

SCIENTIFIC REPORTS



OPEN

Higher FT4 or TSH below the normal range are associated with increased risk of dementia: a meta-analysis of 11 studies

Received: 12 February 2016

Accepted: 26 July 2016

Published: 25 August 2016

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Observational studies of thyroid function and dementia have reported conflicting results. We reviewed cohort and case-control studies from MEDLINE, EMBASE, Web of Science and the Cochrane Library that focused on the association between serum thyroxine, thyrotropin and dementia. A total of 24,952 participants from three case-control and eight cohort studies were included. The relationships between dementia and the per standard deviation (SD) increment of free thyroxine (FT4) (random relative ratio (RR) = 1.08, 95% confidence interval (CI) 1.00–1.17) and thyroid-stimulating hormone (TSH) (fixed RR = 0.91, 95% CI 0.84–0.99) were well established. TSH levels in the low category were associated with an increased risk of dementia (fixed RR = 1.60, 95% CI 1.27–2.00). However, the positive association was confined to TSH levels below the normal range (fixed RR = 1.77, 95% CI 1.31–2.39), not those in the lower tertile of the normal range (fixed RR = 1.39, 95% CI 0.98–1.97). Additionally, dementia was not significantly associated with high TSH levels (fixed RR = 0.99, 95% CI 0.76–1.29). Furthermore, there was no positive association between dementia and the low or high categories of TSH in men. Thus, individuals with higher FT4 levels or those with TSH levels below the normal range have an increased risk of dementia.

Dementia is a clinical syndrome characterized by a cluster of symptoms and signs that results in complex cognitive decline; it has emerged as one of the greatest health threats during old age and has substantial socioeconomic costs. Alzheimer's disease (AD), which is the most common type of dementia, constitutes 50–70% of cases¹ and is one of the top 8 major health problems in the world². Despite recent advances in research, major scientific gaps remain in the understanding of the intrinsic mechanism of dementia. In the absence of medications that effectively cure or slow the progression of these diseases, especially AD^{3,4}, considerable challenges associated with early intervention remain. The development of preventive measures for dementia requires a greater understanding of the risk factors for this disease. Accordingly, we may prevent the elderly from further cognitive decline.

Thyroid hormone (TH) regulates metabolic processes that are essential for normal growth and development as well as neurocognitive function after development⁵. Thyroid-stimulating hormone (TSH) targets the thyroid gland and triggers the release of thyroxine (T4) and triiodothyronine (T3) when stimulated by the hypothalamic secretion of thyrotropin-releasing hormone (TRH)⁶. The relationship between thyroid-related hormones and dementia is controversial, especially regarding TSH (whether outside or within the normal range)^{7–10}. According to laboratory tests, thyroid dysfunction can be classified as overt, with both abnormal TSH and free T4 (FT4) levels, or as subclinical, with abnormal TSH but normal FT4 levels. Some studies have demonstrated a relationship between overt thyroid disease and cognitive disturbances^{11,12}. However, the influence of subclinical thyroid disease on cognition remains unclear. Since Wahlin *et al.*¹³ first reported an association between poor cognition and low serum TSH levels within the normal range, more researchers have become interested in the impact of thyroid hormone levels (within the normal range) on cognition^{7,14}. Moreover, the role of FT4 levels in the development or progression of dementia remains controversial. Certain large prospective studies have observed that higher FT4 levels are related to dementia^{15,16}, whereas other studies have not reported this association^{10,17}. Therefore, it is

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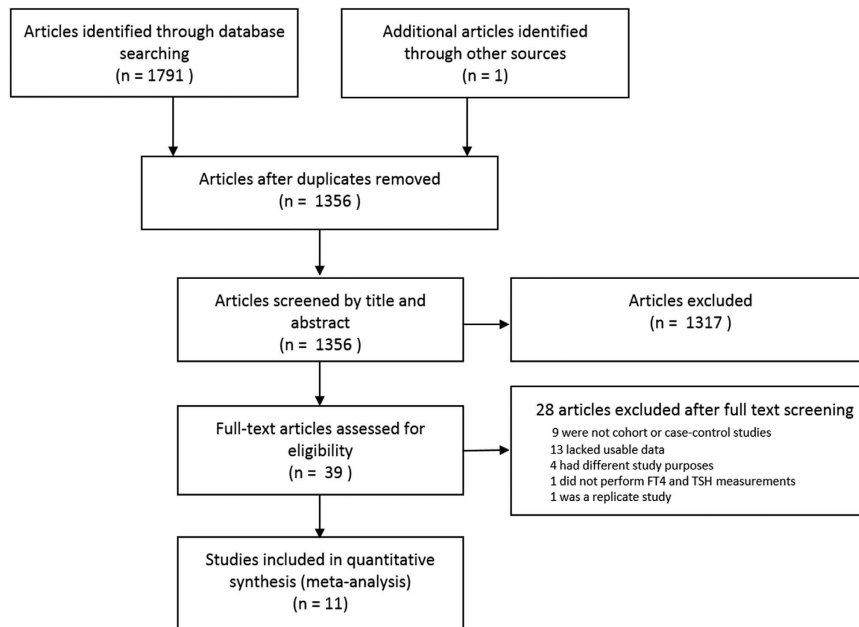


Figure 1. Flow diagram of study retrieval and selection.

necessary to conduct a systematic review and meta-analysis to summarize the published findings and to obtain a better understanding of the association between FT4, TSH and dementia.

