Growing up with Down syndrome

The developing child and its parents

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General discussion
Chapter 7

This thesis focuses on the developing child with Down syndrome (DS) and its parents. Part one of this thesis describes development during the first decade of life, from the perspective of a thyroid hormone treatment trial early in life. Part two describes psychosocial outcomes in mothers and fathers of children with DS. The current chapter provides a reflection on the main findings in this thesis, an overview of the clinical implications, consideration of the limitations of our studies, and suggestions for future research.

REFLECTION ON THE MAIN FINDINGS

Part 1: The developing child with DS

Part one of this thesis describes a follow-up study at the age of 10.7 years, after a randomized controlled trial (RCT) concerning thyroxine (T4) treatment early in life. Newborns with DS show, as a group, lower T4- and higher thyroid stimulating hormone (TSH) concentrations than newborns without DS [1]. Based on this finding, Van Trotsenburg et al. [2] set up a trial to determine the effect of T4 treatment during the first two years of life in children with DS. It was hypothesized that optimal thyroid hormone concentrations during this important period for brain maturation would lead to developmental benefits and, to a more limited extent, growth benefits [2, 3]. Indeed, outcomes at the age of 24 months indicated a subtle, but significant positive effect of T4 treatment on motor development and physical growth. A follow-up study was needed to determine whether T4 treatment would result in long-term benefits, and whether these potential benefits were specifically found in children with neonatal signs of subclinical hypothyroidism [4]. This allowed for a detailed analysis of the developmental outcomes that spanned the first decade of life. An overview of the main findings in part one of this thesis is presented in Table 1.

Long-term developmental benefits of early T4 treatment

The follow-up study first of all suggested no significant long-term developmental benefits in T4 treated children. How the original advantages that translated to around 7 motor index points would translate to long-term outcomes was hard to predict. Due to the lack of other studies concerning early T4 treatment in children with DS, or in children without DS but with subclinical hypothyroidism (SH) [5], there was little clinical evidence that could guide expectations. It could be hypothesized that optimized early brain maturation might result in larger benefits later in life. This could be called ‘growing into benefit’, small differences in early life might lead to larger differences later in life. By contrast, it could also be hypothesized that the observed benefits at 24 months were temporary and had little clinical relevance in the face of other mechanisms that influence development in DS. The latter appeared to be the case, leading to our conclusion that it ineffective to treat all children who have DS with T4 to stimulate development.
Table 1. Main findings in the first part of this thesis: The developing child with DS.

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<th>Long-term effect of early T4 treatment in DS</th>
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<td></td>
<td>123 children with DS; 64 T4 treated, 59 placebo</td>
<td>Single follow-up visit 8.7 years after the end of an RCT concerning T4 treatment in the first two years of life</td>
<td>Primary Intelligence: SON-R 2.5-7 or BSID-II Motor: Movement ABC 2 Secondary Communication: Vineland-Z Fine motor: Beery VMI Growth: height, weight, head circumference</td>
<td>-T4 treatment did not result in long-term developmental benefits -T4 treatment did appear to have a positive long-term effect on growth, particularly in children with elevated TSH concentrations</td>
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</table>

| Chapter 3 | Development in DS: 6 months to 10.7 years | N = 123 children with DS | Detailed analysis of developmental data from an RCT in the first two years of life, and a follow-up study at age 10.7 years: Developmental strengths and weaknesses at the age of 10.7 years Analysis of early life predictors for outcomes at 10.7 years | 6, 12 & 24 months Mental: BSID-II Motor: BSID-II 10.7 years Intelligence: SON-R 2.5-7 or BSID-II Adaptive functioning: Vineland-Z Motor skills: Movement ABC 2 | -Children with DS show a distinct profile of relative strengths and weaknesses in adaptive functioning (socialization > daily living > communication) and motor skills (aiming/catching > manual dexterity > balance) -These profiles vary with developmental level of the child (above average functioning vs below average functioning) -Intelligence and adaptive functioning at the age of 10 years were best predicted by early developmental outcomes (24 months BSID-II), while male gender and the occurrence of infantile spasms additionally predicted poorer functioning later in life -Later motor skills appeared to be harder to predict than intelligence and adaptive functioning |

Abbreviations: Beery VMI, Beery Test of Visual-Motor Integration; BSID-II, Bayley Scales of Infant Development second edition; DS, Down syndrome; M-ABC 2, Movement Assessment Battery for Children second edition; RCT, Randomized Controlled Trial; SON-R 2.5-7, Snijders-Oomen Nonverbal Intelligence Test Revision 2.5-7 years; T4, Thyroxine.
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The above conclusion concerns all children with DS in the trial. That is, children who had normal or at most subclinical thyroid hormone levels. After publication of the original trial results, it was suggested that, rather than all children with DS, only those with SH may profit from early T4 treatment [4]. Therefore we performed a subgroup analysis in children with elevated neonatal TSH concentrations and those with normal neonatal TSH concentrations. This analysis also failed to show statistically significant long-term benefits of T4 treatment in either subgroup.

It should be noted, however, that this was a subgroup of children with relatively mild subclinical hypothyroidism. To define subgroups for the subgroup analysis, we used a TSH cut-off of 5 mIU/liter. Although this is a common cut-off value to define SH [6], a cut-off of 10 mIU/liter is recommended to initiate T4 treatment in the absence of clinical signs of hypothyroidism [5, 7]. We cannot rule out that children with somewhat higher TSH values (e.g. ≥7 mIU/liter or ≥8 mIU/liter) might profit from early T4 treatment. We cannot confirm this, however, due to insufficient numbers of children to perform such analyses. If one would want to study the effect of early T4 treatment in children with DS and clear SH, including sufficient children to get the required statistical power to determine this will be quite a challenge.

The premise of the original trial, however, was that children with DS suffered from mild subclinical hypothyroidism at group level and would benefit from early T4 treatment. The suggestion that children with SH might profit from early T4 treatment is not unique for DS. However, as noted before, high quality evidence for the benefits of early T4 treatment in children (with or without DS) with significantly elevated neonatal TSH concentrations is lacking.

