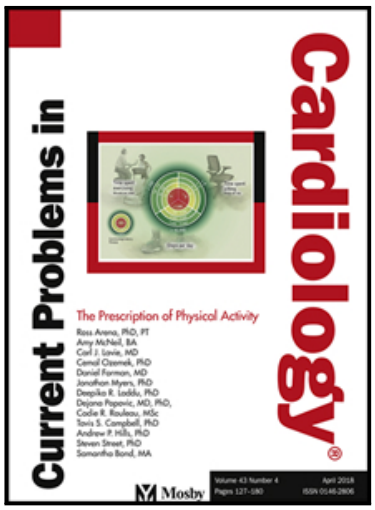

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Relationship of subclinical hypothyroidism on epicardial adipose tissue: a systematic review and meta-analysis

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Abstract: Accumulation of epicardial adipose tissue (EAT) and Subclinical hypothyroidism (SH) are associated with increased cardio-metabolic risk. The objective of this study was to quantitatively compare EAT thickening between patients with SH and healthy controls. Therefore, after searching the PubMed/MEDLINE, Embase, Science Direct, Scopus, Google Scholar, and Cochrane databases; we analyzed a group of observational studies who compare the EAT changes between SH vs control groups. A total of 9 studies were included in the final analysis, for a total of 424 patients with SH and 330 controls. Random or fixed effects models were used. Pooled analysis revealed that HS increased EAT (MD: 1.0 mm [0.40; 1.50]; $P < 0.01$). This meta-analysis suggests that the amount of EAT is significantly increased in SH patients. EAT might be a marker of cardiovascular risk in patients with SH.

Keywords: Epicardial adipose tissue, subclinical hypothyroidism, meta-analysis, cardiovascular diseases

Introduction

Subclinical hypothyroidism (SH) is defined as combination of elevated levels of thyroid-stimulating hormone (TSH) and normal levels of free thyroid hormones. Hypothyroidism is considered to be a risk factor for cardiovascular diseases (CVD) [1]. SH is associated with dyslipidemia, diastolic hypertension, impaired coagulation, carotid artery intima-media thickness and arterial stiffness [2].

The presence of SH seems to be linked with an elevated body mass index (BMI) as this condition it is more common in obese individuals (7-23%). This association is considered an adaptive response to increase resting energy expenditure [3]. As obesity and overweight have become pandemic diseases worldwide in the last decades further research needs to be done to clarify this topic.

The increase in visceral adipose tissue (VAT) and ectopic fat deposition are characteristic in SH. In fact, obesity causes a reduce capacity of lipid storage in the visceral adipose tissue that leads to a lipid spillover to non-adipose tissues such as the skeletal muscle, liver, and heart. This abnormal fat deposition impairs insulin signaling and leads to insulin-resistance [4].

There is evidence about the importance of epicardial adiposity on cardiometabolic risk.Epicardial adipose tissue (EAT) is the adipose tissue depot immediately adjacent to the heart wall, being an anatomic supplier of substrates to the myocardium, given that no fascia separates EAT adipocytes from cardiomyocytes and the coronary blood stream [5].

This VAT, in healthy metabolic states, would act as a buffer for the overload of fatty acids to the myocardium. However, in insulin-resistant states, this buffer function is vanished as EAT expands. Consequently, a proinflammatory profile is expressed, characterized by M1 macrophage infiltration and bioactive lipid species enrichment, as well as proinflammatory cytokine expression [6].

In this context, the secretion of inflammatory mediators such as tumor necrosis factor alpha (TNF-α), Interleukin 6 **(**IL-6), and adipocytokines would play an important role in the development of coronary atherosclerosis, through potential paracrine or endocrine mechanisms [7].

Total amount of body fat as well as its distribution which are thus disturbed in hypothyroidism, a common condition, which is strongly associated with obesity and dyslipidemia [8].

Previous studies have evaluated the association SH and EAT changes although the results were conflicting [9], [10], [11], [12], [13], [14], [15], [16], [17]. To date, there are no published meta-analyses that assess this topic. Therefore, our main objective is to evaluate available published data reporting EAT on SH.

2. Materials and Methods

A systematic review was conducted, based on the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist[18]. Using the PICOS model (patient, intervention, control, outcome, study), inclusion and exclusion criteria were created. Potential risks of bias were evaluated for all included experimental studies, using the Cochrane tool developed for this purpose[19]. The ROBINS-I tool assesses bias in seven different domains: bias due to confounding, bias due to selection of participants, bias in classification of interventions, bias due to deviations from intended intervention, bias due to missing data, bias in measurement of outcomes and bias in selection of the reported result. Each domain was rated as ‘‘Serious’’, ‘‘Moderate’’ or ‘‘Low’’ depending on the judgment of the authors.

The quality of the included studies was assessed by two independent review authors, any discrepancy between the two reviewers was solved through discussion and by involving a third reviewer. All possible combinations of search terms included, PubMed/MEDLINE, Scielo, Google Scholar, Embase and Cochrane Controlled Trials databases using the terms: "Subclinical hypothyroidism" AND "epicardial fat tissue OR epicardial adipose tissue OR subepicardial adipose tissue OR subepicardial fat tissue". No language or publication date restrictions were imposed in this study. Two independent authors analyzed each paper and independently extracted the data. The differences were settled by accordance.

We analyzed studies that reporting EAT thickness. Between the outer wall of the myocardium and the visceral layer of the pericardium, "EAT" is found as the echo-free space. Higher reproducibility and interobserver agreement have been shown by surface measurement [20].

All the analyzed studies meet the following inclusion criteria: a) SH patients b) Observational studies c) Reporting of change in epicardial fat tissue thickness between SH and the control group.

Exclusion criteria included a) Duplicate studies, abstracts from unpublished studies, reviews, cross-sectional studies, case reports, and letters b) Participants diagnosed with severe hypothyroidism or hyperthyroidism; c) Animal studies and reviews d) Studies that did not provide the value of at least one variable (mean and standard deviation) among the predictors.

EAT thickness can be measured by an echocardiographic epicardial fat thickness test; between the outer wall of the myocardium and the visceral layer of the pericardium, EAT is measured as the echo-free space. Due to, higher reproducibility and interobserver agreement have been shown by volumetric measurement, finally, EAT thickness is a parameter that is used in the qualitative analysis[21].

The primary endpoint of the study was the change in EAT measured from SH vs control group and the secondary points were: a) change in lipids levels between SH vs control group; b) change in BMI between SH vs control group. We performed the same analysis comparing TSH ≥10 or TSH<10mIU/L groups.

Statistical analysis

The summary effect on the primary endpoint was estimated. Measures of effect size were expressed as mean difference (MD), and the I^2 statistic was calculated to quantify between trial heterogeneity and inconsistency. Depending on the value of I^2, a fixed effects model ($I^2 < 40\%$) or a random effects model ($I^2 > 40\%$) was chosen. To compare mean effects between subgroups, a Z test was used. Statistical analyses were performed using the R software for statistical computing version 3.5.1 with additional specific packages. A two-tailed p value > 0.05 was considered statistically significant[22].

Analysis of publication bias: The tests for funnel plot asymmetry were not done because this research included a small number of studies. In this context, the power of the tests is too low to distinguish chance from real asymmetry. However, Egger's regression intercept tests were done. A p-value less than 0.1 was considered significant for the linear regression test.

