General discussion

REFLECTION ON THE MAIN FINDINGS

Chapter 2 of this thesis investigated the association of thyroid function with specific aspects of cardiometabolic health, including fatty liver, fibrosis, atherosclerosis, coagulation and epicardial adipose tissue (EAT). Chapter 3 investigated the association of thyroid function with general health, using several multidimensional measures that can reflect the pleiotropic effects of thyroid hormones. The main findings of this thesis are summarized in Table 1.

Thyroid function and specific aspects of cardiometabolic health

Thyroid function and the risk of nonalcoholic fatty liver disease: Nonalcoholic fatty liver disease (NAFLD) comprises a broad spectrum, ranging from steatosis to nonalcoholic steatohepatitis (NASH) with fibrosis.[1] NAFLD is the most common chronic liver condition with a global prevalence of more than 25%.[2,3] The prevalence of NAFLD is rapidly increasing, and NASH-related cirrhosis is becoming the leading cause of liver transplantation worldwide.[4] Therefore, the identification of novel modifiable risk factors of NAFLD is of major importance. Thyroid hormones can influence the intrahepatic lipid metabolism and the development of hepatic steatosis.[5] However, previous cross-sectional population-based studies investigating the association of thyroid function with hepatic steatosis have provided inconsistent results.[6,7] The only prospective study to date was performed by Xu et al, who showed that subclinical hypothyroidism is associated with an increased risk of developing NAFLD.[8] Still, the risk of NAFLD in the remaining categories of thyroid function, other than subclinical hypothyroidism, has not been prospectively explored. To address this gap, we investigated the association between the whole spectrum of thyroid function and the risk of NAFLD, in a large prospective population-based cohort study (Chapter 2.1).

Our results indicated that the association of thyroid function with NAFLD is not only limited to subclinical hypothyroidism, but is extended both within as well as outside the reference range of thyroid function. We found a negative linear association between free thyroxine (FT_4) levels and incident NAFLD, even among euthyroid subjects, as well as a positive linear association for thyroid-stimulating hormone (TSH) levels. The risk of NAFLD progressively decreased from a hypothyroid to a hyperthyroid state.

Aiming to provide some mechanistic insights, we further investigated whether and which cardiovascular risk factors could explain the association of thyroid function with NAFLD. Interestingly, our data indicated that circulating triglyceride levels

Table 1. Overview on the main findings of this thesis

	TSH	FT_4
Thyroid function and specific aspects of cardiometabolic health		
Nonalcoholic fatty liver disease (P)	↑/=	↓
Fibrotic diseases of the liver, lung and heart (C and P)	↑/=	=
Atherosclerosis (P)		
Coronary artery calcification	=	↑
Incident atherosclerotic CV events	=	↑
Atherosclerotic CV deaths	↓/=	↑
Coagulation factors (C)		
Fibrinogen	=	↑
VWF	=	↑
ADAMTS13	=	↓
Epicardial adipose tissue (C)	=	↑*
Potential mediating role (P)		
Fibrinogen & CV outcomes	=	M
VWF & CV outcomes	=	M
ADAMTS13 & CV outcomes	=	=
Epicardial adipose tissue & AF	=	=
Thyroid function and general health		
Frailty index changes (P)	=	↑
Gait aspects related to thyroid function (C)	Tandem, base of support, velocity	=
Life expectancy with and without NCD† (P)	↑	↓
Life expectancy with and without CV disease† (P)	↑	↓

Arrows represent the direction of the associations. Arrows pointing upwards represent positive associations, whereas arrows pointing downwards represent negative associations. Equal signs represent absence of statistically significant associations. *This finding applies only to subjects with large waist circumferences. †This study was performed among euthyroid participants. Abbreviations: TSH, thyroid-stimulating hormone (mIU/L); FT_4, free thyroxine (ng/dL); CV, cardiovascular; VWF, von Willebrand factor; ADAMTS13, a disintegrin and metalloprotease with thrombospondin motif repeats 13; AF, atrial fibrillation; M, mediator; NCD, non-communicable diseases; (P), prospective; (C), cross-sectional.

and body mass index may play an important role in the pathways linking thyroid function to NAFLD (ie, excess risk mediated by triglycerides and BMI, up to 22.2%).