Results

Eligible studies and characteristics. The search strategy identified 1791 citations for evaluation. A manual review of the study references yielded one additional study. After carefully scanning the titles and abstracts, 39 articles that were potentially eligible for inclusion were retrieved. After reading the full texts, 28 articles were excluded for the following reasons: nine studies were not cohort or case-control studies^{18–26}; 13 lacked usable data^{13,14,17,27–36}; four had different study purposes^{37–40}; one did not perform FT4 and TSH measurements⁴¹; and one was a replicate study with a shorter follow-up⁴² than that by de Jong *et al.*¹⁰ (Fig. 1). Eleven studies published from 2003 to 2016 that evaluated a total of 24,952 participants, including 1526 patients with dementia, were finally included. The detailed information is provided in Table 1. Among the included studies, three^{43–45} were case-control studies, and eight^{7–10,15,16,46,47} were cohort studies. Specifically, the work by Tan *et al.*⁹ was analyzed by gender and was treated as two individual studies. Additionally, two studies^{15,16} included only men. Most studies controlled for some conventional risk factors, including age ($n = 11$), gender ($n = 11$) and thyroid medication ($n = 7$). Most of the included studies were of high quality and scored from 7 to 9 on the Newcastle Ottawa Scale (NOS). Only one was of moderate quality, with a score of 6 (Supplementary Table 1). The average score was 7.3, and the follow-up duration ranged from 4 to 17 years.

Meta-analysis. Four studies evaluated the association between serum FT4 concentration and dementia. The pooled results revealed that the per standard deviation (SD) increment of FT4 was associated with an increased risk of dementia (relative ratio (RR) = 1.08, 95% confidence interval (CI) 1.00–1.17) with a heterogeneity (I^2) of 48.5% ($P = 0.120$) using the random effect model (Fig. 2). Five studies considered TSH level as a continuous variable to analyze its association with dementia. Meta-analysis using a fixed effect model showed a significant association between the per SD increment of TSH and dementia (fixed RR = 0.91, 95% CI 0.84–0.99; $I^2 = 0\%$, $P = 0.744$) (Fig. 3). Moreover, ten studies evaluated the risk estimates of different TSH categories and dementia. When comparing the low and middle categories of TSH levels, the fixed model showed that low TSH levels were significantly associated with an increased risk of dementia (fixed RR = 1.60, 95% CI 1.27–2.00; $I^2 = 0\%$, $P = 0.578$) (Fig. 4). Furthermore, the risk estimates for the high and middle categories of TSH levels indicated an inverse but insignificant association between high TSH levels and dementia (fixed RR = 0.99, 95% CI 0.76–1.29; $I^2 = 17.0\%$, $P = 0.291$) (Supplementary Figure 1).

Subgroup analyses. Subgroup analyses were performed on studies with a similar study design (cohort or case-control) and data on TSH levels and gender. Stratified analyses were not performed using the per SD increment of FT4 and TSH levels model because all the included studies were cohort studies. When low and middle categories of TSH levels were compared, the results of analyses stratified by study design were consistent with the overall trend. Additionally, case-control studies showed a positive association between high TSH levels and dementia (fixed RR = 0.54, 95% CI 0.30–1.00; $I^2 = 0\%$, $P = 0.440$), while cohort studies did not show this association. For data types regarding TSH levels, there were two low categories: the lower tertile of TSH levels within the normal range and TSH levels below the normal range. Likewise, there were two high categories: the upper tertile of TSH levels within the normal range and TSH levels above the normal range. Subgroup analyses revealed

First author	Country (race)	Study size (females, %)	Mean age (range)	Follow up (years)	Covariates	Results	NOS score
Case-control studies							
Doberst 2003 ⁴³	Germany (Caucasian)	77 dementia (46.8%); 42 controls (47.6%)	AD, 69.8 Control, 63.9	—	Age, sex, thyroid medication	Positive association between lower TSH and dementia.	7
van Osch 2004 ⁴⁴	UK (Caucasian)	178 AD (43.0%); 291 controls (48.0%)	73.7	—	Age, sex, education, APOE ϵ 4, Hcy, depression, Cr, thyroid medication	Positive association between lower TSH and AD.	7
Hu 2016 ⁴⁵	China (Asian)	154 AD (46.8%); 77 controls (44.2%)	AD, 63.5 Controls, 64.1	—	Age, sex, education, BMI	Negative association between AD and hypothyroidism and SH.	6
Cohort studies							
de Jong 2006 ¹⁰	Netherlands (Caucasian)	1,025 communities (51.2%)	72.3 (60–90)	5.5	Age, sex, education, smoking, Hcy depression, smoking, Cr, APOE ϵ 4, DM, AF, BMI, medication use, cholesterol,	Negative association between TSH/FT4 and dementia.	9
Tan 2008 ⁹	USA (Caucasian)	1864 communities (59.0%)	71	12.7	Age, stroke, education, Hcy, BMI, AF	Positive association between low/high TSH and AD in women.	7
de Jong ¹⁶	Hawaii (Japanese -American)	665 communities (0%)	77.3–78.6 (71–93)	4.7	Age, education, depression, albumin, BMI, TC, HDL-C, DM, smoking, thyroid medication, SBP, DBP	Positive association between higher FT4 and dementia.	7
Annerbo 2009 ⁴⁶	Sweden (Caucasian)	200 communities (79.5%)	81.0 (75–93)	6.7	Age, sex, education	Negative association between TSH and dementia.	7
Forti 2011 ⁸	Italy (Asian)	660 communities (52.9%)	73.3 (65–91)	4	Age, gender, education, BMI, hypertension, cholesterol, Hcy, DM, CVD, GDS	Negative association between TSH and AD.	7
Vadiveloo 2011 ⁴⁷	UK (Caucasian)	12,115 communities (NR)	66.5	5.6	Age, gender, history of dementia and psychiatric disorders, thyroid medication	Positive association between SH and dementia.	7
Yeap 2012 ¹⁵	Australia (Caucasian)	3401 communities (0%)	(70–89)	5.9 (median)	Age, BMI, smoking, education, DM, CVD, hypertension, MMSE, social support, sensorial impairment, thyroid medication	Positive association between higher FT4 and dementia in men.	9
Cappola 2015 ⁷	USA (African 18.6%, Caucasian 81.4%)	2843 communities (56.2%)	74.5	17	Age, sex, race, thyroid medication, hypertension, DM, current smoking, alcohol, BMI, TC, stroke, APOE ϵ 4, claudication	Positive association between higher TSH and lower incidence of dementia.	7

