Psychological consequences of congenital hypothyroidism: Cognitive, motor and psychosocial functioning
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Citation for published version (APA):
van der Sluijs Veer, L. (2013). Psychological consequences of congenital hypothyroidism: Cognitive, motor and psychosocial functioning

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General introduction
1. Introduction

More than 60 years ago, Radwin and colleagues (1949) introduced the term ‘congenital hypothyroidism’ (CH). They described children with hypothyroid-associated features of severe intellectual disability and growth retardation. Nowadays this definition of CH needs a revision since the diagnosis CH as a chronic disease is made before the onset of severe clinical symptoms, and is based on biochemical measurement of thyroid stimulating hormone (TSH) and thyroid hormone levels alone. CH is a chronic life-long disease, which may affect the patient’s daily life because of the hospital visits, the daily thyroxine (T4) administration, the need of regular dose adjustments and sometimes the need of adjuvant medical care such as speech training, remedial therapy and physiotherapy. In CH, thyroid hormone deficiency is present from the prenatal period onwards, until, after birth, adequate T4 supplementation is provided. As the first few months of life are critical for early human brain development, and to prevent brain damage associated with thyroid hormone deficiency, it is important that children with CH are treated as soon as possible after birth.

Therefore since 1974, neonatal CH screening programs have been implemented worldwide, enabling early postnatal detection of CH. To optimize the effect of early treatment on cognitive and motor outcome in CH patients, timing and treatment modality have been adapted several times over the years. For example, treatment modality gradually changed from a relatively low initial T4 dose in the early years of neonatal screening, to higher initial T4 dose in recent years. To evaluate if these changes of treatment achieve optimal effect on development of the children with CH, investigating cognitive and motor outcome over time is necessary.

In this thesis, the results of our study entitled “Effect evaluation of the neonatal screening on CH in The Netherlands” are described. In this study cognitive and motor outcome of three nationwide cohorts of CH patients born in 1981-1982, 1992-1993 and 2002-2004 was investigated. In addition, we examined the social-emotional consequences of children growing up with CH, as little is known on these consequences up till now. We focused on Health Related Quality of Life (HRQoL), Course of Life (CoL), and self-esteem. Furthermore, all outcomes were analyzed in relation to type and severity of CH and to treatment variables, such as timing of initiation of T4 supplementation and initial T4 dose.

This introductory section outlines what is known about the medical and psychological aspects of CH, and the design of the study.
2. Medical aspects of congenital hypothyroidism

2.1 Thyroid gland and thyroid hormone

The human thyroid gland is an endocrine gland and is localized on the anterior side of the neck, in front of the trachea and just below the larynx (Figure 1). During development, the thyroid is actually located in the back of the tongue and has to migrate to the front of the neck before birth. The thyroid gland regulates the metabolism throughout the body and has two lobes connected by the isthmus. The thyroid gland makes two thyroid hormones that it secretes into the blood stream: thyroxine; this hormone contains four atoms of iodine and is often called T4 and tri-iodothyronine, which contains three atoms of iodine and is called T3. Thyroid cells are the only cells in the body which can organify iodine. These cells combine iodine and the amino acid tyrosine to make T3 and T4. T3 and T4 are then released into the blood stream and are transported throughout the body where they control metabolism. The major form of thyroid hormone in the blood is T4, which has a longer half life than T3. The ratio of T4 to T3 released into the blood is roughly 20 to 1. However T3 possesses about four times the hormone ‘strength’ as T4. In contrast to T3, T4 is not physiologically active and has to be transformed into T3, before the cells can use it. T4 is converted to the active T3 within cells by deiodination (5’-iodinase). The activity of the thyroid gland is controlled by the hypothalamus and pituitary.

2.2 The role of thyroid hormones in fetal brain development

In addition to its many functions in growth and metabolism, thyroid hormone is extremely important for normal development of the human central nervous system (CNS).

Figure 1 – Front view of the neck with thyroid gland and thyroid system
Untreated CH implies low levels of circulating thyroid hormone in infancy, when the brain is extremely vulnerable to thyroid deficiencies.\textsuperscript{7,10} The importance of thyroid hormone for brain development has been shown in clinical as well as experimental studies. With the exception of the construction of the neural tube, thyroid hormone is necessary for nearly all processes in the brain development, from the neuroblast formation in the tenth fetal week up to the completion years after the birth. The experimental data demonstrate that hypothyroidism may affect brain development at every level of organisation from the molecular to the gross structural.\textsuperscript{11} Because each brain region has its own unique development schedule, the effects of thyroid hormone deficiency differ for each brain region.

