Graves’ disease and the risk of Parkinson’s disease: a Korean population-based study

Yoon Young Cho, MD, PhD¹, Bongseong Kim, PhD², Dong Wook Shin, MD, PhD³, Jinyoung Youn, MD, PhD⁴,⁵, Ji Oh Mok, MD, PhD¹, Chul-Hee Kim, MD, PhD¹, Sun Wook Kim, MD, PhD⁷, Jae Hoon Chung, MD, PhD⁷, Kyungdo Han, PhD²,†, and Tae Hyuk Kim, MD, PhD⁷,†

¹Division of Endocrinology and Metabolism, Department of Medicine, Soonchunhyang University Bucheon Hospital, Bucheon, Korea, ²Department of Statistics and Actuarial Science, Soongsil University, Seoul, Korea, ³Supportive Care Center/Department of Family Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, ⁴Department of Clinical Research Design & Evaluation, Samsung Advanced Institute for Health Science & Technology, Sungkyunkwan University, Seoul, Korea, ⁵Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, ⁶Neuroscience Center, Samsung Medical Center, Seoul, Korea, ⁷Division of Endocrinology and Metabolism, Department of Medicine, Thyroid Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

Correspondence to:
Tae Hyuk Kim, MD, PhD
Division of Endocrinology and Metabolism, Department of Medicine, Thyroid Center, Samsung Medical Center, Sungkyunkwan University School of Medicine
81 Irwon-ro, Gangnam-gu 06351, Seoul, Korea
Tel: +82-2-3410-6049
Fax: +82-2-3410-6983
Email: taehyukmd.kim@samsung.com
Correspondence may also be sent to:

Kyungdo Han, PhD
Department of Statistics and Actuarial Science, Soongsil University
369 Sangdo-ro, Dongjak-gu, 06978, Seoul, Korea
Tel: +82-2-820-7025
Fax: +82-2-823-1746
Email: hkd917@naver.com

Running title: Graves’ disease and Parkinson’s disease

†Kyungdo Han and Tae Hyuk Kim contributed equally to this study.
Abstract

Two European cohort studies have suggested that Graves’ disease is associated with the development of Parkinson’s disease, although the results were limited and controversial. We evaluated whether patients with Graves’ disease had an increased risk of developing Parkinson’s disease according to treatment modality. We included 65,380 Graves’ disease patients and 326,900 healthy controls matched according to age and sex, using the Korean National Health Insurance database. The primary outcome was the incidences of Parkinson’s disease among Graves’ disease patients and controls. Subgroup analyses of Graves’ disease patients were performed according to anti-thyroid drug treatment, radioactive iodine therapy, and surgery. The cumulative dose and duration values of anti-thyroid drug were calculated for each patient and categorized into highest, middle, and lowest tertiles. Among 65,380 Graves’ disease patients, 301 Parkinson’s disease cases were diagnosed during 453,654 person-years of follow-up. Relative to the controls, and regardless of age, sex, or comorbidities, the Graves’ disease patients had a 33% higher risk of developing Parkinson’s disease (HR: 1.33, 95% CI: 1.17–1.51). Most Graves’ disease patients (96%) had received medical therapy, and increased risks of Parkinson’s disease were observed in the various subgroups for cumulative dose and treatment duration. This study revealed that Graves’ disease was an independent risk factor for developing Parkinson’s disease, and that the risk remained elevated regardless of demographic factors or treatment duration/dosage of anti-thyroid drug. Clinicians should be aware that Graves’ disease patients have an increased risk of developing Parkinson’s disease, even though Graves’ disease patients are often relatively young.

Keywords: Graves’ disease; Parkinson’s disease; population-based study; Korea

Abbreviations:

ATD = anti-thyroid drug; CI = confidence interval; GD = Graves’ disease; HPT = hypothalamic-pituitary-thyroid; HR = hazard ratio; ICD-10 = International Classification of Diseases, 10th revision; IR = incidence rate; PD = Parkinson’s disease; PYs = person-years; NHID = the National Health Information Database; NHIS = the National Health Insurance Service; RAIT =
radioactive iodine therapy; RID = rare intractable diseases; SIR = standardized incidence ratio; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone
Introduction

After Alzheimer’s disease, Parkinson’s disease (PD) is the second most common neurodegenerative disease. The incidence of PD increases with age, affecting 1% of people who are >60 years old. This disease is characterized by progressive motor dysfunction, which can involve bradykinesia, resting tremors, rigidity, and postural instability, as well as non-motor symptoms, such as sleep disturbance, depression, constipation, and dysautonomic symptoms. Early-stage PD leads to degeneration of dopaminergic neurons in the pars compacta of the substantia nigra, and loss of dopaminergic neurons is the most common postmortem finding in brains that are affected by PD.

