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ORIGINAL ARTICLE

Higher initial levothyroxine doses and very early treatment start may lead to better cognitive outcomes in children with congenital hypothyroidism

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Abstract

Aim: This study aimed to assess the cognitive development of individuals with congenital hypothyroidism.

Methods: Using hospital records, we identified 180 patients with congenital hypothyroidism born between 1980 and 2018 in Turku and Kuopio University Hospital catchment areas. Cognitive development was evaluated in 22 adults (7 males and 15 females) and 20 children (8 males and 12 females) using age-specific Wechsler Intelligence Scales. Full-scale IQ (FSIQ) and the four indices were compared to standardisation samples. Simple linear regression was used to test whether treatment-related variables predicted FSIQ.

Results: FSIQ and its four indices differed significantly from the standardisation sample in adults with congenital hypothyroidism (FSIQ 87.64, SD 13.70, $p < 0.001$) but not in children (FSIQ 97.90, SD 15.12). Adults had received a lower initial levothyroxine dose than children (8.1 mg/kg, 95% CI 7.2–9.0 vs. 10.2 mg/kg 9.7–10.7, $p < 0.001$), and their treatment was initiated later (4.8 days, 95% CI 4.0–5.6 vs. 3.6 days, 2.9–4.2, $p = 0.018$).

Conclusion: Adults with congenital hypothyroidism had a significantly lower FSIQ compared to the population standard, while children's FSIQ did not differ. Our findings suggest that a higher initial levothyroxine dose together with very early treatment start may lead to better cognitive outcomes.

KEYWORDS
cognitive development, congenital hypothyroidism, levothyroxine treatment

Abbreviations: FSIQ, full-scale intelligence quotient; fT4, free thyroxine; ICD, International Classification of Diseases; IQ, intelligence quotient; LT4, levothyroxine; T4, thyroxine; TSH, thyroid stimulating hormone; WAIS-IV, Wechsler Adult Intelligence Scale, Fourth Edition; WISC-IV, Wechsler Intelligence Scale for Children, Fourth Edition.

Emmi Danner and Laura Niuro shared first authorship.

1 | INTRODUCTION

Congenital hypothyroidism may lead to irreversible mental and growth retardation if not treated appropriately. Newborn screening enables a prompt start of levothyroxine (LT4) treatment preventing this. The recommended initial dose of LT4 has increased over the decades, due to increasing knowledge about the advantages of a higher dose regimen. Nonetheless, it appears that congenital hypothyroidism may still influence neurodevelopment, regardless of early treatment. Indeed, the current consensus guidelines by The European Reference Network on rare endocrine conditions suggest that the psychomotor development and school progression of children with congenital hypothyroidism should be periodically evaluated.[1] A special focus should be on speech delay, attention and memory problems. However, formal psychological testing is not suggested for all affected children.

The recommended LT4 starting dose is currently 10–15 μg/kg/day. At the start of the screening era in the 1980s the respective dose was 6–8 μg/kg/day, that is only close to half of the current one. The higher LT4 dose seems to be more beneficial for full-scale IQ,[2–4] although contrasting findings have also been reported.[5] Additionally, this higher dose regimen has been shown to close the IQ gap between the severe and moderate forms of congenital hypothyroidism.[6,7] This is important as the severity of the disease has been shown to impact neurodevelopment with more severe form leading to poorer performance in neurocognitive tests.[8–13] Severity was described as markedly low plasma (free) thyroxine values pretreatment and/or low area-of-knee epiphyses. In addition to the initial dose, thyroid function levels during treatment have also been shown to be associated with neurodevelopment.[7,14–16]

However, the higher dose does raise a question of possible overtreatment and its effects on neurodevelopment. Some studies have shown that overtreatment led to lower verbal skills,[17] attention deficit hyperactivity disorder[18] and lower cognitive outcome,[19] whereas others showed that overtreatment might even advance cognitive development.[14]

In addition to full-scale IQ, congenital hypothyroidism seems to influence some indices more than others. These include verbal,[12,16,20,21] performance[12] and motor skills.[8,11–13,16] These difficulties have been shown to largely persist with aging,[11,22] yet verbal skills have been shown to improve with age.[23]

