


Low TSH Is Associated With Frailty in an Older Veteran Population Independent of Other Thyroid Function Tests

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Abstract

Low TSH is associated with frailty in the older adult. We studied whether low TSH is an independent marker of frailty or is an indicator of subclinical hyperthyroidism, which in turn predicts frailty. Of outpatient veterans seen between January 2005 and December 2016, we identified 100 patients aged ≥ 60 years with two low TSH ($< 0.5 \mu\text{IU/ml}$) and one fT3 measurement and 50 matched controls (TSH $0.5\text{--}5.0 \mu\text{IU/ml}$). We used a deficit accumulation approach to create a frailty index (FI). The higher the FI, the more likely ($p < 0.001$) that patients had expired. Patients with low ($0.31 \pm 0.11 \mu\text{IU/mL}$) versus normal ($1.84 \pm 0.84 \mu\text{IU/mL}$) TSH had higher mean FI compared to controls (0.25 ± 0.12 vs. 0.15 ± 0.07 , $p < .001$). Low TSH was significantly associated with frailty ($p < .001$), independent of age. However, lower TSH was not associated with higher fT3 or fT4 levels. There was a nonsignificant inverse association of fT3 levels with FI ($p = .13$), which disappeared when adjusted for age. Similar to prior studies, low TSH was associated with frailty. However, neither fT3 nor fT4 predicted low TSH or FI, suggesting that the association of low TSH with frailty is not due to subclinical hyperthyroidism, but perhaps to effects of comorbidities on TSH secretion.

Keywords

comorbidity, frailty index, free T3, veterans

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Introduction

Thyroid function is often assessed in the older adult in outpatient settings for a wide range of symptoms. Currently thyroid stimulating hormone (TSH) is the most common test used to screen for abnormal thyroid function. Results outside the laboratory range of normal in the absence of symptoms are categorized as subclinical thyroid dysfunction. The prevalence of subclinical hyperthyroidism in a representative sample of US subjects without known thyroid disease is 0.7% (TSH $< 0.1 \mu\text{IU/mL}$) and 1.8% (TSH $< 0.4 \mu\text{IU/mL}$; Hollowell et al., 2002). The 2016 American Thyroid Association Guidelines for the Diagnosis and Management of Hyperthyroidism and Other causes of Thyrotoxicosis recommends treatment of subclinical hyperthyroidism when TSH is persistently $< 0.1 \mu\text{IU/mL}$ in all individuals ≥ 65 years of age; in patients with cardiac risk factors, heart disease or osteoporosis (Strong recommendation, moderate-quality evidence). When

TSH is persistently below the lower limit of normal but $\geq 0.1 \mu\text{IU/mL}$, treatment of subclinical hyperthyroidism should be considered in individuals ≥ 65 years of age and in patients with cardiac disease, osteoporosis, or symptoms of hyperthyroidism (Weak recommendation, moderate-quality evidence) (Ross et al., 2016).

Frailty is a geriatric multidimensional state of increased risk (Morley et al., 2013; Rockwood & Mitnitski, 2007; Urdangarin, 2000) and has been shown to be an independent predictor of mortality (Hope et al., 2015; Zeng et al., 2015). Studies have suggested that subclinical thyroid dysfunction and, in particular, low

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levels of TSH, may be associated in the community dwelling older adult with frailty (Veronese et al., 2017; Virgini et al., 2015). However, most of these studies have failed to distinguish idiopathic, chronic TSH hyposecretion from suppression of TSH by autonomous overproduction of thyroid hormone, producing a state of mild or “subclinical” hyperthyroidism. Moreover, in some reports, higher levels of free T4 (thyroxine), but not low TSH, predicted frailty (Yeap et al., 2012) or mortality (Yeap et al., 2013). Cappola et al. (2015), in a study of 2843 community-dwelling adults, reported that “higher TSH was negatively associated ($p=.03$) and higher free T4 was positively associated ($p=.007$) with mortality.” However, it remains unclear the extent to which aging and associated chronic illness lead to reduced function of the hypothalamic pituitary axis, and hence a non-causal association of low TSH with frailty versus a causal association due to effects of thyroid hormone elevations. Measurement of free T3 (triiodothyronine) is a highly accurate predictor of thyroid hormone status, since free T3 is nearly always increased in thyrotoxicosis even in the approximately 14% of cases in which free T4 is not elevated (Figge et al., 1994). With physiologic aging, there is an increase in TSH levels with an inversely correlated free T3 but relatively stable free T4 level (Clegg & Hassan-Smith, 2018).

