous literature has been on stress, which revealed that parents of children with DS experience more stress than parents of children without DS [68]. Yet, stress is a rather unidimensional concept that captures the experiences of parents raising children with DS only to a limited extent. As highlighted above, the consequences of raising a child with DS concern a variety of domains of life. There is a need for studies that join relevant domains and give a comprehensive overview of the consequences that parents experience.

Health related quality of life

One concept that covers a range of relevant domains is HRQoL. HRQoL refers to the appreciation of functioning in health related domains, including physical, psychological, and social functioning, and the resulting sense of well-being [69]. As such, HRQoL represents what health care ultimately aims to achieve. It is therefore increasingly seen as an important outcome in clinical trials. Nevertheless, few studies have focused on the HRQoL of parents who raise a child with DS.

One of the main studies that reported on HRQoL in parents of children with DS was the so-called ‘Care project’. The Care project aimed to determine the consequences of caring for children with chronic conditions [70]. One of these groups was parents of those children with DS who had participated in the aforementioned T4 trial. Overall, this study found that parents of children with chronic conditions show considerably lower HRQoL than control parents, and recommended a family centered approach in the care for children with chronic conditions. Parents of children with DS showed significantly lower HRQoL in 4 out of 12 domains: cognitive functioning, social functioning, daily activities, and vitality. These
findings were largely in line with Australian and Swedish HRQoL studies, which additionally found lower outcomes in parents of children with DS concerning mental health [71, 72]. Of the studies described above, two relied on the reports of (mainly) mothers [70, 71], while one compared outcomes in mothers and fathers [72]. Interestingly, this revealed that mothers and fathers did not show the same outcomes; mothers reported lower vitality than fathers, and spent significantly more time caring for their child with DS than their spouses. This highlights that the experiences of mothers and fathers are not interchangeable. Nevertheless, the vast majority of studies on parental functioning relies on the reports of mothers. Most likely however, the maternal experience does not necessarily represent the paternal experience, due to e.g. different roles in the family and different perceptions of family life [68, 73]. So, there is a need for specific knowledge about the consequences that fathers experience.

*Predicting HRQoL*

These previous HRQoL findings provided an interesting and rather comprehensive overview of parents’ functioning. To be able to improve parental functioning, however, it is important to understand the dynamics that lead to lower HRQoL. Although general predictive models for parental HRQoL have been developed, we suppose that the raising a child with DS is different from raising a child with a chronic condition. However, none of the previous studies concerning HRQoL in parents of children with DS analyzed predictors, to our knowledge.

*Family functioning*

One of the main conclusions of the Care project was that a family-centered approach is needed in the care for children with chronic conditions, which would ensure attention for the well-being of parents [70]. Yet, parenting a child with DS not only affects the individual parent, it affects the entire family system [74]. This involves for instance the daily family routine, the parenting roles, and the relations within the family and with the outside world [68]. Family functioning and parental functioning provide complementary descriptions of adaptation to raising a child with DS, and strongly interact [75, 76].

Family functioning, however, can refer to a variety of different outcomes [77]. A frequently used Dutch questionnaire approaches family functioning as the relations within the family (partner relation, parenting) and of the family with the outside world (social network of the family) [78]. There is a body of literature describing these areas of family functioning. Findings, however, are inconsistent with some authors arguing that most families adapt well to their challenges [23, 79, 80] and show few if any differences from control families [81, 82], while others report poorer outcomes in several family functioning dimensions [83, 84].

What precisely underlies these inconsistent findings is unclear, yet the wide range of instruments and concepts make it hard to integrate the results. Also, literature first and
foremost pertains to the country and culture where the study took place. Each country and culture has its specific perception of children with DS, health care standards, financial consequences due to differences in health insurance, and availability of supportive services such as respite care [74]. Further, the age of the child may be an important component determining the extent of consequences that parents experience [23, 61, 73, 82]. Each age has its own dynamics, with specific challenges, e.g. puberty or transitioning schools. The age of the child is not always considered when describing family functioning, and most studies have focused on parents of young children with DS, or included parents of children in wide age ranges [68].

In conclusion, family functioning is an important complementary perspective on the parental adaptation to DS. Literature to date on family functioning is inconsistent, and Dutch studies that involve mothers and fathers of children within a limited age range are needed.

**Psychosocial screening**

For parents, professional guidance and support is important to achieve successful adaptation [80, 85]. Therefore, care providers should make an effort to understand the challenges and consequences associated with DS. Not only at group level, but also at the level of each family they see in clinical practice. This can be achieved by using psychosocial screening instruments in clinical practice.

For this purpose, brief measures that give a quick overview of the needs of the parents and family are needed. Using such measures should be a cost- and time-effective way to detect psychosocial problems in an early stage, to be able to refer parents to appropriate assistance. A frequently used measure for this purpose is the Distress Thermometer for Parents (DT-P). The DT-P lets parents rate their experienced distress in the last week on a thermometer ranging from 0 to 10, and inquires various everyday problems that may cause this distress [86]. So, results provide an overview of the overall experienced distress and the everyday problems.

