The Association Between Thyroid Diseases and Alzheimer’s Disease in a National Health Screening Cohort in Korea

Ji Hee Kim1, Heui Seung Lee1, Yoo Hwan Kim2, Mi Jung Kwon3, Joo-Hee Kim4, Chan Yang Min5, Dae Myoung Yoo6 and Hyo Geun Choi5,6*

1 Department of Neurosurgery, Hallym University College of Medicine, Anyang, South Korea, 2 Department of Neurology, Hallym University College of Medicine, Anyang, South Korea, 3 Department of Pathology, Hallym University College of Medicine, Anyang, South Korea, 4 Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, Hallym University College of Medicine, Anyang, South Korea, 5 Hallym Data Science Laboratory, Hallym University College of Medicine, Anyang, South Korea, 6 Department of Otorhinolaryngology-Head & Neck Surgery, Hallym University College of Medicine, Anyang, South Korea

Objectives: Thyroid dysfunction is linked to an increased risk of cognitive impairment. However, studies on the relationships between thyroid diseases and Alzheimer’s disease (AD) have reported conflicting results. We investigated the associations between several thyroid diseases and AD in a nested case-control study.

Methods: A total of 1,977 participants with AD were identified by claims data from 2002-2015 among a random sample of half a million people in the Korean National Health Insurance database. We recruited 16,473 age- and sex-matched (1:4 ratio) control participants and applied conditional logistic regression to estimate the relationships between thyroid diseases and AD, with adjustments for potential confounders, such as basic demographics, lifestyle factors, and various medical conditions or comorbidities.

Results: The prevalence rates of hypothyroidism (odds ratio [OR]=1.14, 95% confidence interval [CI]=1.00-1.30), thyroiditis (OR=1.22, 95% CI=1.05-1.40), and hyperthyroidism (OR=1.13, 95% CI=1.01-1.28) were significantly higher in participants with AD than in control participants after adjustment for confounders.

Conclusion: In this large national sample, we found significant relationships between several thyroid diseases and AD. Despite of the need for further investigation, these findings could better support to appreciate the pathophysiology of AD.

Keywords: Alzheimer’s disease (AD), cognitive decline, neurodegeneration, neurodegenerative diseases, thyroid disease
INTRODUCTION

Thyroid hormones are essential for neuronal development and cellular metabolism, and their dysfunction can lead to potentially devastating health consequences that influence numerous organs in patients of all ages (1). In particular, thyroid hormones regulate neuronal cytoarchitecture, growth and synaptogenesis, and their receptors have a broad distribution in the central nervous system (CNS) (2). Accordingly, thyroid dysfunction, namely, any deficiency or increase in thyroid hormones, can induce a range of changes in mood and cognitive function and, in severe cases, cause anxiety, depression, irritability, and a deficit in executive function (3). Specifically, hypothyroidism can often be accompanied by widespread cognitive decline, particularly memory dysfunction, whereas overt thyrotoxicosis can manifest cognitive decline mainly in the areas of attention, concentration, and executive function (3).

Alzheimer’s disease (AD) is the most prevalent form of dementia and a progressive neurodegenerative disease of the CNS that leads to multidomain cognitive impairment, particularly memory dysfunction. According to the 2010 US Census data, the overall prevalence of AD was estimated to be 14.5% and the annual incidence was 2.3% (4). Pathologically, this disease is known to be attributed to extracellular amyloid deposition and intracellular neurofibrillary tangles of hyperphosphorylated tau (5). However, the causes of these features and those of the disease have not yet been elucidated.

After the link between clinical thyroid dysfunction and cognitive abnormalities was first described by Asher as “myxoedematous madness” in 1949 (6), interest in the association between thyroid disorders and dementia increased. Since neurotransmission, memory, and further vital brain functions require the maintenance of normal energy (glucose)-consuming processes, low thyroid function at any age can debilitate cognitive function (7). Several studies have also disclosed that thyroid hormones regulate the function of the adult brain, which illustrates the tightened arrangement of thyroid hormone transport into the brain, region-specific T4 (thyroxine) to T3 (tri-iodothyronine) conversion and T3 receptor levels (8). Given the theoretically increased risk of cognitive decline with thyroid dysfunction, it is conceivable that thyroid diseases can contribute to the pathophysiology of AD. Clinical observations and experimental studies have indicated a relationship between thyroid hormones and AD or its pathology (9–12). However, many previous studies provided inconsistent results owing to small sizes of the data samples, heterogeneous participant characteristics, or cognitive tests of limited sensitivity. Some studies have shown a positive association (12, 13), while others have reported no relationship between thyroid-stimulating hormone (TSH) or thyroid hormones and AD (14, 15).