We aimed to investigate whether the reported association of low TSH with frailty is due to its being an indicator of subclinical hyperthyroidism, as assessed by Free T3 levels, or whether low TSH is independently associated with frailty, regardless of thyroid hormone production.

Methods

Study Population

This is a single institution retrospective cross sectional study approved by the Phoenix VA Institutional Review Board. The retrospective chart review was completed between January 2017 and December 2018.

Utilizing VA Informatics and Computing Infrastructure (VINCI), VA HSR RES 13-457, U.S. Department of Veterans Affairs (2008), we obtained a subject list of patients at or above the age of 60 years, seen at least once at the Phoenix VA between 2005 and 2016. In March 2018, using additional laboratory code search criteria, we obtained a list of patients with low TSH on at least two separate test dates and a measured free T3 within 6 months of either TSH measurement. Free T3 was ordered at the discretion of the provider. Low TSH was defined as a value below $0.5 \mu\text{IU/mL}$ which is the lower limit of the reference range for our laboratory (Burkhardt et al., 2014). Of the 300 patients allocated to the low TSH group, additional exclusion criteria were applied. These were inpatient status, symptoms or evidence of overt hyperthyroidism, any listed thyroid medications

(including Levothyroxine or Synthroid, Armor thyroid or Nature Thyroid, Amiodarone, recent Lithium use, Methimazole, Propylthiouracil, high dose Corticosteroids, or Radioactive Iodine). Additionally, patients with insufficient data (two or more missing variables) to definitively calculate a frailty index (FI) were excluded. Of the 300 patients with low TSH, 100 patient charts meeting all criteria, were analyzed.

The control group consisted of patients age and sex matched to the low TSH group but with normal TSH measurements (TSH $0.5\text{--}5.0 \mu\text{IU/mL}$). In November 2018, a list of control patients was obtained. Of the 100 patients eligible for the control group, the 50 patient charts best matching age and sex of the low TSH group were selected for analysis after excluding those with insufficient data to definitively assign an FI (Figure 1)

Laboratory Measurements

The Phoenix VA laboratory uses Abbott’s automated Chemiluminescent Microparticle Immunoassay (CMIA) for the quantitative determination of TSH, free thyroxine (free T4) and free triiodothyronine (free T3) in human serum and plasma. The normal reference interval for each of these is set at TSH of 0.5 to $5 \mu\text{IU/mL}$, free T3 of 1.50 to 4.20 pg/mL , and free T4 of 0.70 to 1.48 ng/dL .

Frailty Index

For the purpose of this retrospective study, we used a syndromic or deficit accumulation approach to derive a frailty index (Rockwood & Mitnitski, 2007). This approach assumes that frailty is an age associated, non-specific vulnerability and that symptoms, signs, diseases, and disabilities are considered deficits (Morley et al., 2013). The deficit accumulation frailty index does not require physical testing but correlates well with other phenotypic frailty indices (Drubbel et al., 2013). The validity of this tool improves with a higher number of variables (Theou et al., 2013). We chose 31 variables which could be readily assessed by chart review with further specifications to assign a present or absent status (Supplemental Table 1).

All patient charts reviewed had sufficient information on at least 30 of the 31 items so that no charts were excluded due to inability to calculate FI. For each variable the patient was given a score of 1 if the condition was present and 0 if absent. FI was calculated as the total sum score divided by the number of non-missing items. Thus, each patient was assigned an FI between 0 and 1. We also recorded mortality status at the time of assessment and compared FI values in living versus deceased subjects.

Statistical Analyses

Statistical analyses were performed using the SAS software (version 9.4; Cary, N.C.). Alpha was set at 0.05.