Another novel aspect of our study was the utilization of liver elastography, which allowed us to additionally explore the risk of developing NAFLD with fibrosis. We showed that the risk of developing NAFLD with fibrosis progressively decreases from a hypothyroid to a hyperthyroid state. In line, lower thyroid function was associated with a higher risk of having NAFLD with fibrosis. Based on these findings, we hypothesize that low thyroid function may either accelerate the progression of liver steatosis to fibrosis or may directly stimulate the development of liver fibrosis, independent of steatosis. Further research will need to pinpoint the exact underlying mechanisms linking thyroid function to liver fibrosis. Moreover, future interventional studies in animals and humans are warranted to explore the potential beneficial effects of thyroid hormone supplementation on liver fibrosis.

Thyroid function and the risk of fibrosis: Current research is focused on the identification of novel determinants of fibrosis, which could be further translated into the development of effective antifibrotic drugs. Among other factors, low thyroid function has been implicated in the occurrence and progression of liver, pulmonary and myocardial fibrosis.[9-11] However, evidence is fragmented and inconclusive. In Chapter 2.2, we aimed to summarize the current evidence regarding the link between thyroid function and the risk of developing fibrosis in the human liver, lung and heart. After screening 1764 titles and abstracts, we identified 10 studies meeting the inclusion criteria.[6,12-20] Of the identified studies, 6 reported on liver fibrosis,[6,12-16] 2 on pulmonary fibrosis,[17,18] and 2 on myocardial fibrosis.[19,20] In the setting of diverse study populations, low thyroid function was consistently associated with increased odds of liver fibrosis, pulmonary fibrosis, and myocardial fibrosis. However, most of the evidence on this topic was 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 lead to new avenues regarding the development of new therapies against fibrotic diseases. Lastly, future research is needed to elucidate the exact underlying mechanisms linking low thyroid function to fibrosis.

Thyroid function and the risk of atherosclerotic cardiovascular morbidity and mortality: Atherosclerosis is an accumulation of lipids and fibrous elements in the arterial walls, that can progress insidiously from an asymptomatic luminal narrowing of the arteries known as subclinical atherosclerosis, to the clinical manifestation of serious cardiovascular events to death.[21] Thyroid hormones have been linked to both proatherogenic[22,23] and antiatherogenic processes.[24] Epidemiological studies have so far investigated the association between specific ranges of thyroid function and distinct atherosclerosis events as coronary heart disease or stroke, with inconsistent results.[25-28] However, the role of thyroid function on the different stages of atherosclerosis progression has been unclear. Therefore, Chapter 2.3 examined the association between the full range of thyroid function and atherosclerosis throughout its spectrum, spanning from subclinical atherosclerosis (measured by coronary artery calcification) to clinical atherosclerotic cardiovascular (ASCV) events to ASCV mortality.

We found that FT_4 levels were positively and linearly associated with subclinical and clinical atherosclerosis. Increasing circulating FT_4 levels were associated with twice the odds of elevated coronary artery calcification scores, 87% greater risk of ASCV events, and double the risk of ASCV mortality. After restricting the analyses to euthyroid participants, these associations became even stronger. Specifically, the higher limit of the FT_4 reference range was associated with a 2.70 and a 4.15 times higher risk of incident ASCV events and ASCV mortality, respectively, compared with the lower reference limit. Also, the magnitude of the association for ASCV mortality was greater compared with non-ASCV mortality, which indicates that atherosclerosis plays an important role in the pathways linking high thyroid function to increased mortality risk.

Interestingly, our findings were independent of traditional cardiovascular risk factors such as hypertension or dyslipidemia. This suggests that the link between thyroid hormones and atherosclerosis can be explained by mechanisms that go beyond traditional cardiovascular risk factors. Hemodynamic changes, endothelial damage and increased thrombogenesis might play a role.

Thyroid function and coagulation: Large meta-analyses and systematic reviews of clinical-based studies have shown an increased risk of bleeding in hypothyroidism and an increased risk of thrombosis in hyperthyroidism.[23,29] Previous studies, however, did not investigate whether the anticoagulant effects of hypothyroidism and

the procoagulant effects of hyperthyroidism are extended even within the normal reference range of thyroid function. To address this, large studies in the general population are needed. Therefore, we performed a large population-based cohort study (Chapter 2.4), which investigated the association of thyroid function with several coagulation factors, including fibrinogen, von Willebrand factor (VWF) antigen and ADAMTS13 (a disintegrin and metalloprotease with thrombospondin motif repeats 13) activity.

