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PERSPECTIVE

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Thyroid function in elderly people: The role of subclinical thyroid disorders in cognitive function and mood alterations

1 | INTRODUCTION

Thyroid hormones exert a wide range of functions in several organs, including cardiovascular system,[1,2] lipid metabolism,[3-5] muscular function,[6] erythropoiesis,[7] and oxidative stress.[8] They also exert various effects on nervous system. Overt thyroid disorders are associated with several forms of cognitive impairment, depression, anxiety disorders, and peripheral neuropathies.[9,10]

Cognition consists of several and specific neuronal systems which include attention, perception, memory, language, psychomotor, and executive functions. All these aspects, together with mood decrements, may be deeply affected by thyroid disease. Overt hypothyroidism has been linked with negative effects to various aspects of cognition. Cognitive deficits have also been reported in overt hyperthyroidism, being poorer performance on tests of attention, memory, or mental alertness the cognitive deficits most frequently observed.[11,12] Thyroid function changes with age, and since cognitive decline is often associated with ageing, physiological changes in thyroid function should be considered if changes of cognition during physiological ageing occur.

Studies on the cognitive decline in healthy euthyroid subjects gave disparate and conflicting results.[13] These differences in the results may be because of differences in age ranges, sample selection, or different cognitive tests employed and drug interferences.

Subclinical hypothyroidism, defined as increased thyrotropin (TSH) level with normal free thyroxine (fT4) concentration,[14] and subclinical hyperthyroidism, defined as reduced TSH with normal fT4 level,[14] are common in the elderly people.[15,16]The impact of these clinical conditions on cardiovascular system and lipid metabolism has been recently analysed[17,18] Here, we performed a review of available evidence from studies on the association between subclinical thyroid disorders and cognition in older adults.

2 | METHODS

We reviewed Pubmed database using the following keywords "dementia", "cognitive impairment", "cognitive decline", "subclinical hyperthyroidism", "subclinical hypothyroidism", and "subclinical thyroid disease". Relevant review and original articles published in English during the past 15 years were included. Articles already known to the authors were also included. In sections entitled "subclinical hypothyroidism" and "subclinical hypothyroidism", we included all original studies that analysed the effect of specific subclinical disorders on cognitive impairment. Cross-sectional and longitudinal studies were considered.

2.1 | Thyroid hormones and neuropsychiatric function

The relationships between thyroid hormones and neuropsychiatric function are multifaceted and several mechanisms of thyroid hormone action on brain function have been documented,[19] both during brain development and in adult life. The complex action of thyroid hormones are initiated by the intracellular binding of T3 to nuclear receptor, where they cause alterations in gene expression, either stimulating or repressing the transcriptional activity of target genes.[19] The most abundant hormone secreted by the thyroid gland is thyroxine (T4), which is converted into triiodothyronine (T3), the biologically active compound, by type 1 iodothyronine deiodinases (ID), which is distributed in all tissues. At the brain level, most of T3 originates through the tissue conversion of the T4 precursor by deiodinases, whose distribution and regulation can have important effects on thyroid hormone action. Both deiodinase 2 (D2) and deiodinase 3 (D3) are expressed in the brain. D3 inactivates T4 by converting it into reverse T3, and converts T3 to diiodothyronine (T2), whereas D2 converts T4 to T3. D2 is primarily expressed in glial cells of various regions of the CNS, and plays an important role in CNS development and function. Polymorphisms in the D2 genes might lead to diminished levels of local T3 production in the brain. There are various potential mechanisms of thyroid hormone action on mood and cognition. Many of the limbic system structures have been implicated in the pathogenesis of mood disorders. Moreover, interactions of thyroid function with brain neurotransmitter system, mainly norepinephrine and serotonin, which are generally believed to play a major role in mood and behaviour regulation, may contribute to the function of both developing and mature brain.[20,21] Experimental data demonstrate that thyroid hormones modulate the serotoninergic system through an increase in serotoninergic neurotransmission, since brain serotonin levels correlated positively—in animals models—with T3 levels.[22] D2 activity may also be depressed by the elevated cortisol levels seen in depression and stress, resulting in decreased brain T3 levels.[23] There are also evidences that selective serotonin reuptake inhibitors and tricyclic antidepressants may

promote the activity of D2, thus resulting in an increased conversion of T4 to T3 within the brain tissues.[24] Thyroid hormones also interact with other neurotransmitter involved in mood regulation, including dopamine as well as gene regulatory mechanisms.[25,26] Additional evidence linking thyroid function to mood are (a) the observations that in depressed subjects, the nocturnal surge of TSH is frequently absent, thus resulting in a reduction in thyroid hormone secretion,[27] and (b) a blunted TSH response to TRH has been described,[23] suggesting that functional central hypothyroidism might occur in some depressed patients.

