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

**Abstract**

**Background:** The assessment of thyroid function is based on TSH levels. Subclinical thyroid dysfunction is defined as the combination of normal levels of thyroid hormones with abnormal levels of TSH. Evidence has emerged contradicting the set-point model of thyroid regulation which underlies the concept of TSH based subclinical thyroid dysfunction. 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 33 articles. There was consistent high quality evidence that atrial fibrillation, low bone density, frailty, death, cognition, features of the metabolic syndrome and steatohepatitis were 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 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 clinical parameters with TSH levels are due to the strong negative population correlation between thyroid hormones and TSH.

The concept of subclinical thyroid dysfunction based on TSH levels is not valid. Any borderline thyroid dysfunction would be better defined in terms of thyroid hormone 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.

**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 whether or not there is a disturbance [11-13].

The anomalous situation appears to have arisen in the case of thyroid function because of the strong negative population correlation between thyroid hormones and TSH levels [14, 15]. This correlation is such that determining the TSH level is a very good screening test for overt thyroid dysfunction.

Furthermore current consensus still confirms the set point hypothesis of thyroid regulation [16]. This hypothesis proposes that each individual has a set point or target, ideal level of a given parameter defended by physiological mechanisms [17]. Therefore, for the parameter FT4, 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 [18,19 ]. 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 [4,20]. 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, this concept creating a pleasing concordance with the relationships in overt thyroid dysfunction.

Our previous work, has demonstrated that the negative population correlation between FT4 and TSH within the normal range of FT4 is merely a function of the population variability of thyroid versus pituitary sensitivity [21 ] and furthermore provides evidence against the existence of a set point for thyroid hormones [22]. We have analogously provided evidence that set points also do not exist for other physiological parameters [23,24], and have argued that the evidence therefore suggests that, in general, regulation and homeostasis are not based on set points. Other authors using different methods have come to similar conclusions [25] .

Whereas the current model and practice emphasises the importance of TSH levels in the diagnosis of subclinical thyroid dysfunction, a model of thyroid regulation not emphasising the importance of TSH levels would imply that thyroid hormone levels alone provide a better indicator of the physiological state.

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 correlation between FT4 and TSH 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 models of thyroid regulation and subclinical thyroid dysfunction would be supported, but, if the clinical features correlated better with thyroid hormone levels, further doubt would be cast on, the validity of the set point hypothesis of thyroid regulation, and the current TSH-based conception of subclinical thyroid dysfunction. In this latter circumstance the previously noted correlations of clinical features with TSH levels would merely reflect 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, triiodothyronine/T3/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 free thyroxine/FT4, T3, TSH/thyroid stimulation hormone and subclinical thyroid dysfunction were included. Reports were excluded if the studied population was duplicated or 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 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 [26].

Statistical Analysis

We initially performed a qualitative analysis, examining the summaries of the articles as per the abstracts, as to any differences between levels of thyroid hormones and TSH in terms of correlations with clinical parameters.

We also performed a formal mathematical analysis. From articles which reported clinical or pathological correlations with both thyroid hormones and TSH we examined all reported correlations (Excel Sheet- Supplement).

The relative strengths of FT4 levels, T3 levels, and TSH levels in terms of correlation with clinical and pathological states were determined by.......... We examined the studies to check that studies supporting correlations with thyroid hormones or TSH did not differ by number of subjects or degree of any insignificance..........

Etc...

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)[27-32], osteoporosis [33-37], and cancer [38-40] correlated with higher thyroid function defined using TSH and/or thyroid hormone levels, across and beyond the normal range ], and steatohepatitis [41-43] and the features of the metabolic syndrome [44-57] 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 [58-63], frailty[64-67], total /cardiovascular mortality[66-75] and heart disease (apart from atrial fibrillation)[58,71-73 , 76, 77].

There were many series finding the above correlations in the context of subclinical thyroid dysfunction. Many of these studies [27, 32, 47, 48, 58, 71, 72, 75-77] 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 [58]. We found one study that looked at FT4 alone [47], this study finding a correlation, and another study [56] 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 33 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 [ 29 ].We found 13 studies [28, 35, 36, 39, 41, 42, 45, 51, 53, 55, 62, 66, 67] that examined correlations with FT4, T3 (free or total) and TSH and a further 20 studies [30, 32, 34, 37, 38, 40, 43, 44, 46, 49, 50, 52, 54, 60, 64, 65, 68-70, 74] that examined correlations with FT4 and TSH.

These 33 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 [28, 32, 35, 42, 45, 49, 50, 52, 53, 55, 60, 69, 70,74] subjects either euthyroid or with subclinical thyroid dysfunction[ 34, 36 -38, 44, 46, 51, 62, 64, 65, 66, 68], and subjects euthyroid or with subclinical/overt thyroid dysfunction [30, 39-41, 43, 54, 67].

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 [31], 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 [32], 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 [51] indicated that TSH was 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[ 30,32], osteoporosis [34, 35, 37], cancer [39-40], metabolic syndrome [41,44,], obesity [49,50], dementia, [60,62], frailty, [64, 65] mortality[66, 68], and sudden cardiac death [74] . 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 [30,39, 66, 74] 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 [46, 62, 68, 74]. One of these papers [46] also showed correlations with TSH.

Formal meta-analysis of our data confirmed the superiority of correlations with thyroid hormone levels (FT4, T3 and FT3) as compared to TSH levels to be overwhelming..... We found no evidence of bias to suggest that the evidence favouring the correlations with thyroid hormones was misleading. In particular there was no evidence the above correlations were only to be found in smaller 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. 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 [53,55], or were in the same direction as simultaneous correlations with TSH levels [42,53]. These results were suggestive of reverse causation (see Discussion). Overall, T3 measurement added little to the assessment based on FT4 levels ?????

