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ORIGINAL RESEARCH

The Association of Thyroid Function on Cognition and Neuropsychiatric Symptoms in Patients with Cognitive Impairment

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Introduction: This study aims to investigate the association between thyroid function, cognitive status, and neuropsychiatric symptoms (NPSs) in patients with mild cognitive impairment or dementia.

Methods: This cross-sectional analysis enrolled 2,289 patients newly diagnosed with mild cognitive impairment or dementia. Based on thyroid-stimulating hormone and free thyroxine levels, patients were classified into euthyroid, hypothyroid, and hyperthyroid groups, with subclinical and overt forms incorporated into their respective categories due to group size distribution. NPSs were assessed using the Neuropsychiatric Inventory. Multivariate logistic regression evaluated associations between thyroid function and NPSs, while linear regression examined relationships with cognitive status.

Results: Significant differences in Clinical Dementia Rating–Sum of Boxes (CDRSOB) and Cognitive Abilities Screening Instrument (CASI) scores were observed across the three thyroid function groups (mean CDRSOB: euthyroid = 4.6, hyperthyroidism = 5.4, hypothyroidism = 5.3, p = 0.013; mean CASI: euthyroid = 51.6, hyperthyroidism = 47.2, hypothyroidism = 49.0, p = 0.028). Patients in the hyperthyroid group demonstrated higher odds of experiencing delusion (odds ratio (OR) = 1.61, 95% confidence interval (CI) = 1.12–2.31, p = 0.009), agitation (OR = 1.47, 95% CI = 1.00–2.13, p = 0.048), and moderate to severe hallucination (OR = 1.76, 95% CI = 1.01–2.92, p = 0.037). After adjusting for age, education, and dementia subtypes, patients in the hyperthyroid group had significantly worse CDRSOB scores than those in the euthyroid group (β = 0.66, 95% CI = 0.03–1.3, p = 0.040).

Conclusion: This study provides the first structured evaluation of behavioral and psychological symptoms of dementia across thyroid function states in patients with cognitive impairment. Hyperthyroidism was associated with worse global function and a higher prevalence of delusions, agitation, and moderate-to-severe hallucinations. These findings highlight an association between thyroid dysfunction and BPSD (behavioral and psychological symptoms of dementia) in cognitively impaired populations and underscore the importance of careful clinical evaluation of thyroid status.

Keywords: hyperthyroidism, behavioral and psychological symptoms of dementia, BPSD, dementia, cognitive impairment, Alzheimer's disease

Introduction

According to the World Health Organization, there are currently 55 million people suffering from dementia worldwide,[1] and the prevalence of mild cognitive impairment among community-dwelling adults aged 50 years and older is over 15%.[2] Behavioral and psychological symptoms of dementia (BPSD), including agitation, delusions, appetite change, hallucinations, and sleep disturbances, are associated with increased morbidity and mortality, faster disease progression, higher rates of nursing home admissions, a greater caregiver burden, and increased healthcare costs.[3,4] Given their clinical impact, identifying modifiable or reversible contributors to BPSD is of particular importance. Abnormal thyroid

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function is a common comorbidity of dementia and should be considered as a possible cause of BPSD.[5] According to the American Academy of Neurology, thyroid function tests are an evidence-based recommendation during the workup of dementia diagnosis.[6]

Previous studies have indicated that thyroid dysfunction is associated with an increased risk of various cognitive impairments. Daniel R Wieland et al used population-based data to conclude that hypothyroidism is associated with a 1.81-fold increased risk of developing dementia.[7] In contrast, a recent meta-analysis by Jianbo Ye et al pointed out that overt hypothyroidism is associated with a reduced risk of dementia. Also, overt hyperthyroidism is associated with an increased risk, and subclinical hyperthyroidism correlates with a higher risk of vascular dementia.[8] Similarly, Layal Chaker et al analyzed data from the Rotterdam Study and stated that higher thyroxine level or lower TSH is associated with an increased risk of dementia.[9] This association is also noticed by Vedant Lekurwale et al in their systematic review, which highlighted the association between the increased dementia risk and subclinical hyperthyroidism, low TSH, or high free thyroxine (T4) levels.[10]