Therefore, our hypothesis in this study is that thyroid dysfunction, whether clinical hypothyroidism or clinical hyperthyroidism, may be associated with AD in data from a large sample. To test this hypothesis, we aimed to investigate the associations between several thyroid diseases and AD using nationwide cohort data from Korea.

MATERIALS AND METHODS

Study Population

The study protocol was approved by the ethics committee of Hallym University (2019-10-023). The data source for this nested-case control study was the Korean National Health Insurance Service (NHIS)-Health Screening Cohort, which included all the original claims data. Specific statements from the Korean NHIS-Health Screening Cohort data have been explained in greater detail in our previous report (16).

Participants who received treatment with levothyroxine for more than 3 months or who had goiter, hypothyroidism, thyroiditis, or hyperthyroidism were evaluated as described previously (17), and these conditions were included as independent variables. Participants with AD, which was used as the dependent variable in our analysis, were assessed and included as reported in our previous work (18).

Participant Selection

AD participants were initially enrolled from a population of 514,866 participants with 615,488,428 medical claim codes between 2002 and 2015 (n=20,087). Participants were included as controls if they were not diagnosed with AD from 2002 to 2015 (n=489,735). Participants who were diagnosed with AD in 2002 were omitted from the study to select only participants who had been newly diagnosed with AD (n=168). In other words, the washout period was designated to exclude the participants who were continuously treated after being diagnosed with AD prior to 2002. To limit confounders, we excluded participants who had experienced head trauma (ICD-10 codes: S00 to S09, confirmed by neurologists, neurosurgeons, or emergency medicine doctors) ≥2 times (n=1,369 in AD; n=12,159 in control) and those who had been diagnosed with brain tumors (ICD-10 codes: C70-C72) at least two times (n=80 in AD; n=791 in control). AD participants who had no records of baseline body mass index (BMI), fasting blood glucose or total cholesterol and hemoglobin levels were also excluded (n=20). We matched AD participants and control participants at a 1:4 ratio based on participants’ age, sex, income, and region of residence. To shorten the selection bias, the control participants were assigned a random number order. The index date of each case was determined as the time of the first treatment for AD. Because the index date of control participants was defined as the index date of their corresponding AD participants, each matched AD and control participant had an identical index date. Throughout the matching step, 1,977 AD participants and 410,893 control participants were excluded. Eventually, 16,473 AD participants were matched with 65,892 control participants at a 1:4 ratio (Figure 1).

Covariates

Our study covariates of interest included participant age, sex, income, region of residence, obesity, smoking, alcohol consumption, systolic blood pressure (SBP), diastolic blood pressure (DBS), fasting blood glucose, levels of total cholesterol and hemoglobin, and comorbidity score. Age was stratified into ten groups with intervals of 5 years: from 40–44 to 85+ years old group. Income groups were categorized into 5 classes from class 1 (lowest income) to class 5 (highest income), and each class comprised of 5 self-employment health insurance classes and 5 employment health
insurance classes. The one health aid class was included in the lowest income class. The region of residence was categorized as urban or rural (19). Obesity assessments via BMI (kg/m²) was made in accordance with the Asia-Pacific criteria (20). Missing BMI was substituted by the mean values of variables from the selected people. Assessments of smoking status and alcohol consumption were performed as defined in a previous publication (16). The Charlson Comorbidity Index (CCI) was utilized to assess comorbidity load with a score from 0 to 29, excluding dementia, cancer, and metastatic cancer.

