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Context: With advances in the treatment of congenital hypothyroidism (CH), the neuropsychological functioning of CH patients is considerably improved. Although much is written about cognitive and motor development, little is known about emotional and social consequences for patients growing up with CH, diagnosed by neonatal screening.

Objectives: The objectives of the study were to: 1) compare health-related quality of life (HRQoL), developmental milestones also called course of life (CoL), sociodemographical outcomes, and self-esteem of CH patients with the general population; and 2) explore whether severity of CH was related to these outcomes.

Design/Setting/Patients: A total of 69 young adults with CH, born in The Netherlands in 1981–1982, completed the "TNO-AZL Questionnaire for Adult's Health related Quality of Life" questionnaire, the CoL survey (developmental milestones and sociodemographical outcomes), and a self-esteem questionnaire.

Main Outcome Measures: HRQoL, CoL, social demographical outcomes, and self-esteem in young adults with CH were determined.

Results: CH patients are more often at risk for HRQoL impairment and reported lower HRQoL on several domains (cognitive functioning, $P < 0.0001$; sleeping, $P < 0.004$; pain, $P < 0.0001$; daily activities, $P < 0.004$; vitality, $P < 0.0001$; aggressiveness, $P < 0.0001$; and depressive moods, $P < 0.0001$) compared with healthy adults. Patients reported a lower self-esteem ($P < 0.005$) and had a delayed CoL on the domain of social development ($P < 0.016$). There were no significant within-group differences between the severity groups for HRQoL, CoL, and self-esteem.

Conclusions: Negative consequences in terms of HRQoL, development, and self-esteem are prevalent in young adults with CH. Health care physicians should be attentive to these consequences and provide additional support (emotional and educational guidance) if necessary. **(*J Clin Endocrinol Metab* 93: 2654–2661, 2008)**

Congenital hypothyroidism (CH) is characterized by the insufficient production of thyroid hormone usually due to thyroid dysgenesis or thyroid dyshormonogenesis. Therefore, lifelong treatment with T_4 is of utmost importance because thyroid hormone not only plays an important role in metabolism but also plays a major role in the development of the central nervous system during prenatal life and the first years after birth (1). The aim of neonatal CH screening programs is to prevent cerebral damage through early initiation of T_4 supplementation.

Early treatment has resulted in remarkable improvement in

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Abbreviations: AMC, Academic Medical Center; CH, congenital hypothyroidism; CoL, course of life; HRQoL, health-related quality of life; IQ, intelligence quotient; RSE, Rosenberg Self-Esteem Scale; TAAQoL, TNO-AZL Questionnaire for Adult's Health-Related Quality of Life.

the neuropsychological functioning of CH patients (2–4). Nevertheless, there is ample evidence that CH patients diagnosed by neonatal screening, especially those with severe CH, are still vulnerable to persistent cognitive and motor deficits (5–10).

Although much is written about the cognitive and motor development of children with CH, little is known about the daily functioning and quality of life of patients growing up with CH (11). CH may affect the patient's daily life because of the hospital visits, daily T_4 administration, need of regular dose adjustments, and sometimes the need of adjuvant medical care such as speech training and physiotherapy. In addition to this, the cognitive and motor problems of CH patients might affect their social life, self-esteem, and emotional functioning.

In general literature, there is growing attention for possible late psychological effects in children and young adults with chronic diseases (12). However, the adjustment of young adults with CH, such as health-related quality of life (HRQoL), developmental tasks, and self-esteem, has not been studied thoroughly. 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 (13). The fulfilling of age-specific developmental tasks and achieving developmental milestones in youth, such as searching for contacts outside the family, or acquisition of independence, referred to as the "course of life" (CoL), are of great importance to adjustment in adult life (14). A positive self-esteem is a significant factor influencing overall good mental health and psychological well-being (15, 16), and is regarded by major theorists as a basic psychological need (17).

From 2001 until now, we conducted a national study to evaluate whether the changes in the screening procedure and treatment strategy over two decades (*e.g.* earlier detection, higher initial T_4 dose) have led to the improved development of patients with CH. We investigated intellectual and motor outcome and social-emotional functioning in terms of HRQoL of CH patients born in 1981–1982, 1992–1993, and 2002–2004. The purpose of the present study was to explore the HRQoL, CoL, social demographical outcomes, and self-esteem in young adults with CH born in 1981 and 1982, and compare the results with those of the general (healthy) population. Furthermore, the study examined the influence of severity of CH on these outcomes.

Patients and Methods

Patients

The complete cohort of CH patients born in The Netherlands in 1981 and 1982 consisted of 136 patients (Table 1). Medical data of these patients were available at the Academic Medical Center (AMC) because of previous studies (8, 18). From the original cohort, four patients had died, three had moved abroad, and five had severe mental retardation related to chromosomal abnormalities, or unclassified syndrome with deafness. Patients were tested at a mean age of 21.5 yr (range 21.0–22.3).