Long-term growth benefits after early T4 treatment

Although we found no significant long-term benefits in development, T4 treatment during the first two years of life did result in differences in physical growth. In the total group, T4 treated children showed a significantly larger head circumference. In the elevated TSH subgroup, T4 treated children had both a larger head circumference and were significantly taller. The difference with placebo treated children in height was on average 3 cm, or 0.5 SDS. These findings suggest that early growth was boosted in T4 treated children, who continued in their higher growth curve even after discontinuing T4 treatment at the age of 24 months. This is somewhat similar to catch-up growth that is seen in children who are small for gestational age, who after early life growth hormone treatment continue in their higher growth curve [8]. Unlike brain development, physical growth is considered to continue to depend in part on optimal thyroid hormone levels after the age of 2 years [9]. Therefore, continuation of T4 treatment during childhood might have resulted in even larger growth benefits, although we have no data to support this hypothesis.

These findings indicate that optimal thyroid hormone levels in early life may prove to be more critical for long-term physical growth outcomes in DS than we are currently aware
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of. This may be particular for children with DS, who typically show a large drop in height SDS during their first three years of life [10]. In children with SH but without DS, substantial delays in growth are not a common finding [11]. Nevertheless, in future T4 trials in early life, growth should be taken into account [5, 12].

Gaining 0.5 SD in height after two years of T4 treatment can be called a success if we compare the cost of T4 with that of growth hormone. In idiopathic short stature, for instance, an average treatment of more than 5 years with growth hormone results in an increase in height of 0.65 SD, at a cost of almost €30,000 per gained cm [13]. T4 medication during the first two years of life at an average daily dose of 50 µg would in total cost less than €40,- at current price levels, or around €13,- per gained cm by the age of 10.7 years. Although these costs are very small, the expected benefit in terms of well-being is questionable. A French study among a large, national representative group of adults found a very limited relation between height and quality of life: only SDS of around -4 SDS or lower were associated with a significant reduction in quality of life [14]. The final height of individuals with DS is on average around - 3 SDS [10]. A more substantial effect of height on quality of life in individuals with intellectual disability is not expected. So, although early T4 treatment may stimulate long term growth in children with DS who show early signs of SH, this may in itself be insufficient reason to start treatment.

Developmental outcomes

One of the most striking and consequential characteristics of DS is intellectual disability, which refers to deficits in intelligence and adaptive functioning [15]. The RCT and follow-up study involved prospective collection of developmental data in a large group of children with DS who were assessed at homogeneous ages. This resulted in a unique dataset of longitudinal developmental outcomes, which allowed for a detailed description of developmental outcomes at follow-up, and for analysis of early predictors for developmental outcomes later in life.

Similar to what is described in previous literature [16], we found great variability across individuals with DS in developmental outcomes. In terms of intelligence, the non-verbal test of intelligence at calendar age 10.7 years revealed a mean age equivalent (AE) of 4 years and 3 months, with a range from 10 months to almost 7 years. Interestingly, this mean AE is very similar to what has previously been reported in children with DS around the age of 10 to 11 years. Mean AEs on several measures were 4 years and 1 month to around 4 years and 6 months [17-19]. These studies all started several decades earlier than the current one. Improvements in health care and increased developmental stimulation could be argued to result in better developmental outcomes at a group level over the last decades [20]. Our findings do, however, not support this argument, as the outcomes in terms of intelligence are strikingly similar to those reported before. Similar to what was found concerning intelligence, adaptive functioning shows great variation across individuals, while the mean AE of 4 ½ years is similar to what has previously been published about children with DS
around the age of 10 to 11 years [21, 22]. Beside the domains that define intellectual
disability, we focused on motor skills, which are also one of the key deficits in DS. Here too
we found large variability in outcomes, which are unfortunately not easily compared with
previous outcomes since the Movement ABC 2 does not yield AEs.

Despite the variability across individuals, children with DS are thought to be predisposed
to specific developmental deficits and relative strengths, i.e. their behavioral phenotype
[23]. The overriding assumption is that there is a single behavioral phenotype that is more
or less valid for all children with DS. Our analysis of relative strengths and weaknesses in the
total group of children with DS were in line with previous descriptions of the DS phenotype
regarding motor skills; ball skills were relatively stronger than fine motor skills and balance.
In adaptive functioning, however, we found that socialization was relatively stronger than
communication and daily living skills, the latter being the weakest skill. This contrasts with
previous literature, which generally found that communication is the weakest domain.

Importantly, however, comparing relatively high-functioning children with relatively
lower functioning children revealed considerably different profiles of strengths and
weaknesses in the subgroups. This was particularly the case for adaptive functioning.
The below-average functioning children showed adaptive strengths and weaknesses that
confirmed previous literature (communication and daily living skills relatively weak relative
to socialization). Yet, for the above-average subgroup we found another profile of strengths
and weaknesses (daily living skills weak relative to communication and socialization). This
contrasts with the general assumption of one DS behavioral phenotype.

As we defined our subgroups by the rate of their intellectual disability relative to the
other children with DS, the relative strengths and weaknesses appear to depend on the level
of intellectual disability. Likely, there are more refined ways to distinguish subgroups other
than the somewhat arbitrary division we made. We hypothesized that the different profiles
of motor skills reflected differences in how well children could be instructed; relatively low
functioning children showing markedly stronger ball skills relative to fine motor skills and
balance, with the latter domains requiring more verbal instruction than the ball skills tasks
[24]. The different profiles of adaptive functioning, however, could not be explained this
way. To explore what may underpin the differences between the subgroups, we looked
into the differences in background variables between the subgroups. The most notable
difference concerned educational placement, with children in the above average subgroup
being more frequently and for a longer period enrolled in mainstream education. We
suggested that participation in mainstream education might play a specific role in explaining
the adaptive functioning profile. Also because the differences in adaptive functioning
were strikingly in line with a review concerning the influence of educational placement
on developmental outcomes, which indicated that mainstream education particularly
stimulates communication skills [25]. This could mean that mainstream education provides
a more stimulating environment for developing communication and socialization skills than
special education. However, based on our data we could not determine causality. So, we
cannot conclude whether e.g. relatively strong communication skills result from educational placement, or whether success in educational placement depends on strong communication skills the children already had. In essence, we do not know whether the subgroups we defined result from ‘nature’ or ‘nurture’.