The available data, taken together, clearly demonstrated a critical role of thyroid hormones on brain development and function.

2.2 | Thyroid function in elderly people

Thyroid hormone secretion decreases with age,[28] but thyroid hormone clearance is also reduced, leading to unchanged fT4 concentrations. In contrast to thyroxine (T4), serum triiodothyronine (T3) concentrations decrease in ageing humans probably because of reduced peripheral conversion of T4 to T3, associated with an impaired activity of type I deiodinase.[29] The inactive metabolite reverse T3 (rT3) seems to increase with age.[30] This probably explains why T4 levels remain within the normal range. Data on TSH changes during ageing are not clear. TSH has been reported to decrease in healthy elderly subjects because of an age-related decrease in TSH secretion by the pituitary.[31,32] In contrast, recent reports have convincingly shown that serum TSH levels increase with age,[33,34] independent of the presence of antithyroid antibodies. This may suggest that thyroid function decreases with age. Since fT4 levels are relatively stable with increasing age, TSH and fT4 cannot be regarded as univocal risk predictors in older people. Moreover, the evaluation of thyroid function in the elderly people is commonly confounded by the drug use, nutritional alterations, and/or the increased prevalence of acute or chronic nonthyroid illness.[35]

There is also an age-dependent increase in the prevalence of positive antithyroid peroxidase (anti-TPO) and antithyroglobulin (anti-Tg) antibodies, which is greater in women >60 years of age.[15] Interestingly, thyroid antibodies are rare in centenarians, while they are rather frequently observed in hospitalised elderly subjects and in those with other autoimmune diseases.[31,36-38] An increased risk of declining cognitive function is well known in ageing, particularly with regard to working memory, long-term memory or information processing speed.[39-41] In recent years, there has been increasing interest in the elderly people on the role of differences in thyroid hormone—within the normal range—on cognition and mood.

However, studies assessing different levels of thyroid hormones within the normal range on cognition and mood are rather conflicting.[42-47] Collectively, the available data are rather inconsistent about a possible link between differences in thyroid hormones within the reference range and mood changes. On the contrary, higher fT4 seems to be associated with a higher risk of cognitive dysfunction in old people. As pointed out by Ritchie et al,[47] reference ranges for thyroid hormones should be reconsidered, and age-adjusted when applied to older adults. Collectively, the available data suggest a possible link between subtle variations of thyroid hormone concentrations with certain memory functions, without a clear impact on cognitive functions.

2.3 | Subclinical hypothyroidism

Subclinical hypothyroidism is by definition a laboratory diagnosis, and is defined as an elevated TSH with a normal fT4. The frequency of subclinical hypothyroidism varies from 6.5% to 8.5% in different populations, with an increasing frequency in older subjects.[48,49] In women aged >60 years, this condition may be present in up to 20% of the population.[50] Depending on the size of the increase in serum TSH, subclinical hypothyroidism can be mild (TSH 4.5-9 mU/L), or severe (TSH >10 mU/L). The most frequent causes of subclinical hypothyroidism are chronic lymphocytic thyroiditis, caused by specific risk factors and genetic predisposition,[51] and inadequate L-thyroxine supplementation, poor adherence, drug interactions, or inadequate monitoring of treatment.[52] Subclinical hypothyroidism is usually progressive, especially when serum TSH concentrations are more than 10 mU/L in the presence of anti thyroid autoantibodies, with an annual rate of progression to overt disease of 2%-6%.[53] The symptoms are neither sensitive nor specific. In general, patients with subclinical hypothyroidism may have at least one symptom that could be related to this diagnosis (eg, poor energy level, fatigue, muscle weakness, dry skin, and intolerance to cold).[54] A series of cardiovascular risk factors, such as hypertension, depressed systolic function, and left ventricular diastolic dysfunction, impaired relaxation of vascular smooth muscle cells have been associated with subclinical hypothyroidism.[18] However, only patients with TSH levels higher than 10 mU/L seem to have an increased risk of coronary heart disease and mortality.[55]