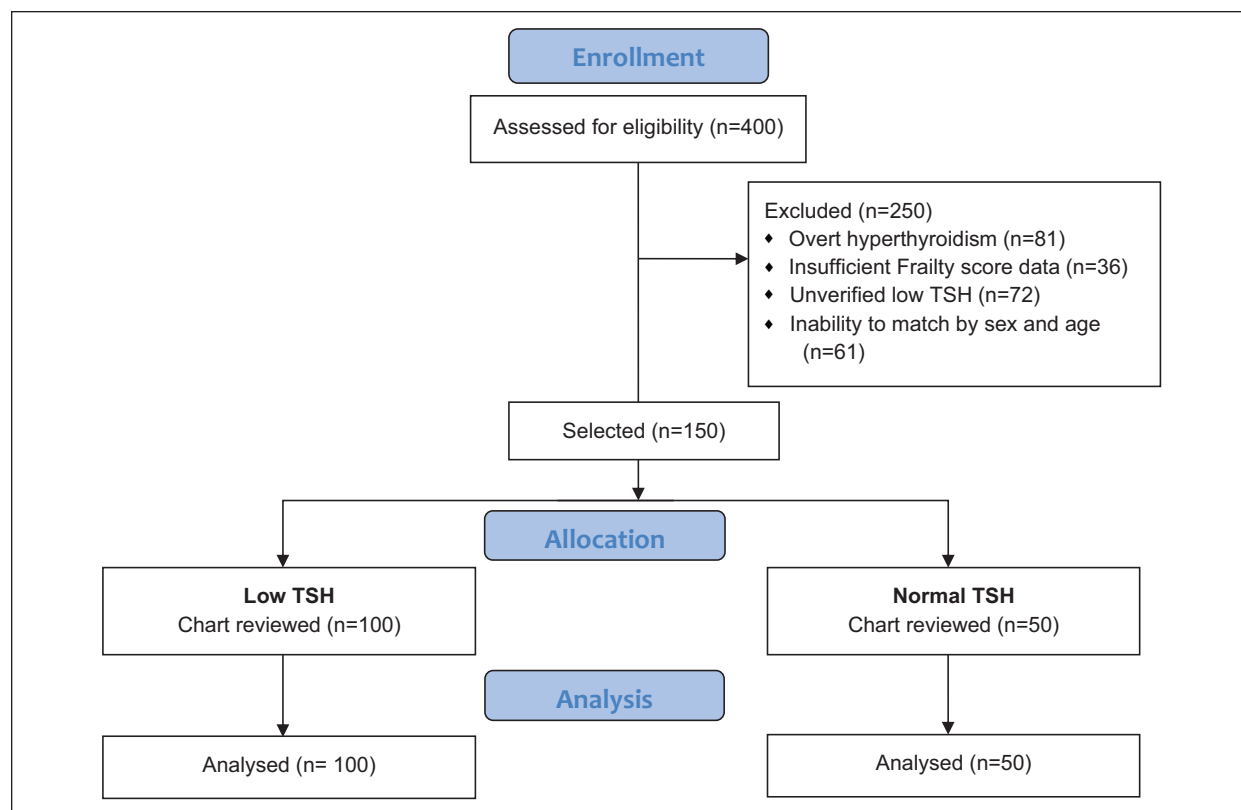


Figure 1. Consort flow diagram.

Table 1. Characteristics of Study Patients.

Variable	Normal TSH ^a	Low TSH ^b
Age (years)	70.7 ± 6.2 (61, 87)	69.6 ± 6.2 (60, 90)
TSH (μIU/mL)	1.84 ± 0.84 (0.77, 4.15)	0.31 ± 0.11 (0.02, 0.49)*
Free T3 (pg/mL)	N/A	2.83 ± 0.47 (1.67, 4.04)
Free T4 (ng/dL)	N/A	1.08 ± 0.14 (0.72, 1.43)
Sex (F/M)	5/45	7/93
Frailty index	0.15 ± 0.07 (0.03, 0.35)	0.25 ± 0.12 (0.03, 0.65)*

Note. Values are presented as mean ± SD (minimum, maximum).

TSH=thyroid stimulating hormone; T3=triiodothyronine; T4=thyroxine.

p-values were calculated by independent *Student's T* test between the two groups.

^aN=50.

^bN=100.

*p < .001.

Data are presented as Mean ± SD. Mean and SD values were calculated for each of FI, TSH, free T4, and free T3, T3/T4 ratio as well as patient age. We compared FI and thyroid function measurements between low TSH and control groups and FI between living and deceased patients by independent *Student's t-test* and sex by χ^2 . Pearson's correlations were used to quantify associations between TSH, free T3, free T4, T3/T4 ratio, age at TSH measurement and FI. Initial univariate regressions were performed using frailty index as the dependent and free T4 and free T3 measurements as the independent variables. Multivariate regression analyses were performed to evaluate the potential effects of likely

confounding variables (Cohen, 1988; Field, 2009; Huberty, 1994; McNeil et al., 2011; Newman et al., 2015).

