Subclinical hypothyroidism in community-dwelling older people: consequences and treatment outcomes

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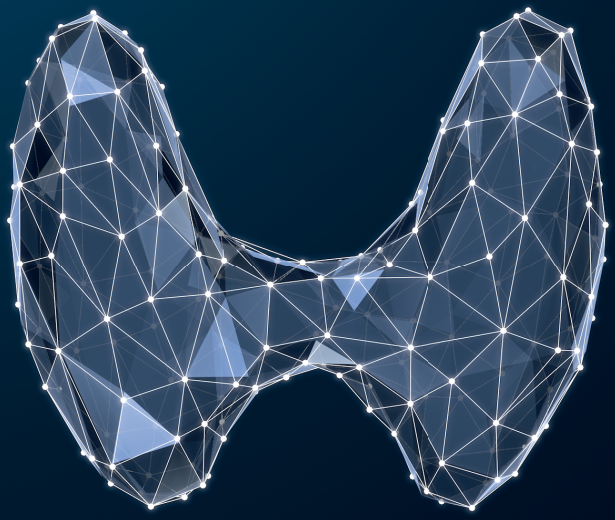

Chapter 9

General discussion

Subclinical hypothyroidism in community-dwelling older people (arbitrarily 65 years and older) is a long-debated subject.[1] In the absence of robust scientific evidence, and with decades of arguably trial-and-error experimentation with levothyroxine treatment, opinions about whether it actually constitutes a diseased state, whether monitoring is required and whether it requires levothyroxine treatment in community-dwelling older people are spread out wide and bolstered, amongst patients, physicians and researchers alike.

This thesis set out to 1) establish whether subclinical hypothyroidism in older people is a neutral, beneficial or detrimental condition by establishing if subclinical hypothyroidism in older people is associated with a) clinically relevant outcomes and b) biologically relevant outcomes, and, 2) investigate if levothyroxine treatment for subclinical hypothyroidism in older people provides long-term benefits in clinically or biologically relevant outcomes. In the next paragraphs, the main findings and their implications from a physician-, patient- and societal-perspective are discussed as well as suggested scientific areas for future exploration.

MAIN FINDINGS

Part 1: subclinical hypothyroidism in older people is a neutral condition not associated with clinically or biologically relevant outcomes

Subclinical hypothyroidism is, by definition, a biochemically defined disease state. However, one may argue that to warrant further physician action, be it monitoring, diagnostic or therapeutic, the definition should not only rely on the traditional reference ranges alone, but should extend to also include clinically or biologically relevant outcomes.

In **chapter 2** we establish that in 4 prospective, international cohorts of community-dwelling oldest old (80 years and older, N=2116), participants with thyroid dysfunction, including subclinical hypothyroidism, had no significant differences in clinically relevant outcomes at baseline and after 5 years of follow-up; i.e. disability in activities of daily living, cognitive functioning, depressive symptoms, grip strength or mortality risk compared to euthyroid age-matched counterparts.

Traditionally, antithyroperoxidase antibody (TPOAb) positivity has always been included in diagnostic and therapeutic algorithms as an additional predictor of poor outcome and a criterion to start levothyroxine treatment. The primary driving force being a potential 2% annual increase in progression from subclinical to overt hypothyroidism.[2] In **chapter 3** we investigate TPOAb positivity in participants in the Leiden 85-plus Study, a population-based cohort study of residents of Leiden aged 85 years and older, and fail to reach the same conclusion. We found that TPOAb levels were indeed associated with higher TSH levels, as

commonly found in subclinical hypothyroidism. Nevertheless, they did not predict a 5-year change in thyroid function (in particular progression to overt hypothyroidism), physical function, disability in ADL, cognitive function or depressive symptoms. Although elevated TPOAb levels were associated with 10-year cumulative survival benefit, suggesting a possible beneficial effect of subclinical hypothyroidism, the effect was independent of circulating fT4 levels making it less likely that any favourable effects are mediated through thyroid function.

One of the most commonly found biological co-occurrences is between subclinical hypothyroidism and erythropoiesis – the production of red blood cells. In **chapter 4,** the results from 16 international longitudinal cohorts in the Thyroid Studies Collaboration (N=42,162) were pooled in an individual participant data meta-analysis to establish whether subclinical thyroid dysfunction was associated with anaemia. Although cross-sectionally the presence of subclinical hypothyroidism was accompanied by a higher odds ratio of having anaemia in subgroup analyses of older adults, the analysis failed to demonstrate an increased hazard of developing anaemia over a median follow-up of 5.7 years.