While overt hypothyroidism has been associated with global cognitive impairment (even if contrasting data have been reported on this issue),[47] a possible role of subclinical hypothyroidism as a predisposing factor for cognitive alterations has been hypothesised.[56] Thus, subtle defect in thyroid hormone action (with thyroid hormones blood levels still in the normal range) might be associated with subtle defects in specific cognitive functions, although psychiatric disturbances may also have a negative impact on assessments of cognitive functions.[57] The results of available cross-sectional studies regarding the association between subclinical hypothyroidism and cognition showed no association with cognitive dysfunction.[47,58-60] Similar negative results have been obtained in a case-control study[61] and in a prospective observational study.[62] More recently, the prevalence of cognitive impairment has been reported to be significantly higher in subclinical hypothyroidism when compared to controls.[63] The presence of cognitive impairment correlated with the level of TSH, as TSH increased cognitive function declined.[64] Recent studies on cognition in subclinical hypothyroidism are summarised in Table 1. Together, the data do not support a clear association between subclinical hypothyroidism with cognitive decline. The effect of L-thyroxine treatment was also studied in these patients, without

TABLE 1 Studies that analyse the effect of subclinical hypothyroidism on cognitive function

Author	Type of study	n	Mean age (yrs.)	Results
Cook[82]	Cross-sectional	15	74	Association with cognitive impairment
Gussekloo[62]	Longitudinal	67	85	No association
Roberts[58]	Cross-sectional	168	74	No association
Jorde[61]	Placebo-controlled, double-blind intervention	89	62	No association
Chueire[66]	Cross-sectional	252	67	Increased risk of depression
Hogervorst[44]	Cross-sectional	33	73	Association with lower cognitive function
Ceresini[74]	Cross-sectional	26	77	No association
Bensenor[80]	Cross-sectional	157	72	No association
Kim[59]	Cross-sectional	37	73	No association
de Jongh[83]	Longitudinal	64	75	No association
Resta[84]	Cross-sectional	42	74	Association with cognitive impairment
Wijsman[85]	Longitudinal	161	76	No association
E Silva[60]	Cross-sectional	43	81	No association
Parsaik[86]	Cross-sectional	141	82	No association
Formiga F 2014[87]	Longitudinal	20	85	No association
Bajaj[64]	Cross-sectional	103	75	Association with cognitive impairment
Hu[76]	Cross-sectional	9	63	No association

a clear effect on mood or cognition when a double-blind placebo-controlled trial was performed in patients with subclinical hypothyroidism.[65] With regards to mood, cross-sectional studies have also shown contrasting results (Table 1). Collectively, the data showed no association between subclinical hypothyroidism and depression or anxiety in older adults,[47] although older adults with higher raised TSH have shown a higher depression rate.[66] Furthermore, a recent systematic review[67] reported that in more than 92% of the population sampled lacks of significant association between subclinical hypothyroidism and cognitive impairment or mood alteration. Given these variable and inconsistent findings, the data do not support the concept that alterations in cognitive functions are associated with subclinical hypothyroidism. More consistent are data on altered mood, such as anxiety or depression,[10] although these symptoms are not usually reported. Taken together, these studies suggest that the degree of cognitive or mood alterations may be related to the degree of thyroid dysfunction, but also demonstrate that subclinical hypothyroidism is unlikely to cause clinically relevant alterations in most patients.

2.4 | Subclinical hyperthyroidism

Subclinical hyperthyroidism is defined as a low serum TSH (eg, TSH concentrations of less than 0.35 mUI/L, which is the lower limit of the reference range), combined with an fT4 and fT3 in the reference range. The prevalence has been reported to vary from 3% to 8%.[17] Subclinical hyperthyroidism may aggravate cardiac dysfunction, and can lead to atrial fibrillation, impaired left ventricular diastolic filling, and other adverse cardiac end-points.[17] Available data support an association between overt hyperthyroidism and cognitive impairment.[47] Patients with hyperthyroidism have been reported to show decrease in attention, verbal memory and concentration, when compared with euthyroid subjects.[68] Other studies found no deficit in neuropsychological testing, although patients self-reported symptoms of cognitive impairment.[69] In particular, studies using fluorodeoxyglucose PET and resting-state MRI revealed that cerebral metabolism in specific brain regions is abnormal in untreated hyperthyroidism.[70,71] More consistent are the findings of increased depressive and anxiety symptoms.[47,70,72] In the last years, there have been a number of studies addressed to assess the relationship between subclinical hyperthyroidism, both in cognition and mood alterations (Table 2), both in cross-sectional and longitudinal approaches. Gussekloo et al[62] found no association of low TSH with cognition or depressive symptoms in a longitudinal study on 599 patients. No association between subclinical hyperthyroidism and cognition (neither with depressive symptoms or anxiety) was also found by Roberts et al[58] in their cross-sectional study. A large population-based study also failed to find cognitive effects of subclinical thyroid dysfunction.[73] On the contrary, Kim et al[59] found, in their cross-sectional study on 495 subjects, that subclinical hyperthyroidism (defined by TSH <0.5 mIU/L) was associated with cognitive