Results

Our initial analysis showed that patients who died in the interim between the time TSH was recorded and our examination of the charts had a higher mean frailty index (0.32 ± 0.12 vs. 0.18 ± 0.08 , $p < .001$) (mean ± SD). Table 1 shows the characteristics of the study patients. Ages of control and low TSH groups were comparable at (70.7 ± 6.2) versus (69.6 ± 6.2)

Table 2. Univariate and Multivariate Correlations.

Variables	β	r^2	F	p -value
Model 1 ^a		0.08		<.0001
TSH	-0.038		13.17	.0004
Model 2 ^a		0.17		
TSH	-0.042		17.91	<.0001
Age	0.005		16.19	<.0001
Model 3 ^b		0.02		.13
fT3	-0.389		2.33	.13
Model 4 ^b		0.10		.0067
fT3	-0.021		0.7	.4
Age	0.005		8.05	.0056
Model 5 ^b		0.01		.39
fT4	0.076		0.76	.39
Model 6 ^b		0.10		.005
fT4	0.094		1.28	.26
Age	0.005		10.38	.0018
Model 7 ^b		0.02		.12
fT3/fT4 ratio	-0.036		2.4	.12
Model 8 ^b		0.10		<.0001
fT3/fT4 ratio	-0.026		1.26	.26
Age	0.005		8.57	.004
Model 9 ^b		0.11		<.0001
Age	0.005		8.21	.0051
TSH	-0.003		0	.98
fT3	-0.267		1.07	.3
fT4	0.108		1.63	.2

Note. All results obtained by linear models, except for fT3, which did not meet criteria for normally distributed data.

fT3=free triiodothyronine; fT4=free thyroxine; TSH=thyroid stimulating hormone.

Units: TSH (μ IU/mL), Age (years), fT3 (pg/mL), fT4 (ng/dL).

^aN=150.

^bN=100.

years respectively. Of controls 10% were women versus 7% of the low TSH patients. TSH levels were higher in the control ($1.84 \pm 0.84 \mu$ IU/ml) versus the low TSH ($0.31 \pm 0.11 \mu$ IU/ml) group ($p < .001$). Thyroid hormone levels were not available for the control patients but were all within the reference ranges for free T3 and free T4 in the low TSH group. Finally, mean FI was significantly lower in the control than in the low TSH group (0.15 ± 0.07 vs. 0.25 ± 0.12 , $p < .001$).

Figure 2 presents the distribution of individual FI values with means and SDs for normal and low TSH patient groups showing significant overlap of values, but with higher mean FI in the low TSH group.

The two graphs in Figure 3 show the relationships of age to frailty index and to thyroid status as indicated by free T3. As assessed by Pearson Correlation coefficients, Figure 3A shows the predictable significant ($p < .001$) association of frailty index with age. Figure 3B shows a significant ($p = .01$), inverse association of free T3 with age.

As shown in Figure 4A there was a highly significant inverse correlation of TSH with FI ($p < .001$). In subsequent multivariate analyses (Table 2), the effects of TSH and age on FI were found to be mutually

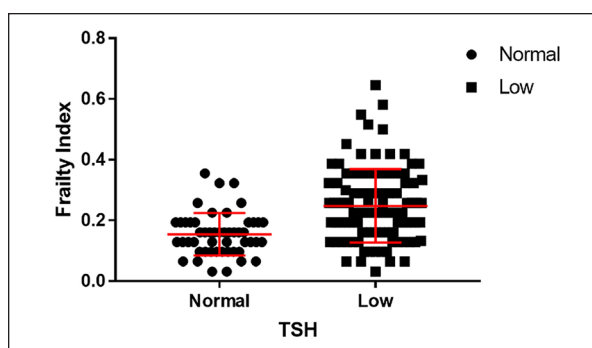


Figure 2. Frailty index and thyroid function for Normal and low TSH groups, distributions, means, and standard deviations. Note the significant overlap of values but the higher mean FI in the low TSH group ($p < .001$) by independent students' t -test.

independent. In Figure 4B there is a trend for decreasing free T3 levels as FI increases, but this apparent inverse relationship was nonsignificant ($p = .13$). The trend completely disappeared when data were adjusted for age ($p = .4$). Not surprisingly, age was consistently a significant predictor of FI in all the models in which age was included. The fT3/fT4 ratio was not correlated to either FI or TSH level in our study. Additionally, TSH values within the low TSH group did not correlate with the degree of frailty, likely due to the limited range of TSH values in this group. In further analysis within the low TSH group, we found that TSH was not significantly correlated with either free T3 ($p = .29$) or free T4 ($p = .70$).

