Association between haemorrhoids and Graves’ disease: a retrospective cohort study using data from Taiwan’s Longitudinal Health Insurance Database

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ABSTRACT
Objective To evaluate the relationship between haemorrhoids and Graves’ disease (GD).
Setting Using the nationwide data from Taiwan’s Longitudinal Health Insurance Database.
Participants We conducted a retrospective study, stratified patients by International Classification of Diseases, Ninth Revision, Clinical Modification disease code and compared the incidence rate of GD between patients with and without haemorrhoids. The study period was from 2000 to 2010, with exclusion of patients with diagnosed haemorrhoids before 2000 or after 2009, and we analysed the HR of GD in the univariable and multivariable models as well as the cumulative incidence curves of GD by using Kaplan-Meier curves.
Result This study included 13 165 and 52 660 patients with and without haemorrhoids, respectively. The mean follow-up duration was approximately 6 years. The incidence rate of GD was 1.57 and 1.13 per 1000 person-years in patients with and without haemorrhoids, respectively. The area under the cumulative incidence curve of GD in patients with haemorrhoids was higher than that of patients without haemorrhoids. The risk of GD increased by 1.39 times (95% CI 1.13 to 1.71) in patients with haemorrhoids compared with patients without haemorrhoids. In the subgroup analysis, women with haemorrhoids had a higher risk of GD (adjusted HR 1.44; 95% CI 1.13 to 1.83). Patients with haemorrhoids aged 30–39 years were more likely to develop GD (adjusted HR 1.73; 95% CI 1.18 to 2.55).
Conclusion The findings of this study indicate that patients with haemorrhoids may have an increased risk of GD compared with other potential confounding factors.

INTRODUCTION
Haemorrhoids are commonly diagnosed on routine health examination,1 and its prevalence has been increasing. The potential risk factors for haemorrhoids include male sex, age <40 years, improper diet, stress, depression, high body mass index, abdominal obesity, pregnancy and increased intra-abdominal pressure.2–5 Although 40% of patients with haemorrhoids are asymptomatic, others may experience rectal bleeding, painful perianal mass, prolapse, faecal incontinence and perianal fullness and irritation. In the USA, haemorrhoid is the fourth leading gastrointestinal disorder diagnosed in outpatient visits, accounting for approximately 4.4% of the overall population.6 The estimated cost of this disease in the employer-insured population was approximately US$800 million in 2014, with a substantial increasing trend.7

Graves’ disease (GD) is an autoimmune disease characterised by abnormal amounts of circulating antibodies that bind to and activate thyrotropin receptors, thus causing hyperthyroidism. It is the most common cause of hyperthyroidism in children and is associated with ophthalmopathy, goitre and dermopathy. Patients with GD typically present with bulging eyes, vision loss, enlarged thyroid, pretibial myxoedema and
other signs of thyrotoxicosis such as palpitations, tremulousness and anxiety. Risk factors include female sex, stress, pregnancy, younger age, smoking, heredity and history of other autoimmune disorders. Global variation in the epidemiology of hyperthyroidism was observed due to differences in population, diagnostic thresholds and iodine nutrition. A US retrospective study reported the incidence of GD to be 30 per 100 000 persons per year from 1935 to 1967.

Our previous work found an increased risk of Hashimoto’s thyroiditis, an autoimmune thyroid disease (AITD), in patients with haemorrhoids. No study has evaluated the correlation between haemorrhoids and GD, another AITD. In this study, we analysed the association between haemorrhoids and GD by using Taiwan’s National Health Insurance (NHI) Research Database (NHIRD).

METHODS
Study population
Since 1995, Taiwan’s NHI programme has >99% of the Taiwanese population, which consists of 98% of Han ethnicity. The original claims data are stored in the NHIRD. For privacy, the identification data are encrypted. Patients aged ≥18 years with at least two outpatient and one admission record of haemorrhoids, as defined using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) disease codes 555.1–555.5 and 455.8 were included as the study group. People without haemorrhoids were enrolled in the control group. The study period was 2000–2010. Patients with haemorrhoids diagnosed before 2000 or after 2009 and those already diagnosed with GD before entering the study were excluded. Patients with and without haemorrhoids were matched by sex, age and comorbidities at a ratio of 1:4 by propensity score matching.