We have previously shown that children with congenital hypothyroidism, irrespective of their initial LT4 dose, grow slightly slower during the first two years of life than healthy children.[24] Moreover, thyroid stimulating hormone (TSH) values normalise significantly quicker if a higher LT4 starting dose is used.[24] However, in other studies, there have been differing findings on the benefits and possible adverse effects of this dose increase on the neurodevelopment of children. Furthermore, it is still somewhat unclear whether congenital hypothyroidism itself, although treated in time and with appropriate LT4 supplementation, influences neurodevelopment. Still, in general, formal psychological testing is not indicated as most patients develop normally.

Key notes

- This study aimed to evaluate how the secular changes in treatment affect cognitive development in congenital hypothyroidism in the Finnish setting, with very early initiation of levothyroxine.
- Adults with congenital hypothyroidism had significantly lower full-scale IQ than the population standard, while the full-scale IQ of children was comparable to the population.
- Children had received a higher initial levothyroxine dose, and their treatment was initiated earlier, which may improve cognitive outcomes.

Finland differs in the screening protocol of congenital hypothyroidism from other Western countries as the first samples are taken from the cord blood opposed to the heel prick at a few days of age. This enables the initiation of LT4 treatment at already 3 to 5 days of age making our cohort unique.

The objective of this study was to investigate the cognitive development of patients with congenital hypothyroidism born in Turku and Kuopio University Hospital catchment areas between the years 1980–2015. We aimed to look at factors possibly affecting the neurodevelopment, including the initial LT4 dose, age at the onset of treatment, the initial and current free thyroxine (fT4) and TSH concentrations, the median thyroid hormone levels during the first two years of age, gender and the aetiology of congenital hypothyroidism.

2 | METHODS

In Finland, nationwide screening for congenital hypothyroidism with complete coverage was implemented in 1980.[25] Finland stands out among Western countries by using cord blood for screening instead of dry blood spot testing. This enables earlier confirmatory testing and initiation of levothyroxine treatment, with the mean age at the start of treatment being 4 days.[24] If the TSH value exceeds the threshold, a confirmatory test (TSH and free thyroxine, fT4) is performed after 72 h of age. The cut-off limits have remained unchanged or have been lowered, depending on the methods used in different laboratories and central hospitals' clinical practice. The cut-off limit for the screening test of primary congenital hypothyroidism has ranged between TSH 25–40 mU/L for cord blood serum sample at birth and between TSH 20–40 mU/L for the confirmatory plasma sample at the mean age of 4 days. We have described in detail the variations in laboratory methods and cut-off limits in the earlier report from our study group.[24]

2.1 | Participants

Patients with congenital hypothyroidism were identified through diagnosis-based searches in the patient records of Kuopio and Turku University Hospitals' catchment areas, using the following International Classification of Diseases (ICD), eighth, ninth and tenth revision codes: ICD-8 code 243, ICD-9 codes 243, 2430A, 2461A, 2534C and ICD-10 codes E03.1, E03.0. The inclusion criteria involved abnormal screening and confirmatory test results. Patients with transient congenital hypothyroidism were excluded. The fulfilment of the inclusion criteria was manually verified from the medical records by two of the authors (ED, LN). A total of 180 patients born between 1980 and 2018 were identified. Of these patients, 168 were over the age of 5 years and were invited to participate in a psychological assessment. 44 patients enrolled in the study.

In borderline cases where screening results were unclear, patients were included in the study if they were diagnosed with primary congenital hypothyroidism by a paediatric endocrinologist or a paediatrician, and LT4 treatment was initiated before 14 days of age. Two adult patients had their treatment temporarily paused for 1–2 months during infancy due to uncertain diagnosis. These patients were excluded from all analysis.

2.2 | Procedure

Participants in the psychological assessment were examined by one of the three psychology master's students, who were trained to perform and interpret used examinations. The test protocols were meticulously followed. Except for name, age and contact information, the examiners received no information about the patients in advance. The assessments were conducted in one session with breaks, if needed.