Sensitivity analyses: A sensitivity analysis was performed. It consists of replicating the results of the meta-analysis, excluding in each step 1 of the studies included in the review.

Results

The search included 163 potentially relevant articles after title screening, 12 studies were excluded after duplicated removed and 115had at least on exclusion criteria. After full textual analysis, 46 studies were removed as these did not include outcomes relevant to our study. Only 9 studies were assessed for quantitative analyses (7 from Turkey, 1 from Brazil and 1 from Korea), all case-control.. A flow diagram of the screening process is shown in **Figure 1**. and the main characteristics of the studies are shown in **Table 1.**

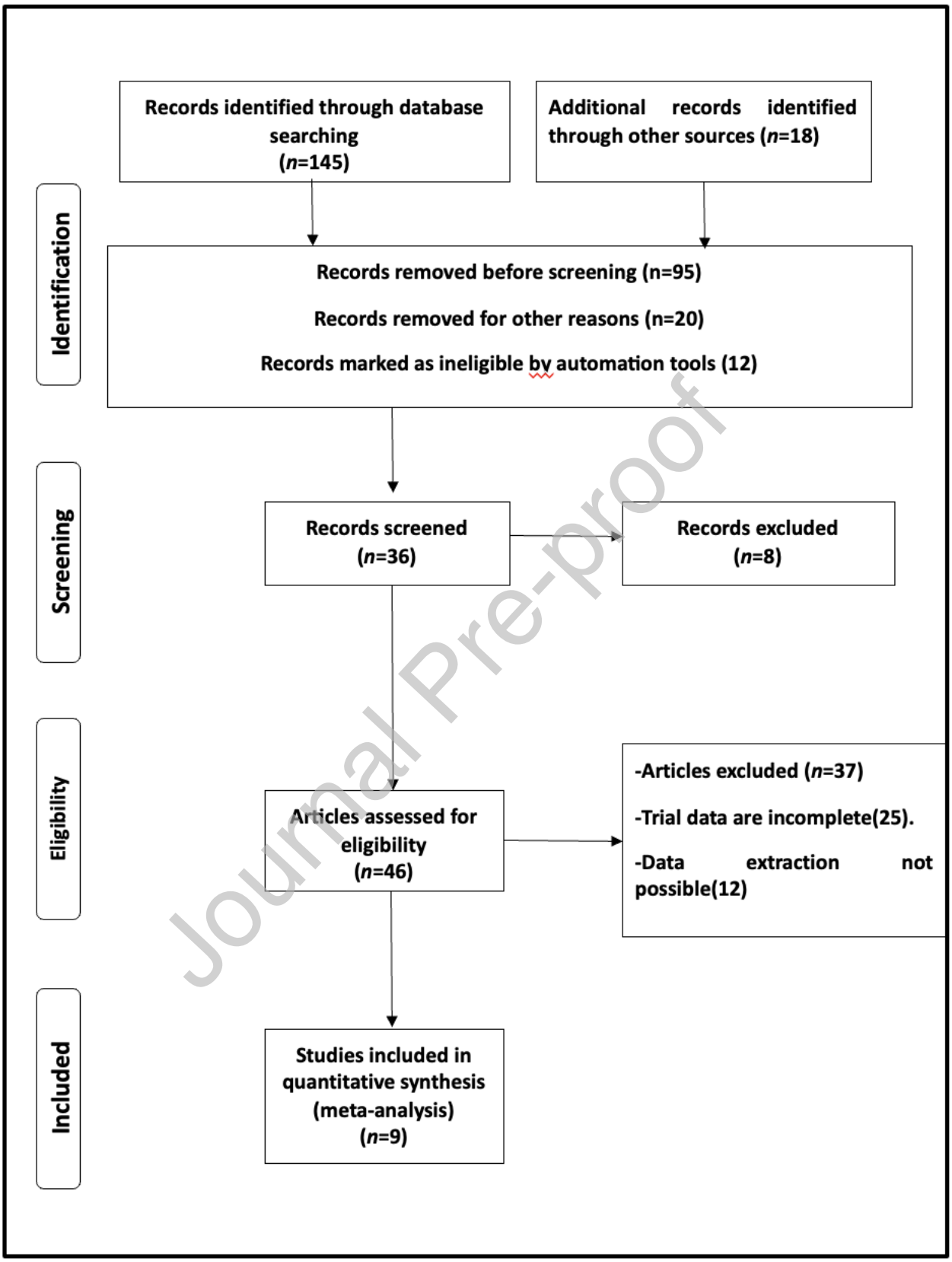


Fig 1. Flow diagram of the study screening process

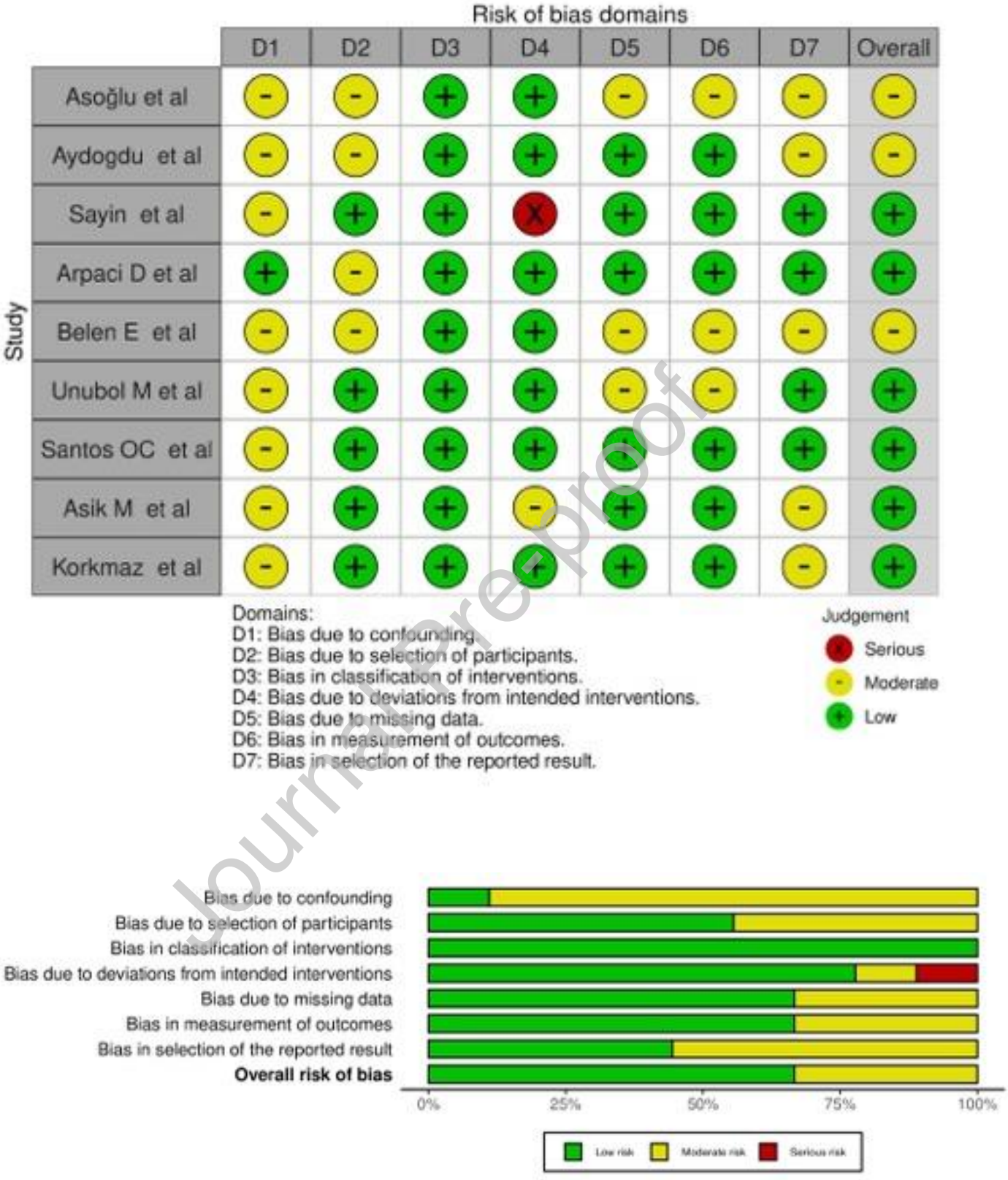


Fig 2. Bias assessment of included studies.

