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

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**Abstract**

**Background:** Whereas other endocrine dysfunctions are not defined on the basis of levels of controlling hormones, the assessment of thyroid function is based on levels of the controlling 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), 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 November 2018, examining correlations of thyroid hormones and TSH with clinical parameters was performed. References of retrieved articles were searched. 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 32 articles. There was consistent high quality evidence that atrial fibrillation, low bone density, frailty, death, cognition, features of the metabolic syndrome and steatohepatitis were significantly more strongly associated with FT4 rather than TSH levels. We were unable to find any consistent evidence suggesting TSH levels correlated better than FT4 levels with any clinical parameter. T3 and FT3 levels were correlated with clinical parameters as strongly as FT4 levels, but there was less literature regarding these correlations available, and some of the FT3/T3 correlations appeared to be due to reverse causation.

**Conclusions**. Thyroid hormone levels have stronger correlations with clinical parameters than do TSH levels. The previously emphasized correlations of TSH levels can be explained by the strong negative population correlation between thyroid hormones and TSH.

The current conception of subclinical thyroid dysfunction is flawed. Any borderline thyroid dysfunction would be better defined in terms of thyroid hormone, rather than TSH, levels.

TSH levels remain sensitive screening tests for overt thyroid dysfunction, but there is no reason to otherwise determine thyroid function or thyroid hormone replacement on the basis of TSH levels.

The conclusions above are consonant with recent advances in the understanding of thyroid hormone regulation and have implications for trials of therapies for borderline thyroid dysfunction.

**Introduction**

Subclinical thyroid dysfunction is defined as the combination of abnormal thyroid stimulation hormone (TSH) levels with normal thyroid hormone levels [1-5]. Subclinical thyroid dysfunction, so defined, is common, and comprises most cases of thyroid dysfunction with a population prevalence of approximately 5% [1], increasing to 15% to 20% in the elderly [5] 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 [1-5]. Therefore, despite the lack of convincing evidence of significant benefit, treatment for subclinical thyroid dysfunction has been recommended in certain circumstances [2, 5-8].

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 [9, 10]. Rather, 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 [11] or parathyroid hormone levels [12] respectively. ACTH levels, though helpful in diagnosing adrenal autonomy are not considered diagnostic for Cushing’s syndrome [13]. 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 [11-13]. We therefore aimed in this work 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 [14, 15] we expected to find correlations between both TSH and FT4 with the clinical features of thyroid dysfunction. We further reasoned however, that if the clinical features correlated better with TSH levels the current definition of subclinical thyroid dysfunction would be supported, but, if the clinical features correlated better with thyroid hormone levels, the current definition of subclinical thyroid dysfunction would warrant review. In this latter circumstance the previously noted correlations of clinical features with TSH levels could be attributed to the strong negative population correlation between FT4 and TSH.

METHOD

Search strategy

Up to 26 November 2018 a systematic search was performed of PubMed/MEDLINE using the following terms: thyroxine /T4, free thyroxine/ FT4, triiodothyronine/T3, free triiodothyronine/FT3, TSH/thyroid stimulation hormone and subclinical. No restrictions were placed on language, country, or publication date. 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 relevant articles were so found the reference lists of these articles were examined for further relevant articles. If repeated study was made of the same cohort the latest only was included. The literature search was conducted independently by two of the authors (SPF and HF), and the included and excluded articles were agreed on by consensus with reference to the criteria described in the next section.

Study selection and data extraction

Studies reporting on FT4, T3/FT3, TSH and subclinical thyroid dysfunction were included. Reports were excluded if the studied population was less than 100 individuals. Review articles, editorials, and meeting abstracts were also excluded.

The literature was first examined to confirm the previously reported general trends of association between clinical parameters and thyroid status.

We then specifically examined studies that reported correlations of clinical parameters with both TSH and thyroid hormone (FT4 +/- FT3/T3) levels. The following information was extracted from each such study: first author, country, number of individuals, sex, age intervals, nature of the study, clinical parameter and any correlations with thyroid hormones and/or TSH, (including the statistical techniques and degrees of significance of any correlations).

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. Papers 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 [16].

Statistical Analysis

We initially performed a qualitative assessment of the literature identifying the general trends as to correlations between clinical parameters and measures of thyroid function.