In 2001, the remaining 124 patients were contacted via their physicians and were asked to participate. A total of 82 patients (66%) gave their written informed consent. To ascertain that patients were euthyroid (*i.e.* TSH, 0.4–4.0 μU/ml) at testing, the most recent measurement of thyroid function before the psychological assessments was evaluated; the T_4 supplementation dose was adjusted when TSH was outside its reference range.

Procedure

All patients were asked to complete the questionnaires, at the AMC (except for four, who were tested at their local hospitals), under the supervision of the same psychologist, who was blinded to the patient's medical details. The assistance of the psychologist was restricted to explaining the meaning of difficult words. The description of the nonparticipants is provided in a previous study (7). The study protocol was approved by the institutional review board of the AMC.

Measures

TNO-AZL Questionnaire for Adult's Health-Related Quality of Life (TAAQoL)

The "TNO-AZL (Netherlands Organization for Applied Scientific Research) Questionnaire for Adult's Health-Related Quality of Life" (TAAQoL) is a validated, generic HRQoL questionnaire for subjects 16 yr and older (19). The questionnaire focuses on health problems in the past month, and, if present, the well-being in relation to this health problem is assessed. The TAAQoL comprises 12 scales: gross motor functioning (*e.g.* difficulty walking, bending); fine motor functioning (*e.g.* difficulty cutting papers or opening a can); cognitive functioning (*e.g.* difficulty remembering or concentrating); sleeping (*e.g.* sleeping restlessly, lay awake a lot); pain (*e.g.* backache, pain in neck-shoulders); social functioning (*e.g.* talk to others, visit friends); limitations of daily activities (*e.g.* difficulties with work, done less work); sexual functioning (*e.g.* had less sex); vitality (*e.g.* feel energetic, tired); happiness (*e.g.* feel joyful, cheerful); aggressiveness (*e.g.* feel angry, aggressive); and depressive moods (*e.g.* feel sad or worried). The scale scores are obtained by adding item scores within scales and transforming crude scale scores to a 0–100 scale; higher scores indicate a better HRQoL. The Cronbach's alphas in the study population were moderate to good for all scales except the fine motor function scale, which was excluded from analysis. From the available database from the original TAAQoL study, young

TABLE 1. Characteristics of the 1981–1982 cohort

Etiology	Total	Nonparticipants		Participants
		Not suitable	Not willing	
Thyroid agenesis	36	2	9	24
Thyroid dysgenesis	59	7	15	37
Thyroid dyshormonogenesis	17	3	6	8
Central CH	19	8	11	0
CH nos	5	4	1	0
Total	136	24	42	69

Four groups are presented: the total group, the group of patients that did not participate divided into patients not suitable or not willing to participate, and the group that did participate. For each group, the subdivision according to etiological classification is given. nos, Not otherwise specified.

adults aged 18–25 yr were selected. Adults with a chronic disease in this population were deleted from this database. This resulted in a norm population of 201 healthy young adults.

The CoL Questionnaire

The CoL Questionnaire, developed by the Psychosocial Department of the Emma Children's Hospital, AMC, assesses the achievement of developmental milestones of young adults, aged 18–30 yr, who have grown up with a chronic or life-threatening disease (20). The items concern behaviors that are characteristic of certain age stages, developmental tasks, and the limitations patients might encounter when they grow up with a chronic disease. Most questions ask retrospectively whether (yes, no) and at what age the respondent had achieved certain developmental milestones. For this study three scales were used, *i.e.* development of autonomy, psychosexual development, and social development. A higher score indicates a more favorable CoL. The questionnaire also measures sociodemographical outcomes in young adulthood, such as living situation, education, and employment. The questionnaire covers a total of 74 items. A comparison group of 274 respondents aged 19–24 yr was available (see Ref. 21 for details).

The validity and the test-retest reliability of the CoL scales are good (20). The internal consistencies (Cronbach's α) in the population under study were small to good: 1) development of autonomy: CH 0.40, comparison group 0.48; 2) psychosexual development: CH 0.83, comparison group 0.67; and 3) social development: CH 0.76, comparison group 0.71.

Self-Esteem Scale

Self-esteem was assessed with the Rosenberg Self-Esteem Scale (RSE), a self-administered, 10-item, 4-point scale with response options ranging from one (strongly agree) to four (strongly disagree) (22). The scale measures the self-acceptance aspect of self-esteem or the overall sense of being capable, worthwhile, and competent. Possible scores range from 10–40. The scoring direction on five negatively phrased items was reversed, so a higher score now is indicative of higher self-esteem. For the study sample, a sufficient Cronbach's α coefficient of 0.89 was obtained. A comparison group of 515 young adults aged 18–25 yr was available (see Ref. 23 for details).