The dopaminergic system interacts with the hypothalamic-pituitary-thyroid (HPT) axis, with dopamine stimulating the production of thyrotropin-releasing hormone (TRH) and inhibiting the production of thyroid-stimulating hormone (TSH) and thyroid hormone. The HPT axis also regulates dopamine release. There is epidemiological evidence that thyroid diseases are associated with PD, and similar genes contribute to both diseases, which may suggest that they share a common pathophysiological mechanism. Graves’ disease (GD) is an autoimmune thyroid disease that can lead to disturbances in dopamine transmission and the loss of dopaminergic neurons. However, we are only aware of two studies that have investigated the association between GD and the subsequent development of PD. Li et al. evaluated a Swedish nationwide database and reported that, relative to the healthy population, patients with GD had an increased risk of developing PD (standardized incidence ratio [SIR]: 1.63, 95% confidence interval [CI]: 1.39–1.90). Furthermore, an even higher risk of developing PD was observed among patients with GD who were <65 years old (SIR: 1.72, 95% CI: 1.02–2.73), although the risk of PD was not significantly increased at 5 years after the GD diagnosis. Rugbjerg et al. performed a Danish population-based case-control study and reported that women with GD had an increased risk of PD (odds ratio [OR]: 2.1, 95% CI: 1.3–3.5), although the development of PD was not associated with any other autoimmune diseases. However, both of these European cohort studies investigated the relationship between >30 autoimmune diseases and subsequent PD, and could not support a detailed analysis of the association between GD and PD. Therefore, the present study evaluated whether Korean patients with GD had an increased risk of developing
PD, using nationally representative data from the National Health Information Database (NHID), as well as whether the risk of developing PD was associated with the GD treatment modality and/or the cumulative dose and duration of anti-thyroid drug (ATD) treatment.

Methods

Data source

Data were retrieved from the Korean NHID, which is maintained by the National Health Insurance Service (NHIS). The NHIS is the only public medical insurance system in Korea and covers approximately 97% of the Korean population, with the other 3% being covered by Medicaid. The NHID contains nationally representative data regarding healthcare utilization, health screening, sociodemographic variables, and mortality, with healthcare utilization and drug prescriptions linked to International Classification of Diseases, 10th revision (ICD-10) diagnostic codes.

Study population

We identified 103,932 individuals who were diagnosed with GD between January 2009 and December 2014 using the ICD-10 code for hyperthyroidism (E05). Patients with GD were grouped according to whether they had received ATDs for ≥60 consecutive days (the ATD group), had undergone radioactive iodine therapy (the RAIT group), or had undergone thyroid surgery (the surgery group). Patients who underwent RAIT or surgery for GD were assigned to the RAIT group or surgery group, regardless of whether they had received ATDs. Definition for detecting GD cases used in this study has been used in the previous epidemiologic studies for GD in Korea. Patients with thyroid carcinoma were excluded (ICD-10 code: C73.9). To exclude pre-existing GD or PD, a washout period was applied from January 2006 to study enrollment. Furthermore, as PD is uncommon among individuals who are <40 years old, we excluded patients who were <40 years old, patients who were diagnosed with PD during the washout period, or patients with missing data. Thus, the analysis included 65,380 GD cases, who were matched with 326,900 controls (1:5 ratio) according to age and sex. The study period ended in December 2018.
The retrospective study protocol was approved by the Samsung Medical Center’s institutional review board (2019-01-034). The requirement for informed patient consent was waived based on the use of publicly available and de-identified patient data. All procedures for this study complied with the relevant patient confidentiality guidelines.

**Clinical variables**

Comorbidities, including diabetes, hypertension, and dyslipidemia, were defined based on ICD-10 codes for diagnoses and drug prescriptions. Household income was classified into quartiles (Q1–Q4) and absolute poverty. The cumulative ATD dose was determined for each patient and classified as <4,953 mg (lowest tertile), 4,953–18,700 mg (middle tertile), and >18,700 mg (highest tertile). The ATD treatment duration was also determined for each patient and classified as <12 months (lowest tertile), 12–35 months (middle tertile), and >35 months (highest tertile).