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. The previously emphasized correlations of clinical parameters with TSH therefore are secondary to the strong negative population correlation between thyroid hormones (chiefly FT4) and TSH. It would therefore appear that clinical features in general result from the exposure of tissues to the combination of thyroid hormones. 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.

Our formal analyses have indicated that our findings are robust. The fact that the quantitative analyses accord with the qualitative analysis serves as a reassurance that the gestalt of the collection of studies has not been distorted by any mathematical manipulation in the meta-analysis.

,whilst providing the empirical conclusion that the assessment of thyroid function in terms of clinical features is better based on thyroid hormone levels than on TSH levels also indicating that the set point model of regulation does not apply to the regulation of thyroid hormones [22]. .

The conventional theoretical basis for the TSH based definitions of thyroid disease is fragile. 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 [16, 18]. This reasoning represents a misreading of the work [78] 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 [79, 80]) but do not have set points [17].

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 hypothyroidism still have significant thyroid associated complaints’[16]. 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 [81].

still further and the difficulty of .

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, 16, 18, 20], relies on the existence of a set point, and 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 [18], indicating that physiologically, an 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 [82 ], parathyroid hormone [83] and erythropoietin [84] 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].

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’ [18] 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.

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 not relevant.

Our data was less consistent with the consideration of clinical parameters associated with lower thyroid function as compared with higher thyroid function. This variability with features of lower thyroid function 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 [55].

In these circumstances there may also be reverse causation [41, 44, 55, 85-89], which may affect correlations with TSH and T3/FT3 more than correlations with FT4. Obesity and insulin resistance may lead to increases in TSH and FT4/FT3 in some populations, perhaps as a thermogenic response [86] to the increased weight itself [87] or to caloric intake [85]. Again, the concept of a set point has been invoked such that obesity resets the ‘central thyrostat’[89], Whatever the cause of such reverse causality, in such populations the associations between clinical features and high TSH would be enhanced whilst the association with low FT4 would be attenuated. TSH enhanced secretion of FT3 [90] might also affect the lipid profile adversely [55, 56].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 [91], 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 fracture (via falls), mortality and frailty may be associated with low T3 levels via reverse causation.

It has been suggested that in elderly individuals the TSH may not be so suppressed by any given rise in FT4 [40, 64] 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).

It remains possible, 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 [37,92], 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.

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.

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 [28- 30, 32, 34, 37, 40, 41, 43-45, 46, 49, 50, 55, 60, 64, 68, 69, 74]. In particular the meta-analysis regarding atrial fibrillation found an association with FT4 but not with TSH [29]. 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’ [30], or ‘tissue’ [44, 50] thyroid status. Our study strengthens and generalizes these propositions.

The superior correlation of clinical parameters with FT4 as compared to TSH levels has however more often been attributed to a putative disturbance of set point physiology [28, 38, 43, 44, 64, 69, 74], to a significant difference between pituitary and peripheral sensitivity to FT4 [29, 43, 49, 45, 60], or to statistical/other factors [34, 37, 41, 46, 55]. Such explanations are denied by, respectively, the evidence that thyroid set points do not exist, 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.

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 [23, 24]. It is this negative relationship, which was again seen in this review [34-37, 42, 67], which is inconsistent with a set point model of regulation [22]. This 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.

The fact that TSH levels reliably identify overt thyroid dysfunction can be explained by the continuation of the negative population relationship between TSH and FT4 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 [93]. This situation differs from other endocrine pathology, for example Cushing’s syndrome, whereby the parameter abnormality is likely to be due to a disorder of the parameter controlling factor [94]. The fact that TSH levels are very sensitive screening tests for overt thyroid dysfunction [20] 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 indicating thyroid dysfunction.

Furthermore, the evidence 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, 28], 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, 28, 95]. 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 [96].

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, in the absence of any evidence to the contrary, the TSH level not be a determinant at all.

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 are result in different senses of wellbeing.

In summary there is matching theoretical and empiric evidence suggesting that the concept of subclinical thyroid dysfunction is flawed, and that even 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. 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, and that if subtle improvements are to be sought within and at the edges of the normal range, FT4, and possibly FT3 levels, may be better targets.

The appreciation of these principles 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.