### 2.3 Prevalence and incidence of congenital hypothyroidism

CH is the most frequent endocrine congenital disorder with an incidence of approximately 1 out of every 3000 children. In The Netherlands, approximately 80 children with permanent CH are detected each year. Prior to the onset of newborn screening programs, the incidence of CH, as diagnosed after clinical manifestations, was in the range of 1: 7.000 to 1: 10.000.\textsuperscript{12,13} With the advent of screening of newborn populations, the incidence was initially reported to be in the range of 1: 3.000 to 1: 4.000.\textsuperscript{13,14} A recent report in the United States showed that the incidence of CH was somewhat lower in Whites (1:1.815) and Blacks (1:1902), somewhat higher in Hispanics (1:1.559), and highest in the Asian population (1:1016).\textsuperscript{15} Besides, this study found the incidence nearly double in twin births (1:876) as compared to singletons (1:1765), and even higher with multiple births (1: 575). Older mothers (> 39 years) had a higher incidence (1:1.328) compared to younger mothers (<20- 29 years, 1:1.608).\textsuperscript{13,16} Nearly all screening programs report a female preponderance, approaching 2:1 female to male ratio and there is an increased risk in infants with Down syndrome.\textsuperscript{13,17,18}

### 2.4 Congenital hypothyroidism and neonatal screening

Until the early 1970s children with CH were diagnosed on the basis of overt clinical signs and symptoms e.g. long-term jaundice, dull look, puffy face, thick tongue, constipation, feeding difficulty, sleepiness etc. As these symptoms are non-specific and develop gradually, diagnosis was often delayed for several months, sometimes years. If CH remains untreated, children are at risk for growth retardation and a delay in motor development. In addition, intellectual disability is the most important and devastating clinical symptom of CH, as it is not reversible.\textsuperscript{2} Therefore from 1974 onwards, neonatal CH screening programs have been implemented worldwide, enabling early postnatal detection of CH. The ultimate aim of neonatal screening is to prevent brain damage due to shortage of thyroid hormone by early initiation of T4 supplementation. In North America, newborn screening for CH was first started on a trial basis during the early mid-1970s. These pilot programs were successful in identifying and treating CH very early in
life, which resulted in the implementation of screening for CH throughout many countries.\(^2\)

The current Dutch neonatal CH screening procedure during the study is presented in Figure 2. It is primarily based on T4 measurement in filter paper blood spots. Sampling is performed between 4 and 7 days after birth. The concentration of T4, expressed as standard deviation (SD) score, is compared to the daily mean. If T4 is \(\leq -0.8\) SD, TSH concentration (expressed in mU/l) is additionally measured. If T4 is \(\leq -1.6\) SD, TBG concentration (expressed in nmol/l) is also measured. A T4/ TBG ratio is calculated \((T4 \text{ SD} + 5.1) \times [\text{TBG}]^{-1} \times 1000\). If T4 \(\leq -3.0\) SD or TSH \(\geq 50\) mU/l, children are immediately referred to a pediatrician. In case of a dubious result (-3 < T4 \(\leq 0.8\)SD in combination with a T4/TBG ratio \(\leq 8.5\) and/or 20 \(\leq\) TSH < 50mU/l), a second heel puncture is performed T4, TSH and TBG are repeated. Children are referred to a pediatrician after a second heel puncture when a result is dubious again, or abnormal.\(^17\)

For children born with a gestational age (GA) \(\leq 36.0\) wk in combination with a birth weight \(\leq 2500\)g the referral criterion is based on TSH; if TSH \(\geq 50\)mU/l, the child is referred, if 20 \(\leq\) TSH < 50mU/l, the result is considered dubious and a second heel puncture is performed after which the child is referred if the result is dubious again or abnormal.\(^17\)

Figure 2 - Dutch neonatal CH screening procedure\(^17\)
2.5 Diagnosis after neonatal screening

