Psychological consequences of congenital hypothyroidism: Cognitive, motor and psychosocial functioning

van der Sluijs Veer, L.

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General discussion and future perspectives

1. Introduction

This thesis presents the results of the Dutch nationwide study "Effect evaluation of the screening on Congenital Hypothyroidism (CH), in The Netherlands," with focus on (1) cognitive and motor consequences of CH and the effect of the changes in timing and treatment modality on cognitive and motor outcome over the years, and (2) psychosocial functioning of children and young adults with CH, including health related quality of life (HRQoL), developmental tasks, and self-esteem. Three cohorts of patients were included (1981-82; tested at 21.5 years of age; 1992-93, tested at the age of 10.5 years and 2002-04, tested at the age of 1 and 2 years). In this final chapter, results of the previous chapters will be summarized and are followed by a reflection on these findings. Furthermore the limitations of the studies, clinical implications and suggestions for future research will be discussed.

2. Main findings

in this paragraph the main findings of each study in this thesis are outlined.

Part 1 describes cognitive and motor consequences of early treated CH in children and young adults. Three cohort studies were performed to (1) assess cognitive and motor functioning in young adults and children with CH diagnosed by neonatal screening in comparison to the general population, (2) examine the effect of the adaptations of the screening procedure and changes in timing and treatment modality on cognitive and motor outcome over the years (from 1981 to 2004) by including three different cohorts of patients, and (3) investigate the impact of disease and treatment factors on cognitive and motor outcome. An overview of the studies presented in this thesis is provided in Table 1 (main findings on cognitive and motor outcome), Table 2 (overview of full scale IQ and mental developmental index in the three cohorts) and Table 3 (main findings on psychosocial outcome). All patients were classified as having 'mild', 'moderate' or 'severe' CH, based on T4 and FT4 concentrations (see Chapter 1).

In all three cohort studies subtle, but relevant cognitive and motor deficits were found in children and adults with thyroidal CH (from now called CH) (Table 2). The patients with severe thyroidal CH born in 1981-82 tested at 9.5 and 21.5 years of age, and born in 1992-93 tested at the age of 10.5 years had lower mean intelligence quotient (IQ) scores compared to the norm population. In the patients with moderate and mild CH no significant differences in IQ scores as compared to the norm population were observed. Similarly, in the third cohort (born in 2002-04), the mean mental developmental index (MDI) scores of the severe CH group at 2 years of age were lower than the norm population, whereas the mean MDI scores of the moderate and mild CH groups were similar compared to the norm population. However, it

should be noted that the tests used to assess intelligence and cognitive development in the three cohorts were different (intelligence versus developmental index[*]). A contrasting result in the third cohort compared to the other cohort studies was that the mean MDI score of the severe patients with CH at the age of 1 year was similar to the population mean. With regard to motor functioning, our findings indicated that regardless of disease severity in all three cohorts motor functioning was worse than in the norm population, with the exception of the mild and moderate CH groups of the 1981-82 cohort.

As reflected in similar cognitive and motor outcomes in all three cohorts, it appears that advancing initiation of T4-supplementation from 27 to 19 to 10 days after birth did not result in improved cognitive and motor outcome in CH patients. Taken these findings through the cohorts into account, our data strongly suggest that the prenatal hypothyroid state is responsible for the postnatal outcome.

In all three cohort studies we investigated the impact of disease and treatment factors (severity; initial T4/FT4 concentration, starting day of T4 supplementation, initial T4 dose) on cognitive and motor outcome. In the 1981-82 and 1992-93 cohort studies we found that only severity appeared to be a significant predictor for total IQ. No correlation was found between starting day of T4 supplementation and IQ, neither was there a correlation between initial T4-dose and IQ. In the 2002-2004 cohort study, severity (initial FT4 concentration) appeared to be a significant predictor for MDI score at the age of 2 years as well. Starting dose of T4 appeared to be a predictor of MDI at the age of 1 year. With respect to motor outcome, severity was only a significant predictor for total motor impairment in the 1981-82 study. In the other cohort studies no significant relation was found between severity and motor functioning and psychomotor developmental index (PDI). Starting dose of T4 appeared to be a predictor of the PDI at the age of 1 and 2 years. In all three cohort studies we could not find any correlation between the starting day of T4 supplementation and cognitive and motor functioning (IQ, MDI, motor scores and PDI).

In conclusion, part 1 of this study has shown cognitive and motor deficits in patients with severe CH. Mildly and moderately affected CH patients had a fair prognosis for cognitive functioning. However, they do also experience motor problems. Furthermore, we conclude that although the development of children with CH is considerably improved by neonatal screening and improvement of treatment, they are still at risk for motor and cognitive problems. This is probably due to the prenatal hypothyroid state or the thyroid hormone deficiency in early life.