Besides the heightened risk of dementia, thyroid abnormalities also lead to various cognitive and psychiatric symptoms. Multiple studies pointed out that patients present with autoimmune thyroiditis have a higher risk of developing depression and anxiety disorders.[11,12] Hypothyroidism itself can present symptoms similar to depression.[13] A severe form of Hashimoto thyroiditis, Hashimoto encephalopathy, is characterized by altered mental status, confusion, hallucinations, and delusions.[14] In a meta-analysis by Marilu Jurado-Flores et al, hypothyroidism may be linked with cognitive deterioration, mood disturbances, and depressive symptoms, whereas hyperthyroidism can result in agitation, acute psychosis, and apathy, particularly affecting older adults more significantly.[15] Another meta-analysis by Henry Bode et al concluded that depression is also associated with hyperthyroidism.[16]

Despite growing evidence linking thyroid dysfunction to dementia risk, existing studies primarily focus on disease incidence rather than symptom phenotypes. In particular, the relationship between thyroid function and BPSD remains poorly characterized, with prior findings being limited, inconsistent, or confined to specific dementia subtypes. A study on Alzheimer's disease (AD) only provided a limited exploration of this topic. Although non-statistically significant, Morag Patterson et al found that patients with AD with higher T4 levels tend to have worse mood symptoms.[17] Given that thyroid dysfunction can mimic or exacerbate neuropsychiatric symptoms and is routinely screened during dementia evaluation, a clearer understanding of its association with BPSD in cognitively impaired populations is clinically relevant yet underexplored. To fill in the gap, this study aims to investigate the association between thyroid function and cognitive status or neuropsychiatric symptoms in patients with cognitive impairment or dementia.

Materials and Methods

Study Population

This study adopts a cross-sectional case-control design and includes patients recently diagnosed with mild cognitive impairment or dementia by neurologists or psychiatrists from January 2014 to November 2024. A total of 2,289 patients in the Changhua Christian Hospital in Central Taiwan were recruited. The subjects of this research were initially interviewed regarding their cognitive status, BPSD, and educational background (in years), and clinical as well as laboratory evaluations were also conducted to assess their thyroid function. The details stated earlier were all recorded in the digital medical records at Changhua Christian Hospital.

This research received approval from the Institutional Review Board of Changhua Christian Hospital (CCH IRB 250215), and informed consent was exempted because the data originated from anonymized electronic files.

Measurement of Patient Features

The preliminary evaluation involved examining the patients' age, gender, educational background, cognitive state, neuropsychiatric inventory (NPI) score, and thyroid function. The study included patients with mild cognitive impairment or dementia. Patients with AD adhered to the diagnostic criteria set by the National Institute on Aging-Alzheimer's Association (NIA-AA). Different dementia types were distinguished according to diverse guidelines. The National Institute on Aging-Alzheimer's Association (NIA-AA) criteria[18,19] apply to AD, while the International Society for

Vascular Behavioral and Cognitive Disorders (VASCOG) guidelines[20] are relevant for vascular cognitive impairment (VCI). The diagnosis of Parkinson's disease dementia (PDD) or Dementia with Lewy bodies (DLB) is based on the Movement Disorder Society-Task Force criteria and the fourth consensus report of the DLB Consortium.[21,22] Patients with Lewy body disease (LBD) included those diagnosed with PDD or DLB.

Measurement of Thyroid Function (Exposure)

All recruited patients underwent laboratory assessments of thyroid function, which included measuring thyroid-stimulating hormone (TSH) and free T4 levels. Based on these TSH and T4 levels, patients were categorized into three distinct groups. Those with a TSH range of 0.38 to 5.33 μIU/mL and a free T4 range of 0.59 to 1.43 ng/dL fell into the euthyroid category. Due to the relatively small number of patients (Supplementary Tables 1 and 2) with overt thyroid dysfunction, subclinical and overt forms were combined into hypothyroid and hyperthyroid categories to maintain statistical stability. Patients with subclinical hypothyroidism (TSH > 5.33 μIU/mL and 0.59 ≤ Free T4 ≤ 1.43 ng/dL) or hypothyroidism (Free T4 < 0.59 ng/dL) were placed in the hypothyroid category. In contrast, individuals with subclinical hyperthyroidism (TSH < 0.38 μIU/mL and 0.59 ≤ Free T4 ≤ 1.43 ng/dL) or hyperthyroidism (Free T4 > 1.43 ng/dL) were grouped under hyperthyroid. All thyroid function tests were conducted at the same institutional laboratory using standardized assays, and reference ranges for thyroid-stimulating hormone and free thyroxine remained consistent throughout the study period.

