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Nonalcoholic Fatty Liver Disease Is Not Associated with Thyroid Hormone Levels and Hypothyroidism: A Systematic Review and Meta-Analysis

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Keywords
Hypothyroidism · Meta-analysis · Nonalcoholic fatty liver disease · Thyroid function

Abstract
Background: Whether hypothyroidism is related to nonalcoholic fatty liver disease (NAFLD) is unclear. Thyroid dysfunction is closely related with components of metabolic syndrome. Given the hepatic manifestation of metabolic syndrome, several studies have investigated the association between NAFLD and thyroid dysfunction and have demonstrated inconsistent results. Thus, we conducted a systematic review and meta-analysis to better characterize the association between NAFLD and thyroid dysfunction. ***Methods:*** MEDLINE and Embase were searched through July 2016. The primary outcome was the association between NAFLD and subclinical, overt, and overall hypothyroidism. The secondary outcome was the difference in thyroid hormone levels (free triiodothyronine [FT_3], free thyroxine [FT_4], or thyroid-stimulating hormone [TSH]) between NAFLD patients and non-NAFLD controls. Pooled odds ratios (OR) and 95% CI were calculated using a random-effects model. All continuous data are summarized as the mean difference along with 95% CI. ***Results:*** Data were extracted from 14 studies involving 7,191 NAFLD patients and 30,003 controls. NAFLD was not associated with subclinical, overt, or overall hypothyroidism compared with non-NAFLD controls. Patients who had NAFLD did not show a significant difference in FT_3, FT_4, or TSH compared with non-NAFLD controls. ***Conclusions:*** Our meta-analysis demonstrates no significant association between NAFLD and subclinical, overt, or overall hypothyroidism, and we also found no significant difference in thyroid hormone levels between participants with and without NAFLD.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a major health problem. It is one of the most common causes of chronic liver disease with a global prevalence of 25% [1]. The presentation of NAFLD ranges from simple steatosis to nonalcoholic steatohepatitis that could progress to cirrhosis and hepatocellular carcinoma. Its prevalence has increased substantially throughout the world in parallel with the growing epidemic of obesity [2, 3]. Moreover, nonalcoholic steatohepatitis-related cirrhosis is expected

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to surpass other causes of chronic liver disease to become the leading indication for liver transplantation in the next 2 decades [4]. Therefore, identifying risk factors for NAFLD to potentially develop new preventive or treatment strategies is of utmost significance.

Metabolic disorders such as hypertension, hyperlipidemia, diabetes, gallstones, and central obesity are known risk factors for NAFLD [2, 5, 6]. Thyroid hormones regulate all metabolic pathways, acting on protein, carbohydrates, and lipid metabolism. Reduced thyroid hormone levels are associated with hypometabolism characterized by reduced resting energy expenditure, weight gain, increased cholesterol levels, reduced lipolysis, and reduced gluconeogenesis [7]. Thyroid hormones also have a role in hepatic lipid metabolism and hepatic insulin resistance [8]. Thyroid dysfunction can lead to hyperlipidemia, obesity, and insulin resistance, which are components of metabolic syndrome [9].

Given the hepatic manifestation of metabolic syndrome, several studies have investigated the association between NAFLD and thyroid dysfunction, but have demonstrated inconsistent results. Therefore, to better characterize this association, we conducted a systematic review and meta-analysis of all published observational studies regarding the association of NAFLD and thyroid dysfunction including hypothyroidism and thyroid hormone levels compared to non-NAFLD subjects.

Methods

This systematic review and meta-analysis was conducted and reported according to the Meta-Analysis of Observational Studies in Epidemiology Statement [10] and was registered in PROSPERO (No. CRD42016041913).

Search Strategy

Two authors (S.U. and V.J.) independently searched published studies indexed in PubMed/MEDLINE and Embase databases from inception to July 2016 using the search strategy that comprised terms for NAFLD and thyroid function without language restriction. References of selected retrieved articles were also manually reviewed.