Table 1. Basal characteristics of included studies.

Author	Number (n)	EAT thickness (mm)	BMI(Kg /m^2)	TG (mg/dl)	HDL (mg/dl)	TC (mg/dl)	LDL (mg/dl)	TSH (mIU/L)
Emin Asoğlu	Control (43)	6.0 ± 2.0	26.2 ± 2.4	205.2 ± 22	42.3 ± 11.4	196.7 ± 36.5	119.2 ± 28.5	3.1 ± 0.7
	Cases (80)	7.0 ± 3.0	26.5 ± 2.4	201.9 ± 39	44.7 ± 8.3	187.0 ± 32.6	118.6 ± 35.6	14.2 ± 6.8
Ali Aydogdu	Control (30)	5.20 ±1.60	37.3 ± 10.5	123 (57–352)	45.2 ±10.5	184.7 ±43.6	108.8 ±40.5	1.5 (0.7–5.3)
	Cases (30)	6.60 ± 2.40	41.8 ± 9.7	144 (45–396)	46.8 ±12.2	197.1 ± 52.9	119.6 ±47.2	7.5 (5.6–22)
Irmak Sayin	Control (42)	4.1 ± 0.90	26.4 ± 4.9	96.6 ± 21.4	47.1 ± 8.6	174.6 ± 28.2	107.1±18.7	2.7 ± 3.0
	Cases (44)	6.30 ± 1.70	27.1 ± 5.2	165 ± 38.8	33.2 ± 5.4	211.2 ± 37.5	116.4±31.4	10.8 ± 12.1
Dilek Arpaci	Control (35)	4.51 ±0.07	23.7 ± 3.0	83.7 ± 27.2	57.32 ± 11.8	NR	104.4 ± 25.5	1.5 ± 0.8
	Cases (41)	4.61 ± 0.06	27.8 ± 5.3	105.9 ± 50.1	55.2 ± 15.4	NR	125.8 ± 31.7	14.5 ± 6.5
Erdal Belen	Control (51)	4.70 ± 1.20	25.4±1.9	129 ± 35.4	50 ± 7.8	156.4 ± 28.4	89 ± 19.5	3.0 ± 1.0
	Cases (51)	6.70 ± 1.40	26.2±2.4	161 ± 49	44.5 ± 6.3	170 ± 41.2	100.7 ± 31	10.1 ± 5.1
Mustafa Unubol	Control (25)	2.81 ± 0.74	24.1 (20.3-28.7)	102 (75-177)	52.1 ± 12.4	196.1 ± 36.2	117.8 ± 32.2	1.71±1.16
	Cases (37)	3.83 ±1.04	28.5 (22.9-32.9)	111 (80-147)	54.4 ± 24.7	212.7 ± 37.9	138.5 ± 31.4	5.78±1.46
Santos OC	Control (48)	3.5 ± 1.20	28.8 ± 6.4	122.1 ± 71	52.5 ± 17.2	205.2 ± 36.0	124.9 ± 32.9	1.7 ± 0.9
	Cases (52)	3.5 ± 1.30	28.5 ± 5.7	153.2 ± 115.7	48.7 ± 14.8	211.2 ± 41.7	130.9 ± 39.5	6.7 ± 1.4
Mehmet Asik	Control (32)	2.89 ± 0.38	27.8 ± 3.6	99.3 ± 38.6	47.5 ± 10.5	176.7 ± 28.5	107.3 ± 24	1.73 ± 1.05
	Cases (33)	3.53 ± 0.92	30.4 ± 0.7	143 ± 84.6	51.9 ± 11.9	196 ± 40.4	131 ± 36.1	9.4 ± 3.9
Levent Korkmaz	Control (24)	2.80 ± 1.4	33.1 ± 6.2	115 ± 46	51 ± 11	186 ± 32	120 ± 28	1.5 ± 0.9
	Cases (61)	3.6 ± 0.90	33.2 ± 6.3	147 ± 68	49 ± 10	191 ± 44	130 ± 31	9.3 ± 5.6

Abbreviations: BMI: Body Mass Index, EAT: Epicardial Adipose Tissue, TG: triglyceride, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, NR: Not Reported, TSH: Thyroid-Stimulating Hormone, TC: Total Cholesterol.

Basal characteristics of cases and controls

Data from 760 patients were evaluated, corresponding to 430 subjects with SH patients and 330 in the control group. The average age was 43 years in the control group and 47.5 years in the group of SH patients, 72.7% of the participants in the control group and 84.07% of the subjects in the SH group were female.

Differences in EAT thickness between patients with SH vs controls

A significant difference in EAT thickness was observed in patients with SH vs control group (mean difference [MD]: 1 mm; 95% confidence interval [95% CI]: 0.4−1.5, p<0.01; statistical heterogeneity was 94%), (Figure 3,A). This difference remained significant regardless of TSH values on subgroup analysis (TSH < 10 mIU/L, MD: 0.7 mm; 95% CI: 0.3−1.1, p<0.01; statistical heterogeneity was 58%) and TSH > 10 mIU/L, MD: 1 mm; 95% CI: 0.5−1.5, p<0.01; statistical heterogeneity was 97% (Figure 4, A).

BMI levels between patients with SH vs controls

BMI levels were not different in SH vs control group (MD: 1.0 kg/m^2; 95% CI: -0.1−2.1, p= 0.58; statistical heterogeneity was 66%), (Figure 3B). These results remained regardless of TSH values on subgroup analysis (TSH < 10 mIU/L, MD: 0.5 kg/m^2; 95% CI: -0.3−1.3, p=0.18; statistical heterogeneity was 0%) and TSH > 10 mIU/L, MD: 1 kg/m^2; 95% CI: -0.5−2.4, p=0.31; statistical heterogeneity was 76% (Figure 4, B).

Total cholesterol (TC), Low-density lipoprotein (LDL), Triglycerides (TG) and High-density lipoprotein (HDL) levels in patients with SH vs controls

SH increased TC levels significantly compared to the control group (MD: 12.4; 95% CI: 1.8−23.1, p< 0.01; statistical heterogeneity was 74%), (Figure 3C). This difference remained significant only TSH >10 IU (TSH < 10 mIU/L, MD: 7.5 mg/dl; 95% CI: -0.3−1.1, p=0.072; statistical heterogeneity was 21%) and TSH > 10 mIU/L, MD: 1 mm; 95% CI: 0.5−1.5, p<0.01; statistical heterogeneity was 71% (Figure 4, C).

