



Rising Incidence and Comorbidities of Endogenous Hypothyroidism in Republic of Korea from 2004 to 2018: A Nationwide Population Study

Chae Won Chung¹, Hwa Young Ahn², Sun Wook Cho³, Ka Hee Yi⁴

¹Department of Internal Medicine, Chung-Ang University Hospital; ²Department of Internal Medicine, Chung-Ang University College of Medicine; ³Department of Internal Medicine, Seoul National University College of Medicine; ⁴Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, Korea

Background: Hypothyroidism, a prevalent endocrine disorder, results from insufficient thyroid hormone production or release, affecting metabolism. However, disparities in comorbidities and treatment trajectories may exist between endogenous and exogenous hypothyroidism.

Methods: Data from the Korean National Health Insurance Service from 2004 to 2018. Endogenous hypothyroidism was defined as cases with two or more diagnostic codes for hypothyroidism coupled with a history of thyroid hormone intake exceeding 60 days. To eliminate iatrogenic hypothyroidism, individuals with diagnosis codes for thyroid cancer, treatment codes for thyroid surgery, or radiotherapy were excluded. Hypothyroidism-related comorbidities were defined as new occurrences of the corresponding diagnosis code after the diagnosis of hypothyroidism during the entire study period.

Results: The age-standardized incidence of endogenous hypothyroidism among men was 0.2 per 1,000 person-years in 2004, increasing to 0.8 in 2018. Among women, the incidence increased from 1.6 per 1,000 person-years in 2004 to 3.7 in 2018. When comparing age groups of 20s–50s and 60s–90s, both sexes in the 60s–90s demonstrated a more rapid increase in incidence than those in the 20s–50s age range. Patients with endogenous hypothyroidism demonstrated a higher incidence of mood disorders across all age groups and cerebrovascular disease in individuals ≥ 60 years old, regardless of sex.

Conclusion: In Republic of Korea, endogenous hypothyroidism incidence has been increased in recent years. The incidence of endogenous hypothyroidism is increasing more rapidly in men than in women, especially in the elderly. Patients with endogenous hypothyroidism seem to have a heightened risk for cerebrovascular disease and mood disorders.

Keywords: Endogenous hypothyroidism; Republic of Korea; Prevalence; Incidence; Comorbidity

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Corresponding authors: Hwa Young Ahn
Department of Internal Medicine, Chung-Ang University College of Medicine,
84 Heukseok-ro, Dongjak-gu, Seoul 06974, Korea
Tel: +82-2-6299-3152, **Fax:** +82-2-6263-2184, **E-mail:** hyahnm@cau.ac.kr

Sun Wook Cho
Department of Internal Medicine, Seoul National University Hospital, Seoul
National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul
03080, Korea
Tel: +82-2-2072-4761, **Fax:** +82-2-2072-7246, **E-mail:** swchomd@snu.ac.kr

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INTRODUCTION

Hypothyroidism—a prevalent endocrine disorder—occurs owing to insufficient production or release of thyroid hormone (TH) [1]. Thyroxine, an essential hormone, regulates diverse metabolic pathways, and its deficiency can cause significant dysfunction throughout the body [2]. The prevalence of hypothyroidism in Western countries ranges from 0.3% to 5.3% [1,3–5], whereas in Republic of Korea, it was 1.6% in 2015 [6].

The etiology of hypothyroidism encompasses intrinsic dysfunction of thyroid gland and extrinsic one from thyroidectomy or radioactive iodine (RAI) therapy. In exogenous hypothyroidism, lifelong TH replacement therapy is required, however, long-term TSH suppression is associated with cardiac and bone complications [7,8]. In endogenous hypothyroidism caused by chronic autoimmune thyroiditis or transient thyroiditis, the duration of hormone replacement therapy varies, and the occurrence of complications is not yet well understood. While a recent study in Republic of Korea investigated prevalence of patients with exogenous hypothyroidism [9], those for endogenous hypothyroidism has not been studied in Republic of Korea.

This study aimed to evaluate the prevalence, incidence, treatment course, and concurrent medical conditions of endogenous hypothyroidism in Republic of Korea.

