Thyroid Function and the Risk of Fibrosis of the Liver, Lung and Heart
A systematic review of human studies

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ABSTRACT

Background Variations in thyroid function may affect the occurrence and progression of liver, pulmonary and myocardial fibrosis. However, evidence is fragmented and inconclusive.

Objective We aimed to systematically appraise the evidence regarding the role of thyroid function on fibrosis of the liver, lung, and heart.

Data Sources Pubmed Publisher, Web-of-Science, Embase and Medline Ovid were searched for studies published from inception to 12.07.2018.

Study Selection Two independent reviewers evaluated and selected observational studies that investigated the association of thyroid function with fibrosis of the liver, lung or heart, in humans.

Data Extraction and Synthesis Data were extracted independently by two reviewers, with disagreement resolved by consensus. PRISMA guidelines were followed. Study quality and risk of bias were evaluated based on the Newcastle-Ottawa Quality Assessment Scale.

Main Outcomes and Measures Fibrotic diseases of the liver, lung and heart, evaluated via noninvasive or invasive measures.

Results After screening 1764 titles and abstracts, we identified 10 studies meeting the inclusion criteria. Of the included studies, 6 studies reported on liver fibrosis, 2 on pulmonary fibrosis, and 2 on myocardial fibrosis. The population sample size ranged from 53 to 4761 subjects. The median mean age was 54 years (range, 36-69), and the median percentage of women was 48 (range, 17-100). The general quality of the data was moderate. Overall, low thyroid function was associated with an increased risk of fibrosis of the liver, lung, and heart. Compared with euthyroidism, hypothyroidism was associated with a higher risk of liver fibrosis (n=2 studies), pulmonary fibrosis (n=2 studies), and myocardial fibrosis (n=1 study). The results were not combined in a quantitative meta-analysis, due to the heterogeneity in the population characteristics, differences in methodology, or differences in fibrotic outcomes of the included studies.

Conclusions and Relevance This systematic review suggests that low thyroid function is associated with an increased risk of chronic fibrotic diseases of the liver, lung, and heart. The evidence, however, is mainly based on cross-sectional data. Therefore, future prospective studies are needed to investigate the long-term effects of thyroid hormones on the occurrence and progression of fibrosis.

INTRODUCTION

Various chronic diseases, including liver cirrhosis, idiopathic pulmonary fibrosis and hypertrophic cardiomyopathy, are characterized by fibrosis.[1] The development of fibrosis is attributable to the accumulation of extracellular matrix proteins such as collagen and fibronectin.[2] Fibrotic elements progressively remodel and destroy the normal tissue architecture, ultimately resulting in organ failure. Hence, nonalcoholic steatohepatitis can progress to decompensated cirrhosis;[3] pulmonary fibrosis contributes to a decline in the lung function;[4] whereas myocardial fibrosis leads to ventricular diastolic dysfunction.[5]

Current research is focused on the identification of novel determinants of fibrosis, which could be further translated into the development of effective antifibrotic drugs.[6-8] Among other factors, hypothyroidism has been implicated in the aetiology of fibrosis. Pronounced hypothyroidism is typically characterized by an increased production of mucopolysaccharides, resulting in interstitial fibrosis and extracellular water retention, also known as myxedema. Yet, the exact role of thyroid hormones on the development of fibrosis remains controversial. Many animal studies have reported profibrotic effects of hypothyroidism.[9-15] Additionally, beneficial effects of thyroid hormone supplementation have been reported on the disease course of the liver,[16-18] lung,[19] or heart[20-23] fibrosis. In contrast, other animal studies have observed an attenuation of fibrosis in experimental hypothyroidism,[24,25] and have shown profibrotic effects of thyroid hormone administration.[26-30] Similar to these animal studies, the results of epidemiological studies are also inconsistent. Some studies report an association of thyroid function with certain fibrotic processes,[31,32] whereas others report no association.[33]