**Statistical Analysis**

The balance of baseline characteristics between study groups was assessed by reporting standardized differences. To compare thyroid diseases between AD participants and control participants, odds ratios (ORs) and 95% confidence intervals (CIs) were computed by using a conditional logistic regression method. We further adjusted the ORs for possible covariates using an adjusted model. The covariates BMI, smoking, alcohol consumption, SBP CCI scores and thyroid cancer were adjusted for in model 1. Levothyroxine treatment, goiter, hypothyroidism, thyroiditis, and hyperthyroidism were additionally included in model 1 to estimate model 2. This is because levothyroxine treatment, goiter, hypothyroidism, thyroiditis, and hyperthyroidism histories were significantly linked to each other (each P <0.001, Table S1).

Subgroup analyses were performed to identify the incidence of thyroid diseases in terms of age and sex (over 75 years of age or under; men or women) and income and region of residence (low or high; urban or rural). Each subgroup was stratified into four groups, and the estimates were conducted using the unadjusted model, model 1, and model 2.

Two-tailed analyses were conducted, and P values less than 0.05 were considered to indicate a statistically significant difference. A standardized difference of ≤0.1 was deemed an ideal balance, and a standardized difference of ≤0.2 was treated as acceptable balance. Statistical analysis was conducted by using SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA).

**RESULTS**

**Characteristics of Participants**

The baseline characteristics of the participants in this study are shown in Table 1. The study groups corresponded to age, sex,
| Characteristics | Total participants |
|-----------------|--------------------|
| **Total number** | 16,473 (100.0)     |
| **Age (years)** |                    |
| 40-44           | 1 (0.0)            |
| 45-49           | 48 (0.3)           |
| 50-54           | 171 (1.0)          |
| 55-59           | 396 (2.4)          |
| 60-64           | 903 (5.5)          |
| 65-69           | 2,075 (12.6)       |
| 70-74           | 3,992 (24.2)       |
| 75-79           | 4,959 (30.1)       |
| 80-84           | 3,419 (20.8)       |
| 85+             | 509 (3.1)          |
| **Sex**         |                    |
| Male            | 6,406 (38.9)       |
| Female          | 10,067 (61.1)      |
| **Income**      |                    |
| 1 (lowest)      | 3,375 (20.5)       |
| 2               | 1,861 (11.3)       |
| 3               | 2,259 (13.7)       |
| 4               | 2,988 (18.1)       |
| 5 (highest)     | 5,990 (36.4)       |
| **Region of residence** |            |
| Urban           | 5,821 (35.3)       |
| Rural           | 10,652 (64.7)      |
| **Obesity**†    |                    |
| Underweight     | 892 (5.4)          |
| Normal          | 6,614 (40.2)       |
| Overweight      | 3,859 (23.4)       |
| Obese I         | 4,620 (28.1)       |
| Obese II        | 488 (3.0)          |
| **Smoking status** |                |
| Nonsmoker       | 12,987 (78.8)      |
| Past smoker     | 1,059 (6.4)        |
| Current smoker  | 2,427 (14.7)       |
| **Alcohol consumption** |        |
| <1 time a week  | 13,558 (82.3)      |
| ≥1 time a week  | 2,915 (17.7)       |
| **Systolic blood pressure** |          |
| <120 mmHg       | 3,700 (22.5)       |
| 120-139 mmHg    | 7,792 (47.3)       |
| ≥140 mmHg       | 4,981 (30.2)       |
| **Diastolic blood pressure** |       |
| <80 mmHg        | 7,290 (44.3)       |
| 80-89 mmHg      | 5,892 (35.8)       |
| ≥90 mmHg        | 3,291 (20.0)       |
| **Fasting blood glucose** |         |
| <100 mg/dL      | 8,960 (54.4)       |
| 100-125 mg/dL   | 5,059 (30.7)       |
| ≥126 mg/dL      | 2,454 (14.9)       |
| **Total cholesterol** |            |
| <200 mg/dL      | 8,912 (54.1)       |
| 200-239 mg/dL   | 5,104 (31.0)       |
| ≥240 mg/dL      | 2,457 (14.9)       |
| **Hemoglobin (g/dL)** |        |
| ≥12 for men and ≥10 for women | 15,765 (95.7) |
| <12 for men and <10 for women | 708 (4.3) |
| **CCI scores‡** |                    |
| 0               | 6,711 (40.7)       |
| 1               | 4,449 (27.0)       |
| ≥2              | 5,313 (32.3)       |
income, and region of residence (each standardized difference = 0.00). The proportions of other baseline characteristics and thyroid diseases were well balanced between the two groups, and the standardized differences were less than 0.2. However, the AD group tended to have slightly higher percentages of participants with levothyroxine treatment over 3 months, goiter, hypothyroidism, thyroiditis, and hyperthyroidism (Table 1).

