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Is thyroid status a common denominator of age-related disease?

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CHAPTER 1

General introduction and outline of the thesis

GENERAL INTRODUCTION

Worldwide, life expectancy has increased impressively over the last centuries, mostly due to better living conditions and by improvements in health care.[1] One of the consequences thereof is an increasingly large proportion of older individuals in the population, which in turn gives rise to numerous societal challenges and opportunities. With the rising number of older individuals, the prevalence of age-related diseases is also on the rise. Age-related disease is an umbrella term for any illness that is more likely to strike older individuals as compared to children and young adults, and it covers a large variety of neurological, musculoskeletal, neoplastic and cardiometabolic diseases. For many conditions the reason for why aging is a major risk factor has not been fully elucidated, although the gradual accumulation of damage over time in conjunction with the body's responses to damage (as captured by the hallmarks of aging) is a popular explanatory model.[2] Over the past decades, it has been hypothesized that settings of endocrinological axes might influence the rate of aging.[3] This thesis focuses on the hypothalamic-pituitary-thyroid (HPT)-axis, which is involved in developmental and maintenance processes and in energy metabolism.

The hypothalamic-pituitary-thyroid-axis

The HPT-axis entails an intricate system of feedforward and feedback signals, from central regulation in the hypothalamus and pituitary to the thyroid gland and peripheral tissues (**Figure 1**). The hypothalamus releases thyrotropin-releasing hormone (TRH) in a pulsatile fashion, which in turn stimulates the pituitary to secrete thyrotropin, also called thyroid-stimulating hormone (TSH). TSH then stimulates production and secretion of thyroid hormones by the thyroid gland. In humans, the vast majority of the thyroid hormones produced by the thyroid gland (approximately 100 microgram per day) is the inactive prohormone thyroxin (T4) and only a small proportion (estimated 30 microgram per day) is the active hormone triiodothyronine (T3).[4]In the blood, more than 99% of T4 and T3 are bound by various binding proteins, leaving only less than 1% unbound and free to enter cells via specialized transporter proteins.[5] Circulating unbound T4 (fT4) signals back to the hypothalamus and pituitary in a negative feedback loop, thus keeping circulating thyroid hormone concentrations stable by inhibiting secretion of TRH and TSH.

In human studies, thyroid status is mostly assessed by measurement of circulating levels of TSH and fT4. On top of the regulation of circulatory concentrations of thyroid hormones, peripheral tissues can locally regulate and finetune their exposure to thyroid hormone signaling, amongst other by specialized enzymes called deiodinases which can activate or deactivate thyroid hormones.[6]

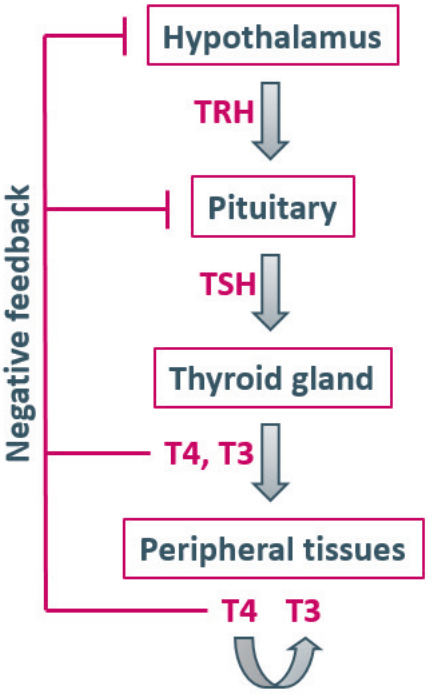

Figure 1. Hypothalamic-pituitary-thyroid-axis
Feed forward and feedback signals between the hypothalamus, pituitary, thyroid gland and peripheral tissues visualized schematically.
Abbreviations: TRH; thyrotropin-releasing hormone, TSH; thyroid-stimulating hormone or thyrotropin, T4; thyroxin, T3; triiodothyronine.

The hypothalamic-pituitary-thyroid-axis and the aging process

In various mammals an association was found between lower circulatory levels of thyroid hormones and increased longevity.[7] Also in exceptionally long-lived human families different tuning of the HPT-axis was observed.[8,9] Interestingly, a similar pattern of higher TSH was found in sporadic octogenarians who had a better functional status.[10] In model organisms, a role for thyroid hormones was discovered in the maintenance of muscle and brain tissue by their effect on cell fate.[11,12] These findings combined gave rise to the hypothesis that thyroid status might influence the apparent tradeoff between optimal development and reproductive capacity versus somatic maintenance and repair.[7]

THYRAGE

This thesis is embedded in the European Commission funded Horizon 2020 project THYRAGE, which started in January 2016. The aim of the project was to investigate the effects of thyroid hormones on a wide range of age-related diseases, including osteoporosis, osteoarthritis, neurological disorders and

sarcopenia. Six partners across five European countries joined forces in a multidisciplinary team of fundamental researchers, chemists, clinicians and epidemiologists. The team at the Leiden University Medical Center led the studies involving human subjects, complementing the basic research performed in model organisms and cell cultures at the other sites in collaboration with industry-based peptide scientists. The objective for this thesis was to investigate the potential causality of associations between circulating concentrations of thyroid parameters and age-related disease or functional decline by optimally exploiting different available data.