**Identification of new PD cases**

The NHIS includes a registration program for rare intractable diseases (RIDs), which include PD. This program was launched in 2006 and offers a copayment rate reduction of up to 10% (vs. 20–30% for other common diseases). The patient is eligible for this RID program after their physician submits a diagnosis certification. For cases of PD, the certification is generally written by neurologists or primary care physicians who have examined the patient. New PD onset was defined as a claim with the ICD-10 code for PD (G20) and with a special RID registration code that indicates PD (V124). This definition has been used in previous Korean epidemiological studies of PD.16-19

**Statistical analysis**

Categorical baseline characteristics were compared using the chi-squared test. Conventional Cox proportional hazard regression analyses were performed to evaluate the association between GD and incident PD. The incidence rate was not adjusted in model 1, while model 2 was adjusted for age, sex, household income, and comorbidities. The P-values for the interaction were calculated according to age, sex, and comorbidities, which included diabetes,
hypertension, and dyslipidemia. All statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA).

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Results

Demographic characteristics

The study included 65,380 GD patients and 326,900 matched healthy controls. The mean age was 54 years, most subjects (83%) were <65 years old, and 29% of subjects in both groups were men (Table 1). The GD patients had higher prevalences of diabetes, hypertension, and dyslipidemia. In GD patient, the majority of patients (95.8%) were treated with ATDs, followed by RAIT (3.4%) and surgery (0.8%). The RAIT group had a higher percentage of male, younger age, and lower prevalences of diabetes and dyslipidemia, compared to those of the ATD and surgery groups. The mean follow-up periods were 7.1 years in groups of GD patients and controls.

Association of GD and incident PD

Among the 65,380 GD patients, 301 cases of incident PD were diagnosed during 453,654 person-years (PYs) of follow-up. Relative to the controls, the GD patients had a 37% higher risk of developing PD (hazard ratio [HR]: 1.37, 95% CI: 1.21–1.56). Furthermore, the GD patients still had an increased risk of developing PD after adjusting for age, sex, household income, and comorbidities (HR: 1.33, 95% CI: 1.17–1.51) (Fig. 1).

Subgroup analyses were performed according to age, sex, and comorbidities, which generally revealed significantly higher risks of PD among patients with GD. However, non-significantly higher risks of PD development were observed among GD patients with diabetes (HR: 1.10, 95% CI: 0.83–1.46) and GD patients without hypertension (HR: 1.20, 95% CI: 0.97–1.47) (Table 2).
Association between GD and incident PD according to treatment modality

Relative to the controls, the ATD group had a 31% higher risk of developing PD (HR: 1.31, 95% CI: 1.15–1.50) and the surgery group had a 208% higher risk of developing PD (HR: 3.08, 95% CI: 1.28–7.43). However, the RAIT group did not have a significantly higher risk of developing PD (HR: 1.34, 95% CI: 0.70–2.59) (Table 3). The risk of developing PD did not vary according to whether the patients achieved GD remission after undergoing RAIT (data not shown).

Subgroup analyses of associations between GD treatment modalities and incident PD

Subgroup analyses were performed according to age, sex, comorbidities, and treatments for GD. Most subgroups of GD patients had similar risks of developing PD, regardless of demographic characteristics or treatment modality (non-significant P-values for interaction). In particular, GD patients who were 40–64 years old (n=54,353, 83% of the GD population) had increased risks of developing PD, regardless of whether their treatment had involved ATDs (HR: 1.27, 95% CI: 1.03–1.58), RAIT (HR: 2.47, 95% CI: 1.17–5.21), or surgery (HR: 4.34, 95% CI: 1.39–13.51) (Table 4). Moreover, subgroup analyses according to cumulative ATD dose and treatment duration revealed relatively consistent increased risks of developing PD, relative to the controls. The one exception was a non-significant difference in the group with the longest ATD treatment duration (HR: 1.03, 95% CI: 0.82–1.29) (Table 5).

Discussion

The present study revealed that Korean GD patients had a 33% higher risk of developing PD, relative to age- and sex-matched healthy controls, based on nationally representative population-based data. During 453,654 PYs of follow-up for 65,380 GD patients, a total of 301 incident PD cases were identified, which corresponded to an incidence rate (IR) of 0.66 cases per 1,000 PYs (vs. 0.48 cases per 1,000 PYs among the healthy controls). Furthermore, the increased risk of developing PD among GD patients remained consistent in various subgroups that were created according to age, sex, or comorbidities. Moreover, the GD treatment modality, except
RAIT and clinical courses did not appear to influence the risk of developing PD, which suggests that GD itself is a risk factor for PD.