Measurement of BPSD and Cognitive Functions (Outcome)

The assessments of BPSD and cognition were performed by psychologists who received referrals from clinicians. BPSD was assessed using the NPI by trained clinicians according to standardized administration procedures,[3] which include 12 categories: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, abnormal motor activity, sleep disturbances, and changes in appetite. For each symptom category, an NPI score (severity multiplied by frequency) of 1 or more indicated the presence of that symptom, while a score of 4 or more indicated moderate to severe symptoms. The aggregate NPI score was the total of the scores across all 12 categories. Cognitive status was evaluated using the Cognitive Ability Screening Instrument (CASI)[23] and the Clinical Dementia Rating scale (CDR).[24] CASI ranges from 0 to 100, with a higher score indicating better cognitive performance. The CDRSOB is a score calculated by the sum of the six aspects of the CDR score, which can be viewed as a composed cognitive and functional assessment.

Statistical Analyses

The study utilized data produced by R software (R Foundation for Statistical Computing). It identified participants' thyroid status as the independent variable, whereas the BPSD and cognitive outcomes, determined by NPI, CASI, and CDRSOB scores, were considered the dependent variable. Covariates were selected a priori based on clinical relevance and prior literature demonstrating their association with cognitive outcomes and neuropsychiatric symptoms.[25] Age, sex, education level, and CDR global score were included to account for demographic factors and baseline dementia severity. Additional covariates were limited to avoid model overfitting and collinearity, given the cross-sectional design. Categorical data were evaluated using Pearson's Chi-square test or Fisher's exact test, while numerical data were examined with the Student's *t*-test or Wilcoxon rank sum test. To explore the relationship between thyroid status and the presence of BPSD, a multivariate logistic regression model was applied. Linear regression models were also used to explore the relationship between thyroid and cognitive status. A p-value under 0.05 was considered statistically significant. All variable definitions, exposure classifications, and outcome measures were predefined before analysis to ensure analytical reproducibility.

Results

A total of 2,289 patients with cognitive impairment were enrolled in this study. The baseline characteristics of the participants are shown in Table 1, while the baseline cognitive and behavioral status are in Table 2. About 129 (90.8%) and 113 (91.1%) patients in the hyperthyroid and hypothyroid groups are subclinical, and the observed associations in subsequent analyses were therefore largely driven by subclinical thyroid dysfunction. The mean age is 77.9, 79.2, and 79.9 years old in the euthyroid,

Table 1 Baseline Characteristics of the Participants

	Euthyroid (N = 2023)	Hyperthyroidism (N = 142)	Hypothyroidism (N = 124)	P Value
Age, mean (SD)	77.9 (8.2)	79.2 (8.8)	79.9 (7.9)	**0.038**
Gender-female	1253 (62%)	102 (72%)	81 (65%)	0.052
Type of cognitive dysfunction				0.9
Alzheimer's disease	1312 (65%)	92 (65%)	82 (66%)	
Vascular cognitive dysfunction	260 (13%)	22 (15%)	19 (15%)	
Lewy body disease	150 (7.4%)	9 (6.3%)	8 (6.5%)	
others	301 (15%)	19 (13%)	15 (12%)	
CDR				0.1768
0.5	1044 (52%)	67 (47%)	62 (50%)	
1	718 (35%)	47 (33%)	36 (29%)	
2	212 (10%)	23 (16%)	21 (17%)	
3	49 (2.4%)	5 (3.5%)	5 (4.0%)	

Notes: Bold values indicate statistical significance ($p < 0.05$).

hyperthyroid, and hypothyroid groups, respectively (77.9 ± 8.2 vs 79.2 ± 8.8 vs 79.9 ± 7.9, p = 0.038). Each group includes different types of cognitive dysfunction, with no significant differences in their distribution (p = 0.9). The severity of cognition is also comparable across the three groups (CDR = 0.5, 52% vs 47% vs 50%, p = 0.1768).