In conclusion, in older community-dwelling people, subclinical hypothyroidism is not associated with clinically relevant outcomes or biologically relevant outcomes.

Part 2: levothyroxine treatment for subclinical hypothyroidism in older people does not provide long-term benefits in clinically or biologically relevant outcomes

Until recently the combined randomised controlled trial evidence for levothyroxine for subclinical hypothyroidism was limited with only 12 trials (with 350 people in total included) in the most recent Cochrane Review[3]; few in numbers, small cohorts, with varying age and reference ranges used, outcomes measured and medications used. The author's recommended that "until better data are available, clinical judgment and patients' preferences remain the best manner to decide" and that large, standardised, international trials were necessary to increase the evidence base.

The TRUST study (**Chapter 5**, N=737, mean age 74 years) shows that after 12 months of levothyroxine treatment the TSH levels in serum had changed significantly in the verum arm, but that the mean change in hypothyroid symptoms, tiredness, quality of life, hand-grip strength, blood pressure, body-mass index or adverse events was no different when compared to the placebo group. Treatment with levothyroxine for persistent subclinical hypothyroidism in participants aged 65 years and older provided no apparent benefits.

There is ample data to suggest that thyroid function, and any possible consequences, are mediated by age. To this end we designed the IEMO 80-plus randomised controlled trial as

an ancillary study to the TRUST study, sharing trial infrastructure and protocols to allow for a joint analysis of all participants aged 80 years and older with persistent subclinical hypothyroidism (**Chapter 6**).

The IEMO 80-plus study (N=251, mean age 85 years) shows, in line with the results from the TRUST trial, that after 12 months of levothyroxine treatment indeed the serum TSH levels had changed significantly, but that no change in hypothyroid symptoms, tiredness, quality of life or any of the other endpoints could be identified compared to the placebo group (**Chapter 7**).

In an additional pre-planned combined analysis using data from both the TRUST and IEMO 80-plus thyroid trials we discovered that treatment with levothyroxine resulted in no increases in haemoglobin levels (**Chapter 8**). The results were not different when stratifying by sex, age, TSH level, or presence of anaemia at baseline, suggesting that in subclinical hypothyroidism, thyroid function and haemoglobin levels is not causally related and should not be used to influence physician practice and policies.

In conclusion, treatment with levothyroxine for subclinical hypothyroidism in older people does not provide benefits in hypothyroid symptoms, tiredness, haemoglobin levels and a range of secondary outcomes.

Is subclinical hypothyroidism in community-dwelling older people a disease?

Considering the aforementioned two conclusions, one may wonder if it's necessary to re-evaluate how we look at subclinical hypothyroidism in community-dwelling older people. Although the International Classification of Diseases version 11 has no code listed for subclinical hypothyroidism,[4] and the International Classification of Primary Care version 1 lists subclinical hypothyroidism as an 'aberrant laboratory result',[5] experts have been disagreeing for years whether subclinical hypothyroidism in older people actually constitutes a disease.

The Oxford medical dictionary defines disease as 'Any illness or abnormal condition of the body with a specific cause (which may or may not be known), excluding physical trauma, that has recognizable signs and symptoms.' The Merriam-webster dictionary extends the definition with 'an impairment of the normal state of the living animal or plant body or one of its parts that interrupts or modifies the performance of the vital functions, is typically manifested by distinguishing signs and symptoms, and is a response to environmental factors (as malnutrition, industrial hazards, or climate), to specific infective agents (as worms, bacteria, or viruses), to inherent defects of the organism (as genetic anomalies), or to combinations of these factors'.

As mentioned earlier subclinical hypothyroidism, particularly in older people, is mostly asymptomatic or is accompanied by varying and unspecific signs and symptoms. The diagnosis is often established after a chance laboratory finding. Keeping the Oxford criteria of disease in mind we may find it difficult to defend that subclinical hypothyroidism fulfils all the criteria required to meet the definition. A more lenient viewpoint could be to include the domains 'defects of the organism' and 'interrupts or modifies the performance of vital functions' according to the Merriam-webster definition. However, as presented in the previous chapters, our research demonstrates that in community-dwelling populations of older people, to the best of our current knowledge, subclinical hypothyroidism is not related to defects of the organism (i.e. continued production of fT4) and does not interrupt or modify vital functions compared to euthyroidism (i.e. no influence on clinically or biologically relevant outcomes).