Table 1. Characteristics of included case-control and cohort studies. Key: NOS: Newcastle Ottawa Scale AD, Alzheimer's disease; Hcy, homocysteine; BMI, body mass index; SH: subclinical hyperthyroidism; Cr, creatinine; DM, diabetes; AF, atrial fibrillation; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; CVD, cardiovascular disease; GDS, Geriatric Depression Scale score; NR, not reported; MMSE, minimum mental state examination.

that only TSH levels below the normal range (fixed RR = 1.77, 95% CI 1.31–2.39; $I^2 = 0\%$, $P = 0.761$, not those in the lower tertile of the normal range (fixed RR = 1.39, 95% CI 0.98–1.97; $I^2 = 22.9\%$, $P = 0.273$) or those in the two high categories, were associated with dementia. Three studies evaluated the relationship between TSH and dementia in men; meta-analyses of the low and high categories of TSH levels showed no association with dementia in men (Supplementary Figure 2). The detailed results are provided in Table 2.

Sensitivity analysis and publication bias. All of the models demonstrated stability in the sensitivity analysis when each study was individually omitted (Supplementary Figure 3). Visual inspection of the funnel plots for each model did not show asymmetry, except for the model of the per SD increment of FT4 (Supplementary Figure 4); however, Egger's test found no statistical evidence of publication bias for all models (per SD increment of FT4, $P = 0.621$; per SD increment of TSH, $P = 0.972$; low vs. middle categories of TSH levels, $P = 0.252$; high vs. middle categories of TSH levels, $P = 0.480$). Funnel plot and Egger's test were not evaluated for subgroup analyses in men, because the numbers of included studies were small.

Discussion

To the best of our knowledge, this study is the first meta-analysis assessing the relationship between FT4 and dementia. In the model of per SD increment of FT4 and dementia, we found an association between higher FT4 levels and an increased risk of dementia in community-dwelling elderly from four prospective studies with high quality. Additionally, FT4 was reported to be related to brain atrophy of the hippocampus and amygdala¹⁰, which is strongly associated with the risk of dementia⁴⁸.

Furthermore, the relationship between the per SD increment of TSH and dementia was well established, showing that lower TSH levels are related to an increased risk of dementia. This finding was supported by the risk estimate of the low category of TSH levels and dementia. Notably, we performed a further subgroup analysis based on the type of data on TSH levels. Interestingly, we found that the positive association between low TSH levels and a high risk of dementia was confined to TSH levels below the normal range, rather than those within the normal range. Due to the limited number of studies on various tertiles of TSH within the normal range, more large studies are urgently needed to obtain a comprehensive and precise conclusion.

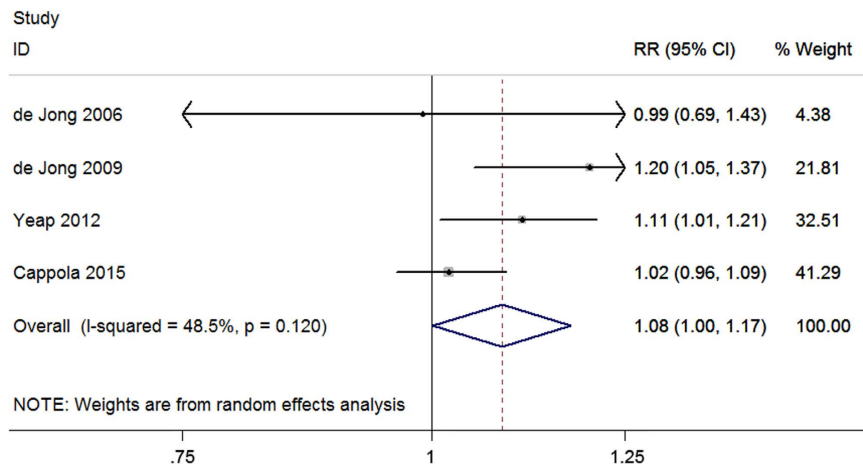


Figure 2. Forest plot of FT4 per SD increment and dementia. The estimated RRs and 95% CIs are plotted with boxes and horizontal lines.