Table 2 shows the baseline cognitive and behavioral status of the patients in each group. There is a significant difference in the CDRSOB and CASI scores among the three groups (CDRSOB, 4.6 ± 3.8 vs 5.4 ± 4.1 vs 5.3 ± 4.1, p = 0.013; CASI, 51.6 ± 23.2 vs 47.2 ± 22.1 vs 49.0 ± 22.4, p = 0.028).

Table 2 Cognitive and Behavioral Status of the Participants

	Euthyroid	Hyperthyroidism	Hypothyroidism	P Value
CDRSOB				**0.013**
N	2023	142	124	
Mean (SD)	4.6 (3.8)	5.4 (4.1)	5.3 (4.1)	
CASI				**0.028**
N	1995	139	121	
Mean (SD)	51.6 (23.2)	47.2 (22.1)	49.0 (22.4)	
Presence of specific NPI symptom				
N	1934	146	113	
Delusion	519 (27%)	57 (39%)	28 (25%)	0.005
Hallucination	299 (15%)	28 (19%)	11 (9.7%)	0.11
Agitation	422 (22%)	44 (30%)	22 (19%)	0.051

(*Continued*)

Table 2 (Continued).

	Euthyroid	Hyperthyroidism	Hypothyroidism	P Value
Depression	669 (35%)	57 (39%)	36 (32%)	0.4
Anxiety	408 (21%)	30 (21%)	22 (19%)	>0.9
Euphoria	72 (3.7%)	7 (4.8%)	4 (3.5%)	0.7
Apathy	485 (25%)	30 (21%)	26 (23%)	0.4
Disinhibition	173 (8.9%)	18 (12%)	6 (5.3%)	0.14
Irritability	555 (29%)	49 (34%)	26 (23%)	0.2
Aberrant motor behavior	334 (17%)	30 (21%)	14 (12%)	0.2
Sleep	808 (42%)	63 (43%)	52 (46%)	0.7
Appetite	441 (23%)	33 (23%)	34 (30%)	0.2
Presence of Moderate to severe specific NPI symptom				
Delusion	289 (15%)	31 (21%)	14 (12%)	0.086
Hallucination	148 (7.7%)	19 (13%)	7 (6.2%)	0.054
Agitation	210 (11%)	20 (14%)	9 (8.0%)	0.3
Depression	329 (17%)	25 (17%)	21 (19%)	>0.9
Anxiety	195 (10%)	18 (12%)	13 (12%)	0.6
Euphoria	18 (0.9%)	2 (1.4%)	2 (1.8%)	0.4
Apathy	299 (15%)	19 (13%)	11 (9.7%)	0.2
Disinhibition	89 (4.6%)	6 (4.1%)	1 (0.9%)	0.2
Irritability	269 (14%)	28 (19%)	11 (9.7%)	0.084
Aberrant motor behavior	199 (10%)	14 (9.6%)	7 (6.2%)	0.4
Sleep	468 (24%)	33 (23%)	31 (27%)	0.7
Appetite	264 (14%)	19 (13%)	19 (17%)	0.6

Notes: Bold values indicate statistical significance ($p < 0.05$).
Abbreviations: CDRSOB, clinical dementia rating scale sum of boxes; N, number; SD, standard deviation; NPI, neuropsychiatric inventory.

Table 3A employs logistic regression models to analyze the relationship between thyroid status and the occurrence of neuropsychiatric symptoms. After adjusting for age, gender, global CDR, and education years, the hyperthyroid group, compared to the euthyroid group, exhibited a higher tendency toward delusions (odds ratio (OR) = 1.61, 95% confidence interval (CI) = 1.12–2.31, p = 0.009), and agitation symptoms (OR = 1.47, 95% CI = 1.00–2.13, p = 0.048). On the other hand, Table 3B displays the findings from logistic regression models regarding thyroid status and the occurrence of moderate to severe neuropsychiatric symptoms. Patients in the hyperthyroid group, as opposed to the euthyroid group, demonstrated a stronger inclination to have moderate to severe hallucinations (NPI score ≥ 4) (OR = 1.76, 95% CI = 1.01–2.92, p = 0.037), whereas no statistically significant association was observed for overall hallucination (NPI score ≥ 1).

Table 4 presents the linear regression models for predicting thyroid status and cognitive scores. Comparing the baseline characteristics, older patients and those with less education come with lower CASI and higher CDRSOB scores ($p < 0.001$). The same trend is also found in vascular cognitive dysfunction in comparison to AD ($p < 0.001$). Patients in the hyperthyroid group had worse CDRSOB scores than the euthyroid group ($\beta = 0.66$, 95% CI = 0.03–1.3, p = 0.040).