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[*] Intelligence (WISC-R, WAIS-III) and Mental Developmental Index (BSID-II-NL)

Table 1 Overview of the three studies in part 1 of this thesis on cognitive and motor outcome in three different cohorts of patients with CH

Chapter	Aim	Sample	Measurements	Main findings
2	1. To assess cognitive and motor functioning in young adults with CH, born in the first 2 years after the introduction of the Dutch screening program. 2. To examine the influence of the severity of CH and start of treatment on cognitive and motor outcome.	Cohort: 1981-1982 N=70 young adults with CH 49 of them were previously tested (9.5 years) Mean age= 21.5 years Median start treatment: 28 days	Intelligence (WISC-R, WAIS-III) Motor skills (TOMI, MABC)	• Patients, particularly those with severe CH, had significantly worse motor scores and lower IQ scores compared with the norm population. • No significant change in IQ from childhood to adulthood was found. • Only severity was correlated with IQ and motor scores.
3	To examine whether advancement of treatment initiation to 20 days has resulted in improved cognitive and motor outcome in children with CH.	Cohort: 1991-1992 N=82 children with CH mean age= 10.5 years Compared with n=58 Cohort 1981-1982 at age of 9.9 years Median start treatment:20 days	Intelligence (WISC-R, WISC-III) Motor skills (TOMI, MABC)	• Patients with severe CH had lower IQ scores compared with the norm population. • IQ-scores of patients with moderate and mild CH were comparable to those of the normative population. • In all three severity groups significant motor problems were observed. • No correlations were found between starting day of treatment and IQ or motor outcome.
4	To examine whether advancement of treatment modality has resulted in improved cognitive and motor development at 1 and 2 years of age compared to normative data.	Cohort: 2002-2004 N=95 toddlers with CH Median start treatment: 9 days	Mental developmental index (BSID-II-NL) Psychomotor developmental index (BSID-II-NL)	• MDI scores of the toddlers with CH at 1 year and the moderate and mild CH group at 2 years were similar to the population mean. • MDI scores of the total CH group and severe CH group at 2 years were significantly lower than the norm population. • In all three severity subgroups significant lower PDI scores were observed. • Severity and initial T4 dose were weak predictors for developmental outcome.

Table 2 Full scale IQ score in the 1992-93 and 1981-82 cohort and mental developmental index scores (MDI) in the 2002-04 cohort of patients with thyroidal CH

	Cohort 1981-82 IQ (95% CI) Mean age: 21.5 years	Cohort 1981-82 IQ (95% CI) Mean age: 9.9 years [b]	Cohort 1992-93 IQ (95% CI) Mean age: 10.5 years	Cohort 2002-2004 MDI (95% CI) Mean age: 1.1 years	Cohort 2002-2004 MDI (95% CI) Mean age: 2.1 years
Severe CH	**91** (86.3-96.3) *	**94** (87.9-100.8)	**93** (89.5-97.9) **	**99** (93.9-103.6)	**88** (83.5-92.6) *** [a]
N	35	22	41	28	26
Mean age at start of T4 supplementation	27	29	19	8.5	8.5
Mean initial T4 dose in µg/kg/day	5.4	5.4	7.0	12.3	12.3
Moderate CH	**99** (91.1-107.1)	**99** (91.6-106.3)	**96** (88.9-103.5)	**104** (98.0-109.3)	**98** (93.3-102.5)
N	16	14	19	24	24
Mean age at start of T4 supplementation.	27	27	19	9.5	9.5
Mean initial T4 dose in µg/kg/day	7.1	7.4	6.6	11.8	11.8
Mild CH	**101** (95.7-106.9)	**99** (89.2-108.2)	**105** (99.5-110.4)	**102** (98.1-103.8)	**100** (96.4-104.3)
N	19	13	22	43	42
Mean age at start of T4 supplementation.	68	68	31	12.7	12.7
Mean initial T4 dose in µg/kg/day	5.2	5.2	5.0	10.3	10.3
Total group CH	**96** (92.3-99.2) *	**97** (92.7-100.9)	**97** (94.2-100.4)	**101** (98.8-103.8) [a]	**96** (93.4-98.8) [a]
N	70	49	82	95	95
Median age at start of T4 supplementation	40	39	23	10.7	10.7
Mean initial T4 dose in µg/kg/day	5.7	5.9	6.4	11.3	11.3

Full scale IQ and MDI expressed as mean with confidence interval between parenthesis.

*p<0.05;**p<0.001; ***p<0.0001 difference between CH patients and normative population.

[a] p<0.0005 difference in change over time between CH patients at 1 year and 2 years of age (based on paired t-test).

[b] ref data Kooistra.[1]

IQ classification: extremely low ≤ 69, borderline 70-79, low average 80-89, average 90-109, high average 110-119, superior 120-129, very superior ≥ 130.

MDI classification: in the norm population MDI has a mean of 100 and a standard deviation of 16.

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Part 2 of this thesis describes the results of the study on psychosocial functioning of young adults, children and toddlers with CH (table 3). Three cohort studies were performed to (1) explore the psychosocial functioning of young adults and children with CH, including health related quality of life (HRQoL), course of life (CoL), and self-esteem, (2) assess the impact of disease and treatment factors on HRQoL, CoL and self-esteem of young adults and children with CH diagnosed by neonatal screening.

The results of the three cohort studies showed that CH has a negative impact on several aspects of HRQoL. The study on young adults (1981-1982) showed that CH patients compared to healthy adults are more often at risk for HRQoL impairment and reported lower HRQoL on several domains: cognitive functioning; sleeping; pain; daily activities; vitality; aggressiveness; depressive moods. The second cohort study in 10-year old children with CH revealed significant differences in mean scores in seven domains of the TACQoL (by child and/ or parent-report): motor functioning; autonomy; cognitive functioning; social functioning; positive emotions; negative emotions. Only for physical functioning no differences were found. In addition, a greater percentage of children with CH, especially patients with severe CH, appeared to be at risk for impaired HRQoL. In the third cohort of investigated children with CH at two years of age most domains of HRQoL appeared similar to the Dutch norm population. This study demonstrated that only the children with severe CH have a lower HRQOL on two of the twelve scales of the TAPQoL: motor functioning and communication.

