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Original Article

Intelligence quotient outcomes in children with early-treated congenital hypothyroidism: a systematic review and meta-analysis

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Abstract

Background Congenital hypothyroidism (CH) is the most common congenital endocrine disorder in childhood and is one of the most preventable causes of intellectual disability (ID). Late initiation of thyroid hormone substitution therapy has a negative impact on intellectual abilities in CH patients.

Objective To compare intelligence quotient (IQ) between children with CH who underwent early treatment among the children without CH.

Methods We performed online literature searches of *ScienceDirect, Pubmed, Cochrane Library,* and *Google Scholar*. We included clinical studies that examined IQ scores in patients with early-treated CH and without CH. *Review Manager 5.4* was used to perform the meta-analysis.

Results Twelve studies comparing pediatric patients with and without CH were included in this meta-analysis, for a total of 808 patients. Based on data analysis, IQ levels of verbal IQ [mean difference (MD) -9.05; (95%CI -14.51 to -3.59); (P<0.00001)], performance IQ [MD -11.70; (95%CI -17.41 to -5.99); (P<0.00001)], and total IQ [MD -10.78; (95%CI -14.03 to -7.54); (P<0.00001)]. While verbal, performance, and total IQ of the early-treated CH group were within the normal range, they were each significantly lower than those in the non-CH group.

Conclusion This meta-analysis reveals that IQ scores in early-treated CH subjects were within normal limits, but significantly lower than that of normal controls. **[Paediatr Indones. 2023;63:290-7; DOI: https://doi.org/10.14238/pi63.4.2023.290-7**].

Keywords: *congenital hypothyroidism; intellectual disability (ID); intelligence quotient (IQ)*

Congenital hypothyroidism (CH) is a general term for thyroid hormone deficiency due to thyroid gland dysfunction or morphological abnormalities of the thyroid gland that develop during the fetal or perinatal stages.[1] The incidence of CH significantly increased after the start of the *New Born Screening* (NBS) program. Prior to NBS, in 1978, CH incidence was estimated to be 1:7,000 to 1:10,000 live births. After implementation of NBS, it increased to 1:3,000 to 1:4,000 live births.[2] *The 2018 Riset Kesehatan Dasar* (*Riskesdas*/Basic Health Survey of Indonesia Ministry of Health) reported that in Indonesia 4.6% of children aged 0-59 months underwent CH screening, while 64.4% did not, 2.9% excluded, and 29.1% loss to follow-up.[3]

Thyroid hormone functions to regulate heart rate, blood pressure, and energy metabolism, and is very important for brain development and growth in children. The most common clinical signs in

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children at diagnosis are delayed motor development (83.3%), constipation (73.3%), decreased activity (70%), macroglossia (70%), and pallor (70%). Late bone maturation (95.5%), hearing loss (22.7%), neuromuscular system disorders (16.7%), and intellectual disability (ID) (62.5%) can also be found.[4] According to the *Diagnostic and Statistical Manual edition IV* (DSM-IV),[5] ID is defined as intellectual functioning that is below average, with an average IQ of 70 or less. Causes of intellectual disability (ID) include chromosomal abnormalities (30%), metabolic and endocrine disorders (3-5%), multiple identified congenital anomalous syndromes (4-5%), injuries (15-20%), and malformations of the central nervous system (10-15%).[6]

Congenital hypothyroidism is the most common congenital endocrine disorder in childhood and is one of the most preventable causes of ID. After diagnosis, if treatment is started within a few weeks of birth, neurodevelopmental outcomes are generally normal. The clinical features of congenital hypothyroidism are often not visible and many newborns are undiagnosed at birth.[7] The CH diagnosis can be made by measuring thyroid stimulating hormone (TSH) and free tetraiodothyronine (FT4). Late initiation of thyroid hormone substitution therapy in CH patients has a negative impact on intellectual abilities.[8] Therefore, we conducted a systematic review and meta-analysis to compare the risk of intellectual disability in children with early-treated CH and without CH.

