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#### **Research Article**

# Sports Games towards Intelligence and Nerve Development of Children in Iodine Deficiency Endemic Area

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#### **ABSTRACT**

**Introduction:** Increased circulation, hormones, and energy metabolism due to exercise are thought to have a positive effect on nerve growth and development. This study aims to examine the effect of addition of sports games on IQ score, TSH, and BDNF levels of elementary school children in IDD en-demic areas. Methods: This research method was a quasi-experiment pre-posttest with control group design. As many as 40 children aged 9 -11 years were divided into 19 children as controls, and 21 children doing sports games for 30 minutes per day, five times a week for eight weeks. Serum TSH and BDNF levels were measured using ELISA and IQ score using Culture Fear Intelligence Test (CFIT) method. Statistical analysis used was T-test, Wilcoxon, and Mann-Whitney test. Results: The mean of serum TSH levels and IQ scores of the treatment group were not significantly different from those of the control group (p>0.05). The mean of BDNF levels in both groups increased significantly, and the increase in BDNF levels in the treatment group was greater than in the control group (p<0.05). Conclusion: It can be con-cluded that the addition of sports games did not significantly change TSH levels and IQ scores (p>0.05), but significantly increase BDNF levels (p<0.05).

Keywords: BDNF, IDD area, Intelligence Quotient (IQ), Sports games

## Introduction

Child growth and development is formed from the result of a balanced interaction between genetic, hereditary, constitutional, and environmental factors. Genetic factors and the environment of the fetus in the womb are early determinants that can be said to be a program for postnatal life. The research shows that brain growth and children's cognition levels are strongly correlated with environmental factors in the form of socio-economic [1], and the adequacy of nutrients needed for nerve growth [2]. Other studies found that environmental factors such as residence, physical

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activity, family income, parental education, and father's work had an impact on children's IQ [3]. Optimal environmental factors are needed to support the development of a child's genetic potential.

Child growth and development in mountain range environment is threatened to be disturbed due to lower iodine contents in the ground caused by glaciation, flood, and deforestation [4]. Iodine is micronutrient that is needed in every stage of growth and development. Childhood, even starting from the womb is the phase that most requires adequate iodine intake [5,6]. Iodine deficiency causes broad spectrum disruption in children's physical and mental development [7] because iodine is needed for the formation of thyroid hormones, namely T4 (tetraiodotironine) and T3 (triiodotironine). Thyroid hormones play an important role in physical and nerve growth and development (Prezioso, Giannini, & Chiarelli, 2018; Rapaport, 2000). Brain growth is strongly correlated with the adequacy of thyroid hormones [10].

The Samigaluh Kulonprogo Yogyakarta plateau area is an IDD replate area [11]. Measurement of TSH and fT4 levels in elementary school children resulted in 42.1% of children experiencing subclinical hypothyroidism [12]. Cases of thyroid disorders found in children in this area are subclinical hypothyroidism. An increase in serum TSH, except in very rare pathological conditions, indicates insufficiency of T3 receptor saturation in the brain and a decrease in serum levels of thyroid hormone. So the increase in serum TSH shows the risk or potential occurrence of thyroxine deficiency by various causes or prematurity [13]. Serum T3 and T4 levels are less specific clues as indicators of deficiency caused by changes in levels affected by age and sex [14].

Children who are in the endemic area of IDD need activities that can improve thyroid function while improving nerve and cognitive function. The results of previous studies found that exercise can improve TSH and thyroid gland function [15]. Physical exercise in hypothyroid patients has been shown to increase T4 and T3 levels and decrease TSH [16]. Research in mice, exercise not only improved the

function of the thyroid gland, but also improved the brain function of hypothyroid mice cub [17]. Treadmill training and running in a spinning wheel in congenital hypothyroid mice cub improved thyroid function, spatial memory and BDNF levels of the hippocampus [18]. Research into the effects of aerobic and anaerobic exercise on adult PTU inducted hypothyroid mice resulted in lethargy and spatial memory abilities improvement and anaerobic exercise had a better effect than aerobic exercise [19]. Swimming can increase blood T4, T3 and TSH levels, mRNA TSH $\beta$  expression in pituitary and TRH in PVN in mice performed adrenalectomy [19].