METHODS

Study population

In this study, we examined claims data obtained from the National Health Insurance Service (NHIS) of Republic of Korea, which comprises a comprehensive nationwide database including age, sex, date of visit, diagnosis codes (International Classification of Diseases, 10th revision codes [ICD-10]) and date, and medication details (name, the number of prescription days, and dosage) [10]. Endogenous hypothyroidism was specifically identified as cases featuring two or more diagnostic ICD-10 codes related to hypothyroidism (E02, E03, E06, E078, or E079), accompanied by a prescription for TH lasting >60 days [9]. This TH treatment includes levothyroxine or liothyronine. Patients with diagnostic codes for thyroid cancer (C73), treatment codes for thyroid surgery (P4551–4554), or RAI therapy (HD071) were excluded from the analysis. Additionally, to focus solely on patients newly diagnosed with endogenous hypothyroidism after 2004, we implemented a 2-year washout period. The study included patients diagnosed with hypothyroidism between 2004 and 2018, with follow-up extending until the end

of 2020.

This study was approved by the Institutional Review Board of Chung-Ang University Hospital (IRB 1911-031-16294) and written informed consent was waived by the board.

Definition of outcomes

To establish the annual incidence of hypothyroidism, we analyzed data from the year before and 1-year following either the diagnosis or initiation of TH treatment. To calculate the standardized population, the standard population of the year 2000 provided by Statistics Korea (<http://kosis.kr>) was used. Age-standardized incidence rates were calculated by categorizing age groups into intervals of 10 years. We assessed the discontinuation and resumption of TH treatment based on the prescription date. Since participants were enrolled until 2018 and follow-up concluded in 2020, the minimum duration for follow-up prescription was 2 years. Hypothyroidism-related comorbidities were defined as new occurrences of the corresponding diagnosis code after the diagnosis of hypothyroidism during the entire study period, and included ischemic heart disease, cerebrovascular disease, mood disorder, cognitive disorder, and dementia, all of which manifested following hypothyroidism diagnosis. Ischemic heart disease was defined operationally as patients hospitalized with one of the following diagnostic codes: I20–I25. Similarly, cerebrovascular disease was defined as patients hospitalized with one of the following diagnostic codes: I60–I69. Mood disorders, cognitive disorders, and dementia were operationalized as patients demonstrating any of the following diagnostic codes on more than two occasions: F30–F39 (for mood disorders), F067 (for cognitive disorders), and F00–F03 (for dementia).

Statistical analysis

The age-standardized incidence rate was a weighted average of the crude age-specific rate, with weights based on the proportion of each age group in the standard population (2000). Incidence rates (per 1,000 person-years) were calculated by dividing the total number of hypothyroidism cases by the total number of person-years of followed at each year. Annual percent changes (APCs) and their 95% confidence intervals (CIs) were determined using linear regression analysis. The difference in age-standardized incidence rates between different time points was analyzed using a Poisson regression. Statistical analyses were conducted using SPSS version 26.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Age-standardized incidence rate and prevalence of endogenous hypothyroidism

Fig. 1 shows the age-standardized incidence rate of endogenous hypothyroidism over the study period. In 2004, the age-standardized incidence rate was 1.6 and 0.2 per 1,000 population person-years in women and men, respectively. By 2018, these rates had risen to 3.7 and 0.8 per 1,000 population person-years in women and men, respectively. The APC of the age-standardized incidence rate was 4.4% (95% CI, 4.2 to 4.6) and 15.2% (95% CI, 14.0 to 16.5) for men and women, respectively.

In 2018, the age-standardized prevalence of endogenous hy-

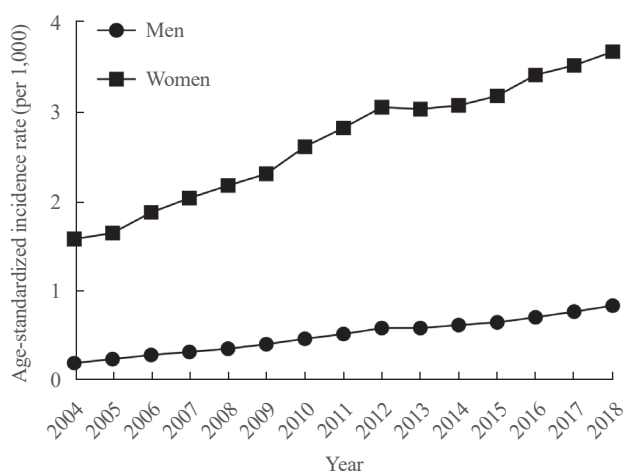


Fig. 1. Nationwide age-standardized incidence rate of endogenous hypothyroidism in South Korea (2004 to 2018) kept increasing in men and women.