These outcomes provide an even more concrete insight into the lives of parents, which is important to further understand the consequences of raising a child with DS. Knowing more of these everyday problems is important, since many of these problems can be alleviated with appropriate support. Very few studies, however, have reported on everyday problems that parents of children with DS experience, although there is an increasing research interest in ‘real-world’ outcomes in parents of children with DS [73].

**Conclusion**

The unique characteristics of DS relate to unique parental experiences. These experiences have been described in various ways, mainly by describing levels of distress. However, a comprehensive overview of consequences across relevant domains of life would be beneficial for an integrated understanding of parental functioning. For this purpose we argue that HRQoL is a relevant outcome, presenting a comprehensive overview of parental
subjective functioning in a variety of relevant domains of life. Family functioning provides a complementary perspective to the individual perspective of HRQoL. Further, psychosocial screening instruments that present real world outcomes and that are feasible for introduction in clinical practice are important to get an understanding of each individual family.

These outcomes should be described within the perspective of the country and culture in which the child with DS is raised. Further, the age of the child with DS should be taken into consideration when describing parental and family adaptation, as each stage of childhood presents unique challenges. Finally, the perspective of fathers is underrepresented in literature and should be taken into account.

Professionals understanding more of the consequences of raising a child with DS, and finding ways to timely detect problems in clinical practice, can make a difference for parents. Providing targeted support to parents of children with DS, both mothers and fathers, is not only relevant for the parental well-being of parents, but ultimately also vital for the well-being and development of the child with DS.

SAMPLE AND DESIGN

Figure 3 shows the participants in each part of this thesis. Part 1 focuses on development of children with DS who enrolled in an RCT studying the effects of T4 vs. placebo treatment during the first two years of life.

- The initial RCT included 196 children with DS who were born between 1999 and 2001. Of these 196 children, 181 fully completed the trial.
- Subsequently, at child’s age 10.7 years, we performed a follow-up study. In the follow up study we included 123 children with DS, a response rate of 68% from the 181 children who completed the initial RCT.

Part 2 focuses on parents raising a child with DS. This part consists of two questionnaire studies:

- The first questionnaire study was conducted when the children with DS were 6 to 8 years old. These pencil-paper questionnaires were completed within the scope of the Care project. The Care project aimed at comparing HRQoL in parents of children with chronic conditions, with HRQoL in parents of children without chronic conditions [70]. Of the parents of children with chronic conditions, 98 parents of 6 to 8 year olds with DS were recruited from the aforementioned RCT.
- The second questionnaire study (Care2 project) was conducted when the children were between 11 and 13 years old. Respondents were recruited among parents whose children (N = 123) participated in the aforementioned T4 follow-up study. For this study, both parents were invited to complete web-based questionnaires concerning HRQoL and family functioning, as well as a psychosocial screening instrument. Parents (N = 124) of 88 children completed the online questionnaires
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in Care2 (response rate 72%).
- A longitudinal analysis was performed in respondents who completed questionnaires in both Care and Care2 (N = 58 parents, predominantly mothers).

Figure 3. Recruitment of participants; part 1 concerns the developing child with DS, part 2 concerns the experience of parents raising a child with DS.

AIMS AND OUTLINE OF THE THESIS

Part 1: the developing child with DS

The first part of this thesis focuses on development in children with DS. In the first part we aimed to determine:
- the long-term effects of early T4 treatment on development and growth in children with DS,
- the long-term effects of early T4 treatment on development and growth in children with DS, separately for children with a normal neonatal thyroid hormone state (TSH < 5 mIU/L) and in children with an abnormal neonatal thyroid hormone state (TSH ≥ 5 mIU/L),
- strengths and weaknesses in adaptive functioning and motor skills in children with DS at the age of 10.7 years,
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- prognostic value of early life characteristics for later intelligence, adaptive functioning and motor skills.

Chapter 2 presents the results of the follow-up study that addressed the first two aims. Chapter 3 addresses the third and fourth aim, by reporting on the longitudinal developmental outcomes that were collected during the first decade of life.

Part 2: parenting a child with DS

The second part of this thesis focuses on the experiences of parents raising children with DS. We aimed to determine:

- which socio-demographics, child functioning and psychosocial variables were related to HRQoL domains in which parents of children with DS scored lower than parents of children without a chronic condition,
- whether mothers and fathers of 11 to 13-year-olds with DS differ from reference parents in HRQoL and family functioning,
- whether HRQoL in parents of children with DS changed over time, from when the child with DS was aged 6 to 8 years to when the child was 11 to 13 years old,
- whether clinical distress and everyday problems were more frequent in mothers and fathers of 11 to 13 year olds with DS than in control parents of age-matched children without chronic disorders,
- to determine whether clinical distress and everyday problems differed between mothers and fathers in parent couples of 11 to 13-year-olds with DS.

Chapter 4, which describes an in-depth analysis of the findings of the Care project in parents of children with DS [70]. Aims B and C are discussed in chapter 5 which reports on an online questionnaire study concerning HRQoL and family functioning in mothers and fathers of children with DS. Aims D and E are addressed in chapter 6, which compares outcomes of a psychosocial screening instrument in mothers and fathers of children with DS versus control parents.

Chapter 7 reflects upon the implications of our findings for clinical practice, the limitations of our studies, and the directions for future research.
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REFERENCES


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