The existence of evidence of the benefits of sports and the presence of problems of children in the area of hypothyroid replete, namely the risk of growth and development, especially nerves [20], it is necessary to examine the effects of hypothesized sports games that can improve the condition of children in endemic areas of IDD. This is based on research that exercise can stimulate angiogenesis [21] to increase blood flow not only to the motion system, but also to the whole body. In addition to increasing circulation, exercise increases hormones for increased metabolism of energy formation including thyroid stimulating hormone (TSH) [16,22]

# Materials and Methods *Materials*

Tools and materials used for blood collection and manufacturing of serum (syringes, cufflinks, tubes, and centrifuge), TSH ELISA kits (HUMAN, German), BDNF ELISA kits (Elabscience), and sports games equipments which were music, balls, sticks, and cords.

#### Methods

This research is a quasi-experimental study with a pre-posttest control group design. The research made at the villages of Purwoharjo and Tukharjo, Samigaluh District, Kulonprogo Regency, DIYogyakarta because this location is a plateau of the IDD replete area [11]. This location is a mild IDD endemic area with a prevalence of 12.5% based on a 2007 survey [23]. Most of the Samigaluh area is a mountainous area causing the low iodine content of

groundwater and during the rainy season it is prone to landslides. Samigaluh District has an area of 6,929.31 hectares, most of which are slopes that cannot be used for residence. Utilization of these slopes is usually planted with plantation or forestry crops and long-term crops, such as teak, sengon, mahogany, cloves, coffee, and cocoa[24]

The subject of this research is 40 children aged 9-12 years old, grades 3-6 elementary school (SD), who received informed consent from their parents. The subjects divided into 19 students as control group and 21 students as treatment group. The subjects are native and settled at the study site.

The serum TSH levels, serum BDNF levels, and IQ were measured at the beginning and end of the research. The TSH and BDNF levels were measured by Elisa method (HUMAN kit ELISA, German), IQ scores were measured using Culture fear intelligence (CFIT) conducted by Lembaga Psikologi Terapan Inspirasi in Wonosari, Gunung Kidul Regency, DIYogyakarta.

The sports games treatment was carried out with duration of 30 minutes between the

hours of 08.30-09.30 AM, 5 times a week, for 8 weeks. Sports performed were the modification of brisk walking. These sports included cross-country brisk walking, ball relay games, fishing nets, running picks, and others. These exercise variations were done so that children were not bored. Outside the program, treatment group children were not restricted to other activities. The control group children got exercise programs from school once a week and were not restricted to other activities.

### Data Analysis

The data obtained was tabulated and edited. Edits were made to retrieve subjects with complete data. The subjects with incomplete data were not included in the data analysis. Figure 1 showed the participant flow through the study. Statistical analysis used Wilcoxon-test, Mann Whitney, and T-test.

#### **Ethical consideration**

This research was carried out after obtaining ethical approval from FKIK UMY number 406/EP-FKIK-UMY/XI2016.

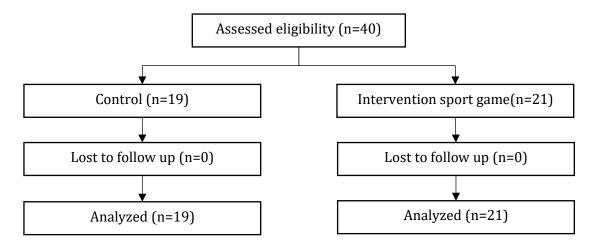


Figure 1. Flow of participants through the study

#### **Result and Discussion**

TSH level measurement results showed that most subjects were euthyroid. The subjects who suffered hypothyroxinaemia were further measured fT4 levels and the results within normal limits. The thyroid subjects' status was divided into two groups that are euthyroid and sub-clinical hypothyroid (SH). Determination of subclinical hypothyroid based

on an increase in serum TSH levels (4-25mU/L) and fT4 levels are in the normal range, which is 0.8-2.0 ng/dL (Ergür et al., 2012). Another reference for SH determination is TSH > 5 mU/L [25]. Based on TSH levels, HS is divided into mild SH with TSH levels of 4-10 mU/L and severe SH with TSH levels > 10mU/L. This division is related to SH management [26].