**Association Between Thyroid Diseases and AD**

Table 2 exhibits the logistic regression results of the analysis of the association between thyroid diseases and AD. Compared with no thyroid disease, all thyroid diseases were significantly associated with AD in multiple logistic regression model 1, which included all the covariates of interest. Among them, hypothyroidism (OR=1.14, 95% CI=1.00-1.30, P=0.046), thyroiditis (OR=1.22, 95% CI=1.05-1.40, P=0.008), and hyperthyroidism (OR=1.13, 95% CI=1.01-1.28, P=0.039) were still identified to have significant associations with AD in multiple logistic regression model 2 with each thyroid disease or condition being controlled.

**Subgroup Analyses Stratified by Age, Sex, Income, and Region of Residence**

We performed subgroup analyses to assess the effect of thyroid diseases on AD within subgroups stratified by age and sex, as indicated in Table 3. Within each subgroup, hypothyroidism, thyroiditis, and hyperthyroidism were consistently associated with a higher likelihood of having AD. Among these subgroups, only the group of men older than 75 years was statistically significant. As displayed in Table 4, the results from the subgroup stratified by income and region of residence indicated that hypothyroidism, thyroiditis, and hyperthyroidism were consistently linked to a higher likelihood of AD in all subgroups except for the subgroup of rural residents with low income.

**DISCUSSION**

This study demonstrated the associations between hypothyroidism, thyroiditis, hyperthyroidism, and AD, with OR values of 1.14, 1.22, and 1.13 after adjusting the model for covariates and each thyroid disease or condition. These findings are consistent with epidemiological studies revealing the effect of clinical hypothyroidism and clinical hyperthyroidism on the risk of dementia in large sample sizes (13, 21–23). George et al. showed that overt hyperthyroidism was related to a higher risk of dementia than euthyroidism in a prospective cohort study of community-dwelling adults who were followed for 22 years (hazard ratio [HR] = 1.40). The authors highlighted the importance of diagnosing and treating hyperthyroidism (22). Forlkestad et al. found an increased

### Table 1

| Characteristics | Alzheimer’s disease patients (n, %) | Total participants | Standardized Difference |
|-----------------|------------------------------------|--------------------|-------------------------|
| Thyroid cancer  | 121 (0.7)                          | 620 (0.9)          | 0.02                    |
| Period of levothyroxine treatment |                     |                    |                         |
| <3 months       | 15,874 (96.4)                      | 63,716 (96.7)      | 0.02                    |
| ≥3 months       | 599 (3.6)                          | 2,176 (3.3)        | 0.01                    |
| Goiter          | 591 (3.6)                          | 2,239 (3.4)        | 0.03                    |
| Hypothyroidism  | 602 (3.7)                          | 2,097 (3.2)        | 0.03                    |
| Thyroiditis     | 280 (1.7)                          | 902 (1.4)          | 0.03                    |
| Hyperthyroidism | 400 (2.4)                          | 1,349 (2.1)        | 0.03                    |

CC, Charlson comorbidity index.

1Obesity (BMI, body mass index, kg/m²) was categorized as <18.5 (underweight), ≥18.5 to <23 (normal), ≥23 to <25 (overweight), ≥25 to <30 (obese I), and ≥30 (obese II).

2CCI scores were calculated excluding dementia, cancer and metastatic cancer.