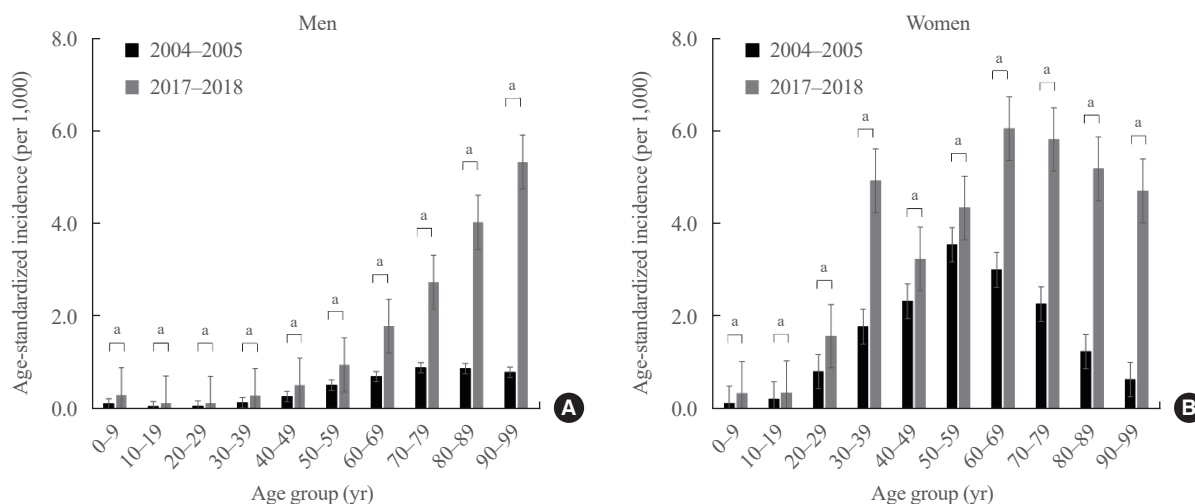


Fig. 2. Incidence of endogenous hypothyroidism was compared between 2004–2005 and 2017–2018 and between (A) men and (B) women. ^a $P < 0.05$.

pothyroidism was 12.63, 5.20, and 19.46/1,000 population for the total, men, and women cohorts, respectively. Women represented 83.4% of all cases. Across all age groups, the highest prevalence of endogenous hypothyroidism was observed among women in their 60s and men aged >80 , with rates of 39.51 and 12.77 per 1,000, respectively (Supplemental Fig. S1).

Investigation of incidence rate across different time points and age groups

Mean incidence of endogenous hypothyroidism was compared between the periods of 2004–2005 and 2017–2018 and between men and women (Fig. 2). In both sexes, the incidence increased across all age groups in 2017–2018 than in 2004–2005 ($P < 0.05$). While men exhibited a higher incidence among the elderly ≥ 70 years (Fig. 2A), women showed peak incidence in earlier age groups (Fig. 2B). In women, the peak incidence shifted from the 50s in 2004 to 60s in 2018, with an additional peak observed in the 30s in 2018 (Fig. 2B). Hypothyroidism incidence in women in their 30s has increased rapidly since 2009, compared to a gradual increase in women in their 20s and 40s (Supplemental Fig. S2A). In contrast, among women beyond middle age, hypothyroidism incidence peaked in their 50s in 2011 and has been gradually decreasing since then. However, for women in their 60s, the incidence continued to increase until 2015 before stabilizing, while for those in their 70s, it continued to increase (Supplemental Fig. S2B).

When comparing age groups of 20s–50s and 60s–90s in each year, the incidence of hypothyroidism in men aged ≥ 60 increased rapidly than in those aged 20s–50s, with APC of 12.4% (95% CI, 11.5 to 13.2) for men aged ≥ 60 and 2.2% (95% CI,

1.9 to 2.5) for men aged 20s–50s, spanning from 2004 to 2018 (Fig. 3A). The increase in incidence was also higher among women aged ≥ 60 than in those aged 20s–50s, with an APC of 24.2% (95% CI, 21.1 to 27.4) for women aged ≥ 60 and 13.1% (95% CI, 11.4 to 14.7) for women aged 20s–50s (Fig. 3B).