REFERENCES

1. Wilson S, Parle JV, Roberts LM, Roalfe AK, Hobbs FDR, Clark P, Sheppard MC, Gammage MD Pattison HM, Franklyn JA. Prevalence of subclinical thyroid dysfunction and its relation to socioeconomic deprivation in the elderly: a community –based cross-sectional survey. J Clin Endocrinol Metab 2006;91(12):4809-4816 DOI: 10.1210/jc.2006-1557 (definition + prevalence)
2. Biondi B, Cooper DS. Subclinical hyperthyroidism. N Engl J Med 2018; 378:2411-9 DOI: 10.1056/NEJMcp1709318( definition-Adverse outcomes – Ix/treatment recommended)
3. Palacios SS, Pascual-Corrales E, Galofre JC. Management of subclinical hyperthyroidism. Int J Endocrinol Metab. 2012;10(2):490-496 DOI:10.5812/ijem.3447(definition subclinical/adverse effects /investigate and treat)
4. Fatourechi V. Subclinical hypothyroidism: an update for primary care physicians Mayo Clin Proc.2009;84(1):65-71 DOI:10.1016/S0025-6196(11)60809-4 (TSH v sensitive as compared with thyroid hormones – necessary for diagnosis + adverse effects need to treat + definition subclinical)
5. Taylor PN, Razvi S, Pearce SH, Dayan CM.A review of the clinical consequences of variation in thyroid function within the reference range. J Clin Endocrinol Metab 2013;98(9)3562-3571 DOI:10.1210/jc.2013-1315
6. Orgiazzi J. Does normal TSH mean euthyroidism in L-T4 treatment? Clinical Thyroidology 2016 DOI:10.1089/ct.2016;28.325-328 (Treatment judged by TSH)
7. The TRUST Study Group. Thyroid hormone therapy for older adults with subclinical hypothyroidism. N Engl J Med 2017;376:2534-2544 DOI: 10.1056/NEJMoa1603825 (No symptomatic benefit treating subclinical hypothyroidism)
8. Villar HC, Sacconato H, Valente O, Atallah AN. Thyroid hormone for subclinical hypothyroidism. Cochrane Database Syst Rev. 2007;18(3):CD003419 DOI:10.1002/14651858.CD00349.pub2 ( no benefit survival/cardiovascular morbidity treating subclinical hypo)
9. Hoermann R, Larisch R, Dietrich JW, Midgley JEM. Derivation of a multivariate reference range for pituitary thyrotropin and thyroid hormones: diagnostic efficiency compared with conventional single reference method. Eur J Endocrinol.2016;174(6):735-743 DOI: 10.1530/EJE-160031
10. Ross HA, den Hejer M, Hermus Ad RMM, Sweep FCGC. Composite reference interval for thyroid-stimulating hormone and free thyroxine, comparison with common cutoff values, and reconsideration of subclinical thyroid disease. Clin Chem DOI:10.1373/clinchem.2009.124560 (Composite reference range FT4/TSH)
11. Cryer PE, Davis SN. Hypoglycemia. Harrison’s Principles of Internal Medicine. 19th edition 2015. Editors Kasper DL, Hauser SL, Jameson JL, Fauci AS, Longo DL, Loscalzo J. Chapter 420:2430-2435. McGraw Hill New York
12. Khosla S. Hypercalcemia and Hypocalcemia. Harrison’s Principles of Internal Medicine. 19th edition 2015. Editors Kasper DL, Hauser SL, Jameson JL, Fauci AS, Longo DL, Loscalzo J. Chapter 65;313-314 McGraw Hill New York
13. Arlt W. Disorders of the adrenal cortex. Harrison’s Principles of Internal Medicine. 19th edition 2015. Editors Kasper DL, Hauser SL, Jameson JL, Fauci AS, Longo DL, Loscalzo J. Chapter 406;2316 McGraw Hill New York
14. Hoermann R, Eckl W, Hoermann C, Larisch R. Complex relationship between free thyroxine and TSH in the regulation of thyroid function. Eur J Endocrinol. 2010;162:1123-1129 DOI: 10.1530/EJE-10-0106
15. Hadlow NC, Rothacker KM, Wardrop R, Brown SJ, Lim EU, Walsh JP. 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. 2013;98(7):2936-2943 DOI:10.1210/jc.2012-4223
16. Cappola AR, Desai AS, Medici M, Cooper LS, Egan D,Sopko G, Fishman GI, Goldman S, Cooper DS, Mora A, Kudenchuk PJ, Hollenberg AN, McDonald CL, Ladenson PW. Thyroid and cardiovascular disease: Research agenda for enhancing knowledge, prevention and treatment. Thyroid 2019; DOI 10.1089/thy.2018.0416
17. Modell H, Cliff W, Michael J, McFarland J, Wenderoth MP, Wright A. A physiologist’s view of homeostasis. Adv Physiol Educ. 2015;39(4):259-266 doi:10.1152/advan.00107.2015 (set point theory
18. Andersen S, Pedersen KM, Bruun NH, Laurberg P. Narrow individual variations in serum T4 and T3 in normal subjects; A clue to the understanding of subclinical thyroid disease. J Clin Endocrinol Metab2002; 87:1068-1072 (Individual set points- those at higher end become more hypothyroid before outside normal range- intra- individual variation< inter-individual variation
19. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. Endocrine Reviews 2008;29(1):76-131 DOI: 10.1210/er.2006-0043 (set point – result abnormal for individual but within laboratory reference range
