

EXPLORING EXERCISE POTENTIAL TO COMPLEMENT THYROID MEDICATIONS THROUGH RECEPTOR MODULATION: A SYSTEMATIC REVIEW AND META-ANALYSES

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ABSTRACT

Thyroid disorders are experienced by millions of people worldwide, and hypothyroidism is a condition which requires the use of lifelong hormone replacement. We performed systematic review and meta-analysis to assess the effect of exercise intervention on thyroid hormone level and their possible as an adjunctive therapy. We conducted a search on Google Scholar, Web of Science, PubMed, and EBSCO using the search terms 'exercise and thyroid stimulating immunoglobulin (TSI), TSH, T3, T4' in English after 2010 (followed the PRISMA guidelines). Using ROB2 guidelines, the risk of bias was evaluated; using MedCalc software for data analysis with standardized average deviation under fixed & random effects models. Eight studies with 266 participants were selected and utilized using a variety of exercise modalities (aerobic, resistance, water-based, core strengthening) and diverse populations. Meta-analysis revealed significant TSH reduction (SMD= -0.567, $p<0.001$) and T3 elevation (SMD=0.768, $p=0.010$), while T4 changes remained non-significant (SMD=0.218, $p=0.324$). There was significant heterogeneity ($I^2=61.65-72.63\%$) but no publication bias was found. The majority of studies were found to be of low risk. The results indicate that exercise is a clinically significant adjunctive therapy for the management of thyroid disorders with a marked beneficial effect on TSH and T3 levels for different types of exercises. But due to the small sample sizes and brief duration of the interventions and heterogeneity of the populations, larger, well-designed trials are required to determine optimal exercise prescriptions for particular patient populations.

KEYWORDS: Exercises, Hypothyroidism, Thyroid Hormones, Thyrotropin.

INTRODUCTION

Disease of Thyroid are among the most common endocrine diseases, impacting millions of people in various populations and age groups. The major hormones released from Thyroid gland are thyroxine (T4) and triiodothyronine (T3) are secreted and are responsible for the regulation of metabolism, energy homeostasis, cardiovascular function, and overall physiological well-being. Thyroid-stimulating hormone(TSH) plays a key role in performing all these major functions secreted by the anterior part of pituitary gland [1]. Hypothyroidism is defined by a deficient amount of thyroid hormone and is seen in about 2-5% of the general population and is linked to metabolic dysfunction, weight gain, tiredness and reduced quality of life [2]. Typically, lifelong treatment with thyroid hormone replacement (usually levothyroxine) is used to restore normal levels of thyroid hormone and reduce symptoms.

There is a recent trend to consider lifestyle changes, including exercise, as useful complementary treatments for thyroid function and clinical outcome in the management of thyroid diseases [3,4]. Exercise has been shown to have a wide range of effects on metabolism such as increased insulin sensitivity, better lipid profiles, and the regulation of many hormonal systems [5]. The interdependence between physical activity and thyroid hormone levels has been examined in several studies and has found promising albeit inconsistent associations between physical activity and thyroid hormones across studies and physical activities. Long-term exercise programs of 8-12 weeks duration have proven effective in lowering TSH levels and increasing T4 levels in adults with hypothyroidism, especially in conjunction with thyroid hormone therapy [6,7]. Aerobic and resistance training have been found to be effective, and a combination of both training modalities may result in the highest benefits for thyroid function and psychological health related standard of living [6].

The mechanism by which exercise increases the sensitivity of thyroid function is still not fully understood, but has been suggested to include an increase in metabolic activity, an increase in tissue responsiveness to thyroid hormones, improvement in regulation of the hypothalamic- pituitary-thyroid axis and favourable alteration in body composition [8,9]. Research has been conducted in a wide range of populations with mixed results.

Moderate exercise levels have been linked to increased T4 levels and decreased TSH in healthy adults [2], but high-intensity exercise does not seem to provide thyroid benefits beyond those of moderate exercise. In obese people and in people with metabolic syndrome, moderate decreases in TSH levels have been seen with exercise intervention [10]. Little evidence exists that exercise improves thyroid hormone levels in pediatric population with thyroid disorders, but there is a potential for this to occur [11,12].

Though there is increasing research on exercise and thyroid function, there are still gaps in the literature. The diverse methodologies used across individual studies, different types of exercise, participant populations, and outcome measures make it difficult to conclude the extent and clinical relevance of exercise on thyroid hormones [4,13]. Additionally, there is no systematic synthesis of the existing literature for a quantitative assessment of the effects of exercise interventions on TSH, T3, and T4 levels among various population groups and exercise types. Moreover, no meta-analysis has been conducted to comprehensively pool the effectiveness of exercise interventions on TSH, T3 and T4 levels across the various populations and exercise types. The purpose of this systematic review and meta-analysis is to fill literature gaps in advancing knowledge to systematically assess the impact of different exercise interventions on thyroid hormones. This investigation aims to draw strong conclusions on whether exercise can be used as a complementary therapeutic modality for the management of thyroid disorders from the available evidence, derived from multiple randomized controlled trials (RCTs) and prospective studies, and therefore help practitioners make decisions in clinical practice and help guide future research directions in this emerging field.