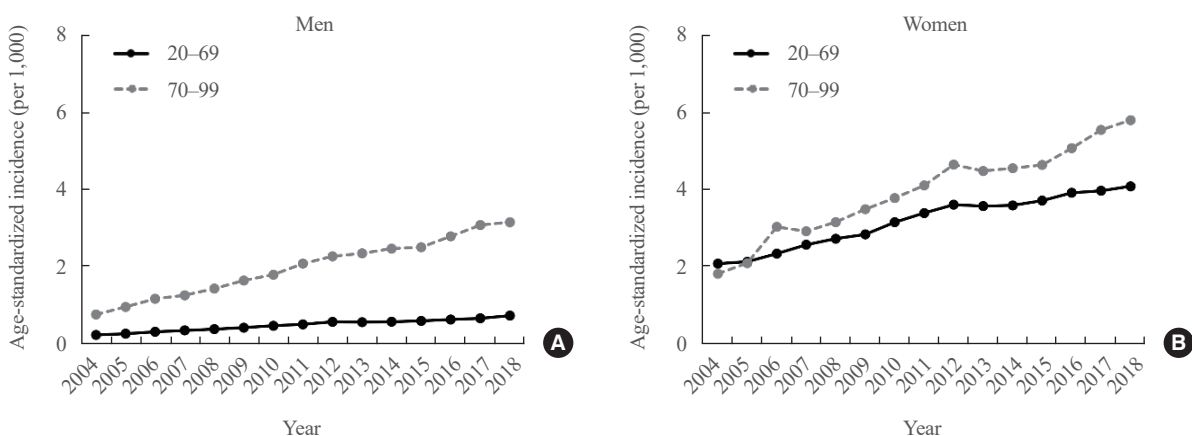


Fig. 3. Incidence of endogenous hypothyroidism was compared between 20s–50s and 60s–90s and between (A) men and (B) women.