Methods

This quantitative study was done by systematic review and meta-analysis. Online literature searches were performed using several main sources, namely, *Science Direct, PubMed, Cochrane Library,* and *Google Scholar*. The meshwords used were "congenital hypothyroidism" OR "cretinism" AND "mental retardation" OR "intellectual disability" AND "IQ" OR "intelligence quotient" The literature search was carried out from August 15 to October 5, 2021.

- We followed the *Preferred Reporting Items for Systematic Reviews and Meta-Analysis* (PRISMA) method to collect and exclude literature systematically.[9] Below are the inclusion criteria for research publications used in this study: Patients: Patients who have been diagnosed with congenital hypothyroidsm and healthy children as a control group
- Intervention: Patients with CH diagnosed on the basis of thyroid function screening in newborns and treated immediately after diagnosis
- Comparison: Patients with CH compared to healthy children as a control group
- Outcomes: To compare the Intelligence Quotient (IQ) scores in CH patients diagnosed by thyroid function screening in newborns and treated immediately after diagnosis to scores of the control group, namely, healthy children without CH.
- Study design: The literature used was not limited by any place or study design, and was published in 2016-2021.

Articles with unsuitable titles, duplicates, could not be accessed, has different aspects of research (such as characteristics, comparisons, or outcomes), without a control group, unsuitable study design, unavailable full text form, unavailable in English or Indonesian, and did not meet the *Newcastle-Ottawa Scale* (NOS) criteria,[10] were excluded from the study.

We included research studies in our meta-analysis that compared pediatric CH patients who had been screened and given initial treatment to a control group, namely, healthy children without CH. The CH patients were diagnosed based on newborn screening (NBS). The study outcome was intelligence quotient (IQ), which was divided into verbal IQ (VIQ), performance IQ (PIQ), and total IQ (TIQ) and evaluated based on standardized assessments, From the included research articles, we collected the characteristics, comparisons, and outcomes using data collection standards that were previously set by the four reviewers. Furthermore, all articles were screened and selected according to the inclusion criteria.

To avoid the risk of bias, evaluation by way of NOS for case-control, cohort, and cross-sectional studies was performed. Prior to inclusion in NOS, the studies must have the correct number of samples calculated and statistically correct hypothesis testing. Studies with the lowest risk of bias can be rated with a maximum of 9 stars which are accumulated in the selection category, comparison category, and exposure category. A rating star was given to each quality attribute according to good, moderate, or poor in

each study. Studies must have a minimum score of "adequate" to be included in the meta-analysis. The author evaluated the quality of the study.

This meta-analysis was conducted using *Review Manager 5.4* software (*The Cochrane Collaboration*, Oxford, UK). Odds ratio (OR) with 95% confidence intervals were used to analyze each variable. Results with P values less than 0.05 indicated statistical significance. Cochrane Q test was used to assess the heterogeneity of the statistical data. Statistical heterogeneity was indicated by the symbol I^2. If the I^2 value was less than 50%, then this meta-analysis used a fixed-effect model, but if I^2 was more than 50%, the meta-analysis used a random-effects model. The overall study hypothesis was analyzed by Z-test.

Results

Our CH literature search yielded 1,468 studies, of which 12 were included in our meta-analysis. The literature search and inclusion process was carried out systematically by the PRISMA method, as shown in **Figure 1**.

The characteristics of the studies are shown in **Table 1**. The 12 included studies were from ten countries in Middle East Asia (8 from Iran, 2 from Egypt) and two countries in South America (1 from Argentina, 1 from Brazil). All the studies had been published between 2011-2021, without limiting the study design. They met the criteria for further analysis by NOS score. As shown in **Table 1**, IQ scores from