Another aspect of psychosocial functioning studied in this thesis is Course of life in young adults (developmental milestones that are necessary in the development of a child). Patients reported a delayed course of life on the domain of social development compared to the norm population. With respect to the milestones of social development, a significantly lower percentage of CH patients than of the comparison group had been a member of a sports club for at least one year during primary school and secondary school. However, the sociodemographical outcomes (living with their parents; marital status; special education at primary school and final educational level) of the assessed young adults in our study did not differ from that of the normal population.

Finally, the results of the 1981-82 and 1991-92 cohort studies showed that having CH had a negative impact on self-esteem. Young adults with CH appeared to have a significantly lower self-esteem than the normgroup. In addition, a greater percentage of the 10 year old patients with CH, especially those with severe CH, appeared to be at risk for impaired self-worth with respect to school performance and athletic performance.

In the 1981-82 and 1991-92 cohort studies, no significant associations of disease and treatment factors on HRQoL, CoL and self-esteem were found. Regarding the impact of the disease factors in the third cohort study, only severity was associated with the domain communication of HRQoL.

Table 3 Overview of the three studies in part 2 of this thesis on psychosocial functioning in three different cohorts of patients with CH

Chapter	Aim	Sample	Measurements	Main findings
5	1. To examine health-related quality of life (HRQoL), developmental milestones (CoL), sociodemographical outcomes, and self-esteem in young adults with CH. 2. To explore whether severity of CH was related to these outcomes.	Cohort:1981-1982 N= 69 young adults Patients were classified to 'severe CH 'or' moderate / mild' CH. Median age start treatment: 28 days	Health related quality of life (TAAQoL) Developmental milestones (the Course of Life questionnaire) Self-esteem Socio-demographic factors	▪ Patients were more often at risk for HRQoL impairment on several domains (cognitive functioning; sleeping; pain; daily activities; vitality; aggressiveness and depressive moods). ▪ Patients reported a lower self-esteem and had a delayed CoL on the domain of social development. ▪ There were no significant within-group differences between the severity groups for HRQoL, CoL, and self-esteem.
6	1. To assess health related quality of life (HRQoL) and self-worth in children with CH. 2. To explore associations of disease factors, IQ and motor skills with the outcomes.	Cohort: 1992-1993 N=82 children Mean age= 10.5 years Median age start treament: 20 days	Health related quality of life (TACQoL: parent and child report) Self-worth (CBSK) Socio-demographic factors	▪ Children and parents reported significantly worse HRQoL on motor, cognitive and social functioning, autonomy, negative and positive emotions. ▪ There were no differences between the severity groups. ▪ Lower IQ was only significantly associated with worse cognitive HRQoL. ▪ Severity, age at onset of therapy, initial T4 dose and motor skills were not significantly associated with HRQoL and self-worth.
7	1. To examine health related quality of life (HRQoL) in toddlers with CH. 2. To explore associations of disease factors, IQ and motor skills with the outcomes.	Cohort: 2002-2004 N=88, 2-year old toddlers Median age start treatment: 9 days	Health related quality of life (TAPQoL: parent report) Socio-demographic factors	▪ Toddlers with severe CH had lowered HRQoL regarding motor functioning and communication. ▪ Worse scores on MDI and PDI were related to lower HRQoL on communication and worse scores on the PDI were related to lower HRQoL on motor functioning. ▪ No significant associations between disease factors, other than severity were found.

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Key messages

In sum, the main findings of part 1 and part 2 lead to four key messages:

1. For children and adults with severe CH, cognitive deficits are a consequence.
2. Deficits in motor functioning are prominent in most children and adults with CH.
3. Impact of treatment factors on cognitive and motor outcome after the implementation of the Dutch neonatal screening program is only limited.
4. Children and adults with CH are at risk for psychosocial problems.

3. Reflections on the key messages

3.1 For children and adults with severe CH, cognitive deficits are a consequence

Neonatal CH screening and early treatment (T4 supplementation) has improved the patient's intellectual potential and developmental prognosis considerably.[2] However this thesis demonstrates that CH in all three cohorts of young adults, children and toddlers of 9.5 and 21, 10 and 2 years of age, is associated with cognitive problems, which persist into adulthood.

The tests used to assess cognitive functioning in the three cohorts were different. Furthermore the 2002-04 cohort was very young at the time of the two effect evaluations. The BSID-II-NL[3] used in this cohort, assesses mental and psychomotor development and not the whole construct 'intelligence' as measured by the Wechsler Intelligence Scale for Children, 3rd Edition (WISC-III)[4] and the Wechsler Adult Intelligence Scale III (WAIS-III)[5] in the other cohorts. Therefore, one should be cautious to generalize our results of the 2002-2004 cohort to older children who nowadays grow up with CH.

Nevertheless, this thesis shows that mildly and moderately affected CH patients had a fair prognosis for IQ and mental developmental index. The significant reduction in timing of treatment in patients with severe CH from 29 days (in 1981-82) via 19 days (in 1992-93) to 8.5 days (in 2002-2004) did not result in improved cognitive development. Thus, regardless optimizing care for CH, early identification and treatment, children with severe CH do have persisting cognitive deficits.