Eligibility Criteria

Our inclusion criteria were (1) published observational studies that addressed the association between NAFLD and thyroid hormone levels (free triiodothyronine [FT_3], free thyroxine [FT_4], or thyroid-stimulating hormone [TSH]) in participants with hypothyroidism, euthyroidism, or hyperthyroidism, or studies that assessed the association between NAFLD and hypothyroidism including either overt hypothyroidism or subclinical hypothyroidism in adult participants; (2) participants without NAFLD were used as a reference group; (3) NAFLD was diagnosed by liver enzyme levels, imaging study, or liver biopsy; and (4) overt and subclinical hypothyroidism were diagnosed by each study's thyroid hormone cutoff levels. To assess the quality of all studies, review articles, case reports, abstracts, and unpublished studies were excluded.

Two authors (S.U. and V.J.) independently reviewed the titles and abstracts of all the citations that were identified. After all the abstracts were reviewed, data comparisons between the 2 investigators were conducted to ensure completeness and reliability. The inclusion criteria were independently applied to all identified studies. Differing decisions were resolved by consensus between the 2 authors.

The quality of each study was independently evaluated by 2 authors (S.U. and V.J.) using the Newcastle-Ottawa Quality Assessment Scale which assessed each study in 3 areas: (1) the selection of the study groups, (2) the comparability of the groups, and (3) the ascertainment of the exposure or outcome of interest for case-control or cohort studies, respectively [11]. Discrepant opinions between authors were resolved by discussion between the authors.

Data Extraction

Full-text versions of potentially relevant papers identified in the initial screening were retrieved. If multiple articles from the same study were found, only the article with the most complete data was included. Data concerning author, year of publication, study design, study location, participant characteristics, diagnostic method of NAFLD, and definition of overt and subclinical hypothyroidism were independently extracted by 2 investigators. We contacted the authors of the primary reports to request any unpublished data. If the authors did not reply, we used the available data for our analyses.

Statistical Analysis

The inverse variance method was used to estimate the pooled odds ratios (OR) and corresponding 95% CI, and data were pooled using a random-effects model given the high likelihood of between-study variance. For studies with several multivariable-adjusted estimates, we extracted those reflecting the greatest degree of control for potential confounders. All continuous data are summarized as the mean difference (MD) along with 95% CI. Sensitivity analysis was performed to evaluate the robustness of results, in which pooled estimates were computed omitting 1 study in each turn. The heterogeneity of effect size estimates across these studies was quantified using the Q statistic, its p value, and I^2 ($p < 0.10$ was considered significant). An I^2 value of 0–25% indicates insignificant heterogeneity, 26–50% low heterogeneity, 51–75% moderate heterogeneity, and 76–100% high heterogeneity [12]. Publication bias was assessed using a funnel plot and the Egger regression test [13]. Data analysis was performed using Comprehensive Meta-Analysis 3.3 software from Biostat Inc. (Englewood, NJ, USA).

Results

The initial search yielded 485 articles; 460 articles were excluded based on the title and abstract review. A total of 25 articles underwent full-length review. Eleven articles were excluded (4 articles had no comparison group, 3 ar-