METHODOLOGY:

We used Databases like google scholar, Web of Science, PubMed and EBSCO were searched using a various key words like exercises and thyroid, aerobic training and TSH, resistance training and TSH etc. to get studies conducted on effects of exercises on thyroid levels including TSH, T3 and T4. The criteria included comprised of all those studies that are available in English language in which the effects of any form of exercises were identified on thyroid hormones levels and was conducted after 2010 so that a good number of studies can be gathered for review and subsequent analyses. However, all those studies that were not available in English language or the full text of the same was not available even after contacting with the author or the outcome measures that were other than thyroid hormone levels like pain, depression anxiety index etc. were all excluded. The quality evaluation of data was performed based on inclusion/exclusion criteria. A data mining form was designed on which various parameters of study finding were registered including author name, target population, study design, intervention given and outcome measure assessed (Table- 1). Likewise, we carry out this investigation according to (PRISMA) criterion (Figure-1). Risk of Bias analyses was performed using a ROB2 guidelines in which all the studies were evaluated on some biased risk, increased risk and decrease risk on three classifications. An excel tool to implement ROB2 was used to perform the analyses [22]. The data collected from the study was analyzed with MDCalc - Medical calculators, equations, scores, and guideline statistical software version 18.11.13.

A standardized average difference (SMD) analyses was performed at random and fixed effects model. A Cohen's rule of thumb was used to interpret the findings of SMD, value of 0.2 to 0.4 indicates low effect size of findings, 0.5 to 0.7 indicates medium effects size of findings and 0.8 and above indicates high effects size at random and fixed effect model [23]. Heterogeneity among the studies was estimated using a I^2 value that was obtained by taking the ratio of the difference of Cochrane's Q and degree of freedom with Cochrane's Q ($I^2 = Q - Df / Q$) to convert heterogeneity into percentage of 0–100%. Low percentages show low heterogeneity and high percentages show high level of heterogeneity among the studies.

Table-1: Characteristics of included study

Author Details	Study Design	Age range	Population Segments	Target Groups	Method of Intervention	Outcome Metrics
Yadav et al 2022[14]	Randomized control trial	Means 30-40 years	Female with decreased thyroid activity normal	Experimental Group (n=10) Control Group (n=10)	EG: Received Resistance Training for 5 days/week each session last for 50 minutes. training was performed using a resistance band or a resistive band CG: Control group received aerobic training of same frequency as of resistance and include jogging or walking as a mode of exercises	TSH

Berahman et al 2021[15]	Randomized control trial	Mean age	65-75 years	Postmenopausal obese	Experimental Group (n=16)	EG: Received 12 weeks of water based rhythmic exercises comprised of 60 minutes of duration/ week. After every 4 week from baseline intensity of exercises were increased on the basis of THR	TSH & T4
					Control Group (n=15)	CG: No distinct protocol of control group was mentioned however the outcome measures were taken from both EG and CG.	
Pancar et al 2020[16]	Randomized control trial	Mean age	20-22 Years	Healthy individuals	Experimental Group (n=12)	EG: For 6 weeks Core strengthening exercises that consist of 7 basic exercises includes: vertical leg crunch and abdominal crunch, , jack knife reverse crunch,	TSH, T3 & T4
					Control Group (n=12)	superman, plank with alternating arm and leg raise and plank jack movements Exercises were performed for three days a week. CG: No details were provided for control group	
Kiani et al 2020[17]	Randomized control trial	Mean age	16 years	High School Girls of Tehran City	Experimental Group (n=15)	EG: Aerobic training performed in the GYM for four weeks Intensity of exercises was measured using a Heart Rate Incremental exercise was performed based on duration started with 10 minutes of aerobic training during first week followed by 5 minutes increase in duration during consecutive 4 weeks taking a duration to 30 minutes during last week. CG: No definite protocol was mentioned for control group	TSH, T3 & T4
					Control Group (n=15)		
Satılmış et al 2020[18]	Randomized control trial	Mean age	13-15 Years	Obese boys of mean BMI 31.1±1.05kg/m ²	Experimental Group (n=10)	EG: Aerobic Exercises for 12 weeks, 3 days/week for a duration of 20–60-minute targeting 400kcal loss/week	
					Control Group (n=10)	CG: No prescribed protocol of exercises for control group	

Jhavar et al 2019[19]	Randomized control trail	18-50 Years	Subclinical Hypothyroidism	Experimental Group (n=50) Control Group (n=50)	EG: Regular Physical Exercises performed on treadmill for 45-60 minutes once weekly for thirty days CG: Only subject to thyroic levels test without any exercise-based intervention	TSH, T3 and T4
Fathi et al 2018[20]	Randomized control trail	35-45 years	Women with a BMI of 30-35kg/m ²	Experimental Group (n=10) Control Group (n=11)	EG: Aerobic Exercises of 45-60 minutes of duration, 3 times week for eight weeks, intensity 65-75% of MHR CG: No prescribed exercise protocol for the group	TSH, T3 and T4
Bansal et al 2015[21]	Randomized control trail	30-40 Years	Male diagnosed with Hypothyroidism	Experimental Group (n=10) Control Group (n=10)	EG: Regular Physical Exercises for 1hour daily for 3 months including jogging or sports CG: Unwilling to perform Physical Exercises	TSH, T3 and T4

