CLINICAL PARAMETERS CORRELATE BETTER WITH THYROID HORMONE LEVELS THAN WITH TSH LEVELS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Stephen P Fitzgerald MB BS FRACP1, 2 (ORCID 0000-0002-9755-2316), Nigel G Bean PhD (Cantab) 3 (ORCID 0000-0002-5351-3104), Henrik Falhammar PhD4, 5, 6 (ORCID 0000-0002-5622-6987), JonoTuke PhD3

1The Departments of General Medicine and Endocrinology, The Royal Adelaide Hospital, Adelaide, South Australia stephen.fitzgerald2@sa.gov.au

2 The University of Adelaide, School of Medicine, Adelaide, South Australia

3School of Mathematical Sciences and ARC Centre of Excellence for Mathematical and Statistical Frontiers, University of Adelaide, Adelaide, SA 5000, Australia [nigel.bean@adelaide.edu.au](mailto:nigel.bean@adelaide.edu.au) and simon.tuke@adelaide.edu.au

4 Department of Endocrinology, Metabolism and Diabetes, Karolinska University Hospital, 171 76 Stockholm, Swedenhenrik.falhammar@ki.se

5 Department of Molecular Medicine and Surgery, Karolinska Institutet, 171 76 Stockholm, Sweden

6 Menzies School of Health Research and Royal Darwin Hospital, Tiwi, NT 0810, Australia

CLINICAL PARAMETERS CORRELATE BETTER WITH THYROID HORMONE LEVELS THAN WITH TSH LEVELS: A SYSTEMATIC REVIEW AND META-ANALYSIS

**Abstract**

**Background:** Though the functional states of other endocrine systems are not defined on the basis of levels of controlling hormones, the assessment of thyroid function is based on levels of the controlling hormone Thyroid Stimulating Hormone (TSH). In particular, subclinical thyroid dysfunction is defined as the combination of abnormal levels of TSH with normal levels of thyroid hormones. We therefore addressed the question as to whether thyroid hormones (free thyroxine (FT4), total triiodothyronine/free triiodothyronine (T3/FT3)), or TSH levels, within and beyond the normal ranges, provide the better guide to the range of clinical parameters associated with thyroid status.

**Methods:** A PubMed/Medline search of papers up to October2019, examining correlations of levels of thyroid hormones and TSH, taken simultaneously in the same individuals, with clinical parameters was performed. We analysed atrial fibrillation, other cardiac parameters, osteoporosis and fracture, cancer, dementia, frailty, mortality, features of the metabolic syndrome and pregnancy outcomes. Papers were assessed for quality using a modified Newcastle-Ottawa score. PRISMA guidelines were followed. A meta-analysis of the correlations was performed.

**Results:** We identified 58 suitable articles, and a total of ... correlations. Atrial fibrillation, low bone density, frailty, death, cognition, features of the metabolic syndrome and steatohepatitis were significantly more often significantly associated with thyroid hormone levels rather than with TSH levels(p<0.0001). The converse was true for no clinical parameter. FT4, T3 and FT3 levels were correlated with clinical parameters equally strongly. There was however less literature regarding FT3/T3 correlations with clinical parameters, and some of these correlations appeared to be due to reverse causation.

**Conclusions**. Thyroid hormone levels have stronger correlations with clinical parameters than do TSH levels. Correlations of clinical parameters with TSH levels can be explained by the strong negative population correlation between thyroid hormones and TSH, whereby TSH levels are an indirect measure of thyroid hormone levels.

Clinical and research components of thyroid medicine currently based on the measurement of TSH levels, including thyroid function testing, the monitoring of thyroid replacement therapy, and the concepts of subclinical thyroid dysfunction and isolated (or euthyroid) hypo/hyperthyroxinemia warrant reconsideration.

**Introduction**

Thyroid function testing is based on the measurement of thyroid stimulating hormone (TSH) levels [1, 2]. Patients are thereby classified as having euthyroidism (normal TSH and thyroid hormone levels), overt thyroid dysfunction (abnormal TSH and thyroid hormone levels), subclinical thyroid dysfunction (abnormal TSH/normal thyroid hormone levels) and isolated hyper/hypothyroxinemia (normal TSH/abnormal thyroid hormone levels).

This classification of thyroid function is based on the concept of TSH levels being the most sensitive indicator of thyroid function such that subclinical thyroid dysfunction as currently defined is thought to be more significant than isolated hyper/hypothyroxinemia, as indicated by the alternative term ‘euthyroid hyper/hypothyroidism’ [3].

Subclinical thyroid dysfunction, so defined, is common, and comprises most cases of thyroid dysfunction with a population prevalence of approximately 5% [4-8], increasing to 15% to 20% in the elderly [8]. Even though it is generally asymptomatic or associated only with non-specific symptoms, subclinical thyroid dysfunction has been associated with many adverse outcomes across a variety of organ systems [4-8]. Therefore, despite the lack of convincing evidence of significant benefit, treatment for subclinical thyroid dysfunction has been recommended in certain circumstances [5, 8-11].

It has previously been suggested by some authors that the above definition of subclinical thyroid dysfunction is overly simple and that its diagnosis should not be based solely on the TSH level being outside of a general population range [12, 13]. Rather, it is claimed that more accuracy may be achieved by defining a normal range for the combination of thyroid hormones and TSH.

However, any model whereby judgement of the thyroid status includes consideration of the TSH level is anomalous, in that the levels of other physiological parameters are not judged by the levels of their controlling hormones. For example, whether or not an individual has hypoglycaemia or hypercalcemia is not determined by reference to insulin [14] or parathyroid hormone levels [15] respectively. ACTH levels, though helpful in diagnosing adrenal autonomy are not considered diagnostic for Cushing’s syndrome [16]. In general the level of a controlling hormone is used to determine the cause of a disturbance rather than identifying whether or not there is a disturbance [14-16].

We therefore aimed to determine whether or not a systematic review of the literature might indicate the relative merits of thyroid hormone levels and TSH levels, in terms of correlations with a broad range of clinical parameters. Because of the strong negative population correlation between FT4 and TSH [17, 18] we expected to find correlations between both TSH and FT4 levels and the clinical features of thyroid dysfunction. We further reasoned that if the clinical features correlated better with TSH levels the current rationale for thyroid function testing and the current definition of subclinical thyroid dysfunction would be supported, but, if the clinical features correlated better with thyroid hormone levels, these concepts would warrant review. In this latter circumstance the previously noted correlations of clinical features with TSH levels could be attributed to the aforementioned strong negative population correlation between FT4 and TSH.

METHOD

Search strategy

Up to 9 October 2019 a systematic search was performed of PubMed/MEDLINE using the following terms: thyroxine/T4, free thyroxine/ FT4, total triiodothyronine/T3, free triiodothyronine/FT3, TSH/thyroid stimulation hormone and subclinical. No restrictions were placed on language, country, or publication date. resulting

On account of the results of this first examination of the literature (see below) we studied atrial fibrillation (AF) and other cardiac parameters, bone density and fracture, cancer, death, frailty, dementia and associated pathology, obesity, features of the metabolic syndrome, and pregnancy outcomes. We specifically sought studies which addressed the correlations of both TSH and thyroid hormone levels, determined simultaneously in the same individuals, with any of the above clinical parameters.

Initially the titles of the articles were screened for relevance and then the abstracts, with full-text reports of potentially relevant reports reviewed. Additional relevant articles were searched for in the reference lists of the retrieved full-text studies. If repeated study was made of the same cohort the latest only was included. The literature search, data extraction and critical appraisal were conducted independently by two of the authors (SPF and HF), and any discrepancies were resolved by consensus with reference to the criteria described in the next section. Should consensus regarding any article not have been achieved the default position was that the article would be included. No study which contradicted the results of our work was knowingly excluded.

Studies reporting on correlations of levels of FT4, T3/FT3, and TSH with clinical features related to thyroid dysfunction were included. We included both T3 and FT3 as there were relatively few studies of FT3. We also included analyses comparing correlations with subclinical hypothyroidism and euthyroid hypothyroxinemia, reasoning that this is a comparison of low thyroid function defined on the basis of TSH levels or thyroid hormone levels respectively. Reports were excluded if the studied population was less than 100 individuals. Review articles, editorials, meta-analyses, and meeting abstracts were also excluded.

The following information was extracted from each such study: first author, country, number of individuals, sex, age intervals, nature of the study and the relevant clinical parameter. We recorded any correlations with thyroid hormones and/or TSH, in addition to the statistical techniques and degrees of significance of any correlations (p values and /or confidence limits). We also recorded the presence of ‘incongruent’ correlations, i.e. correlations in the opposite direction to that normally expected (e.g. obesity correlating with high thyroid function), or correlations of thyroid hormones in the same direction as correlations with TSH, as indicators of reverse causation [19].

As our study was not directed at a collection of works addressing therapeutic outcomes of an intervention, the use of a quality assessment (the Newcastle-Ottawa Scale; available at: www.ohri.ca/ programs/clinical\_epidemiology/oxford.asp) was adjusted to suit this setting. In the main this adjustment consisted of allowing for continuous, as well as binary quantifications, of clinical outcomes and exposure to thyroid hormone levels. Articles were scored according to the representativeness of the subjects, the similarity of the subjects apart from differences in the parameter of interest, the reliability of the classification of thyroid status and parameter status, control for confounding factors, and for prospective studies, the demonstration that outcome was not present at study onset, the adequacy of length and completeness of follow-up. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed [20].

Statistical Analysis

To determine whether thyroid hormone levels or TSH levels correlated better with the examined clinical parameters we analysed the above studies as to the relative frequencies of statistically significant correlations of thyroid hormone and TSH levels with the clinical parameters. We then performed further analyses to confirm that these findings did not result from any systematic bias.

For each result given in the literature, we fitted a logistic regression model. The response variable was whether the analysis indicated a significant or non-significant result. The predictors considered were the type of thyroid test; the clinical parameter under consideration; the number of subjects in the analysis; and the number of covariates in the model. To account for the repeated analysis, we also incorporated a random intercept term. We considered random intercepts for the paper, the cohorts nested with each paper, the type of analysis nested within paper; and the complexity of the models nested within the papers.

Pairwise comparisons of the thyroid tests were performed at a 5% overall significance level for those models where a significant effect of thyroid test was found.

As well, as we were concerned that multiple nested models are often considered within the same paper, we also repeated the analysis under the strict constraint that we only considered a single representative analysis from the series of nested models.