All evidence considered, it may be concluded that in community-dwelling populations of older people, the state we currently describe as subclinical hypothyroidism is not a disease but a strictly biochemical diagnosis that is not associated with detrimental nor beneficial health outcomes, but with neutral health effects at best.

Understanding age-adjusted reference ranges

In parallel with the growing evidence-base that shows that subclinical hypothyroidism in older people is a neutral condition, some experts have solicited that the thyroid function reference ranges should be adjusted. Although the TSH distribution depends among other things on the population studied and assays used, commonly a range between 0.4 and 4.5 mIU/L is defined as normal.[6] Some,[7-9] but not all,[10-15] studies have demonstrated an age-related increase in median TSH levels among presumed healthy older individuals prompting several experts to advocate a change in guidelines towards age- and sex-specific TSH reference ranges that widen in interval and increase in median with increasing age and differ per sex. If this is implemented, a proportion of older people currently diagnosed with subclinical hypothyroidism would be reclassified as euthyroid. There are, however, several caveats to this approach that are sometimes overlooked. Perhaps there is a better alternative.

Currently the TSH reference range serves dual purposes: 1) describing a distribution in the general population, as well as 2) the basis for treatment decisions for physicians. If we consider that these purposes may not necessarily require the same numbers, an alternative, elegant solution presents itself. Given the results in this thesis, it could be perfectly valid to continue describing a population distribution using the 2.5^{th} and 97.5^{th} percentiles like we do today, and nothing would change in the classification. However, subclinically hypothyroid older people do not seem to benefit from levothyroxine treatment, particularly with TSH<10 mIU/L. A secondary set of treatment thresholds, not based on the statistical distribution but based on scientifically substantiated expected benefit or prevention, would then serve as

levothyroxine treatment cut-offs. Much like how the current American and European thyroid guidelines already advocate more leniency towards treatment initiation if TSH levels are >10 mIU/L based on preventing a higher cardiovascular disease risk identified in a landmark IPD-meta analysis.[6] Using this approach doctors can finally start to "treat patients, not numbers".[16] This approach would be very challenging, requiring full international collaboration, discussion and consensus, on top of sufficiently powered and set-up randomised controlled trials and IPD-meta analyses, but is perhaps a more appropriate solution to the reference range dilemma.

IMPLICATIONS OF FINDINGS

Patients, physicians and researchers have been debating the impact and management of subclinical hypothyroidism in older people for decades, and it would be presumptuous to state that the evidence in this thesis ends that debate. Still, the choices and considerations (i.e. inclusion of older people, internationally sampled populations, long follow-up times, harmonised reference ranges and outcomes) that went into the research in this thesis make it of particular value for physicians serving older, community-dwelling patients with subclinical hypothyroidism. For this group as a whole, the main findings of the two research objectives demonstrate that in older community-dwelling people, the presence or resolution of subclinical hypothyroidism is not associated with clinically or biologically relevant outcomes and that routine treatment with levothyroxine does not provide long term benefits.

These findings may be of considerable importance in how care is provided to community-dwelling older people. The provision of high-value care in modern healthcare systems is inextricably linked with coordinating and balancing simultaneous commitments to physicians, patients, and society. In the next few paragraphs several implications for each are discussed.

Subclinical hypothyroidism and implications for physicians

Many physicians struggle with managing subclinical hypothyroidism in older people. A qualitative study by Gibbons *et al.* in 2009 was one of the first to lay bare that although physicians tried a patient-centred approach, they reported having little knowledge of the disease, possibly due to uncertainty regarding prognosis and variations in advice regarding treatment.[17] In 2012 Allport *et al.* concluded that British GPs are potentially uncertain how to interpret symptoms and thyroid function tests in older adults.[18] In 2015 a survey from den Elzen *et al.* confirmed this by establishing large GP treatment variations by country (the Netherlands, Germany, England, Ireland, Switzerland and New Zealand) and by patient characteristics, with some treating patients outside of guideline recommendations.[19] At the time of writing this thesis (2021), the latest international, professional, practice guidelines date from 2012

and 2013 (American Thyroid Association 2012[20], European Thyroid Association 2013[21], Dutch College of General Practitioners 2013[22]). It is a worrying thought that more than 10 years after the first paper of Gibbons demonstrated the difficulties in daily medical practice, the scientific community has not been able to provide physicians with more robust guiding principles and decision support other than 8-year-old low- to moderate-quality recommendations.