The participants were divided into two groups according to age. The cut-off age was 16 years 6 months and participants older than that are referred as adults and younger as children. The cognitive capacity of the adults ($n = 22$) was studied with the Finnish version of the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV). In children ($n = 20$), cognitive capacity was studied with the Finnish version of the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV). The abovementioned tests have been standardised using a random sample of the Finnish population (670 persons aged from 16 to 92 years for WAIS-IV and 910 people aged from 5 years 4 months to 16 years 7 months for WISC-IV).

The Full-Scale IQ (FSIQ) of WAIS-IV and WISC-IV consists of four indices: verbal comprehension, perceptual reasoning, working memory and processing speed. The mean of the indices in both tests is 100, with a standard deviation (SD) of 15. These four indices consist altogether of 10 core subtests and five supplemental subtests, each with a mean of 10 and a SD of 3. All 10 core subtests were conducted with each participant. In two cases, one core subtest was replaced with an equal supplemental subtest.

Information on the aetiology, mother's age, birth data and thyroid-stimulating hormone (TSH) and free thyroxine (fT4) or thyroxine hormone (T4) concentrations at birth, at diagnosis and during the first two years of life were collected from patient records. Current TSH and fT4 concentrations were examined within 2 months of the psychological assessment.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Northern Savo Hospital District (permission number 346/2018).

2.3 | Statistical methods

The mean full-scale IQ of patients by birth year was calculated and a one-sample t-test was used to calculate 95% confidence intervals. An independent samples t-test was used to compare the performance between cases and the standardisation sample of the test as well as to assess differences in characteristics between participants and non-participants, and between WISC and WAIS groups. The Mann–Whitney U test was applied for comparing the median TSH values of the first two years due to their non-normally distributed nature. In addition, a one-way analysis of variance was conducted to compare the mean FSIQ among patients with different aetiologies of congenital hypothyroidism.

Simple linear regression analyses were performed to investigate whether clinical determinants significantly predicted FSIQ. These determinants included gender, age at the onset of treatment and initial LT4 dose. The analyses also considered initial and current fT4 and TSH concentrations, median TSH and fT4 concentrations during the first two years of life and the age at examination.

In a few cases, initial and diagnostic TSH values were reported as being above the laboratory detection limit or simply noted as alerts. These values were excluded from the statistical analyses and included three diagnostic values in children, four initial values in adults and three diagnostic values in adults. All laboratory results of each subject, after confirmatory samples up to 24 months of age, were considered, and a median was calculated for each subject for both TSH and fT4. If the confirmatory cessation of LT4 treatment occurred within this timeframe, TSH and fT4 values during that period were excluded. When calculating the median TSH of the first two years, the values below the laboratory detection limit were modified to be the lower detection limit value.

The data were analysed using SPSS for Windows, version 27 (IBM Corp, New York, USA). A p value <0.05 was considered statistically significant.

3 | RESULTS

The neuropsychological assessment was performed in 22 patients using the WAIS-IV and 20 patients using the WISC-IV. Patients in the WAIS group were born between 1980 and 2004 with a median age of 24 (range 17–41) years. Patients in the WISC group were born

between 2005 and 2015 and their median age was 11.5 years (range: 6 to 16 years). Characteristics of the study populations and comparison with non-participants are presented in Table 1.

Characteristics of the two study groups, adults and children, differed from each other in terms of the initial LT4 dose (8.1 mg/kg, 95% CI 7.2–9.0 vs. 10.2 mg/kg, 9.7–10.7, $p<0.001$) and the age at onset of treatment (4.8 days, 4.0–5.6, vs. 3.6 days, 2.9–4.2, $p=0.018$) as presented in Table 1. Furthermore, the median TSH concentration during the first two years of life was significantly lower in children than in adults.

The mean full-scale IQ of patients with congenital hypothyroidism, categorised by their year of birth, is presented in Figure 1. This figure reveals a trend where the mean full-scale IQ of patients approached the population average in later years. However, this trend was not statistically significant. The cut-off point between adults and children was in the year 2005.