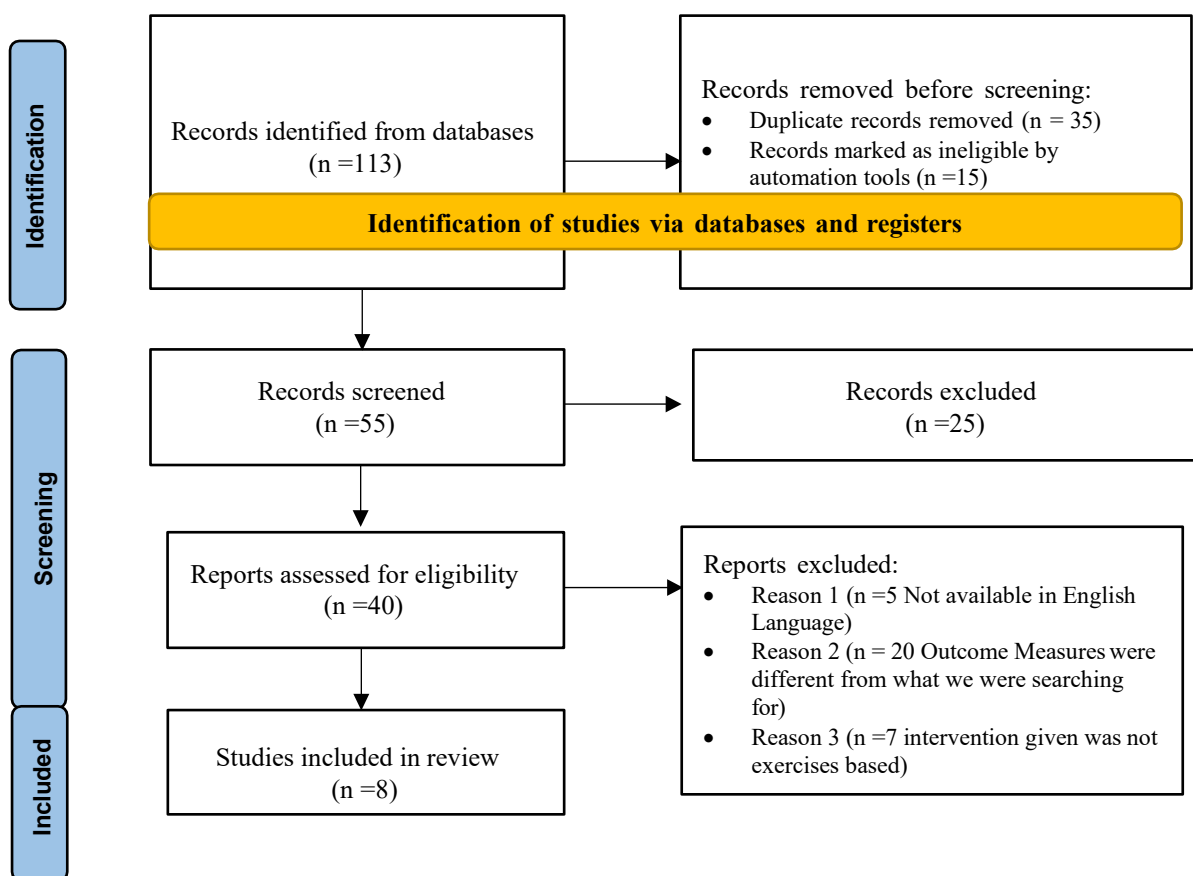


Figure-1: PRISMA 2020 flow diagram for updated systematic review and meta-analysis which included searches of database

RESULTS

This Metanalysis comprises of total eight studies including a collective sample size of n=266 participants encompassing experimental and control group. Studies included a variety of exercise modalities such as aerobic training, resistance training, water-based rhythmic exercises, and core strengthening exercises, and interventions lasted between 4 and 12 weeks. The participants were diverse and ranged from healthy controls to patients with hypothyroidism or subclinical hypothyroidism, obese adolescents and adults, and postmenopausal women, aged 13 to 75 years. Both fixed-effects and random-effects analyses were carried out and heterogeneity was explored by using I^2 statistics while Egger's and Begg's tests were used for examining publication bias.

Effects of Exercise on TSH Levels

How exercise affects TSH levels A total of 246 subjects (123 in exercising groups and 123 in controls) were included in the meta-analysis of the TSH levels. Exercise interventions resulted in statistically significant decreases in TSH in the pooled analysis. Fixed-effects model: standardized average difference = -0.567 (95% Confidence Interval: -0.823 to -0.312; $p < 0.001$) which, according to Cohen's criterion, corresponds to a medium effect size. The results from random effects model yielded were also similar with an SMD of -0.528 (95% CI: -1.010 to -0.0454, This was substantiated by another analysis which showed that this result was robust as $p = 0.032$. There is significant heterogeneity between the individual studies with effect sizes ranging from positive (Yadav et al. 2022, SMD=0.666) to strong negative (Fathi et al. 2018, SMD= -1.234) as seen in the forest plot. The results of heterogeneity testing showed there was a significant level of disagreement between studies ($I^2=67.77\%$, $Q=18.6167$, $p=0.0049$), indicating that the actual effect sizes found in each study vary significantly. This between-study heterogeneity could be due to the differences in the exercise protocols (resistance training, aerobic training, water based, core strengthening), or due to variations in the population (age ranges from 13–75 years, healthy individuals, hypothyroidism, obesity), or due to the duration of the interventions (4 to 12 weeks). Despite this heterogeneity, both Egger's test ($p=0.7445$) and Begg's test ($p=0.8806$) revealed none of publication biases, that strengthen the validity of these findings. (Table-2, Figure-2).