We found that high and high-normal FT_4 levels are associated with increased fibrinogen and VWF levels, which indicate a procoagulant state. In line with our results, a direct role of thyroid hormones on the transcription of fibrinogen and VWF genes has been suggested.[30] Moreover, we found that high and high-normal FT_4 levels are associated with a decreased activity of ADAMTS13. This suggests that thyroid hormones can attenuate the role of ADAMTS13 in cleaving the procoagulant VWF multimers into less procoagulant forms. Future studies are warranted to explore the possibility of a direct effect of thyroid hormones on ADAMTS13.

Thyroid function and epicardial adipose tissue: The role of thyroid hormones on adiposity is complex and depends on the location and composition of adipose tissue. EAT, which surrounds the myocardium, possesses both white and brown adipose tissue properties.[31] A thyroid-hormone dependent gene, namely uncoupling protein 1 gene is recently shown to be highly expressed in EAT, thus suggesting a potential direct effect of thyroid hormones on mitochondrial uncoupling and EAT activation.[31] In line, several small studies (n<100) have suggested a potential role of thyroid dysfunction on EAT activation.[32-36] However, the association of thyroid function with EAT has not been explored in larger studies, nor has it been investigated throughout the full range of thyroid function in the general population. To address this, we performed a large population-based cohort study (Chapter 2.5), in which we evaluated EAT volumes by using well-standardized CT scan measurements. We found that higher FT_4 levels among participants with a large waist circumference are associated with larger EAT volumes. Hypothetically, increased thyroid hormone levels may contribute to the transdifferentiation of white adipocytes to brown adipocytes in the EAT of obese patients.

Mediators linking thyroid function to cardiovascular disease: In Chapters 2.4 and 2.5, we sought to provide mechanistic insights on the cardiovascular effects of thyroid hormones.

Previous evidence suggests that thyroid hormones regulate the synthesis of coagulation proteins, which in turn contribute to blood viscosity.[30] In Chapter 2.4, we investigated the potential mediating role of coagulation factors in the association of thyroid function with cardiovascular disease and mortality. VWF and fibrinogen (but not ADAMTS13) were identified as partial mediators linking FT_4 to cardiovascular events. The observed proportion of mediation was approximately 10%, which is quite considerable given the multiple mechanisms through which thyroid hormones affect cardiovascular health. Besides, it can be assumed that other coagulation factors, such as factors VII, VIII, IX, X, XII, can play an additional mediating role.[23,37,38] Unfortunately, data on these factors were not available in our study. If all the relevant coagulation factors could also be taken into account in our mediation analyses, the expected proportion of mediation related to coagulation may have been even higher than what we observed in our study.

Another explanation of the cardiovascular effects of thyroid hormones can be related to EAT. Thyroid hormones may affect the metabolism of EAT, which is a rapidly emerging risk factor for CVD, and particularly for atrial fibrillation (AF).[31,39] In Chapter 2.5, we investigated the potential mediating role of EAT in the association of thyroid function with AF. No relevant mediating effect of EAT was found, but our study indicated that the combined effects of thyroid hormones and EAT may increase the risk of AF synergistically.

Thyroid function and general health

Thyroid function associated with frailty index, a measure of frailty and general health: In Chapter 3.1, we investigated the association of thyroid function with frailty index, a well-established measure of frailty and general health. Interestingly, higher FT_4 levels were associated with increasing scores of frailty index, thus indicating an increased risk of health deterioration over time. These findings can reflect various deleterious effects of excess thyroid hormones, such as an increased risk of neurodegeneration, arrhythmias, hemodynamic changes, hypercoagulability, and reduction in bone mineral density.[40-43]

Identification of gait aspects related to thyroid function: Thyroid function in the general population has been linked to gait velocity.[44,45] However, it remains unknown whether other gait aspects are related to thyroid function. In Chapter 3.2, we identified tandem and base of support as novel gait domains related to thyroid function. The identification of thyroid-related gait domains may provide valuable hints on the pathways linking thyroid function to gait. Tandem, base of support and velocity have been so far associated with executive functioning, balance, and distinct brain structures (ie, prefrontal regions, parietal cortex, pallidum, putamen, and cerebellum) that may be targeted by thyroid hormones.[46-51]

