CLINICAL PARAMETERS CORRELATE MORE OFTEN WITH THYROID HORMONE LEVELS THAN WITH TSH LEVELS: A SYSTEMATIC REVIEW

**Abstract**

**Context:** 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 free thyroxine (FT4) or TSH levels provide the better guide to the broad range of clinical parameters associated with thyroid dysfunction.

**Evidence Acquisition:** A PubMed/Medline search up to November 2018. References of retrieved articles were searched. Papers were assessed for quality using a modified Newcastle-Ottawa score. PRISMA guidelines were followed.

**Evidence Synthesis:** We identified 35 articles. There was consistent high quality evidence that atrial fibrillation, low bone density, frailty and death, in the context of higher thyroid function, were more strongly correlated with higher FT4levels than with lower TSH levels. In the context of lower thyroid function, the evidence was less consistent, but still, features of the metabolic syndrome and steatohepatitis were more strongly associated with lower FT4 than higher TSH levels. We were unable to find any consistent evidence suggesting TSH levels correlated better than FT4 levels with any parameter.

Conclusions. For subclinical hyperthyroidism and to a lesser extent for subclinical hypothyroidism FT4 levels have a stronger correlation with clinical parameters than do TSH levels. The physiological effects of thyroid status are continuous across the normal and abnormal ranges as judged by FT4, and to a lesser extent, 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, 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].

Underlying the concept of subclinical thyroid dysfunction is the understanding that the intra-individual variation in thyroid hormone levels is less than the inter-individual variation [9]. This has led to the view that individuals may have abnormal thyroid hormone levels for themselves, even though the hormone levels may still lie within a population normal range [9, 10].

Physiologically, each individual has been thought to have a ‘setpoint’, target, reference, or ideal level of thyroid hormones [9-12]. Set point theory proposes that deviation from such a set point generates an error signal to which the body responds [13]. As TSH levels are believed to be the most sensitive marker of thyroid function it has followed that abnormal TSH levels, even in the context of normal free thyroxine (FT4) and free triiodothyronine (FT3) levels, indicate thyroid dysfunction [4, 14], albeit a more subtle dysfunction than that of overt thyroid dysfunction, when there are abnormalities of FT4 and /or FT3 as well as TSH.

TSH levels as well as being the arbiters of the diagnosis of subclinical thyroid dysfunction are also promoted as the parameters that guide therapy when therapy is instituted [6].

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 [15, 16]. 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 [17] or parathyroid hormone levels [18] respectively. ACTH levels are not considered valuable for screening for Cushing’s syndrome [19]. 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 [17-19]. The anomalous situation appears to have arisen in the case of thyroid function because of the strong population correlation between thyroid hormones and TSH levels [11, 20]. This correlation is such that determining the TSH level is a very good screening test for overt thyroid dysfunction.

Our previous work, has demonstrated that the negative population correlation between FT4 and TSH provides evidence against the existence of a set point for thyroid hormones [21]. We have analogously provided evidence that set points also do not exist for other physiological parameters [22], and have argued that the evidence therefore suggests that, in general, regulation and homeostasis are based on balance points rather than set points. Other authors using different methods have come to similar conclusions [23].

In a balance point model the levels of thyroid hormones merely reflect an equilibrium of the various physiological processes at play [24], there being no pre-set reference value, from which any error signal may be generated. In the case of thyroid physiology, the individual’s balance point lies at the intersection of the individual’s T4 curve (the FT4 response to different levels of TSH), and the individual’s TSH curve (the TSH response to different levels of FT4) (Figure 1).There is thus in such a model no particular significance of the level of a controlling hormone such as TSH.

Whereas the current model and practice emphasises the importance of TSH levels in the diagnosis of subclinical thyroid dysfunction, a balance point model of thyroid regulation 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 feature correlated better with thyroid hormone levels, there would be support for the balance point model of thyroid regulation, and doubt would be cast on the validity of the current TSH-based conception of subclinical thyroid dysfunction. In this circumstance the previously noted correlations of clinical features with TSH levels would merely reflect the 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, 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 and so on. 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. The literature search was terminated when it became apparent that our results were so overwhelming that further articles were unlikely to alter our conclusions.

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 less than 100 individuals. Review articles, editorials, and meeting abstracts were also excluded. The following information was extracted from each study: first author, country, number of individuals, sex, age intervals, nature of the study, clinical parameter and statistical significance of any correlations.. The use of a quality assessment (e.g., 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 [25].

From articles which reported clinical or pathological correlations with both FT4 and TSH we extracted all reported correlations and classified them as significant (p<0.05), for FT4 but not TSH, for TSH but not FT4, for both FT4 and TSH, and for neither FT4 or TSH. For the fewer studies also reporting associations with T3 we classified similarly all the permutations.

The relative strengths of FT4 levels, T3 levels, and TSH levels in terms of correlation with clinical and pathological states were determined by the respective numbers of significant correlations found. 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.

RESULTS

We found an extensive literature addressing thyroid function and various clinical features (Figure 1). 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 [26-30], osteoporosis [31-35], and cancer [36-38] correlated with higher thyroid function defined using TSH and/or thyroid hormone levels, across and beyond the normal range ], and steatohepatitis [39-41] and the features of the metabolic syndrome [42-55] 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 [56-61], frailty[62-65], total /cardiovascular mortality[64-73] and heart disease (apart from atrial fibrillation)[56,69-71, 74, 75].

There were many series finding the above correlations in the context of subclinical thyroid dysfunction. Many of these studies [26, 31, 45, 46, 56, 69, 70, 73-75] 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 [56]. We found one study that looked at FT4 alone [45], this study finding a correlation, and another study [54] 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. (Table)

The focus of our study was the relative correlation of clinical states with FT4 (+/- T3/FT3), and TSH. In the end we identified 36 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 15 studies [27, 33, 34, 37, 39, 40, 43, 49, 51, 53, 57, 59, 60, 64, 65] that examined correlations with FT4, T3 (free or total) and TSH and a further 21 studies [28-30, 32, 35, 36, 38, 41, 42, 44, 47, 48, 50, 52, 58, 62, 63, 66-68, 72]that examined correlations with FT4 and TSH.