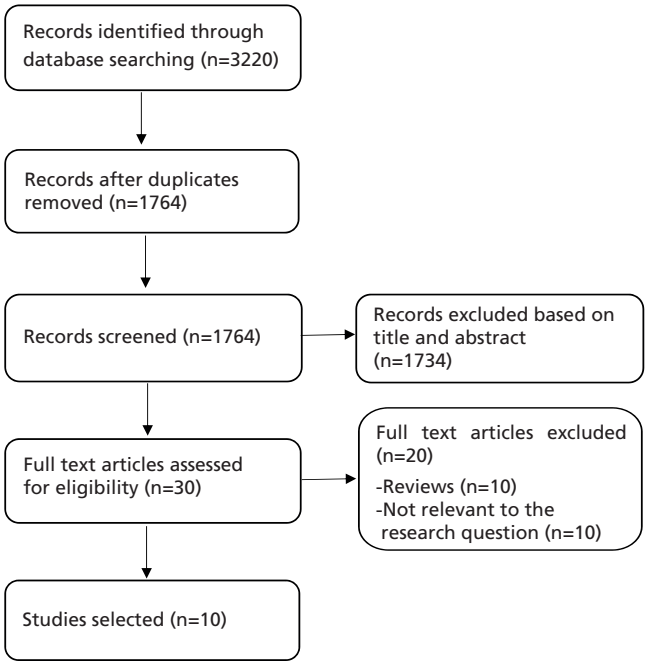
To date, there is a critical lack of literature synthesis concerning the impact of thyroid function on the occurrence and progression of fibrosis. In this context, the present review aims to summarize the current observational evidence regarding the association of thyroid function with fibrosis of the liver, lung and heart in humans.

METHODS

Data sources and search strategy

This systematic review was conducted in accordance with the PRISMA guidelines for transparent reporting.[34] The checklist is provided in Appendix 1. Four electronic databases, including Pubmed Publisher, Web-of-Science, Embase and Medline Ovid, were searched from inception to 12.07.2018, with the help of librarians. The computer-based searches combined terms related to thyroid function and fibrosis of the liver, heart, or lung. An outline of the step-wise inclusion and exclusion procedure is shown in Figure 1. Details of the search strategy are provided in Appendix 2.

Figure 1. Flowchart for study inclusion, adapted from the PRISMA statement.



Example of electronic search strategy (EMBASE): ((exp thyroid gland/ or exp thyroid disease/ or exp thyroxine/ or exp thyroid function/ or thyroid hormone/ or thyrotropin/ or thyroxine/ or exp thyroid hormone blood level/ or exp thyroid gland examination/) or (thyroid* or hyperthyro* or hypothyro* or free thyroxine or Graves or thyrotropin or thyroxin or deiodinase or hashimoto or triiodothyronine or thyronine* or myxedema or thyrotoxicosis or hyperthyroxinemia).ab,ti.) and ((fibrotic or

fibrosis or nonalcoholic steatohepatitis or fibroblast).ab,ti. or (exp fibrosing alveolitis/ or exp fibrosing interstitial pneumonia/ or exp heart muscle fibrosis/ or exp liver fibrosis/ or exp lung fibrosis/)) and ((heart or cardiac or endocardium or myocardium or pericardium or lung or pulmonary or liver or hepatic or cardiovascular).ab,ti.)

Study selection

The titles and abstracts of the citations were screened for: (i) Observational studies (ii) that investigated the role of thyroid function on fibrosis of the liver, lung, or heart, in humans; (iii) reporting effect estimates with 95% confidence intervals, or mean differences with standard deviations (*P* values), or prevalence differences (*P* values). Case-reports, letters to the editor, proceedings, reviews, systematic reviews, meta-analyses, and animal studies were excluded. There were no restrictions on publication year or language. Two independent reviewers screened the titles and abstracts, and selected the eligible studies. Any disagreement regarding inclusion was resolved through consensus. Full texts and reference lists of the selected articles were hand searched to identify additional studies.

A predesigned data collection form was used to extract relevant information from the selected studies, including article source, sample size, demographics of study participants, methods of assessing thyroid function and fibrosis, study results and conclusions. The results were not combined in a quantitative meta-analysis, due to the heterogeneity in the population characteristics, differences in methodology, or differences in fibrotic outcomes of the included studies. The quality of the included studies was assessed by using the Newcastle–Ottawa Scale (NOS) for non-randomized studies in meta-analyses (Appendix 3).[35] The quality of cross-sectional studies was assessed by using an adapted NOS scale (Appendix 4). The NOS scale evaluates the study quality based on 3 domains, namely selection of participants, comparability of study groups, and ascertainment of the outcomes of interest. Each study could have a maximum of 9 stars.