Subclinical hypothyroidism is a mild condition of hypothyroidism or often referred to as compensated hypothyroidism. In this case the body of SH sufferers can still maintain fT4 levels within normal limits, but TSH stimulation needs to be greater than normal individuals. Judging from the daily appearance, subjects look normal, no apparent disturbance [27]. Although there are no manifestations of distractibility and hyperactivity, children with a history of compensated hypothyroidism may have significant deficits in attention and memory, mental and psychomotor [9] If someone with mild hypothyroidism has a real neuropsychiatric disorder, it is necessary to study and re-diagnose the possibility that the disorder is not related to thyroid disorder [28]. Replacement of thyroxine to correct the deficit does not appear to have an impact on neuropsychological function [29].

Table 1 shows that the treatment did not cause significant changes in the average serum TSH level and the percentage of subclinical hypothyroid events between the beginning and end of the study. The percentage of subclinical hypothyroid events in the group of subjects at the end of the study was 27.5%. This percentage is greater than the general percentage in children, which is 1.7%, while the incidence in adults is relatively common, which is 4-20%. Subclinical hypothyroidism in adults often correlates with insulin resistance, dyslipidemia, vascular disorders, and heart disease [27].

Table 1. Average of serum TSH level and total number of subclinical hypothyroid (SH) control and treatment groups at the beginning and end of the study

Group	N	Initial TSH level (ng/dL)	SH TSH >4mIU/L	Final TSH level (ng/dL)	SH TSH >4mIU/L	Change of TSH level (ng/dL)	Wilcoxon
		average ± SD	(N)	average ± SD	(N)	average ± SD	
Control	19	3,01 ± 1,52	5 (26,3%)	4,69 ±3,95	7 (36,8%)	1,75 ± 4,86	0,243
Sports Games	21	2,68 ±1,19	3 (14,3 %)	3,53 ± 2,27	4 (19,0%)	1,68 ± 3,81	0,018
Total	40		8 (20,0%)		11 (27,5%)		
Mann Whitney		0,448		0,256		0,389	

Physical exercise has been accepted as a disease management with "exercise is medicine" initiated in 2007 [30]. Doctors prescribe exercise doses according to the patient's condition, because exercise will only be beneficial if carried out according to the required amount [31]. This study has not been able to answer the role of physical exercise for 8 weeks in improving thyroid function in SH in improving thyroid function in children with SH. SH treatment to improve children thyroid function is still being debated [32]. The existence of various disorders that arise in adult SH, then SH needs to be treated [33]. SH treatment is needed to prevent progression to clinical hypothyroidism.

The addition of sports games in children conducted for 8 weeks in this study has not shown improvement in thyroid function. The time may need to be extended because 16-

week aerobic exercise research improved the quality of life of middle-aged women with SH [34]. Another study concluded that aerobic exercise for 16 weeks in adolescents with disabilities had an impact on increasing plasma levels of thyroid hormone and reducing TSH [35].

Table 2 shows that the addition of sports games to elementary school children significantly increased IQ scores (p=0.007), while the IQ scores of children who did not receive additional sports games increased insignificantly (p=0.083). Difference test in IQ score improvement between the treatment and control groups found no significant difference (p=0.876). Thus, the increase in IQ score that occurs in the treatment group is not only due to the provision of additional sports games, but because of various activities and stimulants given at school, home, and elsewhere.

Table 2. Average of IQ scores in the control and treatment groups at the beginning and end of the study

Croun	N	Initial IQ score	Final IQ score	Change of IQ score	Paired T-test	
Group	IN	Average ± SD	Average ± SD	Average ± SD	raneu i-test	
control	19	92,11 ± 12,24	93,05 ± 10,89	0,95 ± 2,25	0,083	
sports games	21	85,81 ± 13,91	86,67 ± 13,32	0,86 ± 1,31	0,007	
independent T-test		0,139	0,107	0,876	_	

Children who did not get additional sports games experienced an increase in IQ scores. This shows that learning activities in schools contribute to an increase in children's IQ. Educational stimulation through play groups, PAUD, playgrounds in younger children for 3 months increased the development of verbal intelligence, achievement and IQ [36].

Factors influencing a child's IQ are chronic parental disease [37], socio-economic

conditions and nutrition during fetus in the womb [38] as well as after birth. IQ scores of children at the age of 9 years and 11 years correlate more strongly with socio-economic and nutritional factors after birth compared with birth weight [26]. The gender factor in children turns out to affect IQ by obtaining evidence that girls aged 3-6 years have higher levels of intelligence than boys [36].