We performed a sensitivity study minimising the contribution of possible reverse causation, excluding studies with incongruent correlations and /or cross-sectional design.

All modelling was performed by the glmer [21] function in the lme4 package in R [22], and all code is available at <https://github.com/jonotuke/TSH_2019>

RESULTS

We found, in our first examination of the literature, that though the findings were not unanimous, there was general consistency of the data. In general, consistent with prior work [8], atrial fibrillation (AF) [23-29], osteoporosis [30-37], and cancer [38-41] correlated with higher thyroid function defined using TSH and/or thyroid hormone levels, across and beyond the normal range, and steatohepatitis[42-44] and other features of the metabolic syndrome [19, 45-64] correlated with lower thyroid function .Both high and low thyroid function, as compared with mid-range thyroid function, were associated with clinical and pathological features of cognitive decline [65-73], frailty [74-77], total /cardiovascular mortality [78-87] , heart disease (apart from atrial fibrillation) [29, 65, 81-83,-86-89 ] and pregnancy outcomes [90-97].

There were many series finding the above correlations in the context of subclinical thyroid dysfunction. Many of these studies [23, 48, 49, 65, 81-83, 85-87] however did not address the relative correlations of clinical parameters with TSH and thyroid hormone levels, the focus of our study.

In the end we identified 58 studies which addressed this question (Figure 1, Table 1). We found no previous synthesis of the data on the effect of thyroid function, as measured by TSH in comparison to thyroid hormone levels, across a range of organ systems. One meta-analysis restricted to atrial fibrillation [25] was found. This meta-analysis was not included in our analysis. Many of the studies addressed multiple parameters summarised by those indicated in Table 1.

We found 22 studies [19, 24, 28, 29, 32, 33, 37, 39, 42, 53, 58-60, 63, 64, 69, 73, 76, 77] that examined correlations with FT4, T3 ( or FT3) and TSH and a further 36 studies [26, 27, 31, 34-36, 38, 40, 41, 44, 45, 47, 50, 51, 52, 54, 61, 62, 67, 71, 72, 74, 75, 78,-80, 84, 88, 90-97] that examined correlations with only FT4 and TSH levels.

These 58 studies included cross-sectional and prospective cohort studies, diverse populations and both sexes. They were contemporary and of high quality (Table1). The study populations comprised strictly euthyroid subjects [24, 27, 28, 32, 37, 43, 46, 50-53, 53, 60, 67, 79, 80, 84, 88, 89], subjects either euthyroid or with subclinical thyroid dysfunction [19, 31, 33, 34, 36, 38, 40, 45, 47, 58, 63, 69, 71, 73-76, 78, 90, 91, 93, 94, 96, 97], and subjects euthyroid or with subclinical/overt thyroid dysfunction [26, 29, 35, 39, 41, 42, 44, 45, 54, 59, 61, 62, 64, 72, 77, 92]. In some studies different subsets were examined separately.

The 58 articles included in our meta-analysis yielded 1386 results of correlation analysis. The supplement catalogues all of these correlations in terms of clinical parameters, subgroups, number of participants, statistical methods, statistical significance, and p values/confidence limits.

The number of subjects for each analysis ranged from 18 to 10990 with a mean of 3071. The number of results in each paper ranged from 3 [58] to 180 [90]. Formal meta-analysis of all this data confirmed the superiority of correlations with thyroid hormone levels (FT4, T3 and FT3) as compared to TSH levels (Figure 2).

FT4 had a significant association with a clinical parameter in 56% of the articles’ analyses. FT3 and T3 correlations were not significantly different from each other and we therefore combined them. T3/FT3 had a significant association in 50% of the analyses whereas TSH had a significant association in only 22%.For the comparison of FT4 and TSH p<0.0001, for the comparison of FT3 and TSH p<0.0001, and for the comparison of FT4 and T3 p=0.539.

As the number of subjects in the analysis increased, the superior correlations with thyroid hormones appeared to become more apparent (Figure 3). This apparent increase in superiority did not achieve statistical significance. The other chosen predictors, system, and number of covariates, were not significant predictors of the significance of an article’s results. The authors accounted for the dependence within each article by incorporating a statistically significant random intercept.

Our sensitivity studies regarding reverse causation .....

Only a few of the studies included patients on thyroxine therapy. In these studies the proportion of patients on thyroxine was very low such that separate analyses of these patients were not undertaken. Analyses of cohorts with removal of these patients did not affect the results.

DISCUSSION

We believe this is the first systematic review studying TSH and thyroid hormone correlations with various clinical parameters. The results went beyond not finding evidence to support the current paradigm of the superiority of TSH. They indicated that the reverse applies i.e. thyroid hormone levels correlate better than TSH levels with clinical parameters.

In our sample we found no indication of, or reference to any work, that suggested that TSH levels consistently indicate thyroid status more strongly than thyroid hormone levels.

Our meta-analysis methodology differs from usual meta-analysis in that we pooled all statistical results rather than pooling all original data for re-examination of significance. This latter technique is used to determine an overall effect when individual studies (usually of a therapeutic effect) are conflicting and/or do not achieve convincing statistical significance. This was not the case with our work in that many of the individual studies achieved statistical significance and there was no indication of significant conflict in the results.

Potentially the summation of statistically significant results can be unreliable [20], but we have accounted for the possibilities of bias on account of, imbalance in the size of the studies, the nature of the parameters and the possibility of reverse causation. As in all of the studies each subject was his/her own control, and the study populations of many of the studies were unselected members of a community, the risk of bias from these considerations was obviated. The convincing degree of superiority of thyroid hormone levels as compared with TSH levels also provides a buffer against the possibility of some unidentified bias influencing our results.

Our research question differed from many research questions too in its breadth. We aimed to determine whether there was any difference between 2 or 3 valid measures of a whole body thyroid effect. Our analysis encompassed therefore, multiple studies covering various clinical outcomes, using different methodologies, different assays and statistical methods. It would not have been appropriate to combine all of these factors into an individual patient meta-analysis. Theoretically one could do such a meta-analysis of each clinical parameter but still these individual meta-analyses would need to be combined using a method akin to ours (i.e. summing the meta-analyses in some way) to determine whether levels of thyroid hormones or TSH are more likely to be associated **in general** with clinical parameters.

The results of the individual patient meta-analysis of atrial fibrillation [25] do in fact support our conclusions, showing superior correlations with FT4 levels than with TSH levels. Also supportive is a recently published similar meta-analysis of pre-term delivery [98], showing that FT4 levels correlate at least as well as TSH levels. One could even argue that the results of these two conventional meta-analyses alone disprove the general hypothesis that TSH levels provide a better guide to thyroid status than FT4 levels.

Our results indicate that the results of the atrial fibrillation and pre-term delivery meta-analyses can almost certainly be generalized. They indicate that, in general, whatever clinical parameters, assays or statistical methods are chosen, thyroid hormone levels, rather than TSH levels, are more likely to indicate thyroid effect.

Reverse or bi-directional causation may have underlain some of our correlations. Obesity and insulin resistance may lead to increases in TSH and thyroid hormones in some populations, perhaps as a thermogenic response [99], to the increased weight itself [100] or to caloric intake [101]. TSH enhanced secretion of FT3 might affect the lipid profile adversely [55, 56, 102]. Whatever the cause of such reverse causality, in such populations, as these particular correlations concern a low thyroid state, the associations between clinical features and high TSH would be artifactually enhanced whilst the association with low levels of thyroid hormones would be attenuated.

We are not aware of any factors that would artifactually preferentially increase the association of high FT4 with atrial fibrillation, osteoporosis and cancer. If anything, any component of the sick euthyroid state associated with these conditions, by lowering TSH and FT4 [103], should again favour an association with TSH rather than FT4.

The sensitivity of T3/FT3 levels to the sick euthyroid state, generated by altered deiodinase activity [104], may also explain some of the correlations with T3. In particular, mortality and frailty may be associated with low T3/FT3 levels via reverse causation. As the TSH would also be expected to be low in this situation one might expect incongruent correlations between clinical parameters, and T3/FT3 (and possibly FT4) and TSH.

Mendelian randomization studies can provide evidence as to the direction of causation [105]. Because genetic variants may affect TSH levels more than FT4 levels [106] such studies, whilst indicating the direction of causation between the thyroid state and the parameter, cannot add to the discussion as to whether thyroid hormone or TSH levels correlate better with any parameter. There is evidence from such studies that the relationship between increased thyroid function and atrial fibrillation is causal [107,108], but that reverse causation applies with higher BMI/fat mass (i.e. there is an increase in FT3 levels caused by increasing BMI [109]).

Our sensitivity studies also indicate that thyroid hormone levels reflect the thyroid state rather than reflecting reverse causation. Other indicators supporting a causative relationship between thyroid function and at least some of the parameters we examined include, relationships similar to those seen in overt thyroid disease [110-122], basic science evidence of causative mechanisms [123], animal intervention studies indicating causation [124], the relationships being seen in otherwise healthy individuals [89-97]), and the prospective nature of many of our included studies.

There was a consistent as well as a strong association of clinical parameters with FT4 levels. Correlations of FT4 and TSH levels with clinical parameters were concordant in terms of being in the opposite directions (e.g. AF is associated with a high thyroid state- with higher FT4 levels and lower TSH levels). Any discordance only occurred when the clinical parameter was associated with both relatively high and low thyroid states (e.g. death). In such a situation there might be an association with both high FT4 and high TSH levels.

We found T3/FT3 level correlations with fewer parameters than we found for FT4. T3 and FT3 correlated similarly with clinical parameters. Although T3/FT3 levels correlated better than TSH levels, and as well as FT4 levels, with clinical parameters, some of these correlations were, as previously mentioned, incongruous or paradoxical, i.e. they appeared in studies where the direction of association was aberrant as compared with other studies or were in the same direction as simultaneous correlations with TSH levels. These results were suggestive of reverse causation. Overall, T3/FT3 measurement added little to the assessment based on FT4 levels.

It would therefore appear that clinical features in general result from the exposure of tissues to the combination of thyroid hormones, and that the previously emphasized correlations of clinical parameters with TSH levels are secondary to the strong negative population correlation between thyroid hormones (chiefly FT4) and TSH. As FT4 levels provide most of the information, and for reasons detailed below, these results may warrant a change of clinical practice such that levels of thyroid hormones and especially FT4 levels become the main determining parameter in the diagnosis of borderline thyroid function. Further studies may clarify the relative importance of FT4 and FT3 levels.