Main outcome and comorbidities
The incidence of GD (ICD-9-CM code 242.0) was considered the primary event in this study. Patients who were lost to follow-up or died were censored. The potential confounders were coronary artery disease (CAD; ICD-9-CM codes 410–414), heart failure (ICD-9-CM codes 428), diabetes (ICD-9-CM codes 250), depression (ICD-9-CM codes 296.2, 296.3, 300.4 and 311), stroke (ICD-9-CM codes 430–438), hypertension (ICD-9-CM codes 401–405), hyperlipidaemia (ICD-9-CM codes 272), CKD (ICD-9-CM codes 580–589) and constipation (ICD-9-CM codes 564.0).

Statistical analysis
Baseline characteristics between patients with and without haemorrhoids are examined by a standard mean difference (SMD). SMD <0.1 was considered to indicate a negligible difference. The Cox proportional-hazards model was used to estimate the risk of GD. The univariable model was used to estimate the crude HR, and the multivariable model, which involved variables of sex, age, depression and hypertension, was used to estimate the adjusted HR. The cumulative incidence curves were obtained using the Kaplan-Meier method and assessed using the log-rank test. Statistical analysis was performed using SAS (V.9.1, SAS Institute). A two-tailed p<0.05 was set as significant.

There was no patient or public involvement.

RESULTS
We recruited 13 165 patients with haemorrhoids and 52 660 patients without haemorrhoids. The mean follow-up duration was approximately 6 years. Table 1 presents the participants’ baseline characteristics. They were mainly men and aged over 50. The distribution of comorbidities in patients with and without haemorrhoids was similar (all SMDs <0.1).

As presented in table 2, the incidence rate of GD in patients with haemorrhoids was 1.57 per 1000 person-years...
| Variables       | Non-Haemorrhoids | Haemorrhoids       | Gender   | Age, year | Comorbidities |
|-----------------|------------------|-------------------|----------|-----------|---------------|
|                 | N    | PY       | IR     | cHR (95% CI) | aHR† (95% CI) | N    | PY       | IR     | N    | PY       | IR     |
|                 | 349  | 308565  | 1.13  | 1.00 –       | 1.00 –         | 121  | 77286   | 1.57  | 1.39 (1.13 to 1.70)** | 1.39 (1.13 to 1.71)** |
| Gender          |       |         |       |             |                | Female | 345  | 166848 | 2.07  | 1.00 –       | 1.00 –         | Male | 125  | 219002 | 0.57  | 0.27 (0.22 to 0.34)*** | 0.29 (0.24 to 0.36)*** |
| Gender          |       |         |       |             |                | Female | 345  | 166848 | 2.07  | 1.00 –       | 1.00 –         | Male | 125  | 219002 | 0.57  | 0.27 (0.22 to 0.34)*** | 0.29 (0.24 to 0.36)*** |
| Age, year       |       |         |       |             |                | 18-29   | 85   | 56636  | 1.50  | 1.00 –       | 1.00 –         | 30-39 | 122  | 81659  | 1.49  | 1.00 (0.76 to 1.32) | 1.05 (0.79 to 1.38) |
| Age, year       |       |         |       |             |                | 40-49   | 116  | 90231  | 1.29  | 0.85 (0.64 to 1.13) | 0.92 (0.69 to 1.21) | ≥50   | 147  | 157324 | 0.93  | 0.62 (0.47 to 0.81)*** | 0.72 (0.54 to 0.97)* |
| Comorbidities   |       |         |       |             |                | CAD     | 464  | 376766 | 1.23  | 1.00 –       | 1.00 –         | No   | 464  | 376766 | 1.23  | 1.00 –       | 1.00 –         |
| Comorbidities   |       |         |       |             |                | No      | 464  | 376766 | 1.23  | 1.00 –       | 1.00 –         | Yes  | 6    | 9084   | 0.66  | 0.53 (0.24 to 1.18) |
| Comorbidities   |       |         |       |             |                | Heart failure | No   | 459  | 374019 | 1.23  | 1.00 –       | 1.00 –         | Yes  | 11   | 11831  | 0.93  | 0.74 (0.41 to 1.35) |
| Comorbidities   |       |         |       |             |                | DM      | 414  | 341527 | 1.21  | 1.00 –       | 1.00 –         | No   | 414  | 341527 | 1.21  | 1.00 –       | 1.00 –         |
| Comorbidities   |       |         |       |             |                | Yes     | 56   | 44323  | 1.26  | 1.03 (0.78 to 1.36) |
| Comorbidities   |       |         |       |             |                | Depression | No   | 408  | 361161 | 1.13  | 1.00 –       | 1.00 –         | Yes  | 62   | 24689  | 2.51  | 2.18 (1.67 to 2.85)*** | 1.62 (1.57 to 2.70)*** |
| Comorbidities   |       |         |       |             |                | Stroke   | No   | 436  | 355653 | 1.23  | 1.00 –       | 1.00 –         | Yes  | 34   | 30197  | 1.13  | 0.90 (0.64 to 1.28) |
| Comorbidities   |       |         |       |             |                | Hypertension | No   | 380  | 285810 | 1.33  | 1.00 –       | 1.00 –         | Yes  | 90   | 100040 | 0.90  | 0.67 (0.53 to 0.84)*** | 0.79 (0.60 to 1.03) |
| Comorbidities   |       |         |       |             |                | Hyperlipidaemia | No   | 374  | 318869 | 1.17  | 1.00 –       | 1.00 –         | Yes  | 96   | 66981  | 1.43  | 1.19 (0.95 to 1.49) |
| Comorbidities   |       |         |       |             |                | CKD      | No   | 450  | 367610 | 1.22  | 1.00 –       | 1.00 –         | Yes  | 20   | 18240  | 1.10  | 0.88 (0.56 to 1.37) |
| Comorbidities   |       |         |       |             |                | Constipation | No   | 354  | 304702 | 1.16  | 1.00 –       | 1.00 –         | Yes  | 116  | 81148  | 1.43  | 1.20 (0.98 to 1.48) |