Statistical analysis

Data were analyzed using SPSS version 12.0 (SPSS Inc., Chicago, IL). Before conducting the final analyses, several preparation analyses were conducted. First, scale scores were computed and missing data imputed on the basis of the guidelines of the questionnaires. The missing data on the TAAQoL and RSE were imputed at scale level. In calculation of the scale scores, one missing item score was allowed for. The missing score is replaced by the mean value of the nonmissing item scores. The missing data on the CoL questionnaire were not imputed. Second, the internal consistencies (Cronbach's α) of the scales were calculated, and the distributions of the scale scores were considered.

After the preparatory analyses, univariate ANOVAs were conducted to test differences between the CH group and healthy controls on the TAAQoL scales, CoL scales, and RSE, corrected for gender. All CH patients were compared with the norm data, and thereafter the severe and moderate/mild subgroups as well. Comparisons between the severe and moderate/mild CH subgroups, with respect to their scores on the HRQoL scales, CoL scales, and RSE, were also made. To adjust for multiple testing, we used a Bonferroni correction and adjusted the α to 0.004 (0.05/11) for the TAAQoL, 0.016 (0.05/3) for the CoL, and 0.05 (0.05/1) for RSE. For all variables, effect sizes (d) were calculated by dividing the difference in mean score between all CH patients and comparison group by the SD of the scores in the comparison group. We considered effect sizes up to 0.2, 0.5, and 0.8 to be small, moderate, and large, respectively (24).

To create a clinically meaningful distinction between young adults that can be considered "at risk" or "not at risk" for problems, two groups were formed, based on percentile norms in the healthy population. If this is done for groups classified by age and gender, differences between the CH group and norm group are accounted for, and groups can be compared (25). The definition of young adults with problems was based on the value of the 25th percentile for all domains of the TAAQoL, CoL, and the RSE in the norm population. A young adult who scores below the 25th percentile is placed in the quarter of the most impaired population. To determine whether the CH sample was different from the healthy population, percentages at risk were compared using χ^2 tests.

To gain detailed insight into the CoL of CH patients, differences on item level (milestones) were also calculated on the social development scale of the CoL questionnaire because there was a significant difference on this scale between the CH and comparison group. χ^2 tests were conducted at the frequency distributions of the individual items of this scale.

Finally, χ^2 tests were conducted to investigate differences in educational level (low, middle, and high),[1] special education at primary school, living situation, and marital status. We used a significance level of $P < 0.01$ to compensate for multiple testing.

Results

Patient characteristics

A total of 82 CH patients (66% of the original cohort) gave their written informed consent, and their initial thyroid hormone levels and treatment modality were recorded. Of this group, 13 patients were excluded from the study because of central CH (n = 1), because treatment was never initiated (n = 1), an exceptionally late (*i.e.* > 4 yr of age) start of treatment (n = 5), a discontinuation of treatment at a young age (n = 4), or because the patients did not return the questionnaires (n = 2). The remaining 69 patients, 51% of the original cohort (total CH group), were classified into two subgroups according to an arbitrarily chosen cutoff level for severity of postnatal hypothyroidism: "severe CH," with initial T_4 less than 2.3 μg/dl (<30 nmol/liter); and "moderate and mild CH," with initial T_4 more than or equal to 2.3 μg/dl (≥30 nmol/liter).

The baseline characteristics of the participating CH patients are given in Table 2. Of the 69 patients (55 females, 79%), 34 had severe CH, and 35 had moderate/mild CH. The median age of start of T_4 supplementation was 28 d for the total group. The intelligence quotient (IQ) scores of the participating CH patients are given in Table 2. For all details, we refer to a previous publication (7).

Comparison with the healthy population

HRQoL

HRQoL of the total CH group appeared to be significantly worse ($P < 0.004$) than the healthy Dutch population on seven of the 11 scales of the TAAQoL: cognitive functioning, F (1.266) = 61.528, $P < 0.0001$; sleeping, F (1.266) = 8.511, $P < 0.004$); pain, F (1.266) = 15.527, $P < 0.0001$); daily activities, F (1.265) = 10.039, $P < 0.0002$); vitality, F (1.253) = 9.273, $P < 0.0001$); aggressiveness, F (1.253) = 10.803, $P < 0.001$); and depressive moods, F (1.254) = 13.745, $P < 0.0001$. These differences were moderate to large [effect sizes (d) ranged from 0.6–1.3, Table 2)]

HRQoL of the severe CH group appeared to be significantly worse ($P < 0.004$) than the healthy Dutch population on six of the

[1] Low: primary education, technical and vocational training, lower and middle general secondary education; Middle: middle vocational education, higher general secondary education, preuniversity education; and High: higher vocational education, university.