The above applies even though FT4 is not the active thyroid hormone at the cellular nuclear level [104]. The strong relationships of parameters, especially atrial fibrillation (risk increased up to 9x across the normal range [28]), to levels of FT4 indicate that the active intracellular T3 generated by thyroid hormone transporters and deiodinases [104] appears to be, in general, proportional to circulating FT4. Any discrepancy, indicating local regulation of thyroid effect may be more prominent in more severe pathophysiological circumstances [104], and therefore more relevant in the circumstances of multisystem entities such as frailty, death and metabolic disturbance.

Our results do not imply that no information can be gleaned from the presence of an abnormal TSH level with normal thyroid hormone levels. Such levels indicate that the thyroid gland physiology is abnormal and that normal range thyroid hormone levels are being achieved only by dint of the abnormal TSH levels. However, for the function of other tissues and organs, the TSH level required to maintain a given level of thyroid hormones appears generally not to be relevant.

It remains possible too, that additional analyses might find that TSH levels are providing an additional signal to FT4 levels, in some populations for some conditions. It has been suggested that TSH itself may have physiological effects apart from the stimulation of thyroid hormone levels [34, 125], and such effects rather than via the reflection of thyroid status might explain such a TSH signal. Empirically, thus far, the evidence suggests that any of these TSH effects are small.

The association of thyroid hormone and particularly FT4 levels, rather than TSH levels, with clinical features has been noted by many authors, covering many individual parameters [24-26, 28, 31, 33, 40, 42, 44-46, 46, 50, 51, 55, 67, 71, 74, 78, 79, 84]. In particular, the meta-analysis regarding atrial fibrillation noted the association with FT4 but not with TSH [25]. authors have also previously 4769, 7178,8447 We were not able to find authors concluding that there are strong associations of clinical parameters with TSH but not thyroid hormone levels.

Nevertheless this information from the individual studies showing the superiority of thyroid hormone levels as correlates with clinical parameters has not to date, to our knowledge, been synthesised into a general proposition.

It has been suggested that ‘despite TSH being considered a more sensitive indicator of thyroid status, FT4 may be a more sensitive indicator of ‘cardiac’ [26], or ‘tissue’ [45, 51] thyroid status. Our study strengthens and generalizes these propositions, indicating that FT4 **is** the more sensitive indicator of thyroid status **because** it is the better indicator of tissue and organ effects.

The superior correlation of clinical parameters with FT4 as compared to TSH levels has more often been attributed to a putative disturbance of set point physiology [24, 38, 44, 45, 74, 79, 84], to a significant difference between pituitary and peripheral sensitivity to FT4[25, 44, 46, 50, 67], or to statistical/other factors [31, 34, 42, 47, 56].

Such explanations are denied by, respectively, the evidence that thyroid set points do not exist (see below), and the evidence that, at a population level, TSH levels do indeed decrease with rising FT4 levels [17, 18]. Any such disturbance to pituitary sensitivity, in the absence of a corresponding change to peripheral sensitivity, would in any event provide another reason not to diagnose subclinical thyroid dysfunction on the basis of TSH levels.

It has been suggested that in elderly individuals the TSH may not be so suppressed by any given rise in FT4 [40, 74] but in this situation, though the range of TSH may change, any physiological association with greater or lesser TSH levels should remain intact. Furthermore, the greater correlation of clinical parameters with FT4 rather than TSH levels is apparent across a wide age range (Table 1).

The evidence also suggests that, regardless of the method used, the classification of thyroid function into normal, subclinical disease and overt disease is arbitrary. Thyroid hormones, as previously suggested [8, 24], like many other biological parameters, exert a continuum of effects across the normal range. There is no clear border between normal and abnormal. There are advantages and disadvantages associated with all levels [8, 24, 126]. Individuals with relatively low levels of FT4 for example are less likely to develop atrial fibrillation but more likely to develop metabolic syndrome; the converse applies for individuals with higher FT4 levels. At the extremes the disadvantages clearly outweigh the advantages, and individuals are likely to become symptomatic.

On the other hand, any excursion from the middle of the range has an association with some pathology or other. Some individual pathologies, e.g. frailty, mortality and dementia may increase with deviations either side of the middle of the range. It seems likely that evolutionary mechanisms have arisen to minimize variation from the middle of the normal range of thyroid hormones [127].

Our work indicates that if any individuals are to be regarded as having subclinical thyroid dysfunction on the basis of a discrepancy between the normality of TSH and thyroid hormones, it would be more logical to so classify those with abnormal levels of thyroid hormones but with normal levels of TSH (i.e. euthyroid hypo/hyperthyroxinemia), rather than vice versa as currently recommended. We would suggest that it would be more logical still if the TSH level were not a determinant at all, and that borderline thyroid function was defined by borderline levels of thyroid hormones alone. With the current paradigm of screening for thyroid dysfunction by measurement of TSH levels the above patients may well not be identified.

None of the above denies the possibility that some individuals (for example individuals with paroxysmal atrial fibrillation), with thyroid hormone levels within the normal range might have improved outcomes if their thyroid hormone levels were adjusted. It may also be that in some individuals, different levels of thyroid hormones within the normal range result in different senses of wellbeing. Furthermore, in some individuals, thyroid hormone levels may not provide the whole diagnosis, and considerations of hormone sensitivity may also apply. However, the fact that, at a population level, clinical features and TSH levels reflect FT4 levels, argues against central or peripheral sensitivity generally being an important factor in the pituitary or peripheral response to thyroid hormones.

The above conclusions are consistent with, and reinforce, contemporary understanding of thyroid regulation. The conventional TSH - based definitions of thyroid disease on the other hand appear to have arisen and persisted on account of the perpetuation of misunderstandings of thyroid regulation. These misunderstandings concern the set point hypothesis and the greater sensitivity of TSH as compared to FT4 with changes in thyroid function.

The current consensus, despite evidence to the contrary [128], still confirms the set point hypothesis of thyroid regulation [1]. This hypothesis proposes that each individual has a set point or target, ideal level of a given parameter defended by physiological mechanisms [129].

The presence of a set point is said to be supported by there being greater inter-individual variation than intra-individual variation in thyroid hormone levels [1, 130] and by ‘various studies showing that, despite normalized TSH and FT4 levels, approximately 15% of patients treated for hypothyroidism or hyperthyroidism still have significant thyroid associated complaints’[1].

The former argument represents a misreading of the work [131] that purportedly demonstrates this proposition. Illustrative empiric examples to the contrary abound [132,133]. Contradicting the latter argument is the observation that individuals with subclinical thyroid dysfunction, who would have thyroid function even further away from any putative set point levels than the above treated patients, have few if any symptoms [4, 5], i.e. their abnormality is indeed ‘subclinical’. Furthermore any residual symptoms in patients treated for hypo/hyperthyroidism may have another cause, and indeed, one study has suggested that thyroid surgery to remove the offending source of autoimmune inflammation may be helpful in this regard [134].

As there is no reason to believe that any individual’s particular thyroid hormone levels represent a set point, it follows that any deviation away from these levels, within the normal range, is not necessarily deleterious, regardless of the TSH level. Individuals do not so become ‘individually ‘dysthyroid’, and may in fact become more ‘normal’ if any change from baseline is towards the middle of the range. No individual needs to become ‘more hypothyroid’ [130] than other individuals to have hormone levels fall out of the normal range and enable diagnosis. By the same logic, there is no imperative with thyroid replacement therapy to attempt to recreate the exact pre-morbid thyroid status of an individual.

It also does not follow that because TSH levels are more sensitive indicators than FT4 levels in the context of changes in thyroid function, that TSH levels are better indicators of thyroid function [1, 7, 130, 135]

There are proportionally greater changes to levels of the controlling hormones insulin [136], parathyroid hormone [137] and erythropoietin [138] in response to primary changes of levels of the parameters glucose, calcium and hemoglobin respectively, but this provides no justification to rely on the levels of the controlling hormones to define normality of these parameters [14, 15].

The fact that TSH levels reliably identify overt thyroid dysfunction can also be explained by the negative population relationship between TSH and FT4, i.e. its extension into the abnormal ranges of FT4 [17, 18]. This is due merely to the fact that nearly all overt thyroid dysfunction is primary rather than secondary [139]. This situation differs from other endocrine pathology, for example Cushing’s syndrome, where ACTH levels cannot be used as a screening test on account of the likelihood that Cushing’s syndrome may be secondary, i.e. be due to a disorder of ACTH regulation [140]. The fact that TSH levels are thereby very sensitive screening tests for thyroid dysfunction [135] does not imply TSH levels are very specific, i.e. that an abnormal TSH level implies thyroid dysfunction. Our work indicates that an abnormal TSH level per se is an imprecise indicator of tissue or organ hyper/hypothyroidism. Certainly an abnormal FT4 level is more indicative of a dysthyroid state. Testing for an abnormal FT4 would also lessen the chance of error in the circumstances of thyroid dysfunction of central origin [141].

This work addressed diagnosis alone. Randomized trials are necessary to determine whether additional considerations apply in the context of thyroid treatments. One study has reported that TSH levels are important in the treatment of thyroid insufficiency [142], but this was an observational study and it did not fully stratify FT4 levels or exclude factors that might interfere with the FT4/TSH relationship.

Our work has relevance for the interpretation and planning of interventional studies. It may well be that previous trials of the treatment of subclinical thyroid dysfunction have been negative on account of treatment being directed at TSH levels. Not only were these TSH levels inappropriate targets, but in addition, on account of the sensitivity of TSH levels to changing FT4 levels, only minimal changes (approximately 2 pmol/L [10]) in FT4 levels would have followed normalization of the TSH levels. If subtle improvements are to be sought within and at the edges of the normal range, FT4, and possibly FT3 levels, would appear to be better targets, with the aim being to bring them at least to the middle of the range; even at the cost of generating an abnormal TSH level.

As organ effects can be appreciated within the normal range however, it does not necessarily follow that even if treatment can be shown to have a beneficial effect that an abnormality was present in the first place. Improved understanding of which clinical states might have engendered compensatory or secondary changes in thyroid function, rather than having resulted from such changes, might explain any suggestion of a signal of harm with treatment of any borderline thyroid function state [143].