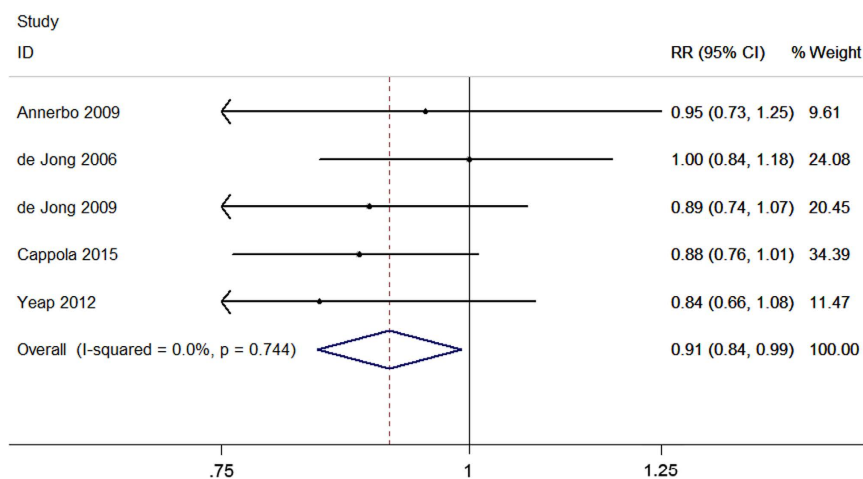


Figure 3. Forest plot of TSH per SD increment and dementia. The estimated RRs and 95% CIs are plotted with boxes and horizontal lines.

In addition, dementia was not significantly associated with TSH levels in the high categories (above the normal range or in the upper tertile within the normal range). Stratified analysis by case-control study showed high TSH levels had a protective tendency for dementia, while the analysis by cohort study showed no association between high TSH levels and dementia, indicating that this association still needs to be investigated. Our observation was also consistent with the two placebo-controlled, double-blind randomized clinical trials of T4 medication administered for 1 year^{49,50}. The two studies both failed to show the effect of T4 replacement therapy on improving cognitive function.

Furthermore, a differential risk by gender in the TSH analyses existed in several studies^{9,36,51}. These studies collectively indicated that women were more susceptible to the effects of TSH on cognition. In our study, the result of the subgroup analysis of gender in three studies showed no relationship between TSH and dementia in men in the high or low categories of TSH levels; however, considering the limited number of studies, caution should be taken when concluding a negative association; additional well-designed studies stratified by gender should be conducted.

Remarkably, some scholars have suggested that low TSH and high FT4 levels may be biomarkers of age, and both parameters are associated with other diseases that occur in patients of advanced age, including dementia. In addition, low TSH levels might be a consequence of AD-related neurodegeneration, which could reduce the secretion of TRH by the hypothalamus or decrease the responsiveness of the pituitary gland to TRH⁵². Moreover, other studies have demonstrated a relationship between thyroid hormone and amyloid, which has an essential role in AD development. These findings raise the question of whether low TSH and high FT4 levels are contributors to, rather than biomarkers or even consequences of, poor cognitive outcomes in older adults. However, our study explored positive associations between higher FT4 levels and TSH levels below the normal range and dementia, and a lack of association between high TSH levels and dementia was noted.

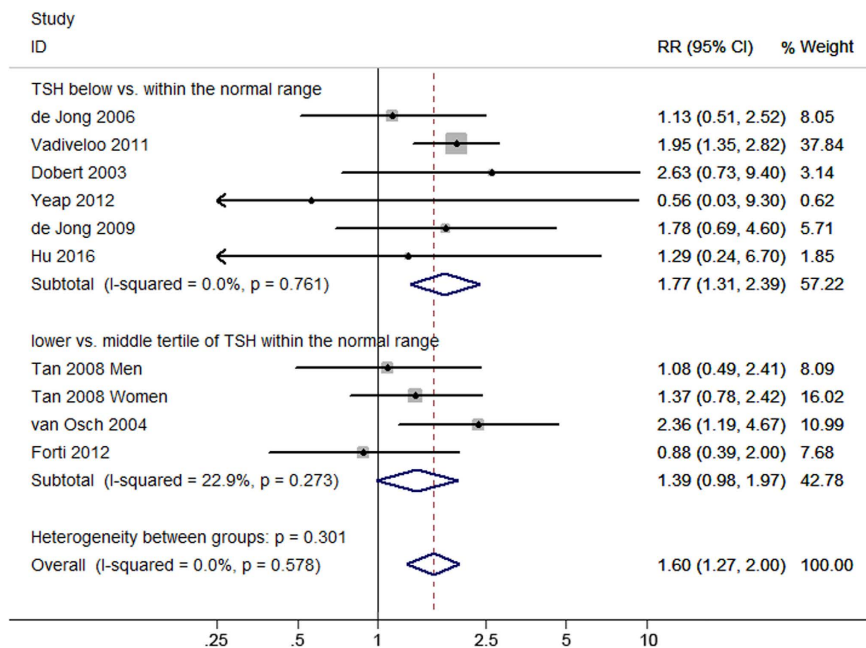


Figure 4. Forest plot of the low vs. middle categories of TSH levels and dementia. Two subgroups were analyzed: TSH levels below vs. within the normal range and the lower vs. middle tertiles of TSH levels within the normal range. The estimated RRs and 95% CIs are plotted with boxes and horizontal lines.