Table-2: Effects of Exercise on TSH Levels

Study	N1	N2	Total	SMD	SE	95% CI	T	P	Weight (%)	
									Fixed	Random
Yadav et al. 2022	10	10	20	0.666	0.441	-0.261 to 1.592			8.64	12.85
Berahman et al. 2021	16	15	31	-0.345	0.353	-1.067 to 0.376			13.50	15.12
Pancar et al. 2020	12	12	24	-1.036	0.422	-1.911 to -0.162			9.45	13.33
Kiani et al. 2020	15	15	30	0.162	0.356	-0.567 to 0.891			13.27	15.03
Jhavar et al. 2019	50	50	100	-0.795	0.206	-1.204 to -0.386			39.49	19.05
Fathi et al. 2018	10	11	21	-1.234	0.461	-2.198 to -0.270			7.92	12.38
Bansal et al. 2015	10	10	20	-1.167	0.466	-2.146 to -0.187			7.73	12.24
Total (fixed effects)	123	123	246	-0.567	0.130	-0.823 to -0.312	-4.378	<0.001	100.00	100.00
Total (random effects)	123	123	246	-0.528	0.245	-1.010 to -0.0454	-2.155	0.032	100.00	100.00
For Testing Heterogeneity										
Q					18.6167					
Degree of Freedom					6					
Significance level					P = 0.0049					
I^2 (inconsistency)					67.77%					
95% Confidence Interval for I^2					28.50 to 85.47					

Publication bias	
Egger's test	
Intercept	0.8181
95% Confidence Interval	-5.2860 to 6.9221
Level of Significance	P = 0.7445

Begg's test	
Kendall's Tau	-0.04762
level of Significance	P = 0.8806

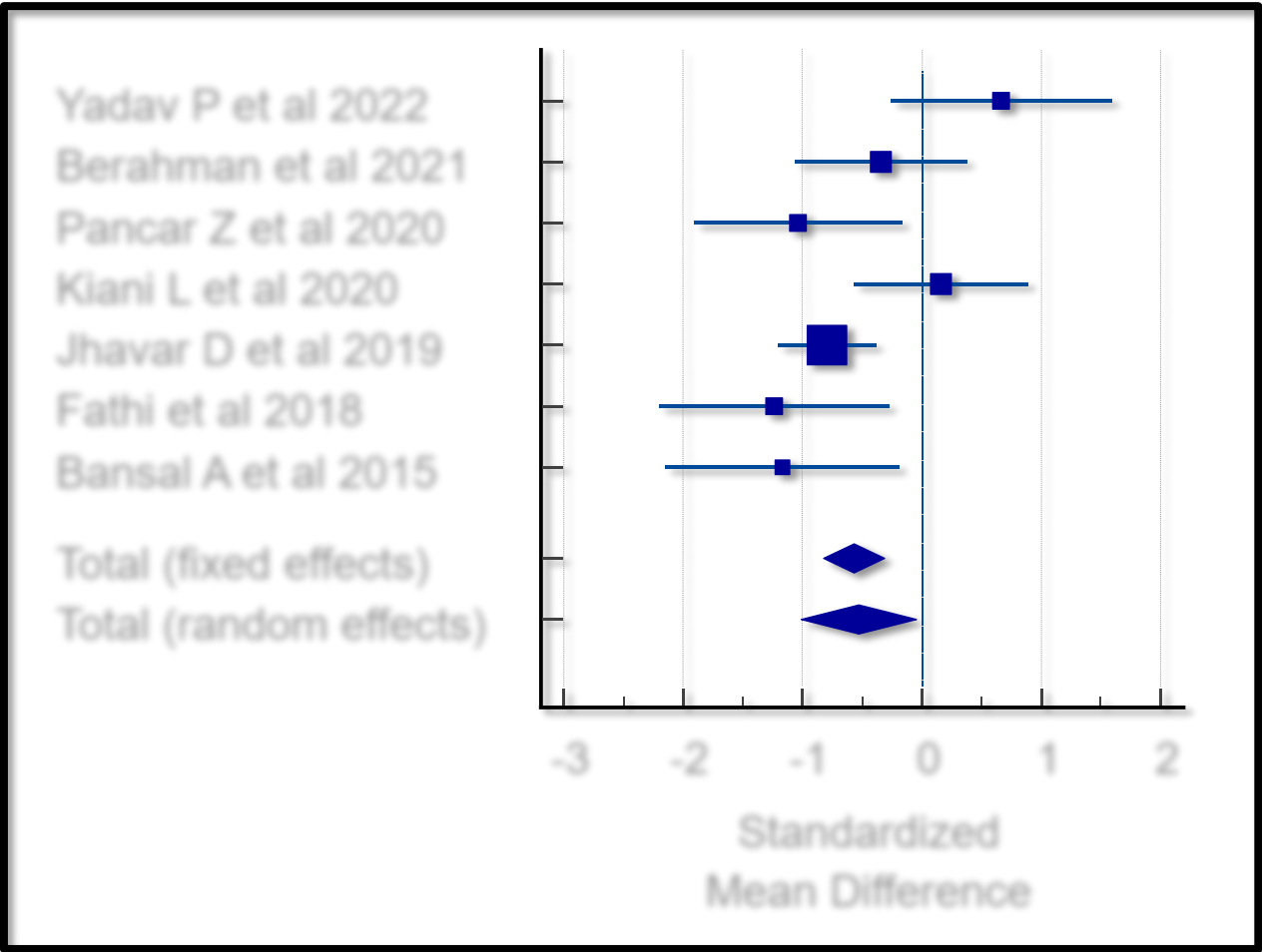


Figure-2: Forest plot showing effects of exercises on TSH levels random and fixed effect model