TABLE 2 Studies that analysed the effect of subclinical hyperthyroidism and cognitive impairment

Author	Type of study	n	Mean age (years)	Results
Kalmijn[67]	Longitudinal	102	69	Increased risk of dementia and Alzheimer's disease
Gussekloo[53]	Longitudinal	17	85	No association
Roberts[49]	Cross-sectional	127	74	No association
Ceresini[63]	Cross-sectional	71	76	Increased risk of cognitive impairment
Bensenor[69]	Cross-sectional	33	72	Increased risk of dementia
Kim[50]	Cross-sectional	14	74	Increased risk of cognitive impairment
Vadiveloo[68]	Longitudinal	2024	66	Increased risk of dementia
De Jongh[71]	Cross-sectional	34	78	No association

impairment, but not with depression. Similar results were obtained by Ceresini et al[74] in another cross-sectional study performed on 1171 adults (age range: 23-102 years). Additional data from a cross-sectional case-control study[75] showed that long-term TSH suppressive therapy in elderly patients with differentiated thyroid carcinoma had no clear effects on cognitive function. In another study performed in China, no association was evident between mild cognitive impairment (or Alzheimer's disease) in old patients with subclinical hyperthyroidism.[76] Finally, other cross-sectional[77] and longitudinal[78,79] studies reported an association of Alzheimer's disease and dementia in adults with TSH <0.4 mU/L. This association was gender-specific in one study[80] since it was present only in men. Although each of these studies employed different cognitive tests, these data, taken together, seem to support a possible association of subclinical hypothyroidism with impairment of cognition, whereas observation data supporting an association of subclinical hypothyroidism with mood disorders are lacking. However, additional studies with randomised controlled trials are required to demonstrate the association and determine whether pharmacological interventions might improve cognitive functions.

2.5 | Limitations

The interpretation of studies which analysed the association between subclinical thyroid disorders and cognitive decline is limited by different factors. First, the duration of the disorder of the thyroid gland is not always assessable. In addition, most of the studies have a cross-sectional design, thus precluding temporality ascertainment. This highlights the importance of a longitudinal examination and randomised controlled trials, which are needed to better understand how thyroid hormone changes or replacement can affect age-related cognitive decline. Finally, the definition of subclinical thyroid disorders is rather arbitrary and different cut-off for TSH has been used in the studies.

3 | DISCUSSION

Since thyroid hormones are important for energy-consuming processes needed for neurotransmission, memory and other brain functions, subclinical thyroid dysfunction and cognitive and mood alterations have been studied in old age.

Given the variable and inconsistent findings on the possible link between subclinical hypothyroidism and mood and cognition alterations, it is clear that these alterations are not distinctive of this clinical condition. It should be noted that the treatment of subclinical hypothyroidism remains controversial.[81] When TSH levels are > 10 mIU/L, only the negative cardiovascular effects of subclinical hypothyroidism might be improved or reversed by replacement therapy.[81] Although only few studies of the cardiovascular effect of L-thyroxine are double-blind and placebo,[61] the data suggest that replacement therapy improves systolic and diastolic function, endothelial function, and carotid intima-media thickness together with a small reduction of LDL cholesterol. Moreover, patients who were treated with thyroxine had significantly lower risk of heart failure events and lower all-cause mortality. Based on the available data, mood alteration and cognitive impairment, when present, are not clinical indications for L-thyroxine replacement.

As for the subclinical hyperthyroidism, the results summarised above suggest that there is no clear association with cognition or mood disorders.

In conclusion, given the available data on subclinical hyperthyroidism and subclinical hypothyroidism on mood and cognition, when these alterations are present and relevant, patients should be evaluated and treated independently from the subclinical thyroid dysfunction.

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DISCLOSURE

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. The manuscript has been seen and approved by all authors. We do not have funding sources to declare.

AUTHOR'S CONTRIBUTION

Alessandro P Delitala helped in article designing and drafting; Marta Manzocco and Federico G Sinibaldi provided support in data collection and article drafting; and Giuseppe Fanciulli did critical revision of the article.

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