When neonatal screening results indicate referral, the child is seen by a pediatrician for further evaluation. In case CH is definite, a diagnostic workup can be done to establish a detailed etiology of CH. When CH is likely, repeated determination of FT4 or TSH, or additional tests might be needed to confirm or reject the diagnosis of CH. Even then it is not always possible to reject the diagnosis of CH within a few days to weeks. Because of the importance of thyroid hormone for brain development T4-supplementation is started as soon as possible to prevent cerebral damage as a consequence of suspected thyroid hormone deficiency. When the diagnosis of CH is not confirmed, it is recommended to search for an (alleged) explanation of the abnormal screening result as well. Establishing a detailed etiology, preferably in the neonatal period, helps to initiate an adequate treatment strategy, to calculate the risk of other defects (endocrine or associated effects), and to inform the parents about the prognosis and the risk of recurrence.

Thyroidal CH (CH-T), the most common form of CH, is permanent and occurs as a result of developmental defects of the thyroid gland, known as thyroid agenesia or dysgenesis or due to disruptions in thyroid hormone biosynthesis, also known as thyroid dyshormonogenesis. Less commonly, the altered neonatal thyroid function is transient, attributable to the transplacental passage of maternal medication, maternal blocking antibodies, or iodine deficiency or excess. In some cases, CH may result from a pituitary or hypothalamic abnormality (central or secondary/tertiary hypothyroidism).

The severity of CH is generally determined by measuring the FT4 concentration in the blood.

2.6 Treatment of congenital hypothyroidism

The overall goal of treatment is ensure that patients with CH are able to have growth, mental and motor development that is as close as possible to their genetic potential. This is achieved by adequate T4 supplementation to restore FT4 and the TSH to the normal range as soon as possible and then maintaining clinical and biochemical euthyroidism. The treatment goals as outlined by European Society for Pediatric Endocrinology (ESPE) guidelines are as follows:

- Serum FT4 or total T4 should be kept in the upper range of normal during the first year of life.
- Target values during the first year are 130 to 206 nmol/l (10-16 µg/dl) for the serum T4 and 18 to 30 pmol/l (1.4 to 2.3 ng/dl) for FT4.
- Serum TSH should be kept under 5 mU/l.
Clinical evaluation should be performed every few months during the first three years of life along with frequent measurements of serum T4 or FT4 and TSH. The American Academy of Pediatrics recommends the following monitoring schedule:\textsuperscript{15,23,24}
- At two and four weeks after the initiation of L-thyroxine (T4) treatment.
- Every 1-2 months during the first 6 months of life.
- Every 3-4 months between 6 months and three years of age.
- Every 6-12 months thereafter.
- Four weeks after any change in dose.

Monitoring should be more frequent if results are abnormal or non-compliance is suspected. The serum (F)T4 should normalize within one to two weeks and the serum TSH should become normal in most infants after one month of treatment.

Successful treatment is achieved by application of a single oral T4 dose in the morning.\textsuperscript{2} Since the introduction of neonatal screening, there has been much discussion on the optimal starting point and dose. The current recommended starting dose is 10-15 µg/kg per day. However, the evidence level supporting this recommendation is still low.\textsuperscript{2}

To optimize the effect of early treatment on cognitive and motor outcome in patients with CH, timing and treatment modality have been adapted several times over the years. For example, treatment modality gradually changed from a relatively low initial T4 dose in the early years of neonatal screening, to higher initial T4 dose in recent years. In order to expand knowledge on optimal treatment, it is important to monitor physical and psychological functioning of the patients with CH.

3. Psychological consequences of congenital hypothyroidism

3.1 Cognitive functioning

Before neonatal screening was introduced, children were diagnosed relatively late in infancy, because overt clinical manifestations of CH were often delayed. As a result, significant brain damage had already occurred, by the time treatment was initiated. Therefore, CH used to be a leading cause of children's mental retardation.