We then examined the summaries of the articles which addressed the specific question of this work, as per the abstracts, summing results and conclusions as to whether they indicated that levels of thyroid hormones or TSH correlated better with clinical parameters.

Then, again addressing the specific question of this work with greater mathematical rigour, 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 are 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 95% 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.

All modelling was performed by the glmer [17] function in the lme4 package in R [18], and all code is available at <https://github.com/jonotuke/TSH_2019>

RESULTS

We found an extensive literature addressing thyroid function and various clinical features (Figure 1(? Diag of literature search)). We found that though there was general consistency of the data, the findings were not unanimous. In general, consistent with prior work [5], atrial fibrillation (AF)[19-24], osteoporosis [25-29], and cancer [30-32] correlated with higher thyroid function defined using TSH and/or thyroid hormone levels, across and beyond the normal range, and steatohepatitis [33-35] and the features of the metabolic syndrome [36-49] correlated with lower thyroid function . One study [47] suggested the metabolic syndrome is associated with higher 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 [50-55], frailty[56-59], total /cardiovascular mortality[58-67] and heart disease (apart from atrial fibrillation)[50, 63-65, 68, 69].

There were many series finding the above correlations in the context of subclinical thyroid dysfunction. Many of these studies [19, 24, 39, 40, 50, 63, 64, 67-69] however did not address the relative associations with TSH and FT4/T3 levels. We also found evidence citing associations with subclinical thyroid dysfunction but not with TSH [50]. We found one study that looked at FT4 alone [39], this study finding a correlation, and another study [48] finding correlations in opposite directions for FT4 and FT3, with TSH not being examined.

We found that in general correlations with FT4 and TSH were congruent, i.e. if a parameter correlated with a high FT4 it would tend to correlate with a low TSH and vice versa. Correlations with T3 were less congruent in terms of correlations with TSH and FT4 when considering metabolic syndrome, frailty and mortality.

The focus of our study was the relative correlation of clinical states with thyroid hormones and TSH. In the end we identified 32 studies which addressed this question. 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. We found one meta-analysis restricted to atrial fibrillation [21].We found 12 studies [20, 27, 28, 31, 33, 34, 37, 43, 45, 54, 58, 59] that examined correlations with FT4, T3 (free or total) and TSH and a further 20 studies [22, 24, 26, 29, 30, 32, 35, 36, 38, 41, 42, 44, 46, 52, 56, 57, 60-62, 66] that examined correlations with FT4 and TSH.

These 32 studies included cross-sectional and prospective cohort studies, diverse populations and both sexes. They were contemporary and of high quality (Table 1). The study populations comprised strictly euthyroid subjects [20, 24, 27, 34, 37, 41, 42, 44, 45, 52, 61, 62, 66] subjects either euthyroid or with subclinical thyroid dysfunction[ 26, 28-30, 36, 38, 43, 54, 56, 57, 58, 60], and subjects euthyroid or with subclinical/overt thyroid dysfunction [22, 31-33, 35, 46, 59].

We found no study summary as per the abstract indicating superior correlations between TSH, rather than thyroid hormones, with the clinical parameters AF, osteoporosis, cancer, steatohepatitis or cognitive decline. The one study that in the text did show significant correlations between TSH rather than FT4, and AF [23], showed the p values for the correlations with FT4 to be borderline at 0.05 and 0.06, and so the association with AF was described as being with ‘high thyroid function’, rather than preferentially with TSH. This study was not included in our analysis because a later analysis of the same cohort was performed [24], this analysis showing a superior correlation of AF with FT4 levels than with TSH levels. We did not find a study conclusion indicating that the metabolic syndrome or its individual components in general, to be better correlated with TSH rather than thyroid hormones. One conclusion [43] implied that though levels of FT4 and TSH were both strongly associated with BMI, TSH levels were more associated with obesity than FT4. Similarly there was no paper conclusion indicating superior correlation with TSH for frailty, mortality, dementia or other cardiac disease.