**Predicting later developmental outcomes**

Although describing developmental outcomes in children with DS at a group or subgroup level is important, one of the major concerns of parents is what the future developmental outcomes in their individual child with DS will be. Only informing them about the wide variability at group level may be of little help. To be able to provide more guidance, it is important to establish early predictors of later developmental outcomes.

Our analyses indicated that by the age of 24 months, developmental testing results are the most important predictor for later developmental outcomes. The predictive value of early assessments increased rapidly through infancy, from an explained variance of 6% at the age of 6 months, 16% at the age of 12 months, to 38% at the age of 24 months, for later intelligence. This is in line with previous findings in children with DS [19] and other children with low IQs, whose early life developmental outcomes were found to be more predictive of later functioning than those of children with higher IQs [26]. Indeed, the relation we found between early developmental outcomes and later functioning is quite substantial compared with similar analysis in children without disabilities. For instance, Roze et al. [27] found an explained variance of around 4% between mental developmental outcome at the age of 18 months and intelligence at the age of 5 years.

This does not mean, however, that IQ or DQ (developmental quotient, defined for this thesis as developmental age/ calendar age * 100) is stable from an early age in children with DS. Quite the contrary is true: like many previous studies [28] we found a significant decreasing mean DQ over time, from around 59 at the age of 24 months to around 40 at the age of 10.7 years. The predictive value rather means that the relative position among the peers with DS at the age of 2 years predicts the relative position in the future. This is shown in Table 2. This table shows the DQ rank of children at the age of 24 months (split in three equal groups) and how this predicted the relative DQ rank at the age of 10.7 years. The majority of children fall in the same category at the age of 10.7 years, as they fell at the age of 24 months. This means that the BSID-II outcome at the age of 2 years can predict to some extent the level of functioning later in life, so whether a child is for instance likely to be a relatively ‘high functioning’ child with DS.

**Table 2.** Category of relatively low, middle, and high DQ at age 24 months versus age 10.7 years

<table>
<thead>
<tr>
<th>24 months/10.7 years</th>
<th>Low</th>
<th>Middle</th>
<th>High</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>26</td>
<td>9</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>Middle</td>
<td>10</td>
<td>19</td>
<td>11</td>
<td>40</td>
</tr>
<tr>
<td>High</td>
<td>3</td>
<td>12</td>
<td>25</td>
<td>40</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>39</td>
<td>40</td>
<td>41</td>
<td>120</td>
</tr>
</tbody>
</table>
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Table 2 does not include some variables that further refine the prediction of the early developmental outcome. Male gender and the occurrence of infantile spasms predicted poorer later functioning alongside the early developmental outcome. Knowing these characteristics of the child adds specificity to the expected outcome later in life based on the early developmental outcome. In other words, for a boy and a girl with identical developmental outcomes at the age of 24 months, the girl is expected to outperform the boy at the age of 10 years. It is expected that predictors like preterm birth or hypothyroidism could further refine the predictive model. Due to the nature of the RCT, however, children with these characteristics were excluded.

Identifying children at risk for relatively poor developmental outcomes may be important even before developmental assessments can predict later outcomes. Therefore, we analyzed predictors of development other than the early developmental outcome. This revealed that, beside infantile spasms and male gender, there was predictive value of high maternal educational level (predicting better intelligence and adaptive functioning), CNS diseases other than infantile spasms (predicting poorer motor skills), and of surgery for the heart condition atrioventricular septum defect (predicting poorer adaptive functioning). This implies that particularly male children, children of lower educated parents, and children with CNS problems or atrioventricular septum defects are at risk for poorer developmental outcomes.

What precisely underlies the relation between these comorbid conditions and developmental outcomes is matter for speculation. Some of these conditions have a conceivable link with poorer developmental prognosis, e.g. conditions that have CNS involvement. Yet even for these conditions cause and effect are not sure [29]. The relation of other comorbid conditions with development is harder to understand. For instance, why atrioventricular septum defect surgery predicts poorer outcomes in adaptive functioning later in life is unclear. We included atrioventricular septum defect as a predictor since it has been found before to predict poorer language development, yet the reason for the effect remains elusive [30]. The invasive medical procedures in itself may not explain these long term effects, since other invasive procedures, like gastrointestinal surgery, did not result in long-term adverse effects on development [29]. There may be unknown underlying mechanisms that result in both the health issue and the developmental outcome [31].

It should be noted that motor skills at the age of 10 years appeared to be harder to predict than intelligence and adaptive functioning. Although this has, to our knowledge, never been published before concerning children with DS, our findings are in line with those in preterm children [32] and children without health conditions [27]. This means that how rapid children with DS acquire their early motor milestones has limited predictive value for the level of more complex motor skills at the age of 10.7 years. This does not necessarily imply that stimulating early motor development is pointless. Although high quality evidence of the effectiveness of early motor interventions in DS is sparse, some studies do indicate positive long term effects of motor interventions in early life [33, 34].
Part 2: Parenting a child with DS

Part two of this thesis concerns the experience of parents raising children with DS. Given the unique characteristics of DS, parents of children with DS deal with unique emotional-, parenting-, and practical challenges. This has implications for the personal and family lives of parents, which should be integrated in the care for these families. In three studies we have focused on the individual functioning of parents in terms of health related quality of life (HRQoL), on family functioning, and on psychosocial screening outcomes. An overview of the main findings in part two of this thesis is presented in Table 3.

Parental health related quality of life

The first impression from the studies that focused on parental HRQoL is that they seem to not allow for uniform conclusions. The premise of the first study, when children were 6 to 8 years old, was that parents of children with DS (mainly mothers) showed lower HRQoL than controls in four domains: cognitive functioning, social functioning, daily activities, and vitality [35]. However, in the second study, which assessed HRQoL in both mothers and fathers when the children were 11 to 13 years old, only one HRQoL domain was significantly lower as compared with controls parents: sexuality in mothers. In fathers none of the HRQoL domains were significantly different from control fathers. So, whereas the first study revealed several HRQoL domains to be lower in parents of children with DS, only one statistically significant difference was found in the second study.