Effects of Exercise on T3 Levels

Six studies with 215 total participants (107 in exercise experimental groups and 108 in control groups) were included in the T3 meta-analysis. The results indicated a significant increase in T3 levels following exercise interventions. The fixed-effects model showed an SMD of 0.751 (95% CI: 0.473 to 1.030, $p < 0.001$), representing a medium to large effect size, while the random-effects model demonstrated an SMD of 0.768 (95% CI: 0.187 to 1.350, $p = 0.010$). Individual study effects varied considerably, with two studies (Pancar et al. 2020 and Kiani et al. 2020) showing minimal or slightly negative effects (SMD = -0.0259 and -0.0265, respectively), while others demonstrated moderate to large positive effects, particularly Fathi et al. 2018 (SMD = 1.965) and Bansal et al. 2015 (SMD = 1.566). The heterogeneity was substantial and statistically significant ($I^2 = 72.63\%$, $Q = 18.2649$, $p = 0.0026$), revealed considerable variation in the true effect sizes across studies (Table-3, Figure-3a). This variation may reflect differences in exercise modalities employed across studies, including core strengthening exercises, aerobic training protocols of varying intensities and durations, and differences in target populations (healthy individuals, obese adolescents, individuals with subclinical hypothyroidism, and obese women). The assessment for publication bias showed no significant evidence of bias in Egger's test ($p = 0.9133$), though Begg's test approached borderline significance ($p = 0.0909$, Kendall's Tau = 0.6000), suggesting possible minor asymmetry in the funnel plot (Figure-3b).

Table-3: Effects of Exercise on T3 Levels

Table-3: Effects of Exercise on T3 Levels										
Study	N1	N2	Total	SMD	SE	95% CI	T	P	Weight (%)	
									Fixed	Rando m
Pancar et al. 2020	12	12	24	-0.0259	0.394	-0.843 to 0.792			12.82	16.82
Kiani et al. 2020	15	15	30	-0.0265	0.355	-0.754 to 0.701			15.78	17.82
Satılmış et al. 2020	10	10	20	0.481	0.435	-0.433 to 1.394			10.53	15.78
Jhavar et al. 2019	50	50	100	0.960	0.210	0.544 to 1.376			45.28	21.43
Fathi et al. 2018	10	11	21	1.965	0.518	0.882 to 3.048			7.44	13.81
Bansal et al. 2015	10	10	20	1.566	0.495	0.526 to 2.605			8.14	14.34
Total (fixed effects)	107	108	215	0.751	0.141	0.473 to 1.030	5.323	<0.001	100.00	100.00
Total (random effects)	107	108	215	0.768	0.295	0.187 to 1.350	2.605	0.010	100.00	100.00
Test for heterogeneity										
Q					18.2649					
DF					5					
Significance level					P = 0.0026					
I ² (inconsistency)					72.63%					
95% CI for I ²					36.96 to 88.11					
Publication bias										
Egger's test										
Intercept					0.3046					
95% CI					-6.9868 to 7.5960					

Significance level	P = 0.9133
Begg's test	
Kendall's Tau	0.6000
Significance level	P = 0.0909