### Table 2

| Characteristics | N of Thyroid disease patients (exposure/total, %) | N of Controls (exposure/total, %) | Crude† | P-value | Odds ratios for Alzheimer’s disease | P-value |
|-----------------|-----------------------------------------------|----------------------------------|--------|---------|-----------------------------------|---------|
| Thyroid cancer  | 121/16,473 (0.7%)                             | 620/65,892 (0.9%)                | 0.033* | 1.15   | 1.04-1.27                         | 0.007*  |
| Period of levothyroxine treatment |                     |                                   |        |         |                                   |         |
| <3 months       | 15,874/16,473 (96.4%)                         | 63,716/65,892 (96.7%)            | 0.033* | 1.15   | 1.04-1.27                         | 0.007*  |
| ≥3 months       | 599/16,473 (3.6%)                             | 2,176/65,892 (3.3%)              | 0.033* | 1.15   | 1.04-1.27                         | 0.007*  |
| Goiter          | 591/16,473 (3.6%)                             | 2,239/65,892 (3.4%)              | 0.033* | 1.15   | 1.04-1.27                         | 0.007*  |
| Hypothyroidism  | 602/16,473 (3.7%)                             | 2,097/65,892 (3.2%)              | 0.033* | 1.15   | 1.04-1.27                         | 0.007*  |
| Thyroiditis     | 280/16,473 (1.7%)                             | 902/65,892 (1.4%)                | 0.033* | 1.15   | 1.04-1.27                         | 0.007*  |
| Hyperthyroidism | 400/16,473 (2.4%)                             | 1,349/65,892 (2.1%)              | 0.033* | 1.15   | 1.04-1.27                         | 0.007*  |

CC, Charlson comorbidity index.

†Conditional logistic regression model. Significance at P < 0.05.

‡Models stratified by age, sex, income, and region of residence.

§Model 1 was adjusted for obesity, smoking, alcohol consumption, systolic blood pressure, diastolic blood pressure, fasting blood glucose, total cholesterol, hemoglobin, thyroid cancer, and CCI scores.

**Model 2 was adjusted for the factors in Model 1 plus levothyroxine treatment, goiter, hypothyroidism, thyroiditis, and hyperthyroidism.
risk of dementia in hyperthyroid individuals in two patient cohorts using large-scale registry-based data (HR=1.17 and 1.06). In addition, the researchers revealed that every 6 months of decreased TSH was correlated with a 16% increased possibility of dementia compared to that of people with normal TSH, suggesting that the longer a patient has hyperthyroidism, the greater the risk of developing dementia is (21). According to a Framingham study by Tan et al. that analyzed prospectively collected data, there was a strong association between hyperthyroidism and the risk of Alzheimer-type dementia, specifying that overt thyroid dysfunction translated to a 2-fold greater risk for the development of Alzheimer-type dementia, compared to that of people with normal TSH, suggesting decreased TSH was correlated with a 16% increased possibility of dementia (23). Formigia et al. reported that subclinical hypothyroidism and hyperthyroidism were not related to a higher risk of cognitive function in their population-based, prospective cohort study consisting of 307 inhabitants (24). They explained that the main limitation of their study was the small number of individuals with abnormal TSH values. Additionally, a recent meta-analysis showed that except for subclinical hyperthyroidism, clinical hyperthyroidism and clinical hyperthyroidism did not influence dementia. The difference between the impact of clinical or subclinical hyperthyroidism on dementia can be clarified by the shortage of treatment and prolonged period of thyroid dysregulation in patients with subclinical hyperthyroidism. However, the authors identified adverse effects of both low and high TSH concentrations in the dose-response meta-analytic study, which inferred that not only hyperthyroidism but also hypothyroidism could cause dementia (25).

Notably, our findings also demonstrated that there was a significant association with thyroiditis and AD. To date, no study has addressed the link between all-cause thyroiditis and dementia and AD. It has been mainly supposed that an increased risk of cognitive dysfunction could pertain to autoimmune disease rather than thyroiditis per se, since the most common cause of thyroiditis is an autoimmune disease. In addition, an increased risk for dementia and AD was noted in patients with Hashimoto’s thyroiditis/hypothyroidism in a previous study, which has been
suggested to be due to thyroid dysfunction (13, 26). Although our analysis could not consider the various etiologies of thyroiditis, such as autoimmune, infection, or drugs, our data confirmed that the relationship between thyroiditis and AD was still statistically significant when controlling for each thyroid disease or condition as well as various comorbidities.

