SYSTEMATIC REVIEW

Effects of exercise on thyroid hormones in children and adolescents with thyroid function disorders: A Systematic Review [version 1; peer review: awaiting peer review]

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Abstract

Background: Exercise leads to changes in hormonal concentration and metabolites which impacts growth and development; during physical activity, energy metabolism is influenced by hormones associated with pubertal development, and characterization of its response to exercise is essential. Therefore, we aimed to identify the effects of exercise on thyroid hormones in children and adolescents with thyroid function disorders.

Methods: A comprehensive literature search was performed in PubMed, Scopus, Web of Science, CINAHL, and Embase based on the search strategy, and the articles were screened based on inclusion criteria, for which two independent reviewers conducted data extraction. The eligible studies were methodologically assessed using a modified Downs and Black's checklist. The extracted data were summarized according to study population, intervention, type and duration, outcome measures, and results.

Results: The total number of screened articles was 1,710, out of which six papers were included for review. Studies included children and adolescents with hypothyroidism, intellectual disabilities, and obesity who received exercise or physical activity as an intervention. The outcomes included thyroid hormones T3, T4, and TSH. Studies were generally of low quality. The findings of the studies throw some light on the benefits of exercise or physical activity.

Conclusions: Structured physical activity and exercise followed for a more extended period showed some thyroid function changes in this population. The intensity of change was directly proportional to exercise intensity. However, this review does not provide sufficient evidence stating that exercise results in changes of thyroid function returning to normal, which requires further higher-quality studies to strengthen the review's findings.
Keywords
Adolescent, Children, Thyroid function disorders, Thyroid hormones, Exercise training, Physical activity

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Introduction

Thyroid hormones play an important role in early neurocognitive development, growth, and tissue maturation throughout childhood and adolescence. Normal thyroid function is essential for regulating metabolic processes such as molecular mechanism, lipid regulation, thermogenesis, and adrenergic stimulation, and thus control energy balance by regulation, storage, and expenditure. Energy expenditure and body weight also correlate with hormonal status. The metabolic pathway regulation involves a direct pathway with bile acid stimulation, and an indirect pathway with nuclear receptors leading to lipolysis and lipogenesis. Thyrotropin-releasing hormone (TRH) from the hypothalamus acts upon the pituitary gland, which increases cAMP and subsequent thyrotropin release. These hormonal signals modulate Thyroid-stimulating hormone (TSH) secretion. Thyroid hormone synthesis and secretion involve the functioning of the hypothalamic-pituitary-thyroid (HPT) axis through a negative feedback mechanism that regulates thyroid functions by converting T4 to T3, which leads to a decrease in TRH and TSH secretion in response to adequate thyroid hormone levels in tissues.

Thyroid function disorders are evaluated based on clinical presentation, thyroid function tests revealing levels of serum TSH, freeT4-thyroxine, and freeT3-thyroid thyroxine. Hormonal status with hyperthyroidism corresponds with excess thyroid hormones showing as weight loss, reduced cholesterol level, increased lipolysis, and gluconeogenesis. On the other hand, hypothyroidism is presented with low plasma levels of thyroid hormones, showing as a hypometabolic state with increased cholesterol levels leading to weight gain.

Functions of thyroid hormones also include regulation of indirect effects of cardiac functions, due to hemodynamic changes by thyroid hormones leading to its dysfunction. At the tissue level, thyroid hormones influence the function of brown and white adipose tissue. Increased fat accumulation alters the normal functioning of the hypothalamic-pituitary-thyroid axis, leading to changes in thyroid function. The pathophysiology of thyroid axis dysfunction is not yet fully understood. Hypotheses have been proposed indicating that thyroid dysfunction is a consequence of excess body weight rather than its cause. In developing children, thyroid hormones and function are essential for brain cell growth and differentiation, and induce neurotransmitter function. Their deficiency in foetal life and early infancy impairs neurocognitive function, which is irreversible, causing retarded brain maturation and intellectual deficits. Congenital hypothyroidism shows an incidence of 1 in 1,500 to 3,000 newborns, most commonly due to thyroid dysgenesis, which is followed by abnormal thyroid hormonal levels due to the defects in thyroid hormone biosynthesis or secretion.