In summary there is now matching theoretical and empiric evidence from a variety of sources suggesting that the concept of subclinical thyroid dysfunction is flawed, and that if it does exist, it should not be diagnosed on the basis of TSH levels. The same applies for the concepts of isolated hypothyroxinemia and hyperthyroxinemia. The borderline thyroid hormone levels in these latter situations indicate borderline normal tissue exposure to thyroid effect, and increased potential for some adverse outcomes, just as they would if the TSH levels were not normal.

There is rather, a continuum of thyroid hormone effect along the continuum of thyroid hormone levels, with a possible optimum around the middle of the range. Though TSH levels remain good screening tests for overt thyroid dysfunction, it is theoretically and empirically more sound to rely on the thyroid hormone, and especially FT4, levels to classify the thyroid state. This applies in principle for all diagnostic, therapeutic, monitoring and research considerations.

This work should result in a simplification of the understanding of thyroid physiology and pathophysiology, and bring it more into line with the understanding of the physiology and pathophysiology of other parameters, whereby the status of a parameter is judged by **its** level rather than the level of any controlling factor. Reconsideration of the TSH-based diagnostic approach to thyroid function, the consequent definitions, and the dependent guidelines appears to be indicated.

REFERENCES

2. Schneider C, Feller M, Bauer DC, Collet T-H, da Costa BR, Auer R, Peeters RP, Brown SJ, Bremner AP, O’Leary PC, Feddema P, Leedman PJ, Aujesky D, Walsh JP, Rodondi N. 2018 Initial evaluation of thyroid dysfunction- are simultaneous TSH and fT4 tests necessary? PLoS One 13(4): e0196631 DOI:10.1371/journal.pone.0196631
3. Ross DS 2019 Euthyroid hyperthyroxinemia and hypothyroxinemia. Cooper DS ed. UpToDate Waltham MA:UpToDate Inc. <https://www.uptodate.com> (accessed November 10, 2019)
4. Wilson S, Parle JV, Roberts LM, Roalfe AK, Hobbs FDR, Clark P, Sheppard MC, Gammage MD Pattison HM, Franklyn JA. 2006 Prevalence of subclinical thyroid dysfunction and its relation to socioeconomic deprivation in the elderly: a community –based cross-sectional survey J ClinEndocrinolMetab91(12):4809-4816 DOI: 10.1210/jc.2006-1557
5. Biondi B, Cooper DS 2018 Subclinical hyperthyroidism. N Engl J Med 378:2411-9 DOI: 10.1056/NEJMcp1709318
6. Palacios SS, Pascual-Corrales E, Galofre JC. Management of subclinical hyperthyroidism2012Int J EndocrinolMetab10(2):490-496 DOI:10.5812/ijem.3447
7. Fatourechi V2009 Subclinical hypothyroidism: an update for primary care physicians Mayo Clin Proc84(1):65-71 DOI:10.1016/S0025-6196(11)60809-4
8. Taylor PN, Razvi S, Pearce SH, Dayan CM 2013 A review of the clinical consequences of variation in thyroid function within the reference range. J ClinEndocrinolMetab98(9)3562-3571 DOI:10.1210/jc.2013-1315
9. Orgiazzi J2016 Dose normal TSH mean euthyroidism in L-T4 treatment? Clinical Thyroidology DOI:10.1089/ct.2016;28.325-328
10. The TRUST Study Group2017Thyroid hormone therapy for older adults with subclinical hypothyroidism. N Engl J Med 376:2534-2544 DOI: 10.1056/NEJMoa1603825
11. Villar HC, Sacconato H, Valente O, Atallah AN2007Thyroid hormone for subclinical hypothyroidism. Cochrane Database Syst Rev18(3):CD003419 DOI:10.1002/14651858.CD00349.pub2
12. Hoermann R, Larisch R, Dietrich JW, Midgley JEM 2016 Derivation of a multivariate reference range for pituitary thyrotropin and thyroid hormones: diagnostic efficiency compared with conventional single reference method. Eur J Endocrinol 174(6):735-743 DOI: 10.1530/EJE-160031
13. Ross HA, den Hejer M, Hermus Ad RMM, Sweep FCGC 2009 Composite reference interval for thyroid-stimulating hormone and free thyroxine, comparison with common cutoff values, and reconsideration of subclinical thyroid disease.ClinChem55(11):2019-2025 DOI:10.1373/clinchem.2009.124560
14. Cryer PE, Davis SN2015 Chapter 420:2430-2435 Hypoglycemia. In: Harrison’s Principles of Internal Medicine. 19th edition. Editors Kasper DL, Hauser SL, Jameson JL, Fauci AS, Longo DL, Loscalzo J. . McGraw Hill New York
15. Khosla S2015 Chapter 65; 313-314 Hypercalcemia and Hypocalcemia. In; Harrison’s Principles of Internal Medicine. 19th edition. Editors Kasper DL, Hauser SL, Jameson JL, Fauci AS, Longo DL, Loscalzo J. McGraw Hill New York
16. Arlt W2015 Chapter 406; 2316 Disorders of the adrenal cortex. In ; Harrison’s Principles of Internal Medicine. 19th edition. Editors Kasper DL, Hauser SL, Jameson JL, Fauci AS, Longo DL, Loscalzo J. McGraw Hill New York
17. Hoermann R, Eckl W, Hoermann C, Larisch R2010Complex relationship between free thyroxine and TSH in the regulation of thyroid function. Eur J Endocrinol162:1123-1129 DOI: 10.1530/EJE-10-0106
18. Hadlow NC, Rothacker KM, Wardrop R, Brown SJ, Lim EU, Walsh JP2013 The relationship between TSH and free T4 in a large population is complex and nonlinear and differs by age and sex. J Clin Endocrinol Metab 98(7):2936-2943 DOI:10.1210/jc.2012-4223
19. Knudsen N, Laurberg P, Rasmussen LB, Bulow I, Perrild H, Ovesen L, Jørgensen T 2005 Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population. J Clin Endocrinol Metab 90(7):4019-24 DOI: 10.1210/jc.2004-2225
20. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group2009 Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med6(7):e1000097
21. Bates D, Maechler M, Bolker B, Walker S2015Fitting linear mixed-effect models using lme4. Journal of Statistical Software 67(1);1-48 DOI:10.18673/jss.v067.i01
22. R Core Team. R: A language and environment for statistical computing. R Foundation for statistical computing, Vienna, Austria. URL https://www.R-project.org/.
23. Selmer C, Olesen JB, Hansen ML, Lindharsen J, Olsen A-MS, Madsen JC, Hansen PR, Pedersen OD, Faber J, Torp-Pedersen C, Gislason GH2012The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. BMJ 345:e7895 DOI:10.1136/bmj.e7895
24. Cappola AR, Arnold AM, Wulczn K, Carlson M, Robbins J, Psaty BM 2015 Thyroid function in the euthyroid range and adverse outcomes in older adults. J ClinEndocrinolMetab100(3):1088-1096 DOI:10.1210/jc.2014-3586
25. Baumgartner C, da Costa BR, Collet TH, Feller M, Floriani C, Bauer DC, Cappola AR, Heckbert SR, Ceresini G, Gussekloo J, den Elzen WPJ, Peeters RP, Luben R, Völzke H, Dörr M, Walsh JP, Bremner A, Iacoviello M, Macfarlane P, Heeringa J, Stott DJ, Westendorp RGJ, Khaw KT, Magnani JW, Aujesky D, Rodondi N; Thyroid Studies Collaboration 2017 Thyroid Studies Collaboration. Thyroid function within the normal range, subclinical hypothyroidism, and the risk of atrial fibrillation. Circulation 136(22):2100-2116. DOI:10.1161/CIRCULATIONAHA.117.028753
26. Gammage MD, Parle JV, Holder RL, Roberts LM, Hobbs FD, Wilson S, Sheppard MC, Franklyn JA2007Association between serum free thyroxine concentration and atrial fibrillation. Arch Intern Med167(9):928-34 DOI: 10.1001/archinte.167.9.928
27. Heeringa J, Hoogendoorn EH, van der Deure WM, Hofman A, Peeters RP, Hop WC, den Heijer M, Visser TJ, Witterman JC2008High-normal thyroid function and the risk of atrial fibrillation: the Rotterdam study. Arch Int Med168(20):2219-24 DOI: 10.1001/archinte.168.20.2219 (FT4- not sig 0.06)
28. Chaker, L, Heeringa J, Deghan A, Medici M, Visser WE, Baumgartner C, Hofman A, Rodondi N, Peeters RP, Franco OH 2015 Normal thyroid function and the risk of atrial fibrillation: the Rotterdam Study J Clin Endocrinol Metab 100:3718-3724 DOI:10.1210/jc.2015-2480
29. Kannan L, Shaw PA, Morley MP, Brandimarto J, Fang JC, Sweitzer NK, Cappola TP, Cappola AR 2018. Thyroid dysfunction in heart failure and cardiovascular outcomes. Circulation: Heart Failure 11(12)e005266 DOI: 10/1161/CIRCHEARTFAILURE.118.005266
30. Yan Z, Huang H, Li J, Wang J2016Relationship between subclinical thyroid dysfunction and the risk of fracture: a meta-analysis of prospective cohort studies. Osteoporosis Int1:115-25 DOI: 10.1007/s00198-015-3221-z
31. Van Rijn LE, Pop VJ, Williams GR 2014Low bone mineral density is related to high physiological levels of free thyroxine in peri-menopausal women. Eur J Endocrinol170(3):461-8 DOI:10.1530/EJE-13-0769
32. Roef G, lapauw B, Goemaere S, Zmierczak H, Fliers T, Kaufman JM, Taes Y2011Thyroid hormone status within the physiological range affects bone mass and density in healthy men at the age of peak bone mass. Eur J Endocrinol 164(6): 1027-34 DOI:10.1530/EJE-10-1113