20. Sheehan MT. Biochemical testing of the thyroid: TSH is the best and, oftentimes, only test needed- a review for primary care. Clin Med Res. 2016;14(2):83-92 DOI: 10.312/cmr.2016.1309 (Individual set point- TSH most sensitive as compare c FT4
21. Fitzgerald SP, Bean NG. The relationship between population T4/TSH set point data and T4/TSH physiology. J Thyroid Research Volume 2016;Article ID 6351473, 7pages
22. Fitzgerald SP, Bean NG, Fitzgerald LN. Population data indicate that thyroid regulation is consistent with an equilibrium-point model, but not with a set point model. Temperature 2017; DOI10.1080/23328940.2017.1281370
23. Fitzgerald SP, Bean NG. Population correlations do not support the existence of set points for blood levels of calcium or glucose- a new model for homeostasis. Physiol Rep, 6 (1), 2018, e13551, <https://doi.org/10.14814/phy2.13551>
24. Fitzgerald SP, Grote Beverborg N, Beguin Y, Artunc F, Falhammar H, Bean NG. Population data provide evidence against the presence of a set point for haemoglobin levels or tissue oxygen delivery. Physiol Rep,7 (12),2019,e14153, https://doi.org/10.14814/phy2.14153
25. Romanovsky AA. Do fever and anapyrexia exist? Analysis of set point-based definitions. Am J Physiol Regul Integr Comp Physiol. 287: R992-R995,2004
26. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med.2009;6(7):e1000097
27. Selmer C, Olesen JB, Hansen ML, Lindharsen J, Olsen A-MS, Madsen JC, Faber J, Hansen PR et al. The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. BMJ 2012;345:e7895 DOI:10.1136/bmj.e7895
28. Cappola AR, Arnold AM, Wulczn K, Carlson M, Robbins J, Psaty BM. Thyroid function in the euthyroid range and adverse outcomes in older adults. J Clin Endocrinol Metab 2015;100(3):1088-1096 DOI:10.1210/jc.2014-3586 (sensitivity difference)
29. 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. Thyroid Studies Collaboration. Thyroid function within the normal range, subclinical hypothyroidism, and the risk of atrial fibrillation. Circulation 2017; 136(22):2100-2116. DOI:10.1161/CIRCULATIONAHA.117.028753 (different sensitivity pit/heart)
30. Gammage MD, Parle JV, Holder RL, Roberts LM, Hobbs FD, Wilson S, Sheppard MC, Franklyn JA. Association between serum free thyroxine concentration and atrial fibrillation. Arch Intern Med. 2007;167(9):928-34 DOI: 10.1001/archinte.167.9.928
31. Heeringa J, Hoogendoorn EH, van der Deure WM, Hofman A, Peeters RP, Hop WC, den Heijer M, Visser TJ, Witterman JC. High-normal thyroid function and the risk of atrial fibrillation: the Rotterdam study. Arch Int Med. 2008;168(20):2219-24 DOI: 10.1001/archinte.168.20.2219 (FT4- not sig 0.06)
32. Chaker, L, Heeringa J, Deghan A, Medici M, Visser WE, Baumgartner C, Hofman A, Rodondi N, Peeters RP, Franco OH. Normal thyroid function and the risk of atrial fibrillation: the Rotterdam Study J Clin Endocrinol Metab.2015; 100:3718-3724 DOI:10.1210/jc.2015-2480
33. Yan Z, Huang H, Li J, Wang J. Relationship between subclinical thyroid dysfunction and the risk of fracture: a meta-analysis of prospective cohort studies. Osteoporosis Int. 2016;1:115-25 DOI: 10.1007/s00198-015-3221-z
34. Van Rijn LE, Pop VJ, Williams GR. Low bone mineral density is related to high physiological levels of free thyroxine in peri-menopausal women. Eur J Endocrinol. 2014;170(3):461-8 DOI:10.1530/EJE-13-0769
35. Roef G, lapauw B, Goemaere S, Zmierczak H, Fliers T, Kaufman JM, Taes Y. Thyroid hormone status within the physiological range affects bone mass and density in healthy men at the age of peak bone mass. Eur J Endocrinol. 2011 164(6): 1027-34 DOI:10.1530/EJE-10-1113
36. Murphy E, Glüer CC, Reid DM, Felsenberg D, Roux C, Eastell R, Williams GR. 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 Clin Endocrinol Metab. 2010;95(7):3173-81 DOI:10.1210/jc.2009-2630
37. Van der Deure, Uitterlinden AG, Hofman A, Rivadeneira F, Pols HA, Peeters RP, Visser TJ. Effects of serum TSH and FT4 levels and the TSHR-Asp727Glu polymorphism on bone: the Rotterdam Study. Clin Endocrinol (Oxf)2008;68(2):175-181 DOI: 10.1111/j.1365-2265.2007.0316.x
38. Chan YX, Knuiman MW, Divitini ML, Brown SJ, Walsh J, Yeap BB. Lower TSH and higher free thyroxine predict incidence of prostate but not breast, colorectal or lung cancer. Eur J Endocrinol 2017;177(4):297-308 DOI:10.1530/EJE-17-0197 (both
39. Tosovic A, Becker C, Bondeson A-G, Bondeson L, Ericsson U-B, Malm J, Manjer J. Prospectively measured thyroid hormones and thyroid peroxidase antibodies in relation to breast cancer risk. Int J Cancer 2012;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. Thyroid function and cancer risk: The Rotterdam Study. J Clin Endocrinol Metab 2016; 12(1):5030-5036. DOI:10.1210/jc.2016-2104