These 36 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 [27, 30, 33, 40, 43, 47, 48, 50, 51, 53, 58, 67, 68, 72 ]subjects either euthyroid or with subclinical thyroid dysfunction[28, 32, 34, 35, 36, 42, 44, 49, 57, 60, 62, 63, 64, 66],and subjects euthyroid or with subclinical/overt thyroid dysfunction [29, 37-39, 41, 52, 65]]. In one study [59] the range of thyroid function was not stated.

We found no study conclusion indicating superior correlations between TSH, rather than FT4 or FT3, with the clinical parameters atrial fibrillation, osteoporosis, cancer, steatohepatitis or cognitive decline. The one study that in the text did show significant correlations between TSH rather than FT4, and AF [30], 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. 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 [49] 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 conclusions indicating superior correlations with thyroid hormones as compared with TSH covering atrial fibrillation[28, 29], osteoporosis [32, 33, 35], cancer[37-38], metabolic syndrome [42,43], obesity [47,48], dementia, [58-60], frailty, [62, 63] mortality[64, 66], and sudden cardiac death [72] . Of the 36 studies, all but 5 showed at least one instance of a correlation with FT4 but not with TSH (Table 2).

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 [44, 60, 66, 72]. One of these papers [44] also showed correlations with TSH.

When we classified all of the correlations reported in the above 36 studies (Table ) we found that regardless of the consistency of the relationship of the clinical parameter to high or low thyroid function there was more likely to be a correlation with thyroid hormones rather than TSH. Triglyceride levels were a possible exception.

Specifically we found......

There was a consistent and strong association of clinical parameters with FT4. We found T3 correlations with fewer parameters. Again T3 seemed to correlate better than TSH with clinical parameters. T3 appeared to correlate at least as well as FT4 but approximately half of the correlations that were positive for T3 but negative for FT4 were paradoxical [40,51,53] and/or likely to be on account of reverse causation (Table) (see Discussion). Overall, T3 measurement added little to the assessment based on FT4 levels ?????

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, or that any lack of significance was less when considering non-significant TSH correlations as compared to non-significant FT4 correlations (Tables].

DISCUSSION

For the first time a systematic review has been performed studying TSH and FT4/T3 level correlation and various features of subclinical thyroid dysfunction. The results indicated that FT4 and T3 levels correlate better with clinical features than TSH levels. It would appear that clinical features in general result from the exposure of tissues to the combination of FT4 and T3 with there being some variability in tissue differential sensitivity and response to these 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 determining parameter in the diagnosis of subclinical thyroid dysfunctions.

In our previous work we have provided evidence that the set point model of regulation does not apply to the regulation of thyroid hormones [21]. A conservative conclusion of this systematic review is that, **regardless of theoretical considerations**, the assessment of thyroid function based on TSH levels alone does not provide a superior assessment to that based on thyroid hormone levels in terms of clinical features. Certainly, for higher thyroid function, and probably for lower thyroid function, assessment on the basis of thyroid hormones appears superior. There is thereby now evidence that the theoretical basis for, and the empirical basis of, TSH based definitions of subclinical thyroid dysfunction, are flawed.

The correlation between FT4 levels (rather than TSH levels) and clinical features, was more consistent for conditions associated with hyperthyroidism rather than hypothyroidism. Specifically, atrial fibrillation, low bone density, death and frailty correlated better with FT4 than TSH levels when considering high thyroid function, as compared with death, metabolic syndrome and its components in the context of low thyroid function. Nevertheless for the latter parameters, and in particular for metabolic syndrome and steatohepatitis, the weight of the correlations still favoured FT4 rather than TSH.

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 [53]. In these circumstances the effects of chance may be more significant.

There may also be reverse causation [39, 42, 53, 76-80], which may affect correlations with TSH and T3 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 [77] to the increased weight itself [78] or to caloric intake [76]. Again, the concept of a set point has been invoked such that obesity resets the ‘central thyrostat’[80], 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 [81] might also affect the lipid profile adversely [53,54].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 [82], 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 [38, 62]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 with lower thyroid function, TSH levels are providing an additional signal to FT4 levels, in some populations for some conditions. This same possibility seems very unlikely for higher thyroid function. It has been suggested that TSH itself may have physiological effects apart from the stimulation of thyroid hormone levels [35], and such effects rather than via the reflection of thyroid status might explain such a TSH signal. Again, in this scenario, empirically, TSH has less physiological effect than thyroid hormones.

Because many 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 [27- 29, 32, 35, 38, 39, 41-43, 44, 47, 48, 53, 58, 62, 66, 67, 72]. 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’ [29], or ‘tissue’ [42, 48] thyroid status. Our study strengthens this proposition.

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 [27, 36, 41, 42, 62, 67, 72], to a significant difference between pituitary and peripheral sensitivity to FT4 [28, 41, 47, 43. 58], or to statistical/other factors [32, 35, 39, 44, 53]. 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 [11, 20]. Any such disturbance to pituitary 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 [22]. It is this negative relationship, which was again seen in this review [32-35, 40, 65], which is inconsistent with a set point model of regulation. 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 [11, 20]. This is due merely to the fact that nearly all overt thyroid dysfunction is primary rather than secondary [83]. This situation differs from other endocrine pathology whereby the parameter abnormality is likely to be due to a disorder of the parameter controlling factor.

Hypercortisolemia, for example, which is most likely due to Cushing’s disease (ACTH excess), cannot reliably be diagnosed on the basis of an ACTH level in the absence of some measure of cortisol excess[19,84]. Analogously, if a significant proportion of cases of hyperthyroidism were due to TSH excess, it would not be possible to screen for hyperthyroidism using TSH levels alone.