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Table 3 Logistic Regression Models to Predict the Association of Thyroid Status and Presence of Moderate to Severe Neuropsychiatric Symptoms*

	Hyperthyroidism		**Hypothyroidism**	
	Odds Ratio, [95% CI] (Ref: Euthyroid)	**p-value**	**Odds Ratio, [95% CI] (Ref: Euthyroid)**	**p-value**
A				
Total NPI				
Delusion	**1.61 [1.12, 2.31]**	**0.009**	0.86 [0.54, 1.34]	0.516
Hallucination	1.22 [0.77, 1.88]	0.386	0.54 [0.26, 1.00]	0.067
Agitation	**1.47 [1.00, 2.13]**	**0.048**	0.83 [0.50, 1.33]	0.454
Depression	1.17 [0.82, 1.66]	0.371	0.90 [0.59, 1.35]	0.607
Anxiety	0.94 [0.61, 1.41]	0.770	0.90 [0.54, 1.43]	0.655
Euphoria	1.30 [0.53, 2.72]	0.524	0.93 [0.28, 2.32]	0.887
Apathy	0.76 [0.49, 1.15]	0.208	0.88 [0.55, 1.38]	0.602
Disinhibition	1.38 [0.79, 2.28]	0.228	0.55 [0.21, 1.17]	0.161
Irritability	1.24 [0.86, 1.78]	0.248	0.73 [0.45, 1.14]	0.177
Aberrant motor behavior	1.14 [0.73, 1.74]	0.549	0.64 [0.34, 1.11]	0.131
Sleep	0.96 [0.68, 1.36]	0.821	1.18 [0.80,1.75]	0.395
Appetite	0.95 [0.62, 1.41]	0.808	1.45 [0.94, 2.18]	0.085
B				
Total NPI				
Delusion	1.42 [0.91, 2.15]	0.111	0.76 [0.41, 1.33]	0.371
Hallucination	**1.76 [1.01, 2.92]**	**0.037**	0.71 [0.29, 1.51]	0.417
Agitation	1.21 [0.71, 1.96]	0.455	0.67 [0.31, 1.30]	0.273
Depression	0.96 [0.60, 1.49]	0.877	1.12 [0.67, 1.80]	0.648
Anxiety	1.18 [0.68, 1.94]	0.537	1.14 [0.60, 2.02]	0.667
Euphoria	1.53 [0.24, 5.50]	0.578	1.95 [0.31, 7.03]	0.378
Apathy	0.79 [0.46, 1.29]	0.362	0.57 [0.28, 1.05]	0.094
Disinhibition	0.85 [0.32, 1.85]	0.713	0.18 [0.01, 0.81]	0.087
Irritability	1.40 [0.89, 2.15]	0.133	0.64 [0.32, 1.17]	0.181
Aberrant motor behavior	0.79 [0.42, 1.38]	0.439	0.52 [0.21, 1.07]	0.106
Sleep	0.83 [0.54, 1.25]	0.388	1.19 [0.76, 1.83]	0.440
Appetite	0.89 [0.52, 1.44]	0.655	1.27 [0.74, 2.09]	0.357

Notes: *All models adjusted age, gender, global CDR, and education. Bold values indicate statistical significance ($p < 0.05$).

Table 4 Linear Regression Models to Predict the Association of Thyroid Status and Cognitive Scores

	CASI		CDRSOB	
	Beta, [95% CI] (Ref: Euthyroid)	**p-value**	**Beta, [95% CI] (Ref: Euthyroid)**	**p-value**
Age	**−0.45 [−0.57, −0.34]**	**<0.001**	**0.06 [0.05, 0.08]**	**<0.001**
Gender (male)	0.93 [−0.98, 2.8]	0.339	0.25 [−0.08, 0.59]	0.142
Education	**1.5 [1.3, 1.7]**	**<0.001**	**−0.08 [−0.12, −0.05]**	**<0.001**
Diagnosis (as opposed to Alzheimer's disease)				
Vascular dementia	**−6.7 [−9.3, −4.1]**	**<0.001**	**1.6 [1.2, 2.1]**	**<0.001**
Lewy body disease	0.49 [−2.9, 3.8]	0.774	0.02 [−0.57, 0.62]	0.938
others	**4.6 [2.1, 7.2]**	**<0.001**	−0.28 [−0.73, 0.17]	0.227
Thyroid status (in comparison to the euthyroid group)				
Hyperthyroidism	−1.8 [−5.4, 1.8]	0.331	**0.66 [0.03, 1.3]**	**0.040**
Hypothyroidism	−1.5 [−5.3, 2.4]	0.451	0.62 [−0.06, 1.3]	0.074