The results of the intellectual and neuropsychological assessments are presented in Table 2. In the adults the mean full-scale IQ was 87.64 (SD 13.70), which differs significantly from the standardisation sample of the test ($p<0.001$). In the WISC group (children), the mean full-scale IQ was 97.90 (SD 15.12).

Compared with the population standard, the adult patients had a significantly lower mean score in all four indices: verbal comprehension (mean 92.09, $p=0.016$), perceptual reasoning (mean 92.05, $p=0.014$), working memory (mean 89.55, $p=0.001$) and processing speed (mean 87.91, $p<0.001$). In the group of children, index scores did not differ from the standardisation sample (Table 2).

To analyse the factors affecting IQ levels, we categorised patients into subgroups of normal (≥85) and low (<85, i.e. 1 SD below the median) full-scale IQ scores. Among adult patients, 41% (9/22) were in the low IQ subgroup, whereas in children, the respective proportion was 15% (3/20). The age at examination, initial or current TSH and fT4 concentrations, or initial dosage of LT4 did not differ between the subgroups. Among children, the LT4 medication was started at a significantly older age in the low IQ subgroup (mean 5.7 days, 95% CI 1.9–9.5) compared to the normal IQ subgroup (mean 3.2 days, 2.6–3.7, $p=0.003$). In adults, the age at the onset of medication was similar in both groups (4.7 vs. 4.9 days, respectively).

Simple linear regression analysis was used to test whether the age at the onset of medication, initial LT4 dosage, initial or current fT4 or TSH concentration or median TSH and fT4 levels during the first two years of life predicted FSIQ. The results indicated that the age at the onset of LT4 treatment significantly predicted FSIQ in children ($R^2=0.30$, F (1, 18) $=7.779$, $p=0.012$, $\beta=-0.55$), but not in adults ($R^2=0.06$, F (1, 20) $=1.272$, $p=0.273$, $\beta=0.24$). Furthermore, none of the other factors significantly predicted full-scale IQ.

In children, male patients had significantly lower full-scale IQ compared to females (WISC-IV mean FSIQ: 88.6, 95% CI 73.9–103.4 vs. 104.1, 98.0–110.2, $p=0.02$). In adults, the difference in FSIQ between males and females was not statistically significant (WAIS-IV mean FSIQ: 81.9, 68.3–95.4 vs. 90.3, 83.2–97.4, $p=0.18$).

Imaging of the thyroid was performed for 20 patients (47.6%). There were no significant differences in full-scale IQ when comparing the nine patients with thyroid aplasia (FSIQ 93.7, 95% CI 85.4–101.9), the seven patients with ectopy or hypoplasia (FSIQ 83.1, 64.2–102.1) or the four patients with normal thyroid gland in situ (FSIQ 87.0, 56.1–117.9, $p=0.451$).

4 | DISCUSSION

This study showed that adults with congenital hypothyroidism had a lower FSIQ and lower performance in all the four indices, verbal comprehension, perceptual reasoning, working memory and processing speed, when compared to the standard population. In contrast, the children with congenital hypothyroidism did not differ from the standard in FSIQ or any of these indices. The two groups differed from each other in the initial LT4 dose, which was higher in children and the age at onset of treatment which was earlier in children. Also, the median TSH of the first two years was lower in children.

A higher initial LT4 dose has been previously associated with normal intellectual development[7] and actually shown to lead to better intellectual outcome when compared to a lower dose.[2–4] Still, opposing findings have also been made.[26] Our results support the benefits of a higher initial LT4 dose on cognitive development as the children in our study did not differ from the population standard, whereas the adults, treated with a lower initial LT4 dose, did. As a whole, children's overall cognitive performance was closer to the population average than that of adults (Figure 1). Additionally, we showed that as many as 41% of adults had a low FSIQ (<85, < -1SD) opposed to only 15% in children, which further supports the benefits of a higher initial dose. We cannot, however, straight forwardly combine or compare the adult and children groups to each other due to different cognitive tests, the WAIS-IV in adults and the WISC-IV in children. Therefore, they were compared to the test appropriate population standard.