41. Ittermann T, Haring R, Wallaschofski H, Baumeister S, Nauck, M, Dörr M, Lerch M, Meyer zuSchwabedissen HE, Rosskopf D, Völzke H. Inverse association between serum free thyroxine levels and hepatic steatosis: results from the study of health in Pomerania. Thyroid 2012; 22(6):568-574 DOI: 10.1089/thy.2011.0279 (DIRECTION OF CAUSALITY)
42. Xu C, Xu L, Yu M, Li Y. Association between thyroid function and non alcoholic fatty liver disease in euthyroid elderly Chinese. Clinical Endocrinology 2011;75:240-246 DOI:10.1111/j.1365-2265.2011.04016.x
43. Bano A, Chaker L, Plompen, EPC, Hofman A, Deghan A, Franco OH, Janssen HLA, Murad SW, Peeters RP. Thyroid function and the risk of non-alcoholic fatty liver disease: the Rotterdam study. J Clin Endocrinol Metab 2016;101(8):3204-3211 DOI: 10.1012/jc.2016-1300 (altered set point)
44. Mehran L, Amouzegar A, Bakhtiyari M, Mansournia MA, Rahimabad PR, Tohidi M, Azizi F. Variations in serum free thyroxine concentration within the reference range predicts the incidence of metabolic syndrome in non-obese adults: a cohort study. Thyroid 2017;27(7):886-893 DOI:10.1089/thy.2016.0557 (SET POINT MODEL- FT4 more impt TSH)
45. Roos A, Bakker SJ, Links TP, Gans RO, Wolffenbuttel BH. Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. J Clin Endocrinol Metab. 2007;92(2):491-6 DOI:10.1210/jc.2006-1718 (PITUITARY SENSITIVITY < PERIPHERAL)
46. Garduño-Garcia J, Alvirde- Garcia U, López-Carrasco G, Mendoza M, Mehta R, Arellano-Campos O, Choza R, Sauque L et al. TSH and free thyroxine concentrations are associated with differing metabolic markers in euthyroid subjects. Eur J Endocrinol. 2010;163:73-278 DOI:10.1530/EJE-10-0312 (Different markers SC H not assoc c metabolic syn; in reality TSH adds little))
47. Lin SY, Wang YY, Liu PH, Lai WA, Sheu WH. Lower serum free thyroxine levels are associated with metabolic syndrome in a Chinese population. Metabolism 2005;54(11):1524-8 DOI: 10.1016/j.metabol.2005.05.020 (T4 + TSH not recorded)
48. 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) Study. Thyroid function and prevalent and incident metabolic syndrome in older adults: The Health, Aging, and Body Composition Study. Clin Endocrinol (Oxf).2012;76(6):911-918 DOI: 10.1111/j.1365-2265.2011.04328.x (ALSO DIRECTION CAUSALITY)
49. Shon HS, Jung ED, Kim SH, Lee JH. Free T4 is negatively correlated with body mass index in euthyroid women. Korean J Intern Med 2008;23(2):53-57 DOI:10.3904/kjim.2008.23.2.53
50. Makepeace AE, Bremmer AP, O’Leary P, Leedman PJ, Feddema P, Michelangeli V, Walsh JP. Significant inverse relationship between serum free T4 concentration and body mass index in euthyroid subjects: differences between smokers and non-smokers. Clin Endocrinol (Oxf) 2008;69(4):648-652 DOI:10.111/j.1365-2265.2008.03239.x
51. Knudsen N, Laurberg P, Rasmussen LB, Bulow I, Perrild H, Ovesen L, Jørgensen T. Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population. J Clin Endocrinol Metab 2005; 90(7):4019-24 DOI: 10.1210/jc.2004-2225 (both)
52. Chaker L, Ligthart S, Korevaar TI, Hofman A, Franco OH, Peeters RP, Deghan A. Thyroid function and risk of type 2 diabetes: a population cohort study. BMC Med.2016;14(1):150 DOI:10.1186/s12916-016-0693-4(both)
53. Jun JE, Jee JH, Bae JC, Jin S-M, Hur KY, Lee M-K, Kim TH, Kim SW, Kim JH. Association between changes in thyroid hormones and incident Type 2 diabetes: a seven- year longitudinal study. Thyroid 2017;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 et al. Association between thyroid dysfunction and lipid profiles differs according to age and sex: results from the Korean National Health and Nutrition Survey. Thyroid 2018; 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. Triiodothyronine levels are independently associated with metabolic syndrome in euthyroid middle-aged subjects. Endocrinol Metab (Seoul). 2016;31(2):311-319 DOI:10.3803/EnM.2016.31.2.311 (RELATION T3 not T4 OR TSH)
56. Strollo F, Carucci I, More M, Marico G, Strollo G, Masini MA, Gentile S. Free triiodothyronine and cholesterol levels in euthyroid elderly T2DM patients. Int J Endocrinol 2012;2012 Article ID 420370, 7 pages DOI:10.1155/2012/420370 (T3 NOT T4/TSH)
57. Svare A, Nilsen TI, Bjøro T, Asvold BO, Langhammer A. Serum TSH related to measures of body mass: longitudinal data from the HUNT Study, Norway. Clin Endocrinol (Oxf) 2011;74(6):769-765. DOI:10.1111/j.1365-2265.2011.04009.x
58. Vadiveloo T, Donnan PT, Cochrane L, Leese G. The Thyroid Epidemiology, Audit, and Research Study (TEARS): Morbidity in patients with endogenous subclinical hyperthyroidism. J Clin Endocrinol Metab. 2011:96(5):1344-1351 DOI: 10.1210/jc.2010-2693 (DEMENTIA/# NOT TSH RELATED)