Thyroid hormones at the skeletal muscle level influence plasma glucose levels, increasing carbohydrate metabolism and reducing white adipose tissue level, corresponding to increased mitochondrial activity due to thyroid hormone levels.

The human body undergoes various modifications to adapt to stress. The endocrine system also undergoes numerous changes when subjected to stress under physical exercise to maintain hormonal balance and normal metabolic processes. Regular physical activity and training have been shown to suppress proinflammatory cytokine production and enhance fibrinolytic activity to improve the chronic inflammatory conditions post-exercise at the muscle level. Additionally, overtraining leads to changes in the central nervous system (CNS) activation of hypothalamic nuclei, influencing Adrenocorticotropic hormone (ACTH) and cortisol release accounting for behavioral changes. It also regulates the effects of thermogenesis and substrate metabolism when excess physical activity with inappropriate intake causes negative energy-balance signalling alterations in HTP axes.

Studies on average athletes concerning changes in thyroid hormonal level with exercise training showed a possible increase in TSH and a late increase in T3 and T4 release. Any modification with external temperature regulation during exercise showed no thyroid hormones changes. Based on the intensity and duration of the training, i.e., low (45%), moderate (70%), and high (90%), TSH showed increased levels in all three intensities, T3 and T4, in submaximal intensity. T4 led to an increased status by 35% during prolonged submaximal exercise. Sedentary males, when compared with athletes, showed reduced T4 plasma levels. Thyroid hormones play a crucial role during and after physical activity, and their control is of utmost importance for the proper metabolic pathway function. Evidence to date shows disputed results concerning thyroid hormone metabolism during exercise in adults and athletes. However, only scarce information provides knowledge regarding thyroid hormone change status in children and adolescents when subjected to strenuous exercise or physical activity. Further, to the aim of the current review is to summarise the available existing evidence to identify the effects of all kinds of exercise and physical activity on thyroid hormones in children and adolescents with thyroid function disorder.

Methods

This systematic review is reported according to the PRISMA guidelines. We did a systematic review of randomized and non-randomized controlled trials on the effects of exercise on thyroid hormones in children with thyroid function-related disorders. The study protocol was set and registered in Open Science Framework.
Search strategy and selection criteria
According to PRISMA, the search strategy for the current review was pre-set and executed before study selection. We used the PICOS strategy (population, intervention, comparison, outcome, and study design). A comprehensive systematic search was performed from May 2021 till June 2021 in the following databases: PubMed (MEDLINE, RRID:SCR_002185), Web of Science (Clarivate Analytics, RRID:SCR_017657), CINAHL, SCOPUS (Elsevier, RRID:SCR_013811) and Embase (EMBASE, RRID:SCR_001650). The identification of the articles was made using the search terms "paediatrics", "child", "children", "adolescent", "thyroid disorders", "hyperthyroidism", "hypothyroidism", "goiter", "physical therapy", "exercise training", "physical activity", "physical function", "exercise therapy", "aerobic exercise", "physical exercise", "thyroid hormones". The search terms were combined with the Boolean operator ‘AND’ or ‘OR’ wherever relevant; secondary searches were carried out using other sources (e.g., Google Scholar, a reference list of the included articles). The current review includes experimental studies (randomised controlled trials [RCTs] and non-randomised controlled trials [non-RCTs]). Investigation studies based on animal populations and non-availability in English were excluded.

Inclusion and exclusion criteria

Inclusion criteria

1) Population: Children aged five to 18 with thyroid function-related disorder.

2) Intervention: Having exercise therapy or any form of physical activity as an intervention. Exercise was defined as “Exercise is a set of physical activity that is planned, structured and repetitive and has a final or intermediate objective of improvement or maintenance of physical fitness”

3) Type of design: RCTs and non-RCTs

4) Type of outcomes: The plasma level of thyroid hormones: triiodothyronine (T3) and thyroxin (T4 & Thyroid-stimulating hormone [TSH]).