The most important role of dopamine involves the inhibition of prolactin synthesis, while TRH stimulates prolactin synthesis in the absence of dopamine. However, the dopaminergic system and HPT axis are also interconnected outside the pituitary gland. For example, dopamine and D2 dopamine receptors mediate the direct stimulation of TRH in the striatum. Dopamine and TRH also upregulate each other, while dopamine inhibits the production of TSH and thyroid hormones. Furthermore, imbalances in thyroid hormones lead to dopamine degradation, downregulation of dopamine hydroxylase, and alterations in dopaminergic receptor sensitivity. Dopamine signaling and HPT axis are linked with sleep. Dopamine promotes sleep and dopamine deficiency leads to the increase in TSH and thyroid hormone secretion. A hypothalamic imbalance between neuro-excitatory thyroid hormones and neuro-inhibitory dopamine secretion has been proposed to be causative mechanism of restless leg syndrome.

Oxidative stress provides important contributions to dopamine neuron loss and PD progression and thyroid dysregulation affects oxidative stress because thyroid hormones affect both oxidant and anti-oxidant activities. As the common environmental factor, vitamin D deficiency has been suggested as a possible risk factor for both GD and PD, however there are controversies for the causal relationship between vitamin D deficiency and GD. In addition, there is evidence regarding common abnormalities that increase susceptibility to both PD and thyroid disease, which may involve RASD2, WSB1, MAPT, and NOX/DUOX.

Two European cohort studies have provided epidemiological evidence that GD may be associated with an increased risk of developing PD. Li et al. evaluated 34,735 GD/hyperthyroidism patients and reported a 63% higher risk of developing PD, which was maintained when they excluded the first year after the GD diagnosis (SIR: 1.42, 95% CI: 1.19–1.68). However, the risk of PD was not significantly increased at 5 years after the index date (SIR: 1.17, 95% CI: 0.94–1.44), which the authors attributed to lead-time bias and earlier diagnosis of PD during the first few years after the GD diagnosis. In contrast, the present study revealed that the cumulative incidence of PD increased steadily, even at 5 years after the GD diagnosis (Fig. 1). This result is likely reliable, as the diagnosis of PD is registered and supervised under the Korean RID program, which ensures that the diagnoses are accurate.
addition, we used age- and sex-matched controls, with correction for comorbidities and household income, which ensures a clearer analysis of the association between two diseases, relative to the SIR values that were reported by Li et al.\textsuperscript{5} Rugbjerg et al.\textsuperscript{6} also reported that GD patients had an increased risk of PD (OR: 2.1), although they did not further evaluate the association between GD and PD. While those studies of Swedish and Danish cohorts\textsuperscript{5,6} were well-designed and used validated data, they evaluated a broad range of >30 autoimmune diseases and were not sufficiently powered to specifically analyze the association between GD and PD.

Older age and a family history of PD are the most important risk factors for developing PD,\textsuperscript{28} although there is controversy regarding other risk factors. We found that the incidence of PD was high among GD patients who were ≥65 years old (IR: 2.63 per 1,000 PYs), even among the healthy controls (IR: 1.92 per 1,000 PYs), relative to among controls who were 40–64 years old (IR: 0.22 per 1,000 PYs), as with the fact that older age is most critical risk factor for developing PD. Of note, elderly people (≥65 years old) with GD had a 34% higher risk of PD, even after statistical correction for their comorbidities that might be contributing factors for PD. In this elderly GD population, only ATD group showed the elevated risk (HR: 1.35, 95% CI: 1.15–1.60) for PD, whereas the RAIT (HR: 0.51, 95% CI: 0.13–2.05) and surgery groups (HR: 1.85, 95% CI: 0.49–7.86) did not. However, non-significant results may be derived from the small number of PD events in the RAIT (2 PD events in 320 patients) and surgery groups (2 PD event in 93 patients); thus, it is cautious to conclude that RAIT and surgical treatment are better than medical treatment for preventing incident PD in this elderly GD population.

Most of the GD patients (83%) were <65 years old and had an increased risk of PD (HR: 1.33), although the absolute increase was not large (IR: 0.3 per 1,000 PYs), which agrees with the SIR of 1.72 reported by Li et al. among patients who were <65 years old.\textsuperscript{5} Furthermore, control subjects with comorbidities (diabetes, hypertension, or dyslipidemia) tended to have a higher incidence of PD, relative to control subjects without comorbidities (Table 2). This also agrees with a previous report that the risk of PD is elevated among patients with diabetes.\textsuperscript{17,29} Nevertheless, the GD patients had elevated risks of PD, regardless of their age, sex, or comorbidities, which suggests that GD may be an independent risk factor for developing PD.
To the best of our knowledge, ours is the first study to evaluate whether the risk of PD was related to the modality used to treat GD. Treatment groups with ATD and surgery had increased risks of developing PD whereas, the risk was not elevated in the RAIT group. Interestingly, although <1% of the GD patients had undergone surgery, they had a substantially higher risk of developing PD (vs. the ATD group), although we do not have a clear explanation for this finding. One assumption is that baseline demographics, including a higher percentage of female, absolute property, diabetes, and hypertension in the surgery group (Table 1) might be linked with the higher risk for incident PD, compared to other two groups, in spite of the statistical correction. In contrast, the RAIT group had a relatively low female incidence, younger mean age, the better economic status, lower rates of diabetes and dyslipidemia compared to those of the ATD and surgery groups, which might be favorable factors for incident PD. Although there has been no evidence regarding incident PD by treatment modality for GD, some literatures have reported that GD patients achieving remission after RAIT had the lower risk of cardiovascular morbidity and mortality.\textsuperscript{30,31} Based on our results, RAIT might be a better treatment option for GD regarding the incident risk of PD, although further research with the larger population for RAIT is needed.