This could imply that parents’ HRQoL improved over time, yet we found no significant improvement over time in any HRQoL. When we consider the effect sizes in both HRQoL studies, those for domains that tended to be poorer in chapter 5 were similar to those of the statistically significant effects in chapter 4. Particularly in fathers, several effect sizes were around 0.5, which has been argued to reflect a clinically meaningful difference [36]. Therefore, both chapters indicate domains in which parents of school-age children with DS may experience somewhat poorer functioning than controls. This concerned everyday activities (social functioning, daily activities), fatigue (vitality, cognitive functioning, sleep), emotional functioning, and sexuality.

Risk and protective factors

Parents of children with DS, as a group, are prone to experiencing lower HRQoL than controls in several domains. To be able to assist parents most effectively, it is important to know what predicts poorer HRQoL outcomes. In chapter 4 we aimed to determine predictors for lower HRQoL in parents (mostly mothers) of children with DS. Socio-demographics, child functioning, and psychosocial variables were assessed as potential predictors, based on the model used by Hatzmann et al. [37].
Table 3. Main findings in the second part of this thesis: Parenting a child with DS.

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Sample</th>
<th>Methods</th>
<th>Outcome measures</th>
<th>Main findings</th>
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<tr>
<td><strong>Chapter 4</strong></td>
<td>HRQoL in parents of 6 to 8-year-olds with DS</td>
<td>( N = 98 ) parents of children with DS; 84 mothers, 14 fathers</td>
<td>Analysis of predictors (socio-demographics, child functioning and psychosocial variables) of HRQoL domains that were lower in parents of children with DS as compared with controls: cognitive functioning, social functioning, daily activities, and vitality</td>
<td>HRQoL: TAAQOL</td>
<td>- Predictors of the poorer HRQoL domains concerned child functioning (sleep, wearing diaper during daytime) and psychosocial variables (emotional support, partner relation quality, personal time, giving up hobbies, loss of friendship, caring for ill friend or relative) - Psychosocial variables were the most consistent and powerful predictors of relevant HRQoL domains; the predictors could be clustered around social support and time pressure.</td>
</tr>
<tr>
<td><strong>Chapter 5</strong></td>
<td>HRQoL and family functioning in parents of 11 to 13-year olds with DS</td>
<td>( N = 124 ) parents of children with DS; 80 mothers and 44 fathers. Results of 58 parents (53 mothers) were analyzed longitudinally.</td>
<td>Comparison of HRQoL and family functioning questionnaires between parents of children with DS and reference data; mothers and fathers separately</td>
<td>HRQoL: TAAQOL</td>
<td>Family functioning: family questionnaire (Dutch: Gezinsvragenlijst) - Analysis of change in HRQOL over time from child's age 6 to 8 years to child's age 11 to 13 years - Mothers and fathers reported few significant HRQoL problems, whereas family functioning problems were frequent. - Family functioning problems concerned the partner relation and social network domain (reported by mothers and fathers), and parenting domains (reported by fathers) - HRQoL showed no significant change over time.</td>
</tr>
<tr>
<td><strong>Chapter 6</strong></td>
<td>Distress and everyday problems in parents of young adolescents with DS</td>
<td>( N = 120 ) parents of children with DS; 76 mothers and 44 fathers; 34 parent couples ( N = 116 ) parents of age matched children without conditions; 64 mothers and 52 fathers</td>
<td>Comparison of psychosocial screening results in parents of children with DS versus controls; mothers and fathers separately</td>
<td>Psychosocial screener: Distress thermometer for parents (DT-P)</td>
<td>- Mothers showed few differences from controls: not in clinical distress and few in everyday problems - Fathers did not differ from controls concerning clinical distress, but reported significantly more everyday problems across a variety of domains - Screening results in mothers and fathers of children with DS did not differ significantly</td>
</tr>
</tbody>
</table>

Abbreviations: DS, Down syndrome; DT-P, Distress Thermometer for Parents; HRQoL, Health Related Quality of Life; TAAQOL, TNO-AZL Adult Quality of Life Questionnaire.
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The most consistent and powerful predictors for lower HRQoL in our model, were psychosocial variables, whereas no socio-demographic and few child functioning variables predicted lower HRQoL. Particularly support from people around the parent, including their partner, appeared to be a protective factor. Further, parents having limited time for themselves and for leisure related to lower HRQoL. Although the relation between child functioning and HRQoL appeared to be limited in this study, this does necessarily mean that having a child with DS has little effect on parental HRQoL. Characteristics in children with DS that show no meaningful variation within that group, may not show up as predictors, even though they may have an important effect. If, for instance, all children with DS need significantly more care than children without DS, the variation of care dependency within the group of children with DS may show little relation with HRQoL, while as a group parents may show lower HRQoL due to the care responsibilities. The significant child functioning predictors that we did find, i.e. sleep of the child and daytime wetting, were hypothesized to represent behavioral problems, which we unfortunately were not able to include as a predictor, even though we expected it to be a relevant predictor [38, 39].

In our study we only assessed direct predictors of HRQoL. We cannot exclude that socio-demographic and child functioning variables have effects on HRQoL that are mediated or moderated by psychosocial variables [40]. To determine this, we would need to verify more elaborate models, which requires larger samples of parents. Even though we did not assess the most complete model to predict HRQoL, our findings have important implications for practice. To improve HRQoL in mothers of children with DS, interventions that strengthen the social network, strengthen the partner relation, or that help parents deal with the time pressure may be effective. Several interventions have been developed to achieve this, so suitable referrals can be made if parents experience problems in these areas.

Family functioning

The family is the core system in which the child develops and is socialized, and in which parents need to integrate the care for their child with DS. As such, family functioning is an important dimension to study if we want to gain a comprehensive understanding what parenting a child with DS entails. There are, however, wide variations in how family functioning is defined and assessed [41]. For our study we relied on the model provided by our outcome measure, the family questionnaire or Gezinsvragenlijst in Dutch [42]. This measure focuses on the partner relation, the social network of the family, and parenting (responsiveness, communication, organization).