Studies that did not include physical activity or exercise as an intervention were excluded, such as those using performance testing and activity questionnaires.

Data extraction and management
The studies eligible for inclusion were screened further based on title and full text independently by BR and VPS (PhD). Any conflict of judgment and agreements were discussed with NSC. A template for data extraction was developed, which included the demographic characteristics of the participants, description of the intervention, comparator, sample size, adverse events, treatment duration, and results in an Excel spreadsheet as reported by the study for all the included articles of this review. Data extraction was done by BR and VPS; any variance was resolved by discussions between the two reviewers and then further with the third reviewer.

Quality assessment
Studies included with the eligibility for the current review were evaluated methodologically and quantified by BR using Downs and Black’s checklist and further reviewed by VPS. The extracted data was updated within the excel sheet based on a pre-set template.

Results
After running a complete search in all the databases with the search strategy, the number of articles obtained was 1713. After merging duplicates using Zotero (Zotero, RRID:SCR_013784) 1,657 articles were accepted for the title and abstract screening, and 20 papers were taken for full-text screening. After all the screening steps, the final eight articles were included in this review.

The PRISMA flowchart (Extended data^32) shows the studies’ identification, screening, and inclusion, given in the following PRISMA chart.

The studies included post-data extraction were evaluated for quality and methodology using Downs and Black’s checklist. The studies included for this review showed low to moderate quality of evidence due to poor study designs, sample size, missing data, poor compliance, and follow-up. Details regarding methodological quality are summarized in Table 1. Amid the included eight studies, three were prospective study design; 2 RCT; 1 pre-post research design, one quasi-experimental study, and a cross-sectional comparative study.
Most studies in this review included children with obesity/overweight with altered thyroid functions. Two studies had children with intellectual disabilities, and another study included girls with hypothyroidism. The outcome measures were TSH level and thyroid hormones T3 and T4; some studies measured the free state thyroid hormones (T3 and T4).

Exercise and physical activity were the interventions included in this review. Out of eight studies, three provided resistance training and aerobic exercise. One study compared two groups with high- and moderate-intensity aerobic

Table 1. Quality assessment using modified Downs and Black’s checklist.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Reporting (11)</th>
<th>External validity (3)</th>
<th>Internal validity-bias (7)</th>
<th>Internal validity-confounding (selection) (6)</th>
<th>Power (1)</th>
<th>Total score (28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sefat et al., 2019</td>
<td>8</td>
<td>0</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Altaye et al., 2019</td>
<td>7</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Zenebe et al., 2019</td>
<td>7</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Wolters et al., 2012</td>
<td>9</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>Reinehr et al., 2006</td>
<td>8</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>Licenziati et al., 2009</td>
<td>8</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>Martins et al., 2020</td>
<td>8</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>Wissal Abassi et al., 2020</td>
<td>8</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>0</td>
<td>18</td>
</tr>
</tbody>
</table>

Table 2. Provides information regarding author, sample characteristics, design, adjunct therapy along with intervention, comparator for intervention and outcomes of the study.