*p<0.05, **p<0.01, ***p<0.001.
†Adjusted for sex, age, depression and hypertension.
aHR, adjusted HR; CAD, coronary artery disease; cHR, crude HR; CKD, chronic kidney disease; DM, diabetes mellitus; IR, incidence rate per 1000 person-years; PY, person-years.
and that in the control group was 1.13 per 1000 person-years. The incidence curve of GD in patients with haemorrhoids was higher than that of patients without haemorrhoids (figure 1). The risk of GD increased by 1.39 times (95% CI 1.13 to 1.71) in patients with haemorrhoids compared with the non-haemorrhoid patients. Women were more likely to develop GD. Patients older than 50 years had a reduced risk of GD relative to patients with age 18–29. Patients with depression had a higher risk of GD than those without depression (adjusted HR 1.62; 95% CI 1.57 to 2.70).

Table 3 presents the risk of GD in different subgroups. Women with haemorrhoids had a higher risk of GD than women without haemorrhoids (adjusted HR 1.44; 95% CI 1.13 to 1.83). Moreover, patients with haemorrhoids aged 30–39 years were more likely to develop GD than control patients aged 30–39 years (adjusted HR 1.73; 95% CI 1.18 to 2.55). The relationship between the treatment of haemorrhoids and GD is illustrated in table 4. Compared with patients without haemorrhoids and corresponding treatments such as suppositories, constipation-relieving tablets and ointment, the HRs of GD for haemorrhoids patients without the treatments was 1.35 (95% CI 1.06 to 1.71), and that for those with treatments was 1.52 (95% CI 1.07 to 2.15).

DISCUSSION
Our data revealed that the risk of GD was 1.39 times higher in participants with haemorrhoids than in those without haemorrhoids. Additionally, follow-up analysis indicated that younger patients (<50 years), women, and patients with depression had a higher risk of GD, which is consistent with current knowledge.

GD, an AITD, is characterised by specific symptoms and signs of overt hyperthyroidism, including weight loss, heat intolerance, fatigue, palpitations, anxiety, and hyperdefecation. It is also often associated with cardiac valve abnormalities, pulmonary arterial hypertension and autoimmune cardiomyopathy and has a long-term risk of increased hospitalisation due to cardiovascular disorders. Risk factors for haemorrhoids include obesity, depressive mood, stress, poor-fibre diet, constipation, chronic diarrhoea, increased intra-abdominal pressure, prolonged forceful Valsalva defecation and history of pregnancy. Population-based studies have indicated that haemorrhoids are also associated with peripheral arterial occlusive disease and coronary heart disease. By considering these findings and those of our previous study, we performed a large database study to evaluate the association between haemorrhoids and GD. Although no direct pathophysiological mechanism linking the two has been identified, future studies should attempt to evaluate relevant gastrointestinal, cardiovascular and psychological factors.

In the subgroup analysis in table 3, higher risks in various subgroups with haemorrhoids diagnosis were noted, especially in women and patients aged 30–39 years, which are also the potential risk factors for GD. Our analysis indicates that haemorrhoids, irrespective of treatment status, seemed to increase GD risk; however, the definite mechanism behind this phenomenon remains unclear.