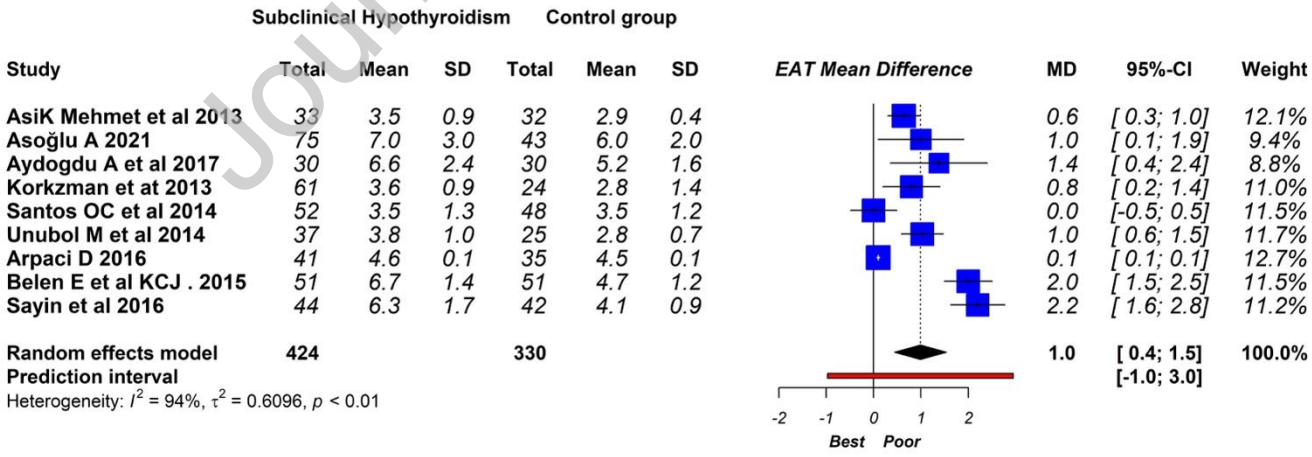
LDL levels increased in SH compared to the control group (MD: 11.7; 95% CI: 7.3−16.1, p<0.01; statistical heterogeneity was 27%), (Figure 3D). This difference remained significant regardless of TSH values on

subgroup analysis (TSH < 10 mIU/L, MD: 9.1 mg/dl; 95% CI: 3.1−15.1, p<0.01; statistical heterogeneity was 18%) and TSH > 10 mIU/L, MD: 11.7 mg/dl; 95% CI: 0.5−1.5, p<0.01; statistical heterogeneity was 45% (Figure 4, D).

Triglycerides (TG) levels increased in SH compared to the control group (MD: 32 mg/dl; 95% CI: 8.5−55.5, p<0.01; statistical heterogeneity was 91%), (Figure 3E). This difference remained significant only TSH >10 mIU/L (TSH < 10 mIU/L, MD: 19.3 mg/dl; 95% CI: -11.2−49.8, p=0.091; statistical heterogeneity was 82%) and TSH > 10 mIU/L, MD: 35.4 mg/dl; 95% CI: 9.0−61.7, p<0.01; statistical heterogeneity was 91% (Figure 4, E).

HDL levels were not difference in SH compared to the control group (MD: -2.1 mg/dl; 95% CI: -6.6−2.3, p = 0.24; statistical heterogeneity was 88%) (Figure 3F). This results were not difference despite of TSH values on subgroup analysis (TSH < 10 mIU/L, MD: 0.9 mg/dl; 95% CI: -1.4−3.2, p=0.081; statistical heterogeneity was 0%) and TSH > 10 mIU/L, MD: -5.0 mg/dl; 95% CI:-10.9−0.9, p=0.32; statistical heterogeneity was 91% (Figure 4, F).

A



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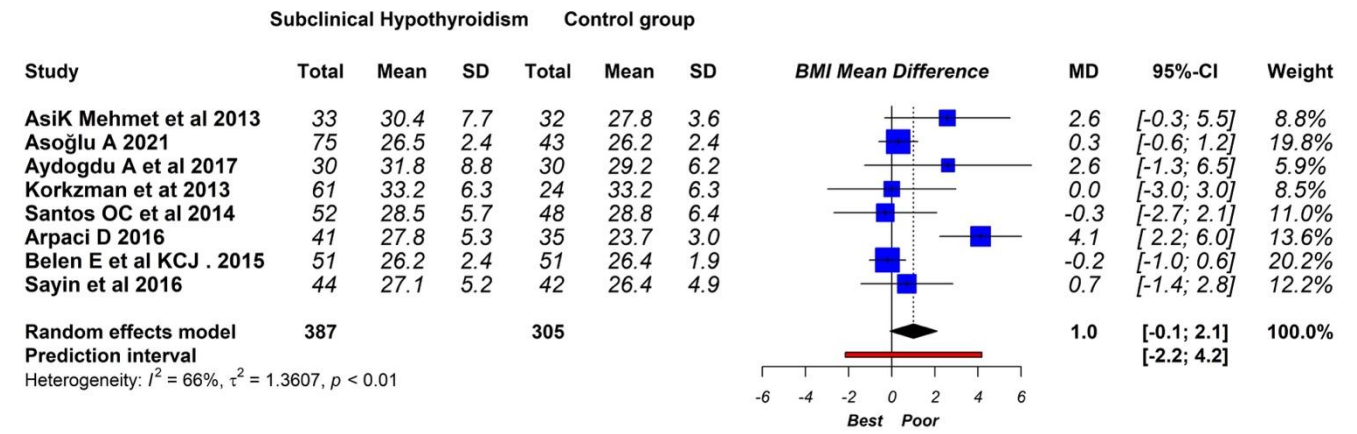

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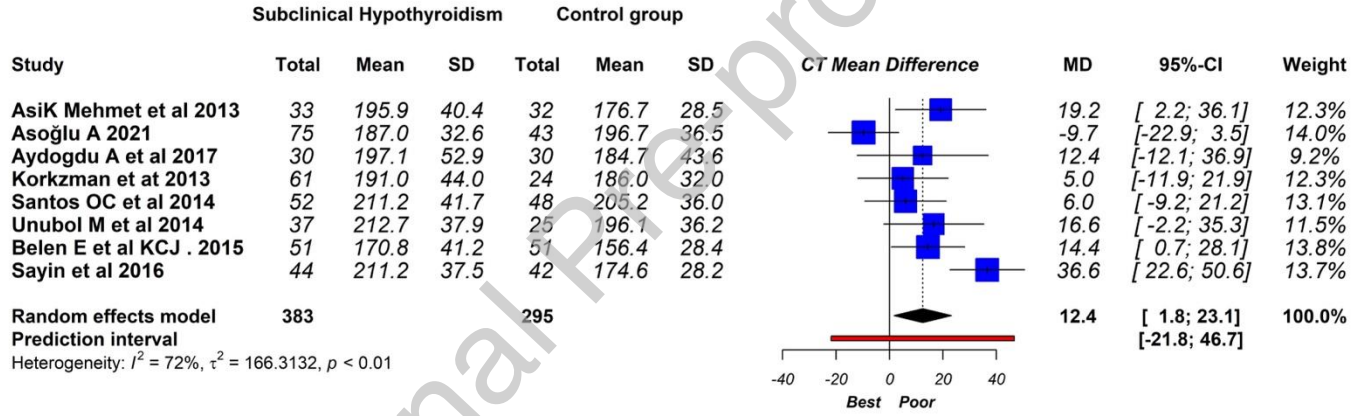