59. Choi HJ, Byun MS, Yi D, Sohn BK, Lee JH, Kim YK, Lee DY; KBASE Research Group. Associations of thyroid hormone levels with in vivo Alzheimer’s disease pathologies. Alzheimer’s Res Ther. 2017;9(1):64 DOI: 10.1186/s13195-017-0291-5
60. Volpato S, Guralnik JM, Fried LP, Remalay AT, Cappola AR, Launer LJ. Serum thyroxine level and cognitive decline in older women. Neurology 2002;58(7): 1055-1061 DOI:10.1212/WNL.58.7.1055
61. Choi HY, Choe YM, Byun MS, Sohn BK, Baek H, Yi D, Han JY, Woo JI, Lee DY. Associations between serum thyroid hormone and cerebral amyloidosis in cognitively diverse elderly. Alzheimer’s and Dementia 2015;11(7) S648-649 DOI:10.1016/j.jatz.2015.06.947 (T3 NOT T4/TSH) !!!
62. de Jong FD, Heijer T, Visser TJ, de Rijke YB, Drexhage HA, Hoffman A, Breteler MMB. Thyroid hormones, dementia, and atrophy of the medial temporal lobe. J Clin Endocrinol Metab 2006;91(7):2569-2573 DOI:10.1210/jc.2006-0449
63. Tan ZS, Beiser A, Ramachandran RS, Au R, Auerbach S, Kiel DP, Wolf PA, Seshadri S. Thyroid function and the risk of Alzheimer’s disease: The Framingham Study. Arch Int Med.2009;168(14):1514-1520 DOI:10.1001/archinte.168.14.1514 (hyper and hypo-TSH high or low)
64. Yeap BB, Alfonso H, Chubb SAP, Walsh JP, Hankey GJ, Almeida OP, Flicker L. Higher free thyroxine levels are associated with frailty in older men: the Health In Men Study. Clin Endocrinol 2012; 76:741-748 DOI: 10.1111/j.1365-2265.2011.04290.x
65. Bano A, Chaker L, Schoufour J, Ikram MA, Kavousi M, Franco OH, Peeters RP, Mattace-Raso FUS. High circulating free thyroxine levels may increase the risk of frailty: The Rotterdam Study. J Clin Endocrinol Metab.2018;103(1):328-335 DOI: 10.1210/jc.2017-01854
66. van den Beld AW, Visser TJ, Feelders RA, Grobbee DE, Lamberts SWJ. Thyroid hormone concentrations, disease, physical function, and mortality in elderly men. [J Clin Endocrinol Metab.](https://www.ncbi.nlm.nih.gov/pubmed/16174720) 2005;90(12):6403-9 DOI:[10.1210/jc.2005-0872](https://doi.org/10.1210/jc.2005-0872)
67. Gussekloo J, van Exel E, de Graen AJM, Meinders AE, Frölich M, Westendorp RGJ. Thyroid status, disability and cognitive function, and survival in old age. JAMA 2004;292:2591-2599 DOI:10.1001/jama.292.21.2591
68. Yeap BB, Alfonso H, Hankey GJ, Flicker L, Golledge J, Norman PE, Chubb SAP. Higher free thyroxine levels are associated with all-cause mortality in euthyroid older men: the health In Men Study. Eur J Endocrinol 2013;169:401-408 DOI: 10.1530/EJE-13-0306
69. 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. Associations between thyroid function and mortality: the influence of age. Eur J Endocrinol. 2014;171(2):183-91 DOI: 10.1530/EJE-13-1070 (mortality- also relation c FT4 not TSH – change in set point)
70. Inoue K, Tsujimoto T, Saito J, Sugiyama T. Association between serum thyrotropin levels and mortality among euthyroid adults in the United States. Thyroid 2016;26(10):1457-1465 DOI:10.1089/thy.2016.0156 (mortality correlates with high FT4 and high TSH)
71. Selmer C, Olesen JB, Hansen ML, von Kappelgaard LM, Madsen JC, Hansen PR, Pedersen OD, Faber J, Torp-Pederson C, Gislason GH. Subclinical and overt thyroid dysfunction and the risk of all-cause mortality and cardiovascular events: a large population study. J Clin Endocrinol Metab 2014;99(7):2372-2382 DOI: 10.1210/jc.2013-4184
72. Moon S, Kim MJ, Yu JM, Yoo HJ, Park YJ. Subclinical hypothyroidism and the risk of cardiovascular disease and all-cause mortality: a meta-analysis of prospective cohort studies. Thyroid 2018; ahead of print, 28(9) DOI:10.1089/thy.2017.0414
73. Razvi S, Weaver JU, Vanderpump MP, Pearce SH. The incidence of ischemic heart disease and mortality in people with subclinical hypothyroidism: reanalysis of the Whickham Survey cohort. J Clin Endocrinol Metab. 2010;95(4):1734-40 DOI: 19.1210/jc.2009-1749
74. Chaker L, van den Berg ME, Niemeijer MN, Franco OH, Deghan A, Hofman A, Rijnbeek PR, Deckers JW, Eijgelsheim M, Stricker, BHC, Peeters RP. Thyroid function and sudden cardiac death: A prospective study. Circulation 2016;134(10):713-722 DOI:10.1161/CIRCULATIONAHA.115.020789 (set point)
75. Asvold BO, Bjøro T, Nilsen TI, Gunnell D, Vatten LJ. Thyrotropin levels and risk of fatal coronary heart disease: the HUNT study Arch Int med 2008;168(8):855-860 DOI:10.1001/archinte.168.8.855 (women not men- inconsistent ie- )