Our meta-analysis had some limitations. First, although bias may exist due to the observational nature of the included studies and different data collection methods (prospective or retrospective), the relatively large combined sample size and good quality of the included studies potentially strengthen the power of the analysis. Second, the methods used to detect thyroid function and covariates differed among the studies. No specific reference range of hormone levels was provided. Moreover, three RRs in the TSH model were calculated manually based on the available data in the respective studies, whereas other data were extracted from the most adjusted regression models. A more precise analysis should be conducted when individual data are available. Third, a subgroup analysis by age was not performed because of insufficient data. The incidence of AD differs with age, and the prevalence doubles every five years after the age of 60⁵³. Fourth, the prevalence of high TSH concentrations is higher in individuals of Caucasian descent than in those of African descent; this difference indicates a genetic influence on TSH secretion⁵⁴. Most individuals included in our study were Caucasians. Thus, a subgroup analysis by race was not conducted.

In conclusion, this report is the first meta-analysis illustrating the contribution of TSH and FT4 to dementia. Based on 24,952 participants including 1526 patients with dementia, an increased risk of dementia in individuals with higher serum FT4 levels and in those with TSH levels below the normal range was found. The present study implied T4 replacement therapy may be administered cautiously, as no specific relationship was shown between high TSH levels and dementia. Moreover, individuals receiving T4 replacement therapy may develop a low or even a suppressed TSH level⁵⁵, which could consequently lead to an increased risk of dementia. However, additional large, prospective, cohort studies and randomized controlled trials are still needed to determine the causal association between thyroid hormones and dementia.

Methods

This meta-analysis was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 Checklist (<http://www.prismastatement.org/statement.htm>) and the Meta-analysis of Observational Studies in Epidemiology group (MOOSE)⁵⁶.

Search strategy and study selection. We searched Medline, Embase, Web of Science and the Cochrane Library for all published studies up to June 7, 2016, that evaluated the relationship between thyroid function and cognitive decline without any restrictions. The key search terms were “thyroxine (T4)”, “thyrotropin (TSH)”, “tri-iodothyronine (T3)”, “hyperthyroidism”, “hypothyroidism”, “euthyroidism”, “subclinical hyperthyroidism”, “subclinical hypothyroidism”, “thyroid dysfunction or disorders”, “dementia”, “Alzheimer’s disease (AD)”, “cognitive decline or impairment or defect”, “mild cognitive impairment (MCI)” and “cohort or case-control or longitudinal or follow-up”. Supplementary Figure 5 contains the MEDLINE search terms. We also manually searched the bibliographies of all qualified studies for other potential articles. Wu Y and Pei Y independently evaluated the retrieved studies by thoroughly reading the titles and abstracts with pre-designed inclusion criteria. Full texts were further checked if necessary. If the required data were not reported in a potential article, we contacted the corresponding author for more details. Any disagreement between the two investigators was resolved by consensus or by discussion with a third reviewer, Wang F.

Subgroup	N	Risk estimate		Heterogeneity	
		Pooled RR (95% CI)	P ₁	I ²	P ₂
TSH: low category vs. middle category	10	1.6 (1.27, 2.00)	<0.001	0.00	0.58
Study type					
Cohort	7	1.5 (1.17, 1.92)	0.001	0.00	0.49
Case-control	3	2.25 (1.28, 3.96)	0.005	0.00	0.78
Data type					
TSH below vs. within the normal range	6	1.77 (1.31, 2.39)	<0.001	0.00	0.76
Lower vs. middle tertile of TSH within the normal range	4	1.39 (0.98, 1.97)	0.062	0.23	0.27
TSH: high category vs. middle category	9	0.99 (0.76, 1.29)	0.923	0.17	0.29
Study type					
Cohort	6	1.14 (0.85, 1.54)	0.385	0.00	0.65
Case-control	3	0.54 (0.30, 1.00)	0.048	0.00	0.44
Data type					
TSH above vs. within the normal range	6	0.91 (0.61, 1.34)	0.619	0.00	0.77
Upper vs. middle tertile of TSH within the normal range	3	1.07 (0.74, 1.54)	0.734	0.70	0.03
Gender: male					
Low category vs. middle category of TSH	3	1.28 (0.70, 2.32)	0.419	0.00	0.62
High category vs. middle category of TSH	3	0.92 (0.60, 1.43)	0.722	0.00	0.57

Table 2. Stratified analysis of the association between TSH and dementia. Key: N, number of studies. P₁ is an evaluation of the statistical significance level of the risk estimate, while P₂ is an evaluation of the heterogeneity among included studies. Subgroup analyses were performed by study design (cohort or case-control) and data types of TSH levels. Three studies evaluating the relationship between TSH and dementia in men were analyzed separately.

Studies were initially included in the detailed assessment if they met the following criteria: 1) sufficient information on the study population; 2) cohort or case-control studies; 3) clear criteria for the outcome (dementia or AD) diagnosed according to internationally accepted criteria for dementia (DSM-III-R⁵⁷ or DSM-IV⁵⁸) and AD (NINCDS-ADRDA⁵⁹), by a multi-disciplinary team (neurologists, psychiatrists, and psychologists) or by record linkage; 4) sufficient data on risk estimates of the association between FT4 or TSH levels and dementia or AD: RR, hazard ratio (HR), or odds ratio (OR) with 95% CIs or the number of outcome events; 5) adjustments for potential confounders; and 6) valid measurements of FT4 and TSH. We excluded studies that were cross-sectional, lacked usable data, or focused on vascular dementia or dementia secondary to other diseases. If multiple reports used the same population, the study with the longest follow-up was included. Reviews, case reports, abstracts and conference proceedings were excluded.