TABLE 2. Characteristics of the subgroups with different severity of CH

	Severe CH	Moderate/mild CH	
No. of patients (male/female)	34 (7/27)	35 (8/27)	
Initial T_4 in ng/dl (95% CI)[a]	1.2 (0.9–1.4)	5.6 (4.6–6.7)	
Initial T_4 in nmol/liter (95% CI)[a]	15.0 (11.9–18.2)	72.7 (59.6–85.8	
Median age at start of T_4 (range)	26 d (8–47)	39 d (4–293)	
Mean IQ scores of the CH patients at 21.5 yr of age recently published in Ref. 7	Severe	Moderate	Mild
Full-scale IQ	91.3 (86.3–96.3)	99.1 (91.1–107.1)	101.3 (95.7–106.9)
Verbal IQ	92.9 (88.1–97.8)	97.8 (89.2–106.3)	101.8 (96.1–107.5)
Performance IQ	90.4 (85.2–95.6)	101.3 (94.8)–107.7)	100.4 (94.7–106.1)

CI, Confidence interval.

[a] Reference range for T_4 in children aged 2–6 wk, 6.5–16.3 μg/dl (84–210 nmol/liter).

11 scales of the TAAQoL: cognitive functioning, F (1.233) = 36.079, $P < 0.0001$; pain, F (1.266)= 15.527, $P < 0.0001$; vitality, F (1.224) = 7.816, $P < 0.004$; social functioning, F (1.230) = 8.750, $P < 0.004$; aggressiveness, F (1.224) = 11.353, $P < 0.004$; and depressive moods, F (1.225)= 12.505, $P < 0.0001$.

HRQoL of the moderate/mild CH group appeared to be significantly worse ($P < 0.004$) than the healthy Dutch population on four of the 11 scales of the TAAQoL: cognitive functioning, F(1.233) = 36.097, $P < 0.0001$; sleeping, F(1.233) = 6.953, $P <$ 0.0001; pain, F (1.233) = 10.275, $P < 0.004$; and vitality, F (1.225) = 8.719, $P < 0.004$.

No significant differences were found between the CH patients and healthy Dutch population on three of the 11 scales on the TAAQoL (gross motor functioning, sexual functioning, and happiness).

CoL

The total CH group and the severe CH group scored significantly lower on one scale of the CoL than the comparison group: social development, total CH group, F (1.334) = 6.191, $P <$ 0.013; severe CH group, F (1.302) = 6.557 (Table 3). This difference was small: effect size (d) = 0.3. No differences were found for the autonomy scale and psychosexual development scale.

With respect to the milestones of social development, we found significant differences between the CH patients and the reference group on two of the 12 milestones (Table 4). A lower percentage of CH patients than the comparison group had been a member of a sports club for at least 1 yr during primary school and secondary school.

No statistically significant differences between CH and the

TABLE 3. Mean scores, SD values, and differences between CH patients and comparison group on HRQoL, CoL, and self esteem, as a function of group, corrected by gender

	Total CH	Severe CH	Moderate/mild CH	Comparison group	Effect size
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Total
TAAQoL	n = 69	n = 34	n = 35	n = 201	
Gross motor functioning	92.4 (14.0)	90.7 (13.7)	93.9 (14.3)	96.8 (9.1)	0.5
Cognitive functioning	65.8 (27.4)[a]	64.0 (27.6)[a]	67.5 (27.4)[a]	89.0 (17.2)	1.3
Sleeping	71.5 (25.3)[b,c]	76.4 (24.6)	67.0 (25.4)[a,b]	81.6 (19.1)	0.5
Pain	74.4 (19.8)[a,b]	74.2 (21.1)[b,c]	74.5 (18.9)[c]	84.7 (16.0)	0.6
Social functioning	86.6 (18.2)	82.2 (20.3)[c]	90.7 (15.0)	91.0 (15.8)	0.3
Daily activities	77.3 (25.8)[c]	78.4 (25.9)	76.3 (26.1)	86.1 (19.1)	0.5
Sexual functioning	84.6 (24.8)	87.9 (23.9)	81.3 (25.6)	91.7 (17.9)	0.4
Vitality	56.5 (21.8)[a,b]	56.6 (22.1)[b,d]	56.3 (22.0)[b,c]	70.1 (19.5)	0.7
Happiness	70.2 (20.0)	67.3 (21.4)	73.2 (18.3)	73.2 (18.9)	0.2
Aggressiveness	78.9 (22.8)[b,c]	76.2 (20.7)[c]	81.6 (24.7)	88.2 (15.5)	0.6
Depressive moods	70.8 (23.4)[a,b]	68.5 (23.4)[a]	73.0 (23.6)	81.9 (15.5)	0.7
CoL	n = 69	n = 34	n = 35	n = 274	
Autonomy development	9.0 (1.4)	8.8 (1.2)	9.2 (1.6)	9.4 (1.5)	0.3
Psychosexual development	7.2 (1.3)	6.8 (1.6)	7.5 (0.9)	7.2 (1.2)	0.0
Social development	20.25 (2.9)[d]	20.0 (2.9)[d]	20.6 (2.9)	21.2 (2.5)	0.4
Self-esteem	n = 63	n = 31	n = 32	n = 515	
Self-esteem	29.9 (4.7)[b,c]	29.0 (4.8)[b,c]	30.8 (4.4)[b]	32.1 (4.7)	0.5

Higher score represents a better HRQoL, CoL, and self-esteem. d, Effect size.

