General introduction

THYROID FUNCTION

The thyroid gland synthetizes and secretes thyroid hormones T_4 (3, 5, 3', 5'-tetraiodothyronine, also known as thyroxine) and T_3 (3, 5, 3'-triiodothyronine).[1] Thyroid hormones are produced in response to the thyroid–stimulating hormone (TSH). TSH is secreted from the anterior pituitary gland in response to the thyrotropin-releasing hormone (TRH), which is secreted from the hypothalamus (Figure 1). The production of TSH and TRH is downregulated by thyroid hormones (Figure 1).[2] T_3, which is mainly derived from the local metabolism of circulating T_4, inhibits the synthesis and secretion of TRH and TSH, via binding to the thyroid hormone receptors in the hypothalamus and pituitary.[2] This negative feedback mechanism ensures the stability of circulating thyroid hormone levels, which is crucial for the biological functioning of all organs.

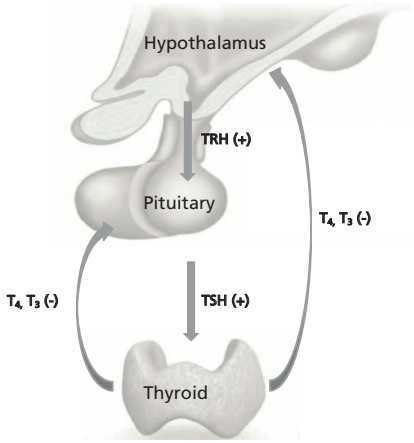


Figure 1. The hypothalamic-pituitary-thyroid axis.
Abbreviations: T_4, thyroxine; T_3, triiodothyronine, TSH, thyroid–stimulating hormone, TRH, thyrotropin-releasing hormone.

Thyroid function is clinically defined by the measurements of TSH and free thyroxine (FT_4) levels. Clinical hypothyroidism is characterized by TSH above the reference range and FT_4 levels below the reference range, whereas clinical hyperthyroidism is characterized by TSH below the reference range and FT_4 levels above the reference range. Subclinical hypothyroidism is defined by FT_4 within the reference range combined with elevated TSH levels. Subclinical hyperthyroidism is defined by FT_4 within the reference range combined with reduced TSH levels. In the adult population, the prevalence of clinical and subclinical hypothyroidism ranges from 0.2 to 5.3% and from 4 to 15%, respectively.[3-9] The prevalence of overt and subclinical hyperthyroid-

ism ranges from 0.8 to 1.3% and from 0.6 to 12.4%, respectively.[5,10-17] This variability may be explained by the different characteristics of the studied populations (eg, different iodine status) and the different assays of thyroid function used.

TSH levels needed to achieve the same thyroid hormone levels vary significantly among individuals,[18] indicating that each individual has a unique pituitary-thyroid set point. Several genetic loci have been linked to the pituitary-thyroid set point, suggesting that the set point is to some extent, genetically determined.[19,20] In addition, the relationship between TSH and FT_4 concentrations can be modulated throughout ageing.[21] Several studies have suggested that increasing age can reduce the sensitivity of the pituitary gland to thyroid hormones.[22-24] As a result, TSH levels needed to maintain the same FT_4 levels are different in younger and older adults.[24]

The reference ranges of TSH and FT_4 levels provide the basis for the diagnosis and treatment of thyroid disease. At present, the reference ranges of thyroid function are determined by a statistical approach, which is based on the 2.5th and 97.5th percentiles of the TSH and FT_4 distributions in an apparently healthy population. That is, TSH (or FT_4) levels above the 2.5th and below the 97.5th percentiles are considered as normal, whereas TSH (or FT_4) levels below the 2.5th and above the 97.5th percentiles are considered as abnormal. However, many studies have reported that the clinical consequences of abnormal thyroid function are extended even within the current reference ranges of TSH and FT_4,[25-28] thus indicating that the statistically defined reference ranges do not properly reflect the risk of developing clinical outcomes. Therefore, over the past years, there has been an ongoing debate on whether the reference ranges of TSH and FT_4 should be reevaluated. While some researchers support a reevaluation of TSH and FT_4 reference ranges, suggested measures are inconsistent varying from a lowering of the upper TSH reference limit (eg, from approximately 4 to 2.5 mIU/L) to an increase of the upper TSH reference limit or a downward shift of the FT_4 reference limit.[25,29-31] Others do not support a reevaluation, suggesting that more robust evidence needs to illustrate the risk of clinical outcomes within the reference ranges of TSH and FT_4.[32-35]