Causal inference in epidemiology

In epidemiology, the ultimate goal is to uncover why some people develop certain diseases and others do not. A first step is to investigate a well-defined group of individuals, a cohort, and simply count whether an outcome of interest occurs more frequently in individuals with certain characteristics compared to those who do not have these characteristics. By these means we can study associations. However, association does not necessarily equal causation. According to Hernán and Robins, inferences about causation are concerned with "what if questions" rather than the actual outcomes observed.[13] Essentially, for causality you would want to know if the outcome had been different if the exposure or characteristic of interest had been different. To answer these types of questions, one would ideally randomize individuals to either being exposed or not being exposed. By randomization, chance decides whether a person is exposed or not. Therefore, if you randomize a sufficiently large group of people, both groups will be equal in every aspect other than the exposure of interest. However, randomization is not always feasible. Observational studies can also approximate causality, though confounding and bias may influence the estimate of the effect.

Multi-cohort studies

Every epidemiological study is prone to errors; these can be divided into random and systematic errors[14]. The magnitude of random errors decreases with an increase in sample size. Systematic errors, also called bias, are not dependent on sample size. Bias is usually a result of study design; the most common types of bias are selection bias and information bias. Selection bias stems from non-random participation, either due to the selection criteria imposed by the researcher or due to factors influencing the choice of individuals to participate in the specific study.[15] Information bias is caused by systematic errors in data collection, which is most problematic when the chance of error differs between the group that develops the outcome and the group that does not.[15] By combining multiple cohorts, the sample size increases which directly reduces random error. In addition, sources of bias usually differ between cohorts. Therefore, if an association is consistent among multiple samples of the population, the estimate

might be closer to the true association in the source population. So, on top of increasing precision by reducing random error through increasing sample size, multi-cohort studies might also improve external validity. To conduct a multi-cohort study, either individual participant data (IPD) or summary-level data can be used. For an IPD approach, the original data for each participant is obtained and reanalyzed, allowing homogenous definitions, standardized analyses and separate analyses for subgroups; however this approach is labor intensive.[16] Summary-level data on the other hand means that data is only available on group level; these data are often publicly available and relatively easy to use, though no subgroups can be investigated and analytical methods are restricted. An intermediate option also explored in this thesis, is to provide a standardized protocol and automated statistical scripts to cohort-affiliated researchers and to request only the group characteristics and the results of the analyses. This hybrid method requires planning of all analyses in advance and presence of sufficient expertise at each research site to execute the protocol. However, with the increasingly restrictive privacy legislation avoidance of sharing individual data is a major advantage.

Mendelian randomization

Confounding and reverse causality always threaten causal inference in observational studies. Despite advances in statistical methods, it remains essentially impossible to rule those out completely in the absence of randomized trials. Mendelian randomization was developed as an alternative method to investigate causal associations, free from most confounding and reverse causality.[17] Mendelian randomization utilizes Mendel's second law of independent inheritance of traits, implying that traits are randomly allocated at conception. Genetic traits can be used as instrumental variables for a given exposure, such as TSH or fT4, thereby circumventing any confounding by lifestyle or other characteristics which might confound the association between the exposure (for example TSH or fT4) and the outcome of interest (for example, a specific age-related disease).[18] However, for this method to be valid three assumptions should be met: 1) the instruments must be associated with the exposure, 2) the instruments must influence the outcome only through the exposure, and 3) the instruments must not associate with measured and unmeasured confounding (**Figure 2**).