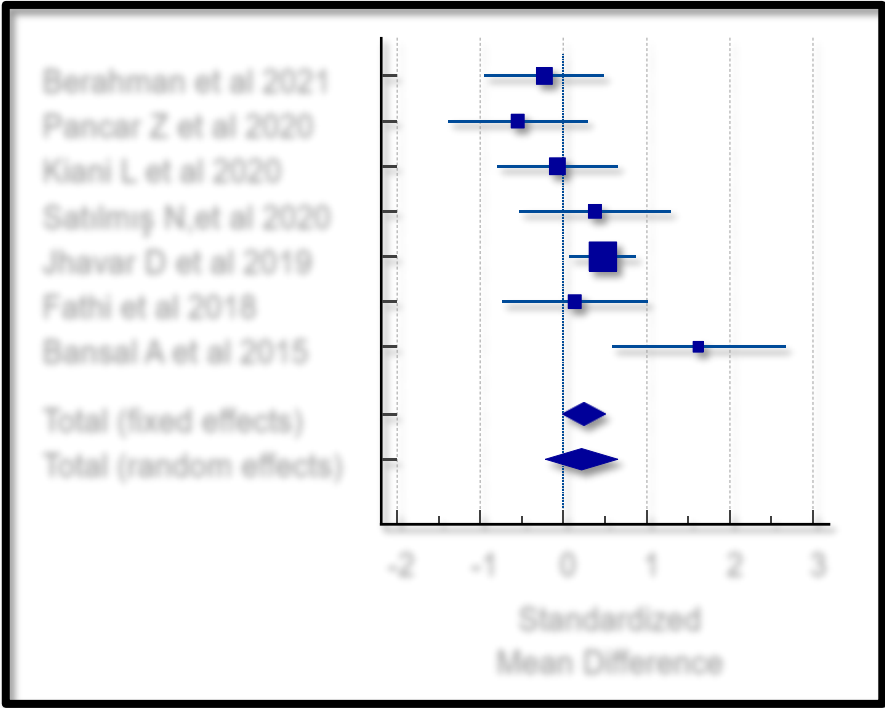


Figure-3a: Forest plot showing fixed and random effect size

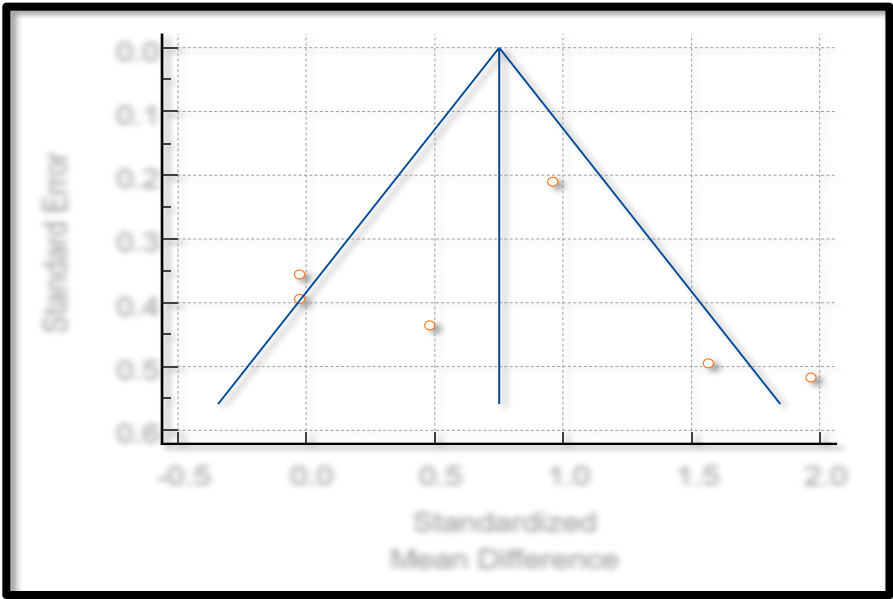


Figure 3b: Funnel plot showing heterogeneity among the findings

Effects of Exercise on T4 Levels

Seven studies encompassing 246 participants (123 in each group) examined the effects of exercise on T4 levels. The meta-analysis revealed more modest and statistically non-significant effects compared to TSH and T3. Under the fixed-effects model, the SMD was 0.246 (95% CI: -0.00438 to 0.496, $p=0.054$), narrowly missing statistical significance and suggesting a small effect size. The random-effects model showed an even smaller and non-significant effect (SMD = 0.218, 95% CI: -0.217 to 0.653, $p=0.324$). The forest plot demonstrates considerable heterogeneity in study findings, with individual study effects ranging from negative (Berahman et al. 2021, SMD= -0.231; Pancar et al. 2020, SMD= -0.546) to strongly positive (Bansal et al. 2015, SMD=1.624). Statistical testing confirmed moderate heterogeneity among the included studies ($I^2=61.65\%$, $Q=15.6440$, $p=0.0158$), though this was somewhat lower than observed for TSH and T3 analyses. The lack of significant overall effect on T4 levels may reflect the fact that T4, as the major thyroid hormone secreted by the thyroid gland, is more tightly regulated by homeostatic mechanisms and less responsive to acute or short-term exercise interventions compared to TSH and T3. There was no evidence of publication bias in both Egger's test ($p=0.8518$) and Begg's test ($p=0.2931$) indicating that the non-significant findings are unlikely to be because of selective reporting of positive results (Table-4, Figure-4).

Table-4: Effects of Exercise on T4 Levels

Study	N1	N2	Total	SMD	SE	95% CI	t	P	Weight (%)	
									Fixed	Random
Berahman et al. 2021	16	15	31	-0.231	0.351	-0.949 to 0.487			13.09	15.05
Pancar et al. 2020	12	12	24	-0.546	0.402	-1.380 to 0.287			10.00	13.46
Kiani et al. 2020	15	15	30	-0.0755	0.355	-0.804 to 0.652			12.79	14.91
Satılmış et al. 2020	10	10	20	0.378	0.432	-0.531 to 1.286			8.64	12.58
Jhavar et al. 2019	50	50	100	0.477	0.201	0.0777 to 0.877			39.85	20.23
Fathi et al. 2018	10	11	21	0.136	0.420	-0.743 to 1.015			9.16	12.93
Bansal et al.2015	10	10	20	1.624	0.499	0.575 to 2.673			6.48	10.83

Total (fixed effects)	123	123	246	0.246	0.127	-0.00438 to 0.496	1.935	0.054	100.00	100.00
Total (random effects)	123	123	246	0.218	0.221	-0.217 to 0.653	0.988	0.324	100.00	100.00

Test for heterogeneity	
Q	15.6440
DF	6
Significance level	P = 0.0158
I ² (inconsistency)	61.65%
95% CI for I ²	12.49 to 83.19
Publication bias	
Egger's test	
Intercept	-0.4266
95% CI	-6.0011 to 5.1478
Significance level	P = 0.8518
Begg's test	
Kendall's Tau	0.3333
Significance level	P = 0.2931