Our previous study based on a similar population and study design found an increased risk of Hashimoto’s thyroiditis in patients with haemorrhoids. AITD is a complex disease spectrum without a clear aetiology; two major AITDs are GD and Hashimoto’s thyroiditis, which have been the targets of our current and previous studies, respectively. A study revealed that the aetiology of AITD is multifactorial, including multiple genetic and environmental factors; environmental triggers, including dietary iodine, smoking, infections, stress and some medications, contribute to approximately 20% of GD risk. The genetic–environmental interaction involved in AITD remains unknown.

Our studies have indicated that haemorrhoid is associated with a significantly increased risk of AITD. Both diseases have common risk factors of stressful lifestyle and depression, which can cause stress to the immune system. Accordingly, a possible mechanism linking the two may be that haemorrhoids stresses the immune system and potentiates its activity against normal tissues, leading to AITD. A prospective study from Denmark involving 145 217 patients found that depression is associated with an increased risk of various autoimmune diseases. Despite the lack of reasonable and credible molecular or genetic explanation for these findings, the significance in the statistical finding is non-negligible; further research should elucidate the aetiology behind the findings.

This study has several limitations. First, data for haemorrhoids, GD, and other comorbidities were retrieved only from the ICD-9-CM codes, which are input by the doctor without strict surveillance. Second, we could...
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not obtain certain critical parameters such as results of thyroid function test, thyroid-stimulating immunoglobulin levels, presence of Graves ophthalmopathy, thyroid ultrasound reports and grades of haemorrhoids because of restrictions or unavailability of the relevant information in the database. Finally, potential confounders like coronary artery disease, constipation, diabetes and depression were discussed in our study, yet other unmeasured confounding factors were still not identified.

Table 3  Stratification analysis of haemorrhoids and Graves’ disease

| Variables          | Non-Haemorrhoids | Haemorrhoids | cHR  (95% CI) | aHR† (95% CI) |
|--------------------|-------------------|--------------|---------------|---------------|
|                    | N    | PY   | IR    | N    | PY   | IR    |                |               |
| Gender             |      |      |       |      |      |       |                |               |
| Female             | 254  | 133785 | 1.90 | 91   | 33063 | 2.75   | 1.45 (1.14 to 1.84)** | 1.44 (1.13 to 1.83)** |
| Male               | 95   | 174780 | 0.54 | 30   | 44222 | 0.68   | 1.25 (0.83 to 1.88)   | 1.25 (0.83 to 1.88)   |
| Age, year          |      |      |       |      |      |       |                |               |
| 18–29              | 65   | 45340 | 1.43 | 20   | 11296 | 1.77   | 1.23 (0.75 to 2.04)   | 1.24 (0.75 to 2.04)   |
| 30–39              | 85   | 65215 | 1.30 | 37   | 16445 | 2.25   | 1.73 (1.18 to 2.55)** | 1.73 (1.18 to 2.55)** |
| 40–49              | 85   | 71896 | 1.18 | 31   | 18245 | 1.70   | 1.44 (0.95 to 2.17)   | 1.44 (0.95 to 2.17)   |
| ≥50                | 114  | 126023 | 0.90 | 33   | 31301 | 1.05   | 1.17 (0.79 to 1.72)   | 1.16 (0.79 to 1.71)   |
| Comorbidities      |      |      |       |      |      |       |                |               |
| CAD                |      |      |       |      |      |       |                |               |
| No                 | 345  | 301668 | 1.14 | 119  | 75098 | 1.58   | 1.39 (1.13 to 1.71)** | 1.39 (1.13 to 1.71)** |
| Yes                | 4    | 6897  | 0.58 | 2    | 2187  | 0.91   | 1.55 (0.28 to 8.47)   | 1.35 (0.24 to 7.47)   |
| Heart failure      |      |      |       |      |      |       |                |               |
| No                 | 341  | 299400 | 1.14 | 118  | 74619 | 1.58   | 1.39 (1.13 to 1.71)** | 1.39 (1.13 to 1.71)** |
| Yes                | 8    | 9164  | 0.87 | 3    | 2667  | 1.13   | 1.27 (0.34 to 4.80)   | 1.23 (0.33 to 4.65)   |
| DM                 |      |      |       |      |      |       |                |               |
| No                 | 305  | 273427 | 1.12 | 109  | 68100 | 1.60   | 1.44 (1.15 to 1.79)** | 1.44 (1.16 to 1.79)** |
| Yes                | 44   | 35137 | 1.25 | 12   | 9185  | 1.31   | 1.05 (0.55 to 1.98)   | 1.01 (0.53 to 1.91)   |
| DM                 |      |      |       |      |      |       |                |               |
| No                 | 302  | 289116 | 1.04 | 106  | 72045 | 1.47   | 1.41 (1.13 to 1.76)** | 1.42 (1.14 to 1.77)** |
| Yes                | 47   | 19449 | 2.42 | 15   | 5240  | 2.86   | 1.19 (0.66 to 2.12)   | 1.19 (0.67 to 2.13)   |
| DM                 |      |      |       |      |      |       |                |               |
| No                 | 324  | 284909 | 1.14 | 112  | 70744 | 1.58   | 1.39 (1.12 to 1.73)** | 1.40 (1.13 to 1.73)** |
| Yes                | 25   | 23656 | 1.06 | 9    | 6541  | 1.38   | 1.31 (0.61 to 2.80)   | 1.21 (0.56 to 2.60)   |
| DM                 |      |      |       |      |      |       |                |               |
| No                 | 277  | 228657 | 1.21 | 103  | 57153 | 1.80   | 1.49 (1.19 to 1.87)** | 1.49 (1.19 to 1.87)** |
| Yes                | 72   | 79907 | 0.90 | 18   | 20133 | 0.89   | 0.99 (0.59 to 1.66)   | 0.98 (0.58 to 1.64)   |
| DM                 |      |      |       |      |      |       |                |               |
| No                 | 276  | 255176 | 1.08 | 98   | 63693 | 1.54   | 1.42 (1.13 to 1.79)** | 1.43 (1.13 to 1.80)** |
| Yes                | 73   | 53389 | 1.37 | 23   | 13593 | 1.69   | 1.24 (0.78 to 1.98)   | 1.21 (0.76 to 1.94)   |
| DM                 |      |      |       |      |      |       |                |               |
| No                 | 334  | 294382 | 1.13 | 116  | 73228 | 1.58   | 1.40 (1.13 to 1.73)** | 1.40 (1.13 to 1.73)** |
| Yes                | 15   | 14182 | 1.06 | 5    | 4057  | 1.23   | 1.16 (0.42 to 3.18)   | 1.07 (0.39 to 2.97)   |
| DM                 |      |      |       |      |      |       |                |               |
| No                 | 258  | 243731 | 1.06 | 96   | 60970 | 1.57   | 1.49 (1.18 to 1.88)** | 1.49 (1.18 to 1.89)** |
| Yes                | 91   | 64833 | 1.40 | 25   | 16315 | 1.53   | 1.09 (0.70 to 1.70)   | 1.08 (0.69 to 1.68)   |