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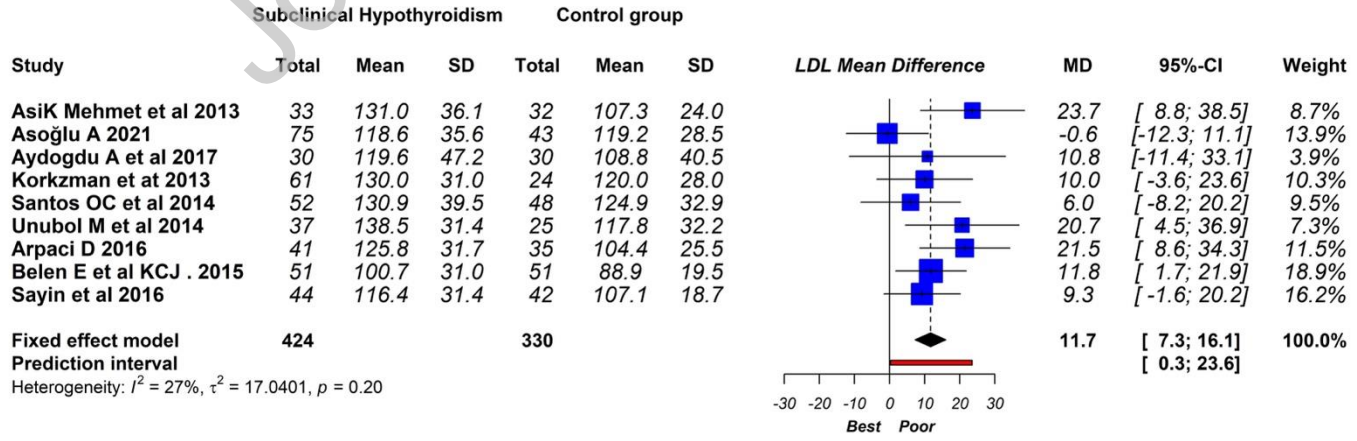

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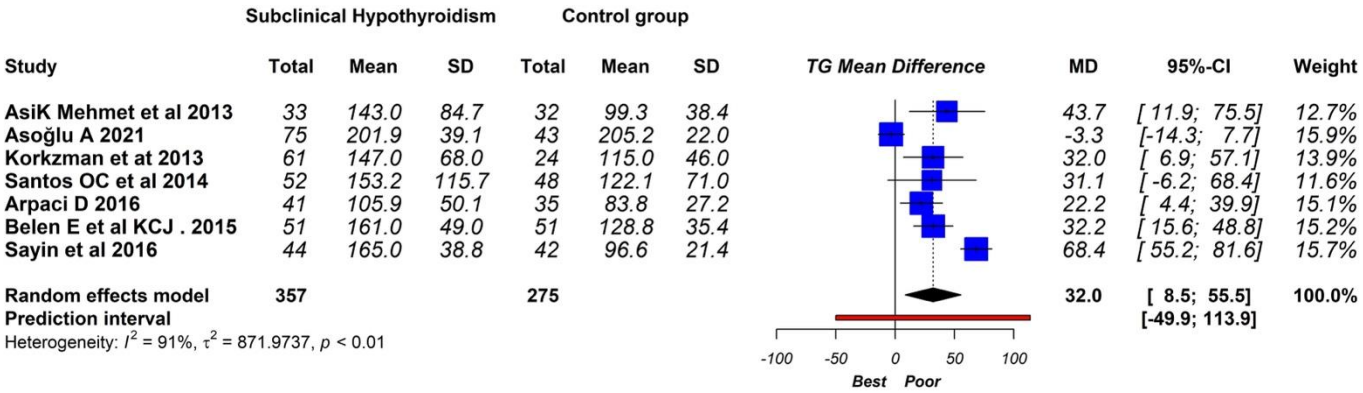

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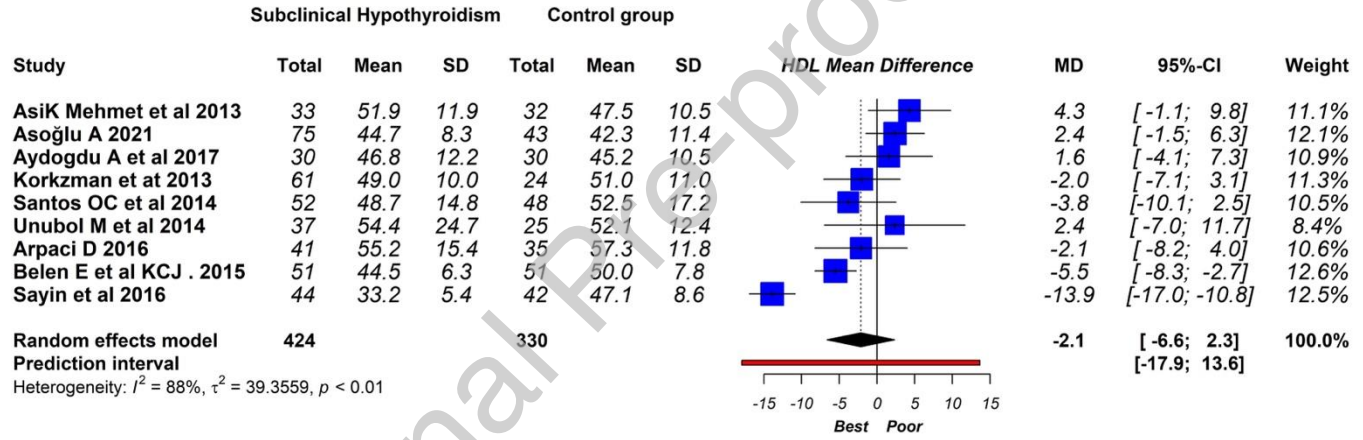
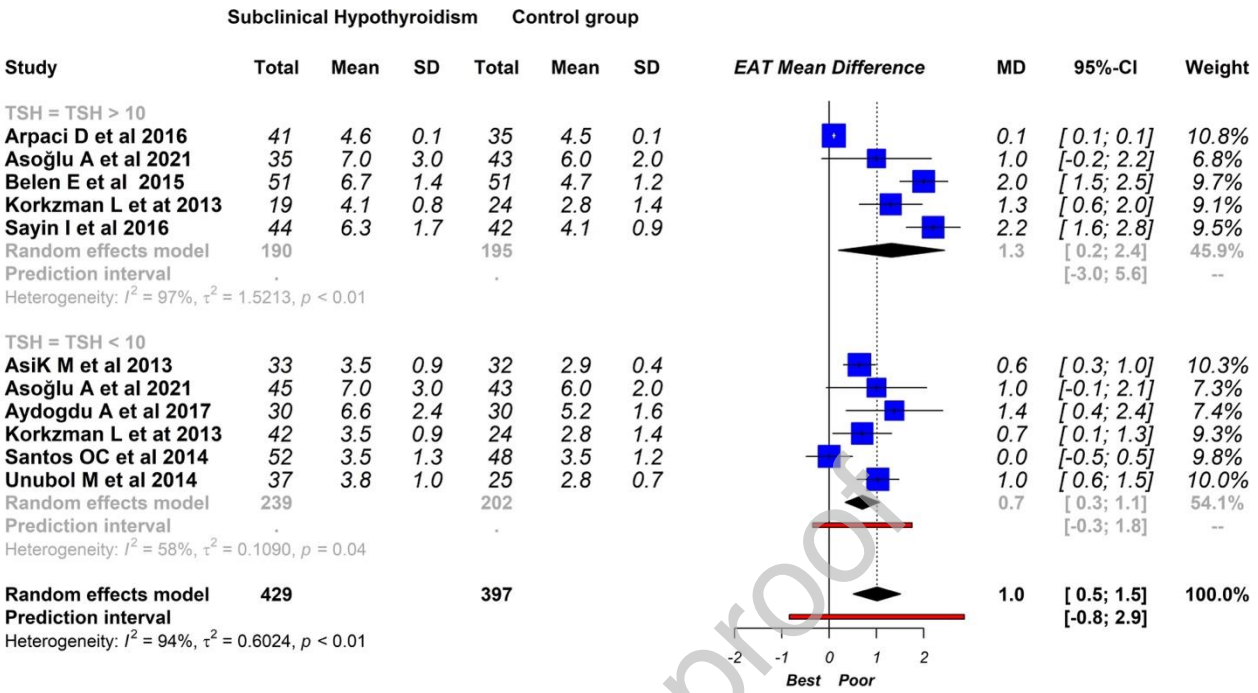