On the other hand we found many study summaries indicating superior correlations with levels of thyroid hormones as compared with TSH covering atrial fibrillation[ 22,24], osteoporosis [26, 27, 29], cancer [30-32], metabolic syndrome [33,36,], obesity [41,42], dementia, [52, 54], frailty, [56, 57] mortality[58, 60], and sudden cardiac death [66] . Table 2 provides a summary of the studies indicating the superior association of clinical parameters with FT4 levels. In general, in the abstracts, the superiority of the correlations with thyroid hormones was reported explicitly; occasionally [22, 31, 58, 66] it was implied.

Tellingly, we found evidence of associations of clinical parameters with FT4 in the absence of an association with subclinical thyroid dysfunction *per se* as currently diagnosed [38, 54, 60, 66]. One of these papers [38] also showed correlations with TSH.

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 and that T3 and FT3 were interchangeable. Although T3/FT3 levels seemed to correlate 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 [45], or were in the same direction as simultaneous correlations with TSH levels [34, 45]. These results were suggestive of reverse causation (see Discussion). Overall, T3 measurement added little to the assessment based on FT4 levels. We found FT3 and T3 levels correlated similarly with clinical parameters.

Formal meta-analysis of our data confirmed the superiority of correlations with thyroid hormone levels (FT4, T3 and FT3) as compared to TSH levels. The results of the statistical modelling of the significance of the papers' analysis were

1. A random intercept for paper and cohort within paper was necessary, but not for type of analysis or complexity of model.

2. There is a statistically significant relationship between thyroid test and a paper's conclusions at the 5% significance level.

3. Thyroid hormones were significantly more likely than TSH to have a positive association with a clinical parameter. (Figure 2)

4. System, number of subjects, and number of covariates are not significant predictors are the significance of a paper's result. As the number of subjects increased the superior correlations with thyroid hormones became more apparent (Figure 3)

5. The significant difference between thyroid hormones and TSH as predictors of disease state in the papers was also replicated when only a randomly selected representative result was used.

DISCUSSION

We believe this is the first systematic review studying TSH and thyroid hormone correlations with various features of subclinical thyroid dysfunction. The results indicated that thyroid hormone levels correlate better with clinical features than TSH levels. Our formal analyses have indicated that our findings are robust. We were unable to find any means by which thyroid hormones could not be regarded a better measure of thyroid effect than TSH. The fact that the semi-formal and formal quantitative analyses accord serves as a reassurance that the individual conclusions from the collection of studies has not been distorted by any mathematical manipulation in the meta-analysis.

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 FT4 levels become the main determining parameter in the diagnosis of borderline thyroid function.

This is not to say 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 is generally not 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 [29, 70], 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.

Our data was less consistent in terms of congruence between TSH, FT4 and T3/FT3 with the consideration of clinical parameters usually associated with lower thyroid function as compared with higher thyroid function.

The variability of correlations between thyroid hormones/TSH and features of the metabolic syndrome may be because of the complexity of the metabolic syndrome, as well as differences in study populations, in the categorization of thyroid function, and in the factors included in the adjustments in the analyses [47].

There may also be reverse causation [33, 36, 47,71-75], which may affect correlations with TSH and T3/FT3 more than correlations with FT4. TSH enhanced secretion of FT3 [76] might affect the lipid profile adversely [47, 48]. Obesity and insulin resistance may lead to increases in TSH and thyroid hormones in some populations, perhaps as a thermogenic response [72], to the increased weight itself [73] or to caloric intake [71]. Whatever the cause of such reverse causality, in such populations the associations between clinical features and high TSH would be artifactually enhanced whilst the association with low FT4 would be attenuated.

We are not aware of any factors that would so 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 [77], should again favour an association with TSH rather than FT4. The sensitivity of T3 levels to the sick euthyroid state may also explain some of the correlations with T3. In particular, mortality and frailty may be associated with low T3 levels via reverse causation. As the TSH would be expected to be low in this situation one might expect a discrepant correlations between clinical parameters, and T3 (and possibly FT4) and TSH.

Because some of the correlations of T3 with clinical parameters may have been driven by the reverse causation, particularly via the sick euthyroid state, and because of the greater consistency of the correlations with FT4, it seems that FT4 provides more reliable correlations with the clinical state than both T3 and TSH in terms of identifying a causal relationship or a potential therapeutic target. The correlations with T3 are equally mathematically valid but, in some circumstances, appear to be, markers or consequences of the clinical state, rather than identifying a therapeutic target.