**p<0.01, ***p<0.001.
†Adjusted for sex, age, depression and hypertension.
aHR, adjusted HR; CAD, coronary artery disease; cHR, crude HR; CKD, chronic kidney disease; DM, diabetes mellitus; IR, incidence rate per 1000 person-years; PY, person-years.
Table 4 Relationship between haemorrhoid treatments and Graves' disease

| Haemorrhoids | Drug | Graves' disease | | |
|--------------|------|-----------------|---|---|---|
| No           | No   | N               | PY | IR | cHR (95% CI) | aHR† (95% CI) |
| Yes          | No   | 349             | 308565 | 1.13 | 1.00 – | 1.00 – |
| Yes          | Yes  | 86              | 56304 | 1.53 | 1.35 (1.06 to 1.70)* | 1.35 (1.06 to 1.71)* |
| Yes          | Yes  | 35              | 20982 | 1.67 | 1.49 (1.06 to 2.12)* | 1.52 (1.07 to 2.15)* |

*p<0.05
†Adjusted for sex, age, depression and hypertension.
aHR, adjusted HR; cHR, crude HR; IR, incidence rate per 1000 person-years; PY, person-years.

CONCLUSION
Patients with haemorrhoids may have an increased risk of GD within 10 years of diagnosis. However, further rigorous laboratory research is required to elucidate the mechanism underlying this association.

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Competing interests
None declared.

Patient and public involvement
Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication
Not applicable.

Ethics approval
This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH104-REC2-115-AR4). The IRB also specifically waived the consent requirement.

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Data availability statement
Data may be obtained from a third party and are not publicly available. The dataset used in this study is held by the Taiwan Ministry of Health and Welfare (MOHW). The Ministry of Health and Welfare must approve our application to access this data. Any researcher interested in accessing this dataset can submit an application form to the Ministry of Health and Welfare requesting access. Please contact the staff of MOHW (email: sctarowu@mohw.gov.tw) for further assistance. Taiwan Ministry of Health and Welfare Address: No.488, Sec. 6, Zhongxiao E. Rd., Nangang Dist., Taipei City 115, Taiwan (R.O.C). Phone: +886-2-8590-6848. All relevant data are within the paper.

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