RESULTS

Literature search

The results of the search strategy are presented in Figure 1. After excluding duplicates, we identified 1764 relevant citations. The citations were screened based on the abovementioned predefined selection criteria. As a result, 30 potentially

relevant articles were identified. After examining the full text of these articles, 10 eligible studies were selected.[31-33,36-42]

Thyroid function and fibrosis of the liver, lung and heart

Table 1A summarizes the main characteristics of the 10 included studies reporting on the association of thyroid function with fibrosis. The population sample size ranged from 53 to 4762 subjects (Table 1A). The median mean age was 54 years (range, 36-69), and the median percentage of women was 48 (range, 17-100) (Table 1A). Of the 10 included studies, 5 studies were performed in the United States,[33,36,37,39,40] 3 in Asia,[32,41,42] and 2 in Europe (Table 1A).[31,38] All the studies recruited patients from hospital units, except for one study which was performed in a population-based cohort (Table 1A).[31] Though 2 studies reported unadjusted estimates,[33,42] most of the included studies controlled for potential confounders (Table 1A).[31,32,36-41]

The included studies reported on blood measurements of thyroid function (TSH, FT_4, FT_3),[31,33,38,41] overt hypothyroidism,[31,36,37,39,40,42] and subclinical hypothyroidism.[31,32] Several definitions of hypothyroidism were used. In 4 studies, the diagnosis of hypothyroidism was based on a self-reported disease history and use of thyroid hormone replacement therapy.[36,37,39,40] Two studies diagnosed overt and subclinical hypothyroidism based on the serum TSH and FT_4 measurements, after excluding the thyroid medication users.[31,32] In another study, overt hypothyroidism was caused by chronic lymphocytic thyroiditis, in the absence of concomitant diseases or medical treatments.[42]

The outcomes were liver fibrosis, fibrotic pulmonary diseases, and myocardial fibrosis. Of the 6 studies assessing liver fibrosis, 5 used liver biopsy,[32,33,36-38] and one study used liver elastography.[31] The fibrotic pulmonary diseases included IPF (idiopathic pulmonary fibrosis) (n=1 study)[40] and chronic hypersensitivity pneumonitis (CHPP) (n=1 study).[39] IPF was diagnosed based on lung biopsy or computed tomography scan,[40] whereas the diagnosis of CHPP was based on the American Thoracic Society criteria.[39] Myocardial fibrosis was assessed by cardiac magnetic resonance imaging, using measurements of myocardial longitudinal relaxation time (T1) mapping (n=1 study),[42] or measurements of late gadolinium enhancement (n=1 study).[41]

Liver fibrosis: We identified 6 studies investigating the association of overt hypothyroidism (n=3 studies),[31,36,37] subclinical hypothyroidism (n=2 studies),[31,32] and thyroid function measurements (TSH, FT_4) (n=3 studies)[31,33,38] with liver fibrosis. Overt hy-

Table 1A. Description of included studies on the association of thyroid function with fibrosis*