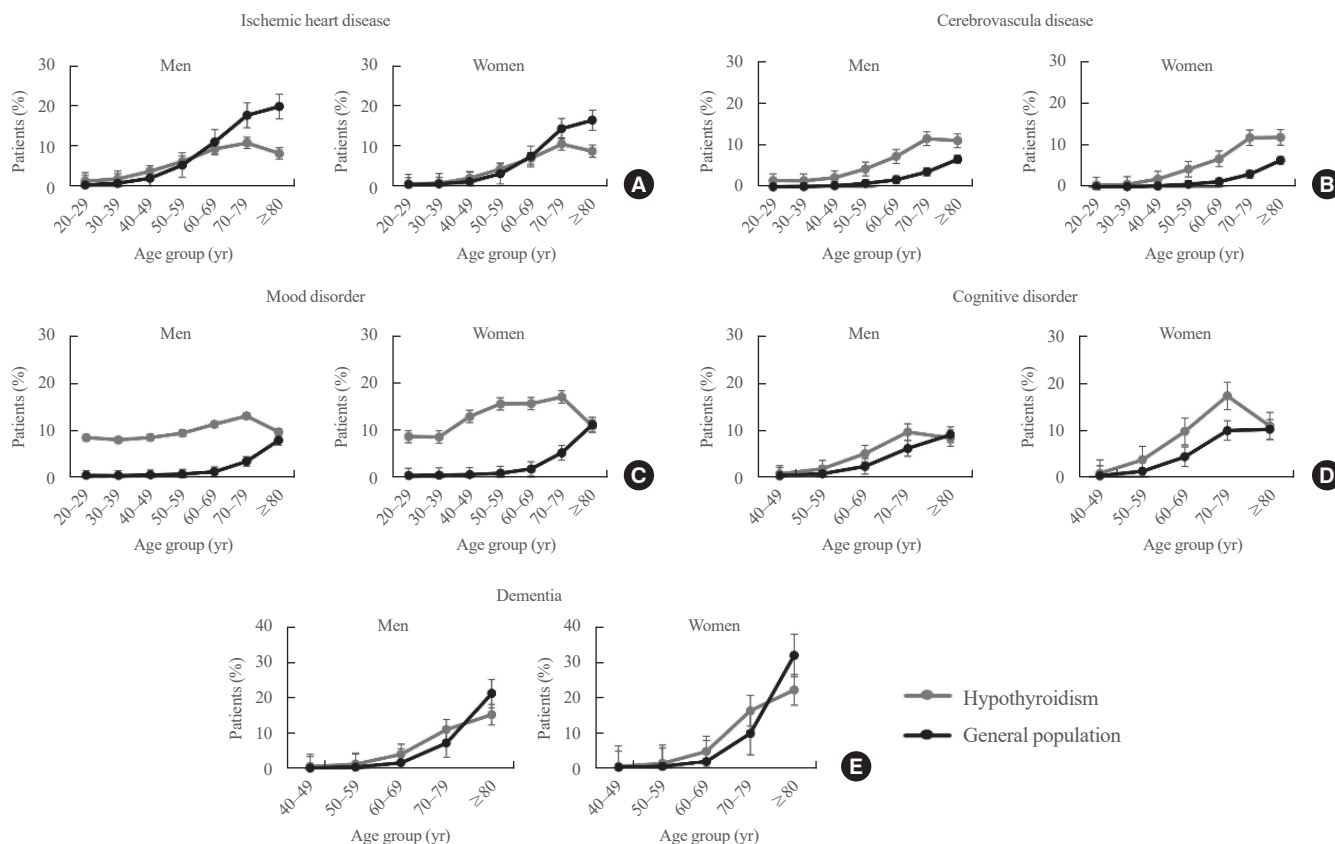


Fig. 4. Occurrence of comorbidities following endogenous hypothyroidism diagnosis was compared between hypothyroidism and the general population in men and women. Comorbidities include (A) ischemic heart disease, (B) cerebrovascular disease, (C) mood disorder, (D) cognitive disorder, and (E) dementia.

cally unfeasible, we investigated the tendency of comorbidity occurrence in this group and the general population. When analyzing the occurrence trend of each comorbidity, it became apparent that ischemic heart disease seemed higher in the general population than in patients with endogenous hypothyroidism in men and women after the age 70 years (Fig. 4A). Conversely, starting from the 40s, cerebrovascular disease occurrence seemed to be higher in patients with endogenous hypothyroidism than in the general population (Fig. 4B). Mood disorder seemed to occur more frequently in patients with endogenous hypothyroidism across ages ranging from the 20s to 70s than in the general population (Fig. 4C). Furthermore, cognitive disorder occurrence among women seemed higher in those with hypothyroidism than in the general population (Fig. 4D). However, dementia rates seemed comparable between patients with endogenous hypothyroidism and the general population (Fig. 4E).

Treatment status of endogenous hypothyroidism

To determine the treatment status of patients with endogenous hypothyroidism in Republic of Korea, we investigated their prescription records. The proportion of patients who maintained TH treatment for >2 years without interruption was 30.2%. Among those who experienced an interruption in TH treatment, nearly half (44.7%) had not been prescribed TH for >1 year (Supplemental Fig. S3). The proportion of patients who resumed TH treatment within 6 months, between 6 months and 1 year, and after 1 year were 31.8%, 7.4%, and 16.1%, respectively (Supplemental Fig. S3).

DISCUSSION

To our knowledge, this study represents the first comprehensive investigation of endogenous hypothyroidism in Republic of Korea conducted over an extended period. From 2004 to 2018, our findings offer valuable insights into shifts in prevalence and age-standardized incidence across diverse age groups (20s–50s vs. 60s–90s) and distinct years (2004–2005 vs. 2017–2018). Furthermore, we explored the incidence of other health conditions that manifested following endogenous hypothyroidism diagnosis and their treatment status.

Previous research on the Korean population documented an overall prevalence of hypothyroidism cases arising from thyroid surgery, ranging from 14.28–15.94/1,000 population [6,9]. In our study, we observed a prevalence of 12.63/1,000 population, indicating that a significant proportion of hypothyroidism cases in Republic of Korea originated from endogenous causes. Addi-

tionally, the prevalence of endogenous hypothyroidism in our study is consistent with that reported in the United States (range, 0.3%–3.7%) and Europe (range, 0.2%–5.3%) [3–5,11].