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample Population</th>
<th>Age Gender</th>
<th>Study design</th>
<th>Adjunct therapy</th>
<th>Comparator</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sefat et al., 2019</td>
<td>Hypothyroidism and overweight</td>
<td>8-15 y Females</td>
<td>RCT</td>
<td>levothyroxine</td>
<td>Control no exercise training</td>
<td>TSH and T4</td>
</tr>
<tr>
<td>Altaye et al., 2019</td>
<td>Adolescents with intellectual disabilities</td>
<td>12-14 y</td>
<td>quasi-experimental design</td>
<td>NA</td>
<td>Control group</td>
<td>TSH, T3, and T4</td>
</tr>
<tr>
<td>Zenebe et al., 2019</td>
<td>intellectual disabilities</td>
<td>12-14 y Females</td>
<td>Pre-post research design</td>
<td>NA</td>
<td>NA</td>
<td>TSH, T3, and T4</td>
</tr>
<tr>
<td>Wolters et al., 2012</td>
<td>Obese children</td>
<td>8-12 y</td>
<td>Prospective study</td>
<td>Nutrition education</td>
<td>No comparator</td>
<td>TSH, ft3, and ft4</td>
</tr>
<tr>
<td>Reinehr et al., 2006</td>
<td>Obese children</td>
<td>8-12 y</td>
<td>cross-sectional comparison</td>
<td>Nutrition education</td>
<td>lean children</td>
<td>TSH, ft3, and ft4</td>
</tr>
<tr>
<td>Licenziati et al., 2009</td>
<td>Obese children</td>
<td>4-18 y</td>
<td>Longitudinal study</td>
<td>Diet</td>
<td>No comparator</td>
<td>TSH, ft3 and ft4</td>
</tr>
<tr>
<td>Martins et al., 2020</td>
<td>Obese children</td>
<td>8-11 y</td>
<td>Longitudinal study</td>
<td>Nutrition education</td>
<td>No comparator</td>
<td>TSH, ft3, and ft4</td>
</tr>
<tr>
<td>Wissal Abassi et al., 2020</td>
<td>Obese children</td>
<td>15-17 y</td>
<td>Randomized control trial</td>
<td>No adjunct</td>
<td>No exercise</td>
<td>TSH, T4</td>
</tr>
</tbody>
</table>
training,\textsuperscript{22–24} two with Obeldicks weight loss program,\textsuperscript{9,25} and the other two with supervised physical activity as intervention. The intervention and follow-up period in the included studies ranged from eight weeks to 16 months.

Details regarding the population, study design, sample size, adjuvant treatment, comparator agent, and outcome measures assessed in these studies are summarized in Table 2, and the details of interventions and results are given in Table 3.

Discussion
Studies on the effect of exercise on thyroid hormones in the pediatric population are scarce. Earlier studies depicted a transient picture of either increased, decreased or practically unchanged results. The level of alterations in thyroid hormones due to exercise or physical activity depended highly on its type and duration. In addition, adequate nutrition intake is required to negate the negative energy balance, absence of this can alter the endocrine and metabolic profiles. This review summarizes the effects of different types of exercise and physical activity and their duration in a heterogeneous population with thyroid hormonal imbalance in children.

Hypothyroidism
The clinical syndrome of hypothyroidism is caused by a defective production of thyroid hormones; its prevalence among children and adolescents is <2\% and is more common in females.\textsuperscript{12} Complications of undermanaged hypothyroidism lead to abnormalities of lipid metabolism and reduced insulin sensitivity and glucose tolerance. An RCT conducted by Sefat \textit{et al.} (2019) evaluated the effect of exercise training on TSH thyroxine (T4) in adolescent girls with hypothyroidism. After eight weeks of aerobic resistance training, the results showed no significant change, with the p-value $\leq 0.05$ (TSH $\mu\text{u/mL}$ -0.360 and T4 $\mu\text{g/mL}$ - 0.593). The study found no effect on thyroid hormones post-concurrent training but showed significant body fat percentage, BMI, and weight changes. Since the population included was overweight, changes in weight, body composition, and body temperature were associated with thyroid disorders.\textsuperscript{22}

Two other studies conducted by Zenebe \textit{et al.} (2019) in children with intellectual disabilities in adolescents and females also reported that the included population was overweight and obese; this is due to children with intellectual disabilities being usually less physically active and with lower levels of thyroid hormones.\textsuperscript{24,26} The studies reported the effects of 16 weeks of aerobic exercise training with a frequency of three sessions/week for 30-45min, on changes in plasma concentrations of thyroid hormones. Following previous studies, the results of the studies showed significantly improved T3, T4 (T3: p-value=0.005, T4: p-value=0.0001) levels and decrease in TSH (p-value=0.0001) post-intervention in a study conducted on adolescents and T3, T4 (p-value=0.022 and 0.015, respectively) and p-value=0.28 for TSH in the study conducted on females with intellectual disabilities. The results showed that moderate intensity, i.e., 55-75\% of maximum heart rate was an efficient method to improve plasma concentrations of T3, T4, and TSH. Moreover, a four-month duration was too long for achieving equilibrium in TSH and thyroid hormones homeostasis in children with intellectual disabilities. The studies noted that aerobic exercise improves lung function and cognitive changes, leading to a better quality of life.\textsuperscript{23,24}