Table 1. Main characteristics of the studies included in this meta-analysis

Study	Country	Study design	NAFLD	Controls	Study sample	Definition of overt hypothyroid	Definition of subclinical hypothyroid	Diagnosis of NAFLD	Mean age, years ± SD	Female, %	Confounder adjustment	Quality (Newcastle-Ottawa Scale)
Liang-Punsakul, 2003 [23]	USA	CC	174	442	All patients with NASH	N/A	N/A	Liver biopsy	49 ± 13	59	DM, HLD, HTN	3,1,3
Moustafa, 2009 [24]	Egypt	CC	13	20	Patients presented to outpatient clinics	N/A	N/A	USG	55 ± 4.6	30.9	N/A	2,2,2
Xu, 2011 [22]	China	CS	227	651	Annual health check-up	TSH >4.5 mIU/L FT_4 7.8 – 14.4 pmol/L	TSH >4.5 mIU/L FT_4 <7.8 pmol/L	USG	71.7 ± 4.1	36.8	Age, BMI, WC, Cr, FBG, uric acid, FT_4	4,2,3
Ittermann, 2012 [18]	Germany	CS	508	3,153	Population-based study in West Pomerania	TSH >3 mIU/L FT_4 <7.7 pmol/L	TSH >3 mIU/L FT_4 7.7 – 23.2 pmol/L	USG	Male: 50.5 ± 16.6 Female: 48.1 ± 16.1	47.5	Age, physical activity, WC, alcohol use, food intake pattern	4,2,3
Zhang, 2012 [26]	China	CC	266	1,056	Community-based sample of adult population	TSH >2.5 mIU/L	TSH >2.5 mIU/L	USG	Male: 44.7 ± 15.1 Female: 44.9 ± 14.7	59	Age, gender, BMI, percentage of body fat, TSH, TG, SBP, DBP, FBG	3,1,2
Chung, 2012 [14]	Korea	CS	1,156	3,492	Subjects who underwent health check-up	TSH >4.1 mIU/L FT_4 <0.7 ng/dL	TSH >4.1 mIU/L FT_4 0.7 – 1.8 ng/dL	USG	48.6 ± 11.8	62.4	Age, gender, BMI, WC, TG, HLD, HTN, DM	4,2,3
Eshraghian, 2013 [16]	Iran	CS	127	705	Clustered random sampling from adult healthy population	TSH >5.2 mIU/L FT_4 <11.5 pmol/L	TSH >5.2 mIU/L FT_4 11.5 – 23 pmol/L	USG	48.2 ± 12.8	N/A	HTN, DM, HLD, ischemic heart disease	4,2,1
Tao, 2015 [21]	China	CS	196	543	Subjects who underwent health check-up	TSH >4.5 mIU/L FT_3 <3.1 pmol/L FT_4 <12.0 pmol/L	TSH >4.5 mIU/L FT_3 3.1 – 6.8 pmol/L FT_4 12.0 – 22.0 pmol/L	USG	47.8 ± 8.1	38.7	Age, gender, smoking, BMI, SBP, DBP, TC, LDL, FT_3, FT_4, TSH, FBG, WC, HDL	4,2,3
Liu, 2015 [19]	China	CS	988	1,588	Subjects who underwent health check-up	TSH >4.78 mIU/L FT_3 <3.5 pmol/L FT_4 <11.5 pmol/L	TSH >4.78 mIU/L FT_3 3.5 – 6.5 pmol/L FT_4 11.5 – 22.7 pmol/L	USG	45.4 ± 10.3	38.5	Age, gender, smoking, HTN, BMI, FBG, TG, TC, LDL, HDL, blood urea nitrogen, Cr, uric acid	4,2,3
Ding, 2015 [15]	China	CS	270	884	Chronic hepatitis B-infected subjects who underwent health check-up	TSH >5.3 mIU/L FT_3 <3.8 pmol/L FT_4 <7.8 pmol/L	TSH >5.3 mIU/L FT_3 3.8 – 6.0 pmol/L FT_4 7.8 – 14.4 pmol/L	Liver biopsy	33.6 ± 9.2	20.4	Gender, HBeAg, HBV-DNA, hepatic inflammation grade, liver fibrosis stage	4,2,3
Parikh, 2015 [25]	India	CC	500	300	Subjects who presented to the outpatient department.	TSH >10 IU/mL	TSH >10 IU/mL	Liver biopsy	NAFLD: 44.3 ± 3.2	65.1	AST, ALT, BMI, NASH	4,2,3
Lee, 2015 [27]	Korea	Retrospective cohort study	2,348	16,196	Subjects who underwent health check-up	TSH >4.2 mIU/L FT_4 <0.9 ng/dL	TSH >4.2 mIU/L FT_4 0.9 – 1.6 ng/dL	USG	NAFLD: 39.2 ± 5.9	53.3	Age, gender BMI, TG, HDL	3,2,3
Ludwig, 2015 [20]	Germany	CS	349	927	Randomly selected from the adult population	TSH >34 IU/mL	TSH >34 IU/mL Total T_4 12.8 – 20.4 pmol/L Total T_3 3.9 – 6.7 pmol/L	USG	Male: 40.7 ± 12.7 Women: 41.3 ± 12.6	51.7	Age, gender, BMI, WHR	4,2,1
Gokmen, 2016 [17]	Turkey	CS	69	46	Subjects who were admitted to the hospital clinic for routine care	TSH >4.1 mIU/L	TSH >4.1 mIU/L	USG	NAFLD: 49.9 ± 12.5	65.2	N/A	3,2,3

AST, aspartate aminotransferase; ALT, alanine aminotransferase; BMI, body mass index; CC, case control study; Cr, creatinine; CS, cross-sectional study; DBP, diastolic blood pressure; DM, diabetes mellitus; FBG, fasting blood glucose; FT_3, free triiodothyronine; FT_4, free thyroxine; HDL, high-density lipoprotein; HLD, hyperlipidemia; HTN, hypertension; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; TSH, thyroid-stimulating hormone; USG, ultrasonography; WC, waist circumference; WHR, waist-hip ratio.

