

# Relationship between Hypothyroidism and Non-Alcoholic Fatty Liver Disease: A Systematic Review and Meta-analysis

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## Abstract

**Background:** Previous studies propose that hypothyroidism might play a crucial role in the pathogenesis of non-alcoholic fatty liver disease (NAFLD), but findings from published studies on the relationship between hypothyroidism and NAFLD are still controversial. Our study aimed to make a comprehensive evaluation of the relationship between hypothyroidism and NAFLD through a meta-analysis.

**Methods:** The pooled odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated to evaluate the strength of the relationship between hypothyroidism and NAFLD through meta-analysis.

**Results:** Thirteen articles were ultimately included in our meta-analysis. Meta-analysis of the 13 studies found a high correlation between hypothyroidism and NAFLD (OR = 1.52, 95% CI 1.24-1.87,  $P < 0.001$ ). Meta-analysis of 9 studies providing adjusted ORs found that hypothyroidism was independently correlated with NAFLD (OR = 1.72, 95% CI 1.32-2.23,  $P < 0.001$ ). Subgroup analysis found that both overt hypothyroidism and subclinical hypothyroidism were significantly correlated with NAFLD, and the pooled ORs were 1.70 (95% CI 1.23-2.36,  $P = 0.002$ ) and 1.40 (95% CI 1.10-1.77,  $P = 0.006$ ), respectively. Besides, meta-analysis of studies providing adjusted ORs also found that both overt hypothyroidism and subclinical hypothyroidism were independently correlated with NAFLD, and the pooled ORs were 1.81 (95% CI 1.30-2.52,  $P < 0.001$ ) and 1.63 (95% CI 1.19-2.24,  $P = 0.002$ ), respectively.

**Conclusion:** The meta-analysis provides strong epidemiological evidence for the relationship between hypothyroidism and NAFLD. Both individuals with subclinical and overt hypothyroidism are at higher risk for NAFLD than euthyroid subjects.

**Keywords:** hypothyroidism, euthyroid, non alcoholic fatty liver

## Introduction

The prevalence of non-alcoholic fatty liver disease (NAFLD) has increased substantially during the past decades, and it has become the leading cause

of liver disease worldwide, which may be partly attributed to the rising prevalence of obesity <sup>(1)</sup>. NAFLD is a chronic liver disease defined as hepatic accumulation of fat in the absence of excess alcohol consumption and not only insulin resistance (IR)

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but also genetic predisposition play a key role in its pathogenesis. NAFLD can be divided into two main histological categories, namely nonalcoholic fatty liver and nonalcoholic steatohepatitis, which is the progressive subtype of NAFLD and can further induce liver cirrhosis and hepatocellular carcinoma<sup>(2)</sup>. An increasing number of diseases have been reported to be linked to NAFLD, such as cardiovascular disease, type 2 diabetes, chronic kidney disease, and cancer<sup>(3-5)</sup>. The prevention and treatment of NAFLD have become the focus of medical research in recent years, and identifying the risk factors for NAFLD is critical to develop effective preventive interventions against NAFLD.

Hypothyroidism is a common disease of the endocrine system that affects lifelong health. The physiological role of the thyroid gland has been taken seriously by many scholars, not just because of the critical role of thyroid hormones in cell metabolism and energy homeostasis<sup>(6)</sup> but also for the more important fact that thyroid dysfunction is associated with numerous diseases<sup>(7)</sup>. Hypothyroidism comprises subclinical hypothyroidism and overt hypothyroidism. Subclinical hypothyroidism is considered as a disease with an elevated thyroid-stimulating hormone (TSH) level than normal range, normal serum free thyroxine (fT4) level and absence of obvious clinical manifestation. Overt hypothyroidism is defined as a disease with an elevated TSH level and a lower fT4 level, and it may be accompanied by obvious clinical symptoms. Some studies have found that both overt hypothyroidism and subclinical hypothyroidism are associated with cardiovascular diseases and mortality. Other studies also have found that either overt hypothyroidism or subclinical hypothyroidism may be associated with other diseases, such as chronic kidney disease, dementia, and fractures<sup>(8-10)</sup>.

## Materials and Methods

### Inclusion and Exclusion Criteria

Our inclusion criteria were as follows: (1) cohort, cross-sectional, or case-control studies which investigated the association between hypothyroidism and NAFLD; (2) all studies must report odds ratios (ORs) with 95% confidence intervals (95% CIs) values or other values which could be converted into ORs; (3) included NAFLD patients must be diagnosed with

an ultrasound examination or pathologic examination to make a clear definite diagnosis, and other diseases that could cause hepatic steatosis were excluded; and (4) the diagnosis of hypothyroidism must be based on biochemical tests including TSH levels and T4/FT4 levels.

## Results

### Study Selection

We searched the databases from mentioned above and found 670 articles, while 634 articles were excluded according to the title and abstract for the following reasons: animal studies, the main purpose of these studies unrelated to the content of the present study. Thirty-six studies were evaluated by reviewing full-texts. Twenty-three articles were excluded after reading full-texts, for there were no data on the outcomes of interest. There were 13 articles included in our meta-analysis ultimately. Following the aforementioned search, a total of 13 studies with 42,143 participants were incorporated into our final analysis studies.