One of the first studies on the degree of impairment associated with hypothyroidism appeared in 1936 by Gesell and colleagues. They found that in cretins early and adequate treatment resulted in less severe retardation.\textsuperscript{24,25} In 1957, Smith et al. were the first to emphasize the importance of early therapy in severely affected patients.\textsuperscript{26} Since then, many retrospective studies have emerged. These studies agreed on the fact that treatment had to be started within 3 months after birth to prevent mental retardation.\textsuperscript{25-27} Klein and colleagues (1972) were the first to show that intelligence of a child with CH depends on the time of clinical diagnosis and
initiation of replacement therapy. They showed that mean Intelligence Quotient (IQ) was 89 in those patients treated before the age of 3 months, mean IQ was 70 in those patients treated between 3 and 7 months and IQ was 54 in those patients treated after the age of 7 months. Similar results were obtained in other studies.28

Neonatal screening programs leading to early postnatal start of T4 supplementation have resulted in the prevention of severe cerebral damage and a large decrease in morbidity in these patients.31 One of the first reports on outcome of CH patients detected by screening was published in The Lancet in 1981.32 This study showed that the mean mental developmental outcome at the age of 3-4 years in a 'total' group of patients with CH, treated from a mean age of 25 days, was comparable to that of controls. However, in this study, no distinction was made for severity of CH. Thereafter, several studies on the effect of the screening and early treatment have shown that most children with CH achieve scores for intelligence within the normal range, however those with severe CH often show, significant deficits in mean IQ scores despite early treatment.9,33 Thus, even in patients with CH who receive early treatment, intellectual, motor and neurocognitive deficits have been reported.9,33-37 In addition, next to negative effects on general cognitive functioning children with CH are also at risk for learning disabilities/difficulties particularly in math and learning to read,38-41 hearing impairment and visual problems 40 and subtle and specific neurocognitive impairments, such as memory and attention problems.37,42,43

3.2 Motor functioning

Besides general cognitive impairments, deficits in motor functioning are commonly seen in children with CH.27,44 Rovet and colleagues (1999) have shown that the sensorimotor domain was the most strongly affected domain in school-aged children with CH.45 Kooistra and colleagues (1994; 1995) have shown that children with CH, especially those with severe CH experienced motor deficiencies. In general, these children appear to have problems with skills in which a sequence of movements must be made using one or more parts of the body. These problems were observed both in fine motor skills (drawing and stacking pins) and in gross motor skills (ball catching and throwing). Children with CH also have problems with static balance, another important aspect of movement control.27,44

3.3 Effect treatment and disease factors on cognitive and motor consequences

Despite the important results obtained in terms of standardization of screening procedures and improvements in time and dose at starting treatment, controversy exists in literature worldwide on the effect of these changes on the development of the child. Some claim early treatment

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* 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
with high T4 dose will lead to normal development,\textsuperscript{36,47} others state that timing does not have a favorable effect on cognitive and motor development.\textsuperscript{5,35} Therefore, the optimal treatment modality for children with CH is still in debate.

Many disease and treatment factors (e.g. etiology, severity CH, starting day of treatment, long-term treatment strategy, thyroid hormone status at time of assessments, treatment compliance, maternal thyroid function, initial dose of T4, adequacy of T4 supplementation, adjuvant care), might influence cognitive and motor outcome. In this thesis we focus on the following important disease and treatment factors:

**Severity**

Children with severe CH are at greater risk for developmental delay. This has been illustrated in many studies done over the world.\textsuperscript{9,18,39,48-50} Commonly, severity of CH is determined by measuring the postnatal pretreatment (F)T4 concentration in the blood. Fuggle and colleagues found that IQ scores for the total group CH patients were not significantly different from the normative population. However, those children with the lowest initial T4 concentration (<20 nmol/l) tended to have significantly lower IQ scores compared to children with higher initial T4 concentrations (>60 nmol/l).\textsuperscript{51} Many studies have found similar results and show that IQ scores of CH patients studied as a group are within the reference range but observe differences when distinctions are made according to severity.\textsuperscript{34,50,51} However, there is no clear definition for severity in the literature. In our study severity of CH was based on the pre-treatment FT4 concentration: ‘severe CH’: initial FT4 ≤0.4ng/dl (≤5 pmol/l), ‘moderate CH’:0.4<initial FT4 ≤0.8ng/dl (5.0<initial FT4 ≤10.0pmol/l) or ‘mild CH’: initial FT4>0.8ng/dl (>10.0 pmol/l).