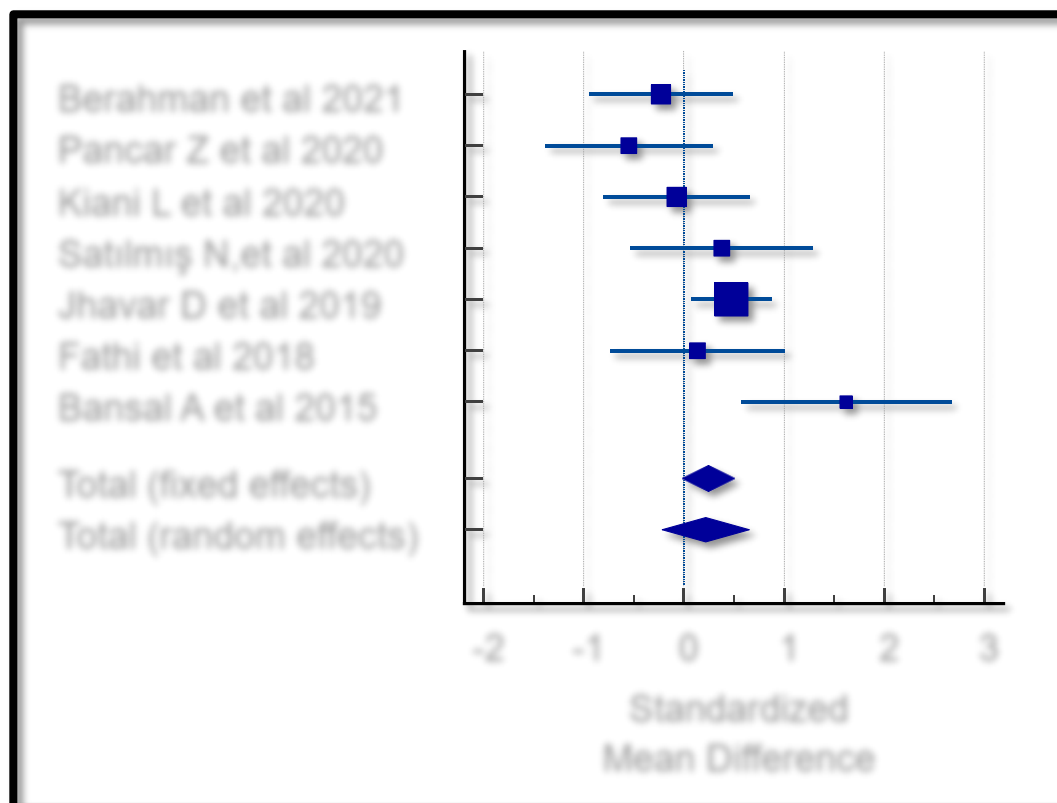


Figure-4: Forest plot showing effects of exercises on T4 levels random and fixed effect model

Risk of Bias Assessment for Determining Methodological Quality of Studies

The methodological quality of the included studies was assessed with the Cochrane Risk of Bias 2 (ROB2) tool in five domains [22]. Overall, most studies had a low risk of bias – 7 studies (Berahman et al. 2021, Pancar et al. 2020, Kiani et al. 2020, Satılmış et al. 2020, Jhavar et al. 2019, Fathi et al. 2018, and Bansal et al. 2015) achieved an overall low risk rating. There was only one study (Yadav et al. 2022) which raised some concern about overall bias, mostly because of randomization and outcome measure concerns (Table-4).

Bias Arising from Randomization Process

Association of the studies with the low risk of bias on the randomization procedure showed that they allocate their studies appropriately with an adequate sequence generation and the concealment of the allocation process. Six studies had low risk of bias in the randomization procedure which suggests adequate sequence generation and concealment of the allocation process. Two studies, however, (Yadav et al., 2022 and Fathi et al., 2018) did raise some concerns about their randomization methods, indicating possible baseline comparability issues between groups due to randomization process.

Bias Deviations from Intended Interventions

The eight studies included in this review all had a low risk of bias on this domain, suggesting good compliance with intervention protocols by participants and personnel. This indicates that there was not a lot of deviation from the exercise interventions as intended, which may limit the validity of the results.

Bias Reduction Due to Missing Outcome Data

In some cases, the data is missing from the outcomes and the results are biased.

There was a reduction in risk of bias shown in all studies, there was minimal attrition and missing outcome data were handled appropriately. This means that the follow-up of subjects was complete or almost complete, and that all investigations included were reported with extensive reporting of thyroid hormones.

Bias in Measurement of Outcome

Outcome measurement had low risk of bias in five studies (Kiani et al. 2020, Satılmış et al. 2020, Jhavar et al. 2019, Fathi et al. 2018, and Bansal et al. 2015). Two studies (Berahman et al. 2021

and Pancar et al. 2020) raised some concerns regarding measurement procedures. Specifically, the study “Yadav et al. 2022” was given a high-risk rating indicating high concerns regarding the reliability and validity of thyroid hormone assessment in this study.

Bias in Selection of Reported Results

In this domain all eight studies had a low risk of bias, suggesting that all pre-specified outcomes were reported fully and transparently. This indicates that selective reporting was not an issue and that all thyroid hormone parameters measured were well reported, irrespective of the direction or size of the effect.

Table-5: Risk of Bias assessment to determine methodological quality of included studies						
Studies	D1	D2	D3	D4	D5	Overall
Yadav et al. 2022	-	+	+	-	+	-
Berahman et al. 2021	+	+	+	?	+	+
Pancar et al. 2020	+	+	+	?	+	+
Kiani et al. 2020	+	+	+	+	+	+
Satılmış et al. 2020	+	+	+	+	+	+
Jhavar et al. 2019	+	+	+	+	+	+
Fathi et al. 2018	-	+	+	+	+	+
Bansal et al. 2015	+	+	+	+	+	+
D1: Bias arising from randomization process + low D2: Bias due to deviations from intended intervention ? Some Concerns D3: Bias due to missing outcome data - High D4: Bias in measurement of the outcome D5: Bias in selective reporting of result						

DISCUSSION

This systematic review and meta-analysis pooled findings from eight studies to assess exercise interventions' effects on thyroid hormones in different populations. The results provide evidence that exercise interventions have a significant effect on reducing TSH levels and increasing T3 levels, with no effect on T4 levels. The findings add to a trend of studies that indicates the value of exercise as a useful complementary therapy in the treatment of thyroid disorders, but with considerable variation between studies, the results must be interpreted with caution.