Thus, there has been an illusion that there is something inherently special about the TSH level in terms of individual thyroid function. TSH is merely a good population correlate of thyroid hormone levels, the parameters responsible for the physiological effects. The correlation of TSH levels with the features of thyroid dysfunction merely reflects the correlation between FT4 and TSH.

It is in fact this population correlation between FT4 and TSH which leads to the association of abnormal TSH values with FT4 values at the edges of the normal range. On account of there being a dependence of TSH on FT4 there is a different normal range of TSH levels for different levels of FT4. The TSH range corrected for FT4 indicates the normality of the pituitary response to the FT4 level. The population range for TSH reflects the population range for FT4. Thus a TSH level may be within the population range but outside of the range for a given FT4, and vice versa (Figure 2).Given that thyroid function can be defined as normal in terms of TSH levels, FT4 levels and also as we suggest in terms of the TSH and T4 curves, and given that these different indices do not correlate perfectly with each other, there can be multiple combinations of normal and abnormal indices (Figure2).

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, 27], 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, 27]. 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 (Table). It seems likely that evolutionary mechanisms have arisen to minimize variation from the middle of the normal range of thyroid hormones [85].

It follows from all of the above that it would be more logical to monitor FT4 levels, rather than TSH levels in patients on replacement (not suppressive) thyroxine; i.e. it would be preferable, as a general rule, to aim for FT4 levels in the mid to upper, (if the relative deficiency of T3 is a concern), range rather than aiming for TSH levels in the lower part of the range.

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 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. In the design of any trials of intervention for subclinical thyroid dysfunction it would appear more logical to target FT4 levels as compared with TSH levels.

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, in general, clinical features and TSH levels reflect FT4 levels, argues against central or peripheral sensitivity being an important factor.

Furthermore, as there is no reason to believe that any individual’s particular thyroid hormone levels represent a set-point, 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’ [9] 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.

In summary there is 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, as this systematic review showed, 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 and therapeutic 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 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.

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Figure 1. The generation of individual balance point values of FT4/TSH. Each individual has individual TSH and T4 curves that cross at the individual’s balance point. This point is not independently pre-set.



Figure 1. The generation of individual balance point values of FT4/TSH. Each individual has individual TSH and T4 curves that cross at the individual’s balance point. This point is not independently pre-set.



Figure 2. In diagrammatical form the normal ranges of TSH (pink area) and T4 (green area) curves. The population range of FT4/TSH approximates the range of the TSH curves. It can be seen that as the FT4 level rises, the TSH level falls. There is thus a different normal range for TSH for different FT4 levels. Thus whilst person A has a normal FT4 in the context of normal TSH, T4 and TSH curves, Person B has a normal FT4 level with a TSH levels which is below the population range, but within the range determined by a normal TSH curve. Persons C, D and E demonstrate other combinations of normal/abnormal.