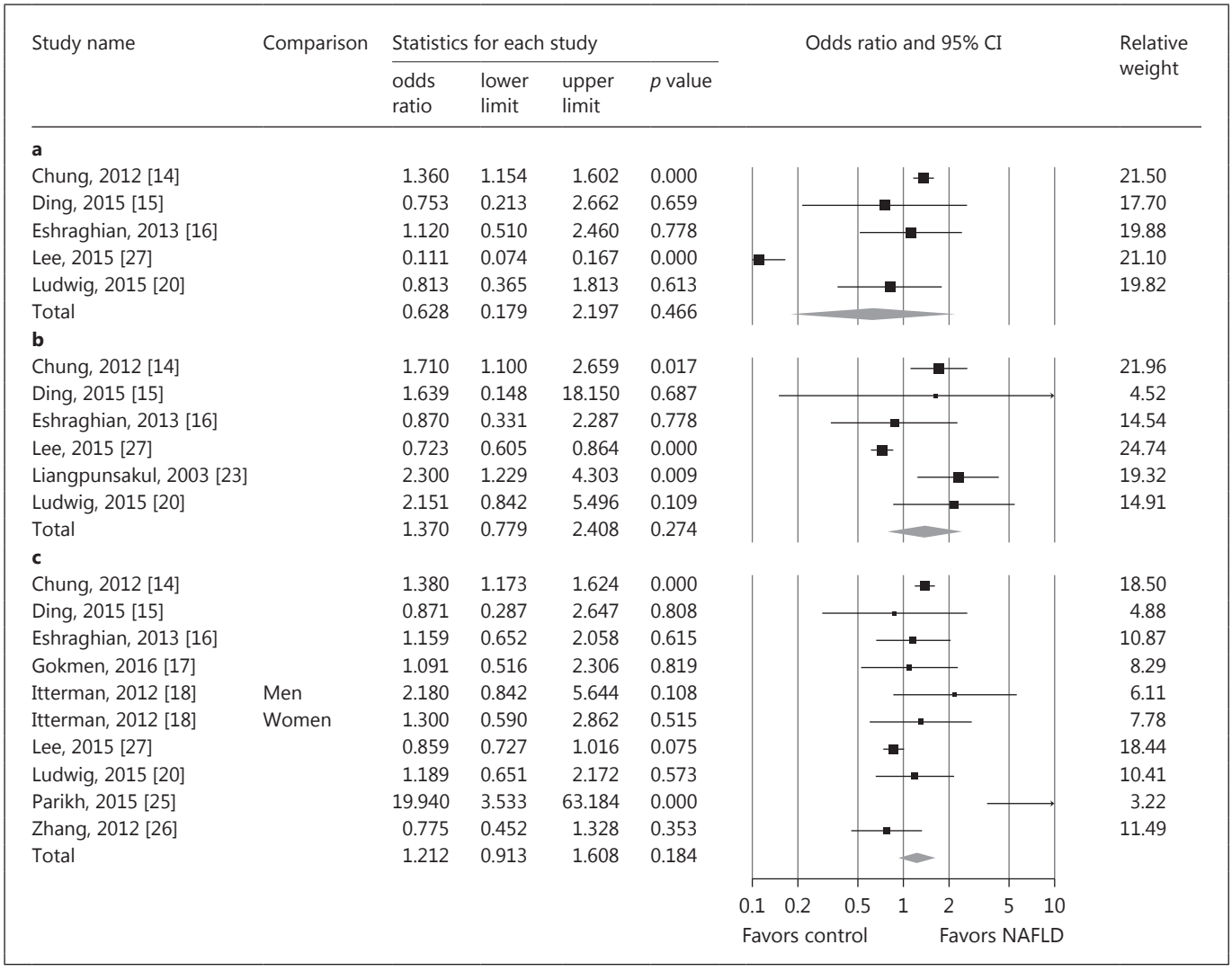

Fig. 1. Forest plot of the included studies assessing the association between NAFLD and subclinical hypothyroidism (**a**), overt hypothyroidism (**b**), and hypothyroidism (**c**). A diamond data marker represents the overall OR and 95% CI for the outcome of interest.

ticles did not report a subject of interest, and 4 articles did not report an outcome of interest). Fourteen observational studies (9 cross-sectional studies [14–22], 4 case-control studies [23–26], and 1 cohort study [27]) involving 7,191 NAFLD patients and 30,003 controls were included in the meta-analysis. Table 1 describes the detailed characteristics and quality assessment of the included studies.