76. Rodondi N, Bauer DC, Cappola AR, Cornuz J, Robbins J, Fried LP, Ladenson PW, Vittinghoff E, Gottdiener JS, Newman AB. Subclinical thyroid dysfunction, cardiac function and the risk of heart failure: The Cardiovascular Health Study. J Am Coll Cardiol 2008;52(14):1152-1159 DOI: 10.1016/jack.2008.07.009
77. Walsh JP, Bremner AP, Bulsara MK, O’Leary P, Leedman PJ, Feddema P, Michelangeli V. Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. Arch Int Med 2005;165:2647-2472 DOI: 10.1001/archinte.165.21.2467 (ALSO TSH ONLY- CVS studies inconsistent)
78. Harris EK. Effects of intra- and interindividual variation on the appropriate use of normal ranges. Clin Chem 1974;20(12):1535-1542
79. Reinhard M, Erlandsen EJ, Randers E. Biological variation of cystatin C and creatinine. Scand J Clin Lab Invest 2009;69(8);831-836 DOI:10.3109/00365510903307947
80. Lazo M, Selvin E, Clark JM. Brief communication: Clinical implications of short-term variability in liver function test results. Ann Int Med 2008;148(5)348-352 DOI: 10.7326/0003-4819-148-5-200803040-00005
81. Guldvog I, Reitsma LC, Johnsen L, Gibbs C, Carlsen E, Lende TH, Narvestad JK, Omdal R, Kvaløy JT, Hoff G, Bernklev T, Søiland H. Thyroidectomy versus medical management for euthyroid patients with Hashimoto disease and persisting symptoms: a randomized trial. Ann Int Med 2019 DOI:10.1089/ct.2019;31.178-181
82. Dickinson S, Colagiuri S, Faramus E, Petocz P, Brand-Miller JC. Postprandial hyperglycemia and insulin sensitivity differ among lean young adults of different ethnicities. The Journal of Nutrition 2002;132(9):2574-2579 DOI:10.1093/jn/132.9.2574
83. Felsenfeld AJ, Rodriguez M, Aguilera-Tejero E. Dynamics of parathyroid hormone secretion in health and secondary hyperparathyroidism. Clinical Journal of American Society of Nephrology 2007;2(6) 1283-1305 DOI:10.2215/CJN.01520407
84. 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 P. Erythropoietin in the general population: reference ranges and clinical, biochemical and genetic correlates. PLOS One 2015;DOI:10.1371/journal.pone.0125215
85. Matzen LE, Kvetny J, Pedersen KK. TSH, thyroid hormones and nuclear binding of T3 in mononuclear blood cells from obese and non-obese women. Scandinavian Journal of Clinical and laboratory Investigation 1989;49(3):249-253 DOI: 10.1080/00365518909089090 (Reverse causation-caloric intake))
86. Rotondi, M, Leporati P, La Manna A, Pirali B, Mondello T, Fonte R, Magri F, Chiovato L. Raised serum TSH levels in patients with morbid obesity: is it enough to diagnose subclinical hypothyroidism? European Journal of Endocrinology 2009;160:403-408 DOI:10.1530/EJE-08-0734 (thermogenic)
87. Rotondi M, Magri F, Chiovato L. Thyroid and obesity: not a one-way interaction J Clin Endocrinol Metab.2011;96(2)344-346 DOI:10.1210/jc.2010-2515 (wt causes inc TSH)
88. Longhi S, Radetti G. Thyroid function and obesity. J Clin Res Pediatr Endocrinol 2013;5(S1):40-44 DOI:10.4274/Jcrpe.856 (Reverse causation)
89. Michalaki MA, Vagenakis AG, Leonardou AS, Argentouloannis MN, Habeos G, Makri MG, Psyrogiannis AI, Kalfrarentzos FE, Kyriazopoupou VE. Thyroid function in humans with morbid obesity. Thyroid 2006;16(1):73-78 DOI: 10.1089/thy.2006.16.73 (higher FT3, T4, TSH- reset ‘thyrostat’)
90. Köhrle J. Thyrotropin (TSH) action on thyroid hormone deiodination and secretion: one aspect of thyrotropin regulation of thyroid cell biology. Horm Metab Res Suppl. 1990;23:18-28 (TSH inc T3 secretion
91. Ross DS, Thyroid function in nonthyroidal illness. Cooper DS (Ed) UpToDate Waltham, MA: UpToDate Inc. <http://www.uptodate.com> accessed 17 Sept 2018
92. 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, BassaniRA, Medel EH, Casis O. High thyrotropin is critical for cardiac electrical remodelling and arrhythmia vulnerability in hypothyroidism. Thyroid 2019 DOI: 10.1089/thy.2018.0709
93. [Hyperthyroidism.](https://www-ncbi-nlm-nih-gov.proxy.kib.ki.se/pubmed/27038492) De Leo S, Lee SY, Braverman LE. Lancet. 2016 Aug 27; 388(10047):906-918. DOI: 10.1016/S0140-6736(16)00278-6. Epub 2016 Mar 30
94. Lacroix A, Feelders RA Stratakis CA, Nieman LK. Cushing’s syndrome. Lancet 2015;386(9996):913-927 DOI:10.1016/S0140-6736(14)61375-1
95. Walsh JP. Setpoints and susceptibility: do small differences in thyroid function really matter? Clin Endocrinol. 2011;75:158-159 DOI: 10.1111/j.1365-2265.2011.04036x (differences across the range- individual set point- BMI, BP,, chol, insulin resistance, AF, cvs mortality, AF, bones )
96. Fitzgerald SP, Bean NG. Thyroid stimulating hormone (TSH) autoregulation reduces variation in the TSH response to thyroid hormones. Temperature 2018: [DOI: 10.1080/23328940.2018.1513110](http://dx.doi.org/10.1080/23328940.2018.1513110)