Proposed neuropathologic mechanisms contributing to the association of thyroid dysfunction with AD have been established in the probable roles of endogenous thyroid hormones and thyrotropin-releasing hormone (TRH). The first potential mechanism is amyloid plaque accumulation. This is due to increased amyloid precursor protein gene expression by low CNS thyroid hormone levels, as thyroid hormones are involved in the regulation of amyloid beta and amyloid beta precursor genes (11). The second potential mechanism is excessive thyroid hormone levels, which have been associated with toxic effects, such as increased oxidative stress on neuronal viability and enhanced neuronal death, which additionally increase vulnerability of the brain to amyloid toxicity (11, 27, 28). The third potential mechanism is the direct adverse effect of thyroxine (T4) reduction on cholinergic neurons. Several experimental studies have indicated the significant function of thyroid hormones in the development and preservation of the basal forebrain cholinergic neurons involved in AD (29, 30). The fourth potential mechanism is the elucidation of the relationship between TRH and the phosphorylation of tau protein. A number of studies have confirmed that a decrease in TRH could improve the phosphorylation of tau and other proteins, which are theoretically involved in the pathogenesis of AD (10, 31). The fifth potential mechanism is the induction of acetylcholine synthesis and release by TRH, which has been observed in rats, indicating that a decrease in TRH may prompt a reduction in acetylcholine, which plays a significant role in the development of AD (32, 33).

The strengths of the present study involved the numerous participants who were recruited from a representative, nationwide population sample and the detailed information regarding the various covariates adjusted as confounding factors in the analyses. Thus, we were able to adjust for plausible confounding factors and perform stratified subgroup analyses to identify potentially relevant interactions. Although the diagnosis of AD was based on ICD-10 coding, the coding of AD from NHIS data had good accuracy and validity, as described in our previous literature (18, see File S2). We calculated the interaction for each relationship indicated that there was little interaction between them in these analyses. The last strength of the present study is that this work simultaneously addresses hypothyroidism and hyperthyroidism in a single study and includes adjustment for

### Table 4: Subgroup analyses of crude and adjusted odds ratios (95% confidence intervals) associated with levothyroxine treatment, goiter, hypothyroidism, thyroiditis, and hyperthyroidism in Alzheimer’s disease patients compared to control participants stratified by income and region of residence.