First author, year (Reference)	Country	N	Age (mean)	% Women	Study design	Population	Additional	Covariates adjusted for*
Thyroid function and liver fibrosis								
Liangpunsakul, 2003[36]	United States	616	49	59	Case-control	General medicine unit	174 NASH cases; 442 non-NASH controls matched for age, sex, race, body weight	Diabetes, hyperlipidemia, hypertension
Pagadala, 2012[37]	United States	246	54	56	Cross-sectional	NAFLD patients	168 events	Diabetes, dyslipidemia, hypertension†
Carulli, 2013[38]	Italy	69	44.4	24	Cross-sectional	Euthyroid NAFLD patients	44 events	Age, sex, chol, BMI, HOMAIR†
Bano, 2016[31]	Netherlands	4762	65	57	Prospective	General population	69 events	Age, sex, cohort, alcohol, smoking, hypolipidemic drugs, chol, Tg, BMI, hypertension, diabetes
Bril, 2016[33]	United States	NR	57	17	Cross-sectional	Euthyroid diabetic NAFLD patients	-	-
Kim, 2017[32]	South Korea	425	53	48	Cross-sectional	NAFLD patients	180 events	Age, sex, BMI, smoking, diabetes, hypertension, Tg, chol, ratio of visceral and subcutaneous tissue area
Thyroid function and pulmonary fibrosis								
Oldham, 2015[40]	United States	392	69	25.5	Case-control	IPF patients and COPD patients	196 IPF cases, 196 COPD controls matched for age, sex, race	BMI, smoking, diabetes, gastroesophageal reflux, CS use
Adegunsoye, 2017[39]	United States	484	65	58	Case-control	CHPP patients and asthma patients	121 CHPP cases, 363 asthma controls matched for age, sex, race	BMI, smoking, diabetes, CS use
Thyroid function and myocardial fibrosis								
Gao, 2016[42]	China	53	36	100	Cross-sectional	Hypothyroid patients and healthy subjects	-	-
Wang, 2016[41]	China	71	54	33.2	Cross-sectional	Patients with IDCM	-	Age, diabetes, renal dysfunction, hypertension†

*Information is related to the analyses of interest for our particular research question. †Stepwise strategy: Statistically significant predictors were kept in the model. Abbreviations: N, total number; NASH, nonalcoholic steatohepatitis; NAFLD, nonalcoholic fatty liver disease; chol, total cholesterol; Tg, triglycerides; BMI, body mass index; HOMAIR, insulin resistance; NR, not reported; IPF, idiopathic pulmonary fibrosis; COPD, chronic obstructive pulmonary disease; CS, corticosteroid; CHPP, chronic hypersensitivity pneumonitis; IDCM, idiopathic dilated cardiomyopathy.

pothyroidism was associated with a higher risk of liver fibrosis than euthyroidism, with odds ratios (ORs) ranging from 2.3 to 6.64.[31,36,37] Subclinical hypothyroidism was associated with a higher risk of liver fibrosis than euthyroidism, with ORs ranging from 2.17 to 2.3.[31,32] Increasing TSH levels were associated with higher odds of liver fibrosis (OR, 1.49 per 1 log TSH).[31] In euthyroid subjects, results varied from a positive association[38] to no association[31,33] of thyroid function with liver fibrosis.

Pulmonary fibrosis: Two case-control studies investigated the association of overt hypothyroidism with fibrotic diseases of the lung, providing similar results.[39,40] Overt hypothyroidism was associated with a 2.39 and a 2.70 times higher risk of CHPP and IPF, respectively (Table 1B).[39,40]

Myocardial fibrosis: Two studies investigated the association of hypothyroidism and thyroid function measurements with myocardial fibrosis (Table 1A).[41,42] One of the studies showed that hypothyroidism is associated with a higher degree of diffuse fibrosis than euthyroidism (Table 2B).[42] The other study showed a negative linear association between FT_3 levels and the risk of myocardial fibrosis among patients with idiopathic dilated cardiomyopathy (Table 1B). TSH and FT_4 levels, on the other hand, were not associated with myocardial fibrosis (Table 1B).[41]

Quality assessment

Study bias assessment scores are shown in Table 4. The general quality of the included studies was moderate. 2 studies scored 7/9 stars, 4 studies scored 6/9 stars, 3 studies scored 5/9 stars, and 1 study scored 4/9 (Table 4).

DISCUSSION

This systematic review summarizes the current evidence regarding the role of thyroid function on fibrosis of the liver, lung and heart in humans. Of the 10 identified studies, 6 reported on liver fibrosis, 2 on pulmonary fibrosis, and 2 on myocardial fibrosis. The general quality of the data was moderate. Overall, low thyroid function was associated with increased odds of liver fibrosis, pulmonary fibrosis, and myocardial fibrosis. Results were consistent, despite the diversity of the study populations, the different methodologies of the included studies and the different locations of

Table 1B. Description of included studies on the association of thyroid function with fibrosis