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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Author/year | Parameter | Cohort Study | Population | NOS |
| Gammage 2007[29] | Atrial Fibrillation | Cross-section | UK community  n=5860; age72(65-98);female 51% | 9/9 |
| Baumgartner 2017\*[28] |  | Meta-analysis  Prospective | Various communities  n= 30,085 | \* |
| Cappola 2015[27] |  | Prospective | US community  N=2843; age 75±5; female56% | 9/9 |
| Heeringa[30] |  | Cross-section | Dutch community;n=1455;age 68±8; male 41% | 9/9 |
| Chaker 2016 [72] | Sudden cardiac death | Prospective | Dutch community age≥45  n=10,318;age 65±10;female 57% | 9/9 |
| van de Ven 2014[67] | Mortality | Prospective | Dutch community  n=5816; age 56±18;female 53% | 9/9 |
| Inoue 2016[68] |  | Prospective | U.S. community  n=5257; age 46±17 | 8/9 |
| Yeap 2013 [66] |  | Prospective | Australian community men  n=3885; age 77±3 | 9/9 |
| Chan [36] | Cancer | Prospective | Australian community n=3649;age 51±15; female 56% | 8/9 |
| Tosovic [37] |  | Prospective | Swedish community, n=17035,women born 1932-1950, | 9/9 |
| Khan [38] |  | Prospective | Dutch community;n=10318 ;age 61 (57-68);female 57% | 8/9 |
| van den Beld 2005 [64] | Frailty | Prospective+ cross-section | Dutch community men age≥73 years  n=403; age 78 (73-94) | 9/9 |
| Yeap 2012 [62] |  | Cross-section | Australian community men  n=3943; age 75±4 | 8/9 |
| Bano 2018 [63] |  | Prospective | Dutch community  n=9419 ;age 65±10;female 57% | 9/9 |
| Gussekloo [65] |  | Prospective | Dutch community;n=558;all age 85;female 66% | 8/9 |
| Volpato 2002 [58] | Dementia | Prospective | U.S. community women age≥ 65  n=464;age 77± 0.6 | 8/9 |
| de Jong 2006 [60] |  | Cross-section | Dutch community  n=489, age 73±8; female 48% | 9/9 |
| Choi 2017 [57] |  | Cross-section | Korean, no cognitive impairment  n= 148; age 69±8; female 62% | 9/9 |
| Choi 2015 [59] |  | Cross-section | n = 116 | 5/9 |
| Roef 2011 [33] | osteoporosis | Cross-section | Belgian community , men age 25-45  n=677;age 34±6 | 9/9 |
| van der Deure 2008 [35] |  | Cross-section | Dutch community age≥55  n=1151;age 69±8;female 58% | 9/9 |
| Murphy 2010 [34] |  | Cross-section | European post-menopausal women;  n=1278; age 68 ±7 | 7/9 |
| van Rijn 2014 [32] |  | Cross-section | Dutch post-menopausal women  n=1477; age 50±2 | 9/9 |
| Makepeace 2008 [48] | Obesity/Metabolic syndrome | Cross-section | Australian community  n=1853;age 49±17;female 47% | 9/9 |
| Mehran 2017[42] |  | Prospective | Iran community  n=2393;age38±13;female 61% | 9/9 |
| Shon 2007 [47] |  | Cross-section | Korean women Medical Centre-primary health screening; n=1572; age 46±11 |  |
| Roos 2007 [43] |  | Cross-section | Dutch community  n=1581; age 48 ±12; female 46% | 9/9 |
| Jun 2017 [51] |  | Cross-section | Korean medical centre attendees  n=6235;age 50±8;female 42% | 9/9 |
| Xu 2011[40] |  | Cross-section | Chinese community  n=878;age 72± 4; female 37% | 9/9 |
| Bano 2016 [41] |  | Prospective | Dutch community  n=9640;age 65±10; female 57% | 9/9 |
| Ittermann 2012 [39] |  | Cross-section | German community; n=3661; female 48%,age 48±16;male age 51±16 | 9/9 |
| Knudsen [49] |  | Cross section | Danish community=4082 ‘preponderance of women” | 9/9 |
| Oh [52] |  |  | Korean community; n=4275;age 49; female 50% | 9/9 |
| G- Garcia [44] |  | Cross-section | Mexican community n=3033;age 42±10;female 51% | 9/9 |
| Kim [53] |  | Cross section-retrospective | Korean medical centre attendees; n=13496;age 51±7; male 60% | 9/9 |
| Chaker[50] | 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.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 1st author and year | Studied outcome | ‘Crude’P- value TSH | ‘Crude’P-value FT4 | adjusted P-value TSH | adjusted P-valueFT4 |
| **Studies with hyperthyroidism** | | | | | |
| Gammage 2007 [29 | Atrial Fibrillation | 0.82 | <0.001 | 0.94 | 0.004 |
| Baumgartner 2017 [28] | Atrial Fibrillation | NS | <0.001 | NS | < 0.001 |
| Cappola 2015 [27] | Atrial Fibrillation | 0.09 | 0.001 | 0.12 | 0.02 |
|  | Heart failure | 0.17 | 0.004 | 0.09 | 0.03 |
|  | Composite cardiovascular outcome | 0.05 | 0.008 | 0.04 | 0.02 |
| Chaker 2016 [72] | Sudden cardiac death | 0.17 | 0.008 | 0.18 | 0.022 |
| Van de Ven 2014 [67] | Mortality |  |  | NS | <0.005 |
| Inoue 2016[68] | Mortality | NS | <0.05 | NS | NS |
| Yeap 2013 [66] | Mortality | 0.250 | <0.001 | NS | 0.025 |
| van den Beld 2005 [64] | Mortality | NS | <0.05 |  |  |
| Gussekloo [65] | Mortality | 0.17 | 0.001 |  |  |
|  | Low physical function | NS | 0.006 |  |  |
| Yeap 2012 [62] | Frailty | 0.621 | <0.001 | 0.533 | 0.010 |
|  | Frailty (TSH normal) |  | <0.001 |  | 0.026 |
| Bano 2018 [63] | Change in frailty | 0.5 | 0.001 |  |  |
|  |  |  |  |  |  |
| de Jong 2006[60] | Hippocampal atrophy | NS | <0.05 |  |  |
|  | Amygdala atrophy | NS | <0.05 |  |  |
|  |  |  |  |  |  |
| Roef 2011 [33] | 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 [35] | 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 [34] | Bone density hip | 0.286 | 0.004 |  |  |
|  | Change in bone density hip | 0.065 | 0.015 |  |  |
| Van Rijn 2014 [32] | Bone density lumbar spine | 0.34 | 0.03 |  |  |
|  | Osteoporosis/osteopenia | 0.87 | 0.004 |  |  |
| **Studies with hypothyroidism** | | | | | |
|  |  |  |  |  |  |
| Volpato 2002 [58] | Cognitive decline | 0.97 | <0.001 | 0.99 | 0.02 |
| Choi 2017 [57] | Alzheimer’s disease pathologies | NS | 0.017 | NS | 0.022 |
| Makepeace 2008 [48] | Obesity | 0.29 | <0.001 | 0.53 | <0.001 |
| Oh [52] | High Triglycerides | 0.006 | <0.001 | 0.510 | 0.003 |
| Kim [53] | Obesity (paradoxical) | NS | 0.019 |  |  |
|  | Systolic BP | NS | <0.001 |  |  |
|  | Diastolic BP | NS | <0.001 |  |  |
| G-Garcia [44] | 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 [42] | 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 [47] | Obesity | NS | <0.01 |  |  |
|  | Triglycerides |  |  | NS | 0.005 |
| Roos 2007 [43] | 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 [51] # (paradoxical result) | >/= 2 metabolic risk factors | NS | <0.001 |  |  |
| Xu 2011 [40] | 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 [41] | 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 [39] | 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).