Data extraction and quality assessment. Two investigators (Wu Y and Pei Y) independently extracted the data from the eligible studies with a common form. The outcome was dementia or AD. The following data were extracted: first author, publication year, study type, country or race, study size, age of participants, gender distribution, duration of follow-up, covariates, and results (Table 1). Generally, the levels of TSH can be divided into three categories: TSH below the normal range, TSH within the normal range, and TSH above the normal range. While in the normal range, TSH levels can be further divided into three tertiles: lower, middle and upper. Thus, the overall TSH levels were classified into three categories in our meta-analysis models: TSH below the normal range or the lower tertile within the normal range, denoted as low; TSH within the normal range or the middle tertile within the normal range, denoted as middle; and TSH above the normal range or the upper tertile within the normal range, denoted as high. Because the data regarding thyroid function varied among the studies, we extracted the following information for the meta-analysis: 1) risk estimates per SD increment of FT4/TSH levels; 2) risk estimates for TSH levels below or above the normal range compared with TSH levels within the normal range; and 3) risk estimates for lower or upper tertiles compared with the middle tertile of TSH levels within the normal range. Of the studies that reported risk estimates with multiple-level adjustments, we included those that adjusted for the most covariates.

The Newcastle Ottawa Scale, a measure of the quality of observational studies, was used to assess the quality of the selected studies. This scale consists of three domains, including the selection of cases, comparability of populations, and ascertainment of exposure. Scores of 0–3, 4–6, and 7–9 indicate low, moderate, and high quality, respectively. Two investigators independently performed the quality assessment, and disagreements were resolved by discussion.

Data synthesis and statistical analyses. Dichotomous data were calculated as the OR and 95% CI. In the meta-analysis, the RRs were used for risk estimates. ORs and HRs were also treated as RRs. Heterogeneity between studies was assessed using the I² statistic: I² < 25%, low; between 25 and 50%, moderate; and >50%, high⁶⁰. If moderate or high heterogeneity was found, a random effect model was used⁶¹; otherwise, the fixed effect model was applied⁶². Subgroup analyses based on study design, data type regarding TSH levels and gender were performed to explore the sources of heterogeneity. To assess the stability of the results, a one-way sensitivity analysis was performed by omitting each study in turn from the analysis. Publication bias was assessed by funnel plots

and Egger's linear regression test⁶³. All analyses were conducted using STATA 12.0 (StataCorp, College Station, TX, USA), and a two-sided $P < 0.05$ was considered significant, except for Egger's test, in which the P value was set at 0.10 to be more conservative.