Potential for changes in clinical practice

The results presented in this thesis reinforce the recommendations that physicians may serve their older community-dwelling patients with subclinical hypothyroidism best through:

1) resolving the uncertainty of potential future health consequences; i.e. not attributing subclinical hypothyroidism to clinically or biologically relevant outcomes and preventing medicalization,
2) unburdening patients and practices from lifelong, periodic and invasive diagnostic schemes; i.e. exercising restraint when it comes to follow-up thyroid function or TPOAb testing, and by
3) protecting patients from unnecessary lifelong pharmaceutical management and from potential overtreatment; i.e. not initiating routine thyroid hormone substitution therapy.

In 2019 an international group of researchers published an independent and unendorsed clinical practice guideline, based on a systematic review of 21 trials (including some reported in this thesis) performed in (older) adults with subclinical hypothyroidism.[23,24] They concluded that 'almost all adults with subclinical hypothyroidism would not benefit from treatment with thyroid hormones', in line with the findings of this manuscript. To this date, however, the aforementioned official international guidelines remain unaltered. Updating these should be a first step in giving physicians a major advantage in the expected increase in subclinical hypothyroidism-related daily practice cases. If not for the entire subclinically hypothyroid group as a whole yet, then at least, based on the outcomes of this thesis, for older people.

Subclinical hypothyroidism and implications for patients

Medical professionals have had debates about subclinical hypothyroidism for decades, but perhaps it's patients that struggle with their affliction and opposing opinions the most. Unfortunately, patient perspectives are not always incorporated in research or guidelines. To avoid paternalistic medical care, researchers will have to reallocate some of their focus into understanding how our older patients actually feel, think and act[25], to tailor medical care to the needs and wants of older patients with subclinical hypothyroidism. Regardless of whether subclinical hypothyroidism is or is not detrimental to health, and regardless of whether levothyroxine treatment is or isn't indicated. Although guideline experts have ad-

vocated incorporating patient values, preferences and perspectives into practice guidelines for years,[26,27] no formal qualitative studies for subclinical hypothyroidism are available to date.

To bridge the gap, researchers will need to properly investigate how older patients feel about subclinical hypothyroidism, including, but not limited to: Would they experience lifelong pill taking and attending periodic testing as burdensome and a dependency? How would their lives be affected if a prominent supplier of levothyroxine suddenly stops shipments? Would they consider a trial of deprescribing levothyroxine in time?

This is potentially an area where most is to be gained. In an online survey of 11.166 American hypothyroid patients, participants scored their satisfaction with their treating physician (both GP and specialist) a disappointing 5 out of 10 (10 = 'completely satisfied'), the doctor´s knowledge 5 out of 10 (10 = 'very knowledgeable') and 71% had switched doctors at least once due to thyroid-related dissatisfaction.[28] It is not unlikely that older patients with subclinical hypothyroidism experience a similar divide between them and their treating physician. This may drive patients away, for instance to explore alternatives to levothyroxine treatment. Any such trend is inherently perpendicular to the values and standards of good medical care.

Additionally, the gap between patients and physicians may be expected to widen over time. For example, several countries including America, Canada, the UK, Australia and the Netherlands, have made their primary care electronic healthcare records (EHR) available for online access by patients and caregivers. Evaluation studies of early open EHR experiments have demonstrated that patients expressed a particular interest in accessing laboratory test results including thyroid function tests.[29] Some studies found this phenomenon to have no effect on anxiety levels,[30,31] while other studies report more negative emotions, more uncertainty and increased anxiety.[32] In half of all test results outside of the reference ranges, participants carried out online searches for additional information, and only half called the physician's office for advice. It is unclear where and how patients with abnormal thyroid function tests will find the sources on which to base any future decision and how this will affect them and their caregivers but it is likely that tensions between patients and physicians will resultingly increase. A striking example can be found in the use of T4+T3-combination therapy. In recent years the number of patients with thyroid dysfunction using a combined therapy of T4 and T3 has increased,[33] although this is not advocated in the guidelines. The narrative has changed from a constructive dialogue, to simply asking for this treatment to sometimes outright demanding this treatment modality, often caused by 'indiscriminate statements on the internet'.[34] By reopening the dialogue, and listening to patient perspectives and preferences, physicians may be able to address these issues appropriately, with or without medication.

Subclinical hypothyroidism and implications for society

Subclinical thyroid (dys-)function has a large impact on most healthcare systems worldwide and its global impact is expected to rise, both diagnostically and therapeutically. If screening, follow-up and treatment are not warranted perhaps the current medical practices leave room for improvement.