Figure 3. Effect of SH on epicardial adipose tissue (EAT) (A), body mass index (BMI) (B), TC (C), LDL (D), TG (E) and HDL (F). Random or Fixed model, mean difference (MD), 95% confidence intervals (CI), and I2 statistics.

A



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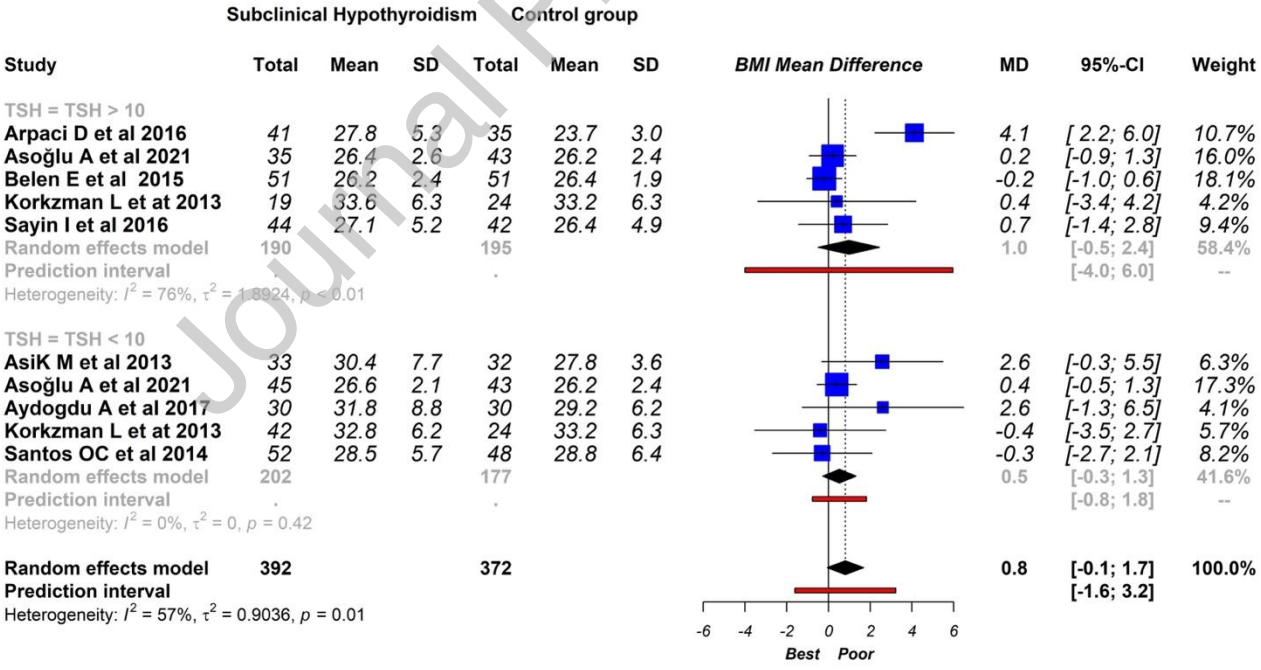

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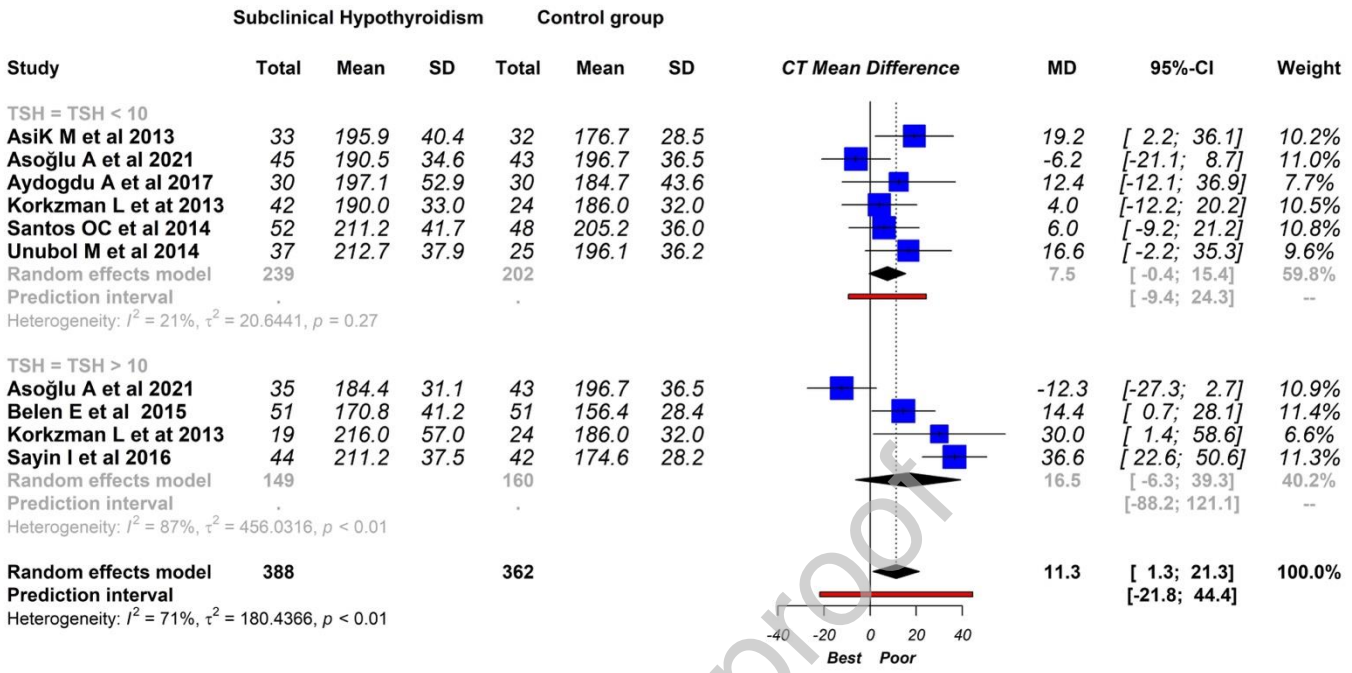