References

- Burns, A. & Iliffe, S. Dementia. *Bmj* **338**, b75 (2009).
- Cornuti, G. The Epidemiological Scale of Alzheimer's Disease. *J. Clin. Med. Res.* **7**, 657–666 (2015).
- Mitchell, S. L. Clinical Practice. Advanced Dementia. *N. Engl. J. Med.* **372**, 2533–2540 (2015).
- Haas, M. *et al.* The European Medicines Agency's strategies to meet the challenges of Alzheimer disease. *Nat. Rev. Drug Discov.* **14**, 221–222 (2015).
- Cheng, S. Y., Leonard, J. L. & Davis, P. J. Molecular aspects of thyroid hormone actions. *Endocr. Rev.* **31**, 139–170 (2010).
- Ritchie, M. & Yeap, B. B. Thyroid hormone: Influences on mood and cognition in adults. *Maturitas* **81**, 266–275 (2015).
- Cappola, A. R. *et al.* Thyroid function in the euthyroid range and adverse outcomes in older adults. *J. Clin. Endocrinol. Metab.* **100**, 1088–1096 (2015).
- Forti, P. *et al.* Serum thyroid-stimulating hormone as a predictor of cognitive impairment in an elderly cohort. *Gerontology* **58**, 41–49 (2012).
- Tan, Z. S. *et al.* Thyroid function and the risk of Alzheimer disease: the Framingham study. *Arch. Intern. Med.* **168**, 1514–1520 (2008).
- de Jong, F. J. *et al.* Thyroid hormones, dementia, and atrophy of the medial temporal lobe. *J. Clin. Endocrinol. Metab.* **91**, 2569–2573 (2006).
- Tan, Z. S. & Vasan, R. S. Thyroid function and Alzheimer's disease. *J. Alzheimers Dis.* **16**, 503–507 (2009).
- Davis, J. D. & Tremont, G. Neuropsychiatric aspects of hypothyroidism and treatment reversibility. *Minerva Endocrinol.* **32**, 49–65 (2007).
- Wahlin, A., Bunce, D. & Wahlin, T. B. R. Longitudinal evidence of the impact of normal thyroid stimulating hormone variations on cognitive functioning in very old age. *Psychoneuroendocrinology* **30**, 625–637 (2005).
- Moon, J. H. *et al.* Lower-but-normal serum TSH level is associated with the development or progression of cognitive impairment in elderly: Korean longitudinal study on health and aging (KLOSHA). *J. Clin. Endocrinol. Metab.* **99**, 424–432 (2014).
- Yeap, B. B. *et al.* Higher free thyroxine levels predict increased incidence of dementia in older men: the Health in Men Study. *J. Clin. Endocrinol. Metab.* **97**, E2230–E2237 (2012).
- de Jong, F. J. *et al.* Thyroid function, the risk of dementia and neuropathologic changes: the Honolulu-Asia Aging Study. *Neurobiol. Aging* **30**, 600–606 (2009).
- Gussekloo, J. *et al.* Thyroid status, disability and cognitive function, and survival in old age. *JAMA* **292**, 2591–2599 (2004).
- Park, Y. J. *et al.* Subclinical hypothyroidism (SCH) is not associated with metabolic derangement, cognitive impairment, depression or poor quality of life (QoL) in elderly subjects. *Arch. Gerontol. Geriatr.* **50**, e68–e73 (2010).
- Ganguli, M., Burmeister, L. A., Seaberg, E. C., Belle, S. & DeKosky, S. T. Association between dementia and elevated TSH: A community-based study. *Biol. Psychiatry* **40**, 714–725 (1996).
- Luboshitzky, R., Oberman, A. S., Kaufman, N., Reichman, N. & Flatau, E. Prevalence of cognitive dysfunction and hypothyroidism in an elderly community population. *Isr. J. Med. Sci.* **32**, 60–65 (1996).
- Prinz, P. N. *et al.* Thyroid hormones: positive relationships with cognition in healthy, euthyroid older men. *J. Gerontol. A Biol. Sci. Med. Sci.* **54**, M111–M116 (1999).
- Resta, F. *et al.* Subclinical hypothyroidism and cognitive dysfunction in the elderly. *Endocr. Metab. Immune Disord. Drug Targets* **12**, 260–267 (2012).
- Stern, R. A. *et al.* Preliminary study of the relationship between thyroid status and cognitive and neuropsychiatric functioning in euthyroid patients with Alzheimer dementia. *Cogn. Behav. Neurol.* **17**, 219–223 (2004).
- van Bostel, M. P., Menheere, P. P., Bekers, O., Hogervorst, E. & Jolles, J. Thyroid function, depressed mood, and cognitive performance in older individuals: the Maastricht Aging Study. *Psychoneuroendocrinology* **29**, 891–898 (2004).
- Kim, J. M. *et al.* Thyroid stimulating hormone, cognitive impairment and depression in an older Korean population. *Psychiatry Investig.* **7**, 264–269 (2010).
- Ojala, A. K., Schalin-Jääntti, C., Pitkälä, K. H., Tilvis, R. S. & Strandberg, T. E. Serum thyroid-stimulating hormone and cognition in older people. *Age Ageing* **45**, 155–157 (2016).
- Wijsman, L. W. *et al.* Subclinical thyroid dysfunction and cognitive decline in old age. *PLoS One* **8**, e59199 (2013).
- Formiga, F. *et al.* Thyroid status and functional and cognitive status at baseline and survival after 3 years of follow-up: the OCTABAIX study. *Eur. J. Endocrinol.* **170**, 69–75 (2014).
- Formiga, F. *et al.* Predictors of cognitive decline in 85-year-old patients without cognitive impairment at baseline: 2-year follow-up of the Octabaix study. *Am. J. Alzheimers Dis. Other Dement.* **28**, 147–153 (2013).
- De Jongh, R. T. *et al.* Endogenous subclinical thyroid disorders, physical and cognitive function, depression, and mortality in older individuals. *Eur. J. Endocrinol.* **165**, 545–554 (2011).
- Yong-Hong, L., Xiao-Dong, P., Chang-Quan, H., Bo, Y. & Qing-Xiu, L. Hypothalamic-pituitary-thyroid axis in patients with Alzheimer disease (AD). *J. Investig. Med.* **61**, 578–581 (2013).
- Lillevang-Johansen, M., Petersen, I., Christensen, K., Hegedus, L. & Brix, T. H. Is previous hyperthyroidism associated with long-term cognitive dysfunction? A twin study. *Clin. Endocrinol. (Oxf)* **80**, 290–295 (2014).
- Nuray Ulusu, N. *et al.* A comparative study on thyroid function in Alzheimer's disease: Results from a Turkish multi-centre study. *J. Neurol. Sci. Turk.* **32**, 335–347 (2015).
- Castellano, C. A. *et al.* Thyroid function and cognition in the euthyroid elderly: a case-control study embedded in Quebec longitudinal study - NuAge. *Psychoneuroendocrinology* **38**, 1772–1776 (2013).
- Zhang, N., Du, H. J., Wang, J. H. & Cheng, Y. A pilot study on the relationship between thyroid status and neuropsychiatric symptoms in patients with Alzheimer disease. *Chin. Med. J. (Engl)* **125**, 3211–3216 (2012).
- Beydoun, M. A. *et al.* Thyroid hormones are associated with longitudinal cognitive change in an urban adult population. *Neurobiol. Aging* **36**, 3056–3066 (2015).
- Hogervorst, E., Huppert, F., Matthews, F. E. & Brayne, C. Thyroid function and cognitive decline in the MRC Cognitive Function and Ageing Study. *Psychoneuroendocrinology* **33**, 1013–1022 (2008).
- Volpato, S. *et al.* Serum thyroxine level and cognitive decline in euthyroid older women. *Neurology* **58**, 1055–1061 (2002).
- Annerbo, S., Wahlund, L. O. & Lökk, J. The significance of thyroid-stimulating hormone and homocysteine in the development of Alzheimer's disease in mild cognitive impairment: a 6-year follow-up study. *Am. J. Alzheimers Dis. Other Dement.* **21**, 182–188 (2006).
- Quinlan, P. *et al.* Thyroid hormones are associated with poorer cognition in mild cognitive impairment. *Dement. Geriatr. Cogn. Disord.* **30**, 205–211 (2010).
- Suhanov, A. V. *et al.* Risk factors for Alzheimer's disease in Russia: a case-control study. *Eur. J. Neurol.* **13**, 990–995 (2006).
- Kalmijn, S. *et al.* Subclinical hyperthyroidism and the risk of dementia. The Rotterdam study. *Clin. Endocrinol. (Oxf)* **53**, 733–737 (2000).