First author, year	Outcome	Assessment	TSH/FT_4/FT_3	Overt hypothyroidism (unless otherwise specified)
Liver fibrosis				
Liangpunsakul, 2003 [a]	NASH	85% liver biopsy 25% radiologic	NA	**OR (CI), 2.3 (1.2-4)**
Pagadala, 2012 [b]	NASH	Liver biopsy	NA	**OR (CI), 3.8 (2-6.9)**
Carulli, 2013	NASH	Liver biopsy	TSH: **OR (CI), 2.74 (1.15-6.53)**	NA
Bano, 2016 [b]	Combined NAFLD and fibrosis	Ultrasound and elastography	*All participants:* LogTSH: **OR (CI), 1.49 (1.04-2.15)** FT_4 (ng/dL): OR (CI), 0.59 (0.13-2.59) *Euthyroid participants:* LogTSH: OR (CI), 1.13 (0.63-2.03) FT_4 (ng/dL): OR (CI), 0.81 (0.11-5.75)	**OR (CI), 6.64 (1.04-23.98)** Subclinical hypothyroidism: **OR (CI), 2.30 (1.12-4.31)** Subclinical hyperthyroidism: OR (CI), 0.80 (0.04; 3.91)
Bril, 2016	NASH	Liver biopsy	Prevalence of NASH was not different among the FT_4 quintiles (71%, 59%, 61%, 76%, 80%; *P* value, 0.28)	NA
Kim, 2017 [c]	NASH	Liver biopsy	NA	Subclinical hypothyroidism: **OR (CI), 2.17 (1.17-4.01)**
Pulmonary fibrosis				
Oldham, 2015 [a]	IPF	Lung biopsy or CT	NA	**OR (CI), 2.70 (1.31-5.54)**
Adegunsoye, 2017 [a]	CHPP	ATS criteria	NA	**OR (CI), 2.39 (1.36-4.2)**
Myocardial fibrosis				
Gao, 2016 [d]	T1-Mapping [e]	Cardiac MRI	NA	Hypothyroid cases had higher T1-values than controls[f]
Wang, 2016	↑ LGE	Cardiac MRI	TSH: OR (CI), 0.98 (0.93-1.04) FT_4: OR (CI), 0.37 (0.05-2.75) FT_3: **OR (CI), 0.14 (0.04-0.57)**	NA

[a]The diagnosis of hypothyroidism was based on self-reported history of hypothyroidism and/or use of thyroid hormone replacement. [b]Thyroid status categories were defined based on FT_4 and TSH measurements. Euthyroidism as reference. [c]Thyroid function was categorized into strict-normal thyroid function (reference), low-normal thyroid function, and subclinical hypothyroidism. Patients with past history of overt thyroid dysfunction, and/or using thyroid medications were excluded. [d]Hypothyroid patients had overt hypothyroidism caused by chronic lymphocytic thyroiditis, free from concomitant disease and without medical treatment. [e]T1-mapping of the myocardium assesses diffuse myocardial fibrosis. Increased T1-values reflect a longer relaxation time and a more advanced stage of diffuse fibrosis. [f]*T1-left ventricular anterior wall (ms):* controls, 1083±51.28; hypothyroid, 1220±75.85 (*P* value<0.001). *T1-interventricular septum (ms):* controls, 1048±66.29; hypothyroid, 1175±81.87 (*P* value<0.001). *T1-left ventricular inferior wall (ms):* controls, 1062±56.56; hypothyroid, 1179±80.21 (*P* value<0.001). *T1-left ventricular lateral wall (ms):* controls, 1066±47.69; hypothyroid, 1185±81.79 (*P* value<0.001). Abbreviations: TSH, thyroid-stimulating hormone; FT_4, free thyroxine; FT_3, free triiodothyronine; NASH, nonalcoholic steatohepatitis; NA, not applicable; OR, odds ratio; CI, confidence interval; NAFLD, nonalcoholic fatty liver disease; IPF, idiopathic pulmonary fibrosis; CT, computed tomography; CHPP, chronic hypersensitivity pneumonitis; ATS, American Thoracic Society; T1, myocardial longitudinal relaxation time; MRI, cardiac magnetic resonance; LGE, late gadolinium enhancement. NB: Lighter grey highlight indicates a negative association between thyroid function and the risk of fibrosis. Darker grey highlight indicates no association.