Diagnostics

TSH testing (interestingly, not fT4 testing) is listed in the World Health Organization list of Essential In Vitro Diagnostic laboratory tests and is one of the most ordered lab tests worldwide. For example in the United States of America, TSH testing was responsible for $484 million of Medicare spending in 2017, higher than any other laboratory test.[35] In the Netherlands over 2.7 million TSH tests were performed in over 2.2 million individual Dutch people in primary care in 2017,[36] and this number is expected to have risen since. In only 725.000 people however, additional fT4 tests were performed when TSH was found to be abnormal. The large number of TSH tests, relative to the small number of subsequent fT4 tests and users of levothyroxine medication, suggests that the majority of the TSH tests was performed from a screening perspective.[36] This is in contrast with the traditional Bayesian approach where, based on a priori suspicion of disease, laboratory testing is used to make a diagnosis more or less likely. The screening approach, rather than a diagnostic approach, suggests a fundamental uncertainty in physicians and potential patients that impacts healthcare systems and that is hard to correct without additional and robust scientific evidence. There is no telling how much more tests will be performed in the future if the over-the-counter TSH home testing kits for self-diagnosis, that have recently become available on the market, gain in popularity.

As the global demographic continues to age, and TSH levels have been shown to rise with age, screening practices for thyroid disease, both physician-requested and commercially, increases the odds of incidental medical findings, likely causing an overestimation of (mild) subclinical hypothyroidism in primary care. This may cause increased levels of anxiety and uncertainty for patients, increased costs, time consumption and work for physicians, and increased burden on healthcare systems through additional diagnostics, follow-up or treatment.

Optimizing thyroid function screening practices

Historically TSH measurements have always come first in screening practices due to better laboratory assays. A log-linear relationship between TSH and fT4 makes that little variations in TSH-levels correspond with major changes in fT4 and are therefore more sensitive. Only when TSH levels are identified outside of the normal reference ranges do we measure the fT4 levels to properly diagnose the amount of thyroid dysfunction; a process called reflex-testing. However, if for the majority of the general older population, subclinical thyroid disease is of

little clinical importance (only TSH results abnormal), yet identifying overt thyroid disease is (both fT4 and TSH results abnormal), it may be interesting to explore new diagnostic screening strategies. Including, for instance, a diagnostic algorithm that measures fT4 first and, in the event of it being high or low, reflex test TSH levels. This new and bold approach may reduce the number of identified people with subclinical hypothyroidism, reduce the amount of unnecessarily alarmed patients, reduce unnecessary lab analyses, reduce unnecessary treatment for subclinical thyroid disorders and improve limited resource spending. A Leiden-based initiative dubbed the "RESTORE"-study has been proposed to investigate a similar new diagnostic strategy.

Treatment

Levothyroxine is one of the most prescribed drugs worldwide. In the United States of America 122 million prescriptions for levothyroxine were dispensed in 2017, more than any other prescription drug.[37] In the Netherlands the amount of users of levothyroxine drugs in the Netherlands has risen from 447.880 in 2014 to 501.170 in 2018, with more than half of all patients (227.629) aged 65 years and older.[38] The total costs amount to 9.3 million Euro's per year and these have risen by over 800.000 euros over the past few years.

It is currently unknown how many of these prescriptions are given for subclinical hypothyroidism but it stands to reason that this constitutes a significant proportion. In older populations, up to 60% of patients with subclinical hypothyroidism revert back to a euthyroid state within 5 years without any intervention at all, and our results in chapters 5, 7 and 8 demonstrate that even in the case of persistent subclinical hypothyroidism treatment with levothyroxine is not associated with beneficial health effects. This indicates that a sizeable proportion of people with subclinical hypothyroidism is treated with levothyroxine unnecessarily, and could even suffer negative health consequences from it.

Possibility for deprescribing

Since international thyroid guidelines do not recommend regular re-evaluation of treatment indications, levothyroxine supplementation is usually continued for life,[39,40] often even without treatment evaluation.[41] The risk of levothyroxine overtreatment increases with age and years of treatment duration and it is estimated that up to 41% of older levothyroxine users show signs of over-suppletion.[42] Without compelling evidence of effect and with a high risk for overtreatment, guidelines may need to be evaluated to reduce the amount of routine thyroid function tests ordered and to decrease the ever-growing amount of levothyroxine prescriptions for older people with subclinical hypothyroidism.