43. Dobert, N. *et al.* Subclinical hyperthyroidism in dementia and correlation of the metabolic index in FDG-PET. *Acta Med. Austriaca* **30**, 130–133 (2003).
44. Van Osch, L. A. D. M., Hogervorst, E., Combrinck, M. & Smith, A. D. Low thyroid-stimulating hormone as an independent risk factor for Alzheimer disease. *Neurology* **62**, 1967–1971 (2004).
45. Hu, Y., Wang, Z. C., Guo, Q. H., Cheng, W. & Chen, Y. W. Is thyroid status associated with cognitive impairment in elderly patients in China? *BMC Endocr. Disord.* **16**, 11 (2016).
46. Annerbo, S., Kivipelto, M. & Lokk, J. A prospective study on the development of alzheimer's disease with regard to thyroid-stimulating hormone and homocysteine. *Dement. Geriatr. Cogn. Disord.* **28**, 275–280 (2009).
47. Vadiveloo, T., Donnan, P. T., Cochrane, L. & Leese, G. P. The Thyroid Epidemiology, Audit, and Research Study (TEARS): morbidity in patients with endogenous subclinical hyperthyroidism. *J. Clin. Endocrinol. Metab.* **96**, 1344–1351 (2011).
48. den Heijer, T. *et al.* Use of hippocampal and amygdalar volumes on magnetic resonance imaging to predict dementia in cognitively intact elderly people. *Arch. Gen. Psychiatry* **63**, 57–62 (2006).
49. Parle, J. *et al.* A randomized controlled trial of the effect of thyroxine replacement on cognitive function in community-living elderly subjects with subclinical hypothyroidism: the Birmingham Elderly Thyroid study. *J. Clin. Endocrinol. Metab.* **95**, 3623–3632 (2010).
50. Jorde, R. *et al.* Neuropsychological function and symptoms in subjects with subclinical hypothyroidism and the effect of thyroxine treatment. *J. Clin. Endocrinol. Metab.* **91**, 145–153 (2006).
51. Chaker, L. *et al.* Thyroid function and the risk of dementia. The Rotterdam Study. *Thyroid* **25**, A3–A4 (2015).
52. Luo, L., Yano, N., Mao, Q., Jackson, I. M. & Stopa, E. G. Thyrotropin releasing hormone (TRH) in the hippocampus of Alzheimer patients. *J Alzheimers Dis* **4**, 97–103 (2002).
53. Nussbaum, R. L. & Ellis, C. E. Alzheimer's disease and Parkinson's disease. *N. Engl. J. Med.* **348**, 1356–1364 (2003).
54. Hollowell, J. G. *et al.* Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J. Clin. Endocrinol. Metab.* **87**, 489–499 (2002).
55. Taylor, P. N. *et al.* Falling threshold for treatment of borderline elevated thyrotropin levels—balancing benefits and risks: evidence from a large community-based study. *JAMA Intern. Med.* **174**, 32–39 (2014).
56. Stroup, D. F. *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* **283**, 2008–2012 (2000).
57. Association Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Revised* third Edition. Washington, DC: American Psychiatric Association (1987).
58. Association Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. DSM-IV. Washington, DC: American Psychiatric Association (1994).
59. McKhann, G. *et al.* Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**, 939–944 (1984).
60. Higgins, J. P., Thompson, S. G., Deeks, J. J. & Altman, D. G. Measuring inconsistency in meta-analyses. *BMJ* **327**, 557–560 (2003).
61. DerSimonian, R. & Laird, N. Meta-analysis in clinical trials. *Control. Clin. Trials* **7**, 177–188 (1986).
62. Mantel, N. & Haenszel, W. Statistical aspects of the analysis of data from retrospective studies of disease. *J. Natl. Cancer Inst.* **22**, 719–748 (1959).
63. Egger, M., Davey Smith, G., Schneider, M. & Minder, C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* **315**, 629–634 (1997).

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 81071418 and No. 81472029) and the Peking Union Medical College Innovation Fund for Graduate Students (No. 2015-1002-01-02).

Author Contributions

Y.W. contributed to the study design, data analysis and interpretation; drafted part of the manuscript; and prepared the tables and figures. Y.P. participated in collecting and analyzing the data and drafting part of the manuscript. F.W. revised the manuscript. D.X. searched the related papers and extracted data. W.C. designed this study and revised the manuscript. All the authors reviewed the manuscript.

Additional Information

Supplementary information accompanies this paper at <http://www.nature.com/srep>

Competing financial interests: The authors declare no competing financial interests.

How to cite this article: Wu, Y. *et al.* Higher FT4 or TSH below the normal range are associated with increased risk of dementia: a meta-analysis of 11 studies. *Sci. Rep.* **6**, 31975; doi: 10.1038/srep31975 (2016).



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