For the indices, initial LT4 dose has been shown to predict verbal IQ.[16] Similarly, Bongers-Schokking et al. showed that verbal performance was lower in patients with a lower initial LT4 dose and an older age at the start of LT4 treatment.[14] In contrast, another study reported that the higher initial LT4 dose did not lead to a better performance in verbal or performance IQ.[26] Additionally, congenital hypothyroidism itself has been shown to lead to a lower processing speed index.[27] In our study, the children did not differ from the population-standard in any of the indices, including processing speed or verbal comprehension, whereas the adults did. Therefore, our results support the use of a higher LT4 dose.

Our study found no association between the aetiology of congenital hypothyroidism and cognitive development, supporting previous findings.[26] Contrasting findings have previously been made where athyreosis and/or dyshormonogenesis have been associated with poorer outcome.[3,28] However, the availability of imaging data was scarce in our study population and this aspect should be studied further.

Additionally, the severity of hypothyroidism, judged from the diagnostic TSH and fT4 levels, did not affect the patients' intellectual

TABLE 1 Characteristics of the study populations.

	WAIS-IV group ($n=22$)	Non-participants born at the same period ($n=73$)	WISC-IV group ($n=20$)	Non-participants born at the same period ($n=51$)
Sex (male/female) (*n*)	7/15	30/43	8/12	18/33
Born from a multiple Pregnancy (*n*)	0	2	0	0
Parity (birth order), mean (95% CI)	1.9 (1.4–2.3)	2.2 (1.9–2.5)	1.9 (1.5–2.4)	1.9 (1.5–2.4)
Mother's age at birth, Mean (years) (95% CI)	28.6 (26.3–30.9)	28.7 (27.3–30.1)	30.8 (27.0–34.5)	29.2 (27.6–30.8)
Duration of pregnancy, mean (days from due date) (95% CI)	4.1 (−0.5–8.7)	−1.2 (−3.8–1.4)	3.6 (−2.4–9.6)	2.2 (−0.9–5.3)
Birth weight, mean (SDS) (95% CI)	−0.05 (−0.6–0.5)	0.0 (−0.2–0.3)	−0.1 (−0.6–0.4)	0.1 (−0.3–0.4)
Apgar 1 min/5 min, mean (95% CI)	7.4/8.2 (6.1–8.7/7.3–9.2)	8.4/8.6 (8.1–8.7/8.3–8.9)	8.6/8.9 (8.1–9.0/8.6–9.1)	8.0/8.4 (7.5–8.6/7.9–8.9)
TSH concentration at the birth, mean (mU/L) (95% CI)	294 (214–375)	340 (286–393)	279 (197–361)	265 (214–315)
TSH concentration at the diagnosis, mean (mU/L) (95% CI)	337 (217–457)	361 (302–421)	281 (162–399)	235 (170–300)
fT4 concentration at the diagnosis, mean (pmol/L) (95% CI)	8.5[a] (5.8–11.1)	11.8[b] (6.3–17.2)	11.6 (8.8–14.3)	12.9 (10.5–15.3)
T4 concentration at the diagnosis, mean (nmol/L) (95 %CI)	71.0[c] (34.2–108)	48.0[d] (34.8–61)	N/A	N/A
Age at the onset of treatment, mean (days) (95% CI)	**4.8*** (4.0–5.6)	4.4 (4.0–4.9)	**3.6*** (2.9–4.2)	3.7 (3.2–4.3)
Initial dosing of levothyroxine, mean (mg/kg) (95% CI)	**8.1**** (7.2–9.0)	7.8 (7.4–8.1)	**10.2**** (9.7–10.7)	10.2 (9.6–10.9)
Median TSH concentration during the first two years of life, Median (mU/l) (IQR)	**2.3***** (0.4–6.3)	1.7 (0.3–5.8)	**0.3***** (0.03–1.5)	0.4 (0.2–1.3)
Median fT4 concentration during the first two years of life, Mean (pmol/L) (95% CI)	22.5[e] (21.0–24.1)	21.3[f] (20.5–22.0)	24.2 (22.8–25.5)	22.9 (22.2–23.7)
Age at the study, mean (years) (95 %CI)	**26.7****** (23.1–29.9)	25.8 (24.3–27.2)	**11.4****** (9.9–12.9)	10.8 (9.9–11.6)
TSH concentration at the study[g], mean (mU/L) (95% CI)	3.1 (1.8–4.4)	N/A	3.3 (2.0–4.5)	N/A
fT4 concentration at the study[g], mean (pmol/L) (95% CI)	20.7 (18.9–22.5)	N/A	20.3 (19.2–21.4)	N/A

Note: There are no significant differences ($p<0.05$) between participants and non-participants. Significant differences between WAIS-IV group and WISC-IV group are marked in bold.