These results are in line with several previous and recent (outcome) studies on patients who were diagnosed by neonatal screening. These also showed that children still had persistent subtle deficits, despite early treatment.[5-11]

These objective findings equates with the patient's perception of cognitive functioning, as measured with the HRQoL questionnaires. In all three studies patients reported lower HRQoLon the cognitive functioning scale, also confirmed by (for the young adults and children with CH) a high percentage of patients considered at risk. In addition, a greater percentage of children with CH, especially patients with severe CH, appeared to be at risk for impaired self-worth with respect to school. Cognitive functioning was assessed by asking if patients had

problems with learning, attention and memory. When answered yes, patients were asked to report the degree to which they were actually bothered by that problem. We also found that lower IQ and mental developmental index scores were associated with lower scores on HRQoL on cognitive functioning.

The results of this thesis strongly suggest that brain damage in (severe) CH dates from the prenatal period. It is known that maternal hypothyroidism during pregnancy can result in cognitive and motor deficits in offspring.[12] CH is already expressed in fetal life, and apparently maternal T4 transferred via the placenta, is too little to fill the gap in fetal T4 production.

3.2 Deficits in motor functioning are prominent in children and adults with CH

The results of this thesis show that substantial motor problems were observed in all three cohorts, even in the 2002- 2004 cohort, with the earliest treatment and highest initial T4 dose. Furthermore, in the 2002- 2004 and 1992-93 cohort, differences were found in all severity groups between the children with CH and the norm population. In the 1981-82 cohort, motor functioning was most affected in those with severe CH. However, given de results of all cohorts, motor functioning appears to be impaired in most children with CH, regardless of disease severity. Thus, despite optimization of care for CH, early identified and treated children do have persisting motor deficits.

Motor skills in the 1981-82 and 1991-1992 cohort were assessed with the Movement ABC designed for identification of impairments of motor function in children. In both cohorts overall motor performance and fine motor functioning were affected most. These findings are in line with recent studies reporting motor problems in patients with CH.[13,14] The study of Arenz et al. (2008), investigated 5-year old children with CH with an early (range 4-15 d) high-dose treatment (range 7.2-17 μg/kg/d). They showed that reactivity and speed of movement was significantly reduced in children with CH, especially in those with pretreatment SH-values of > 200 mU/L. Hauri-Hahl and colleagues (2011) reported significant lower pure and adaptive fine motor functioning, tested with the Zurich Neuromotor Assessment (ZNA) in 63 children (median starting dose 14.7 μg/kg/d), tested at a median age of 13.8 years (range 7.0-14.2 y).

Unfortunately, with the BSID-II,[15] it was not possible to split motor function in specific motor areas. With the new version of the BSID, version III (not yet available during our inclusion period), it has become possible to examine motor development more in depth. In a recent study of Komur and colleagues (2012) [9], motor development of young children (6-42 months of age) was evaluated with the BSID-III test. Fine motor and gross motor sub scores in children with CH were significantly lower than those in the control group.[9] These findings are in line with the results of our third cohort study. We hypothesize that similar to our hypothesis regarding cognitive development, poorer motor functioning cannot be completely explained by postnatal treatment and is probably due to prenatal brain injury. Thus poorer motor function

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probably results from hormonal influences on neurodevelopment in intrauterine period.

The objective results on motor functioning are consistent with our findings on psychosocial functioning of young adults, children and toddlers with CH. As expected, (severe) patients with CH are at greater risk for impaired HRQoL regarding motor functioning. Children and toddlers of 10 and 2 years of age reported lower HRQoL on motor functioning compared to the Dutch norm population. Furthermore, children showed higher percentages at risk for impaired self-worth with regard to athletic competence, young adults reported a lower level of participation in sport clubs.

Our consistent findings over time warrant for sensitive monitoring of motor functioning. It has been shown that motor problems in childhood can be associated with visuomotor and visuoperceptual impairments.[14,16] Children with fine motor problems could have problems in writing, performing crafts and drawing. Gross motor problems may impair social participation in class and during leisure time. This possibly will lead to secondary behavioral problems and impaired quality of life.[14]

3.3 Impact of treatment factors on cognitive and motor outcome after the Implementation of the Dutch neonatal screening program is only limited

Despite optimization of care for CH, early identified and treated children do have persisting cognitive and motor deficits. Many disease and treatment factors might influence cognitive and motor outcome. In this thesis we focus on the following medical factors:

3.3.1. Severity

As we might expect, based on previous and recent literature,[1,13,14,17-22] the results of this thesis demonstrate that children and adults with severe CH are more at risk for cognitive deficits. With regard to motor functioning, all children and young adults were at risk for substantial motor problems, which were slightly more pronounced in severe CH-T patients, although this effect was not as strong as for cognitive deficits. This could, as previously mentioned, be the consequence of the limited (yet substantial) maternal-fetal transfer of T4. It is likely that this maternal contribution to the fetal thyroid hormone is a major factor in protecting brain development, but is not known whether it is always sufficient to completely protect prenatal brain development.