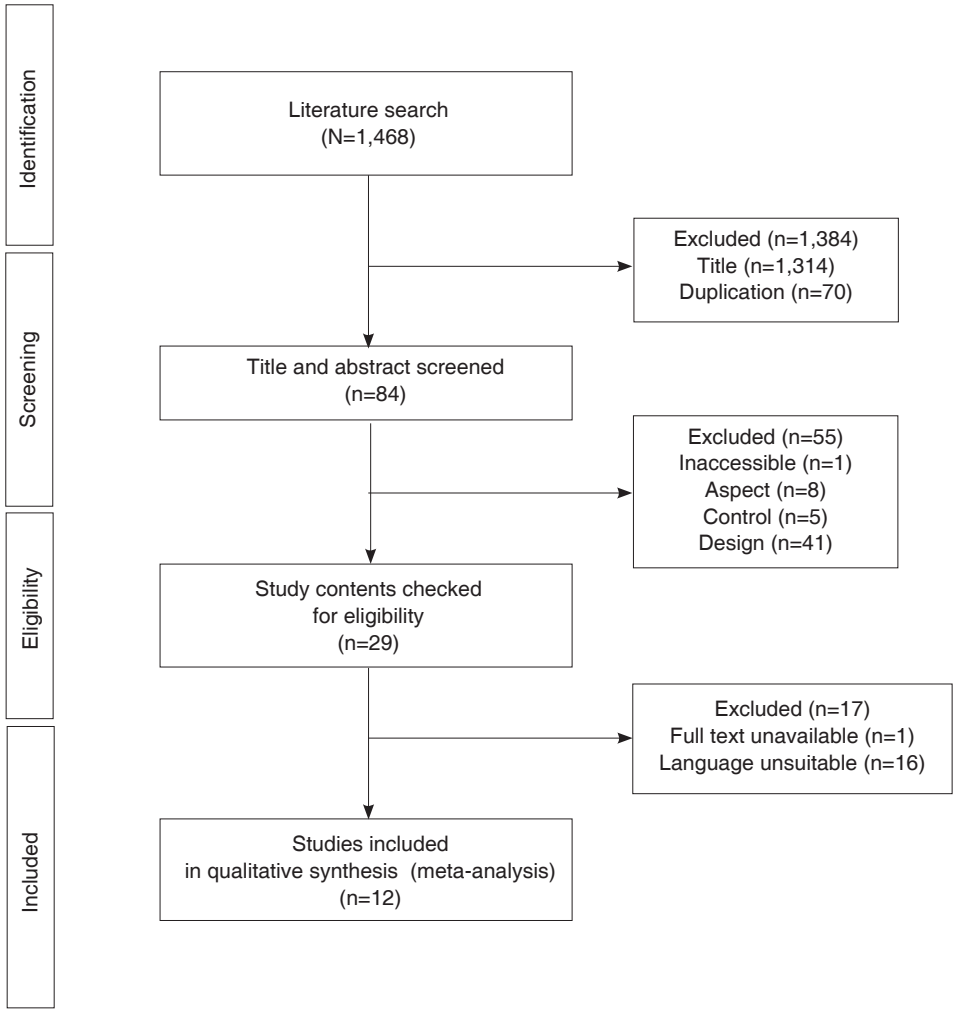

Figure 1. Literature search according to PRISMA

Table 1. Study characteristics and comparison of mean (SD) verbal IQ, performance IQ, and total IQ in the early-treated CH and non-CH groups