Table 2. Quality Assessment Scale

First author, year (Reference)	Selection	Comparability	Exposure/Outcome	Total
Liangpunsakul, 2003[36]	3/4	2/2	1/3	6/9
Pagadala, 2012[37]	1/4	2/2	3/3	6/9
Carulli, 2013[38]	2/4	2/2	3/3	7/9
Bano, 2016[31]	3/4	2/2	2/3	7/9
Bril, 2016[33]	2/4	0/2	3/3	5/9
Kim, 2017[32]	1/4	2/2	3/3	6/9
Oldham, 2015[40]	2/4	2/2	1/3	5/9
Adegunsoye, 2017[39]	1/4	2/2	2/3	5/9
Gao, 2016[42]	1/4	0/2	3/3	4/9
Wang, 2016[41]	1/4	2/2	3/3	6/9

fibrosis. However, the number of identified studies and the amount of prospective evidence were limited.

Hypothyroidism was consistently associated with an increased risk of fibrosis. The magnitudes of the associations differed across studies, which may be partly attributable to the different definitions of hypothyroidism used across studies. In general, the studies that excluded the thyroid medication users[31,32] reported larger effect estimates compared with the studies that included hypothyroid patients under thyroid medications.[36,37,39,40] In the latter group, the levothyroxine treatment may have reduced the risk of fibrosis, further resulting in an underestimation of the observed associations. In addition, the different magnitudes of the associations can be derived from the heterogeneity of fibrotic outcomes and the different population characteristics across the included studies.

We identified several studies investigating the association of thyroid function parameters with the risk of fibrosis.[31,33,38,41] Overall, there was a trend towards a positive association of circulating TSH levels with the risk of fibrosis.[31,38] FT_4 levels, on the other hand, tended to be negatively associated with the risk of fibrosis, but not significantly.[31,41] These results could be explained by the lack of sufficient statistical power to detect an association between serum FT_4 levels and the risk of fibrosis. Alternatively, it is also likely that the risk of fibrosis may be more sensitive to fluctuations in serum TSH rather than FT_4 levels. Furthermore, we identified a limited number of studies investigating the association between thyroid function within the reference range and the risk of fibrosis. Results varied from a negative association[38] to no association,[31,33] and the inconsistencies are likely due to the insuf-

ficient sample sizes. Future larger studies are therefore needed to clarify whether the risk of fibrosis is affected by the fluctuations within the reference ranges of TSH or thyroid hormone levels.

The extracellular matrix, which represents one of the targets of thyroid hormone action, is a likely candidate to be involved in the pathways linking hypothyroidism to fibrosis. Animal studies have shown that experimental hypothyroidism can lead to fibrosis via upregulation of the collagen gene expression.[12-14] Accordingly, the administration of thyroid hormones is shown to reduce the collagen gene expression in the liver[16,17] and myocardium.[20-22] Thyroid hormones enhance the matrix metalloproteinase activity, further resulting in a collagen breakdown. Another factor that may play a mediating role in the pathways linking hypothyroidism to fibrosis is the transforming growth factor beta (TGFβ), which represents one of the most potent fibrogenic cytokines.[43] Animal data have shown that thyroid hormones antagonize hepatic and pulmonary fibrosis through inhibiting the TGFβ/SMAD-dependent transcriptional activation.[18] Besides, the expression of deiodinases is likely altered in fibrotic tissues. In humans, the fibrotic lung has been characterized by an increased expression of DIO2 gene, which further increases the local conversion of T_4 to T_3.[19,44] Moreover, research in animal models of experimental hypothyroidism has shown that DIO2 plays a protective role against lung injury.[45] Overall, these data suggest that the increased expression of DIO2 gene may represent a compensatory mechanism which tends to improve the stressed environment of the fibrotic lung. Still, the expression of DIO2 in other fibrotic organs, such as the heart, remain to be clarified. Future studies may also examine the expression of deiodinases type 1 and type 3 in fibrotic tissues.

To the best of our knowledge, this is the first systematic review which combines the literature regarding the role of thyroid function on fibrosis of the liver, lung and heart, in humans. In accordance with the NOS scale, we used strict criteria for the quality assessment of the risk of bias. Most of the included studies adjusted for potential confounders, including age and sex. Another strength is the consistency of the results in the setting of diverse study populations. The wide range of ages (mean age ranging from 36 to 69) and ethnicities of participants may increase the generalizability of our conclusions.