THE ROLE OF THYROID FUNCTION ON CARDIOMETABOLIC HEALTH

Thyroid hormones play a critical role in maintaining cardiometabolic homeostasis, via regulating cardiac and vascular physiology, as well as lipid, glucose and protein metabolism.[36] Besides, thyroid hormones influence energy expenditure by

accelerating basal metabolic rate, mitochondrial oxygen consumption and thermogenesis.[37] In the heart, thyroid hormones exert genomic effects via binding to the thyroid hormone receptors that are located in the nucleus of cardiomyocytes, further promoting the expression of target genes.[38] Thyroid hormones also exert non-genomic effects on various ion channels in the membranes of cardiomyocytes.[38] These genomic and non-genomic effects are translated into inotropic, chronotropic and bathmotropic cardiac effects of thyroid hormones.[38] Previous studies have extensively explored the association of thyroid function with various cardiometabolic conditions, including atrial fibrillation (AF), coronary heart disease (CHD), stroke, heart failure, hypertension, diabetes mellitus, dyslipidemia, and obesity.[25,28,32,39-48] Interestingly, even minimal fluctuations in TSH and FT_4 concentrations have been associated with remarkable alterations in cardiometabolic health.[27,49-53]

Atrial fibrillation: High and high-normal thyroid function constitute an increased risk of AF. An individual participant data (IPD) meta-analysis from the Thyroid Studies Collaboration showed that subclinical hyperthyroidism is associated with a 1.68 times higher risk of AF compared with euthyroidism.[39] Prospective studies focusing on the normal range of thyroid function have also consistently reported an association between high-normal thyroid function and increased AF risk.[28,40]

Coronary heart disease: Three large IPD meta-analyses from the Thyroid Studies Collaboration have focused on the risk of CHD and CHD mortality in subclinical hypothyroidism, subclinical hyperthyroidism and euthyroidism, respectively.[32,39,41] The first reported that subclinical hypothyroidism with TSH levels above 10 mIU/L is associated with a 1.89 and 1.58 times higher risk of CHD events and CHD mortality than euthyroidism, respectively.[41] The second reported that subclinical hyperthyroidism is associated with a 1.21 and 1.29 times higher risk of CHD events and CHD mortality than euthyroidism, respectively.[39] The third IPD meta-analysis, performed among euthyroid subjects, showed no association between thyroid function within the reference range and CHD risk.[32]

Stroke: The association of thyroid function with stroke has been investigated in two IPD meta-analyses from the Thyroid Studies Collaboration.[43] One of them found no overall effect of subclinical hypothyroidism on the risk of stroke events or fatal stroke.[43] However, age-stratified analyses (younger versus older than 65 years) revealed that in

younger participants, subclinical hypothyroidism was associated with a higher risk of stroke than euthyroidism. The other IPD meta-analysis, which included only euthyroid participants, showed that low-normal TSH levels and high-normal FT_4 levels are associated with an increased risk of stroke.[42]

Hypertension: Overt and subclinical hyperthyroidism often lead to systolic hypertension via increasing cardiac output.[45,54] Overt and subclinical hypothyroidism, on the other hand, promote diastolic hypertension via increasing systemic vascular resistance.[55,56] Even in euthyroid subjects, higher TSH levels have been associated with both systolic and diastolic hypertension.[51,52]

Heart failure: In an IPD meta-analysis from the Thyroid Studies Collaboration, both higher and lower TSH levels showed a significant trend for an increased risk of heart failure.[44] Participants with TSH levels ≥10 and <0.1 mIU/L had a 1.86 and 1.94 times higher risk of heart failure than euthyroid participants, respectively. Several mechanisms can explain the role of thyroid function on heart failure. Subclinical thyroid dysfunction can increase the risk of CHD, which is a common cause of heart failure. Moreover, alterations in thyroid function affect heart rate, cardiac contractility, cardiac output and vascular resistance, that can all contribute to the development of heart failure.[57] On the other hand, a potential influence of heart failure on the metabolism of thyroid hormones is also likely. Heart failure-related hypoxia increases the gene expression of type 3 deiodinase, which promotes the degradation of thyroid hormone, eventually reducing the local availability of T_3 in cardiomyocytes.[58,59] Low levels of T_3 further contribute to a progressive deterioration of cardiac function in heart failure and have been proposed as an independent predictor of New York Heart Association functional class.[60]