NAFLD and Hypothyroidism

A total of 5 studies [14–16, 20, 27] involving 26,454 participants, 6 studies [14–16, 20, 23, 27] involving 27,070 studies, and 9 studies [14–18, 20, 25–27] involving 32,347 participants were included in our meta-analyses for assessing the association between NAFLD and subclinical hypothyroidism, overt hypothyroidism, and overall hypothyroidism, respectively. NAFLD was not associated with subclinical hypothyroidism (pooled OR = 0.63, 95% CI: 0.18–2.20, $p = 0.47$, $I^2 = 97\%$, $p_{\text{heterogeneity}} < 0.01$), overt hypothyroidism (pooled OR = 1.37, 95% CI: 0.78–2.41, $p = 0.27$, $I^2 = 81\%$, $p_{\text{heterogeneity}} = 0.08$), or overall hypothyroidism (pooled OR = 1.21, 95% CI: 0.91–1.61, $p = 0.18$, $I^2 = 72\%$, $p_{\text{heterogeneity}} = 0.02$) compared with non-NAFLD controls (Fig. 1).

In order to assess the stability of the results of our meta-analyses, we performed a 1-study removed sensitivity analysis. For subclinical hypothyroidism, removal of Lee

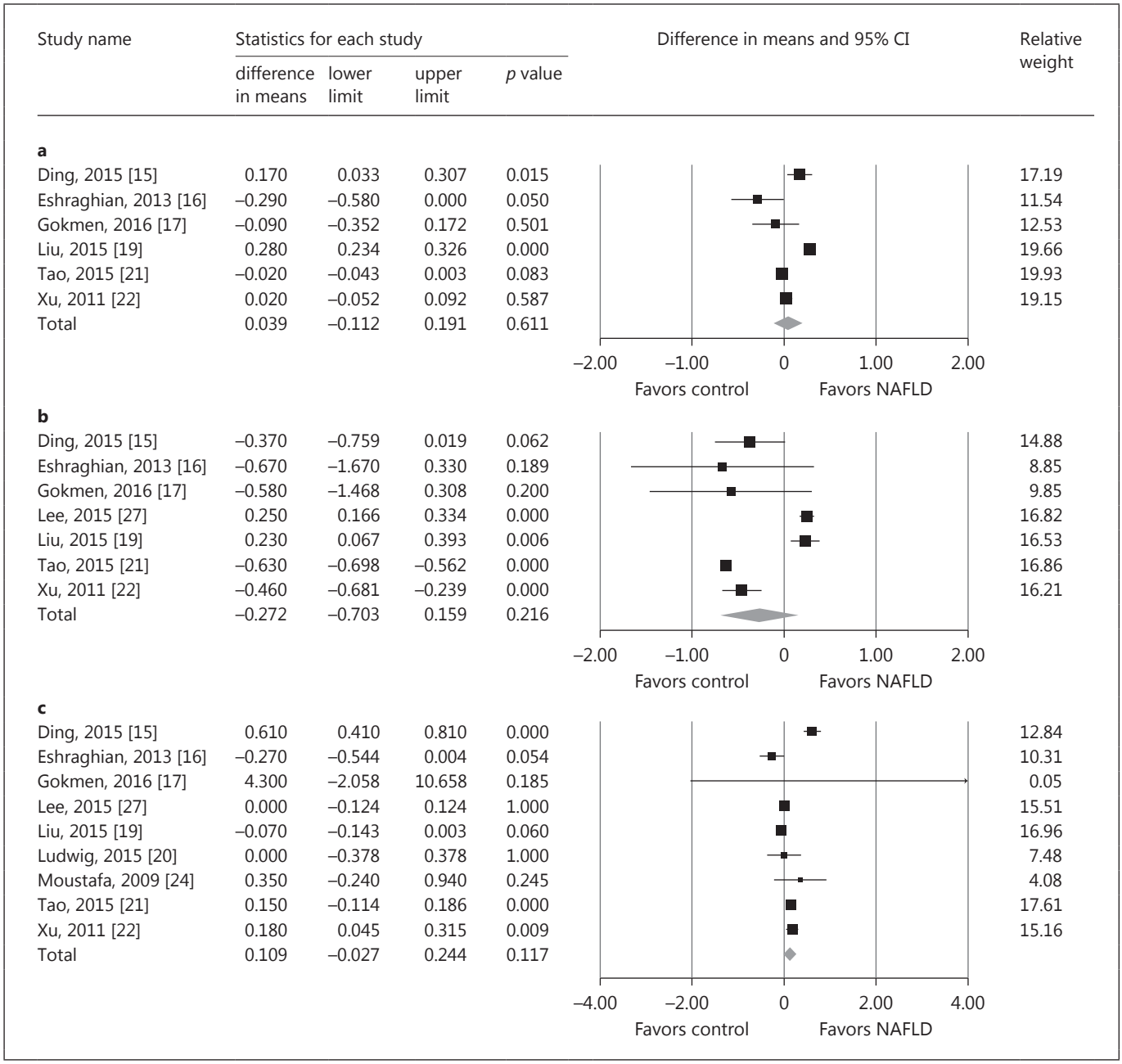

Fig. 2. Forest plot of the included studies assessing the association between NAFLD and free triiodothyronine (**a**), free thyroxine (**b**), and thyroid-stimulating hormone (**c**). A diamond data marker represents the overall RR and 95% CI for the outcome of interest.

et al. [27] moved the overall effect to favor NAFLD with an OR of 1.31 (95% CI: 1.12–1.53), suggesting that Lee et al. was partly the reason for the high between-study heterogeneity. For overt hypothyroidism, removal of Lee et al. moved the overall effect to favor NAFLD with an OR of 1.76 (1.28–2.41), suggesting that Lee et al. also could contribute to the presence of heterogeneity. For overall hypothyroidism, statistically similar results were obtained after sequentially excluding each study in all meta-analyses, suggesting the results were robust.

To investigate potential publication bias, we examined the contour-enhanced funnel plot of the included studies.