Table 3. Average of serum BDNF levels control and treatment groups at the beginning and end of the study

group	N _	Initial BDNF level (ng/dL) Average ± SD	Final BDNF level (ng/dL) Average ± SD	Change of BDNF level (ng/dL) Average ± SD	paired T-test
control 1	19	1649,78 ± 150,09	1805,94 ± 114,14	174,36 ± 168,64	0,002
sports games	21	1568,61± 171,08	1895,21 ± 116,73	326,57 ± 191,41	0,0001
independent T-test		0,121	0,019	0,011	

Table 3 shows that the serum BDNF levels in the treatment group increased significantly, as did the control group. A significant increase in BDNF levels in the control group means that learning and playing activities at school, home, and their environment are stimulants to the nervous system and stimulate growth and development. The vital role of BDNF for cognitive task performance is needed. Observations from rodent studies showed the benefits of BDNF if added and the resulting deficit in learning if BDNF was blocked. In addition, one training session had been shown to increase peripheral BDNF concentrations although there was no apparent improvement in memory [39].

Physical activity is likely to have a longer lasting effect on the brain which is still in developmental stages [40]. Research on normal children proved that motor skills correlated with cognitive learning abilities [41]. It turns out

that physical activity and play are not only beneficial in normal children, but the intelligence of children with mental retardation had been successfully improved with play therapy programs [42]. One factor that can repair nerves from growth retardation or damage is an increase in BDNF. Various neurodegenerative diseases of the brain due to age or due to excess reactive oxygen species that are triggered by neurotoxic agents and injury to the brain due to trauma can be corrected with neurotrophin [43]. The multipotent effect on brain signaling and synaptic plasticity is a key factor in the effect of BDNF work [44].

Increasing BDNF will not only improve IQ, but also improve neuropsychiatric disorders [45]. Individuals with lower IQs have an increased risk of psychological disorders, mental health problems, and suicide; similarly, children with low IQ scores are more likely to have

behavioral, emotional and anxiety disorders. Therefore it is necessary to continue to study various stimulants that can improve brain function and improve cognition [46].

#### Conclusion

The addition of sports games for 8 weeks did not cause significant changes in thyroid function and IQ scores in subclinical hypothyroid children, but significantly increased BDNF levels (p<0.05). Simpler nerve function parameters such as nerve reaction time, short-term, medium-term, and long-term memory may be more appropriate to assess the effects of sports stimulus in a relatively short time.

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#### References

- Jednoróg, K., Altarelli, I., Monzalvo, K., Fluss, J., Dubois, J., Billard, C., Dehaene-Lambertz, G., & Ramus, F. (2012). The Influence of Socioeconomic Status on Children's Brain Structure. *PLOS ONE*, 7(8), e42486. <a href="https://doi.org/10.1371/journal.pone.004248">https://doi.org/10.1371/journal.pone.004248</a>
- Nyaradi, A., Li, J., Hickling, S., Foster, J., & Oddy, W. H. (2013). The role of nutrition in children's neurocognitive development, from pregnancy through childhood. *Frontiers in Human Neuroscience*, 7. <a href="https://doi.org/10.3389/fnhum.2013.00097">https://doi.org/10.3389/fnhum.2013.00097</a>
- Makharia, A., Nagarajan, A., Mishra, A., Peddisetty, S., Chahal, D., & Singh, Y. (2016). Effect of environmental factors on intelligence quotient of children. *Industrial Psychiatry Journal*, 25(2), 189. <a href="https://doi.org/10.4103/ipj.ipj\_52\_16">https://doi.org/10.4103/ipj.ipj\_52\_16</a>
- Pandav, C. S., Yadav, K., Srivastava, R., Pandav, R., & Karmarkar, M. G. (2013). Iodine deficiency disorders (IDD) control in India. *Indian J Med Res*, 138(3), 418–433.
- 5. Glinoer, D. (2004). The regulation of thyroid function during normal pregnancy: importance of the iodine nutrition status. *Best Pract. Res. Clin. Endocrinol. Metab.*, 18(2), 133–152. https://doi.org/10.1016/j.beem.2004.03.001