Discussion

We investigated the association of subclinical hyperthyroidism and frailty in a population of older Veterans enrolled at the Phoenix VA Health Care System. We created a novel frailty index using a deficit accumulation approach based on 31 variables (Searle et al., 2008). A similar frailty index was created in another veteran population using at least 30 of 44 variables in a recently published study (Baskaran et al., 2020). We recorded mortality data at the time of our assessment and demonstrated higher mortality with higher FI, a finding consistent with prior studies (Hope et al., 2015; Zeng et al., 2015). Our results comparing our FI with TSH concentrations confirm previous findings (Veronese et al., 2017; Virgini et al., 2015; Yeap et al., 2012) that low TSH is associated with frailty. Our finding that patients with normal TSH levels were less frail than those with low TSH levels is further evidence for this relationship. In prior studies (Bano et al., 2018), it was hypothesized that the relationship of low TSH to frailty and/or mortality was actually mediated by increased thyroid hormone levels, that is, subclinical hyperthyroidism, which suppressed the TSH. However, none of these studies evaluated free T3, which is probably the best measurement for diagnosing thyrotoxicosis (Figge et al., 1994). One study looked at low free T3 as a possible marker

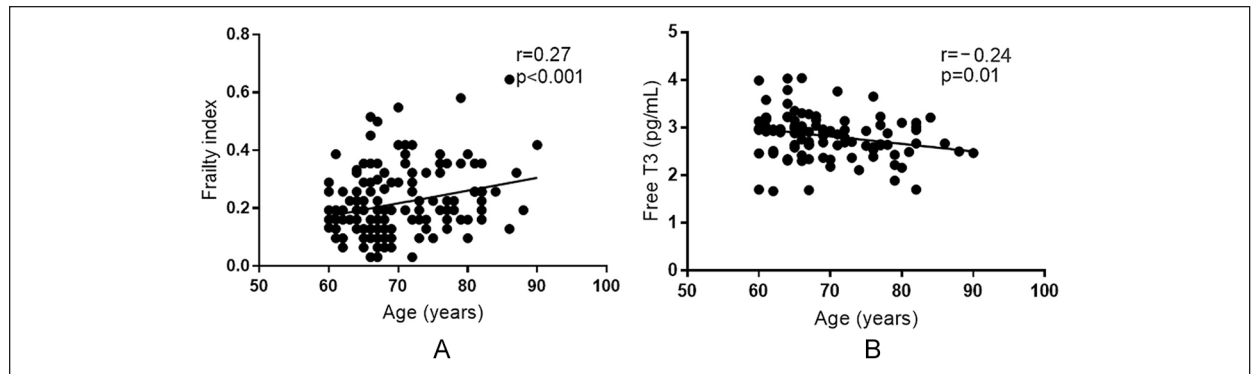


Figure 3. Age influence on Frailty Index (A) and free T3 (B). Scatterplot diagrams where the continuous line shows a positive association of FI with age ($p < .001$) in 3A and inverse association of free T3 with age ($p = .01$) in 3B by Pearson correlation coefficient.