The most striking finding is the high rate of clinical and subclinical family functioning in families of children with DS. Compared with the norm, clinical family functioning outcomes were almost twice as frequent in families of children with DS, both according to the reports of mothers and fathers. By contrast, several authors have stressed that family functioning in families of children with DS is marked by normality [43, 44]. A possible explanation for this discrepancy in conclusions may be attributed to a difference in perspective. For instance, Cunningham [44] concluded that normality was the overriding impression from his studies.
of family functioning, since the majority (around 65 to 70%) showed normal functioning. In essence, such findings were contrasted with the historical view that raising a child with intellectual disability is “a tragedy and inevitably detrimental to couples and families” [43]. The idea that having a child with DS entails a certain disaster for family life should indeed be countered. Our results also indicated that the majority of families of children with DS reported normal family functioning, yet abnormal family functioning was far more frequent in families of children with DS as compared with normative data. If we aim to support families where and when needed, we should not be oblivious to the issues that parents of children with DS are more likely to struggle with than parents of children without DS.

Both among mothers and fathers, problematic outcomes concerning partner relation and social network were frequent. This supports the notion that social functioning is challenged in families of children with DS, as suggested by our HRQoL findings and previous literature [43, 45, 46]. The high rate of partner relation problems, however, was surprising in the light of previous literature [43, 44, 47, 48]. This may reflect a difference in age of the children in these studies, since age of the child has been suggested to be an important factor in the partner relation of parents [47]. The finding of frequent partner relation problems does, however, underscore the importance of the partner relation as suggested by the study of predictors for HRQoL. Moreover, both social support and the partner relation are important resources for successful adaptation [49, 50]. Therefore attention to poorer outcomes in these domains is warranted.

Besides the unfavorable outcomes concerning partner relation and social functioning, fathers reported problems related to parenting. Previous literature on parenting yielded inconsistent outcomes, with some indicating more parenting problems in parents of children with DS [51, 52], while others did not find this [53, 54]. For fathers in particular, interacting with older children with DS may give some difficulty [46, 55]. Whether there are indeed statistically significant differences between mothers and fathers in how they experience parenting could not be determined in the current study. These findings do underscore that attention for the fathers is needed.

Psychosocial screening
Repeatedly we have suggested that attention for a range of topics is needed. Clinicians may be intimidated by this, as this comes on top of all other things they need to attend to following the guidelines for DS [56]. Systematic screening for psychosocial problems may be a feasible solution to systematically pay attention to psychosocial topics in clinical practice [57]. To detect potential problems, brief and easily interpreted questionnaires are needed. In chapter 6 we describe the outcomes of such a frequently used psychosocial screening measure, the Distress Thermometer for Parents (DT-P, in Dutch Last Thermometer voor Ouders - LTO). Results in mothers and fathers of children with DS were compared with those in mothers and fathers of children without a chronic condition. This study showed, unexpectedly, that mothers and fathers of children with DS did not
report more clinical distress than control parents, and mothers did also not report more everyday problems than controls. Fathers, however, did report more everyday problems and more frequently wished to consult a professional about their situation. A wide range of various problems was reported more frequently by fathers of children with DS. Many of these problems underscored what we found in the HRQoL and family functioning studies. Fathers reported more social problems, emotional problems, physical problems (including sexuality), and cognitive problems. The latter were also abundant among mothers and were interpreted to relate not necessarily to cognitive functioning, but rather to experienced problems in memory or concentration due to e.g. emotional problems or fatigue.

The most striking finding was the apparent discrepancy between the normal distress and the elevated rate of everyday problems in fathers. In practice, which of these should guide whether the parent requires professional assistance? One of the additional questions of the DT-P inquired just this, whether the parents would wish to talk to a professional about their situation. Fathers of children with DS showed significantly more interest in this, suggesting that a high number of everyday problems is indicative for the need for professional assistance. We concluded therefore that paying attention to psychosocial needs of parents of children with DS should consist of probing for concrete problems. This can be facilitated by psychosocial screening instruments like the one used in this study.

Subjective evaluation of consequences
In the above sections we have discussed several relevant issues for parents of children with DS, which concerned social functioning, the partner relation, vitality, daily and leisure activities, and emotional functioning. In addition, a relatively high proportion of fathers reported parenting problems. Nevertheless, our results appeared to be inconsistent in some regards. As discussed above, fathers of children with DS did not report more clinical distress than control fathers, yet they did report more everyday problems. Also, the family questionnaire evidently indicated social network problems, whereas the simultaneously completed HRQoL questionnaire revealed only a tendency towards poorer social functioning in parents of children with DS. There appears to be an underlying mechanism explaining these apparent inconsistencies.

Parents appear to respond differently to questions that inquire concrete consequences as compared with questions that assess their subjective evaluation of these consequences. Raising a child with DS is associated with several challenges, which may result in concrete consequences for everyday functioning. In turn, these concrete consequences are subjectively evaluated by the parent within the framework of his or her values and expectations. For instance, a child needing constant supervision may have concrete consequences for the social functioning of the parents. These consequences may or may not be subjectively evaluated by the parent as bothersome, depending on what the parent expects and values in life.

If we fit our various findings in this framework, the HRQoL assessment is argued to inquire both concrete consequences and the subjective evaluation of these consequences.
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For instance, the TAAQOL inquires concerning social functioning ‘If you needed it, was it possible for you in the last month to visit friends?’ - If not - ‘how much did that bother you?’ [58]. The TAAQOL weighs both the concrete consequence and the subjective evaluation in the scoring. The family functioning questionnaire on the other hand appears to emphasize concrete consequences. Concerning the social network of the family, the family questionnaire states: ‘We regularly meet with friends or acquaintances’ [42]. The DT-P focuses on concrete consequences in the problem list, and on an overall subjective evaluation of the experienced burden in the thermometer score concerning distress.