**Starting day of treatment**

Besides severity, the timing of initiation of treatment seems an import factor in predicting cognitive functioning. Although effects of thyroid hormones on the brain development starts from the intrauterine life and continues until 2–3 years of age, first 6 months in the postnatal period is known to be a very important time interval.\textsuperscript{52} 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.\textsuperscript{37}

However, studies evaluating timing of initiation of treatment have presented contrasting results. In a Dutch Study of Bongers and colleagues (2000), a sample of patients born between 1993 and 1996 and tested between 11 and 30 months of age, no correlation was found between developmental scores and age at start of treatment. Though, subdivision in groups showed that a treatment delay of 6 days in children with severe CH receiving a mean initial dose of 10.8µg/
kg per day resulted in a loss of 25 developmental index score points. However, retesting the same patients between 5.5 and 7 years of age showed no differences anymore in IQ among the 4 initial treatment groups. Furthermore, many studies have not been able to demonstrate a clear effect of the age which treatment started on outcome. The discrepancy between studies which showed or failed to show an effect of age at start of treatment might be caused by relative small patient groups and a limited variation in age at start of treatment.

**Initial dose of T4**

Some researchers have questioned whether effects of severe CH can be compensated for very early onset of high-dose treatment, suggesting that more optimal treatment may be possible. Therefore, the importance of the initial T4-dose as a key factor for preservation of brain development has become a subject of major interest. Both American and European treatment guidelines have changed during the past 15 years, recommending higher initial T4 dosage (10-15 µg/kg per day versus previous 5-8 µg/kg per day. A controversy regarding the appropriate T4 starting dose still exists. A striking example is that in one study the same initial starting dose gave a favorable outcome if it was defined as high, and a suboptimal outcome when defined as a low dose.

However, a systematic review of Ng et al. (2009) determined the effects of high versus low dose of initial thyroid hormone replacement for CH. They concluded that at present, there is inadequate evidence to suggest that a high dose is more beneficial compared to a low dose initial thyroid hormone replacement in the treatment of CH.

**Adequacy of T4 supplementation**

Another important factor to consider when evaluating outcome of CH patients is the adequacy of T4 supplementation during the first years of life. Because the critical period of thyroid hormone dependent brain development endures the first years of life, it is likely that adequacy of treatment contributes to outcome.

The relationship between adequacy of treatment throughout childhood and cognitive functioning is not clear. A main problem is that adequacy of treatment is hard to determine or quantify. An international guideline to define adequate treatment is not available. Time take to achieve and maintain the target ranges for (F)T4 and TSH seems also an indicator for better outcome. In one study, T4 normalization beyond two weeks resulted in patients scoring lower on behavioral and cognitive testing than patients who normalized in less than two weeks. Recent literature provides recommendations regarding the treatment of children with CH.
In conclusion, the possible effects of the starting day of treatment, initial dose of T4, CH-T severity and adequacy of T4 supplementation during the first year of life on developmental outcome of patients detected by neonatal CH screening have been studied extensively. However, the results are often difficult to compare, since screening method, guidelines for treatment (starting day of treatment and initial T4 dose, quality of treatment), sample size and criteria for CH-T severity differ among these studies.

3.4 Psychosocial functioning

In general literature, there is a growing attention for the psychological effects of chronic diseases in children.\(^5^7\)\(^-\)\(^6^1\) Chronic diseases of childhood may have implications for the psychosocial well-being of children and their families. Many psychological studies conclude that children and young adults with different chronic diseases are at heightened risk for the development of psychosocial problems. They tend to suffer more than healthy children from behavior problems, especially internalizing problems such as depression, anxiety, and social withdrawal.\(^5^7,\)\(^6^1\)\(^-\)\(^6^4\)

Over the years, much has been reported about the cognitive and motor development of children with CH while little is known about social-emotional functioning of patients growing up with CH.\(^6^5\) The possible cognitive and motor problems in patients with CH may result in worse academic abilities or learning difficulties. As a result, cognitive and motor deficits possibly will influence the psychosocial well-being of patients with CH. In addition suboptimal thyroid state may affect well-being. Simons et al.\(^6^6\) show that children with CH had more internalized problems such as anxiety and depression, which tended to increase with the child’s age and was connected to the severity of the disease.\(^6^6,\)\(^6^7\) Rovet et al. found that CH can lead to more difficult temperament in infancy and more behavior problems in middle childhood.\(^6^8\)

CH is a chronic life-long disease,\(^6^9\) which may effect the patient’s daily life because of the hospital visits, the daily T4 administration, the need of regular dose adjustments and sometimes the need of adjuvant medical care such as speech training and physiotherapy. 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. In the next subparagraphs, we will explain these concepts in more detail.