The association of FT4 levels, rather than TSH levels, with clinical features has been noted by some authors of the cited papers [20-22, 24, 26, 29, 32, 33, 35-37, 38, 41, 42, 47, 52, 56, 60, 61, 66]. In particular the meta-analysis regarding atrial fibrillation found an association with FT4 but not with TSH [21]. 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’ [22], or ‘tissue’ [36, 42] 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 [20, 30, 35, 36, 56, 61, 66], to a significant difference between pituitary and peripheral sensitivity to FT4 [21, 35, 41, 37, 52], or to statistical/other factors [26, 29, 33, 38, 47].

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 [14, 15]. 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 [32, 56] 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 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 [5, 20], 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 [5, 20, 78]. 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 [79].

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, rather than vice versa as is 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. 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, the greater sensitivity of TSH as compared to FT4 with changes in thyroid function, and the strong negative population correlation between FT4 and TSH [14, 15].

The current consensus, despite evidence to the contrary, still confirms the set point hypothesis of thyroid regulation [80]. This hypothesis proposes that each individual has a set point or target, ideal level of a given parameter defended by physiological mechanisms [81]. Therefore, according to this hypothesis, individuals can have FT4 (and TSH) levels within the population normal range that are nevertheless abnormal for those individuals, and in these circumstances thyroid dysfunction, though masked, is present [82, 83]. It is also believed that on account of the different ways TSH and FT4 levels change with any change in thyroid function, TSH levels are the more sensitive marker of thyroid function [4, 84]. By extension an abnormal TSH level in the absence of abnormalities in the levels of FT4 or FT3 has come to imply that there is an abnormality of thyroid function, albeit an abnormality more subtle than that of overt thyroid dysfunction.

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 [80, 82]. This reasoning represents a misreading of the work [85] that purportedly demonstrates this proposition. In this work it was shown that if there is greater inter-individual variation than intra-individual variation of a given parameter, the population normal range can be an unreliable guide to individual normality. That is, the work relies on the premise of there being an individual normal level or set point. The reasoning is by definition not applicable in the absence of a set point, and cannot be used to indicate the presence of a set point. Illustrative empiric examples abound (e.g. serum creatinine and alkaline phosphatase exhibit greater inter-individual variation than intra-individual variation [86, 87] but do not have set points [81]).

The hypothesis of there being an individual thyroid set point has also been reported as being supported 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’[80]. Contradicting this observation 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 patients, have few if any symptoms [1, 2], i.e. their abnormality is indeed ‘subclinical’. Furthermore any residual symptoms in treated patients may well be due to other factors rather than to thyroid replacement not achieving individual set points. Indeed, one study has suggested that thyroid surgery to remove the offending source of autoimmune inflammation may be helpful in this regard [88].

The fact that TSH levels reliably predict FT4 values within the normal range and that the correlation between TSH and FT4 in the population is negative is consistent with the relationships between other parameters and their controlling hormones [89-91]. It is this negative relationship, a function of the population variability of thyroid versus pituitary sensitivity [92], again seen in this review [26-29, 34, 59], which is inconsistent with a set point model of regulation [89].The negative TSH/FT4 population relationship is consistent with a balance point model of regulation, this model of regulation rendering redundant the need to seek further explanations for the superior correlation of clinical features with FT4 levels as compared with TSH levels. Other authors investigating yet another parameter (body temperature) using different methods have come to similar conclusions [93] regarding the existence of a set point.

The set point hypothesis has still further problems, including the difficulty of determining the set point [80], and the difficulty of isolating the tissue substrate of set point functioning [81]. All of this supports the contemporary view of homeostatic regulation ‘that there is no basis for invoking a central controller that purposefully coordinates responses to attain a desired set point....’[94].

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 with baseline thyroid function towards the upper end of the range must have a greater decline in thyroid function to become hypothyroid as compared with individuals with baseline function at the lower end of the range because this reflects the true physiology; they are starting at a ‘slightly hyperthyroid’ point. These former individuals with a small drop in FT4 levels are not becoming ‘individually’ hypothyroid, but are, in fact becoming more ‘normal’. They do not need to become ‘more hypothyroid’ [82] than other individuals so as to have hormone levels fall out of the normal range and enable diagnosis. Conversely these individuals with upper normal range levels of FT4 need little disturbance upwards to become truly, overtly hyperthyroid.