Meaningful differences in life expectancy within the reference range of thyroid function: In view of the ongoing debate on redefining the reference ranges of TSH and FT_4 levels, several population-based studies have shown that variations in thyroid function within the reference range are associated with an increased risk of chronic diseases and mortality.[26,27,40,52-54] In Chapters 3.3 and 3.4, we extended the previous knowledge, by revealing meaningful differences in total life expectancy and life expectancy with and without diseases within the reference range of thyroid function. We found that subjects with low-normal thyroid function lived more years with and without non-communicable diseases than those with high-normal thyroid function. As a result, low-normal thyroid function was also associated with a prolonged life expectancy compared with high-normal thyroid function. These differences in life expectancy can reflect differences in the risk of adverse outcomes within the reference range of thyroid function. So far, low-normal TSH and high-normal FT_4 levels have been prospectively linked to an increased risk of AF, ASCV disease, heart failure, dementia and fractures, which are all associated with an increased risk of mortality.[27,55,56]

METHODOLOGICAL CONSIDERATIONS

Population-based cohort studies, strengths and pitfalls

Most studies included in this thesis were embedded within the framework of the Rotterdam Study, a prospective population-based cohort study in middle-aged and older adults.[57] Major strengths of our studies are the well-characterized population-based study sample, the large number of eligible participants, and the extensive

information on covariates including exposures, outcomes, potential confounders and mediators. Multiple sensitivity analyses provided consistent findings.

The following considerations should also be taken into account. Due to the observational character, population-based studies may be subject to bias including healthy volunteer bias or attrition bias. However, the possibility of these biases within the Rotterdam Study is minimized because of the random sampling of participants from the general population, the high response rate of participants and the nearly complete follow-up. Another type of bias in observational studies is the information bias, which can be either differential or non-differential. However, the possibility of information bias in our studies is minimized because of the utilization of standardized procedures of data collection, blinding of both participants and investigators to thyroid function measurements, and the adjudication of events in accordance with the current guidelines. Another concern in observational studies is related to the possibility of confounding. To address confounding, we adjusted our analyses for potential confounders, that were selected based on biological plausibility and previous literature.[58] However, the possibility of residual confounding cannot be ruled out. Potential confounders as smoking status, alcohol consumption and diet were self-reported and therefore could have been affected by measurement errors. Furthermore, the Rotterdam Study includes predominantly white Northern Europeans older than 45 years.[57] Therefore, we cannot ascertain the generalizability of our findings to other ethnicities or younger subjects.

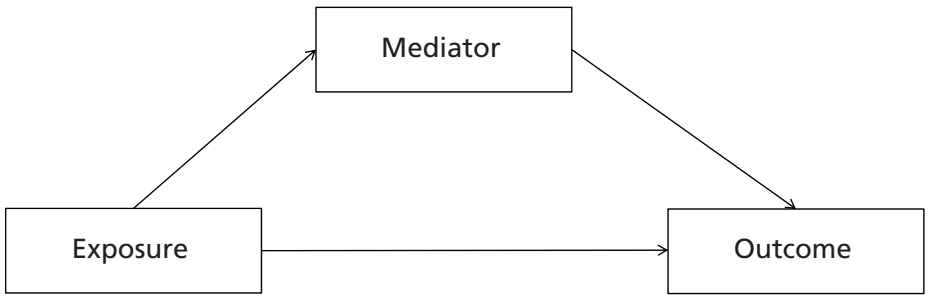
The studies of this thesis are mostly characterized by a prospective design with a long term follow-up time. Prospective designs provide evidence for a temporal relation between the exposure and outcome, thus reducing the possibility of reverse causation.[59] When applicable (eg, in Chapters 2.3, 3.3, 3.4), we additionally addressed reverse causation by excluding the events that occurred within the first two years of follow-up. However, some analyses in this thesis had a cross-sectional character, which does not provide evidence on the temporality of an association. This specifically applies to Chapter 3.2, in which we reported a nonlinear association of TSH levels with global gait. Similarly, the cross-sectional analysis in Chapter 3.1 revealed a nonlinear association of TSH levels with frailty index. Taken together, the cross-sectional analyses in Chapters 3.1 and 3.2 indicated that subjects with low and high thyroid function are more likely to have a worse heath state than those with normal thyroid function. On the other hand, the prospective analysis in Chapter 3.1 suggested that subjects with low thyroid function do not have an increased risk of

health deterioration over time. This discrepancy between the cross-sectional and prospective results can be attributed to the condition of "non-thyroidal illness", which is typically characterized by low thyroid function secondary to a poor health status.[60] The cross-sectional association between low thyroid function and poor health may reflect an alteration of thyroid parameters due to health-related issues rather than vice-versa. Therefore, the possibility of reverse causation due to the "non-thyroidal illness" needs to be taken into consideration when interpreting the results of cross-sectional studies on thyroid function.