[a] *$P < 0.0001$ difference between CH patients and comparison group (based on univariate F tests according to ANOVA, TAAQoL scales by group and gender).*

[b] Univariate effects were found on gender ($P < 0.01$).

[c] $P < 0.005$ difference between CH patients and comparison group (based on univariate F tests according to ANOVA, TAAQoL scales by group and gender).

[d] $P < 0.01$ difference between CH patients and comparison group (based on univariate F tests according to ANOVA, TAAQoL scales by group and gender).

TABLE 4. Milestones of social development (CoL questionnaire) CH patients *vs.* comparison group

Social development	CH (n = 69)	Comparison (n = 297)
At least 1-yr membership in a sports club, primary school		
Yes	73.9[a]	86.8
No	26.1	13.2
No. of friends in first-third grade, primary school		
<4	40.6	27.9
≥4	59.4	72.10
No. of friends in fourth-sixth grade, primary school		
<4	36.2	25.3
≥4	63.8	74.7
Best friend, primary school		
Yes	77.9	74.1
No	22.1	25.9
Most of the time playing with….., primary school		
Friends	85.3	89.3
Brothers and/or sisters, parents, on your own	14.7	10.7
At least 1-yr membership in a sports club, secondary school		
Yes	55.9[b]	77.4
No	44.1	22.6
No. of friends, secondary school		
<4	36.2	25.3
≥4	63.8	74.7
Best friend, secondary school		
Yes	72.5	71.3
No	27.5	28.7
Belonging to a group of friends, secondary school		
Yes	70.6	82.7
No	29.4	17.3
Leisure time, mainly with ….., secondary school		
Friends	76.1	85.8
Brothers and/or sisters, parents, on your own	23.9	14.2
Going out to a bar or disco, secondary school		
Sometimes/often	75.4	86.2
Never	24.6	13.8
At least 1-yr membership in a sports club, after secondary school		
Yes	42.0	49.1
No	58.0	50.9

[a] $P < 0.001$ based on χ^2 test.

[b] $P < 0.01$ based on χ^2 test.

comparison group were found in the number of patients still living with their parents or in marital status. In addition, no significant difference was found with respect to current educational level and in patients receiving special education at a primary school compared with the comparison group (Table 5).

Self-esteem

CH patients in the total and severe CH group appeared to have a significantly lower self-esteem than the comparison group: total CH group, $F(1.572) = 5.224$, $P < 0.005$; and severe CH group, $F(1.542) = 8.513$, $P < 0.004$) (Table 3). These differences had moderate effect sizes (d = 0.5).

Within-group differences according to severity

There were no significant differences found between the severity groups for HRQoL, CoL, and self-esteem (Table 3).

Prevalence of young adults with CH at risk

Table 6 shows the percentages of young adults at risk for all impaired HRQoL, CoL, and self-esteem domains. χ^2 tests comparing the CH patients with healthy controls on HRQoL, CoL, and self-esteem showed significant differences for six scales of the TAAQoL. The total group of CH patients showed significantly higher percentages of patients at risk for HRQoL than the comparison group on five scales of the TAAQoL (cognitive functioning, social functioning, daily activities, vitality, and depressive moods), ranging from 41–68%. In the severe group, CH patients were considered at risk for problems on six scales of the TAAQoL (gross motor functioning, cognitive functioning, social functioning, aggressiveness, vitality, and depressive moods), ranging from 42–70%. In addition, CH patients in the moderate/mild CH group were only considered at risk on two scales of the TAAQoL (sleeping, cognitive functioning), ranging from 54–66%.

Discussion

To our knowledge, this is the first study describing the developmental and HRQOL consequences in early treated young adult

TABLE 5. Percentages and differences between CH group and comparison group with respect to living situation and employment status

	% CH (n = 69)	% Comparison (n = 297)
Living with their parents		
Yes	43.5	41.2
Marital status		
Married/living together	24.2	18.8
Single	75.8	81.2
Special education at primary school		
Yes	13.0	5.4
Educational level[a]		
Low	29.9	30.4
Middle	65.7	61.8
High	12.0	7.8
Educational level[b]		
Low	14.5	17.2
Middle	46.4	38.0
High	39.1	44.8

$P < 0.01$ based on χ^2 test. High, Higher vocational education, university; Low, primary education, technical and vocational training, lower and middle general secondary education; Middle, middle vocational education, higher general secondary education, preuniversity education.