The observed significant decrease in TSH levels (SMD= -0.567, $p<0.001$) is consistent with some of the investigations retrieved from this meta-analysis. One study found that males with hypothyroidism who exercised regularly for 3 months had a significant lowering of TSH levels and lost weight [21]. The same study found that another group of patients with subclinical hypothyroidism had significant decrease in TSH after 30 days of the exercises on the treadmill [19]. In one study, comparing aerobic and resistance training, resistance training was found to be superior to aerobic training for TSH levels in those with hypothyroidism [14]. The mechanism by which exercise leads to reduced TSH levels could be related to improved regulation of the hypothalamic-pituitary-thyroid axis, increased sensitivity of peripheral tissues to thyroid hormones, and favorable metabolic changes which decrease the need for stimulation by thyroid hormones [24]. It seems that the answer depends on the type of exercise performed, however, because a single study demonstrated small changes in TSH in obese postmenopausal women with rhythmic exercises that were water-based [15]. This difference might be due to the methodological factors, as well as the intensity of the exercise, the characteristics of the population involved, and the length of time of the intervention, which should be taken into account.

The clinically relevant increase in T3 level (SMD=0.768, $p=0.010$) was found in our analysis, and this is the

most metabolically active thyroid hormone which is important for energy metabolism, thermogenesis and cardiovascular function. One study evaluating aerobic activity in obese boys showed that there was a significant increase in T3 levels, and positive changes in lipid profiles [18]. In another study, investigating core strengthening exercises in healthy men, positive results on thyroid metabolism were seen after 6 weeks of core training [16].

A population-based cohort study has recently been undertaken that provides evidence of the thyroid function-physical activity relationship being bidirectional and complex, since physical activity may influence thyroid function levels in addition to exerting effects on them [25]. The significant heterogeneity found for T3 responses ($I^2=72.63\%$) may be attributed to the difference in exercise protocols as different modalities have different metabolic requirements. The aerobic training studies in high school girls yielded inconclusive results for T3, with only slight changes in other metabolic measures observed, [17] and greater increases in T3 levels were observed in studies that used longer duration, higher intensity training, [20]. These data indicate that the intensity and amount of exercise can be important factors in determining the thyroid hormone response.

The result that T4 was not significantly affected (SMD=0.218, $p=0.324$) should be approached with caution. T4 is the major secretory product of the thyroid gland and is tightly regulated by negative feedback mechanisms related to the activity of the hypothalamic-pituitary-thyroid axis. However, a population-based study did not show an association between total physical activity and thyroid function levels, indicating that there may not be a strong exercise-induced modulation of T4 in the general population without marked thyroid disease [26]. Recent Mendelian randomization (MR) studies have shown that thyroid function has an effect on daily activity patterns, a greater amount of sedentary time was observed with higher TSH, suggesting that the relationship between physical activity and thyroid hormone is not a straightforward one [27]. Acute exercise did not significantly influence thyroid hormone levels in healthy, active male athletes, indicating that thyroid hormone is well controlled under normal physiological conditions [24] in agreement with the present idea that the ingestion of melatonin during the day has no effect on thyroid hormone levels. It is also possible that the small and not significant T4 changes we observed in our analysis might be due to the relatively few and short interventions that were included in the studies (4-12 weeks), since longer-term exposure to exercise may be required to elicit structural changes in thyroid gland function and capacity to synthesize hormones.

The significant heterogeneity found in all meta-analyses ($I^2=61.65-72.63\%$) provides a limitation and an opportunity to gain insight into the complex effects of exercise on thyroid function.

Several factors may contribute to the heterogeneity, such as different exercise modalities used in the studies included, [16] different types of exercises (water-based or land-based), [15] different intensities and durations of interventions, and substantially different participant groups including healthy women, [16] hypothyroid, [14,21] obese, [18,20] adolescents, [17] and postmenopausal women. [15] A recent, extensive literature review of the relationship between thyroid disorders and physical activity found that thyroid disorders may have an adverse effect on physical activity capacity and physical activity could be used to treat some disorders linked to thyroid dysfunction [13]. Such heterogeneity implies that some exercise responses to the thyroid may be individual and thus specific interventions should be tailored according to an individual's characteristics and therapeutic needs. Although no publication bias was found in any of the analyses, there may be some uneven distribution of tests with small numbers of subjects in each and a relatively small number of studies; larger, well-designed trials with standardized outcome assessment protocols are needed for the results of these analyses to be interpreted with caution.

CONCLUSION

This systematic review and meta-analysis yielded strong evidence to support the use of exercise interventions to decrease TSH levels and increase T3 levels, but no significant effects were observed when measuring T4 levels. The moderate effect sizes seen with the effects of exercise on TSH and increase in T3 indicate that exercise is a clinically more significant adjunctive treatment for thyroid disorders, especially in conjunction with standard thyroid hormone replacement therapy. The positive outcomes seem to be similar regardless of the type of exercise program, such as aerobic, resistance, or combination, but there is significant variation in response to exercise, depending on the participant, the characteristics of the exercise program, and the baseline thyroid status.

While these findings are promising, there are several important constraints and areas of research that need to be noted. Findings from individual studies may be limited to generalizability and definite conclusions about optimal exercise prescriptions for specific patient populations are not available due to relatively small sample sizes and short lengths of interventions. Large randomized controlled trials with an appropriate exercise protocol, adequate power and long-term follow-up, and measurement of all thyroid function markers, and quality of life and adverse effects are recommended for the future.

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