| Characteristics | N of Thyroid disease patients | N of Controls | Odds ratios for Alzheimer’s disease |
|-----------------|------------------------------|---------------|----------------------------------|
|                 | (exposure/total, %)         | (exposure/total, %) | Crude† P-value | Model 1† P-value | Model 2† P-value |
| Low income, urban (n = 11,730) |                            |               |                    |                    |                    |
| Levothyroxine   | 87/2,346 (3.7%)             | 350/9,384 (3.7%) | 0.99 (0.78-1.26)    | 0.961 (0.76-1.29) | 0.927 (0.59-1.13) |
| Goiter          | 86/2,346 (3.7%)             | 350/9,384 (3.7%) | 0.98 (0.77-1.28)    | 0.897 (0.68-1.23) | 0.867 (0.50-1.47) |
| Hypothyroidism  | 86/2,346 (3.7%)             | 350/9,384 (3.7%) | 1.09 (0.86-1.38)    | 0.500 (0.37-0.68) | 0.360 (0.18-0.69) |
| Thyroiditis     | 45/2,346 (1.9%)             | 141/9,384 (1.5%) | 1.28 (0.91-1.80)    | 0.150 (0.11-1.93) | 0.167 (0.09-0.29) |
| Hyperthyroidism | 53/2,346 (2.3%)             | 193/9,384 (2.1%) | 1.10 (0.81-1.50)    | 0.540 (0.40-0.72) | 0.570 (0.40-0.82) |
| Low income, rural (n = 25,745) |                            |               |                    |                    |                    |
| Levothyroxine   | 165/5,149 (3.2%)            | 530/20,596 (2.6%) | 1.24 (1.04-1.48)    | 0.019* (1.04-1.55) | 0.019* (0.97-1.28) |
| Goiter          | 144/5,149 (2.8%)            | 529/20,596 (2.6%) | 1.09 (0.91-1.32)    | 0.356 (0.27-0.46) | 0.311 (0.23-0.42) |
| Hypothyroidism  | 171/5,149 (3.3%)            | 506/20,596 (2.5%) | 1.37 (1.15-1.63)    | 0.001* (1.14-1.66) | 0.001* (1.05-1.72) |
| Thyroiditis     | 78/5,149 (1.5%)             | 240/20,596 (1.2%) | 1.32 (1.02-1.71)    | 0.039* (1.07-1.80) | 0.039* (1.07-1.80) |
| Hyperthyroidism | 98/5,149 (1.9%)             | 378/20,596 (1.8%) | 1.06 (0.84-1.31)    | 0.677 (0.55-0.85) | 0.636 (0.50-0.82) |
| High income, urban (n = 17,375) |                            |               |                    |                    |                    |
| Levothyroxine   | 160/3,475 (4.6%)            | 567/13,900 (4.1%) | 1.14 (0.95-1.36)    | 0.165 (1.01-1.50) | 0.107 (0.83-1.35) |
| Goiter          | 163/3,475 (4.7%)            | 610/13,900 (4.4%) | 1.08 (0.90-1.28)    | 0.428 (0.35-0.51) | 0.386 (0.31-0.48) |
| Hypothyroidism  | 163/3,475 (4.7%)            | 572/13,900 (4.1%) | 1.15 (0.96-1.37)    | 0.130 (0.99-1.44) | 0.106 (0.87-1.35) |
| Thyroiditis     | 65/3,475 (1.9%)             | 213/13,900 (1.5%) | 1.23 (0.93-1.62)    | 0.155 (0.98-1.57) | 0.098 (0.88-1.58) |
| Hyperthyroidism | 104/3,475 (3.0%)            | 326/13,900 (2.3%) | 1.29 (1.03-1.61)    | 0.028* (0.99-1.55) | 0.061 (0.93-1.49) |
| High income, rural (n = 27,351) |                            |               |                    |                    |                    |
| Levothyroxine   | 188/5,503 (3.4%)            | 729/22,012 (3.3%) | 1.04 (0.88-1.22)    | 0.645 (0.71-1.30) | 0.340 (0.75-1.23) |
| Goiter          | 198/5,503 (3.6%)            | 750/22,012 (3.4%) | 1.06 (0.90-1.24)    | 0.478 (0.44-1.53) | 0.304 (0.89-1.30) |
| Hypothyroidism  | 79/5,503 (3.3%)             | 690/22,012 (3.1%) | 1.04 (0.89-1.23)    | 0.653 (0.54-1.21) | 0.296 (0.84-1.53) |
| Thyroiditis     | 91/5,503 (1.7%)             | 308/22,012 (1.4%) | 1.19 (0.94-1.50)    | 0.158 (0.93-1.51) | 0.172 (1.08-1.35) |
| Hyperthyroidism | 144/5,503 (2.6%)            | 452/22,012 (2.1%) | 1.28 (1.06-1.55)    | 0.010* (1.06-1.56) | 0.011* (1.03-1.53) |

CCI, Charlson comorbidity index.
*Conditional logistic regression model. Significance at P < 0.05.
†Models stratified by age, sex, income, and region of residence.
‡Model 1 was adjusted for obesity, smoking, alcohol consumption, systolic blood pressure, diastolic blood pressure, fasting blood glucose, total cholesterol, hemoglobin, thyroid cancer, and CCI score.
§Model 2 was adjusted for the factors in Model 1 plus levothyroxine treatment, goiter, hypothyroidism, thyroiditis, and hyperthyroidism.
CONCLUSION

The current results demonstrated that clinical hypothyroidism, thyroiditis, and hyperthyroidism were significantly associated with AD, although the biological mechanisms remain unclear. Furthermore, our findings imply that there may be a role for the treatment of these thyroid diseases in prevention of the development or progression of AD. Further research is warranted to elucidate causality and the directions of these associations.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The current article used a national sample cohort and does not involve data that can be available. Requests to access these datasets should be directed to https://nhiss.nhis.or.kr/ bd/ay/bdaya001iv.do.

ETHICS STATEMENT

This study was approved by the ethics committee of Hallym University (2020-07-022). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JK and HL participated in the interpretation of the data and drafted and revised the manuscript. YK, MK, J-HK, CM, and DY participated in data collection and data interpretation. HC designed the study, participated in data collection and data interpretation, and revised the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.815063/full#supplementary-material
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