It is also interesting that the risks of PD were similar between the subgroups that were classified according to cumulative ATD dose or ATD treatment duration, despite the fact that a higher cumulative dose or prolonged treatment would suggest the cases involved obstinate GD. Therefore, although we had limited information regarding whether the GD was persistent or in remission, it appears that GD itself may be a potential risk factor for PD.

The present study has several limitations. First, the diagnosis of hyperthyroidism was based on ICD-10 codes and information regarding the etiology of hyperthyroidism was lacking. To exclude transient thyrotoxicosis, the definition of consecutive ATD prescription was also used for the ATD group. The etiology of hyperthyroidism in an iodine-sufficient area, including Korea is known as GD, and toxic adenoma account for less than 1% of the etiology of hyperthyroidism in Korea.\textsuperscript{32} Therefore, the present results may be interpreted as the results of GD. Second, we identified PD cases using the RID database. An epidemiologic study for the incidence of PD in Korea using the NHIS-RID database\textsuperscript{16} reported the gradual increase in the
incidence of PD from 23.2 to 27.8 per 100,000 (2010–2015) in Korean population (male, 18.9 to 23.3 per 100,000 and female, 27.4 to 32.2 per 100,000). In our population, the incidence of PD was 48 per 100,000 in controls and the incidence was somewhat higher than that of the study by Park et al.’s, although the direct comparison of the incidence of PD between our study and the previous study by Park et al. seems to be inappropriate because, controls in this study were matched with GD population by age and sex. Female predominance and elderly population excluding individuals <40 years old in this study might affect the incidence of PD. Third, the NHID does not include data regarding relevant clinical parameters, such as thyroid function or autoantibody titers (e.g., antibodies to TSH receptor), which precluded related analyses. Fourth, the mechanisms underlying the increased risk of PD that is associated with GD remain unclear. Fifth, approximately 96% of the Korean GD patients had received ATDs, which is substantially higher than the proportion of American patients that receive ATDs (approximately 60%). Thus, our findings might be influenced by the large proportion of patients who received medical treatment for GD, and the findings might not be replicated in larger studies of patients who underwent RAIT or surgery for GD. Nevertheless, the prevalences of GD and PD are both <1% in the general population, and a population-based database is likely needed to evaluate the relationship between GD and PD, despite the innate limitations of the NHID.

Conclusions

The present study revealed that Korean patients with GD had an increased risk of developing PD, even at relatively young ages. Furthermore, the risk of PD did not substantially change in subgroup analyses according to demographic characteristics or treatment duration/dosage of ATDs. Therefore, although the absolute incidence is low, we suggest that clinicians should remain aware of the possibility that GD patients may develop PD, even at relatively young ages.

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**Figure legend**

**Figure 1. Cumulative incidence of Parkinson's disease among patients with Graves’ disease and controls**

Cox proportional hazard regression analyses was conducted and results were adjusted for age, sex, household income, diabetes, hypertension, and dyslipidemia.
### Table 1. Baseline demographics of patients with Graves’ disease and controls