[a] Highest level completed.

[b] Highest level completed/or ongoing study.

patients with CH using validated and reliable instruments. We have shown that having CH does negatively influence the HRQoL, social development, and self-esteem. However, the sociodemographical outcomes and their final educational level until now did not differ from that of the normal population.

This study shows that patients with CH born in 1981–1982 do not experience more problems with autonomy development and sexual functioning, and they have similar feelings of happiness as the healthy Dutch population controls. Despite these positive findings, CH has a negative impact on the daily life of the patients. They experienced more problems concerning cognitive 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. To add clinical meaning to these differences, we divided the young adults into two groups, one at risk for an impaired HRQoL, CoL, and self-esteem, and one not at risk. This division shows that young adults with CH, especially in patients with severe CH, are more often at risk for HRQoL impairment. The definition of young adults as being at risk was based on the value of the 25th percentile of all scales in the norm population. There is no gold standard for good or bad HRQoL, CoL, and self-esteem, however, this definition is considered to be a suitable way to differentiate between individuals with higher scale scores from individuals with lower scale scores (25).

The most salient result is that CH patients reported a considerable lower HRQol on the cognitive functioning scale of the TAAQoL, also presented in a high percentage of patients considered at risk. Cognitive functioning was assessed as the occurrence of problems with attention and memory, and if such a problem was indicated, the degree to which the patient is actually bothered by that problem was assessed subsequently. The lower scores on the cognitive function scale of the TAAQoL are in line with the results of neuropsychological studies, which showed that children and young adults with CH scored significantly poorer on overall attention and had more problems with memory than controls (26–29). Our results indicate that problems in cognitive functioning trouble most CH patients and hamper their daily life.

As expected, severe CH patients are more at risk for problems with gross motor functioning than patients with moderate/mild CH. This is consistent with our recent findings that the total CH

TABLE 6. Percentage of patients with CH at risk for HRQoL impairment

	Total CH	Severe CH	Moderate/mild CH	Comparison group
Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
TAAQoL	n = 68	n = 33	n = 35	n = 201
Gross motor functioning	32%	42%[b]	23%	25%
Cognitive functioning	68%[a]	70%[a]	66%[a]	25%
Sleeping	43%	31%	54%[b]	25%
Pain	46%	48%	20%	25%
Social functioning	46%[b]	58%[a]	34%	25%
Daily activities	41%	39%	43%	25%
Sexual functioning	34%	25%	40%	25%
Vitality	44%[b]	50%[b]	38%	25%
Happiness	29%	36%	15%	25%
Aggressiveness	47%[a]	57%[b]	38%	25%
Depressive moods	46%[b]	50%[a]	41%	25%
CoL	n = 69	n = 34	n = 35	n = 274
Autonomy development	39%	41%	37%	25%
Psychosexual development	26%	35%	17%	25%
Social development	30%	36%	25%	25%
Self-esteem	n = 69	n = 33	n = 35	515
Self-esteem	27%	36%	19%	25%

Twenty-fifth percentiles of healthy young adults are not exactly 25% due to distribution of scale scores. Percentiles approach 25th, ranging from 18th-31st percentile.

[a] $P < 0.0001$ χ^2 test in comparison with healthy children.

[b] $P < 0.004$ χ^2 test in comparison with healthy children.

group born in 1981/1982 had substantial motor problems (7). This is also in line with the findings on the items of the social development scale of the CoL questionnaire, which showed that CH patients reported a lower level of participation in sport clubs.

Although more significant differences between the severity group and the comparison group than the moderate/mild CH group compared with the healthy population were found, we did not find significant within-group differences on severity for CoL, HRQoL, or self-esteem. It may be considered that the existence of a chronic disease as such, regardless of its severity, influences functioning in daily life.

The negative consequences of CH on the HRQoL, social development, and self-esteem might also be explained by the fact of living with a chronic disease. CH affects the patient's daily life because of the daily T_4 administration, the need of regular T_4-dose adjustments, frequent T_4 and TSH measurements, consciousness of having a chronic disease, and sometimes the need of adjuvant medical care such as speech training and physiotherapy. It is also possible that parents of a child with CH were more protective, which resulted in less stimulation of social development. In addition, the cognitive and motor problems of CH patients may have affected their social life, self-esteem, and emotional functioning. From this study and our previous study (7), it is apparent that CH patients seem to be vulnerable in this area. Besides, one has to keep in mind that a suboptimal thyroid hormone state may affect well-being. Whereas the goal of long-term T_4 treatment is to maintain euthyroidism, this remains challenging because of the continuous need to adapt T_4 dose in a growing child and the need of treatment compliance. Recently, it has been shown that differences in free T_4 and TSH concentration, even within the reference range, may be a determinant of psychological well-being in treated hypothyroid patients (30).