33. Murphy E, Glüer CC, Reid DM, Felsenberg D, Roux C, Eastell R, Williams GR 2010 Thyroid function within the upper normal range is associated with reduced bone mineral density and an increased risk of nonvertebral fractures in healthy euthyroid postmenopausal women. J ClinEndocrinolMetab95(7):3173-81 DOI:10.1210/jc.2009-2630
34. Van der Deure, Uitterlinden AG, Hofman A, Rivadeneira F, Pols HA, Peeters RP, Visser TJ2008Effects of serum TSH and FT4 levels and the TSHR-Asp727Glu polymorphism on bone: the Rotterdam Study. Clin Endocrinol (Oxf)68(2):175-181 DOI: 10.1111/j.1365-2265.2007.0316.x
35. Waring AC, Harrison S, Fink H, Samuels MH, Cawthorn PM, Zmuda JM, Orwoll ES, Bauer D. 2013 A prospective study of thyroid function, bone loss, and fractures in older men: The MrOS Study J Bone Miner Res 28(3):472-479 DOI: 10.1002/jbmr.1774
36. Siru R, Alfonso H, Chubb SAP, Golledge J, Flicker L, Yeap BB. 2017. Subclinical thyroid dysfunction and circulating thyroid hormones are not associated with bone turnover markers or incident hip fracture in older men. Clin Endocrinol 89:93-99 DOI:10.1111/cen.13615
37. Lambrinoudaki I, Armeni E, Pliatsika P, Rizos D, Kaparos G, Augoulea A, Alexandrou A, Flokatoula M, Creatsa M, Panoulis C, Triantafyllou N, Papacharalambous X 2017. Thyroid function and autoimmunity are associated with the risk of vertebral fractures in postmenopausal women. J Bone Miner Metab 35:227-233 DOI:19.1007/s00774-016-0752-0
38. Chan YX, Knuiman MW, Divitini ML, Brown SJ, Walsh J, Yeap BB2017Lower TSH and higher free thyroxine predict incidence of prostate but not breast, colorectal or lung cancer. Eur J Endocrinol 177(4):297-308 DOI:10.1530/EJE-17-0197
39. Tosovic A, Becker C, Bondeson A-G, Bondeson L, Ericsson U-B, Malm J, Manjer J 2012 Prospectively measured thyroid hormones and thyroid peroxidase antibodies in relation to breast cancer risk. Int J Cancer 131(9):226-2133 DOI:10.1002/ijc.27470
40. Khan SR, Chaker L, Ruiter R, Aerts JGJV, Hoffman A, Deghan A, Franco OH, Stricker BHC, Peeters RP 2016 Thyroid function and cancer risk: The Rotterdam Study. J Clin Endocrinol Metab12 (1):5030-5036. DOI:10.1210/jc.2016-2104
41. Kuijpens JLP, Nykličtek I, Louwman MWJ, Weetman TAP, Pop VJM, Coebergh J-W W 2005. Hypothyroidism might be related to breast cancer in post-menopausal women. Thyroid 15(11):1253-1259 DOI:10.1089/thy.2005.15.1253
42. Ittermann T, Haring R, Wallaschofski H, Baumeister S, Nauck, M, Dörr M, Lerch M, Meyer zuSchwabedissen HE, Rosskopf D, Völzke H2012 Inverse association between serum free thyroxine levels and hepatic steatosis: results from the study of health in Pomerania. Thyroid 22(6):568-574 DOI: 10.1089/thy.2011.0279
43. Xu C, Xu L, Yu M, Li Y2011Association between thyroid function and non alcoholic fatty liver disease in euthyroid elderly Chinese. Clinical Endocrinology 75:240-246 DOI:10.1111/j.1365-2265.2011.04016.x
44. Bano A, Chaker L, Plompen, EPC, Hofman A, Deghan A, Franco OH, Janssen HLA, Murad SW, Peeters RP 2016 Thyroid function and the risk of non-alcoholic fatty liver disease: the Rotterdam study. J ClinEndocrinolMetab101(8):3204-3211 DOI: 10.1012/jc.2016-1300
45. Mehran L, Amouzegar A, Bakhtiyari M, Mansournia MA, Rahimabad PR, Tohidi M, Azizi F2017Variations in serum free thyroxine concentration within the reference range predicts the incidence of metabolic syndrome in non-obese adults: a cohort study. Thyroid 27(7):886-893 DOI:10.1089/thy.2016.0557
46. Roos A, Bakker SJ, Links TP, Gans RO, Wolffenbuttel BH2007 Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. J ClinEndocrinolMetab92(2):491-6 DOI:10.1210/jc.2006-1718
47. Garduño-Garcia J, Alvirde- Garcia U, López-Carrasco G, Mendoza M, Mehta R, Arellano-Campos O, Choza R, Sauque L, Garay-Sevilla ME, Malacara JM, Gomez-Perez FJ, Aguilar-Salinas CA 2010TSH and free thyroxine concentrations are associated with differing metabolic markers in euthyroid subjects. Eur J Endocrinol163:73-278 DOI:10.1530/EJE-10-0312
48. Lin SY, Wang YY, Liu PH, Lai WA, Sheu WH 2005 Lower serum free thyroxine levels are associated with metabolic syndrome in a Chinese population. Metabolism 54(11):1524-8 DOI: 10.1016/j.metabol.2005.05.020
49. Waring AC, Rodondi N, Harrison S, Kanava AM, Simonsick EM, Milkovic I, Satterfield S, Newman AB, Bauer DC, for the Health, Aging and Body Composition (Health ABC) Study2012 Thyroid function and prevalent and incident metabolic syndrome in older adults: The Health, Aging, and Body Composition Study. Clin Endocrinol (Oxf).76(6):911-918 DOI: 10.1111/j.1365-2265.2011.04328.x
50. Shon HS, Jung ED, Kim SH, Lee JH2008 Free T4 is negatively correlated with body mass index in euthyroid women. Korean J Intern Med 23(2):53-57 DOI:10.3904/kjim.2008.23.2.53
51. Makepeace AE, Bremmer AP, O’Leary P, Leedman PJ, Feddema P, Michelangeli V, Walsh JP 2008 Significant inverse relationship between serum free T4 concentration and body mass index in euthyroid subjects: differences between smokers and non-smokers. Clin Endocrinol (Oxf) 69(4):648-652 DOI:10.111/j.1365-2265.2008.03239.x
52. Chaker L, Ligthart S, Korevaar TI, Hofman A, Franco OH, Peeters RP, Deghan A2016Thyroid function and risk of type 2 diabetes: a population cohort study. BMC Med14(1):150 DOI:10.1186/s12916-016-0693-4
53. Jun JE, Jee JH, Bae JC, Jin S-M, Hur KY, Lee M-K, Kim TH, Kim SW, Kim JH2017Association between changes in thyroid hormones and incident Type 2 diabetes: a seven- year longitudinal study. Thyroid 27(1):29-38 DOI:10.1089/thy.2016.0171
54. Oh H-S, Kwon H, Ahn J, Song E, Park S, Kim M, Han M, Jeon MJ, Kim WG, Kim WB, Shong YK, Rhee E-J, Kim TY2018 Association between thyroid dysfunction and lipid profiles differs according to age and sex: results from the Korean National Health and Nutrition Survey. Thyroid 28(7):849-856 DOI: 10.1089/thyr.2017.0656.
55. Kim HH, Bae JC, Park HK, Byun DW, Suh K, Yoo MH, Kim JH, Min Y-K, Kim SW, Chung JH 2016Triiodothyronine levels are independently associated with metabolic syndrome in euthyroid middle-aged subjects. Endocrinol Metab (Seoul)31(2):311-319 DOI:10.3803/EnM.2016.31.2.311
56. Strollo F, Carucci I, More M, Marico G, Strollo G, Masini MA, Gentile S2012 Free triiodothyronine and cholesterol levels in euthyroid elderly T2DM patients. Int J Endocrinol 2012 Article ID 420370, 7 pages DOI:10.1155/2012/420370
57. Svare A, Nilsen TI, Bjøro T, Asvold BO, Langhammer A 2011 Serum TSH related to measures of body mass: longitudinal data from the HUNT Study, Norway. Clin Endocrinol (Oxf) 74(6):769-765. DOI:10.1111/j.1365-2265.2011.04009.x
58. Proces S, Delgrange E, Vander Borght T, Donckier J, Donckier JE 2001 Minor alterations in thyroid-function tests associated with diabetes and obesity in outpatients without known thyroid illness. Acta Clinica Belgica 56(2):86-90 DOI:10.1179/acb.2001.015
59. Wolide AD, Zawdie B, Alemayehu T, Tadesse S 2017. Association between thyroid hormone parameters and dyslipidemia among type 2 diabetes mellitus parameters: Comparative cross-sectional study. Diab Metab Syndr Suppl1 S257-S262 DOI:10.1016/j.dsx.2016.1.041
60. Temizkan S, Balafoulou B, Ozderya A, Avci M, Aydin K, Karaman S, Sargin M 2016. Effects of thyrotrophin, thyroid hormones and thyroid antibodies on metabolic parameters in a euthyroid population with obesity. Clin Endocrinol 85:616-623 DOI:10.1111/cen.13095
61. Jain 2017. Associations between the levels of thyroid hormones and lipid/lipoprotein levels: Data from national Health and Nutrition Examination Survey 2007-2012. Environ Toxicol Pharmacol 53:133-144 DOI: 10.1016/j.etap.2017.05.002
62. Boekholdt SM, Titan SM, Wiersinga WM, Chatterjee K, Basart DCG, Luben R, Wareham NJ, Khaw K-T 2009 Initial thyroid status and cardiovascular risk factors: The Epic-Norfolk prospective population study. Clin Endocrinol 72:404-410 DOI:10.1111/j.1365-2265.2009.03640.x
63. Udenze,I, Nnaji I, Oshodi T. 2014 Thyroid function in adults with metabolic syndrome Pan Afr Med J 18:352 DOI: 10.11604/pami.2014.18.352.4551
64. Elgazar EH, Esheba NE, Shalaby SA, Mohamed WF 2019.Thyroid dysfunction prevalence and relation to glycemic control in patients with type 2 diabetes mellitus. Diabetes Metab Syndr. 13(4)2513-2517 DOI:10.1016/j.dsx.2019.07.020
65. Vadiveloo T, Donnan PT, Cochrane L, Leese G 2011The Thyroid Epidemiology, Audit, and Research Study (TEARS): Morbidity in patients with endogenous subclinical hyperthyroidism. J ClinEndocrinolMetab:96(5):1344-1351 DOI: 10.1210/jc.2010-2693