| Variables                  | Controls (n=326,900) | Graves’ disease (n=65,380) | P-value | ATD (n=62,615) | RAIT (n=2,237) | Surgery (n=528) | P-value * |
|----------------------------|----------------------|----------------------------|---------|----------------|----------------|----------------|-----------|
| Male sex                   | 95,175 (29%)         | 19,035 (29%)               | 1       | 18,148 (29%)   | 766 (34%)      | 121 (23%)      | <0.000    |
| Mean age, years            | 54.2±10.1            | 54.2±10.1                  | 1       | 54.3±10.1      | 53.0±9.8       | 54.0±10.0      | <0.000    |
| Age of ≥65 years           | 55,135 (17%)         | 11,027 (17%)               | 1       | 10,614 (17%)   | 320 (14%)      | 93 (18%)       | 0.004     |
| Household income           |                      |                            | <0.000  | 4,045 (6%)     | 133 (6%)       | 48 (9%)        | 0.009     |
| Absolute poverty           | 19,615 (6%)          | 4,226 (6%)                 |         |               |                |                |           |
| First quartile             | 61,810 (19%)         | 11,932 (19%)               |         | 11,459 (18%)   | 389 (17%)      | 84 (16%)       |           |
| Second quartile            | 61,620 (19%)         | 11,689 (18%)               |         | 11,194 (18%)   | 384 (17%)      | 111 (21%)      |           |
| Third quartile             | 74,678 (23%)         | 14,700 (22%)               |         | 14,065 (23%)   | 506 (23%)      | 129 (24%)      |           |
| Fourth quartile            | 109,177 (33%)        | 22,833 (35%)               | <0.000  | 21,852 (35%)   | 825 (37%)      | 156 (30%)      |           |
| Diabetes                   | 26,117 (8%)          | 8,291 (13%)                | <0.000  | 7,978 (13%)    | 234 (10%)      | 79 (15%)       | 0.002     |
| Hypertension               | 78,202 (24%)         | 24,139 (37%)               | <0.000  | 22,932 (37%)   | 963 (43%)      | 244 (46%)      | <0.000    |
| Dyslipidemia               | 44,564 (14%)         | 10,518 (16%)               | <0.000  | 10,157 (16%)   | 273 (12%)      | 88 (17%)       | 1         |

ATD, anti-thyroid drug; RAIT, radioactive iodine therapy.

* P-value was calculated among three groups according to the treatment modality.
Table 2. Subgroup analyses of Parkinson’s disease risk among patients with Graves’ disease and controls

| Subgroup | GD  | n    | PD  | PYs   | IR per 1,000 PYs | Hazard ratio (95% CI) * | P for interaction |
|----------|-----|------|-----|-------|------------------|--------------------------|------------------|
|          | GD  |      | PD  | PYs   |                  |                          |                  |
| 40–64 years | No  | 271,765 | 417 | 1,911,919 | 0.22              | Reference               |                  |
|          | Yes | 54,353  | 115 | 382,998   | 0.30              | 1.33 (1.08–1.64)        | 0.92             |
| ≥65 years | No  | 55,135  | 680 | 354,584   | 1.92              | Reference               |                  |
|          | Yes | 11,027  | 186 | 70,655    | 2.63              | 1.34 (1.13–1.57)        |                  |
| Male     | No  | 95,175  | 285 | 653,355   | 0.44              | Reference               |                  |
|          | Yes | 19,035  | 84  | 131,059   | 0.64              | 1.43 (1.12–1.83)        | 0.53             |
| Female   | No  | 231,725 | 812 | 1,613,148 | 0.50              | Reference               |                  |
|          | Yes | 46,345  | 217 | 322,594   | 0.67              | 1.29 (1.11–1.50)        |                  |
| No diabetes | No | 300,783 | 897 | 2,095,931 | 0.43              | Reference               |                  |
|          | Yes | 57,089  | 236 | 398,425   | 0.59              | 1.40 (1.21–1.61)        | 0.15             |
| Diabetes | No  | 26,117  | 200 | 170,572   | 1.17              | Reference               |                  |
|          | Yes | 8,291   | 65  | 55,229    | 1.18              | 1.10 (0.83–1.46)        |                  |
| No hypertension | No | 248,698 | 582 | 1,741,618 | 0.33              | Reference               |                  |
|          | Yes | 41,241  | 107 | 288,571   | 0.37              | 1.20 (0.97–1.47)        | 0.18             |
| Hypertension | No | 78,202  | 515 | 524,885   | 0.98              | Reference               |                  |
|          | Yes | 24,139  | 194 | 165,083   | 1.18              | 1.41 (1.19–1.67)        |                  |
| No dyslipidemia | No | 282,336 | 803 | 1,972,689 | 0.41              | Reference               |                  |
|          | Yes | 54,862  | 193 | 384,279   | 0.50              | 1.22 (1.04–1.43)        | 0.15             |
| Dyslipidemia | No | 44,564  | 294 | 293,814   | 1.00              | Reference               |                  |
|          | Yes | 10,518  | 108 | 69,375    | 1.56              | 1.55 (1.24–1.93)        |                  |

GD, Graves’ disease; PD, Parkinson’s disease; PYs, person-years; IR, incidence rate.