3.3.2. Starting day of treatment

In contrast with the expectations in all studies of this thesis, there was no correlation found between the starting day of treatment and cognitive, motor and psychosocial functioning.
Since the start of the national institution of the Dutch neonatal screening program, treatment initiation has changed from a mean age of 29 days (in 1981- 1982) via a mean age of 19 days

(1992-1993) to 10 days (born in 2002-2004). However, all cohorts had subtle deficits in cognitive and motor outcome. Apparently this advancement did not result in an improvement of cognitive and motor functioning. This shows timing of treatment initiation is not a predictor of long-term motor and cognitive outcome. Again it appears that brain development is not only thyroid hormone dependent in the neonatal period, but as well prior to birth. Apparently, maternal T4, transferred via the placenta, is not sufficient to prevent brain damage. The thyroid gland develops very early in gestation and T4 synthesis of the fetus begins at about mid-gestation.[14] Our findings on cognitive and motor functioning, severity and starting day of treatment raise the question whether irreversible brain damage occurs prenatally in children with CH. In the first trimester maternal thyroid hormones are effective on development of fetal brain, while continuing development of the brain in the second and third trimesters relies increasingly on thyroid hormones produced by both the fetus and mother.[9,23] Although effects of thyroid hormone on brain development starts during intrauterine life and continues until 2–3 years of age, the first 6 months in the postnatal period is known to be a very important time interval.[9,23] Because thyroid hormone is essential for normal brain development with different brain regions requiring thyroid hormone at different specific times pre- or postnatally, children with CH suffer varying degrees of brain impairment depending on when and how long they were without thyroid hormone. Generally, the longer children with CH are without thyroid hormone, the more extensive is their brain damage.[24]

It has become clear that early diagnosis and treatment of CH does not eliminate all deficits. The rationale of the neonatal CH screening programs is to enable early start of treatment in order to prevent brain damage. Only few studies of screening samples have found associations between age at start of treatment and outcome measures.[9,10,13] The lack of associations between age at start of treatment and outcome in other studies could be the result of methologic issues (i.e., either the limited variation in age at start of treatment is confounded with CH severity). Age at start of treatment is most likely associated with CH severity in a number of studies, because some newborns with severe CH have obvious clinical symptoms and are diagnosed prior to the result of the neonatal screening.[18]

3.3.3. Initial dose of T4

Only in the third cohort we found an effect of T4 dose on outcome. Our results indicate that (higher) T4 starting dose appears to be a predictor of MDI at the age of 1 year and of the PDI at the age of 1 and 2 years. Despite many studies on the effect of the initial dose of T4 it remains unclear whether high dose thyroid hormone replacement is more effective than low dose in the treatment of CH.[25] Even recent reports about this issue give contradictory results.[25-28] Based on currently available outcome data, which do not reach high level of evidence, most guidelines recommend a high dose of T4 of 10-15 μg/kg body weights started within the first 2 weeks of life.[26]

3.3.4. Adequacy of T4 supplementation (during the first year of life)
Thyroid function determinants (TSH and FT4 concentrations) during follow-up and at the time of cognitive and motor assessments are important factors for evaluating treatment adequacy. Possible, the deficits found may not only be the result of prenatal thyroid hormone deficiency, but inadequate long term treatment may play a role as well. In our studies, all CH patients, independent of severity, were treated with T4 according to criteria of good clinical practice, by pediatricians who followed the Dutch national guidelines, published in three editions (1980,1986,1997). In addition, at the time of psychological assessments, all patients had plasma TSH concentrations within the reference range. However, for several reasons it is difficult to assess treatment solely based on intermittently measured FT4 and TSH concentrations.[29] In the last cohort study toddlers were treated according to current screening practice. Furthermore, in this study we evaluate "adequate treatment" as a control variable in our analysis. Analysis showed that the majority of our patients were adequately treated during the first 2 years of life. Moreover, no differences were found in developmental outcomes between the patients with >20% of blood values deviating from the norm and those with <20% of blood values deviating from the norm. This makes it unlikely that deficits in cognitive functioning as observed in patients with severe CH were related with long-term treatment insufficiency.[29]

Some other studies measured the effect of adequacy of treatment on outcome.[14,20] Hauri Hohl and colleagues (2011) found that static balance may be an indicator for poorer substitution and/or compliance. A consistent negative relationship was found between TSH levels for children older than 1 year and static balance: higher TSH levels were associated with poorer static balance performance. Results of the study of Leger et al. (2011) showed that the risk of not graduating from high school was significantly related to the adequacy of long-term hypothyroidism control during childhood.[20]

3.4. Children and adults with CH are at risk for psychosocial problems
In order to be able to adequately support the development of children with CH, insight in their social-emotional functioning is necessary. Psychosocial functioning of young adults and children with CH, such as HRQoL, CoL, and self-esteem has not been studied thoroughly. Nevertheless, detailed knowledge on these topics can be highly relevant for optimizing support of children with CH.

The results in this thesis show that CH has impact on the daily life of the patients and does negatively influence the HRQoL, social development en self-esteem. Patients experienced more problems concerning cognitive, motor and social functioning, pain, daily activities, aggressiveness, self-esteem, and they appeared to be less vital and more depressed compared with the (healthy) Dutch population. This is a source of concern that deserves attention.

An important finding between the studies is that the patient's perception of cognitive

functioning, as measured with the TAAQoL, TACQoL and TAPQoL, equates with objective findings measured with the WAISIII, WISC-III and BSID-II. Clearly, children and young adults with CH have to cope with cognitive problems. As a consequence they experience problems in learning, functioning at school and at work. We also found that lower IQ and mental developmental index scores were associated with lower scores on HRQoL on cognitive functioning. However, worse IQ and motor skills did not explain the presence of impaired functioning in most other domains of HRQoL and self-worth, as the results of the regression analyses demonstrated. So, we can conclude that patients with CH are at risk for impaired HRQoL and self-worth, independent of their IQ and motor skills.