Parents of children with DS tend to differ from controls if concrete consequences are inquired, but not if their subjective evaluation is assessed. This is suggestive of a shift in expectations, standards and values in these parents. In essence, parents of children with DS may show a response shift in their subjective evaluations [59]. Of interest, several studies have noted a change in values in parents of children with DS, with parents remarking that their view of what is important in life changed, while learning tolerance and patience [60, 61]. This is precisely what is described in relation to response shift [59]. However, little research is done concerning response shift among parents of children with intellectual disability.

As discussed above, many parents report positive effects of raising a child with DS, as they experience affection for their child with DS and personal or even spiritual growth that they associated with raising their child with DS [61, 62]. It is important to have a balanced view of the experiences of parents of children with DS, which has been described as a paradoxical experience [62, 63], marked by challenges and by rewards, for instance in experiencing love for the child and a sense of purpose in raising their child [55].

For clinical practice it is important to consider whether the concrete consequences or the subjective evaluation should guide the decision to offer assistance. Based on our findings we concluded that the concrete consequences appear to be more indicative for the need for professional support. Also, if parents report problems concerning their partner relation or social network, professional attention is warranted given the importance for the well-being of all family members, and even for the child’s development [47, 64-68]. This again underscores the need to pay attention to concrete problems that parents may struggle with, which can be facilitated by psychosocial screening instruments. This can improve early detection of potential problems leading parents to timely and fitting practical or psychosocial support.

The child’s age

Several previous studies have suggested that the age of the child is an important factor determining consequences for parents [64, 69]. This makes sense if we consider that each stage of childhood and adulthood comes with specific challenges. In our studies we accounted for the age of the child by describing outcomes as reported by parents of children within relatively limited age ranges. In addition, we have assessed the effect of age on HRQoL in two different ways. First, it was one of the potential predictors for
parental HRQoL, which revealed little effect of age. Second, we compared the parental HRQoL at child’s age 6 to 8 years with parental HRQoL at child’s age 11 to 13 years, which revealed no significant change over time. In sum, we found very limited effects of age of the child on parental HRQoL.

We do not exclude, however, that age may play an important role for parental and family functioning. In our analyses the age ranges were quite small, which means that we cannot exclude important changes over the entire period of life that parents care for their child with DS. This also means that, for instance our findings in chapter 5 and 6 should primarily be considered to represent parents of children in the studied age range.

Fathers

In chapter 6 we compared outcomes in mothers and fathers of children with DS. This revealed no statistically significant differences. This is in line with relatively recent studies that also found similar outcomes in mothers and fathers [51, 69], whereas older studies typically found less favorable outcomes in mothers as compared with fathers [46, 55, 70]. In chapter 5 we analyzed mothers and father separately, without comparing them. Yet, the findings in the latter chapter also give little reason to assume that fathers’ functioning is substantially better than that of mothers. By contrast, results of the family questionnaire suggested that fathers in particular reported parenting problems. This suggests even that psychosocial outcomes in fathers may even be unfavorable as compared with those of mothers. This is surprising in the light of previous literature, which, if anything, found that fathers showed more favorable outcomes than mothers [46, 55]. It is possible that the role of fathers has changed, with fathers and mothers sharing care responsibility and experiencing similar psychosocial consequences [69].

An interesting question, which we unfortunately cannot answer, is whether the absence of differences in outcomes between mothers and fathers suggests that fathers are relatively worse off than mothers. In studies of HRQoL, for instance, men typically show better HRQoL than women. Also in the outcomes of chapter 6, the results in the control group suggested that in the general population, men show more favorable outcomes than mothers. So, fathers showing similar outcomes as mothers may be at a disadvantage as compared with fathers of children without DS. To analyze this, a dataset that includes parent couples of children with DS and control parent couples would be needed.

Whatever the precise differences as compared with the general population are, our findings underscore that fathers should not be ignored, in research nor in care. To date, fathers are underrepresented in research, and may also be less likely to accompany their child to health care visits [71]. Further, fathers may need more encouragement than mothers to seek support for psychosocial problems [72]. Therefore, professionals should make an effort to involve fathers and gauge their psychosocial needs.
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CLINICAL IMPLICATIONS

The developing child with DS

Intervene

Improving developmental outcomes in children with DS was the aim of the early T4 trial. This appeared to be ineffective in terms of long-term developmental benefits, while the possible gain in height may not be the burden of treatment. Therefore, our findings imply that intervention with early life T4 treatment in children with DS who have normal thyroid hormone concentrations is not recommended.

Although T4 treatment could not achieve long-term developmental benefits, our finding that early development shows substantial relations with outcomes later in life underscores the importance of stimulating development early in life. For this purpose, early intervention programs are recommended [73, 74]. Through these family-centered programs parents are guided to structurally stimulate their child’s early development across a range of domains. This provides the parent with support during the early years, and may be beneficial for the child’s development as well as for their own adaptation [75]. Since we found that particularly boys with DS, children from relatively lower educated mothers, children with CNS disorders and children with atroventricular septum defect are at risk for poorer long-term developmental outcomes, parents of these children in particular should be encouraged to participate in early intervention programs. Positive effects of early intervention programs have been found for the child’s development and for the adaptation of families [74, 76, 77], yet high quality evidence for long term effects is sparse.

Beside early intervention, physical therapy and speech therapy are advised for all children with DS [56]. Our findings of particular weaknesses concerning balance and fine motor skills at the age of 10 years suggest that targeted stimulation of these skills may be needed. Such stimulation programs for children with DS have been developed [78, 79]. Typically, however, children stop receiving physical therapy after their early childhood [80], whereas improving motor skills throughout childhood can help in acquiring better self-help skills, which may ultimately improve their ability to live more independently [81]. Therefore, targeted interventions to improve motor performance in school-age children with DS are recommended.

Screen

Our finding that early developmental outcomes are the best predictor for later functioning, can be a compelling reason to screen for developmental outcomes in early life. Regular evaluation of early development can help identify children who are at risk to show relatively poor long-term outcomes. This may also provide some guidance in making educational choices. There is, however, controversy surrounding the use of developmental testing in the context of educational or interventional planning [82], possibly due to rigid use of such results in the past. It should be realized indeed that, at least up until the age of 24 months, the majority of variance in future developmental outcomes remains
unexplained by our predictive models. From a pragmatic point of view, however, these predictors are the best we have got in early life, and if handled with caution, they may prove to be valuable to quantify delay, inform caregivers, and plan for developmental interventions [83].