Notes: Bold values indicate statistical significance ($p < 0.05$).
Abbreviations: CASI, cognitive ability screening instrument; CDRSOB, clinical dementia rating scale sum of boxes.

Baseline cognitive and behavioral characteristics across detailed thyroid function categories are summarized in Supplementary Tables 1 and 2.

Discussion

This study revealed notable differences in BPSD and cognitive functions among patients across different thyroid function groups. Patients in the hyperthyroid group are associated with worse CDRSOB than those in the euthyroid group. Furthermore, the hyperthyroid group was linked to delusion, agitation, and moderate to severe hallucinations. However, the observed associations were generally modest in magnitude, and findings approaching borderline statistical significance should be interpreted with caution.

The present study found that patients in the hyperthyroid group are associated with worse cognitive function based on CDRSOB ($\beta = 0.66$, 95% CI = 0.03–1.3, $p = 0.040$). The results are consistent with the meta-analysis by Jianbo Ye et al,[8] the Rotterdam Study by Layal Chaker et al,[9] and the systematic review by Vedant Lekurwale et al,[10] as mentioned in the introduction. Multiple hypotheses have been suggested to explain the underlying cause. For starters, the cardiovascular effect of thyroid hormone is most discussed,[8–10,26,27] has been proposed to contribute to vascular brain changes and, in turn, present as cognitive dysfunction.[9] Another theory is that changes in gene expression[28,29] and the alteration of beta-amyloid precursor proteins[30–32] have been proposed to be associated with excess thyroid hormones. Thyroid hormone-related neurotoxicity[33] and acetylcholine depletion by low thyrotropin-releasing hormone in hyperthyroidism[8] have also been mentioned as a positive contributor. Lastly, due to incomplete evaluation of causal relationships, the observed association between hyperthyroidism and cognitive impairment may be attributable to preclinical dementia-related behaviors, such as malnutrition-induced hyperthyroidism,[9] or to age-related alterations in thyroid hormone levels.[10]

The primary novelty of this study lies in the systematic evaluation of behavioral and psychological symptom profiles across thyroid function groups in patients with cognitive impairment, rather than in the magnitude of individual effect sizes. Most importantly, our study reveals that hyperthyroidism is linked to delusion, agitation, and moderate to severe hallucinations in patients with cognitive impairment. The result confirms some of the results of the meta-analysis by Marilu Jurado-Flores et al that hyperthyroidism can result in agitation and acute psychosis.[15] However, increased symptoms like apathy,[15] mentioned in the same article, or depression[16] in another meta-analysis by Henry Bode et al,[16] are not

observed in our study. Moreover, depression[11–13,15] linked with hypothyroidism is also not seen in this study. The meta-analysis by Henry Bode et al[34] demonstrated that the association between hypothyroidism and depression is weaker than previously suggested and is markedly attenuated in subclinical hypothyroidism, which predominates in our hypothyroid group. Consistent with this, recent meta-analyses have reported that subclinical hypothyroidism is not significantly associated with depression[35] or that the relationship remains inconclusive.[36] Also, in cognitively impaired populations, overlapping neurodegenerative pathology and symptom burden may attenuate or obscure the neuropsychiatric effects attributable to hypothyroidism alone. These variations may be attributable to the fact that the referenced studies focus exclusively on the relationship between thyroid function and general psychiatric symptoms, whereas our study emphasizes the association between thyroid function and BPSD, evaluating only individuals with cognitive impairment.

Currently, there is little research on the pathophysiology of BPSD occurrence in hyperthyroid patients. However, possible mechanisms accounting for the increased prominence of delusion, hallucination, and agitation may be hypothesized to be related to some of the manifestations of thyroid hormone effects.