Abbreviations: CI, confidence interval; fT4, free thyroxine; IQR, interquartile range, 25th and 75th percentile; T4, thyroxine; TSH, thyroid stimulating hormone.

[a] $n=14$.

[b] $n=43$.

[c] $n=8$.

[d] $n=30$.

[e] $n=17$.

[f] $n=61$.

[g] Within 2 months of the examination.

*$p=0.018$. **$p<0.001$. ***$p=0.021$. ****$p<0.001$.

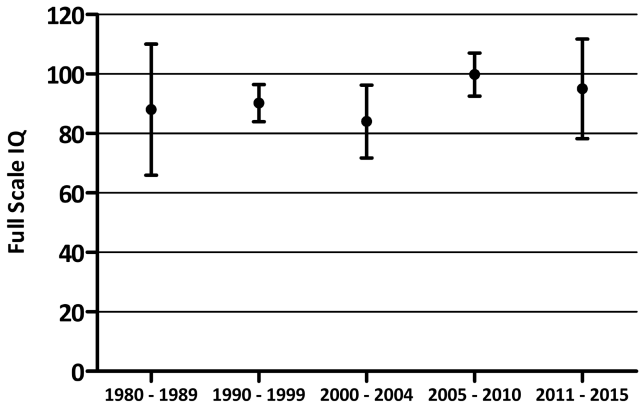

FIGURE 1 The mean full-scale IQ of patients with congenital hypothyroidism by year of birth with 95% confidence intervals. Number of studied patients: 1980–1989 $n=6$, 1990–1999 $n=9$, 2000–2004 $n=7$, 2005–2010 $n=12$, 2011–2015 $n=8$. Cognitive capacity of patients born between 1980 and 2004 was assessed using the Finnish version of the Wechsler Adult Intelligence Scale, Fourth Edition, while the Finnish version of the Wechsler Intelligence Scale for Children was used for younger patients.

outcome. In earlier reports patients with more severe form of the disease have been shown to do more poorly in FSIQ[8,13,29] as well as in verbal and performance indices.[11,12] Tillotson et al. have even found a threshold effect in the severity of the disease: children with diagnostic thyroxine values below 42.8 nmol/L had lower IQ than those with higher values and controls.[9] On the other hand, a higher LT4 dose regimen has been shown to narrow or even close this cognitive development gap between the severe and less severe forms of congenital hypothyroidism.[2,6,17,30] In our study, the adults and children had similar mean initial thyroid hormone values. Thus, the difference between the adults' and children's cognitive performance compared to the standard population cannot be explained by the severity of the disease.

In the current study, psychological tests were performed once for each subject. It has been shown before that there is no significant decline in cognitive development during childhood[22] or from childhood to adulthood[11] in patients with congenital hypothyroidism. Furthermore, other studies have shown that especially verbal skills might even improve with age.[23] We could, hence, anticipate that our children's group would maintain their cognitive performance also at an older age, especially because children in our study had skills comparable to the standards in all, including verbal, indices.