Table of correlations

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Parameter | SCH+  SCH- | Author-year | n | FT4+  TSH- | FT4-  TSH+ | FT4+  TSH+ | FT4-  TSH- |
| Atrial Fibrillation (AF) | SCH+ | Gammage-2007 [29] | 5860 | 3 |  |  |  |
|  |  | Baumgartner- 2017 [28] | 30085 | 30 |  |  | 8 |
|  |  | Cappola-2015 [27] | 2843 | 3 |  |  |  |
|  |  | Heeringa-2008[30] | 1455 |  | 2 |  |  |
|  |  | **Total** |  | **36** | **2** |  | **8** |
|  |  |  |  |  |  |  |  |
| Other Cardiac | SCH+ |  |  |  |  |  |  |
| Heart Failure |  | Cappola-2015 [27] | 2843 | 1 |  |  | 2 |
| Composite outcome |  | Cappola-2015 [27] | 2843 | 1 |  | 1 |  |
| Coronary Heart Disease |  | Cappola-2015 [27] | 2843 | 1 |  |  | 2 |
| Sudden Cardiac Death |  | Chaker-2016 [72] | 10318 | 21 |  |  | 5 |
|  |  | **Total** |  | **24** |  | **1** | **9** |
|  |  |  |  |  |  |  |  |
| Mortality | SCH+ | Van de Ven-2014 [67] | 5816 | 1 |  |  | 3 |
|  |  | Inoue- 2016 [68] | 5257 | 1 |  |  |  |
|  |  | Van den Beld-2005 [64] | 403 | 1 |  |  |  |
|  |  | Cappola-2015 [27] | 2843 | 1 |  | 1 | 1 |
|  |  | Yeap-2013 [66] | 3885 | 18 |  |  | 2 |
|  |  | Gussekloo-2004[65] | 558 | 1 |  | 2 |  |
|  | SCH- | Van de Ven-2014 [67] | 5816 |  | 1 |  |  |
|  |  | Inoue-2016 [68] | 5257 |  | 1 |  |  |
|  |  | **Total** |  | **23** | **2** | **3** | **3** |
|  |  |  |  |  |  |  |  |
| Frailty | SCH+ |  |  |  |  |  |  |
| Frailty |  | Yeap-2012 [62] | 3943 | 2 |  |  | 1 |
| Frailty | SCH+/- | Bano-2018 [63] | 9419 | 1 |  | 4 |  |
| Change in frailty |  | Bano-2018 [63] | 9419 | 4 |  |  | 1 |
| Change in instrumental ADL | SCH+/- | Gussekloo-2004 [65] | 558 |  | 1 |  |  |
|  |  | **Total** |  | **7** | **1** | **4** | **2** |
|  |  |  |  |  |  |  |  |
| Dementia |  |  |  |  |  |  |  |
| Dementia | SCH+ | Cappola-2015 [27] | 2843 |  | 1 |  | 2 |
|  | SCH+ | De Jong-2006 [60] | 489 |  |  |  | 1 |
|  | SCH- |  |  |  |  |  | 1 |
|  | SCH+ | Choi-2015 [59] | 116 |  |  |  | 1 |
| Cognitive decline | SCH- | Volpato-2002 [58] | 464 | 5 |  |  | 5 |
|  |  | Gussekloo-2004 [65] | 558 |  |  |  | 1 |
| Dementia (pathology) | SCH+ | De Jong-2006 [60] | 489 | 2 |  |  |  |
|  |  | Choi-2015 [59] | 116 |  |  |  | 6 |
|  | SCH- | Choi-2017 [57] | 148 | 1 | 1 |  |  |
|  |  | **Total** |  | **8** | **2** |  | **17** |
|  |  |  |  |  |  |  |  |
| Low bone density |  |  |  |  |  |  |  |
| Low bone density | SCH+ | Roef -2011 [33] | 677 | 1 |  |  | 6 |
|  |  | Van der Deure-2008 [35] | 1151 | 8 |  | 3 | 3 |
|  |  | Murphy-2010 [34] | 1278 | 9 | 2 | 1 | 10 |
|  |  | Van Rijn-2014 [32] | 1477 | 4 |  |  |  |
| Fracture |  | Murphy-2010 [34] | 1278 | 1 |  | 1 | 4 |
|  |  | Cappola-2015 [27] | 2843 |  |  |  | 2 |
|  |  | **Total** |  | **23** | **2** | **5** | **25** |
|  |  |  |  |  |  |  |  |
| Cancer | SCH+ | Chan-2017 [36] | 3649 |  | 1 | 5 | 24 |
|  |  | Khan-2016 [38] | 10318 | 6 |  | 1 | 3 |
|  |  | Tosovic 2012 [37] | 17035 | 8 |  |  | 6 |
|  |  | **Total** |  | **14** | **1** | **6** | **33** |
|  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |
| Obesity | SCH- |  |  |  |  |  |  |
| Obesity |  | Makepeace -2008 [48] | 1853 | 7 |  |  | 1 |
|  | SCH+ | Kim-2016 [53] | 13496 | 1 |  |  |  |
|  | SCH- | Shon-2008 [47] | 1572 | 1 |  |  |  |
|  |  | Knudsen-2005 [49] | 4082 |  | 1 | 1 | 1 |
| Waist circumference |  | Mehran-2017 [42] | 2393 | 2 |  | 2 |  |
|  |  | Roos-2007 [43] | 1581 | 2 |  |  |  |
|  |  | Xu-2011 [40] | 878 | 1 |  |  |  |
|  |  | Garduno-Garcia-2010 [44] | 3033 |  |  | 1 |  |
| BMI |  | Xu-2011 [40] | 878 | 1 |  |  |  |
|  | SCH+ | Kim-2016 [53] | 13496 |  | 1 |  |  |
|  |  | Shon-2008[47] | 1572 | 2 |  |  |  |
|  |  | Knudsen-2005 [49] | 4082 |  |  |  |  |
|  |  | Jun-2017[51] | 6235 | 1 |  | 1 |  |
| Abdominal /bodyfat |  | Jun-2017 [51] | 6235 |  |  | 1 | 3 |
|  |  | **Total** |  | **18** | **2** | **6** | **5** |
|  |  |  |  |  |  |  |  |
| NAFLD | SCH- | Xu-2011 [40] | 878 | 1 |  | 2 |  |
|  |  | Bano-2016 [41] | 9640 | 2 | 2 | 2 |  |
|  |  | Itterman-2012 [39] | 3661 | 4 |  |  | 2 |
|  |  | **Total** |  | **7** | **2** | **4** | **2** |
|  |  |  |  |  |  |  |  |
| Hypertriglyceridemia | SCH- | Mehran-2017 [42] | 2393 | 3 | 3 |  |  |
|  | SCH+ | Kim-2016[53] | 13496 |  |  |  | 1 |
|  | SCH- | Shon-2008 [47] | 1572 | 1 |  |  |  |
|  |  | Roos-2007 [43] | 1581 |  |  | 3 |  |
|  | SCH+ | Jun-2017 [51] | 6325 |  | 2 |  |  |
|  | SCH- | Oh-2018 [52] | 4275 | 1 |  | 2 | 1 |
|  |  | Garduno-Garcia-2010 [44] | 3033 |  | 5 |  |  |
|  |  |  |  |  |  |  |  |
|  | SCH+ | Xu 2010 [40] | 878 |  |  | 1 |  |
|  |  | **Total** |  | **5** | **10** | **6** | **2** |
|  |  |  |  |  |  |  |  |
| Diabetes | SCH- |  |  |  |  |  |  |
| Diabetes | SCH- |  |  |  |  |  |  |
|  |  | Chaker-2016 [72] | 8452 |  |  | 20 |  |
|  |  |  |  |  |  |  |  |
|  |  | Jun-2017 [51] | 6325 | 9 | 3 | 13 | 2 |
| Fasting glucose |  | Mehran-2017 [42] | 2393 |  |  |  | 6 |
|  |  | Shon-2008 [47] | 1572 |  |  |  | 1 |
|  |  | Roos-2007 [43] | 1581 | 1 |  |  | 2 |
|  |  | Xu-2011 [40] | 878 |  |  |  | 1 |
|  |  | Kim [53] | 13496 |  | 1 |  |  |
|  |  | Garduno-Garcia-2010 [44] | 3148 | 1 |  |  |  |
|  |  | **Total** |  | **11** | **4** | **34** | **12** |
|  |  |  |  |  |  |  |  |
| Other metabolic syndrome | SCH- |  |  |  |  |  |  |
|  |  | Jun-2017 (51) | 6325 | 9 |  | 4 | 4 |
|  |  | Shon-2008 (47) | 1572 | 1 |  |  | 4 |
|  |  | Roos-2007 [43] | 1581 | 13 | 4 | 2 | 6 |
|  |  | Mehran-2017[42] | 2393 | 7 |  | 6 | 11 |
|  |  | Garduno-Garcia-2010 [44] | 3148 | 14 | 5 | 5 | 1 |
|  |  | Oh-2018 [52] | 4275 |  | 2 | 2 | 8 |
|  |  | Xu-2011 [40] | 878 |  | 1 | 1 | 4 |
|  |  | Kim -2016 [53] | 13496 | 2 | 1 |  | 6 |
|  |  | **Total** |  | **46** | **13** | **26** | **44** |
|  |  |  |  |  |  |  |  |
| Metabolic syndrome | SCH+ | Kim-2016 [53] | 13496 |  |  |  | **2** |
|  |  |  |  |  |  |  |  |
| Total |  |  |  | 222 | 41 | 95 | 164 |
|  |  |  |  |  |  |  |  |