### Study Characteristics

Nine studies reported outcomes on the association between subclinical hypothyroidism and NAFLD, and six studies reported outcomes on the association between overt hypothyroidism and NAFLD. Those 13 studies were published from 2003 to 2017, and the number of recruited participants was from 332 to 18,544. Nine studies provided adjusted ORs and four studies only provided native ORs.

### Meta-Analysis

Meta-analysis of the 13 studies found a high correlation between hypothyroidism (including both overt hypothyroidism and subclinical hypothyroidism) and NAFLD (OR = 1.52, 95% CI 1.24–1.87,  $P < 0.001$ ). After excluding 4 studies without adjusted ORs, meta-analysis of 9 left studies found that hypothyroidism was significantly and independently correlated with NAFLD (OR = 1.72, 95% CI 1.32–2.23,  $P < 0.001$ ).

Meta-analysis of nine studies found that subclinical hypothyroidism was significantly correlated with NAFLD (OR = 1.40, 95% CI 1.10–1.77,  $P < 0.006$ ). After excluding three studies without providing adjusted

ORs, meta-analysis of six left studies found that overt hypothyroidism was significantly correlated with NAFLD (OR = 1.63, 95% CI 1.19–2.24,  $P < 0.002$ ).

Funnel plots did not show obvious indications of publication bias. The  $P$  values of Egger's test in the meta-analyses relating overt hypothyroidism and subclinical hypothyroidism were 0.35 and 0.17, respectively.

## Discussion

Although previous studies propose that hypothyroidism might play a crucial role in the pathogenesis of NAFLD, some observational studies fail to find an obvious association between hypothyroidism and NAFLD. However, based on the results of the present meta-analysis, hypothyroidism plays an important role in the pathogenesis of NAFLD. The meta-analysis suggests epidemiological evidence for the obvious relationship between hypothyroidism and NAFLD, and the impact of hypothyroidism is independent from other known risk factors for NAFLD. Besides, both subclinical hypothyroidism and overt hypothyroidism are independently related to NAFLD. It is more remarkable that our study, which comprised 13 available studies from 11 countries, is the first meta-analysis integrating the evidence for the relationship between hypothyroidism and NAFLD.

According to our study, hypothyroidism independently increases the risk of NAFLD, which has some implications in the screening of hypothyroidism and NAFLD. It may be helpful for the screening of NAFLD among hypothyroidism patients since those patients are at higher risk of developing NAFLD. Meanwhile, it may also be helpful to identify hypothyroidism in patients with NAFLD and to give an appropriate treatment for hypothyroidism. Therefore, the results of this study is of great significance in the preventive medicine of hypothyroidism and NAFLD.

Our results demonstrate that either overt hypothyroidism or subclinical hypothyroidism independently increases the risk of NAFLD. Some studies have laid the foundation for the findings of the meta-analysis by providing some possible explanations for the molecular mechanism underlying the relationship between hypothyroidism and NAFLD. There are several possible mechanisms which can explain the relationship between hypothyroidism and NAFLD. First, obvious relations between

hypothyroidism and metabolic changes have been reported, which include IR, dyslipidemia and obesity and they have important roles in the development of NAFLD. Both IR and obesity are vital factors in the development of NAFLD, which are also common in hypothyroidism patients compared to those general population. IR can accelerate liver injury in NAFLD. Besides, Demir et al. found that hypothyroidism can cause NAFLD in rat models, and pointed out that obesity is one of the key factors in the relationship between hypothyroidism and NAFLD. The metabolic changes aforesaid among hypothyroidism patients can thus further result in the development of NAFLD. Second, thyroid hormones can regulate lipid metabolism in the liver *via* thyroid hormone receptor  $\beta$ , and they can decrease cholesterol and triglyceride levels. It is worth mentioning that lower levels of thyroid hormones in hypothyroidism can increase the levels of cholesterol, low-density lipoproteins and triglyceride due to the delivery of hepatic fatty acids, but decrease the level of high-density lipoprotein (HDL), and thus can affect lipid metabolism. Therefore, patients with overt hypothyroidism often have fatty infiltration of the liver and thus have a higher risk for NAFLD. Hypercholesterolemia caused by hypothyroidism also plays an important role in the pathogenesis of NAFLD. According to the results of the present research, we found an obvious phenomenon that the correlation between overt hypothyroidism and NAFLD was more significant than that between subclinical hypothyroidism and NAFLD. As mentioned above, overt hypothyroidism is defined as having a much higher TSH level and lower T4 and T3 levels compared to subclinical hypothyroidism. The more significant correlation between overt hypothyroidism and NAFLD may be explained by the synergistic effects of higher TSH level and lower thyroid hormones in the pathogenesis of NAFLD, because TSH itself may induce hepatocyte steatosis *via* TSH receptor signal.

## Conclusion

Our meta-analysis provides strong epidemiological evidence for the significant relationship between hypothyroidism and NAFLD. Both individuals with subclinical hypothyroidism and overt hypothyroidism are at a higher risk for the development of NAFLD than those with normal thyroid function. More prospective cohort studies are needed to further strengthen the relationship between NAFLD and hypothyroidism.

Ethical clearance- taken from institutional committee

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**Conflict of Interest -** Nil

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