Furthermore, except for the HRQoL study in toddlers, we did not find a significant association of severity of CH and HRQoL. HRQoL and CoL have become important outcome measures in research about effects of chronic diseases.[30-38] Our findings are in line with several studies that have demonstrated that chronic illness could lead to poor HRQoL in different domains compared to healthy peers. Furthermore many psychological studies conclude that children with different chronic diseases are at higher risk for emotional and behavior problems.[39-43] Some studies found behavior disorders and psychiatric disturbances in children with CH.[44-47] Few studies were directed at assessing HRQoL in patients with CH. Sato et al. showed that the HRQoL of young adults with CH did not differ from healthy controls.[48] However in a recent study of Leger et al.,[20] young adults with CH had a lower HRQoL (vitality, social functioning, role-emotional and mental health) than their healthy peers, as in our study. Furthermore a larger proportion of the CH group than of the general population declared they had other moderate or severe chronic pathological diseases, hearing impairment or visual problems and BMI was significantly higher in CH patients, than in the general population. Moreover, patients with CH were less likely to attain the highest level of education or the highest-intermediate socioeconomic category, were more often unemployed than the general population, or still in education. In addition, a significant higher percentage of CH patients were still living with their parents or did not live with a partner.[20] These authors underlined the need of early and consequent monitoring patients with CH. Several other studies showed that children and adolescents with CH were at risk of social-emotional problems, such as behavioral disorders and psychiatric disturbances. Tinelli et al. found that adolescents (> 12 years) scored significantly higher than controls on withdrawal, anxiety/depression, thought problems, attention problems and aggressive behavior.[49] Bisacchi et al. found more internalizing and externalizing problems in 6-10 years patients with CH. However, they found no differences between patients and controls in other age groups. The results of our study can be considered in line with a growing body of literature that suggests that overall, children with chronic illness are at heightened risk for adjustment problems.[50]

Except for the HRQoL study in toddlers, we did not find a significant association of

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severity of CH and HRQoL and self-esteem. No significant association of the other disease factors (intial T4 dose and age at onset of therapy) and psychosocial functioning in all three studies were found. So, we can conclude that patients with CH are at risk for impaired HRQoL and self-worth, independent on treatment factors. Therefore, it could be assumed that living with a chronic disease as such, influences functioning in daily life. CH affects the child's daily life because of the need for regular T4-dose adjustments, the daily T4 administration that creates a state of dependence, frequent T4 and TSH measurements, consciousness of having a chronic disease, and sometimes the need for adjuvant medical care such as speech training and physiotherapy. In addition, the cognitive and motor problems of patients with CH may affect their social life, self-worth and emotional functioning. From this study and our previous studies it is apparent that patients with CH are vulnerable in these areas**.** Besides, one has to keep in mind that a suboptimal thyroid hormone state may affect well-being. Whereas the goal of long-term T4 treatment is to maintain euthyroidism, this remains challenging because of the continuous need to adapt T4 dose in a growing child and the need for treatment compliance. It has been shown that differences in serum FT4 and TSH concentrations, even within the reference range, may be determinants of psychological well-being in treated hypothyroid patients.[51]

4. Strengths and limitations

The strength of this thesis is the assessment of large national cohort samples of screened patients with CH. We measured the same constructs in three cohorts of CH patients. One psychologist, who was blinded for the patient's medical details, carried out all psychological tests and questionnaires. To avoid an inclusion bias, all patients born within three selected time periods (1981-82, 1992-93, 2002-04) were recruited nationwide. Furthermore, to avoid a bias by suboptimal treatment at the time of the assessments, all patients of whom data were analyzed had their assessments under euthyroid conditions (plasma TSH concentrations within the reference range). This is an important point, known that even a slightly abnormal thyroid function can influence mood and may therefore have an effect on the answers the patient gives when completing a questionnaire. In addition, all cohorts were carefully characterized in terms of etiology and initial disease characteristics and were treated by pediatricians who followed the national guidelines for treatment.

Findings of the present thesis should be considered in light of a number of limitations. First, the 2002-04 cohort was very young at the first evaluation. Testing of a young child is difficult and the predictive value of outcomes for future cognitive and motor functioning increases with age. The BSID-II-NL assesses mental and psychomotor development and not

the whole construct 'intelligence' as measured by the Wechsler Intelligence Scale for Children, 3rd Edition (WISC-III) and the Wechsler Adult Intelligence Scale III (WAIS-III) in the other cohorts. Therefore definite conclusions about children's cognitive and motor capabilities can be more accurately assessed at an older age. Furthermore, a surprising result in the present study was that the mean MDI score of the severe CH patients at the age of 1 year was similar to the population mean whereas their mean MDI score at the age of 2 years was significantly lower than the population mean. An explanation for these findings could be that cognitive problems only become evident at older age and the psychological tests used in older children are more sensitive to detect differences. This explanation is confirmed by the study of Westra et al. They found that the Dutch normative values of the BSID are not sufficiently reliable for use at the ages of 6 and 12 months.[52] Therefore it is considered untrustworthy to draw conclusions based on the outcome at 1 year of age. The norms are more reliable at the age of 2 years. With this in mind the developmental quotients should not be considered the exact equivalent of the intellectual and motor quotients obtained in the other cohorts. Therefore caution is needed in generalizing our results to children who are nowadays growing up with CH.

Second, caution is also needed for generalizing our psychosocial results to children who are nowadays growing up with CH. The question is, whether the impaired HRQoL of the young adults and the 10-year old CH patients in our study could be assigned to suboptimal treatment years ago, as lower initial T4 dose and older age at onset of therapy compared to the current treatment protocols. In the studies on HRQoL and self-worth however, we did not find any significant association of initial T4 dose and age at onset of therapy with HRQoL and self-worth, which might be an indication that the contribution of treatment factors to psychosocial outcomes in CH patients is limited. So, it could be assumed that also CH children being treated nowadays should be considered at risk of impaired HRQoL and self-worth.