The thyroid hormone is closely linked to neurodevelopment.[37] In adult brains, multiple gene expressions can be disturbed by thyroid hormone,[15] and the increased oxidative stress[15] from it can also take a toll on the neuro-signaling function of the cerebrum. Disruption of thyroid hormone signaling leads to neurobehavioral abnormalities, pathological brain changes, and altered gene expression profiles in aging mice.[38] Additionally, Hyperthyroidism can exacerbate into thyrotoxicosis, and even when mild, neuropsychiatric symptoms can occur.[39] Thyroid hormone excess alters astrocyte-related transcription pathways involved in neuroimmune regulation.[38] Excess thyroid hormone in this condition can affect the central nervous system and manifest as psychosis.[40] As a result of the altered mental status, psychotic symptoms such as delusions, hallucinations, and agitation may be observed. Third, elevated thyroid hormone levels can induce changes in regional cerebral glucose metabolism.[41,42] When the limbic system is affected,[42] psychotic symptoms like delusions, hallucinations, and agitation may consequently manifest in patients within the hyperthyroid group. These pathophysiological mechanisms are discussed as hypotheses derived from prior literature and should be interpreted as exploratory, given the observational and cross-sectional nature of the present study. Interpretation of these potential mechanisms should be made cautiously, as the present study did not adjust for psychotropic medication use, cardiovascular risk factors, or more granular dementia severity measures beyond the CDR.

The present study showed lower cognitive and functional ability in patients who are older, with less education, or those with a vascular cognitive impairment. Evidence of ageing-induced cognitive decline is well-documented in current literature. Older adults tend to have a decline in processing speed of information, attention, or visuospatial concepts in complex tasks, memory, naming ability, verbal fluency, and some executive functions.[43] On the other hand, similarly, the study by Claudia K. Suemoto et al, using CDRSOB, supports our finding that lower educational attainment is associated with poorer cognitive abilities.[44] Sean A P Clouston pointed out that education reduces the risk of dementia-related cognitive decline,[45] and likewise, Sonali Arora et al emphasized that schooling has a delaying effect on cognitive decline.[46] In addition, contrary to the findings of Grazia D'Onofrio et al in 2015, which indicated that AD is associated with a higher degree of cognitive decline in comparison to vascular dementia,[47] our results suggest an opposite pattern. Due to more acute presentation in VCI, Grazia D'Onofrio et al[47] concluded that the pattern they found might be related to delayed care in AD patients. However, a decade has passed since their results, advancements in understanding the health of older adults and dementia suggest that the diagnostic time gap between the two should now be reduced. Patients with AD have been diagnosed at a milder disease stage in 2023 when compared with 2010 in Taiwan.[48] More AD patients have been diagnosed at the mild cognitive impairment stage, which may explain the worse cognitive score in the VCI group in the present study.

The strength of our study lies in that 1) this is the first study to evaluate NPS in patients with dementia across different thyroid statuses. 2) BPSD was assessed using the standardized NPI score. Nonetheless, several limitations should also be taken into account: 1) This retrospective, cross-sectional design is subject to inherent bias and precludes causal inference between thyroid function and cognitive or neuropsychiatric outcomes. 2) The combination of subclinical and overt thyroid dysfunction may obscure physiologically distinct effects between these conditions. 3) Information on thyroid-related medications, psychotropic agents, and medical comorbidities—including apoE4 genotype, vascular risk factors, and antipsychotic use—was unavailable, which may introduce residual confounding. 4) Additionally, although thyroid function tests were performed as part of routine clinical care, subtle assay-related variability over the 10-year study period cannot be completely excluded.

Conclusion

This study is the first structured analysis to examine BPSD across different thyroid function states in patients with cognitive impairment, demonstrating significant differences in neuropsychiatric symptom profiles. Patients with hyperthyroidism exhibited worse global function compared with euthyroid individuals and showed higher prevalence of delusions, agitation, and moderate-to-severe hallucinations. These findings highlight an association between thyroid dysfunction and BPSD in cognitively impaired populations and underscore the importance of careful clinical evaluation of thyroid status in this context.

Ethical Declaration

This study complies with the Declaration of Helsinki.

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Disclosure

The authors report no conflicts with any product mentioned or concept discussed in this article. Yu-Ru Lin, Ming-Che Chang, Wen-Fu Wang, and Yu-Chun Tung share first authorship.

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