66. Choi HJ, Byun MS, Yi D, Sohn BK, Lee JH, Kim YK, Lee DY; KBASE Research Group 2017 Associations of thyroid hormone levels with in vivo Alzheimer’s disease pathologies. Alzheimer’s Res Ther 9(1):64 DOI: 10.1186/s13195-017-0291-5
67. Volpato S, Guralnik JM, Fried LP, Remalay AT, Cappola AR, Launer LJ 2002 Serum thyroxine level and cognitive decline in older women Neurology 58(7): 1055-1061 DOI:10.1212/WNL.58.7.1055
68. Choi HY, Choe YM, Byun MS, Sohn BK, Baek H, Yi D, Han JY, Woo JI, Lee DY2015 Associations between serum thyroid hormone and cerebral amyloidosis in cognitively diverse elderly. Alzheimer’s and Dementia 11(7) S648-649 DOI:10.1016/j.jatz.2015.06.947
69. de Jong FD, Heijer T, Visser TJ, de Rijke YB, Drexhage HA, Hoffman A, Breteler MMB2006 Thyroid hormones, dementia, and atrophy of the medial temporal lobe. J ClinEndocrinolMetab91(7):2569-2573 DOI:10.1210/jc.2006-0449
70. Tan ZS, Beiser A, Ramachandran RS, Au R, Auerbach S, Kiel DP, Wolf PA, Seshadri S 2009 Thyroid function and the risk of Alzheimer’s disease: The Framingham Study. Arch Int Med168(14):1514-1520 DOI:10.1001/archinte.168.14.1514
71. Yeap BB, Alfonso H, Chubb SA, Puri G, Hankey GJ, Flicker L, Almeida OP 2012. Higher free thyroxine levels predict increased incidence of dementia in older men: the Health in Men Study. J Clin Endocrinol Metab. 97(12) E2230-7. DOI 10.1210/jc.2012-2108
72. Chaker L, Wolters, FJ, Korevaar TI, Hofman A, van der Lugt A, Koudstaal PJ, Franco OH, Deghan A, Vernooij MW, Peeters RP, Ikram MA 2016. Thyroid function and the risk of dementia: The Rotterdam Study. Neurology 87(16):1688-1695 DOI: [10.1212/WNL.0000000000003227](https://doi.org/10.1212/WNL.0000000000003227" \t "_blank)
73. Ittermann T, Wittfeld K, Nauck M, Bülow R, Hosten N, Völzke H, Grabe HJ 2018. High thyrotropin is associated with reduced hippocampal volume in a population –based study from Germany. Thyroid 28(11):1434-1442 DOI:10.1089/tyh.2017.0561
74. Yeap BB, Alfonso H, Chubb SAP, Walsh JP, Hankey GJ, Almeida OP, Flicker L2012 Higher free thyroxine levels are associated with frailty in older men: the Health In Men Study. Clin Endocrinol 76:741-748 DOI: 10.1111/j.1365-2265.2011.04290.x
75. Bano A, Chaker L, Schoufour J, Ikram MA, Kavousi M, Franco OH, Peeters RP, Mattace-Raso FUS2018High circulating free thyroxine levels may increase the risk of frailty: The Rotterdam Study. J Clin Endocrinol Metab103(1):328-335 DOI: 10.1210/jc.2017-01854
76. van den Beld AW, Visser TJ, Feelders RA, Grobbee DE, Lamberts SWJ2005 Thyroid hormone concentrations, disease, physical function, and mortality in elderly men. [J ClinEndocrinolMetab](https://www.ncbi.nlm.nih.gov/pubmed/16174720" \o "The Journal of clinical endocrinology and metabolism.)90(12):6403-9 DOI:[10.1210/jc.2005-0872](https://doi.org/10.1210/jc.2005-0872" \t "_blank)
77. Gussekloo J, van Exel E, de Graen AJM, Meinders AE, Frölich M, Westendorp RGJ2004Thyroid status, disability and cognitive function, and survival in old age. JAMA 292:2591-2599 DOI:10.1001/jama.292.21.2591
78. Yeap BB, Alfonso H, Hankey GJ, Flicker L, Golledge J, Norman PE, Chubb SAP2013 Higher free thyroxine levels are associated with all-cause mortality in euthyroid older men: the Health In Men Study. Eur J Endocrinol 169:401-408 DOI: 10.1530/EJE-13-0306
79. Van de Ven AC, Netea-Maier RT, de Vegt F, Ross HA, Sweep HA, Sween FC, Kiemeney LA, Smit JW, Hermus AR, den Heijer M 2014 Associations between thyroid function and mortality: the influence of age. Eur J Endocrinol171(2):183-91 DOI: 10.1530/EJE-13-1070
80. Inoue K, Tsujimoto T, Saito J, Sugiyama T2016 Association between serum thyrotropin levels and mortality among euthyroid adults in the United States. Thyroid 26(10):1457-1465 DOI:10.1089/thy.2016.0156
81. Selmer C, Olesen JB, Hansen ML, von Kappelgaard LM, Madsen JC, Hansen PR, Pedersen OD, Faber J, Torp-Pederson C, Gislason GH2014 Subclinical and overt thyroid dysfunction and the risk of all-cause mortality and cardiovascular events: a large population study. J ClinEndocrinolMetab99(7):2372-2382 DOI: 10.1210/jc.2013-4184
82. Moon S, Kim MJ, Yu JM, Yoo HJ, Park YJ2018 Subclinical hypothyroidism and the risk of cardiovascular disease and all-cause mortality: a meta-analysis of prospective cohort studies. Thyroid 28(9):1101-1110 DOI:10.1089/thy.2017.0414
83. Razvi S, Weaver JU, Vanderpump MP, Pearce SH 2010. The incidence of ischemic heart disease and mortality in people with subclinical hypothyroidism: reanalysis of the Whickham Survey cohort. J ClinEndocrinolMetab95(4):1734-40 DOI: 19.1210/jc.2009-1749
84. Chaker L, van den Berg ME, Niemeijer MN, Franco OH, Deghan A, Hofman A, Rijnbeek PR, Deckers JW, Eijgelsheim M, Stricker, BHC, Peeters RP2016 Thyroid function and sudden cardiac death: A prospective study. Circulation 134(10):713-722 DOI:10.1161/CIRCULATIONAHA.115.020789
85. Asvold BO, Bjøro T, Nilsen TI, Gunnell D, Vatten LJ2008Thyrotropin levels and risk of fatal coronary heart disease: the HUNT study Arch Int Med 168(8):855-860 DOI:10.1001/archinte.168.8.855
86. Rodondi N, Bauer DC, Cappola AR, Cornuz J, Robbins J, Fried LP, Ladenson PW, Vittinghoff E, Gottdiener JS, Newman AB2008 Subclinical thyroid dysfunction, cardiac function and the risk of heart failure: The Cardiovascular Health Study. J Am CollCardiol52(14):1152-1159 DOI: 10.1016/jack.2008.07.009
87. Walsh JP, Bremner AP, Bulsara MK, O’Leary P, Leedman PJ, Feddema P, Michelangeli V2005 Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. Arch Int Med 165:2647-2472 DOI: 10.1001/archinte.165.21.2467
88. Peixoto de Miranda EJF, Bittencourt MS, Staniak HL, Sharovsky R, Pereira AC, Foppa M, Santos IS, Lotufo PA, Benseñor IM 2018. Thyrotropin and free thyroxine levels and coronary artery disease: cross-sectional analysis of the Brazilian longitudinal Study of Adult Health (ELSA-Brasil). Braz J med Biol Res. 51(5):e7196 DOI:10.1590/1414-431X20177196
89. Roef GL, Taes YE, Kaufman J-M, Van Daele CM, De Buyzere ML, Gillebert TC, Rietzschel ER 2013. Thyroid hormone levels within reference range are associated with heart rate, cardiac structure, and function in middle aged men and women. Thyroid 23(8) 947-954 DOI:10.1089/thy.2012.0471
90. Vrijkotte TGM, Hrudey E, Twickler MB. 2017 Early maternal thyroid function during gestation is associated with fetal growth, particularly in male newborns. J Clin Endo Metab 102(3):1059-1066 DOI 10.1012/jc.2016-3452
91. Korevaar, TIM, Schalekamp-Timmermans S, de Rijke YB, Visser WE, Visser W, de Muinck Keizer-Schrama SMPF, Hofman A, Ross HA, Hooijkaas H, Tiemeier H, Bongers-Schokking JJ, Jaddoe VW, Visser TJ, Steegers EA, Medici M, Peeters RP 2013. Hypothyroxinemia and TPO- antibody positivity are risk factors for premature delivery: the generation R study. J Clin Endocrinol Metab 98(11) 4382-4390 DOI: 10.1210/jc.2013-2855
92. Medici M, de Rijke YB, Peeters RP, Visser W, de Muink Keizer-Schrama SM, Jaddoe VV, Hofman A, Hooijkaas H, Steegers EA, Tiemeiei H, Bongers-Schokking JJ, Visser TJ . 2012 Maternal early pregnancy and newborn thyroid hormone parameters: the Generation R study. J Clin Endocrinol Metab 97(2):646-652 DOI: 10.1210/jc.2011-2398
93. Cleary-Goldman J, Malone FD, Lambert-Messerlain G, Sullivan L, Canick J, Porter TF, Luthy D, Gross S, Bianchi DW, D’Alton ME 2008. Maternal thyroid hypofunction and pregnancy outcome. Obstet and Gynecol 112(1):85-92 DOI:10.1097/AOG.obo13e3181788dd7
94. Breathnach FM, Donnelly J, Cooley SM, Geary M, Malone FD 2013. Subclinical hypothyroidism as a risk factor for placental abruption: Evidence from a low-risk primigravid population. Australian and New Zealand Journal of obstetrics and Gynaecology 53(6):553-560 DOI:10.1111/ajo.12131
95. Ashoor G, Maiz N, Rotas M, Jawdat, F, Nicolaides KH 2010. Maternal thyroid function at 11-13 weeks of gestation and subsequent fetal death. Thyroid 20(9):989-993 DOI:10.1089/tyy.2010.0058
96. Knight BA, Shields BM, Hattersley AT, Vaidya B 2016. Maternal hypothyroxinaemia in pregnancy is associated with obesity and adverse maternal metabolic parameters. Eur J Endocrinol 174:51-57 DOI:10.1530/EJE-15-0866
97. Li Y, Shan Z, Teng W, Yu X, LI Y, Fan C, Teng X, Guo R, Wang H, Li J, Chen Y, Wang W, Chawinga M, Zhang L, Yang L, Zhao Y, Hua T 2010. Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25-30 months. Clin Endocrinol 72:825-829 DOI:10.1111./j.1365-2265.2009.03743.x
98. Jackson K, Cooper DS. 2019 Subclinical hypothyroidism and thyroid autoimmunity are associated with preterm delivery in an individual participant meta-analysis. Clinical Thyroidol;31:410-416 DOI:10.1089/ct.2019,31.410-416