We found that the age at onset of LT4 treatment predicted FSIQ in children. Indeed, the children with a low FSIQ were significantly older at the start of LT4 treatment than the ones with a normal FSIQ. Such a difference was not observed in the adults. Additionally, in our study the adults and children differed from each other in the age at onset of treatment. All our study subjects had LT4 treatment started promptly and at a younger age than in studies performed in other countries and much earlier than the oldest recommended age of 2 weeks.[1] This is due to unique umbilical cord blood screening of congenital hypothyroidism in Finland which allows the confirmation of the diagnosis at only a few days of age enabling very early start of LT4 treatment. Other studies have a broader age range and a higher mean age at the start of treatment. Before screening, a benefit in intellectual development was evident if LT4 treatment was started before the age of 3 months.[31] Boileau et al. considered 21 days of age at the start of LT4 treatment to be a threshold for global IQ[32] and Bulus et al. showed better results when treatment was started before 15 days of age.[33] On the other hand, some studies have not found a connection in the cognitive development and age at start of treatment.[12,25] Our results support a fast start of treatment as the results were better with a prompt start of treatment even in the children's group, all of whom were started with LT4 at the latest at 7 days of age and who were treated with a higher initial LT4 dose. Still, these differences in the starting age were subtle and only a matter of days. However, our results suggest that every single day might be critical in terms of the turnaround time from sample to result and from result to the start of treatment. Further investigation is warranted into the neurodevelopmental outcomes resulting from initiating treatment earlier than is currently recommended, particularly in larger cohorts and population-based studies.

The timing of thyroid hormone insufficiency affects neurodevelopment in different ways.[34,35] Children with congenital hypothyroidism are mostly protected by the maternal thyroid hormone supply during pregnancy, although especially athyreosis has been shown to lead to a lower IQ, especially on the performance scale.[34] Thyroid hormone deficiency occurring after birth affects mostly language and memory skills.[35] Thus, the normalisation of thyroid hormone levels can be expected to influence neurodevelopment and, indeed, previous studies have shown that thyroxine levels during the first years[15] as well as the normalisation of thyroid function levels[28,36] are related to intellectual outcome. Additionally, in some studies subnormal TSH has been shown to correlate with poorer cognitive outcome,[17] although there are also contrasting findings.[14] The median thyroid hormone levels during the first two years of life did not predict FSIQ in our study. However, our study's children had significantly lower median TSH during the two years of age compared to the adults. Indeed, the first two years' median TSH was under the reference range in children, whereas it was within the reference range in adults. The first two years' median fT4 did not differ significantly between the groups and was within the reference range in both groups. Hence, the subnormal TSH did not lead to a supranormal fT4. In addition, the children did better compared to standard than adults.

Male patients had a significantly lower FSIQ compared to females in the children's group and also lower FSIQ in the adults, although this was not significant. The gender difference in patients with congenital hypothyroidism has been shown before in mental development, although in markedly younger children of 2 years of age.[15] Interestingly, such a gender difference was recently also observed in a Finnish study of 9 year old children whose mothers had had gestational diabetes.[37] However, our cohort size was quite small

TABLE 2 Neurocognitive performance of patients with congenital hypothyroidism compared to the standardisation sample.

Adults: WAIS-IV ($n=22$)	Mean score (95% CI)	SD	mean difference	p value	Children: WISC-IV (n = 20)	mean score (95% CI)	SD	mean difference	p value
Full-scale IQ	**87.64 (81.56–93.71)**	**13.70**	**−12.36**	**<0.001**	*Full-scale IQ*	97.90 (90.83–104.97)	15.12		
Verbal comprehension index	**92.09 (84.08–100.10)**	**18.06**	**−7.91**	**0.016**	*Verbal comprehension index*	100.70 (95.92–105.48)	10.20		
Similarities	9.45 (7.91–11.00)	3.49			*Similarities*	9.70 (8.74–10.66)	2.06		
Vocabulary	9.32 (7.69–10.95)	3.68			*Vocabulary*	10.35 (9.15–11.55)	2.56		
Information	**7.27 (5.79–8.75)**	**3.34**	**−2.73**	**<0.001**	*Comprehension*	10.30 (9.04–11.56)	2.70		
Perceptual reasoning index	**92.05 (86.20–97.89)**	**13.19**	**−7.95**	**0.014**	*Perceptual reasoning index*	99.00 (91.45–106.55)	16.14		
Block design	8.86 (7.44–10.29)	3.21			*Block design*	9.70 (8.49–10.91)	2.58		
Visual puzzles	**8.09 (6.67–9.51)**	**3.21**	**−1.91**	**0.004**	*Picture concepts*	10.20 (8.46–11.94)	3.72		
Matrix reasoning	9.18 (8.16–10.20)	2.30			*Matrix reasoning*	9.60 (8.40–10.80)	2.56		
Working memory index	**89.55 (82.46–96.64)**	**16.00**	**−10.45**	**0.001**	*Working memory index*	99.10 (91.85–106.35)	15.49		
Digit span	**8.32 (6.89–9.75)**	**3.23**	**−1.68**	**0.01**	*Digit span*	9.75 (8.57–10.93)	2.53		
Arithmetic	**8.09 (6.79–9.39)**	**2.93**	**−1.91**	**0.003**	*Letter-number sequencing*	10.00 (8.53–11.47)	3.06		
Processing speed index	**87.91 (81.85–93.97)**	**13.67**	**−12.09**	**<0.001**	*Processing speed index*	95.80 (89.08–102.52)	14.35		
Coding	**8.36 (7.10–9.63)**	**2.85**	**−1.64**	**0.012**	*Coding*	8.95 (7.53–10.37)	3.03		
Symbol search	**7.05 (5.87–8.23)**	**2.60**	**−2.95**	**<0.001**	*Symbol search*	9.65 (8.48–10.82)	2.50		