Table of consistency of correlations

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Parameter | author | FT4 | TSH | FT3 |
|  |  |  |  |  |
| AF | Gammage [29] | + | 0 |  |
|  | Baumarttgner 28] | + | 0 |  |
|  | Cappola [27] | + | 0 |  |
|  | Heeringa [30] | 0 | - |  |
|  | *Selmer [26]* |  | - |  |
| ‘dysrhythmia’ | *Vadiveloo [56]* |  | - |  |
| Osteoporosis | Roef [33] | + | 0 | + |
|  | Van der Deure [35] | + | - |  |
|  | Murphy [34] | + | - | + |
|  | Van Rijn [32] | + | 0 |  |
|  | *Yan[31]* |  | *-* |  |
|  |  |  |  |  |
|  |  |  |  |  |
| Cancer | Chan [36] | + | - |  |
|  | Khan [38] | + | 0 |  |
|  | Tosovic [37] | + | 0 |  |
|  |  |  |  |  |
| Obesity | Makepeace [48] | - | 0 |  |
|  | Shon [47] | - | + |  |
|  | Knudsen [49] | - | + |  |
|  | Mehran [42] | - | + |  |
|  | Jun [51] | - | + | + |
|  | G-Garcia [44] | - | + |  |
|  | Roos [43] | - | 0 |  |
|  | Xu [40] | - | 0 | + |
|  | Kim [53] | + | - | + |
|  | *Lin [45]* | - |  |  |
|  | *Svare [55]* |  | + |  |
|  |  |  |  |  |
| Metabolic syn | *Waring [46]* |  | + |  |
|  |  |  |  |  |
|  |  |  |  |  |
| NAFLD | Xu [40] | - | + |  |
|  | Bano [41] | - | + |  |
|  | Itterman [39] | - | 0 |  |
|  |  |  |  |  |
| TG | Mehran [42] | - | + | - |
|  | Roos [43] | - | + | - |
|  | Jun [51] | - | + | + |
|  | Shon [47] | - | 0 |  |
|  | G- Garcia [44] | 0 | + |  |
|  | Xu [40] | - | + | + |
|  | Kim [53] | 0 | 0 | + |
|  | Oh [52] | - | + |  |
|  | *Lin [45]* | - |  |  |
|  |  |  |  |  |
| Low HDL | Jun [51] | - | + | - |
|  | Roos [43] | - | + |  |
|  | Xu [40] | - | + |  |
|  | Kim [53] | 0 | - | + |
|  | G Garcia [44] | - | 0 |  |
|  |  |  |  |  |
| Diabetes | Chaker [50] | - | + |  |
|  | Jun [51] | - | + | - |
|  |  |  |  |  |
| Fasting glucose | Jun [51] | - | 0 | + |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
| Mortality | Van de Ven [67] | + | + |  |
|  | Inoue [68] | + | +/- |  |
|  | Van den Beld [64] | + | 0 |  |
|  | Cappola [27] | + | 0 |  |
|  | Yeap [66] | + | 0 |  |
|  | Gussekloo [65] | + | - | - |
|  | *Moon [70]* |  | + |  |
|  | *Selmer [69]* |  | + |  |
| Dementia | Cappola [27] | 0 | + |  |
|  | Volpato [58] | - | 0 |  |
|  | *Tan[61]* |  | +/- |  |
| Dementia (pathology) | Choi 2015 [59] | - | + |  |
|  | Choi 2017 [57] | 0 | 0 | + |
|  | De Jong [60] | + | 0 |  |
|  |  |  |  |  |
| Frailty | Yeap [62] | + | 0 |  |
|  | Bano [63] | +/- | -/+ |  |
|  | Gussekloo [65] | 0 | - | +/- |
|  |  |  |  |  |
| Other cardiac | Chaker [72] | + | 0 |  |
|  | Cappola [27] | + | - |  |
|  | *Moon [70]* |  | + |  |
|  | *Razvi [71]* |  | + |  |
|  | *Selmer[69]* |  | - |  |
|  | *Vadiveloo [56]* |  | - |  |
|  | *Asvold[73]* |  | + |  |
|  | *Walsh [75]* |  | + |  |
|  | *Inoue [68]* |  | + |  |
|  |  |  |  |  |