Obesity
Obesity in the pediatric population shows altered thyroid functions, including hyperthyrotropenemia, a condition characterised by an increase of TSH and freeT3 (fT3) concentrations.\textsuperscript{9} Furthermore, subclinical hypothyroidism shows increased TSH concentrations with normal fT3 and free T4(fT4) concentrations.\textsuperscript{27}

Wolters \textit{et al.} (2012) studied the relationship between TSH and thyroid hormones fT3 fT4 and weight status, as well as their changes, during and after lifestyle intervention. The baseline values in the study of TSH and fT3 were high, and the study results showed differences in TSH and fT3 but not fT4 during the intervention period, which was not significant. The TSH and T3 concentration changes are highly dependent on resting energy expenditure (REE) changes since it is directly proportional to Thyroid hormone concentration.\textsuperscript{25} In addition, a decrease in energy expenditure due to weight loss has been proven.\textsuperscript{29} Since the study did not measure REE, it shows that TSH and T3 concentrations may represent an adaptation process of obesity; that is, returning to normal with weight loss and assuming that increase REE to reduce the availability of energy for conversion of fat. Although this study could not show whether thyroid hormones play a role in weight regain, it showed that exercise-induced weight loss showed changes in thyroid hormone production.\textsuperscript{9}

Reinehr \textit{et al} (2006) did not find significant results in TSH p=0.081, fT4 p=0.156 and fT3 p= 0.386 after intervention. Clinically, TSH and fT3 comparatively decreased but in fT4 levels did not. Since T3 regulates both resting metabolic rate and thermogenesis, changes in thyroid hormones could reflect an adaptation process in obesity, i.e., REE directly proportional to TH changes.\textsuperscript{9,25} This represents a factor in the difficulty to maintain weight loss. The authors also hypothesized that hyperthyrotropenemia in obesity required no treatment.\textsuperscript{8}
Table 3. Changes in Thyroid hormones pre- and post-intervention, * in results indicates significant changes with p <0.05.