101. Fliers E, Kalsbeek A, Boelen A 2014. Beyond the fixed setpoint of the hypothalamus- pituitary-thyroid axis. Eur J Endocrinol 171(5) R197-208 DOI:10.1530/EJE-14-0285
102. Burgess S, Scott RA, Timpson NJ, Davey Smith G, Thompson SG, Epic-InterAct Consortium 2015. Using published data in Mendelian randomisation: a blueprint for efficient identification of causal risk factors. Eur J Epidemiol 30(7):543-552 DOI:10.1007/s10654-015-0011-z
103. Medici M, [van der Deure WM](https://www.ncbi.nlm.nih.gov/pubmed/?term=van%20der%20Deure%20WM%5BAuthor%5D&cauthor=true&cauthor_uid=21367965), [Verbiest M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Verbiest%20M%5BAuthor%5D&cauthor=true&cauthor_uid=21367965), [Vermeulen SH](https://www.ncbi.nlm.nih.gov/pubmed/?term=Vermeulen%20SH%5BAuthor%5D&cauthor=true&cauthor_uid=21367965), [Hansen PS](https://www.ncbi.nlm.nih.gov/pubmed/?term=Hansen%20PS%5BAuthor%5D&cauthor=true&cauthor_uid=21367965), [Kiemeney LA](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kiemeney%20LA%5BAuthor%5D&cauthor=true&cauthor_uid=21367965), [Hermus AR](https://www.ncbi.nlm.nih.gov/pubmed/?term=Hermus%20AR%5BAuthor%5D&cauthor=true&cauthor_uid=21367965), [Breteler MM](https://www.ncbi.nlm.nih.gov/pubmed/?term=Breteler%20MM%5BAuthor%5D&cauthor=true&cauthor_uid=21367965), [Hofman A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Hofman%20A%5BAuthor%5D&cauthor=true&cauthor_uid=21367965), [Hegedüs L](https://www.ncbi.nlm.nih.gov/pubmed/?term=Heged%C3%BCs%20L%5BAuthor%5D&cauthor=true&cauthor_uid=21367965), [Kyvik KO](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kyvik%20KO%5BAuthor%5D&cauthor=true&cauthor_uid=21367965), [den Heijer M](https://www.ncbi.nlm.nih.gov/pubmed/?term=den%20Heijer%20M%5BAuthor%5D&cauthor=true&cauthor_uid=21367965), [Uitterlinden AG](https://www.ncbi.nlm.nih.gov/pubmed/?term=Uitterlinden%20AG%5BAuthor%5D&cauthor=true&cauthor_uid=21367965), [Visser TJ](https://www.ncbi.nlm.nih.gov/pubmed/?term=Visser%20TJ%5BAuthor%5D&cauthor=true&cauthor_uid=21367965), [Peeters RP](https://www.ncbi.nlm.nih.gov/pubmed/?term=Peeters%20RP%5BAuthor%5D&cauthor=true&cauthor_uid=21367965) 2011.A Large-scale association analysis of 68 thyroid hormone pathway genes with serum TSH and FT4 levels [Eur J Endocrinol.](https://www.ncbi.nlm.nih.gov/pubmed/21367965" \o "European journal of endocrinology.)  May; 164(5):781-8. doi: 10.1530/EJE-10-1130
104. [Ellervik C](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ellervik%20C%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Roselli C](https://www.ncbi.nlm.nih.gov/pubmed/?term=Roselli%20C%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Christophersen IE](https://www.ncbi.nlm.nih.gov/pubmed/?term=Christophersen%20IE%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Alonso A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Alonso%20A%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Pietzner M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Pietzner%20M%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), Sitlani CMO, [Trompet S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Trompet%20S%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Arking DE](https://www.ncbi.nlm.nih.gov/pubmed/?term=Arking%20DE%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Geelhoed B](https://www.ncbi.nlm.nih.gov/pubmed/?term=Geelhoed%20B%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Guo X](https://www.ncbi.nlm.nih.gov/pubmed/?term=Guo%20X%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Kleber ME](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kleber%20ME%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Lin HJ](https://www.ncbi.nlm.nih.gov/pubmed/?term=Lin%20HJ%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Lin H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Lin%20H%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [MacFarlane P](https://www.ncbi.nlm.nih.gov/pubmed/?term=MacFarlane%20P%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Selvin E](https://www.ncbi.nlm.nih.gov/pubmed/?term=Selvin%20E%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Shaffer C](https://www.ncbi.nlm.nih.gov/pubmed/?term=Shaffer%20C%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Smith AV](https://www.ncbi.nlm.nih.gov/pubmed/?term=Smith%20AV%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Verweij N](https://www.ncbi.nlm.nih.gov/pubmed/?term=Verweij%20N%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Weiss S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Weiss%20S%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Cappola AR](https://www.ncbi.nlm.nih.gov/pubmed/?term=Cappola%20AR%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Dörr M](https://www.ncbi.nlm.nih.gov/pubmed/?term=D%C3%B6rr%20M%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Gudnason V](https://www.ncbi.nlm.nih.gov/pubmed/?term=Gudnason%20V%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Heckbert S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Heckbert%20S%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Mooijaart S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Mooijaart%20S%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [März W](https://www.ncbi.nlm.nih.gov/pubmed/?term=M%C3%A4rz%20W%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Psaty BM](https://www.ncbi.nlm.nih.gov/pubmed/?term=Psaty%20BM%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Ridker PM](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ridker%20PM%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Roden D](https://www.ncbi.nlm.nih.gov/pubmed/?term=Roden%20D%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Stott DJ](https://www.ncbi.nlm.nih.gov/pubmed/?term=Stott%20DJ%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Völzke H](https://www.ncbi.nlm.nih.gov/pubmed/?term=V%C3%B6lzke%20H%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Benjamin EJ](https://www.ncbi.nlm.nih.gov/pubmed/?term=Benjamin%20EJ%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Delgado G](https://www.ncbi.nlm.nih.gov/pubmed/?term=Delgado%20G%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Ellinor P](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ellinor%20P%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Homuth G](https://www.ncbi.nlm.nih.gov/pubmed/?term=Homuth%20G%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Köttgen A](https://www.ncbi.nlm.nih.gov/pubmed/?term=K%C3%B6ttgen%20A%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Jukema JW](https://www.ncbi.nlm.nih.gov/pubmed/?term=Jukema%20JW%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Lubitz SA](https://www.ncbi.nlm.nih.gov/pubmed/?term=Lubitz%20SA%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Mora S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Mora%20S%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Rienstra M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Rienstra%20M%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Rotter JI](https://www.ncbi.nlm.nih.gov/pubmed/?term=Rotter%20JI%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Shoemaker MB](https://www.ncbi.nlm.nih.gov/pubmed/?term=Shoemaker%20MB%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Sotoodehnia N](https://www.ncbi.nlm.nih.gov/pubmed/?term=Sotoodehnia%20N%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Taylor KD](https://www.ncbi.nlm.nih.gov/pubmed/?term=Taylor%20KD%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [van der Harst P](https://www.ncbi.nlm.nih.gov/pubmed/?term=van%20der%20Harst%20P%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Albert CM](https://www.ncbi.nlm.nih.gov/pubmed/?term=Albert%20CM%5BAuthor%5D&cauthor=true&cauthor_uid=30673084), [Chasman DI](https://www.ncbi.nlm.nih.gov/pubmed/?term=Chasman%20DI%5BAuthor%5D&cauthor=true&cauthor_uid=30673084)2019Assessment of the relationship between genetic determinants of thyroid function and atrial fibrillation A Mendelian Randomisation Study [JAMA Cardiol.](https://www.ncbi.nlm.nih.gov/pubmed/30673084" \o "JAMA cardiology.) F1; 4(2):144-152. doi: 10.1001/jamacardio.2018.4635
105. Larsson SC,  [Allara E](https://www.ncbi.nlm.nih.gov/pubmed/?term=Allara%20E%5BAuthor%5D&cauthor=true&cauthor_uid=30702347)3, [Mason AM](https://www.ncbi.nlm.nih.gov/pubmed/?term=Mason%20AM%5BAuthor%5D&cauthor=true&cauthor_uid=30702347)3, [Michaëlsson K](https://www.ncbi.nlm.nih.gov/pubmed/?term=Micha%C3%ABlsson%20K%5BAuthor%5D&cauthor=true&cauthor_uid=30702347)1, [Burgess S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Burgess%20S%5BAuthor%5D&cauthor=true&cauthor_uid=30702347). 2019 Thyroid function and dysfunction in relation to 16 cardiovascular diseases. A Mendelian Randomisation Study. [Circ Genom Precis Med.](https://www.ncbi.nlm.nih.gov/pubmed/30702347" \o "Circulation. Genomic and precision medicine.)  Mar; 12(3):e002468. DOI: 10.1161/CIRCGEN.118.002468.