3.4.1 Health Related Quality of Life

HRQoL is becoming a key component in research about effects of chronic diseases and therefore commonly used as outcome measure in psychological research. The World Health Organization (WHO) defines QoL as: ‘individual’s perceptions of their position in live in
the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns.” The concept of HRQoL emerged as a way of defining the multidimensional concept of Quality of life in the field of health. The evaluation of HRQoL implies evaluations of the impact of a disease and its treatment on all relevant dimensions of the patient’s life. HRQoL can be used as an indicator of adjustment, which comprises elements of physical, functional, social and psychological health, as well as the patient’s perceived health status and well-being.71 HRQoL in children with CH has not been studied thoroughly. Overall, children with a chronic disease are at a greater risk of HRQOL problems than their healthy peers, but not in all cases, and not on all domains.72-74

3.4.2 Course of Life
Concern has risen about the consequences of chronic pediatric diseases later in life. The fulfilling of age specific developmental tasks and achieving developmental milestones that are necessary in the development of a child, such as having friends, participating in sports, having tasks at home, first boy-/girlfriend during childhood, or acquisition of independence, referred to as the Course of Life (CoL), are of great importance to adjustment in adult life.75 The normal developmental tasks of childhood and adolescence involve the achievement of social and academic competence, the development of peer relationships and increasing independence from the parents.76,77 Growing up with CH might have impact on the psychosocial development into adulthood. However little is known about patients with CH in adulthood. Findings from other studies have shown that chronic diseases (e.g. fabry disease, childhood cancer, end stage renal disease, children with anorectal malformations, Hirschprung’s disease and galactosaemia) are likely to achieve fewer psychosocial milestones, or to achieve the milestones at an older age compared to their peers.64,78,79 In a study about the impact of the course of life of children with end-stage renal disease on their quality of life in adulthood it was found that patients who achieved fewer social milestones while growing up experiences more emotional problems and had a lesser overall mental quality of life.72

3.4.3 Self-esteem
Self-concept represents important aspects of our perceived identity that are formed through experiences with the environment and the expectations and perceptions of significant others.80,81 Self-concept is seen as a main aspect of adolescent psychological health 80,82 embedded in the evaluation of personal characteristics such as social acceptance, behavior, physical ability and appearance, and academic capability.80,83 Self-esteem is the evaluative component of self-concept. It is recognized as a sub-domain analogous to the notion of general self-worth in the hierarchical model of self-concept.80,84 Positive self-worth is a significant factor influencing overall good mental health and psychological well-being 85 and is regarded by major theorists as
a basic psychological need. Growing up with a chronic disease can limit children in achieving every day successes (social, athletics and academic), which are necessary to develop a positive view of the self. Some studies demonstrated that children with chronic diseases compared with healthy peers often reveal no significant differences in overall self-worth. Though, there are also studies that indicate that self-worth is negatively associated with internalizing behavior problems in children with various chronic diseases. However, there are no studies that report on self-esteem in children with CH.

4. Aim, design and outline of the thesis

This thesis reports part of the results of the Dutch nationwide study “Effect evaluation of the screening on CH in The Netherlands”.

Part one of this thesis aimed 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 changes in timing and treatment modality on cognitive and motor outcome over the years by including three different cohorts of patients, (3) investigate the impact of disease and treatment factors (severity, starting day at treatment, initial dose of T4 and adequacy of T4 supplementation) on cognitive and motor outcome.