By the same logic, there is no imperative with thyroid replacement therapy to attempt to recreate the exact thyroid status of an individual prior to any thyroid disease or surgery that led to the need for such replacement therapy.

The concept that TSH levels are more sensitive indicators than FT4 levels in the context of changes in thyroid function, (based on changes in TSH and FT4 levels), and therefore are better indicators of thyroid function [4, 80, 82, 84], relies on the existence of a set point from which a change is important. It also depends on whether or not a log scale is employed, and whether TSH is generating, or responding to, any change to FT4 levels. In normal individuals, changes to TSH and thyroid hormones are positively correlated [82], indicating that physiologically, any increase in TSH may be driving an increase in thyroid hormone levels (away from equilibrium), rather than responding to a drop in thyroid hormone levels and restoring equilibrium i.e. one cannot even surely predict the direction of any change in thyroid function in the normal range by reference to the change in the TSH level.

Regardless of the above, whether or not TSH or thyroid hormones are the more sensitive indicator of a change to thyroid function, does not necessarily indicate the better indicator of abnormal thyroid function. There are proportionally greater changes to levels of the controlling hormones insulin [95], parathyroid hormone [96] and erythropoietin [97] 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 [11, 12].

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 [14, 15]. This is due merely to the fact that nearly all overt thyroid dysfunction is primary rather than secondary [98]. 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 secondary, i.e. be due to a disorder of ACTH regulation [99]. The fact that TSH levels are thereby very sensitive screening tests for thyroid dysfunction [84] does not imply TSH levels are very specific, i.e. that an abnormal TSH level implies thyroid dysfunction. An abnormal TSH level in the presence of normal levels of thyroid hormones more likely indicates a false-positive TSH result in terms of tissue or organ hyper/hypo-thyroidism.

In summary there is matching theoretical and empiric evidence 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. 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. TSH levels remain good screening tests for overt thyroid dysfunction, but this systematic review has shown that to determine thyroid status within and around the normal range, it is theoretically and empirically more sound to rely on the level of FT4. This applies in principle for all diagnostic, therapeutic and monitoring considerations.

This work however addressed diagnosis alone; randomized trials are necessary to determine whether additional considerations apply in the context of thyroid treatments. One study [100] has reported that TSH levels are important in the treatment of thyroid insufficiency, 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 planning and interpretation 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 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.

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 [101].

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. A change in the diagnostic criteria of borderline normal/subclinical thyroid dysfunction appears indicated.

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**Table 1** Description and quality assessment of included studies