Diabetes mellitus: Hypothyroidism is associated with an increased risk of diabetes, most likely due to a decreased insulin sensitivity and glucose tolerance.[46,61] Accordingly, restauration of euthyroidism after treatment of hypothyroidism has been shown to improve insulin sensitivity.[62,63] These negative consequences of hypothyroidism on glucose metabolism can also be extended within the reference range of thyroid function. In a large prospective population-based cohort study, even low-normal thyroid function was associated with an increased risk of type 2 diabetes and progression from prediabetes to diabetes.[27]

Dyslipidemia: Overt hypothyroidism commonly leads to hypercholesterolemia and hypertriglyceridemia,[36] via decreasing the expression of hepatic LDL receptors, reducing cholesterol clearance and modulating fatty acid metabolism.[47] The role of subclinical hypothyroidism on dyslipidemia is less clear. Some studies have suggested that thyroid hormone replacement may improve the lipid parameters.[64-66] This, however, was not confirmed in a meta-analysis of randomized clinical trials, that showed no overall effects of thyroid hormone replacement in the lipid profiles of patients with subclinical hypothyroidism.[67] Levothyroxine treatment did not result in a reduction of total cholesterol, HDL cholesterol, triglycerides, apolipoprotein A and B, and lipoprotein A, though there was a trend towards reducing LDL cholesterol >155 mg/dl.[67]

Obesity: In some,[48,53,68] but not all[69] population-based studies, high and high-normal TSH levels have been associated with an increased body weight. The association between thyroid function and body weight is likely bidirectional. On one hand, low thyroid function is typically characterized by decreased energy expenditure and low metabolic rate, resulting in weight gain.[70] On the other hand, adipose tissue has been recognized as an endocrine organ because it secretes leptin,[70-72] which is known to stimulate TSH release.[70]

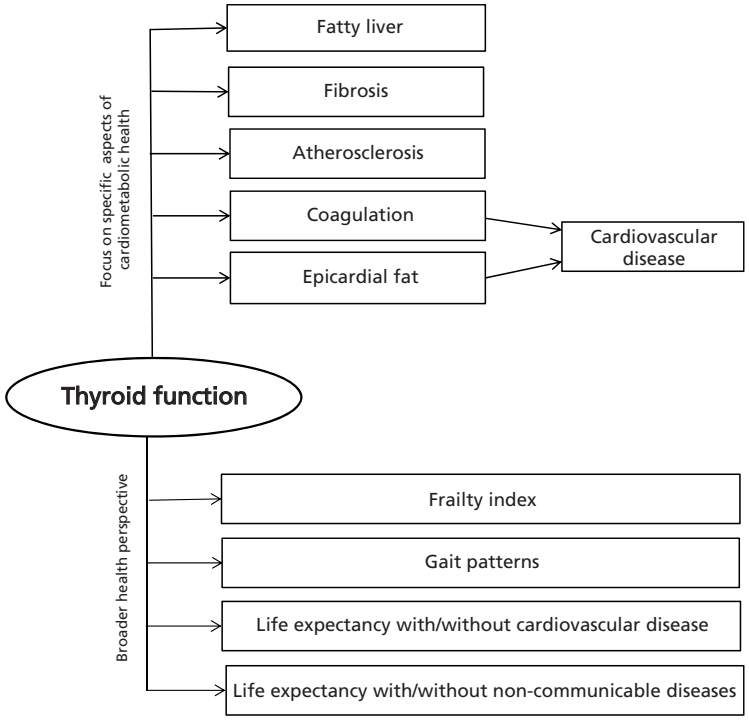
THE PLEIOTROPIC EFFECTS OF THYROID HORMONES

Thyroid hormones have complex pleiotropic effects in nearly all tissues and organs.[73,74] Clinical, epidemiological and experimental evidence suggests that even subtle changes in circulating thyroid hormone levels can adversely affect cardiovascular, musculoskeletal and neurocognitive functioning.[26,28,73,74] The effects of thyroid hormones vary in character, some being stimulatory and others inhibitory. This is illustrated by several prospective studies, showing that circulating thyroid hormones are negatively associated with the risk of diabetes or dyslipidemia[27,49] and are positively associated with the risk of cognitive decline or atrial fibrillation.[26,28] The effects of thyroid hormones also vary in magnitude, depending on the targeted tissues and organs. For example, in middle-aged and older adults, increasing FT_4 levels have been prospectively associated with an increased risk of dementia, and even higher risk of AF.[26,28]