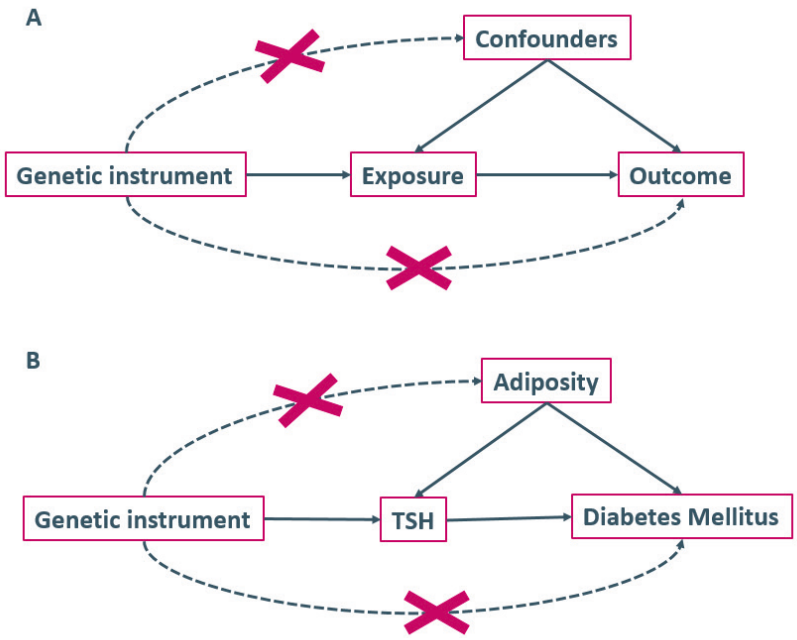

Figure 2. Assumptions of Mendelian randomization
Visualization of the assumed relations investigated in Mendelian randomization studies.
A. Conceptual visualization,
B. Example with TSH (exposure) and risk of diabetes mellitus (outcome) as explored by Bos et al.[19]

Oftentimes the magnitude of the association between the genetic instruments and the exposure is estimated in another study population than the population in which the association with the outcome is assessed; this strategy is called two-sample Mendelian randomization.[20] In a one-sample or single-sample design both estimates are derived from the same study population; this approach is vulnerable to bias towards the observational association when weaker genetic instruments are used.[21]

Triangulation

Despite all efforts, each study design has its flaws. That is one of the reasons why new knowledge is built on several different pieces of evidence, usually from different branches of research. Triangulation attempts to formalize this multi-disciplinary evidence by explicitly combining different research approaches with unrelated sources of bias.[22] The main idea is that if different approaches point in the same direction, the findings are more likely to be true.

Aim of this thesis

The aim of this thesis was to investigate the potential causal role of thyroid status in the development of age-related diseases in humans using multiple sources of available, observational data.

OUTLINE OF THIS THESIS

In **Chapter 2** we put forward the viewpoint that disturbances in tissue maintenance might be at the interface between the classic hallmarks of aging and the development of age-related diseases. We present a selection of potential biomarkers of tissue maintenance that could be used to address this hypothesis. In **Chapter 3** we prospectively studied the association between different measures of thyroid status and mortality in two populations of nonagenarians. The participants of the Leiden Longevity Study were selected based on familial longevity, while the nonagenarians of the Leiden 85-plus Study were selected for survival to 90 years and living in the city of Leiden. In **Chapter 4** we investigated the association between thyroid dysfunction and cognitive function using an individual participant data analysis approach. In **Chapter 5** we performed a Mendelian randomization study and a candidate gene study on thyroid stimulating hormone and bone mineral density using summary-level data of the GEFOS (GEnetic Factors for Osteoporosis) consortium. In **Chapter 6** the relationship between thyroid function and anemia was assessed at three levels; (i) diagnosis of thyroid dysfunction, (ii) genetically determined circulating levels and (iii) genetic variants of enzymes regulating intracellular thyroid hormone availability. All analyses were performed using data from the UK Biobank; a population-based study with information on genetics, health and lifestyle of half a million inhabitants of the United Kingdom. In **Chapter 7** we investigated the interplay of thyroid status, body mass index (BMI) and diabetes mellitus with Mendelian randomization in the UK Biobank. In **Chapter 8** we explored the association between thyroid parameters and coronary artery disease with Mendelian randomization in summary-level data of the multi-ancestry CARDIoGRAMplusC4D (Coronary ARtery DIsease Genome wide Replication and Meta-analysis [CARDIoGRAM] plus The Coronary Artery Disease [C4D] Genetics) consortium. In **Chapter 9** we aimed to add to the evidence on the role of thyroid status in cardiovascular disease by triangulation of the metabolomic profile associated with thyroid parameters and multi-cohort Mendelian randomization on thyroid parameters and coronary artery disease. For the triangulation, we performed multivariable regression analyses in six cohorts embedded in BBMRI-NL (Biobanking and BioMolecular resources Research Infrastructure the Netherlands), and Mendelian randomization in four cohorts with genetics data and data on the metabolomic platform used in BBMRI-NL (MAGNETIC consortium, NEO [Netherlands Epidemiology of Obesity] study,

Oxford Biobank, and PROSPER [PROspective Study of Pravastatin in the Elderly at Risk]). The Mendelian randomization study on coronary artery disease was performed with the summary-level data of three European ancestry cohorts (CARDIoGRAM [Coronary ARtery DIsease Genome wide Replication and Meta-analysis] consortium, the UK Biobank and FinnGen [a concerted effort of Finnish universities, hospitals and national institute for health and welfare to combine different registries to a research source]).

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