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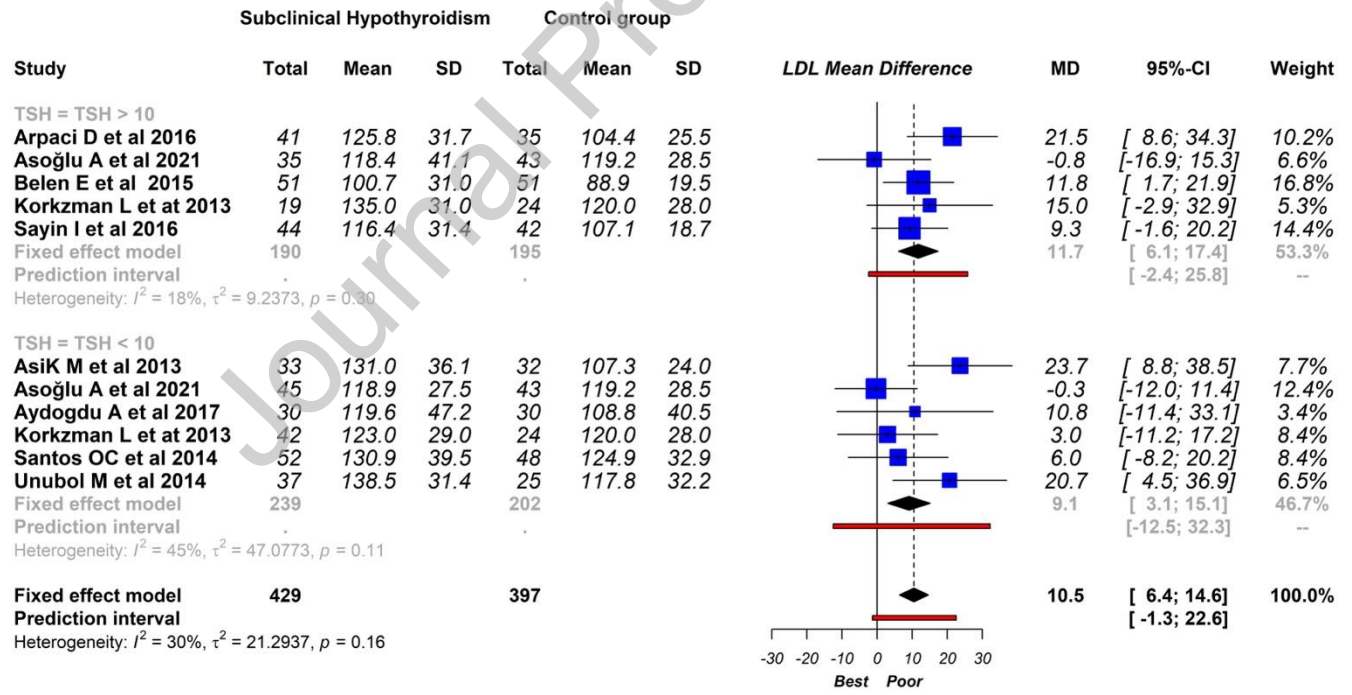

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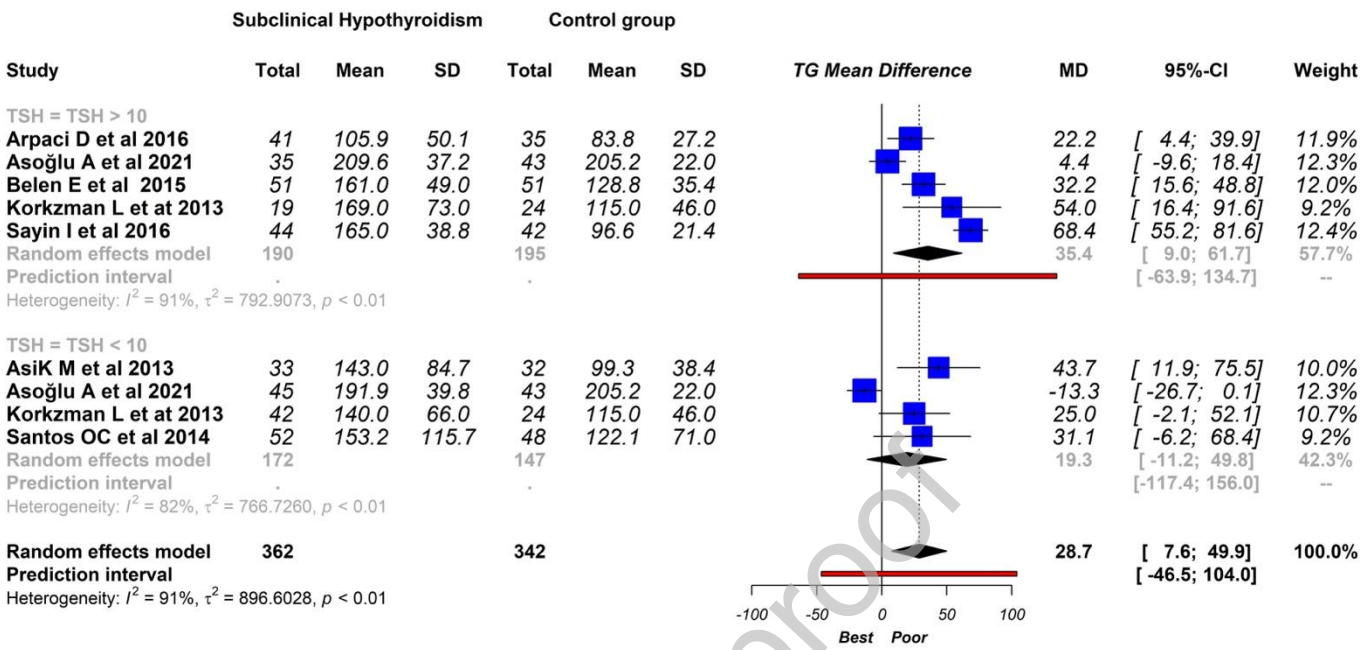