Note: Only significant differences compared to the normative sample are shown. Significant differences ($p<0.05$) are bolded.

Abbreviations: CI, confidence interval, SD = standard deviation, WAIS-IV = Wechsler Adult Intelligence Scale, Fourth Edition, WISC-IV = Wechsler Intelligence Scale for Children.

when divided according to gender limiting the significance of this result. The possible gender difference especially in patients treated with the now recommended higher LT4 initial dose should still be investigated further with larger sample size.

The limitations included the small number of participants. Only part of the subjects in our cohort attended the cognitive and psychological tests which might lead to selection bias. They were, however, comparable to the non-participants in the tested variables as shown in Table 1. To maximise the participation in the study, the whole cohort was initially contacted by postal service mail. If no response was achieved, the patients were contacted twice again at 4- and 8-week intervals. An additional limitation is that we do not know the socioeconomic status of the subjects, which has been shown to significantly influence cognitive development.[38–40] Neither in this test setting did we have access to the school performance, education or professional careers of participants and non-participants. However, in the previous report of our study group, socioeconomic status did not differ from that of their controls.[41] Considering aetiology, only half of the subjects had imaging done as this is not routinely performed in Finnish patients. In addition, here we did not study the possible previously shown adverse effects of the higher dose (such as attention and behavioural problems) nor did we study the motor skills, which have been shown to be affected by congenital hypothyroidism.

5 | CONCLUSION

Adults with congenital hypothyroidism had a significantly lower FSIQ compared to the standardisation sample of the test while the FSIQ of children born during the era of higher initial dose regimen did not differ from the standard population. Moreover, a faster initiation of LT4 treatment was shown to optimise the outcome. We found no connection between the cognitive outcome and the severity or the aetiology of the disease. Our study results support the higher LT4 dose protocol. Possible benefits of a faster start of treatment than currently recommended urges further studies.

AUTHOR CONTRIBUTIONS

Emmi Danner: Conceptualization; writing – original draft; writing – review and editing; formal analysis; data curation; methodology; investigation. **Laura Niuro:** Conceptualization; writing – original draft; writing – review and editing; formal analysis; data curation; methodology; investigation. **Sonja Lapinoja:** Writing – review and editing; investigation; methodology. **Hanna Huopio:** Conceptualization; writing – review and editing; supervision. **Liisa A. Viikari:** Conceptualization; supervision; writing – review and editing. **Jukka Kero:** Conceptualization; supervision; writing – review and editing. **Jarmo Jääskeläinen:** Conceptualization; supervision; project administration; writing – review and editing. **Harri Niinikoski:** Conceptualization; project administration; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Restrictions apply to the availability of all data generated or analysed during this study to preserve patient confidentiality. However, data access may be permitted on a case-by-case basis upon request only. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided. Data sharing outside the group requires a data-sharing agreement.

ETHICS STATEMENT

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Northern Savo Hospital District (permission number 346/2018). In addition all participants and/or their guardians have given their informed consent.

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