**Inform**

For clinical practice, our findings provide first of all referential information about developmental outcomes in a large sample of children with DS who were assessed within narrow age ranges. This is important for an up-to-date idea of what developmental outcomes can be expected in children with DS. Although important at the group level, parents are often more anxious to learn how their individual child will perform in the future. As mentioned above, early life characteristics can provide some more specific indication of future development. When used with the caution we outlined above, this can inform parents about what to expect for their son or daughter with DS.

The finding that there may be more than one profile of typical strengths and weaknesses, at least concerning adaptive functioning, should inform clinical practice. For instance, professionals working with relatively high functioning children with DS cannot assume that the typical strengths and weaknesses in adaptive functioning that are described in literature applies to their population. Rather, they may want to aim to stimulate daily living skills rather than communication skills in their population.

**Parenting a child with DS**

**Inform**

New or future parents of children with DS have the right to be reliably informed about what raising a child with DS entails. Current leaflets informing parents about raising a child with DS could be more specific, and should be based on the reports of Dutch parents. It is important that parents are presented with a balanced view that acknowledges both the ups and the downs; and that is based on the experiences of Dutch parents. This should not serve to discourage parents, but to make them aware of the specific challenges for families of children with DS, and to inform them about ways to navigate these challenges. They should for instance be made aware of the importance of maintaining their social support and their partner relation, and of the services that can support them in relevant areas.

The same is true for professionals supporting these families. They need to be aware of the psychosocial aspects of raising a child with DS throughout childhood. This can be done through incorporating information on guiding families of children with DS in the Dutch guideline. Currently, the guideline only provides information on psychosocial functioning of families around the birth of their child, while psychosocial issues remain relevant throughout childhood [56].
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Screen
Beyond being aware of psychosocial aspects of raising a child with DS, professionals should take a proactive approach to guiding families of children with DS in this regard. This can be facilitated by using psychosocial screening instruments, as used in, for instance, the KLIK program in many medical centers in the Netherlands [84]. Psychosocial screening results that are made available to the pediatrician prior to the consultation can facilitate targeted discussion of psychosocial issues which may otherwise remain uncovered. Our findings suggested that screening should use a family-centered approach, that moves beyond the individual well-being of mothers and fathers, but that also includes measures of family functioning. Further, in order to uncover the potential needs of parents the screening instruments need to (also) probe for concrete consequences. If professionals understand the psychosocial situation of a family, targeted support or referrals can be initiated.

Intervene
Based on screening results, parents can be referred to relevant services. This can be a referral to a psychologist, but likely low-key, practical interventions are more frequently needed. Respite care, for instance, may allow parents to invest time in their social relations or in their partner relation. Respite care provides temporary care for the child for a limited number of days [85, 86], and has shown promising results [87]. For parents struggling with parenting, mindful parenting programs may be effective [88].

Parents of children with DS may be reluctant to pursue such services; they may see the concrete consequences as ‘part of the deal’. In the long run, however, sustaining the well-being of parents will benefit not only the parents themselves, but all family members, including the child with DS.

LIMITATIONS
The findings in this thesis must be considered in the light of some limitations. First of all, the sample size of the initial RCT was powered to detect an improvement of 0.5 SD in developmental outcomes in the entire group. Therefore, the study was not powered for the subgroup analysis we performed. Nevertheless, we deemed it important to explore whether the long-term effects were different in the subgroups of children with or without elevated neonatal TSH. Notwithstanding the limited power, the subgroup analysis provided outcomes that shed more light on the effectiveness of T4 treatment in these subgroups.

Further, the fact that the initial RCT was designed with the primary aim to compare T4 and placebo early in life limited the representativeness of our findings for all children with DS and their parents. For the purpose of the RCT, several inclusion and exclusion criteria were defined. These, however, excluded children with characteristics that are quite common among DS, such as premature birth or hypothyroidism. This means for the study of developmental outcomes, that these represent a relatively healthy group of children with DS. The predictive models for later developmental outcomes were also limited by excluding
premature birth and hypothyroidism, since these can be expected to influence long-term developmental outcomes. Further, the RCT in itself may have influenced development, both in the T4 and the placebo group. Even aside from the treatment effect at young age, the frequent medical check-ups and contact with health professionals such as a psychologist may have had a positive influence on development. Also for the studies that included the parents of children with DS, we should consider that these were parents of relatively healthy children with DS, who received intensive medical support for their child with DS during the first years after the birth. For a more representative overview of the functioning of children and their parents, population-based studies are needed.

In terms of outcome measures, our choice of intelligence test limited our analyses. We aimed to choose a test that would allow as much children as possible to participate in, without having to switch tests. Given the wide variation in the abilities of children with DS, this was not easy. We chose the SON-R, which has a broad age range and was, at the time, the only Dutch intelligence test with acceptable psychometric properties in that age range. The SON-R however is limited by its non-verbal character. It is argued to be a non-verbal test of fluid intelligence rather than a test of non-verbal intelligence [89]. Still, it essentially does not capture language skills. Given the importance of language outcomes in DS in particular, and given the importance of thyroid hormone for developing language skills, a test that included language skills would have been preferable. Moreover, an intelligence test with more distinguishable domains would have allowed for analysis of strengths and weaknesses in intelligence. We deemed analysis of strengths and weaknesses on the SON-R as not particularly meaningful.

The study of predictors for HRQoL suffered from the fact that the data were gathered within the scope of a study that focused on a wide variety of chronic conditions [35]. As a result, predictors that would have been of interest for parents of children with DS were not always included. One important example concerns behavioral problems of the child, which may predict HRQoL in parents of children with DS, but not in parents of children with DS in general.

Finally, for the study of HRQoL and family functioning we did not employ a matched control group. A control group of parent couples who have children without DS in the same age range would allow for comparison of mothers and fathers whilst correcting for gender differences that are common in the general population.