Journal	Year	Location	IQ coring measurement	n	NOS score	Mean verbal IQ (SD)	Mean performance IQ (SD)	Mean total IQ (SD)
Arad *et al.*[11]	2020	Iran	Wechsler Intellegence Scale for Children 3rd ed. (WISC-III)[23]		8			
CH				78		85.73 (13.54)	89.44 (13.66)	87.01 (13.47)
Non-CH				90		106.86 (10.18)	110.62 (9.82)	107.45 (10.49)
Rahmani *et al.*[12]	2018	Iran	Wechsler Preschool and Primary Scale of Intellegence (WPPSI)[24]		7			
CH				240		101.0 (15.8)	100.3 (14.7)	101.1 (13.7)
Non-CH				240		104.2 (16.5)	103.4 (14.5)	104.5 (14.5)
Nili *et al.*[13]	2015	Iran	Goodenough Draw-a-Man Test[25]		7			
CH				100		n.r	n.r	103.4 (16.9)
Non-CH				100		n.r	n.r	103.4 (15.4)
Saeidinejat *et al.*[14]	2020	Iran	Wechsler Preschool and Primary Scale of Intellegence 4ed (WPPSI-IV)[26]		7			
CH				64		n.r	n.r	86.01 (0.548)
Non-CH				1906		n.r	n.r	98.91 (0.095)
Farahat *et al.*[15]	2017	Egypt	Stanford-Binet 5th ed.[27]		8			
CH				61		n.r	n.r	81.705 (21.56)
Non-CH				78		n.r	n.r	94.11 (19.75)
Campos *et al.*[16]	2017	Argentina	Wechsler Intellegence Scale for Children 3rd ed. (WISC-III)[23]		6			
CH				60		100 (9.1)	85.3 (7.2)	94.4 (8.6)
Non-CH				60		104.8 (8.4)	98.8 (8.2)	102.7 (7.1)
Nekouei *et al.*[17]	2020	Iran	Wechsler Intellegence Scale for Children 3rd ed. (WISC-III)[23]		7			
CH				46		114.04 (9.9)	105.79 (10.6)	110.69 (9.2)
Non-CH				44		118.77 (11.8)	116.10 (10.4)	118.91 (10.9)
Nekouei *et al.*[17]	2020	Iran	Wechsler Intellegence Scale for Children 3rd ed. (WISC-III)[23]		7			
CH				45		104.87 (11.3)	113.81 (11.3)	110.25 (10.4)
Non-CH				44		118.77 (11.8)	116.10 (10.4)	118.91 (10.9)
Najmi *et al.*[18]	2013	Iran	Wechsler pre-school and primary scale of intelligence (WPPSI)[24]		7			
CH				30		89.5 (17.9)	95.9(16.1)	92.4 (16.3)
Non-CH				60		97.8 (14.2)	113.3 (14.6)	105.9 (12.9)
Najmi *et al.*[18]	2013	Iran	Wechsler pre-school and primary scale of intelligence (WPPSI)[24]		7			
CH				30		90.5 (13.7)	97.9 (18.3)	93.0 (15.8)
Non-CH				60		97.8 (14.2)	113.3 (14.6)	105.9 (12.9)
Ahmed *et al.*[19]	2019	Egypt	Stanford-Binet 4th ed.[28]		8			
CH				20		n.r	n.r	66.95 (22)
Non-CH				100		n.r	n.r	94.98 (10)
De Andrade *et al.*[20]	2021	Brazil	Wechsler Intellegence Scale for Children 4th ed. (WISC-1V)[26]		9			
CH				34		n.r	n.r	88.9 (17.8)
Non-CH				29		n.r	n.r	97.0 (14.7)

n.r=not reported

both groups were compared, including verbal IQ (VIQ), performance IQ (PIQ), and total IQ (TIQ), and presented in mean and standard deviation (SD).

The verbal IQ analysis results are shown in **Figure 2**. Forest plot analysis of 7 studies revealed significant results because they did not touch the vertical line. The comparison of verbal IQ in patients with and without CH resulted in a value of I^2=92%, an indication of heterogeneous data ($I^2 \geq 50\%$), thus, a random effects model was used for analysis. The total mean difference (MD) of verbal IQ was -9.05 (95%CI -14.51 to -3.59) (P<0.00001), and it was significantly lower in the CH group than in the non-CH group.

The performance IQ analysis results are shown in **Figure 3**. The forest plot of performance IQ in children with and without CH resulted in I^2=93%, indicating heterogeneity, so a random effects model was used to analyze the data. The total MD was -11.70 (95%CI -17.41 to -5.99); (P<0.00001), and it was significantly lower in the CH group than in the non-CH group.

The total IQ analysis results are shown in **Figure 4**. The forest plot analysis of 12 articles, revealed that 11 studies had significant differences in outcomes because they did not touch the vertical line, and one study did not have significant differences in outcomes. The forest plot of total IQ in children with and without CH resulted in I^2=92% indicating heterogeneity, so a random effects model was used to analyze the data. The total mean difference (MD) was -10.78 (95%CI -14.03 to -7.54) (P<0.00001), and indicating that total IQ was significantly lower in the CH than in the non-CH group.