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| --- | --- | --- | --- | --- |
| Author/year | Parameter | Cohort Study | Population | NOS |
| Gammage 2007[30] | Atrial Fibrillation | Cross-section | UK community  n=5860; age72(65-98);female 51% | 9/9 |
| Cappola 2015[28] |  | Prospective | US community  N=2843; age 75±5; female56% | 9/9 |
| Chaker [32] |  | Prospective | Dutch community n = 9166, age 65± 9.9, female 57% |  |
| Chaker 2016 [74] | Sudden cardiac death | Prospective | Dutch community age≥45  n=10,318;age 65±10;female 57% | 9/9 |
| van de Ven 2014[69] | Mortality | Prospective | Dutch community  n=5816; age 56±18;female 53% | 9/9 |
| Inoue 2016[70] |  | Prospective | U.S. community  n=5257; age 46±17 | 8/9 |
| Yeap 2013 [68] |  | Prospective | Australian community men  n=3885; age 77±3 | 9/9 |
| Chan [38] | Cancer | Prospective | Australian community n=3649;age 51±15; female 56% | 8/9 |
| Tosovic [39] |  | Prospective | Swedish community, n=17035,women born 1932-1950, | 9/9 |
| Khan [40] |  | Prospective | Dutch community;n=10318 ;age 61 (57-68);female 57% | 8/9 |
| van den Beld 2005 [66] | Frailty | Prospective+ cross-section | Dutch community men age≥73 years  n=403; age 78 (73-94) | 9/9 |
| Yeap 2012 [64] |  | Cross-section | Australian community men  n=3943; age 75±4 | 8/9 |
| Bano 2018 [65] |  | Prospective | Dutch community  n=9419 ;age 65±10;female 57% | 9/9 |
| Gussekloo [67] |  | Prospective | Dutch community;n=558;all age 85;female 66% | 8/9 |
| Volpato 2002 [60] | Dementia | Prospective | U.S. community women age≥ 65  n=464;age 77± 0.6 | 8/9 |
| de Jong 2006 [62] |  | Cross-section | Dutch community  n=489, age 73±8; female 48% | 9/9 |
| Roef 2011 [35] | osteoporosis | Cross-section | Belgian community , men age 25-45  n=677;age 34±6 | 9/9 |
| van der Deure 2008 [37] |  | Cross-section | Dutch community age≥55  n=1151;age 69±8;female 58% | 9/9 |
| Murphy 2010 [36] |  | Cross-section | European post-menopausal women;  n=1278; age 68 ±7 | 7/9 |
| van Rijn 2014 [34] |  | Cross-section | Dutch post-menopausal women  n=1477; age 50±2 | 9/9 |
| Makepeace 2008 [50] | Obesity/Metabolic syndrome | Cross-section | Australian community  n=1853;age 49±17;female 47% | 9/9 |
| Mehran 2017[44] |  | Prospective | Iran community  n=2393;age38±13;female 61% | 9/9 |
| Shon 2007 [49] |  | Cross-section | Korean women Medical Centre-primary health screening; n=1572; age 46±11 |  |
| Roos 2007 [45] |  | Cross-section | Dutch community  n=1581; age 48 ±12; female 46% | 9/9 |
| Jun 2017 [53] |  | Cross-section | Korean medical centre attendees  n=6235;age 50±8;female 42% | 9/9 |
| Xu 2011[42] |  | Cross-section | Chinese community  n=878;age 72± 4; female 37% | 9/9 |
| Bano 2016 [43] |  | Prospective | Dutch community  n=9640;age 65±10; female 57% | 9/9 |
| Ittermann 2012 [41] |  | Cross-section | German community; n=3661; female 48%,age 48±16;male age 51±16 | 9/9 |
| Knudsen [51] |  | Cross section | Danish community=4082 ‘preponderance of women” | 9/9 |
| Oh [54] |  |  | Korean community; n=4275;age 49; female 50% | 9/9 |
| G- Garcia [46] |  | Cross-section | Mexican community n=3033;age 42±10;female 51% | 9/9 |
| Chaker[52] | diabetes | Prospective | Dutch community; n=8542;age 65±10;female 58% | 9/9 |

NOS, adapted Newcastle-Ottawa quality assessment scale (the higher number out of 9, the better study). \*NOS not applied since a meta-analysis.