Several limitations of this systematic review warrant consideration. The limited number of identified studies illustrates the scarcity of evidence in this topic. Most of the included studies were characterized by a cross-sectional design, which does

not provide evidence with regard to the temporality of the associations. The large heterogeneity across studies, including different definitions of thyroid dysfunction and various measures of fibrotic outcomes, did not allow us to perform summary statistics. Nevertheless, the results of the included studies were overall consistent.

Conclusions

This systematic review of human studies suggests that low thyroid function is associated with an increased risk of chronic fibrotic diseases of the liver, lung, and heart. Results were consistent in the setting of diverse study populations. However, most of the current evidence on this topic is based on cross-sectional data. In the future, adequately powered studies are needed to prospectively investigate the long-term effects of thyroid hormones on the occurrence and progression of fibrosis. Furthermore, future interventional studies in humans are needed to explore whether thyroid hormones or thyroid hormone analogues can prevent the progression of fibrosis. These investigations could eventually lead to new avenues regarding the development of therapies against fibrotic diseases. Lastly, future research is needed to elucidate the exact underlying mechanisms linking low thyroid function to fibrosis.

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SUPPLEMENTAL MATERIAL

Appendix 1. PRISMA 2009 checklist.

Section/Topic		Checklist item	Page
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	54
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	55-56
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	57
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	57
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, Web address), and, if available, provide registration information including registration number.	x
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	59
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	58
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	58-59
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	59
Data collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	59
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	58, Appendix 2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	58-59, Appendix 3, Appendix 4
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in means).	x
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I^2) for each meta-analysis.	x

Appendix 1. PRISMA 2009 checklist. (continued)

Section/Topic		Checklist item	Page
Methods			
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	x
Additional analyses	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	x
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	59, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	58, Table 1A
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	60, Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 1B
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	x
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	x
Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see Item 16]).	x
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, healthcare providers, users, and policy makers).	62
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review-level (eg, incomplete retrieval of identified research, reporting bias).	64-65
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	65-66
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	66

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Appendix 2. Supplemental information on Search strategy

Search in Pubmed

(((Thyroid*[Title/Abstract] or hyperthyro* [Title/Abstract] or hypothyro* [Title/Abstract] or thyronine* [Title/Abstract] or Hashimoto[Title/Abstract] or thyroid-stimulating hormone [Title/Abstract] or "free thyroxine"[Title/Abstract] or Graves[Title/Abstract] or thyrotropin[Title/Abstract] or deiodinase[Title/Abstract] or triiodothyronine[Title/Abstract] or myxedema [Title/Abstract] or thyrotoxicosis[Title/Abstract] or hyperthyroxinemia [Title/Abstract])) AND (fibrosis[Title/Abstract] or fibrotic[Title/Abstract] or fibrosing[Title/Abstract] or fibroblast[Title/Abstract] or "nonalcoholic steatohepatitis"[Title/Abstract])) AND (heart [Title/Abstract] or cardiac [Title/Abstract] or cardiovascular[Title/Abstract] or lung [Title/Abstract] or pulmonary [Title/Abstract] or liver [Title/Abstract] or hepatic[Title/Abstract] or endocardium [Title/Abstract] or myocardium [Title/Abstract] or pericardium[Title/Abstract])

Search in Medline

((exp thyroid gland/ or hyperthyroxinemia/ or hyperthyroidism/ or hypothyroidism/ or thyroid function tests/ or thyroxine/ or thyroid hormones/ or thyrotropin/ or thyroxine/) or (thyroid* or hyperthyro* or hypothyro* or free thyroxine or thyroid-stimulating hormone or Graves or thyrotropin or thyroxin or deiodinase or Hashimoto or triiodothyronine or thyronine* or myxedema or thyrotoxicosis or hyperthyroxinemia).ab,ti.) AND ((fibrotic or fibrosis or nonalcoholic steatohepatitis or fibrosing).ab,ti. or fibroblast.mp or fibrosis/ or exp pulmonary fibrosis/ or exp endomyocardial fibrosis/ or idiopathic pulmonary fibrosis/) AND (heart or cardiac or endocardium or myocardium or pericardium or lung or pulmonary or liver or hepatic or cardiovascular).ab,ti.