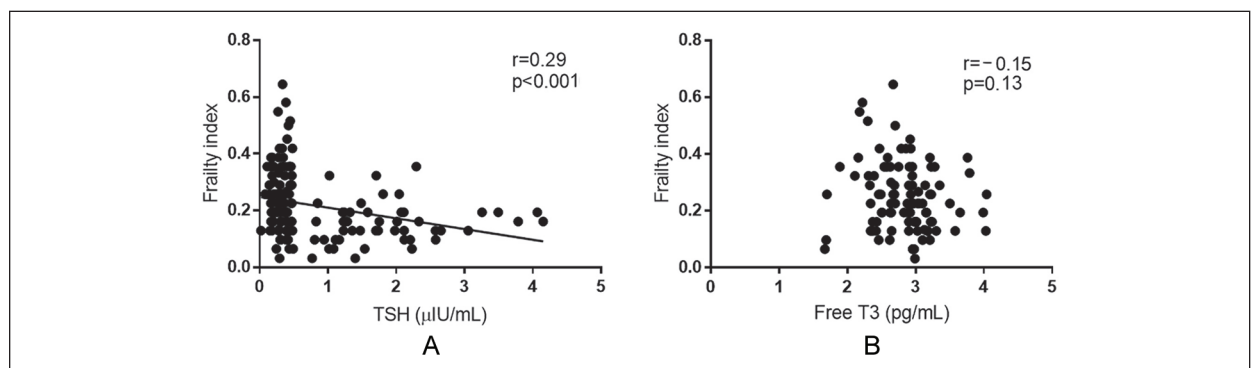


Figure 4. The association of Frailty Index with thyroid function as assessed by TSH (A) and free T3 (B). Scatterplot diagrams where the continuous line shows an inverse correlation of TSH with FI ($p < .001$) in 4A and no significant relationship of FI with free T3 in 4B by Pearson correlation coefficient.

of frailty and concluded that measuring free T3 can be a useful laboratory parameter in frailty assessments (Bertoli et al., 2017).

In contradiction of the above hypothesis, we found that neither free T3 nor free T4 was associated with frailty, nor was either thyroid hormone concentration correlated with TSH within our low TSH group, independent of age. These findings suggest that the association of low TSH with frailty may be due to the effects of comorbidities on TSH secretion, rather than low TSH serving as an indicator of subclinical hyperthyroidism.

Another hypothesis recently proposed is that the peripheral degradation of thyroxine, as indicated by $\text{ft3}/\text{ft4}$ ratio is a more accurate indicator of frailty and possibly of early mortality than is free T3 alone (Pasqualetti et al., 2018). Our results did not confirm this finding. We postulate that the difference results from the clinical setting in which the patients were tested. The above study looked at older hospitalized patients in whom more severe nonthyroidal illness was driving $\text{ft3}/\text{ft4}$ ratios lower. The ratio in this setting may be an indicator of acute illness rather than of frailty. Our patient population on the other hand, was mainly outpatient with various chronic conditions, but not acute illness.

Our finding that aging and frailty were, if anything, correlated with lower free T3 levels could be taken as further evidence against the subclinical hyperthyroidism hypothesis and is consistent with the known effects of age and illness to shift the metabolism of T4 from T3 to rT3 (reverse T3) production (Peeters et al., 2005).

It remains to be elucidated how low TSH is linked to frailty. With aging, healthy individuals typically have lower free T3 and higher TSH levels (Clegg & Hassan-Smith, 2018). The reduction in free T3, a catabolic hormone, is likely beneficial. A possible reason why free T3 failed to correlate with frailty in our study may lie in the fact that its value is highly variable and may be dependent on factors such as iodine consumption and genetic makeup. Our study justifies further investigation, possibly a longitudinal clinical trial to determine whether treatments to improve overall health and lower FI increase TSH in this high-risk population.

Strengths of our study included reliable measurements of thyroid hormones in a sufficiently large group of Veterans to allow us to age-match patients with low versus normal TSH measurements and the availability of extensive clinical data in our electronic medical record, which allowed complete characterization of our

frailty variables in nearly all patients. Weaknesses of our study include the facts that it was comprised of mainly male Veterans with only 8% female patients due to our older veteran population's demographics. This may also limit generalizability of our findings to the older community dwelling population in the United States. Our study was cross-sectional, so that the longitudinal association of frailty and mortality by one or more low TSH levels could not be evaluated. Finally, we did not have sufficient measurements of free T4 and free T3 in our controls with normal TSH levels to allow us to evaluate thyroid hormone relationships in this group.

In conclusion, our data strongly suggest that low TSH is associated with frailty, and likely also mortality, independent of its relationship to free T3 or free T4. Therefore, low TSH in this context is almost certainly not, as has been supposed by some (Davey et al., 1996; Ross et al., 2016) an indicator of subclinical hyperthyroidism.

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Author Contributions

Nalini S Bhalla: literature search, study design, data collection, and drafting of manuscript. Karyne Lima Vinales: data analysis, data interpretation, graphs, and revision of manuscript. Ming Li: literature search and revision of manuscript. Richa Bhattarai: data collection. Janet Fawcett: literature search and data collection. Sherman Mitchell Harman: literature search, study design, data interpretation, drafting, and revision of manuscript. All authors read and reviewed the final manuscript.

Declaration of Conflicting Interests

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Impact Statement

We certify that this work is novel and may improve our understanding of thyroid function studies.

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Supplemental Material

Supplemental material for this article is available online.

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