The incidence of endogenous hypothyroidism in Republic of Korea significantly increased in 2018 than in 2004. This rise could potentially be attributed to a right shift in the incidence peak within age groups, possibly influenced by an increased proportion of elderly individuals and more frequent visits to medical institutions [12].

Between 2017 and 2018, another peak was observed in the incidence of endogenous hypothyroidism among women in their 30s. The average age of mother at the birth of their first child has shifted from the 20s to 30s, coinciding with an elevated infertility rate in Republic of Korea [13]. Since the implementation of a nationwide infertility support program in 2006, an increase has been observed in visits to infertility-related medical institutions and the number of procedures conducted [13]. Several reports have indicated the effect of hypothyroidism and thyroid autoimmunity on infertility [14,15]. Therefore, including thyroid screening in the examination of women experiencing infertility is crucial. This could potentially explain the highest occurrence of endogenous hypothyroidism observed among women in their 30s. Supplemental Fig. S2A illustrates a gradual rise in the occurrence of endogenous hypothyroidism among women in their 30s starting in 2006, with a sharp increase observed after 2009. This supports the idea that thyroid function tests for pregnancy and infertility may have influenced the rise in endogenous hypothyroidism cases.

When examining the increased incidence rate across different sex and age groups, we found a more rapid increase in incidence among the elderly, particularly pronounced in men than in women. A nationwide study on dietary iodine status in Republic of Korea conducted from 2013 to 2017 revealed that individuals over the elderly >65 years, specifically in the 95 percentile group, consumed 2,336 µg of iodine daily, whereas younger adults ingested 1,911 µg [16]. In another study using data from the Korea National Health and Nutrition Examination Survey from 1998 to 2014, the mean daily dietary iodine intake was higher in men since 2007. The intake ranged from 326.2–566.6 µg and 257.0–400.4 µg in men and women, respectively [17]. Therefore, while the increase in medical visits and aging might be the major cause of the increased endogenous hypothyroidism among the elderly, variations in iodine intake could have influenced the differing rates of hypothyroidism increase between men and women and between the elderly and young individuals. Endogenous hypothyroidism, unlike exogenous forms

caused by procedures including RAI or surgery, presents an opportunity for treatment discontinuation [18]. Our study supports this notion, revealing that 44.7% of patients who discontinued their TH prescription did not resume medication for over 1 year. Regarding TH prescription discontinuation among a relatively large proportion of patients, one potential explanation is that a significant subset of individuals diagnosed with subclinical hypothyroidism underwent TH treatment for a brief duration before discontinuing it. However, since distinguishing between subclinical and overt hypothyroidism is impossible using the NHIS data, we cannot ascertain the proportion of patients who discontinue TH treatment and exhibit subclinical hypothyroidism. In contrast, another limitation is the inability to distinguish whether TH cessation is attributed to hypothyroidism recovery or poor compliance. Therefore, this warrants further well-designed studies that specify TH prescription duration and each interruption period.

Regarding comorbidities, ischemic heart disease occurrence seemed lower in patients with endogenous hypothyroidism than in the general population in their 70s to 80s. However, interpreting this result with caution is essential owing to the absence of a matched control group that accounts for other risk factors, including dyslipidemia, hypertension, family history, or smoking. Given the conflicting findings regarding the influence of subclinical hypothyroidism on cardiovascular disease [19-21], further studies with appropriate matched control with similar risk factors are warranted.

Cerebrovascular disease tends to occur more frequently in patients with endogenous hypothyroidism than in the general population, specifically in men and women after the age of 40 years. A previous large-scale cohort study using health insurance data in Taiwan reported findings consistent with ours, indicating a higher risk of cerebrovascular disease in the hypothyroid group (hazard ratio, 1.89; 95% CI, 1.61 to 2.22) than in the matched control group [22].

Mood disorders are a common feature associated with hypothyroidism. As anticipated, their prevalence was higher among patients with endogenous hypothyroidism. Regarding cognitive function and dementia, guidelines recommend thyroid examination, as thyroid dysfunction is among the reversible causes [23]. However, our findings indicated no clear trend of cognitive disorders and dementia in patients with endogenous hypothyroidism. This finding is consistent with several meta-analyses investigating the relationship between cognitive dysfunction and hypothyroidism [24-26]. Statistical analyses were not feasible; however, the observed trends in comorbidities compared to the

general population highlight the importance of closely monitoring patients with endogenous hypothyroidism.