- Leung, A. M., Pearce, E. N., & Braverman, L. E. (2011). Iodine nutrition in pregnancy and lactation. *Endocrinol Metab Clin North Am*, 40(4), 765–777. <a href="https://doi.org/10.1016/j.ecl.2011.08.001">https://doi.org/10.1016/j.ecl.2011.08.001</a>
- Zimmermann, M. B. (2011). The role of iodine in human growth and development. In *Seminars in Cell and Developmental Biology* (Vol. 22, Issue 6, pp. 645–652). Elsevier Ltd. <a href="https://doi.org/10.1016/j.semcdb.2011.07.00">https://doi.org/10.1016/j.semcdb.2011.07.00</a>
   9
- 8. Rapaport, R. (2000). Congenital hypothyroidism: Expanding the spectrum. *The Journal of Pediatrics*, 136(1), 10–12. https://doi.org/10.1016/S0022-3476(00)90041-6
- 9. Prezioso, G., Giannini, C., & Chiarelli, F. (2018). Effect of Thyroid Hormones on Neurons and Neurodevelopment. *Hormone Research in Paediatrics*, 90(2), 73–81. <a href="https://doi.org/10.1159/000492129">https://doi.org/10.1159/000492129</a>
- Rovet, J. F. (2014). The Role of Thyroid Hormones for Brain Development and Cognitive Function. In *Endocrine Development* (Vol. 26, pp. 26–43).
  S. Karger AG. https://doi.org/10.1159/000363153
- 11. Wibowo, R. A., Wahyuningrum, S. N., & Hidayat, T. (2015). Profil Genetik Iodotironin Deiodenase dan Status Tiroid pada Wanita Usia Subur Penderita Hipotiroid dan Hipotiroid Subklinik. *Media Gizi Mikro Indonesia*, 6(2), 133–144.
- 12. Noor, Z., & Darmawati, I. (2016). Kajian Efek Jalan Cepat terhadap Fungsi Tiroid, Neurogenesis dan Perkembangan Fungsi Otak Anak SD di Daerah Endemik GAKI Kulonprogo Yogyakarta.
- 13. Bhavani, N. (2011). Transient congenital hypothyroidism. *Indian J Endocrinol Metab*, 15(Suppl2), S117--S120. https://doi.org/10.4103/2230-8210.83345
- 14. Brent, G. A. (2012). Mechanisms of thyroid hormone action. *Journal of Clinical Investigation*, 122(9), 3035–3043. https://doi.org/10.1172/JCI60047
- 15. Ciloglu, F., Peker, I., Pehlivan, A., Karacabey, K., İlhan, N., Saygin, O., & Ozmerdivenli, R. (2005). Exercise intensity and its effects on thyroid hormones. *Neuroendocrinology Letters*, *26*(6), 830–834.

- 16. Bansal, A., Kaushik, A., Singh, C., Sharma, V., & Singh, H. (2015). The effect of regular physical exercise on the thyroid function of treated hypothyroid patients: {An} interventional study at a tertiary care center in {Bastar} region of {India}. Archives of Medicine and Health Sciences, 3(2), 244. <a href="https://doi.org/10.4103/2321-4848.171913">https://doi.org/10.4103/2321-4848.171913</a>
- 17. Shin, M.-S., Ko, I.-G., Kim, S.-E., Kim, B.-K., Kim, T.-S., Lee, S.-H., Hwang, D.-S., Kim, C.-J., Park, J.-K., & Lim, B.-V. (2013). Treadmill exercise ameliorates symptoms of methimazole-induced hypothyroidism through enhancing neurogenesis and suppressing apoptosis in the hippocampus of rat pups. *International Journal of Developmental Neuroscience*, *31*(3), 214–223. <a href="https://doi.org/10.1016/j.ijdevneu.2013.01.00">https://doi.org/10.1016/j.ijdevneu.2013.01.00</a>
- 18. Shafiee, S. M., Vafaei, A. A., & Rashidy-Pour, A. (2016). Effects of maternal hypothyroidism during pregnancy on learning, memory and hippocampal BDNF in rat pups: Beneficial effects of exercise. *Neuroscience*, *329*, 151–161. <a href="https://doi.org/10.1016/j.neuroscience.2016.04.048">https://doi.org/10.1016/j.neuroscience.2016.04.048</a>
- 19. Park, S.-H., & Song, M. (2016). Effects of aerobic and anaerobic exercise on spatial learning ability in hypothyroid rats: a pilot study. *Journal of Physical Therapy Science*, *28*(12), 3489–3492. <a href="https://doi.org/10.1589/jpts.28.3489">https://doi.org/10.1589/jpts.28.3489</a>
- 20. Ergür, A. T., Taner, Y., Ata, E., Melek, E., Bakar, E. E., & Sancak, T. (2012). Neurocognitive functions in children and adolescents with subclinical hypothyroidism. *J Clin Res Pediatr Endocrinol*, 4(1), 21–24. https://doi.org/10.4274/Jcrpe.497
- 21. Kwak, S.-E., Lee, J.-H., Zhang, D., & Song, W. (2018). Angiogenesis: focusing on the effects of exercise in aging and cancer. *J Exerc Nutrition Biochem*, 22(3), 21–26. <a href="https://doi.org/10.20463/jenb.2018.0020">https://doi.org/10.20463/jenb.2018.0020</a>
- 22. Bloor, C. M. (2005). Angiogenesis during exercise and training. *Angiogenesis*, 8(3), 263–271. <a href="https://doi.org/10.1007/s10456-005-9013-x">https://doi.org/10.1007/s10456-005-9013-x</a>
- Dinas Kesehatan Kabupaten Kulon Progo. (2007). Profl Kesehatan Kabupaten Kulon Progo Tahun 2007. BPS Kabupaten kulonprogo, 2023. Dinkes Kulonprogo.
- 24. Badan Pusat Statistik. (2023). *Demografi Kabupaten Kulon Progo*.