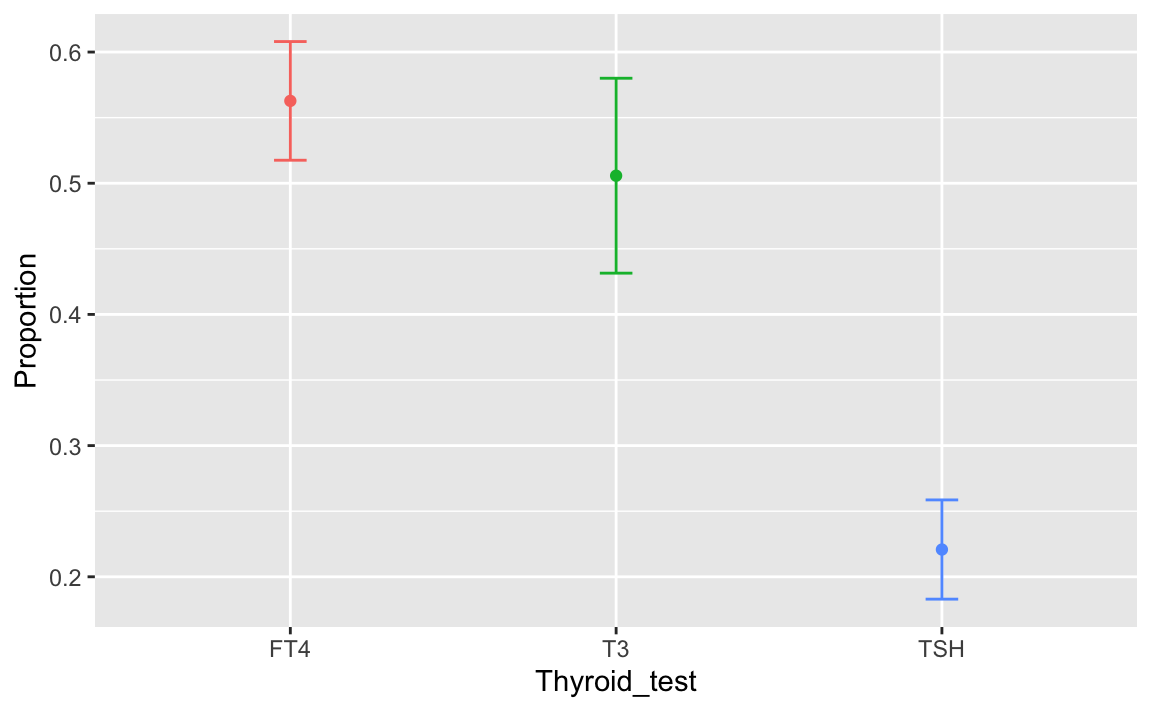


Figure 2- overall results

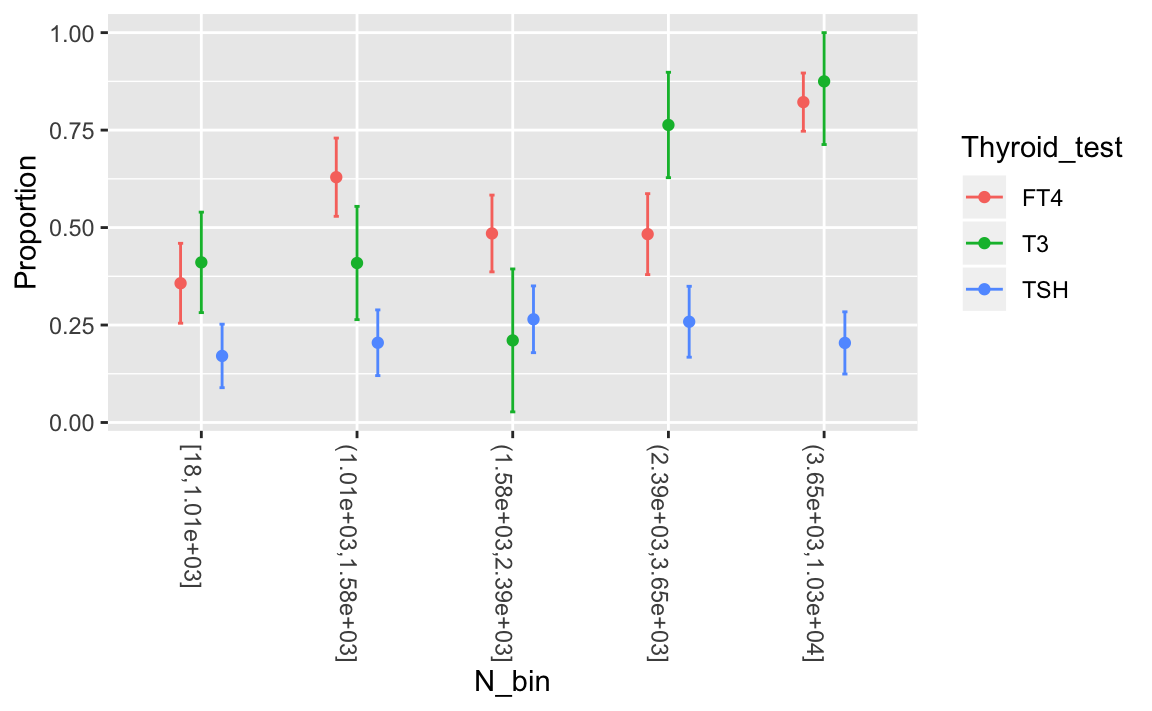


Figure 3- correlations of clinical parameters with FT4/T3/ TSH, with increasing n