Discussion

We performed a meta-analysis on 12 studies that analyzed the risk of intellectual disability (ID) in patients with congenital hypothyroidism who had been screened early and given treatment after diagnosis. Our results were in line with the results of several previous studies,[11-20] which all stated

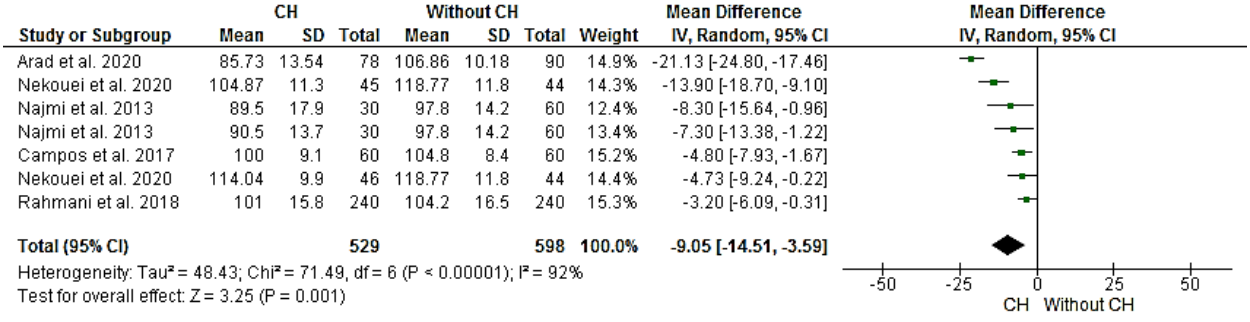

Figure 2. Forest plot of mean verbal IQ in the early-treated CH and non-CH groups

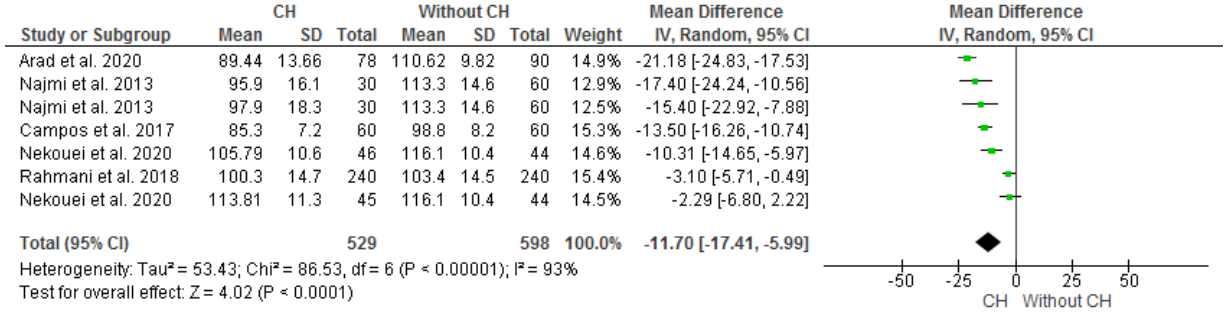

Figure 3. Forest plot of performance IQ in the early-treated CH and non-CH groups