* Adjusted for age, sex, household income, diabetes, hypertension, and dyslipidemia.
Table 3. Risks of Parkinson’s disease among patients with Graves’ disease according to treatment modality

|                      | n    | PD  | PYs    | IR per 1,000 PYs | Model 1 *     | Model 2 **     |
|----------------------|------|-----|--------|------------------|--------------|--------------|
| Controls             | 326,900 | 1,097 | 2,266,503 | 0.48            | Reference    | Reference    |
| Graves’ disease      | 65,380  | 301  | 463,654 | 0.66            | 1.37         | 1.33         |
|                      |       |     |        |                  | (1.21–1.56)  | (1.17–1.51)  |
| Treatment modality   |      |     |        |                  |              |              |
| ATD                  | 62,615 | 287 | 434,451 | 0.66            | 1.37         | 1.31         |
|                      |       |     |        |                  | (1.20–1.55)  | (1.15–1.50)  |
| RAIT                 | 2,237  | 9   | 15,634  | 0.58            | 1.19         | 1.34         |
|                      |       |     |        |                  | (0.62–2.29)  | (0.70–2.59)  |
| Surgery              | 528   | 5   | 3,569   | 1.40            | 2.91         | 3.08         |
|                      |       |     |        |                  | (1.21–6.99)  | (1.28–7.43)  |

PD, Parkinson’s disease; PYs, person-years; IR, incidence rate; ATD, anti-thyroid drug; RAIT, radioactive iodine therapy.

* Not adjusted.

** Adjusted for age, sex, household income, diabetes, hypertension, and dyslipidemia.
Table 4. Subgroup analyses of Parkinson’s disease risk among patients with Graves’ disease and controls according to treatment modality

| Subgroup | Treatment | n   | PD | PYs    | IR per 1,000 PYs | Hazard ratio (95% CI) * | P for interaction |
|----------|-----------|-----|----|--------|------------------|--------------------------|------------------|
| 40–64 years | Controls | 271,765 | 417 | 1,911,919 | 0.22 | Reference | |
|          | ATD      | 52,001 | 105 | 366,430  | 0.29 | 1.27 (1.03–1.58) | 0.20 |
|          | RAIT     | 1917   | 7   | 13,566   | 0.52 | 2.47 (1.17–5.21) |  |
|          | Surgery  | 435    | 3   | 3,002    | 0.99 | 4.34 (1.39–13.51) |  |
| ≥65 years | Controls | 55,135 | 680 | 354,584  | 1.92 | Reference | |
|          | ATD      | 10,614 | 182 | 68,021   | 2.68 | 1.35 (1.15–1.60) |  |
|          | RAIT     | 320    | 2   | 2,067    | 0.97 | 0.51 (0.13–2.05) |  |
|          | Surgery  | 93     | 2   | 567      | 3.53 | 1.85 (0.49–7.86) |  |
| Male sex | Controls | 95,175 | 285 | 653,355  | 0.44 | Reference | |
|          | ATD      | 18,148 | 81  | 124,883  | 0.65 | 1.43 (1.12–1.84) | 0.51 |
|          | RAIT     | 766    | 1   | 5,368    | 0.19 | 0.58 (0.08–4.15) |  |
|          | Surgery  | 121    | 2   | 808      | 2.48 | 5.25 (1.31–21.12) |  |
| Female sex | Controls | 231,725 | 812 | 1,613,148 | 0.50 | Reference | |
|          | ATD      | 44,467 | 206 | 309,567  | 0.67 | 1.27 (1.09–1.48) |  |
|          | RAIT     | 1471   | 8   | 10,266   | 0.78 | 1.62 (0.81–3.26) |  |
|          | Surgery  | 407    | 3   | 2,761    | 1.09 | 2.38 (0.77–7.39) |  |
| No diabetes | Controls | 300,783 | 897 | 2,095,931 | 0.43 | Reference | |
|          | ATD      | 54,637 | 224 | 381,315  | 0.59 | 1.38 (1.19–1.60) | 0.64 |
|          | RAIT     | 2,003  | 7   | 14,036   | 0.50 | 1.39 (0.66–2.90) |  |
| Condition          | Group          | Surgery | Controls | ATD       | RAIT     | Surgery |
|--------------------|----------------|---------|----------|-----------|----------|---------|
|                    |                |         |          |           |          |         |
| Diabetes           |                |         |          |           |          |         |
|                    |                | 21.15   | 21.15    | 21.15     | 21.15    | 21.15   |
|                    |                | 3.45    | 3.45     | 3.45      | 3.45     | 3.45    |
|                    |                | 1.63    | 1.63     | 1.63      | 1.63     | 1.63    |
|                    |                | 4.20 (1.74–10.12) |          |          |          |         |
| No hypertension    |                |         |          |           |          |         |
|                    |                | 21.48   | 21.48    | 21.48     | 21.48    | 21.48   |
|                    |                | 3.45    | 3.45     | 3.45      | 3.45     | 3.45    |
|                    |                | 1.63    | 1.63     | 1.63      | 1.63     | 1.63    |
|                    |                | 0.28    | 0.28     | 0.28      | 0.28     | 0.28    |
| Hypertension       |                |         |          |           |          |         |
|                    |                | 21.48   | 21.48    | 21.48     | 21.48    | 21.48   |
|                    |                | 3.45    | 3.45     | 3.45      | 3.45     | 3.45    |
|                    |                | 1.63    | 1.63     | 1.63      | 1.63     | 1.63    |
|                    |                | 0.37    | 0.37     | 0.37      | 0.37     | 0.37    |
| No dyslipidemia    |                |         |          |           |          |         |
|                    |                | 21.48   | 21.48    | 21.48     | 21.48    | 21.48   |
|                    |                | 3.45    | 3.45     | 3.45      | 3.45     | 3.45    |
|                    |                | 1.63    | 1.63     | 1.63      | 1.63     | 1.63    |
|                    |                | 0.37    | 0.37     | 0.37      | 0.37     | 0.37    |
| Dyslipidemia       |                |         |          |           |          |         |
|                    |                | 21.48   | 21.48    | 21.48     | 21.48    | 21.48   |
|                    |                | 3.45    | 3.45     | 3.45      | 3.45     | 3.45    |
|                    |                | 1.63    | 1.63     | 1.63      | 1.63     | 1.63    |
|                    |                | 0.37    | 0.37     | 0.37      | 0.37     | 0.37    |