106. [Taylor PN](https://www.ncbi.nlm.nih.gov/pubmed/?term=Taylor%20PN%5BAuthor%5D&cauthor=true&cauthor_uid=26595101), [Richmond R](https://www.ncbi.nlm.nih.gov/pubmed/?term=Richmond%20R%5BAuthor%5D&cauthor=true&cauthor_uid=26595101), [Davies N](https://www.ncbi.nlm.nih.gov/pubmed/?term=Davies%20N%5BAuthor%5D&cauthor=true&cauthor_uid=26595101), [Sayers A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Sayers%20A%5BAuthor%5D&cauthor=true&cauthor_uid=26595101), [Stevenson K](https://www.ncbi.nlm.nih.gov/pubmed/?term=Stevenson%20K%5BAuthor%5D&cauthor=true&cauthor_uid=26595101), [Woltersdorf W](https://www.ncbi.nlm.nih.gov/pubmed/?term=Woltersdorf%20W%5BAuthor%5D&cauthor=true&cauthor_uid=26595101), [Taylor A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Taylor%20A%5BAuthor%5D&cauthor=true&cauthor_uid=26595101), [Groom A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Groom%20A%5BAuthor%5D&cauthor=true&cauthor_uid=26595101), [Northstone K](https://www.ncbi.nlm.nih.gov/pubmed/?term=Northstone%20K%5BAuthor%5D&cauthor=true&cauthor_uid=26595101), [Ring S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ring%20S%5BAuthor%5D&cauthor=true&cauthor_uid=26595101), [Okosieme O](https://www.ncbi.nlm.nih.gov/pubmed/?term=Okosieme%20O%5BAuthor%5D&cauthor=true&cauthor_uid=26595101), [Rees A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Rees%20A%5BAuthor%5D&cauthor=true&cauthor_uid=26595101), [Nitsch D](https://www.ncbi.nlm.nih.gov/pubmed/?term=Nitsch%20D%5BAuthor%5D&cauthor=true&cauthor_uid=26595101), [Williams GR](https://www.ncbi.nlm.nih.gov/pubmed/?term=Williams%20GR%5BAuthor%5D&cauthor=true&cauthor_uid=26595101), [Smith GD](https://www.ncbi.nlm.nih.gov/pubmed/?term=Smith%20GD%5BAuthor%5D&cauthor=true&cauthor_uid=26595101), [Gregory JW](https://www.ncbi.nlm.nih.gov/pubmed/?term=Gregory%20JW%5BAuthor%5D&cauthor=true&cauthor_uid=26595101), [Timpson NJ](https://www.ncbi.nlm.nih.gov/pubmed/?term=Timpson%20NJ%5BAuthor%5D&cauthor=true&cauthor_uid=26595101), [Tobias JH](https://www.ncbi.nlm.nih.gov/pubmed/?term=Tobias%20JH%5BAuthor%5D&cauthor=true&cauthor_uid=26595101), [Dayan CM](https://www.ncbi.nlm.nih.gov/pubmed/?term=Dayan%20CM%5BAuthor%5D&cauthor=true&cauthor_uid=26595101).2016 Paradoxical relationship between body mass index and thyroid hormone levels: a study using Mendelian randomisation [J Clin Endocrinol Metab.](https://www.ncbi.nlm.nih.gov/pubmed/26595101" \o "The Journal of clinical endocrinology and metabolism.)  Feb; 101(2):730-8. doi: 10.1210/jc.2015-3505
107. DeGroot LJ. Grave’s disease and the manifestations of thyrotoxicosis. [Updated 2015 Jul 11]. In Feingold KR, Anawalt B, Boyce a, et al., editors. Endotext [Internet]. South Dartmouth (MA):MDText.c0m, Inc.; 2000. Available from <https://www.ncbi.n1m.nih.gov/books/NBK285567/>
108. Stabouli S, Papakatsika S Kotsis V 2010 Hypothyroidism and hypertension. Expert Rev Cardiovasc Ther 8(11):1559-1565 DOI: 10.1586/erc.10.141
109. Ryödi E, Salmi J, Jaatnen P, Huhtala H, Saaristo R, Välimäki M, Auvinen A, Metso S. 2013 cardiovascular morbidity and mortality in surgically treated hyperthyroidism- a nation –wide cohort study with a long-term follow-up Clin Endocrinol 80(5) :743-750 DOI:10.1111/cen.12359
110. Gorka J, Taylor-Gjevre RM, Arnason T. 2013.Metabolic and clinical consequences of hyperthyroidism on bone density. International journal of endocrinology 2013,article ID 638727, 11pages DOI:10.1155/2013/638727
111. Fukui T, Hasegawa Y, Takenaka H. 2001 Hyperthyroid dementia: clinicoradiological findings and response to treatment J Neurol Sci. 184(1):81-88 DOI:10.1016/s0022-510x(00)00487-1
112. Duntas LH 2002. Thyroid disease and lipids. Thyroid 1294):287-293 DOI:10.1089/10507250252949405
113. Nikkilä EA, Kekki M 1972 Plasma triglyceride metabolism in thyroid disease. J Clin Invest 51(8):2103-2114 DOI: 10.1172/JCI107017
114. Prisant LM, Gujral JS, Mulloy AL 2007. Hyperthyroidism: a secondary cause of isolated hypertension J Cin Hypertension 8(8) 2103-2114. DOI:10.1111/j.1524-6175.2006.05180x
115. Dimitriadis GD, Raptis SA .2001 Thyroid hormone excess and glucose intolerance. Exp Clin Endocrinol Diabetes 109: Suppl 2 S225-239 DOI:10.1055/s-2001-18584
116. Sato A, Shirota,T, Shinoda T, Komiya I, Alawa T, Takemura Y, Yanada T 1995. Hyperuricemia in patients with hyperthyroidism due to Grave’s disease. Metabolism 44(2) 2017-2011 DOI:10.1016/0026-0495(95)90266-x
117. Anantarapu S, Vaikkahura S, Sachan A, Phaneendra BV, Suchitra MM, Reddy AP, Epuri S, Mukka A, Vemvakam D.2015 Effects of thyroid hormone replacement on glycated hemoglobin levels in non-diabetic subjects with overt hypothyroidism. Arch Endocrinol Metab. 59(6):495-500 DOI: 10.1590/2359-3997000000065
118. Andersen SL, Olsen J, Wu CS, Laurberg P. 2014 Spontaneous abortion, stillbirth and hyperthyroidism: A Danish population- based study. Eur Thyroid J 3(3):164-172 DOI:10.1159/000365101
119. Sahay RK, Sri Nagesh V 2012. Hypothyroidism in pregnancy. Indian J Endocrinol Metab. 16(3):364-370 DOI:10.4103/2230-8210.95667
120. Moeller LC, Führer D 2013.Thyroid hormone, thyroid hormone receptors, and cancer: a clinical perspective. Endocr Relat Cancer 20(2):R19-29 DOI:10.1530/ERC-12-0219
121. Theodossiou C, Schwarzenberger P 2000 Propylthiouracil reduces xenograft tumour growth in athymic nude mouse prostate cancer model. Am J Med Sci 319(2):96-99 DOI:10.1097/00000441-200002000-00005
122. Fernandez-Ruocco J, Gallego M, Rodriguez-de-Yurre A, Zayas-Arrabal J, Echeazarra L, Alquiza A, Fernández-López V, Rodriguez-Robledo JM, Britto O, Schleier Y, Sepulveda M, Oshiyama NF, Vila-Petroff M, Bassani RA, Medel EH, Casis O. 2019 High thyrotropin is critical for cardiac electrical remodelling and arrhythmia vulnerability in hypothyroidism. Thyroid 29(7):934-945 DOI: 10.1089/thy.2018.0709
123. Modell H, Cliff W, Michael J, McFarland J, Wenderoth MP, Wright A 2015 A physiologist’s view of homeostasis. Adv Physiol Educ39(4):259-266 doi:10.1152/advan.00107.2015
124. Andersen S, Pedersen KM, Bruun NH, Laurberg P 2002 Narrow individual variations in serum T4 and T3 in normal subjects; A clue to the understanding of subclinical thyroid disease. J Clin Endocrinol Metab87:1068-1072
125. Harris EK 1974 Effects of intra- and interindividual variation on the appropriate use of normal ranges. Clin Chem 20(12):1535-1542
126. Reinhard M, Erlandsen EJ, Randers E 2009 Biological variation of cystatin C and creatinine. Scand J Clin Lab Invest 69(8);831-836 DOI:10.3109/00365510903307947
127. Lazo M, Selvin E, Clark JM2008 Brief communication: Clinical implications of short-term variability in liver function test results. Ann Int Med 148(5)348-352 DOI: 10.7326/0003-4819-148-5-200803040-00005
128. Guldvog I, Reitsma LC, Johnsen L, Gibbs C, Carlsen E, Lende TH, Narvestad JK, Omdal R, Kvaløy JT, Hoff G, Bernklev T, Søiland H2019 Thyroidectomy versus medical management for euthyroid patients with Hashimoto disease and persisting symptoms: a randomized trial. Ann Int Med DOI:10.1089/ct.2019;31.178-181
129. Sheehan MT 2016 Biochemical testing of the thyroid: TSH is the best and, oftentimes, only test needed- a review for primary care. Clin Med Res14(2):83-92 DOI: 10.312/cmr.2016.1309
130. Dickinson S, Colagiuri S, Faramus E, Petocz P, Brand-Miller JC2002 Postprandial hyperglycemia and insulin sensitivity differ among lean young adults of different ethnicities. The Journal of Nutrition 132(9):2574-2579 DOI:10.1093/jn/132.9.2574
131. Felsenfeld AJ, Rodriguez M, Aguilera-Tejero E2007 Dynamics of parathyroid hormone secretion in health and secondary hyperparathyroidism. Clinical Journal of American Society of Nephrology 2(6) 1283-1305 DOI:10.2215/CJN.01520407
132. Grote Beverborg N, Verweij N, Jsbrand I, Klip T, van der Wal HH, Voors AA, van Veldhuisen DJ, Gansevoort RT, Bakker SJL, van der Harst P, van der Meer P2015 Erythropoietin in the general population: reference ranges and clinical, biochemical and genetic correlates. PLOS One DOI:10.1371/journal.pone.0125215
133. De Leo S, Lee SY, Braverman LE 2016 [Hyperthyroidism.](https://www-ncbi-nlm-nih-gov.proxy.kib.ki.se/pubmed/27038492)Lancet. Aug 27; 388(10047):906-918. DOI: 10.1016/S0140-6736(16)00278-6. Epub 2016 Mar 30
134. Lacroix A, Feelders RA, Stratakis CA, Nieman LK 2015 Cushing’s syndrome. Lancet 386(9996):913-927 DOI:10.1016/S0140-6736(14)61375-1
135. Beck-Pecozz P, Perani, L, Lania A. 2019 Jan 11.Thyrotropin- Secreting pituitary adenomas. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK278978/
136. Akirov A, Gimbel H, Grossman A, Shochat T, Shimon I 2017 Elevated TSH in adults treated for hypothyroidism is associated with increased mortality. Eur J Endocrinol 176(1):57-66 DOI:10.1530/EJE-16-0708
137. Bekkering G, Agoritsas T, Lytvyn L, Heen A, Feller M, Moutzouri E, Abdulazeem H, Aertgeerts B, Beecher D, Brito J, Farhoumand P, Singh Ospina N, Rodondi N, van Driel M, Wallace E, Snel M, Okwen P, Siemieniuk R, Vandvik P, Kuijpers T, VermandereM 2019 Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. BMJ 365:12006. DOI:[10.1136/bmj.12006](https://doi.org/10.1136/bmj.l2006)

There were no conflicts of interest for any of the authors, and none of them received any funding for this work.

Corresponding author- Dr Stephen Paul Fitzgerald, The Department of General Medicine, The Royal Adelaide Hospital, Port Road, Adelaide, South Australia.