AIMS OF THIS THESIS

This thesis has two main aims. The first aim is to extend the current knowledge on the specific effects of thyroid function on cardiometabolic health. In view of the inconsistent results of previous studies,[32,42,75-78] we investigate the association of thyroid function with cardiometabolic diseases, such as nonalcoholic fatty liver disease, fibrotic disease, and atherosclerosis. Furthermore, we focus on the association of thyroid function with some aspects of cardiometabolic health that have been studied less extensively so far, such as coagulation and epicardial adipose tissue. To provide some mechanistic evidence, we also investigate whether and to what extent coagulation factors and epicardial adipose tissue can explain certain cardiovascular effects of thyroid hormones. The second aim is to yield novel insights about the qualitative and quantitative impact of thyroid function on general health. We thus adopt a broader perspective, using multidimensional measures

Figure 2. Implications of thyroid function among middle-aged and older adults: Focused versus broader perspective.



that can reflect the pleiotropic effects of thyroid hormones, such as frailty index, global gait, and measurements of life expectancy with and without diseases. The conceptual framework of this thesis is presented in Figure 2.

RATIONALE OF THIS THESIS

Beyond thyroid status categories

The classification of thyroid status in categories of euthyroidism, clinical and subclinical hypothyroidism, clinical and subclinical hyperthyroidism, is useful in clinical decision making. However, thyroid status categories are based on arbitrary cutoffs of TSH and FT_4 levels. As a result, cohort studies exclusively investigating thyroid status categories or arbitrary cutoffs of thyroid function may not properly account for potential nonlinear effects of thyroid function. Hypothetically, variations throughout the full spectrum of TSH and FT_4 levels may be associated with the risk of adverse outcomes. Therefore, our investigations were mainly focused on the risk of adverse outcomes throughout the continuous range of TSH and FT_4 levels, beyond the above described thyroid status categories.

Thyroid function, a potential risk factor for cardiometabolic conditions

The burden of diseases that affect cardiometabolic health can be reduced by identifying and modifying their determinants. High thyroid function, for example, is a well-established risk factor for AF, and thyroid function measurements are routinely performed in patients diagnosed with newly-onset AF.[79] Yet, the association of thyroid function with some other aspects of cardiometabolic health is less established. Previous studies focusing on the role of thyroid function on fatty liver, fibrosis or atherosclerosis have yielded inconsistent results.[32,42,75-78] Moreover, current data on the role of thyroid function on coagulation or epicardial adipose tissue are scarce. Therefore, we aimed to extend the current knowledge about the role of thyroid function on several aspects of cardiometabolic health, including fatty liver, fibrosis, atherosclerosis, coagulation, and epicardial adipose tissue.

Potential mediators linking thyroid function to cardiovascular disease

The influence of thyroid function on cardiovascular events, such as AF, CHD, and stroke, seems to be independent of hypertension, dyslipidemia, obesity, and diabetes.[25] This suggests that alternative factors beyond traditional cardiovascular risk

factors can mediate the effects of thyroid function on the cardiovascular system. The elucidation of these mediators is important, not only for a better pathophysiological understanding of cardiovascular diseases, but also for establishing novel preventive and treatment strategies. Therefore, we hypothesized that coagulation factors and epicardial adipose tissue can partially explain the effects of thyroid function on cardiovascular disease and AF, respectively.

The need for a broader health perspective

Thyroid hormones have stimulatory or inhibitory, major or minor effects, depending on the targeted tissues and organs. The resultant of all the specific effects of thyroid hormones is likely reflected in general health. However, the role of thyroid hormones on general health remains unclear. This information could help improve the prevention and possible prediction of health deterioration, and would also be relevant in view of the ongoing debate on the optimal reference ranges of thyroid function. Therefore, we sought to provide novel insights regarding the qualitative and quantitative impact of thyroid function on general health. Given that a "golden standard" measure of general health is lacking, we used several multidimensional measures that can reflect the pleiotropic effects of thyroid hormones, such as frailty index (measure of general health and frailty), global gait (measure of general health and functional mobility), and measurements of life expectancy with and without diseases.