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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 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 |
| Kim [55] |  | Cross section-retrospective | Korean medical centre attendees; n=13496;age 51±7; male 60% | 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.

**Table 2** Indicative summary of studies showing at least one significant correlation of clinical state with FT4 but not with TSH. The complete tabulation of results is on the spread sheet supplement.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 1st author and year | Studied outcome | ‘Crude’P- value TSH | ‘Crude’P-value FT4 | adjusted P-value TSH | adjusted P-valueFT4 |
| **Studies of higher thyroid function** | | | | | |
| Gammage 2007 [30] | Atrial Fibrillation | 0.82 | <0.001 | 0.94 | 0.004 |
| Cappola 2015 [28] | Atrial Fibrillation | 0.09 | 0.001 | 0.12 | 0.02 |
| Chaker 2015 [32] | Atrial Fibrillation | 0.71 | 0.008 | 0.60 | 0.005 |
|  | Heart failure | 0.17 | 0.004 | 0.09 | 0.03 |
|  | Composite cardiovascular outcome | 0.05 | 0.008 | 0.04 | 0.02 |
| Chaker 2016 [74] | Sudden cardiac death | 0.17 | 0.008 | 0.18 | 0.022 |
| Van de Ven 2014 [69] | Mortality |  |  | NS | <0.005 |
| Inoue 2016[70] | Mortality | NS | <0.05 | NS | NS |
| Yeap 2013 [68] | Mortality | 0.250 | <0.001 | NS | 0.025 |
| van den Beld 2005 [66] | Mortality | NS | <0.05 |  |  |
| Gussekloo [67] | Mortality | 0.17 | 0.001 |  |  |
|  | Low physical function | NS | 0.006 |  |  |
| Yeap 2012 [64] | Frailty | 0.621 | <0.001 | 0.533 | 0.010 |
|  | Frailty (TSH normal) |  | <0.001 |  | 0.026 |
| Bano 2018 [65] | Change in frailty | 0.5 | 0.001 |  |  |
|  |  |  |  |  |  |
| de Jong 2006[62] | Hippocampal atrophy | NS | <0.05 |  |  |
|  | Amygdala atrophy | NS | <0.05 |  |  |
|  |  |  |  |  |  |
| Roef 2011 [35] | Bone density -hip | 0.40 | 0.15/0.002/0.02\* |  |  |
|  | Bone density- total body | 0.83 | 0.053/0.006/0.007\* |  |  |
|  | Bone density- radius trabecular |  | 0.04 |  |  |
| Van der Deure 2008 [37] | Bone density lumbar spine | 0.24 | 0.009 | 0.59 | 0.04\*\* |
|  | Bone density femoral neck | 0.06 | 0.01 | 0.20 | 0.05 |
| Murphy 2010 [36] | Bone density hip | 0.286 | 0.004 |  |  |
|  | Change in bone density hip | 0.065 | 0.015 |  |  |
| Van Rijn 2014 [34] | Bone density lumbar spine | 0.34 | 0.03 |  |  |
|  | Osteoporosis/osteopenia | 0.87 | 0.004 |  |  |
| **Studies of lower thyroid function** | | | | | |
|  |  |  |  |  |  |
| Volpato 2002 [60] | Cognitive decline | 0.97 | <0.001 | 0.99 | 0.02 |
| Makepeace 2008 [50] | Obesity | 0.29 | <0.001 | 0.53 | <0.001 |
| Oh [54] | High Triglycerides | 0.006 | <0.001 | 0.510 | 0.003 |
| Kim [55] | Obesity (paradoxical) | NS | 0.019 |  |  |
|  | Systolic BP | NS | <0.001 |  |  |
|  | Diastolic BP | NS | <0.001 |  |  |
| G-Garcia [46] | Glucose | 0.775 | 0.010 |  |  |
|  | Insulin | 0.016 | <0.001 | NS | <0.001 |
|  | HOMA-IR | 0.046 | <0.001 | NS | <0.001 |
|  | HDL | 0.120 | <0.001 |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
| Mehran 2017 [44] | Metabolic Syndrome | NS | <0.05 | NS | NS |
|  | Waist circumference | NS | <0.05 | NS | <0.05 |
|  | High blood pressure | NS | <0.05 | NS | <0.05 |
|  | High Triglycerides | NS | <0.05 | NS | <0.05 |
| Shon 2008 [49] | Obesity | NS | <0.01 |  |  |
|  | Triglycerides |  |  | NS | 0.005 |
| Roos 2007 [45] | Waist circumference | 0.079 | 0.093 | 0.162 | 0.038 |
|  | Triglycerides | 0.008 | 0.003 | 0.002 | 0.023 |
|  | High density lipoprotein | 0.016 | 0.122 | 0.098 | 0.007 |
|  | Blood pressure -systolic | 0.396 | 0.105 | 0.690 | 0.019 |
|  | Blood pressure -diastolic | 0.610 | 0.023 | 0.634 | 0.035 |
| Jun 2017 [53] # (paradoxical result) | >/= 2 metabolic risk factors | NS | <0.001 |  |  |
| Xu 2011 [42] | Body mass Index | 0.063 | 0.010 |  |  |
|  | Waist circumference | 0.156 | 0.003 |  |  |
|  | Triglycerides | <0.001 | <0.001 |  |  |
|  | Serum uric acid | 0.05 | 0.018 |  |  |
|  | Nonalcoholic fatty liver | 0.011 | 0.<001\*\* | NS | 0.013 |
| Bano 2016 [43] | Nonalcoholic fatty liver(total group) | <0.05 | <0.05 | NS | <0.05 |
|  | Nonalcoholic fatty liver low Fatty liver Index (low risk) | 0.05 | <0.05 | NS | <0.05 |
| Ittermann 2012 [41] | Hepatic steatosis- men/women | 0.069/0.594 | <0.001/0.004 |  |  |

As the statistical methods vary between the studies only the significance of the results is tabulated. When 95% confidence intervals rather than p-values were provided in the referenced articles we translated these confidence intervals simply to p-values less than 0.05 or NS (non-significant).Tabulated is the ‘crude’ correlation and the correlation when adjusted for other factors- again the methodology of the ‘crude’ correlations and adjusted correlations varied study to study, i.e., in some studies the ‘crude’ correlation was partially corrected e.g. for age. FT4, free thyroxine.FT3, free triiodothyronine. \*FT4/Total T4/FT3. \*\* Multivariate regression- association with FT4, but not TSH. NS - not significant (p>0.05).