Mediation analyses

Mediation analyses are helpful tools to explore and identify the underlying mechanisms of an association.[61] Besides the potential direct effect of the exposure on the outcome, the model proposes that the exposure influences a mediator, which in turn influences the outcome (Figure 1). In this thesis, mediation analyses were used to explore some of the pathways through which thyroid hormones affect cardiovascular health. In Chapter 2.4, we investigated the potential mediating role of several coagulation factors, including fibrinogen, VWF, and ADAMTS13 activity. We found evidence of partial mediation, implying that the coagulation factors account for some, but not all, of the association between FT_4 and cardiovascular events. In Chapter 2.5, we used the four-way decomposition approach, that unifies within a single framework the methods using mediation and interaction.[62] Although we did not describe a mediating role of EAT, we found evidence for a suggested interaction of FT_4 with EAT volumes on AF risk.

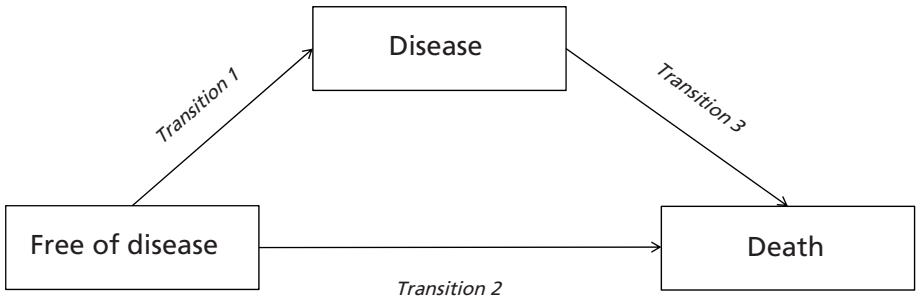
Figure 1. A statistical mediation model.



Multistate life tables

Multistate life tables is a demographic tool that is often used to estimate the total life expectancy and disease-specific life expectancies.[63] This tool combines the information of individuals in three possible health states, namely "free of disease", "disease" and "death". Potential transitions of participants are: (1) from free of disease to disease, (2) from free of disease to death, (3) from disease to death (Figure 2). The age of each individual is measured at the study entry, when the event occurs and at the end of the follow-up.[64] Age-specific rates of disease and mortality probabilities are used to calculate the total life expectancy and disease-specific life expectancies. A limitation of this approach is related to the arbitrary categorization of participants into health states, thus not accounting for the potential amelioration or aggravation of disease over time. Hence, the results derived from the multistate life table analysis are only an approximation of the real disease burden. In Chapters 3.3 and 3.4, the multistate life table analysis was used to investigate the association of thyroid function with total life expectancy and disease-specific life expectancies among euthyroid subjects. We found considerable differences in life expectancy within the reference range of thyroid function. These findings provide supporting evidence for a reevaluation of the current reference ranges of thyroid function.

Figure 2. Transitions in multistate life tables.



POTENTIAL IMPLICATIONS AND FUTURE DIRECTIONS

Causality

In this thesis, the biological plausibility of the research questions, the strength and consistency of the associations, the prospective designs of most studies and the various sensitivity analyses addressing reverse causation strongly suggest a causal

relation between exposures and outcomes.[65] Yet, the observational character of our studies does not allow us to establish causality.

In the future, methods of causal inference can be useful to gain further insights on the direction of the associations. Mendelian Randomization (MR) is a pragmatic method of causal inference which uses genetic variants in non-experimental data.[66,67] This approach is based on the principle that genetic variants are generally not associated with confounders owing to the random independent assortment of DNA at meiotic segregation of alleles.[68] Given that genetic variants are immune to reverse causation, MR can be useful to clarify the direction of an association. However, the following considerations need to be taken into account. First, MR studies are based on the critical assumption that the genetic variants should be associated with the exposure. To satisfy this assumption, a large proportion of TSH and FT_4 heritability needs to be explored and explained by future research. Second, genetic variants in MR can sometimes have multiple phenotypic effects, also known as pleiotropic effects.[69] Third, the effects of genetic variants may be buffered by compensatory developmental processes. Fourth, MR studies require very large sample sizes in order to obtain sufficient statistical power.