Ultimately policy and guideline committees may also want to reassess whether the older, community-dwelling patients with subclinical hypothyroidism that are already on levothy-

roxine treatment for many years can safely be withdrawn from treatment while maintaining their health and well-being. Currently one self-controlled observational study ("RELEASE"-study), undertaken by the LUMC (The Netherlands), is investigating to what extent 360 levothyroxine users aged 60 years and older can successfully and safely be deprescribed. The results from this analysis should prove instrumental in optimizing thyroid care for older people.

LIMITATIONS TO GENERALIZABILITY

Although the results from this thesis may help shape the discourse of subclinical hypothyroidism in older people in medical care in general, it is hardly the be-all and end-all of subclinical thyroid dysfunction. It should be noted that the conclusions reached apply primarily to community-dwelling populations of older people; i.e. the vast majority of people with subclinical hypothyroidism. Because thyroid function is a continuum it cannot be excluded that in subgroups of patient populations on either end of the subclinical hypothyroidism spectrum, such as those under the direct care of an endocrinologist, other clinical and biological outcomes or levothyroxine treatment effects may be identified. This limitation extends to more subgroups including, but not limited to, iodine-, selenium- or iron-deficient populations, patients with significant pre-existent cardiovascular disease,[6,43] patients using thyroid influencing therapies (amiodarone, lithium or radiotherapy) or patients with TSH levels >10 mIU/L.[44] Although resource-intensive and time-consuming, additional studies aiming particularly at more specialised groups are needed before the results of this thesis can be fully generalised to these groups that are by and large more the exception than the rule.

FUTURE RESEARCH

Understanding subclinical hypothyroidism in older people is complex and we have only just uncovered the tip of the proverbial iceberg, with the majority of our understanding still left hidden below the water level. The findings from research objectives 1 and 2 demonstrate that for older community-dwelling people with subclinical hypothyroidism currently employed diagnostic and levothyroxine treatment strategies are not routinely indicated but this, however, does not mean that researchers can now comfortably sit on their hands. In order to optimise the management of subclinical hypothyroidism researchers may want to focus on generalizing findings to younger age groups, on particular populations (such as more marked thyroid dysfunction with TSH >10 mIU/L) that may or may not warrant particular management strategies and on the potential for deprescribing for current levothyroxine users. Without presuming to be exhaustive, a list of especially interesting future research ideas

may include understanding age-adjusted reference ranges, optimizing thyroid function screening practices and how to move forward with the results from this thesis.

Understanding the biology of the ageing thyroid

A future research area of particular interest is how and why subclinical hypothyroidism in old age happens in the first place. Many experts agree that in general median TSH levels increase with age (regardless of clinical significance). How these thyroid ageing processes actually work 'in vivo', however, has proven hard to investigate. Regardless of ethical limitations (for example requiring invasive biopsies), older people are generally exposed to a myriad of non-physiological mediators, both presently and over the course of their life. These include, but are not limited to, thyroid-influencing medication (such as tyrosine kinase inhibitors in cancer treatment), thyroid-influencing therapies (such as head/neck radiation), reduced intake of nutrients (such as iodine and selenium, both crucial for thyroid hormone function), thyroid-influencing comorbid conditions (such as autoimmune diseases like rheumatoid arthritis or vascular disease like atherosclerosis) and chronic low-grade inflammation (dubbed 'inflammaging').[45,46] Currently the complex series of events and interactions that ultimately lead to subclinical hypothyroidism in old age are yet to be uncovered but may prove vital to understanding the condition and its consequences in full. The European research project THYRAGE is currently attempting to elucidate the effects of thyroid hormone on a wide range of age-related diseases.[47] One particularly appealing theory is that the increased TSH levels and reduced thyroid hormone signalling in old age are actually the hallmarks of an evolutionary advantageous natural selection in which after the reproductive phase, the focus shifts from sexual maturity and fitness to functional optimization and somatic repair, leading to increased health and longevity in old age.[46]

CONCLUDING REMARKS

The findings from this thesis demonstrate that in older community-dwelling people, subclinical hypothyroidism is a neutral condition not associated with clinically or biologically relevant outcomes. Levothyroxine treatment does not provide long-term benefits. Physicians provide the best possible medical care by employing a more conservative management style reducing thyroid function testing and levothyroxine prescriptions. Reflecting on the statements in the general introduction, physicians: 'should not handle this elevated TSH level finding as a disease, may want to reassure their patients that this is not abnormal and does not explain any potential symptoms, may want to conservatively monitor thyroid function over time and should not start levothyroxine treatment instead.'

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