This study had some limitations. First, the absence of a matched control group restricts our ability to establish definitive causal relationships between endogenous hypothyroidism and comorbidities. Hence, future research should explore the underlying causes of the observed trends, including potential environmental factors and changes in diagnostic criteria. Second, since the study relied on data from the NHIS, the absence of actual laboratory values, including TSH and free thyroxine, renders it impossible to distinguish between subclinical and overt hypothyroidism. Despite these limitations, our study holds significance as an epidemiological investigation into the prevalence of endogenous hypothyroidism across almost the entire Republic of Korean population.

In conclusion, endogenous hypothyroidism is on the rise in Republic of Korea, potentially owing to aging population, iodine intake variations, and increase in screening tests. Patients with endogenous hypothyroidism may have a higher risk of cerebrovascular disease and mood disorders than those without the condition.

CONFLICTS OF INTEREST

Sun Wook Cho is the deputy editor of the journal. However, she was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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This study used the National Health Insurance Database created by the National Health Insurance Service (NHIS). The authors declare no conflict of interest with the NHIS.

AUTHOR CONTRIBUTIONS

Conception or design: C.W.C., H.Y.A., S.W.C., K.H.Y. Acquisition, analysis, or interpretation of data: C.W.C., H.Y.A., S.W.C., K.H.Y. Drafting the work or revising: C.W.C., H.Y.A., S.W.C., K.H.Y. Final approval of the manuscript: C.W.C., H.Y.A., S.W.C., K.H.Y.

ORCID

Chae Won Chung <https://orcid.org/0000-0002-8781-858X>

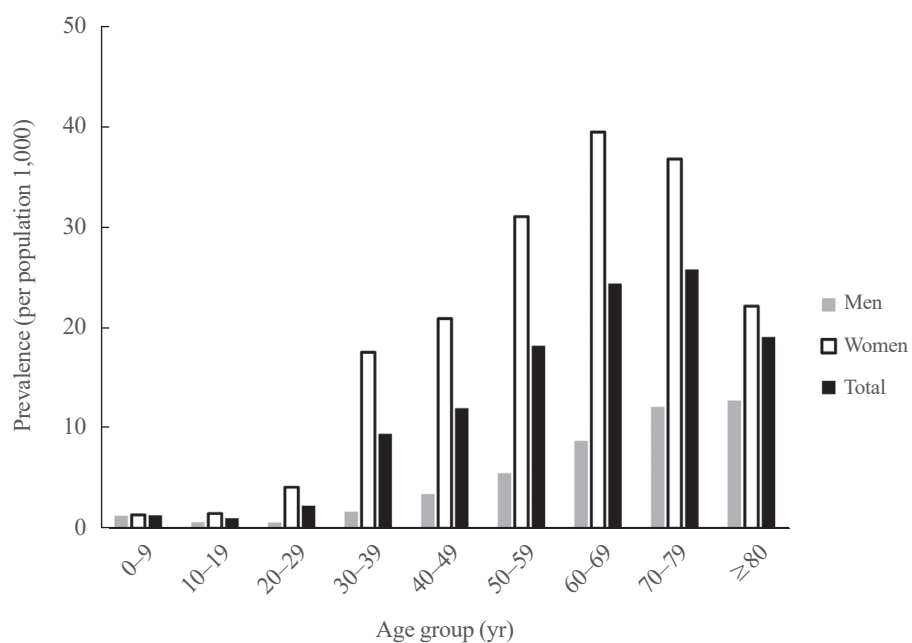
Hwa Young Ahn <https://orcid.org/0000-0002-2737-6759>