Randomized clinical trials (RCTs) can provide important evidence on the effects of treatment and can help overcome some limitations of the observational studies.[70] One of the major strengths of RCTs is randomization, which addresses the issue of confounding. However, the randomization of individuals to specific interventions can be unethical. Besides, RCTs are expensive and require a long time to be completed. Therefore, before designing new RCTs, data from previous RCTs and observational studies need to be carefully evaluated.[71] To date, guidelines for the treatment of subclinical thyroid dysfunction[72,73] are mainly based on the results of observational research and short-term small RCTs.[74-78] The long-term risks related to the treatment of subclinical thyroid dysfunction have not been comprehensively explored. Moreover, it remains unclear whether the optimal treatment thresholds for TSH and FT_4 levels are similar to the TSH and FT_4 reference ranges. As a result, thyroid patients often carry the risk of being overtreated or undertreated. In order to minimize this risk, adequately powered RCTs are warranted to explore the risks and benefits of the thyroid disease treatment and eventually establish the optimal treatment targets for the TSH and FT_4 levels.

Mechanisms

The mediation analyses in Chapters 2.1, 2.4, 2.5 of this thesis provide some novel insights on the pathways through which thyroid hormones affect cardiometabolic health. Specifically, our results in Chapter 2.1 suggest that even slight reductions in circulating thyroid hormone levels can increase the risk of NAFLD via affecting the metabolism of triglycerides and fat. Furthermore, our results in Chapter 2.4 indicate that high and high-normal thyroid hormones may increase the risk of cardiovascular diseases via altering the activity of circulating coagulation factors, such as VWF, ADAMTS13, and fibrinogen. Future observational studies are needed to replicate the results of our mediation analyses in other populations. In addition, *in vitro* and *in vivo* experimental studies are also needed to explore the exact mechanisms that can explain the role of thyroid function on cardiometabolic health and general health. Once identified, the modifiable mediators can be further targeted to eventually reduce the burden of the clinical implications of thyroid dysfunction.

Circulating thyroxine, a potential predictive marker?

Observational studies provide evidence for either the presence or absence of an association. Once an association is reported, additional research may further head towards new avenues regarding causation and underlying mechanisms. Regardless of whether an association is causal or not, it can still be very useful to make predictions.

The studies included in this thesis showed that variations in thyroid function are associated with specific aspects of cardiometabolic health (Chapter 2) and with several measures of general health (Chapter 3), independently of traditional cardiovascular risk factors. Remarkably, our observed associations among euthyroid participants were similar and sometimes even stronger than in the general population, indicating the robust consistency of our findings. Overall, our results suggest that thyroid function measurements among middle-aged and older adults can be considered as potential predictive markers for cardiometabolic health and general health.

FT_4 measurements may even represent a better predictive marker than TSH measurements. In line with other studies among middle-aged and older adults, we consistently showed that the association between FT_4 and clinical outcomes is generally stronger compared with the association between TSH and clinical outcomes (Table 1).[12,55,79] One potential explanation for these results is that the direct effects

of thyroid hormones on various organs may be independent from the effects of thyroid hormones on the pituitary gland. Another potential explanation is related to the ageing process, which may modify the TSH-FT_4 set point of the negative feedback mechanism.[80] In order to maintain the same FT_4 levels, older persons (such as the Rotterdam Study participants) may need different TSH levels compared with the younger persons.

Risk prediction modelling can become a new line of thyroid-related research. Presumably, the discrimination abilities of some current predictive models can be improved after adding FT_4 measurement as a potential predictor. Hence, future studies may aim to assess the potential role of FT_4 in predicting the risk of adverse outcomes. Besides, future studies may aim to identify potential subgroups at high risk for developing adverse outcomes. Once identified, subgroups at risk may further receive additional testing and care.

Reference ranges of TSH and FT_4 levels

Previous population-based studies have reported that variations in thyroid function within the reference range are associated with several diseases such as AF, stroke, and diabetes.[26,54,79] Studies included in this thesis extend the previous literature by showing that variations in thyroid function within the reference range are also associated with other clinical outcomes, such as NAFLD and atherosclerosis. These data, taken together, suggest that the effects of thyroid dysfunction are extended even within the reference ranges of TSH and FT_4 levels. Based on this evidence, future studies may need to perform a reevaluation of the current reference ranges of thyroid function.