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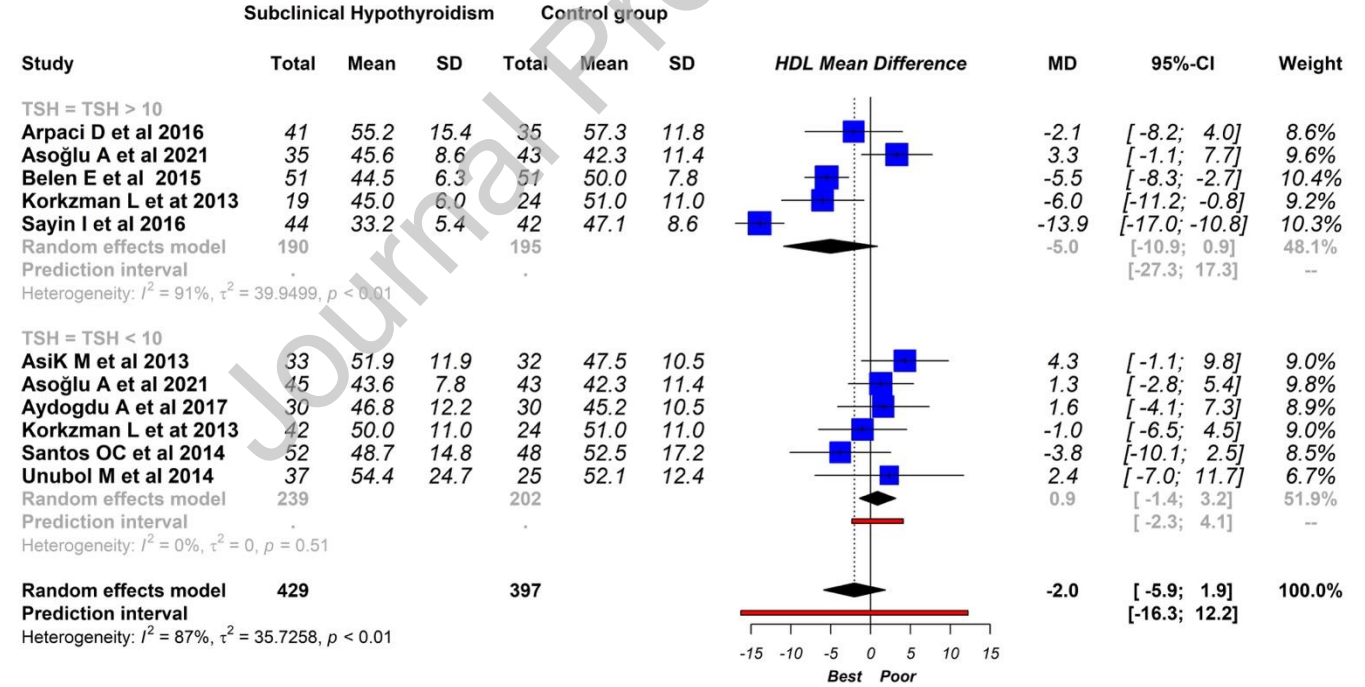


Figure 4. Effect of SH with TSH>10 or TSH <10 mIU/L on epicardial adipose tissue (EAT) (A), body mass index (BMI) (B), TC (C), LDL (D), TG (E) and HDL (F). Random or Fixed model, mean difference (MD), 95% confidence intervals (CI), and I2 statistics.

Discussion

To our knowledge, this is the first meta-analysis that evaluates the relationship of SH on EAT expansion, demonstrating that SH was associated with EAT independently of TSH levels. These findings may explain the pathological mechanisms of CVD in SH patients. It is well-known that SH is a factor to produce insulin-resistant and inflamed adipose tissue (AT) whose phenotype and secretion pattern are deleterious, with the predominance of pro-inflammatory and pro-atherogenic adipokines [23].

EAT, is the heart's visceral adipose tissue, which surrounds and infiltrates myocardium and coronary arteries, lying contiguously without a fascial barrier, therefore allowing crosstalk through paracrine and vasocrine pathways [24]. Nowadays, EAT is considered not only fat storage as well as a very active endocrine organ with the capacity to produce a huge variety of cytokines with harmful or protective effects according to the microenvironment [25]. A previous study reported that EAT can bind TSH as it has TSH receptors, this characteristic may affect cardiac function [26]. There is a relation between VAT and TSH level and the presence of TSH receptors on adipocytes during differentiation and fully differentiated adipocytes have been demonstrated as well [27]. The expansion of EAT would be different from visceral and subcutaneous adipose tissues. It must be considered that EAT has a higher adipocyte density with lower adipocyte size [7]. These properties are in line with those found by Aitken-Buck et al, who proposed that EAT expansion would be mainly dependent on hyperplasia but not hypertrophy [28]. SH can alter body fat distribution by different mechanisms of sympathetic and parasympathetic stimulation with consequent lipolytic and lipogenic action, respectively.

Given that EAT has a differential tissue specific remodeling, and it presents an intrinsically high lipolytic and lipogenic capacity, we hypothesize that this could be one of the mechanisms through which SH modifies EAT volume and therefore increases cardiovascular risk [29]. EAT expansion is related to increased lipoprotein lipase (LPL) activity characteristic of states of insulin resistance in association with decreased plasma LPL activity [30].

Thyroid hormone is master regulator of cell metabolism and this involves crucial actions on lipid metabolism, in contrast, subclinical hypothyroidism has a decrease LPL activity in peripheral tissues that could explain the increase in TG levels, reflecting the insulin resistance typically of the patients with SH. We also found an increase in LDL and TC, that is associated with an increase in major atherogenic lipoproteins and this should be viewed as a cardiovascular risk factor[31].

We have recently shown that in insulin-resistant patients the greater expansion of EAT was due to greater expression of LPL in EAT with a decrease of LPL activity in peripherical tissue[30]. Contrariwise, we have found an increase in bioactive lipid markers such as ceramide in patients with high cardiovascular risk, the inflammatory effect of ceramide is recognized[32].

This meta-analysis presented several limitations; firstly, even though the results were robust when performing the sensitivity analysis, the statistical heterogeneity was high, particularly due to the large proportion of studies in Turkish.. Secondly, the analysis included only trial-level data without individual data. Thirdly, our analysis included only observational studies. Moreover, the presence of biases and confounding factors was greater than we expected. Finally, since randomized clinical trials on this topic have not been performed yet, relatively few studies were included in our analysis.

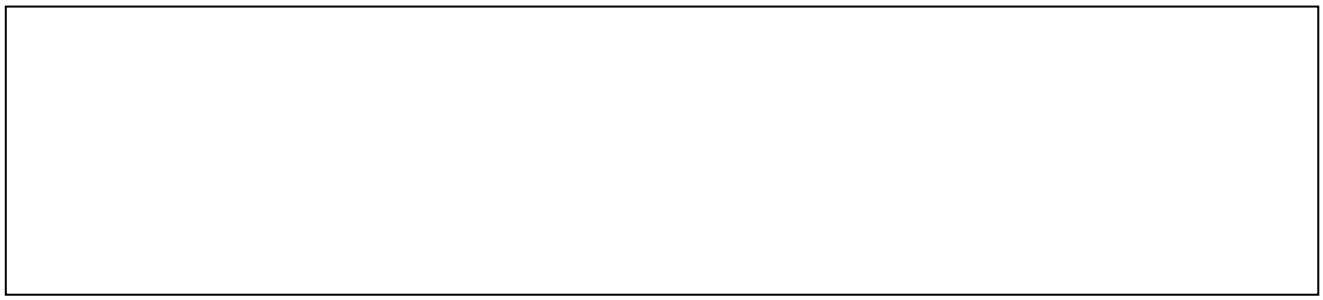
Conclusions

SH has a significant association with EAT expansion and the risk of CVD. Therefore, whether SH patients can benefit from early assessments of measures of EAT like CV risk markers may require large-scale, long-term clinical studies to further confirmation.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:



Author Contribution

Nogueira Juan Patricio was the main coordinator of the project and was responsible for the study design. Closs Cecilia, drafted the manuscript of the present paper. Hernando Vargas-Uricoechea, Eddison Godinez-Leiva and Diego Schwarzstein were involved in the supervising of data collection and stratification. Lobo Martin and Nogueira Juan Patricio contributed to data assembly and analysis. Lagranja Elena contributed with manuscript revision. All authors contributed intellectually to this manuscript and have approved this final version.

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