Third limitation is the loss of subjects from the original cohorts, which restricts the representativeness of the current samples. We clarified the etiology of both the excluded patients and the patients not willing to participate in all three cohorts (Chapters 2, 3 and 4). However, no information about outcome and the socio- demographic status was available for the non-participants.

Fourth, adequacy of long-term T4 supplementation was not studied explicitly in the first two cohorts. However all studied patients were treated according to criteria of good clinical practice by pediatricians who rely on (inter)national guidelines (preserving euthyroidism primarily by maintaining plasma TSH concentrations within the reference range with regular T4 dose adjustments). In the last cohort we analyzed whether the patients were treated well, to define "adequate treatment". Analysis showed that only a minority of patients during the first or second year of life had >20% of the vena punctures with values deviating from the norm. So, we can conclude that the vast majority of our patients of the last cohort were treated adequately

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during their first two years of life.

Fifth, the interpretation of HRQoL is difficult. As a standardized definition for bad HRQoL and self-worth is lacking, we tried to add clinical meaning to the differences between CH and healthy children on HRQoL and self-worth. We divided the children in two groups, one at risk for an impaired HRQoL and self-worth and one not at risk. Although there is no gold standard for good or bad HRQoL yet, this definition is considered to be a suitable way to differentiate between individuals with higher scale scores from individuals with lower scale scores.[53]

5. Clinical implications

Our findings show that several children and young adults with CH are prone to substantial motor, cognitive and psychosocial problems. Therefore, we can conclude that children with CH are vulnerable and that there is need for systematic evaluation and specific care. In this regard, several recommendations are made.

5.1 Be aware of possible consequences of CH and provide relevant information
The results of this thesis deserve proper attention and awareness of health care professionals treating children with CH. Pediatricians should be informed about the increased risk of the cognitive, motor and psychosocial problems in CH patients of all ages.
They should in addition to medical evaluation be aware of the psychological consequences of CH and provide adequate information and thereby psycho-education to the parents. Furthermore, information about the possible psychological, cognitive, motor and psychosocial consequences of CH for patients and their parents needs also be available in leaflets and on websites. This will make parents more aware of the possible consequences of their child growing up with CH.

5.2 Monitor and screen patients with CH
In addition to awareness of the consequences of CH, it seems also important to monitor these patients. Our consistent findings over time highlight the need for careful monitoring long-term treatment adequacy, cognitive, motor and psychosocial functioning of patients with CH throughout childhood and adulthood. Pediatricians should allow early identification, more detailed psychosocial/developmental assessment and therapeutic intervention by paying more attention on school performances, motor and psychosocial functioning.

The use of patient reported outcomes (PROs) in daily clinical practice will be helpful to routinely monitor psychosocial functioning (HRQoL) and refer them to the needed care if necessary. In the past ten years there has been a growing interest in these PROs as a tool for pediatricians to discuss psychosocial issues during medical consultation.[54] For example, a

recent study investigating the effectiveness of the use of Health Related Quality of life (HRQoL) assessments for children in clinical practice, showed that the use of PROs leads to significantly more discussion of emotional and social functioning during outpatient consultation and improves the identification of emotional and cognitive problems.[55] When pediatric psychologists and pediatricians work together, PROs can be used to closely monitor children with chronic illnesses in a multidisciplinary context and referral to psychosocial support can be facilitated more easily.[56,57] In addition, the use of valid and reliable screening instruments to detect patients with CH with social, emotional and behavior problems are recommended, for example the Strength and Difficulties Questionnaire (SDQ).

Furthermore, our results underscore the importance of routine (neuro)cognitive assessments for all children with a severe form of CH and routine motor assessments for all children with CH. Routine screening could distinguish those children with severe problems and will enable timely referral to targeted care. Additional remedial therapy or psycho-education of teachers at the children's school might be a result of routine screening.

5.3 Refer to targeted care if necessary

First, patients could be motivated to engage in sport activities. When motor problems are present, tailored support with respect to movement and sports should be considered as an early intervention. In addition, we recommend referring all children with deficits in motor functioning to a physiotherapist or child physical therapist as part of standard health care. Furthermore with respect to cognitive functioning, intervention programs that improve cognitive functions such as memory and attention or speech training might be offered to children if needed. Finally, it seems important to stimulate children's social performance and to support children with their social skills to continue peer-related activities as much as possible, to stimulate their social performance and with that their self-esteem. Awareness about patients HRQoL and possible gaps in the course of life can be useful in clinical practice because it enables health care providers to select and adjust coaching programs in order to aim at a most favorable course of life in these patients, throughout their development. During the last decades, studies have suggested that adjustment in children with chronic diseases may be promoted using cognitive behavioral therapeutic techniques.[58-61] Children with CH with social- emotional and adjustment problems could be referred to a cognitive behavioral group intervention for a heterogeneous population of children with various chronic diseases (called 'Op Koers'). A recent study investigating this intervention showed positive effects on child adjustment.[62]

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6. Future research

Part 1:

6.1 Neuropsychological consequences of CH

The findings of our study have implications for future research. In this thesis we only examined 'overall' cognitive functioning. It seems important to study cognitive functioning of patients with CH in more detail, for example to examine additional neuropsychological domains like attention and memory. Although neurocognitive functioning in CH is described in the current literature,[11,24,63,64] further work is needed to advance the understanding of the functional impact of different neurocognitive long-term sequelae, especially processing speed, visual motor skills, attention and executive functioning (working, memory, shifting). Furthermore the use of magnetic resonance imaging (MRI) could be used to determine whether children and adolescents with CH have brain damage. Rovet and colleagues showed with the use of MRI that patients with CH had smaller hippocampal volumes than controls. In addition, unlike controls, who showed a positive relationship between age and hippocampal volumes, age was unrelated to hippocampal size in the CH group.[65,66]

6.2 Effect of interventions

Because of the deficits in cognitive and motor functioning in patients with CH and therefore advised possible interventions like physiotherapy, remedial therapy and speech therapy, it seems important to examine the effect of these interventions. With respect to motor functioning, in our study it was not possible to split motor function with the BSID-II in specific motor areas. With the new version of the BSID, version III, it is possible to examine motor development more in depth. Furthermore, with the new version of the BSID, it is also possible to assess social development or behavioral problems. However this version was not yet available during our inclusion period. Future studies should take in consideration the use of tests that are able to study motor functioning more specifically.

6.3 Neonatal screening and treatment of CH

Children with CH, even when treated within a few days after birth, still suffer from subtle but significant cognitive and motor deficits. Because our data strongly point to the prenatal hypothyroid state being responsible for the postnatal outcome it may be concluded that the current neonatal screening program on CH is optimal as it is. Future research should include neonatal brain imaging and focus on improvements of the prenatal thyroid hormone state.

Despite the important results obtained in terms of standardization of screening procedures and improvements in time and dose at starting treatment,[28,68,78] controversy exists in literature worldwide on the effect of these changes on development.[18,25,67-76] Hence, international guidelines

for optimal treatment (starting day of treatment, initial T4-dose, treatment adequacy) are desirable and needed. Only with (international) consensus with respect to treatment and criteria for CH-T severity, best practice will be available for all children. Therefore, recent literature provides recommendations regarding the treatment of children with CH.[28,68] However, pursuing research in this area seems still important.

Furthermore, promising new ESPE guidelines are underway, so it is important to take these in consideration in clinical practice and future research, when published.

Part 2:

6.4 Risk and protective factors

An important goal of this study was to evaluate psychosocial functioning of children with CH and compare functioning to healthy peers. We only explored the influence of disease factors, IQ and developmental scores on HRQoL and self-esteem. Evidence on psychosocial functioning in children with other chronic illnesses suggests that not medical, but mainly psychosocial factors (e.g. parenting, family functioning, coping) contribute to variance in psychosocial functioning.[43,77] Therefore, it seems important for future research to identify more risk- and protective factors such as socio-economic status and psychosocial factors (e.g parenting, family functioning, coping) that influence HRQoL, self-worth and cognitive-, motor- and social functioning, in order to be able to detect and support the children and adolescents who are at risk and to prevent maladjustment and help those patients who encounter problems.

6.5 Parents of children with CH

Future studies should also include parents of children with CH. In this study we did not study the consequences for parents of children with CH as well as the interplay of parent and child variables. Hatzmann et al. described lower HRQoL scores of parents of chronically ill children compared to parents of healthy children.[79] A recent study showed that 13% of the parents of children with CH had parenting stress above the clinical cut-off. Furthermore, the emotional-behavioral problems of the children were significantly associated with overall parental stress.[44] When parents establish a supportive, caring and positive environment, this will have a positive effect on developmental outcomes for children, also in a population of children growing up with a chronic disease.[80] Parental psychological adjustment can be essential factor of chronically ill child's psychological adjustment.[45] Parental psychological adjustment can influence children's psychological adjustment indirectly through efficacy of the treatment that is affecting as an organic factor, as the parents of very young chronically ill children are mostly responsible for the treatment compliance. The results of the study of Jusiene et al. confirmed that parental psychological maladjustment predicts the psychological maladjustment of children with CH

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and phenylketonuria. Parents who tend to use more emotion-oriented coping in everyday stress situations and who indulge their sick children also rate them as having more psychological problems.[45]

6.6 Other psychosocial outcomes in patients with CH

Psychopathology of children and young adults with CH was not measured in the present study. Since CH patients appeared to be less vital and have more negative emotions compared to the healthy Dutch population, it seems interesting to study the relation between CH and psychopathology like anxiety and depression in more detail. Depression and anxiety are more often signalled in adults with hypothyroidism as well as in children with other chronic diseases. Future research should also address these topics.

A remarkable result in the present study was that CH patients did not differ in educational level compared to controls. Most patients were 21 years of age at time of testing. Therefore most patients have not yet completed their education at the moment of testing. For that reason, it is unclear whether CH patients will be able to function on the same level in society (after completion of their education) as their healthy peers. For future research this is an important aspect to take in consideration when testing adult patients, who already fulfil a certain role in society.

7. Conclusion

In conclusion, results of this thesis show that although the development of children with CH is considerably improved by early treatment as a result of by neonatal screening, they are still at risk for motor and cognitive problems. This applies especially for children with severe CH. Finetuning of treatment and timing does not seem to further improve the positive effect of the screening program. This is probably due to the prenatal hypothyroid state or the thyroid hormone deficiency in early life.

Results of this thesis also show that CH has a negative impact on several aspects of HRQoL, developmental milestones (CoL) and self-esteem. Patients reported more problems with cognitive, motor and psychosocial functioning. This is a source of concern that deserves attention. Therefore awareness of psychological consequences among health care physicians, screening, monitoring and referring of patients to targeted care is of utmost importance.

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