- Calaciura, F., Motta, R. M., Miscio, G., Fichera, G., Leonardi, D., Carta, A., Trischitta, V., Tassi, V., Sava, L., & Vigneri, R. (2002). Subclinical Hypothyroidism in Early Childhood: A Frequent Outcome of Transient Neonatal Hyperthyrotropinemia. *The Journal of Clinical Endocrinology & Metabolism*, 87(7), 3209–3214. https://doi.org/10.1210/jcem.87.7.8662
- 26. Pearce, M. S., Deary, I. J., Young, A. H., & Parker, L. (2005). Growth in early life and childhood IQ at age 11 years: the Newcastle Thousand Families Study. *Int J Epidemiol*, *34*(3), 673–677. <a href="https://doi.org/10.1093/ije/dvi038">https://doi.org/10.1093/ije/dvi038</a>
- Gallizzi, R., Crisafulli, C., Aversa, T., Salzano, G., De Luca, F., Valenzise, M., & Zirilli, G. (2018). Subclinical hypothyroidism in children: is it always subclinical? *Italian Journal of Pediatrics*, 44(1), 25. <a href="https://doi.org/10.1186/s13052-018-0462-4">https://doi.org/10.1186/s13052-018-0462-4</a>
- 29. Aijaz, N. J., Flaherty, E. M., Preston, T., Bracken, S. S., Lane, A. H., & Wilson, T. A. (2006). Neurocognitive function in children with compensated hypothyroidism: lack of short term effects on or off thyroxin. *BMC Endocrine Disorders*, 6(1). https://doi.org/10.1186/1472-6823-6-2
- 30. Tipton, C. M. (2014). The history of "Exercise Is Medicine" in ancient civilizations. *Adv Physiol Educ*, 38(2), 109–117. https://doi.org/10.1152/advan.00136.2013
- 31. Billinger, S. A., Boyne, P., Coughenour, E., Dunning, K., & Mattlage, A. (2015). Does Aerobic Exercise and the FITT Principle Fit into Stroke Recovery? *Curr Neurol Neurosci Rep*, *15*(2), 519. <a href="https://doi.org/10.1007/s11910-014-0519-8">https://doi.org/10.1007/s11910-014-0519-8</a>
- 32. Tng, E. L. (2016). The debate on treating subclinical hypothyroidism. *Singapore Med J*, *57*(10), 539–545. https://doi.org/10.11622/smedj.2016165
- 33. McDermott, M. T., & Ridgway, E. C. (2001). Subclinical Hypothyroidism is Mild Thyroid Failure and Should be Treated. *J Clin Endocrinol Metab*, 86(10), 4585–4590. <a href="https://doi.org/10.1210/jcem.86.10.7959">https://doi.org/10.1210/jcem.86.10.7959</a>
- 34. Werneck, F. Z., Coelho, E. F., Almas, S. P., Garcia, M. M. do N., Bonfante, H. L. M., Lima, J. R. P. de,