The strength of our study is that all patients were treated by pediatricians who followed the national guidelines and that at psychological assessments, all patients had plasma TSH concentrations within the reference range.

There are some limitations in the present study that need to be mentioned. First, "course of life" encompasses more than the achievement of developmental milestones and encompasses more accomplishment during childhood than we have been able to assess with the questionnaire. It is the only (Dutch) questionnaire concerning this issue, and test-retest reliability has proved to be satisfactory (20). However, the internal consistency of the autonomy scale is small, probably because the items concern diverging aspects of autonomy. The disadvantage of using scales with low internal consistency is that detecting differences between groups is more difficult. Considering our findings, this did not apply. Second, CH patients described in this study differ from more recently diagnosed patients because the screening and treatment strategy has been changed over the past two decades (*e.g.* earlier detection, higher initial T_4 dose). Therefore, we need to be cautious in generalizing our results toward more recently diagnosed CH patients. In addition, it is important to investigate the HRQoL, CoL, social demographical outcomes, and self-esteem in more recent cohorts. Another limitation is the loss of subjects from the original cohort, which restricts the representativity of the current sample. Besides, we have no information about the socio-economic status, we clarified the etiology of both the excluded patients and the patients not willing to participate (Table 1). At last we should take notice of the use of different questionnaires of which norm data were acquired in different studies. This should be considered when comparing the data.

The findings of the study have implications for future research. It is important to study cognitive functioning in more detail, *e.g.* to determine attention and memory of CH patients. Intervention programs that improve memory and attention functioning might thereafter be offered to particular individuals.

A remarkable result in the present study was that CH patients were not different in educational level compared with controls. Most patients were 21 yr of age at 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 consider when testing adult patients who already fulfill a certain role in society.

Because CH patients appeared to be less vital and more depressed compared with the healthy Dutch population, it seems interesting to study the relation between CH, and anxiety and depression in more detail. From a developmental, psychological point of view, the fulfilling of age-specific developmental tasks in childhood is of great importance for adjustment in adult life (14, 31). For this reason it is important to direct future research on the predictors of a hampered social development to be able to detect the children and adolescents who are at risk at an early stage.

Communication about problems in clinical practice should be studied in more detail to get insight into whether problems are adequately assessed. Computer-scored individual measurement of HRQoL, to inform the physician about the patient's HRQoL (32, 33), should be considered for clinical practice. The computer output, usually a graphical summary of HRQoL outcomes, assists the physician to focus at the HRQoL domains that correspond with the patient's needs. Using HRQoL measurement can facilitate patient-physician communication and can identify patients with the greatest needs so that a focused action, *e.g.* referring to other health care providers, can be performed.

In summary, we conclude that young adults with CH reported a lower HRQoL and had a lower self-esteem compared with healthy peers. CH patients also had a delayed social development. Therefore, it is important for parents and clinicians to encourage children with CH to continue peer-related activities as much as possible to stimulate their social performance and, with that, their self-esteem. An awareness about patients' HRQoL and possible gaps in the CoL can be useful in clinical practice because it enables health care providers to select and adjust coaching programs to aim at a most favorable CoL in these patients, throughout their development. Most of all, our findings add to the evidence for cognitive problems in relation to CH. Health care physicians should be observant for cognitive problems and refer for more detailed psychosocial assessment if necessary.