SETTING

The study presented in Chapter 2.2 is a systematic review of the literature. Two reviewers independently screened the titles and abstracts, further selecting the eligible studies. The Newcastle-Ottawa Scale for non-randomized studies was used to assess the quality of the included studies based on 3 predefined domains, namely selection of participants, comparability of study groups, and ascertainment of the outcomes of interest.

The other studies presented in Chapters 2 and 3 of this thesis were performed within the framework of the Rotterdam Study. The Rotterdam Study is an ongoing prospective population-based cohort study that investigates the determinants, occurrence, and progression of chronic diseases among middle-aged and older adults.[80] In 1989, the Rotterdam Study enrolled participants into its first cohort (RS

cohort I), which was further extended in 2000 (RS cohort II) and 2006 (RS cohort III). Study participants are followed-up for the occurrence of chronic diseases. Extensive medical examinations are performed every 3 to 5 years. Thyroid function tests were measured in the three Rotterdam Study cohorts using the same method and assay.

OUTLINE OF THIS THESIS

Chapter 1 provides a general background on the pleiotropic effects of thyroid hormones, with a particular focus on cardiometabolic health. The objectives, rationale and outline of the thesis are further described.

Chapter 2 aims to extend the knowledge on the association of thyroid function with specific aspects of cardiometabolic health, including fatty liver, fibrosis, and atherosclerosis. Most studies examining the role of thyroid function on fatty liver are characterized by inconsistent results, that can be explained by cross-sectional designs and small sample sizes.[75,76] Therefore, Chapter 2.1 prospectively investigates the association of thyroid function with the risk of nonalcoholic fatty liver disease, in a large population-based cohort.
Furthermore, it has been suggested that variations in thyroid function may affect the occurrence and progression of fibrosis, but the data are fragmented and inconclusive.[77,78,81,82] In this context, Chapter 2.2 systematically appraises the evidence regarding the role of thyroid function on fibrosis of the liver, lung, and heart.

Thyroid hormones have been linked to both proatherogenic[83,84] and antiatherogenic[36] processes, but the role of thyroid function on the different stages of atherosclerosis progression has not been investigated. The cohort study presented in Chapter 2.3 examines the association of thyroid function with different stages of atherosclerosis, from subclinical atherosclerosis to atherosclerotic cardiovascular events to atherosclerotic cardiovascular mortality.

The effects of thyroid hormones on the cardiovascular system seem to be independent of traditional cardiovascular risk factors, such as hypertension or dyslipidemia.[25] In Chapters 2.4 and 2.5, we aim to identify potential mediators linking thyroid function to cardiovascular events. In Chapter 2.4, we hypothesize that blood coagulation can be one of the underlying mechanisms through which thyroid hormones affect cardiovascular health. Using a four-way decomposition approach,

Chapter 2.5 explores whether epicardial adipose tissue mediates the association of thyroid function with atrial fibrillation.

Thyroid hormones exert specific effects on nearly all tissues and organs, the resultant of which can be reflected in general health. In ***Chapter 3***, we aim to provide novel insights on the qualitative and quantitative impact of thyroid function on general health. We therefore evaluate conditions that can reflect the pleiotropic effects of thyroid hormones, including general health, vulnerability to adverse outcomes, functional mobility, and life expectancy. In Chapter 3.1, we cross-sectionally and longitudinally investigate the association of thyroid function with frailty index, a well-established measure of frailty and general health. Chapter 3.2 seeks to identify the spatiotemporal gait aspects that are related to thyroid function. Comprehensive measurements of gait patterns, including global gait, rhythm, variability, phases, pace, base of support, tandem, turning, and velocity, are used. In view of the current debate on the reference ranges of TSH and FT_4 levels, Chapters 3.3 and 3.4 investigate whether there are meaningful differences in total life expectancy and disease-specific life expectancy within the reference range of thyroid function. Given the important role of thyroid hormones on cardiovascular health, Chapter 3.3 focuses on the association between thyroid function within the reference range and life expectancy with and without cardiovascular disease. Meanwhile, Chapter 3.4 provides a broader perspective by investigating the association between thyroid function within the reference range and life expectancy with and without non-communicable diseases.

Chapter 4 summarizes the principal findings of this thesis, elaborates on the main methodological considerations, and further discusses the clinical implications and potential directions for future research.

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