FUTURE RESEARCH

Our findings concerning early T4 treatment highlight the lack of other high-quality evidence concerning T4 treatment in children with SH in early life. It is important to determine what could be gained by early T4 treatment and what the cut-off hormone concentrations for treatment would need to be. T4 treatment would first and foremost aim to improve developmental outcomes, but growth should be analyzed as well. Our findings suggested an important role of T4 for growth in children with DS and SH, which
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warrants future research to better understand the substantially lower final height in DS [90].

We have followed a relatively large cohort of children with DS over the first decade of their lives. Carr et al. [91] have shown that even longer longitudinal studies, albeit in a smaller sample, can yield important insights in life with DS. In their impressive project a group of (eventually) 30 individuals with DS were followed from the age of 6 weeks to 45 years. Our sample too provides the opportunity of extended follow-up, which can focus on how these individuals end up in terms of work and living situation, how they fare during transitions, for instance to adult health care which does not know specialized Down teams, and which individuals develop dementia.

Concerning the developmental outcomes at the age of 10 years we found that there may be more than one profile of strengths and weaknesses in DS. Our subgroups were somewhat arbitrary, so a more refined understanding of subtypes in the behavioral phenotype of DS is needed. Studies should focus on various developmental outcomes, and consider how the behavioral phenotypes develop over time. A more elaborate understanding of the DS behavioral phenotype is essential to be able to accommodate to the relative strengths and weaknesses in children with DS and to ensure optimal developmental outcomes [92]. Moreover, evidence is needed for the role of educational placement for the developing child with DS. Particularly with legislation aiming to include more children with disabilities in mainstream education [93].

We showed that there is considerable consistency in development throughout childhood, which can be predicted to some extent in early life. Future studies can further refine the predictive model by adding predictors like preterm birth and hypothyroidism. The effect of interventions, such as early intervention, physical therapy or speech therapy should also be incorporated in this model. Further, longitudinal studies that assess children at more intermediate time points, may even allow for ‘developmental growth charts’ [94], similar to what is used to chart physical growth. This would facilitate the process of informing parents about the development of their child and the range of expected future outcomes.

The current studies were among few other studies reflecting on HRQoL in parents of children with DS, and to our knowledge the first to do so in the Dutch situation. However, several important issues could not be addressed in the current thesis. More knowledge is needed about differences in psychosocial outcomes between mothers and fathers and how these evolve over time. For this purpose, prospective studies of HRQoL and family functioning as reported by parent couples over a longer period of time, preferably starting in infancy, with a control group consisting of parent couples would be optimal. Further, more elaborate models of predictors for these outcomes in mothers and fathers, assessing moderators and mediators can provide more specific information on starting points for interventions.

We noted that parents appear to show a response shift in the subjective evaluation of their situation. This has not been studied as such among parents of children with DS,
although some studies touch upon the subject [60, 62, 95]. These previous studies focus on the changed perspective and the setting of new, realistic goals for the life of the parent and the child. These dynamics and how this influences questionnaire studies is an important topic that may place apparently contrasting findings in previous literature in perspective.

Psychosocial screening is recommended for families of children with DS. An interesting approach to this is found in pediatric oncology practice. Based on evidence of risk and protective factors, a screening instrument has been developed that provides a risk assessment for psychosocial problems. Subsequently a level of psychosocial care is indicated; basic (e.g. psycho-education), targeted (interventions aimed at symptoms), or clinical (intensive treatment) [96]. A similar screening approach could be developed for parents of children with DS or developmental disabilities. To do so, the evidence concerning risk factors and evidence based interventions and treatment would need to be integrated.

CONCLUSION

We described developmental outcomes in children with DS over the first decade of their lives. Although the variety in developmental outcomes after these first 10 years is wide, there appears to be relative stability among children with DS. In the sense that many of those who perform relatively well early in life, continue to perform relatively well compared with their peers with DS. This suggests that early development is important for long-term developmental outcomes in children with DS. Our findings indicated, however, that the beneficial effects of early T4 treatment on development were undetectable by the age of 10 years. Although T4 treatment appeared stimulate long-term growth, particularly in children with neonatal signs of subclinical hypothyroidism, growth benefits alone may not justify early T4 treatment in these children with DS. Detailed analysis of the follow-up results challenged the general assumption that there is one profile of relative strengths and weaknesses in DS. Rather, relatively high-functioning and low-functioning children with DS showed different profiles of strengths and weaknesses in adaptive functioning.

Beside the developing children with DS, we focused on their parents. From the dimensions of personal HRQoL, family functioning, and psychosocial screening outcomes several unfavorable outcomes emerged in parents of school-age children with DS. These revolve around the themes of social functioning, partner relation, vitality, participation in activities, and emotional functioning. Fathers of young adolescents in particular appeared to be at risk for parenting problems. Parents of children with DS appear to show a response shift; parents may report concrete consequences, but their subjective evaluation of functioning is often similar to that of parents of children without DS. Psychosocial screening that facilitates the discussion of concrete consequences is recommended in clinical practice. This should help professionals in taking a proactive approach to the psychosocial challenges for these families, and providing them with fitting and timely support when needed. Essentially, a family centered approach which aims to sustain the well-being of all family-members is needed for families of children with DS.
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KEY MESSAGES

- Early T4 treatment in children with DS does not result in significant long-term developmental benefits.
- Early T4 treatment does appear to have long-term effects on growth, particularly in children with neonatal elevated TSH.
- There may more than one single profile of relative strengths and weaknesses in adaptive functioning in children with DS.
- Early developmental assessments, combined with gender and the occurrence of infantile spasms can predict the level of intellectual functioning at the age of 10 years to some extent.
- Parents’ subjective evaluation of functioning is often similar to that of parents of children without DS, but when prompted parents of children with DS may report concrete consequences.
- Important themes for parents of school age children with DS that appeared from this thesis, are social functioning, partner relation, vitality, participation in activities, and emotional functioning.
- Fathers of children with DS should not be forgotten; they report no less consequences than mothers.
- A proactive approach to psychosocial guidance for families of children with DS is needed; this can be facilitated by psychosocial screening with special attention for concrete consequences.
REFERENCES


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