The vertical axis represents study size (standard error by log OR), while the horizontal axis represents effect size (log OR). When assessing the studies for OR of overt hypothyroidism, publication bias is present as there are more studies that favor a positive log OR (positive results), but the *p* value for the Egger regression test is not significant ($p = 0.12$). When assessing the studies for OR of subclinical hypothyroidism and overall hypothyroidism, the plots exclude bias since there are symmetrical distributions of studies on both sides of the mean. The Egger tests were not significant ($p = 0.49$ and 0.61, respectively).

NAFLD and Thyroid Hormone Levels

A total of 6 studies [15–17, 19, 21, 22] involving 6,294 participants, 7 studies [15–17, 19, 21, 22, 27] involving 24,838 studies, and 9 studies [15–17, 19–22, 24, 27] involving 26,147 participants were included in our meta-analyses for assessing the association between NAFLD and FT_3, FT_4, and TSH, respectively. Patients who had NAFLD did not show a significant difference concerning FT_3 (pooled MD = 0.04, 95% CI: –0.11 to 0.19, $p = 0.61$, $I^2 = 96\%$, $p_{\text{heterogeneity}} < 0.01$), FT_4 (pooled MD = –0.27, 95% CI: –0.70 to 0.16, $p = 0.22$, $I^2 = 98\%$, $p_{\text{heterogeneity}} < 0.01$), and TSH (pooled MD = 0.11, 95% CI: –0.03 to 0.24, $p = 0.12$, $I^2 = 88\%$, $p_{\text{heterogeneity}} = 0.03$) compared with non-NAFLD controls (Fig. 2).

As we performed sensitivity analysis, statistically similar results were obtained after sequentially excluding each study at a time in all meta-analyses for FT_3, FT_4, and TSH, suggesting the results were robust. For assessing the studies for the MD of FT_3 and FT_4, publication biases are present as there are more studies that favor negative results (decreased FT_3 and FT_4 in NAFLD compared with controls) but the Egger regression tests showed nonsignificant publication bias ($p = 0.73$ and $p = 0.86$, respectively). For assessing the MD of TSH, the plot excludes bias with the nonsignificant Egger test ($p = 0.98$).