AF, osteo cancer SCH+

Nafld, diab SCH-

Obesity low HDL, TG - mostly SCH-

Dementia, mortality, frailty mixed

T3 congruent- osteoporosis, diabetes

T3 incongruent- obesity,

T3 mixed-TG, HDL, frailty

T4 consistent- AF, osteoporosis,cancer ,obesity, NAFLD, TG, HDL , Diabetes

F4 mixed- frailty , dementia, mortality

AF, osteo cancer SCH+

Nafld, diab SCH-

Obesity low HDL, TG - mostly SCH-

Dementia, mortality, frailty mixed

T3 congruent- osteoporosis, diabetes

T3 incongruent- obesity,

T3 mixed-TG, HDL, frailty

T4 consistent- AF, osteoporosis,cancer ,obesity, NAFLD, TG, HDL , Diabetes

F4 mixed- frailty , dementia, mortality

Table P values of not significant correlations

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Author | parameter | p value TSH+/FT4- | Odds ratio  TSH+/FT4- | Confidence range TSH+/FT4- | p value FT4+/TSH - | Odds ratio  FT4+/TSH- | Confidence range FT4+/TSH- |
|  | AF |  |  |  |  |  |  |
| Gammage [29] |  |  |  |  | 0.82,0.94 |  |  |
| Baumgartner [28]] |  |  |  |  |  | 1.09 (ave. Of 14)# | (0.88- 1.34) (ave. Of 14)# |
| Cappola [27] |  |  |  |  | 0.40,0.24 |  |  |
| Heeringa [30] |  | 0.05,0.06 |  |  |  |  |  |
|  |  |  |  |  |  |  |  |
|  | Heart failure |  |  |  |  |  |  |
| Cappola [27] |  |  |  |  | NS |  |  |
|  | Composite |  |  |  |  |  |  |
| Cappola [27] |  |  |  |  | 0.43,0.78 |  |  |
|  | Sudden cardiac death |  |  |  |  |  |  |
| Chaker [72] |  |  |  |  |  | 0.91,0.80,  0.87,0.78  (all x3); 0.74,0.85, 0.83,0.83, 0.81, 0.91 (all x2) | (0.80-1.04),( 0.63-1.04), (0.65-1.16), (0.58-1.06), (all x3); (0.53-1.04), ( 0.65-1.16),(0.64-1.08); (0.64-1.08), (0.62-1.06), (0.65-1.28) (all x2) |
|  | Death |  |  |  |  |  |  |
| Van de Ven [67] |  |  | 1.0 | (0.6-1.8) |  | 1.1 | (0.9-1.3) |
| Inoue [68] |  |  | 0.9 | (0.60-1.36) |  | 0.94 | (0.61-1.43) |
| van den Beld [64] |  |  |  |  | NS |  |  |
| Cappola [27] |  |  |  |  | NS |  |  |
| Yeap [66] |  |  |  |  |  | 0.98, 1.01, 0.99 (all x5); 1.03 (x3)\* | (0.84-1.15),( 0.84-1.23),(0.84-1.17) (all x5), (0.82-1.29) (x3)\* |
| Gussekloo [65] |  |  |  |  | 0.17 |  |  |
|  | Frailty |  |  |  |  |  |  |
| Yeap [62] |  |  |  |  | 0.621,0.533 |  |  |
| Bano [63] |  |  |  |  | 0.3; 0.5,0.5,0.2, |  | (-0.03-0.42) |
| Gussekloo [65] |  | 0.09 |  |  |  |  |  |
|  | Dementia |  |  |  |  |  |  |
| Cappola [27] |  | NS |  |  |  |  |  |
| Volpato [58] |  |  |  |  | 0.48,0.48, 0.97, 0.99, NS |  |  |
| de Jong [60] |  |  |  |  |  | 0.04,0.03^ | (-0.02-0.11),(-0.03-0.08) |
| Choi [59] |  | NS |  |  | NS |  |  |
|  |  |  |  |  |  |  |  |
|  | Low bone density |  |  |  |  |  |  |
| van der Deure [35] |  |  |  |  | 0.24,0.06,0.10, 0.59,0.20,0.07, 0.10,0.07,0.26, NS |  |  |
| Murphy [34] |  | 0.443,0.362 |  |  | NS,NS,0.167, 0.556,0.190, 0.065,0.761, 0.062,0.115 |  |  |
| Van Rijn [32] |  |  |  |  | 0.34, 0.87, NS, 0.39 |  |  |
| Roef [33] |  |  |  |  | NS |  |  |
|  | Fracture |  |  |  |  |  |  |
| Murphy [34] |  |  |  |  | 0.167 |  |  |
|  |  |  |  |  |  |  |  |
|  | Cancer |  |  |  |  |  |  |
| Chan [36] |  | 0.089 |  |  |  |  |  |
| Khan [38] |  |  |  |  | NS x 6 |  |  |
| Tosovic [37] |  |  |  |  | 0.2, 0.14,0.28. 0.38 | 0.86,0.90, 1.00, 0.94 | (0.69-1.08),(0.77-1.06),(0.67-1.07), (0.76-1.09) |
|  |  |  |  |  |  |  |  |
|  | Obesity |  |  |  |  |  |  |
| Makepeace [48] |  |  |  |  | 0.29,0.53, 0.59, 0.50, 0.87,0.52 0.84 |  |  |
| Shon [47] |  |  |  |  | NS x3 |  |  |
| Knudsen [49] |  | NS |  |  |  |  |  |
| Roos [43] |  |  | 1,1.01 | (0.99-1.01)  X2 | 0.162,0.993 |  |  |
| Mehran [42] |  |  |  |  |  |  |  |
| Xu [40] |  |  |  |  | 0.063,0.156 |  |  |
|  |  |  |  |  |  |  |  |
|  | Triglcerides |  |  |  |  |  |  |
| Shon [47] |  |  |  |  | NS |  |  |
| Mehran [42] |  | 0.87,0.11, 0.093 |  |  |  | 1x3 | (0.99-1.01),(0.99-1.03),0.99-1.01) |
| Jun [51] |  | NSx2 |  |  |  |  |  |
| Oh [52] |  |  |  |  | 0.510 |  |  |
| Garduno-Garcia [44] |  | 0.053, NSx4 |  |  |  |  |  |
|  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |
|  | Diabetes |  |  |  |  |  |  |
| Jun [51] |  | 0.146,0.8380.589 |  |  | 0.078,0.148  0.157,0.133NS | 1.55,1.27 | (0.76-3.14),(0.86-1.90) |
| Roos [43] |  |  |  |  | 0.075 |  |  |
| Garduno-Garcia [44] |  | 0.775 |  |  |  |  |  |
|  | Other metabolic syn |  |  |  |  |  |  |
| Shon [47] |  |  |  |  | NS |  |  |
| Jun [51] |  |  |  |  | NSx6,0.5240.176,0.154 |  |  |
| Roos [43] |  | 0.122,0.1400.6910.587 |  |  | 0.670,0.490  0.594,0.224  0.501,0.401  0.098,0.411  0.758,0.690  0.610,0.634NS |  |  |
| Mehran [42] |  |  |  |  | 0.92,0.49, 0.71 | 1,0.99 x3 | (0.99-1.02),(0.96-1.1),(0.99-1) |
| Oh [52] |  | 0.168,0.883 |  |  |  |  |  |
| Garduno-Garcia [44] |  | NSx5 |  |  | NS x 11,0.120 0.108, 0.85 |  |  |
| Xu [40] |  | 0.143 |  |  |  |  |  |
|  |  |  |  |  |  |  |  |
| Kim [53] |  | NS x2 |  |  | NS x2 | 0.888  0.919  0.926 | (0.747-1.055)  (0.772-1.095) (0.727-1.178) |
|  | Steatohepatitis |  |  |  |  |  |  |
| Xu [40] |  |  |  |  | NS |  |  |
| Itterman [39] |  |  |  |  | 0.928,0.069  0.509,0.594 |  |  |
| Bano [41] |  |  | 0.41,0.59 | (0.09-1.73)  (0.13-2.59) |  | 1.07,1.08 | (0.98-1.17),(0.95-1.23) |
|  |  |  |  |  |  |  |  |