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention Details</th>
<th>Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sefat et al., 22</td>
<td>Resistance and aerobic training Intensity: Resistance- to 60–65% of a maximum replication Aerobic- 70–80% HHR. TIME: 75 min: resistance training 30-min: aerobic training TYPE: Resistance-muscular endurance training and muscular strength training. Aerobic- rhythmic movements of the upper body in series of 4 pulses and lower body performed in the series eight pulses</td>
<td>8 weeks</td>
<td>TSH showed a change response from 4.12±1.9 to 6.38±5.2 and T4 value from 6.96±1.1 to 7.62±1.0*</td>
</tr>
<tr>
<td>Altaye et al., 23</td>
<td>Aerobic exercises Frequency: 3 sessions a week TIME: 30–45min TYPE: 10 min of warm-up exercises, 15–30 min of main aerobic workout and 5min cool-down exercises Provided by- Fitness trainer</td>
<td>16 weeks</td>
<td>The change response in TSH 1.097±0.157, T3-1.713±0.224 and T4-8.349±1.043</td>
</tr>
<tr>
<td>Zenebe et al., 24</td>
<td>aerobic exercises Frequency: 3 sessions a week TIME: 30–45min TYPE: 10 min of warm-up exercises, 15–30 min of main aerobic workout and 5min cool-down exercises Provided by- Fitness trainer</td>
<td>16 weeks</td>
<td>The change response in TSH -1.142±0.059, T3-1.812±0.182 and T4-8.27±1.741 *</td>
</tr>
<tr>
<td>Wolters et al., 25</td>
<td>‘Obeldicks’ Weight loss program: Nutrition program Physical activity and counseling</td>
<td>1-year</td>
<td>TSH value post-intervention changed from 5±1.4 to 3±1.5, T3 from 4.2±0.8 to 4.3±1.1 and T4 1.2±0.3 to 1.2±0.4 *</td>
</tr>
<tr>
<td>Reinehr et al., 29</td>
<td>‘Obeldicks’ Weight loss program: Nutrition program Physical activity and counseling</td>
<td>1-year</td>
<td>The change response was seen with intervention in TSH- 2.6(1.6-3.3), in T3 4.3(3.8-4.9) and T4 1.2(1.1-1.3)*</td>
</tr>
<tr>
<td>Licenziati et al., 26</td>
<td>Regular physical activity</td>
<td>1-year</td>
<td>TSH value post-intervention changed from 5.4±1±4 to 4.9±1.5 to 1.2±0.4</td>
</tr>
<tr>
<td>Martins et al., 27</td>
<td>Supervised physical activity</td>
<td>16 months</td>
<td>TSH showed change response from 1.48(1.34-1.62) to 0.6 (-4.5-1.63), T3 from 5.26(5.10-5.36) to -0.15(-2.46-1.38) and T4 12.17(11.93-12.42) to -0.90(-4.89-2.96)</td>
</tr>
<tr>
<td>Wissal Abassi et al., 30</td>
<td>HIIT and MIIT F-3 sessions/week I- HIIT: 100-110% of MAS &amp; recovery at 50% of MAS  I- MIIT- 70–80% MAS &amp; active recovery at 50% of MAS  T- Two sets of six repetitions of 30 s running followed by 30 s of active recovery  T: 35-40min</td>
<td>12 weeks</td>
<td>TSH changed from 2.2±0.4 to 1.6±0.47 and T3 from 15.3±2.01 to 13.4±1.35</td>
</tr>
</tbody>
</table>
Licenziati and Martin et al. (2009) studied thyroid function changes in children subjected to regular physical activity with lifestyle modifications. Children who showed a decrease in BMI showed a decrease in TSH (p <0.0001), where the decrease depended on the extent of weight loss, hence proving an association between BMI and TSH. They also observed structural changes in the thyroid gland, which returned to normal.27,29

Wissal Abassi et al. (2020) showed improving thyroid function status in children post-high-intensity interval training compared with moderate-intensity interval training and no exercise. The change in the response witnessed can be due to intensity- and leptin production-induced hypothalamic hormonal regulation.5 The reduction in body fat corresponds to reduced resting metabolism energy, increasing basal metabolism, and regulating thyroid function level.5,28 Based on these reasons, the group subjected to high-intensity training showed better change response when compared to other groups, thus showing exercise intensity is directly proportional to changes in thyroid functions.28

Exercise, or any form of regular physical activity leads to changes in BMI related to thyroid hormones.9,25,27 No significant study evidenced thyroid hormones returning to normal within the intervention period or post it. However, studies showed some changes in thyroid hormones due to exercise or physical activity linked with weight loss. Weight loss can be achieved through diet, bariatric surgery, or exercise.

Exercise benefits in decreased BMI with changes in cardiovascular adaptations, increase in muscular strength, and improve the quality of life of children and adolescents with thyroid function disorders.9,22,25–27,90–31

Conclusions
Studies with aerobic exercise training for eight to 16 weeks show benefits in improving thyroid functions. However, the study quality was low-level. Regular exercise or physical activity practiced for a longer duration helped reduce weight, influencing thyroid functions to be normal in this population. The extent of change was directly proportional to exercise intensity. However, this review does not provide sufficient evidence stating that exercise results in changes in thyroid function returning to normal, which requires further higher-quality studies to strengthen the review’s findings.

Data availability
Underlying data

This project contains the following underlying data:
- Data extraction (AutoRecovered).xlsx
- PRISMA_2020_checklist.docx
- Study protocol.docx
- PRISMA flow chart

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

References

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