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References

1. **Bernal J, Guadano-Ferraz A, Morte B** 2003 Perspectives in the study of thyroid hormone action on brain development and function. Thyroid 13:1005–1012
2. **Heyerdahl S** 2001 Longterm outcome in children with congenital hypothyroidism. Acta Paediatr 90:1220–1222
3. **Rovet JF, Ehrlich RM, Sorbara DL** 1992 Neurodevelopment in infants and preschool children with congenital hypothyroidism: etiological and treatment factors affecting outcome. J Pediatr Psychol 17:187–213
4. **Tillotson SL, Fuggle PW, Smith I, Ades AE, Grant DB** 1994 Relation between biochemical severity and intelligence in early treated congenital hypothyroidism: a threshold effect. BMJ 309:440–445
5. **Bargagna S, Canepa G, Costagli, Dinetti D, Marcheschi M, Millepiedi S, Montanelli L, Pinchera A, Chiovato L** 2000 Neuropsychological follow-up in early-treated congenital hypothyroidism: a problem-oriented approach. Thyroid 10:243–249
6. **Derksen-Lubsen G, Verkerk PH** 1996 Neuropsychologic development in early treated congenital hypothyroidism: analysis of literature data. Pediatr Res 39:561–566
7. **Kempers MJ, van der Sluijs Veer L, Nijhuis-van der Sanden MW, Kooistra L, Wiedijk BM, Faber I, Last BF, de Vijlder JJ, Grootenhuis MA, Vulsma T** 2006 Intellectual and motor development of young adults with congenital hypothyroidism diagnosed by neonatal screening. J Clin Endocrinol Metab 91:418–424
8. **Kooistra L, Laane C, Vulsma T, Schellekens JM, van der Meere JJ, Kalverboer AF** 1994 Motor and cognitive development in children with congenital hypothyroidism: a long-term evaluation of the effects of neonatal treatment. J Pediatr 124:903–909
9. **Rovet JF** 1999 Long-term neuropsychological sequelae of early-treated congenital hypothyroidism: effects in adolescence. Acta Paediatr Suppl 432:88–95
10. **Salerno M, Militerni R, Di Maio S, Bravaccio C, Gasparini N, Tenore A** 1999 Intellectual outcome at 12 years of age in congenital hypothyroidism. Eur J Endocrinol 141:105–110
11. **Northam EA** 2004 Neuropsychological and psychosocial correlates of endocrine and metabolic disorders–a review. J Pediatr Endocrinol Metab 17:5–15
12. **Stam H, Hartman EE, Deurloo JA, Groothoff J, Grootenhuis MA** 2006 Young adult patients with a history of pediatric disease: impact on course of life and transition into adulthood. J Adolesc Health 39:4–13
13. **de Haan RJ** 2002 Measuring quality of life after stroke using the SF-36. Stroke 33:1176–1177
14. **Garber J** 1984 Classification of childhood psychopathology: a developmental perspective. Child Dev 55:30–48
15. **Coopersmith S** 1981 The antecedents of self-esteem. Palo Alto, CA: Consulting Psychologists Press
16. **Shavelson RJ, Bolus R** 1982 The interplay of theory and methods. J Educ Psychol 74:3–17
17. **Stanwyck DJ** 1983 Self-esteem through the life span. Fam Community Health 6:11–28
18. **Vulsma T** 1991 Etiology and pathogenesis of congenital hypothyroidism. Evaluation and examination of patients detected by neonatal screening in The Netherlands. University of Amsterdam, Amsterdam, The Netherlands (Thesis)
19. **Bruil J, Fekkes M, Vogels T, Verrips GHW** 2004 TAAQOL-manual. Leiden Center for Child Health and Pediatrics-TNO Prevention and Health. Leiden, The Netherlands
20. **Grootenhuis MA, Stam H, Destrée-Vonk A, Heijmans HSA, Last BF** 2003 Levensloop Vragenlijst voor Jong-Volwassenen (The Course of life Questionnaire of young adults). Gedrag & Gezondheid 31:336–350
21. **Stam H, Grootenhuis MA, Last BF** 2005 The course of life of survivors of childhood cancer. Psychooncology 14:227–238
22. **Rosenberg M** 1965 Society and the adolescent self-image. Princeton, NJ: Princeton University Press
23. **Langeveld NE, Grootenhuis MA, Voute PA, de Haan RJ, van den Bos C** 2004 Quality of life, self-esteem and worries in young adult survivors of childhood cancer. Psychooncology 13:867–881
24. **Cohen J** 1977 Statistical power analysis for the behavioral sciences. New York: Academic Press
25. **Rose MS, Koshman ML, Spreng S, Sheldon R** 1999 Statistical issues encountered in the comparison of health-related quality of life in diseased patients to published general population norms: problems and solutions. J Clin Epidemiol 52:405–412
26. **Oerbeck B, Sundet K, Kase BF, Heyerdahl S** 2005 Congenital hypothyroidism: no adverse effects of high dose thyroxine treatment on adult memory, attention, and behaviour. Arch Dis Child 90:132–137
27. **Rovet J, Daneman D** 2003 Congenital hypothyroidism: a review of current diagnostic and treatment practices in relation to neuropsychologic outcome. Paediatr Drugs 5:141–149
28. **Rovet JF, Hepworth S** 2001 Attention problems in adolescents with congenital hypothyroidism: a multicomponential analysis. J Int Neuropsychol Soc 7:734–744
29. **Song SI, Daneman D, Rovet J** 2001 The influence of etiology and treatment factors on intellectual outcome in congenital hypothyroidism. J Dev Behav Pediatr 22:376–384
30. **Saravanan P, Visser TJ, Dayan CM** 2006 Psychological well-being correlates with free thyroxine but not free 3,5,3′-triiodothyronine levels in patients on thyroid hormone replacement. J Clin Endocrinol Metab 91:3389–3393
31. **Lewis M, Miller SM** 1990 Handbook of developmental psychopathology. New York: Plenum Press
32. **Varni JW, Burwinkle TM, Lane MM** 2005 Health-related quality of life measurement in pediatric clinical practice: an appraisal and precept for future research and application. Health Qual Life Outcomes 3:34
33. **Velikova G, Booth L, Smith AB, Brown PM, Lynch P, Brown JM, Selby PJ** 2004 Measuring quality of life in routine oncology practice improves communication and patient well-being: a randomized controlled trial. J Clin Oncol 22:714–724