# Conservative approximation

\*Similar values grouped

Correlations summed FT4/T3/TSH

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Parameter | Author | T3/FT4/TSH+ | T3/FT4+/TSH- | T3+/FT4-/TSH+ | T3+ /FT4/TSH- | T3- / FT4/TSH+ | T3-/FT4+ /TSH- | T3-/FT4-TSH+ | T3/FT4/ TSH- |
| Bone density | Murphy [34] | 1 | 3 | 1 | 2 |  | 4 |  | 6 |
|  | Roef [33] |  |  |  | 7 |  | 1 |  | 4 |
|  | Cappola [27] |  |  |  |  |  |  |  | 2 |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  | 3 |  |  |
| AF | Cappola [27] |  |  |  |  |  |  |  |  |
| Other heart |  |  |  |  |  | 1 | 3 |  | 4 |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
| Mortality | Cappola [27] |  |  |  |  |  | 1 |  |  |
|  | Van den Beld [64] |  |  |  |  |  | 1 |  |  |
|  | Gussekloo [65] | 1 |  |  |  |  |  | 1 |  |
|  |  |  |  |  |  |  |  |  |  |
| Dementia | Cappola [27] |  |  |  |  |  |  |  |  |
|  | Choi [59] |  |  |  |  |  |  |  | 1 |
|  | De Jong [60] |  |  |  |  |  |  |  | 2 |
| (path) | De Jong [60] |  |  |  |  |  | 2 |  |  |
|  | Choi [57] |  |  |  |  |  | 1 | 1 |  |
|  | Choi [59] |  |  |  | 4 |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
| Cancer | Tosovic [37] |  |  |  |  |  | 5 |  | 4 |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
| Met S/fatty liver |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  | Knudsen [49] |  |  |  |  | 1 |  |  |  |
|  | Xu [40]\* | 1 | 2 |  | 2 | 1 | 2 | 1 | 2 |
|  | Jun [51]\* | 10 | 12 | 6 | 9 | 2 |  |  | 1 |
|  | Itterman [39] |  |  |  |  |  | 2 |  | 1 |
|  | Roos [43] | 3 | 8 |  | 3 |  | 6 | 2 | 6 |
|  | Kim [53]\* | 1 | 4 | 2 | 1 | 1 |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
| Frailty | Gussekloo [65]# |  |  |  | 10 |  |  | 1 | 5 |
|  | Van den Beld [64] |  |  |  |  |  |  |  | 3 |
|  |  |  |  |  |  |  |  |  |  |
| Total |  | 17 | 29 | 9 | 38 | 7 | 31 | 6 | 41 |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |

* \* T3 correlations paradoxical – reverse causation- responding to metabolic syndrome [51]
* # T3 correlations reverse causation – manifestation of sick euthyroid syndrome [65]