Search in Embase

((exp thyroid gland/ or exp thyroid disease/ or exp thyroxine/ or exp thyroid function/ or thyroid hormone/ or thyrotropin/ or thyroxine/ or exp thyroid hormone blood level/ or exp thyroid gland examination/) or (thyroid* or hyperthyro* or hypothyro* or free thyroxine or Graves or thyrotropin or thyroxin or deiodinase or Hashimoto or triiodothyronine or thyronine* or myxedema or thyrotoxicosis or hyperthyroxinemia).ab,ti.) AND ((fibrotic or fibrosis or nonalcoholic steatohepatitis or fibroblast).ab,ti. or (exp fibrosing alveolitis/ or exp fibrosing interstitial pneumonia/ or exp heart muscle fibrosis/ or exp liver fibrosis/ or exp lung fibrosis/)) AND ((heart or cardiac or endocardium or myocardium or pericardium or lung or pulmonary or liver or hepatic or cardiovascular).ab,ti.)

Search in Web-of-Science

(TS=(thyroid* or hyperthyro* or hypothyro* or "free thyroxine" or thyroid-stimulating hormone or Graves or thyrotropin or deiodinase or triiodothyronine or myxedema or thyrotoxicosis or hyperthyroxinemia or thyronine* or Hashimoto)) AND (TS=(fibrosis or fibrotic or fibroblast or nonalcoholic steatohepatitis or fibrosing)) AND (TS=(heart or cardiovascular or cardiac or endocardium or myocardium or pericardium or lung or pulmonary or liver or hepatic))

Appendix 3. Newcastle-Ottawa Quality Assessment Scale for case-control studies

Selection (max 4 stars)

1) *Is the case definition adequate?*
   a. yes, with independent validation*
   b. yes, eg, record linkage or based on self-reports
   c. no description

2) *Representativeness of the cases*
   a. consecutive or obviously representative series of cases*
   b. potential for selection biases or not stated

3) *Selection of controls*
   a. community controls*
   b hospital controls
   c. no description

4) *Definition of controls*
   a. no history of disease (end point)*
   b. no description of source

Comparability (max 2 stars)

1) *Comparability of cases and controls on the basis of the design or analysis*
   a. study controls for the most important factors*
   b. study controls for any additional factor**

Exposure (max 3 stars)

1) *Ascertainment of the exposure*
   a. secure record (eg, surgical records)*
   b. structured interview where blind to case/control status*
   c. interview not blinded to case/control status
   d. written self-report or medical record only
   e. no description

2) *Same method of ascertainment for cases and controls*
   a. yes*
   b. no

3) *Non-response rate*
   a. same rate for both groups*
   b. non-respondents described
   c. rate different and no designation

Appendix 4. Adapted Scale from the Newcastle-Ottawa Quality Assessment Scale for cohort studies

Selection (max 4 stars)

1) Representativeness of the exposed cohort
   a. Truly representative of the average in the target population (all subjects or random sampling)*
   b. Somewhat representative of the average in the target population (non-random sampling)*
   c. Selected group of users
   d. No description of the derivation of the cohort

2) Sample size
   a. Justified and satisfactory*
   b. Not satisfied

3) Ascertainment of the exposure
   a. Secure record (*eg*, medical records)*
   b. Structured interview *
   c. Written self-report
   d. No description of the measurement tool

4) Non-respondents
   a. Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory*
   b. The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory
   c. No description of the response rate or the characteristics of the respondents and the non-respondents

Comparability (max 2 stars)

1) The subjects in the different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.
   a. Study controls for the most important factors (age, sex)*
   b. Study controls for additional relevant factors**
   c. Inadequate degree of control

Outcome (max 3 stars)

1) Assessment of the outcome
   a. Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (eg, X-rays, medical records)**
   b. Record linkage (eg, identified through ICD codes on database records)**
   c. Self-report (ie, no reference to original medical records or X-rays to confirm the outcome)*
   d. No description

2) Statistical test
   a. The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including the probability level (*P* value)*
   b. The statistical test is not appropriate, not described or incomplete.