The reevaluation of TSH and FT_4 reference ranges may have important clinical implications on the diagnosis and treatment of thyroid disease. Therefore, the criteria of reevaluation need to be carefully established. One approach of reevaluation can redefine the reference ranges of TSH and FT_4 levels based on the risk of developing adverse outcomes. This approach has two main challenges. First, an expert group will need to specify the relevant adverse outcomes that are related to thyroid function. To achieve this, inconsistent literature reports on the effects of thyroid function will need to be reconciliated. Second, risk estimates of all relevant adverse outcomes will need to be further combined into an integrated risk estimate. This is complex, because the beneficial effects of specific TSH and FT_4 levels on one system can be counterbalanced by their harmful effects on another system. Previ-

ous prospective population-based studies have reported that high-normal thyroid function constitutes a decreased risk of metabolic diseases (eg, diabetes), but an increased risk of cardiovascular diseases (eg, AF).[54,79] Additionally, we report that high-normal thyroid function constitutes a decreased risk of NAFLD, but an increased risk of ASCV events.[12,55] It is therefore challenging to determine the balance of overall benefits and risks for specific cutoffs of TSH and FT_4 levels. Moreover, the observed associations of thyroid function with various adverse events are generally linear, thus making it difficult to propose specific cutoffs.

Another approach for reevaluating the thyroid function reference ranges could be based on the measures of general health that reflect the pleiotropic effects of thyroid hormones. The major challenge of this approach is that a "golden standard" measure of general health does not exist. In these circumstances, future research can take into consideration our results in Chapters 3.3 and 3.4, which imply the possibility of a downward shift of FT_4 reference ranges.

Identification of novel thyroid hormone agonists

In line with previous studies,[54,79] our findings suggest that thyroid hormones exert either beneficial or harmful effects depending on the targeted organs (eg, Chapters 2.1, 2.3). Given the complexity of thyroid hormone action, researchers over the last years have been intrigued by the possibility of discovering novel thyroid hormone analogues that can maximize the beneficial effects of thyroid hormones and minimize their deleterious effects. Several interventional studies to date have suggested potential beneficial effects of thyroid hormone analogues in reducing the risk of metabolic diseases as hepatic steatosis, diabetes, hyperlipidemia, and obesity.[81-84] Unfortunately, detrimental effects of thyroid hormone analogues in various systems, including the cardiovascular system, have been reported.[85] The most promising thyroid hormone analogue, eprotirome, was not approved for clinical use in humans due to its adverse effects on the cartilage of animals.[85] In this context, one of the major challenges for future research remains the identification of novel effective thyroid hormone analogues. In particular, future studies may need to identify the thyroid hormone receptor genes that are responsible for the specific beneficial and deleterious effects of thyroid hormones.

Additional measurements

The Rotterdam Study is characterized by extensive and detailed information regarding the measurements of exposures, outcomes, potential confounders and mediators. Future studies may consider performing several additional measurements. First, repeated measurements of TSH and FT_4 levels could provide additional information on the strength and consistency of the associations. However, studies using only one measurement of TSH and FT_4 can underestimate the association of thyroid function with morbidity and mortality by approximately one third, due to the regression dilution bias.[86] Hence, repeated measurements of thyroid function would be expected to strengthen even more our risk estimates. Second, although TSH and FT_4 concentrations are currently considered as the most relevant measurements of thyroid function in clinical practice, measurements of free triiodothyronine (FT_3) levels could provide more comprehensive information on the action and bioavailability of thyroid hormones. Available FT_3 measurements allow the calculation of the FT_3/FT_4 ratio, which is a marker of peripheral thyroxine deiodination. Third, longitudinal measurements of EAT, coagulation factors and gait patterns would be expected to minimize the possibility of reverse causation that derives from cross-sectional designs.

CONCLUSIONS

This thesis extends the current knowledge on the association of thyroid function with specific aspects of cardiometabolic health. Adopting a broader perspective, we further present novel insights on the association of thyroid function with markers of general health. Our results suggest that the clinical consequences of thyroid dysfunction are extended even within the reference ranges of TSH and FT_4 levels, thus providing supporting evidence for a reevaluation of the current reference ranges of thyroid function. Further studies may consider incorporating thyroid function measurements in models for predicting the risk of adverse outcomes. Moreover, future research is needed to replicate our results, establish causality, and explore additional underlying mechanisms.

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