- Vigário, P. D. S., Mainenti, M. R. M., Teixeira, P. de F. D. S., & Vaisman, M. (2018). Exercise training improves quality of life in women with subclinical hypothyroidism: a randomized clinical trial. *Arch Endocrinol Metab*, 62(5), 530–536. <a href="https://doi.org/10.20945/2359-3997000000073">https://doi.org/10.20945/2359-39970000000073</a>
- 35. Altaye, K. Z., Mondal, S., Legesse, K., & Abdulkedir, M. (2019). Effects of aerobic exercise on thyroid hormonal change responses among adolescents with intellectual disabilities. *BMJ Open Sport & Exercise Medicine*, *5*(1), e000524. <a href="https://doi.org/10.1136/bmjsem-2019-000524">https://doi.org/10.1136/bmjsem-2019-000524</a>
- 36. Siswina, T. (2016). Pengaruh stimulasi pendidikan terhadap perkembangan kecerdasan anak usia 3-6 tahun. *Jurnal Ilmiah Bidan*, *1*(2), 27–33.
- 37. Barker, R. L. (2003). *The social work dictionary*. NASW press.
- 38. Morgane, P. J., Austin-LaFrance, R., Bronzino, J., Tonkiss, J., Díaz-Cintra, S., Cintra, L., Kemper, T., & Galler, J. R. (1993). Prenatal malnutrition and development of the brain. *Neuroscience & Biobehavioral Reviews*, 17(1), 91–128. <a href="https://doi.org/10.1016/S0149-7634(05)80234-9">https://doi.org/10.1016/S0149-7634(05)80234-9</a>
- 39. Etnier, J. L., Wideman, L., Labban, J. D., Piepmeier, A. T., Pendleton, D. M., Dvorak, K. K., & Becofsky, K. (2016). The Effects of Acute Exercise on Memory and Brain-Derived Neurotrophic Factor (BDNF). *Journal of Sport and Exercise Psychology*, 38(4), 331–340. https://doi.org/10.1123/jsep.2015-0335
- 40. Macpherson, H., Teo, W. P., Schneider, L. A., & Smith, A. E. (2017). A life-long approach to physical activity for brain health. *Frontiers in Aging Neuroscience*, 9(MAY). https://doi.org/10.3389/fnagi.2017.00147

- 41. Abdelkarim, O., Ammar, A., Chtourou, H., Wagner, M., Knisel, E., Hökelmann, A., & Bös, K. (2017). Relationship between motor and cognitive learning abilities among primary school-aged children. *Alexandria Journal of Medicine*, 53(4), 325–331. https://doi.org/10.1016/j.ajme.2016.12.004
- 42. Machmudah, & Santy, W. H. (2017). The influence of play therapy in developing the intelligence of school age children with mental retardation. *Proceeding of Surabaya International Health Conference*, *6*, 5–9.
- 43. Habtemariam, S. (2018). The brain-derived neurotrophic factor in neuronal plasticity and neuroregeneration: new pharmacological concepts for old and new drugs. *Neural Regeneration Research*, 13(6), 983. <a href="https://doi.org/10.4103/1673-5374.233438">https://doi.org/10.4103/1673-5374.233438</a>
- 44. Kowiański, P., Lietzau, G., Czuba, E., Waśkow, M., Steliga, A., & Moryś, J. (2018). BDNF: A key factor with multipotent impact on brain signaling and synaptic plasticity. *Cell Mol Neurobiol*, *38*(3), 579–593. https://doi.org/10.1007/s10571-017-0510-4
- 45. Autry, A. E., & Monteggia, L. M. (2012). Brain-Derived Neurotrophic Factor and Neuropsychiatric Disorders. *Pharmacol Rev*, 64(2), 238–258. https://doi.org/10.1124/pr.111.005108
- 46. Whitley, E., Gale, C. R., Deary, I. J., Kivimaki, M., & Batty, G. D. (2011). Association of maternal and paternal IQ with offspring conduct, emotional and attention problem scores: transgenerational evidence from the 1958 {British} birth cohort study. *Arch Gen Psychiatry*, 68(10), 1032–1038.
  - https://doi.org/10.1001/archgenpsychiatry.20 11.111