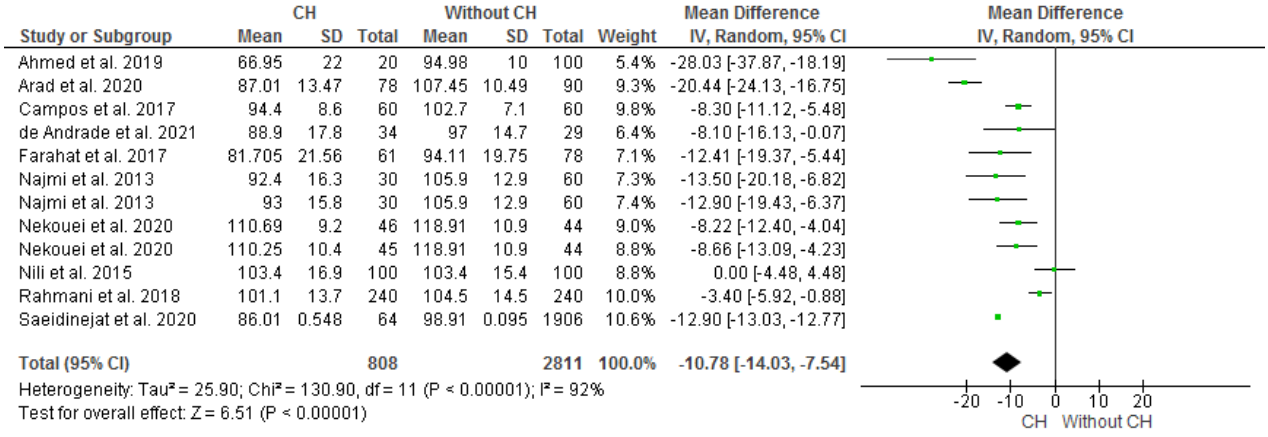

Figure 4. Forest plot of total IQ in the early-treated CH and non-CH groups

that newborns who had been screened and treated immediately had similar IQs to children without CH.

However, in this meta-analysis, newborns who had been screened and given immediate treatment had significantly lower IQs as children without CH. According to a previous study, late diagnosis and initiation of CH treatment had a negative effect on intellectual ability. In that study, most CH patients IQ scores <70 (intellectual disability).[8] Arad *et al.*[11] stated that there was a difference in mean IQ at the start of treatment, i.e., in patients who received treatment <21 days had a better IQ result than treatment given >21 days after birth. This finding was in agreement with a study, which stated that patients who received treatment at <21 days had better results than patients who received treated at >21 days.[21]

Forest plots of verbal IQ, performance IQ, and total IQ, revealed that performance IQ were all significantly lower than that of the non-CH controls. Similarly, another study noted that children with CH generally had normal intellectual intelligence if given initial treatment after diagnosis, but in terms of performance, such children had lower processing speed, reaction times, attention, cognitive flexibility, visuoconstruction, and long-term memory, even though the performance IQ scores were in the normal range. This may have been due to inadequate myelination, both quantitatively and qualitatively.[16]

Several studies stated that children with CH treated with levothyroxine at a dose of 10-15 μg/kg/day resulted in a good IQ.[13,16,18] This finding was in line with the 2017 recommendations by the *Ikatan Dokter Anak Indonesia* (IDAI/*Indonesian Pediatric Association*),[22] of levothyroxine dose of 10-15 μg/kg/day. A study reported that an initial dose of levothyroxine ≥ 7 μg / kg / day gave better IQ results.[21]

Two studies in our meta-analysis, looked at IQ based on the classification of CH (permanent CH and transient CH), namely, Najmi *et al.*[18] and Nekouei *et al.*[17] However, for our purposes, we did not differentiate CH by classification in our inclusion criteria. The reason was supported by Arad *et al.*[11] and Nili *et al.*,[13] who stated that there was no significant difference in IQ in permanent CH and transient CH.

A previous study conducted an IQ assessment of suspected CH, namely, patients with TSH levels of 5-9 mU/L on the first examination, < 5 mU/L on the second examination (normal), and compared them to the control group of children without CH and normal TSH levels (< 5 mU/L at first examination). They found no significant difference in IQ between the suspected and control groups.[14] Moreover, a study noted that the mean IQ in the CH patient group was 66.95 (SD 22), indicating a significant decrease in IQ in the CH patient group, as this score was interpreted to be an intellectual disability (ID) in the mild category (IQ=55-70). This was likely caused by non-compliance in drug administration in CH patients who had been diagnosed.[19]

In conclusion, this meta-analysis reveals that IQ scores in early-treated CH subjects are within normal limits, but significantly lower than that of normal controls.

Conflict of interest

None declared.

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