Discussion

This is the first meta-analysis on the association between NAFLD and thyroid dysfunction involving around 7,000 NAFLD patients and 30,000 controls, and showed that NAFLD patients had no significant differences in thyroid hormone levels including FT_3, FT_4, and TSH compared to non-NAFLD controls. We also found no associations between NAFLD and subclinical, overt, and overall hypothyroidism.

Liangpunsakul and Chalasani [23] published the first study in 2003 demonstrating the significantly higher prevalence of hypothyroidism in a nonalcoholic steatohepatitis group in comparison to a control group in a case-control study involving around 600 subjects. Since then, there have been a number of studies addressing this potential association, but most of them were conducted on a small scale. There are a few large-scale studies that have demonstrated significant results. Ittermann et al. [18] conducted a population-based study in Germany including 3,600 healthy individuals that found only a significant association between NAFLD and FT_4, but not FT_3, TSH, hypothyroidism, or hyperthyroidism. Chung et al. [14] performed a population-based study in Korea involving 4,648 healthy subjects and showed that the prevalence of NAFLD was independently associated with hypothyroidism and the grade of hypothyroidism in a dose-dependent manner. Liu et al. [19] performed another health survey study in China including almost 2,600 participants and showed that FT_3 was independently associated with NAFLD, but FT_4 was only significantly associated with NAFLD in a subgroup of postmenopausal women. However, there have also been a few large trials that found no association. Zhang et al. [26] conducted a population-based study involving more than 1,300 Chinese subjects and showed that TSH is not an independent risk factor for NAFLD. Lee et al. [27] conducted a study involving almost 20,000 healthy Korean subjects and found no association between NAFLD and hypothyroidism in all subtypes (overt and subclinical hypothyroidism). Interestingly, both studies that demonstrated significant and nonsignificant results comparably included variables in multivariate models including age, gender, alcohol, smoking, and metabolic parameters and both were comparably comprised of Asian and Caucasian populations. However, there are variations in the definition of hypothyroidism and the measurement of thyroid hormones.

Although hypothyroidism is associated with components of metabolic syndrome [9] and NAFLD is considered as the hepatic manifestation of metabolic syndrome, and even though there are several plausible mechanisms that could explain this possible link, our meta-analysis, which included all published observational studies, could not find any association between NAFLD and hypothyroidism. Leptin is considered as one of the explanations of this association because it is found to be increased in patients with hypothyroidism [28] and it is also found to be higher in NAFLD as it can promote hepatic insulin resistance and be involved in hepatic fibrogenesis [29, 30].

Fibroblast growth factor-21, a member of fibroblast growth factor family, could also provide a role in this association as increased serum fibroblast growth factor-21 levels were observed in patients with hypothyroidism [31]. Its level was also correlated with intrahepatic triglyceride content and associated with increased vulnerability to metabolic stressors that could accelerate the progression of NAFLD [32]. Further large-scale studies are needed to clarify this potential association and should adjust for all potential confounding factors and include comparisons between different ethnicities and gender.

Several limitations of this study should be acknowledged. First, statistical heterogeneity is present in this study. This might be explained by the differences in the populations enrolled, definitions of hypothyroidism, methods used to check thyroid hormone profile, and study designs. Second, this is a meta-analysis of observational studies, which can only demonstrate an association, not causality, between NAFLD and hypothyroidism. Third, most of the included studies used imaging studies to detect hepatic steatosis. Although these imaging techniques are widely accepted as the diagnostic tools of choice for screening NAFLD because they are widely available and easy to perform, they have limited accuracy in detecting mild steatosis compared to liver biopsy, which is considered the gold standard [33].

In conclusion, our meta-analysis demonstrates no significant association between NAFLD and subclinical, overt, or overall hypothyroidism, and we also found no significant difference in thyroid hormone levels between participants with and without NAFLD.

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Statement of Ethics

This article does not contain any studies with human participants or animals performed by any of the authors. No informed consent was obtained.

Disclosure Statement

The authors have nothing to disclose. There are no potential competing interests.

Author Contributions

V.J. conceived the study, assessed the quality of the studies, and drafted the manuscript. S.U. searched the literature, assessed the quality of the studies, performed the statistical analysis, and drafted the manuscript. A.S. participated in the statistical analysis and drafted the manuscript. All authors read and approved the final manuscript.

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