Sun Wook Cho <https://orcid.org/0000-0002-7394-3830>

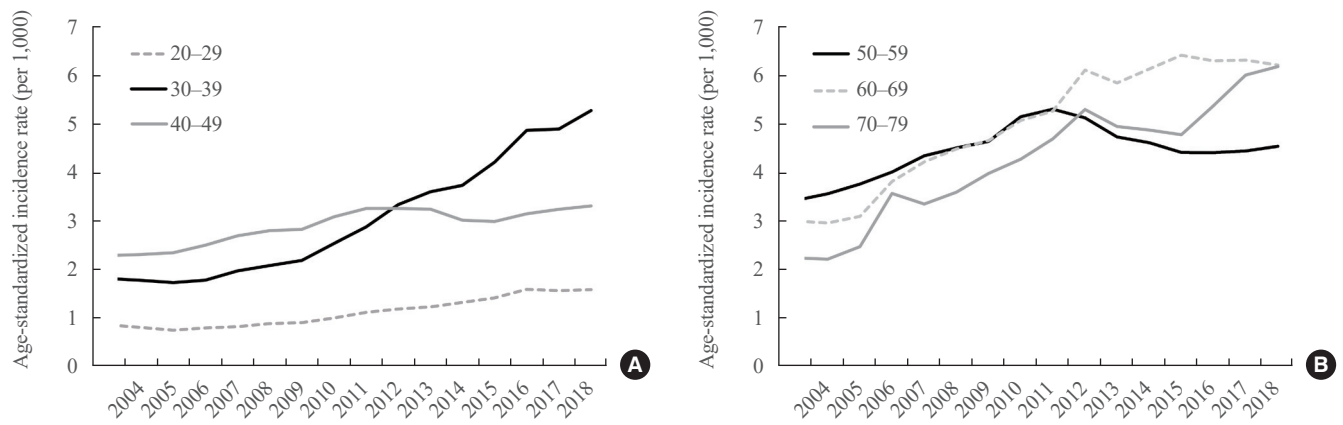
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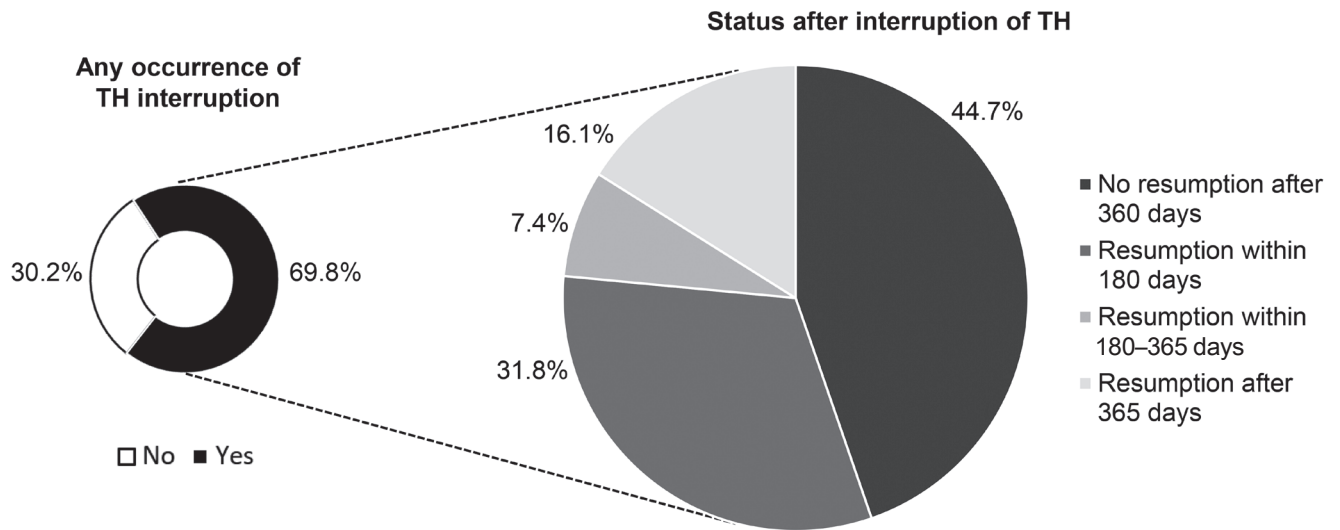
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Supplemental Fig. S1. Prevalence of endogenous hypothyroidism in South Korea (2018).



Supplemental Fig. S2. Incidence of hypothyroidism in women in each age group (A: 20s, 30s, 40s; B: 50s, 60s, 70s) was depicted.



Supplemental Fig. S3. Proportion of patients who maintained thyroid hormone (TH) treatment for >2 years without interruption was 30.2%. Among those who experienced an interruption of TH treatment, nearly half of them (44.7%) were not prescribed TH for >1 year.