Part two of this thesis aimed to (1) explore the psychosocial functioning of young adults and children with CH, HRQoL, 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 main outcomes of part 1 and part 2 of the study are cognitive, motor and psychosocial functioning. In order to explore the association between disease related variables, socio-demographic factors, cognitive, motor and psychosocial functioning we constructed a research model, based on the biopsychosocial model (figure 3). The biopsychosocial model combines biological, psychological, and social perspectives on a child's health and well being. Within our research model we focused on disease related factors and socio-demographic factors, as these are considered to determine cognitive, motor and psychosocial functioning, whereas cognitive and motor functioning are subsequently regarded as determinants of psychosocial functioning.
4.1 Study design
In the Dutch nationwide study “Effect evaluation of the screening on CH in The Netherlands”, three cohorts of patients were investigated. The specific years of the cohorts were deliberately chosen; 1981-82 because these patients were born the first years after the introduction of national screening, moreover, this cohort was tested previously at the age of 7.5 and 9.5 years and the patients had reached adult age; 1992-93 because initiation of treatment was significantly different from the 1981-82 cohort, and because their results at 10.5 years of age could be compared to the results of previous studies in the 1981-82 cohort; 2002-04 because both initiation of treatment was earlier and initial T4 dose higher as compared to the other cohorts. 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. Furthermore, all cohorts were well characterized in terms of etiology and initial disease characteristics. In Cohort I (1981-82) cognitive and motor outcome of patients was tested at 21.5 years of age. Cohort II (1992-93) was tested at the age of 10.5 years. Cohort III (2002-2004) was tested at the age of 1 and 2 years. The variety of medical and treatment factors of the three different age groups representing specific time periods of the screening was used to evaluate cognitive, motor and psychosocial functioning. The factors and corresponding measures that were used in the Dutch nationwide study are presented in Table 1.

4.2 Outline of the thesis
The general introduction of this thesis is covered in chapter 1. In Part 1 of this thesis the results of the cognitive and motor outcome in three different cohorts of patients with CH are reported. All outcomes were analyzed in relation to treatment variables.
In **Chapter 2** the results are presented of the cognitive and motor outcome of 70 young adults with CH, born in the first 2 years after the introduction of the Dutch neonatal screening program. 49 of them were previously tested at 9.5 years. Their median age at start of treatment was 28 days (range 4-293 days). **Chapter 3** describes the cognitive and motor outcome of 82, 10.5-year old children with CH born in 1992-1993, in which treatment was initiated at a median age of 20 days (range 2-73 days). In **Chapter 4** we examined whether the advancement of treatment modality has resulted in improved cognitive and motor outcome. 95 Toddlers with

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**Table 1** Factors and corresponding measures used in this thesis

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<td>- Performance IQ (WISC-R/ WAIS-III)</td>
<td>- Performance IQ (WISC-III)</td>
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<tr>
<td>Motor functioning</td>
<td>Total motor impairment (TOMI/MABC)</td>
<td>Total motor impairment (TOMI/MABC)</td>
<td>Motor Developmental Index (BSID-II-NL)</td>
</tr>
<tr>
<td>- Manual Dexterity</td>
<td>- Manual Dexterity</td>
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</tr>
<tr>
<td>- Ball Skills Score</td>
<td>- Ball Skills Score</td>
<td>-</td>
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</tr>
<tr>
<td>- Balance Score (MABC)</td>
<td>- Balance Score (MABC)</td>
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<tr>
<td>Health-related Quality of Life</td>
<td>TAAQoL (self-report)</td>
<td>TACQoL (self-and parent report)</td>
<td>TAPQoL (parent-report)</td>
</tr>
<tr>
<td>Self-esteem</td>
<td>Self-Esteem Scale (self-report)</td>
<td>CBSK (self-report)</td>
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<tr>
<td>Course of Life</td>
<td>Development of autonomy</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>- Psychosocial development</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>- Social Development (Course of Life Questionnaire)</td>
<td>-</td>
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</table>
CH-T at 13 and 25 months of age and treated at a median age of 9 days were studied. In Part 2 of this thesis the psychosocial consequences of CH are reported. Outcomes were analyzed in relation to treatment variables. Chapter 5 describes HRQoL, CoL, social demographical outcomes, and self-esteem in 69 of young adults from the 1981-1982 cohort. In chapter 6 the HRQoL and self-esteem in 82 10.5-year old children with CH, reported by children and their parents is studied. The purpose of chapter 7 was to explore HRQoL in the third cohort of 88 investigated toddlers with CH at two years of age and compare the results to those of the norm population. This thesis ends in chapter 8 with a general discussion including main findings, key messages, and the limitations of the studies, clinical implications and suggestions for future research.
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