1 PD, Parkinson’s disease; PYs, person-years; IR, incidence rate; ATD, anti-thyroid drug; RAIT, radioactive iodine therapy.

* Adjusted for age, sex, household income, diabetes, hypertension, and dyslipidemia.
Table 5. Risks of Parkinson’s disease among patients with Graves’ disease according to cumulative ATD dose and treatment duration

|                  | n   | PD  | PYs       | IR per 1,000 PYs | Model 1 * | Model 2 ** |
|------------------|-----|-----|-----------|------------------|-----------|------------|
| Controls         | 326,900 | 1,097 | 2,266,503 | 0.48             | Reference | Reference  |
| ATD              | 62,615 | 287  | 434,451   | 0.66             | 1.37      | 1.31       |
|                  |      |      |           |                  | (1.20–1.55)| (1.15–1.50)|
| Cumulative dose  |      |      |           |                  |           |            |
| Lowest           | 20,871 | 96   | 136,217   | 0.70             | 1.48      | 1.33       |
|                  |      |      |           |                  | (1.20–1.83)| (1.08–1.60)|
| Middle           | 20,875 | 91   | 142,299   | 0.64             | 1.33      | 1.31       |
|                  |      |      |           |                  | (1.07–1.65)| (1.06–1.62)|
| Highest          | 20,869 | 100  | 155,935   | 0.64             | 1.30      | 1.31       |
|                  |      |      |           |                  | (1.06–1.60)| (1.06–1.61)|
| Cumulative duration |      |      |           |                  |           |            |
| Lowest           | 20,889 | 109  | 142,228   | 0.77             | 1.59      | 1.49       |
|                  |      |      |           |                  | (1.30–1.93)| (1.23–1.82)|
| Middle           | 20,857 | 95   | 143,451   | 0.66             | 1.37      | 1.46       |
|                  |      |      |           |                  | (1.11–1.69)| (1.19–1.81)|
| Highest          | 20,869 | 83   | 148,772   | 0.56             | 1.15      | 1.03       |
|                  |      |      |           |                  | (0.92–1.43)| (0.82–1.29)|

PD, Parkinson’s disease; PYs, person-years; IR, incidence rate; ATD, anti-thyroid drug.

Cumulative ATD doses were <4,953 mg (lowest), 4,953–18,700 mg (middle), and >18,700 mg (highest).

Cumulative ATD treatment durations were <12 months (lowest), 12–35 months (middle), and >35 months (highest).

* Not adjusted.

** Adjusted for age, sex, household income, diabetes, hypertension, and dyslipidemia.
Figure 1

HR 1.33 (95% CI 1.17–1.51), $p < 0.0001$

| Number of patients | Time (years) |
|--------------------|--------------|
| Controls           | 0, 2, 4, 6, 8, 10 |
| Graves’ disease    | 0, 2, 4, 6, 8, 10 |
| Controls           | 326,900, 323,017, 318,930, 213,134, 101,741, 700 |
| Graves’ disease    | 65,380, 64,595, 63,825, 42,712, 20,393, 139 |

180x115 mm (6.9 x DPI)