



BMJ Open 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

Strengths and limitations of this study

- Data for haemorrhoids, Graves' disease and other comorbidities were retrieved only from the International Classification of Diseases, Ninth Revision, Clinical Modification codes, which are input by the doctor without strict surveillance.
- We could not obtain certain critical parameters, because of restrictions or unavailability of the relevant information in the database.
- This data analysis of this study revealed the association between the two diseases that was not mentioned directly in the literature to our knowledge.
- Potential confounders like constipation, diabetes and depression were discussed, yet other unmeasured confounding factors were still not identified.

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



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other signs of thyrotoxicosis such as palpitations, tremulousness and anxiety.^{8 9} Risk factors include female sex, stress, pregnancy, younger age, smoking, heredity and history of other autoimmune disorders.^{10 11} Global variation in the epidemiology of hyperthyroidism was observed due to differences in population, diagnostic thresholds and iodine nutrition.¹² A US retrospective study reported the incidence of GD to be 30 per 100 000 persons per year from 1935 to 1967.¹³

Our previous work found an increased risk of Hashimoto's thyroiditis, an autoimmune thyroid disease (AITD), in patients with haemorrhoids.¹⁴ 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 455.1–455.5 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

Table 1 Baseline characteristics of patients with and without haemorrhoids

Variables	Haemorrhoids				SMD
	No (N=52660)		Yes (N=13165)		
	n	%	n	%	
Gender					0.01
Female	22995	44	5688	43	
Male	29665	56	7477	57	
Age, year					
18–29	7536	14	1888	14	0.001
30–39	10645	20	2684	20	0.004
40–49	12182	23	3082	23	0.01
≥ 50	22297	42	5511	42	0.01
Mean, (SD)	48.5	(16.8)	48.2	(16.5)	0.02
Comorbidities					
CAD	1271	2.4	39	3.0	0.04
Heart failure	1773	3.4	500	3.8	0.02
DM	6587	13	1687	13	0.01
Depression	3934	7.5	1023	7.8	0.01
Stroke	4483	8.5	1213	9.2	0.03
Hypertension	14612	28	3640	28	0.002
Hyperlipidaemia	10525	20	2635	20	0.001
CKD	2817	5.4	782	5.9	0.03
Constipation	12545	24	3114	24	0.004

Follow-up: control: 5.87(2.87) case: 5.86(2.89).

CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; SMD, standard mean difference.

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 13165 patients with haemorrhoids and 52660 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

Table 2 Incidence rate and HR of Graves' disease

Variables	Graves' disease			cHR	(95% CI)	aHR†	(95% CI)
	N	PY	IR				
Non-Haemorrhoids	349	308 565	1.13	1.00	–	1.00	–
Haemorrhoids	121	77 286	1.57	1.39	(1.13 to 1.70)**	1.39	(1.13 to 1.71)**
Gender							
Female	345	166 848	2.07	1.00	–	1.00	–
Male	125	219 002	0.57	0.27	(0.22 to 0.34)***	0.29	(0.24 to 0.36)***
Age, year							
18–29	85	56 636	1.50	1.00	–	1.00	–
30–39	122	81 659	1.49	1.00	(0.76 to 1.32)	1.05	(0.79 to 1.38)
40–49	116	90 231	1.29	0.85	(0.64 to 1.13)	0.92	(0.69 to 1.21)
≥50	147	157 324	0.93	0.62	(0.47 to 0.81)***	0.72	(0.54 to 0.97)*
Comorbidities							
CAD							
No	464	376 766	1.23	1.00	–		
Yes	6	9084	0.66	0.53	(0.24 to 1.18)		
Heart failure							
No	459	374 019	1.23	1.00	–		
Yes	11	11 831	0.93	0.74	(0.41 to 1.35)		
DM							
No	414	341 527	1.21	1.00	–		
Yes	56	44 323	1.26	1.03	(0.78 to 1.36)		
Depression							
No	408	361 161	1.13	1.00	–	1.00	–
Yes	62	24 689	2.51	2.18	(1.67 to 2.85)***	1.62	(1.57 to 2.70)***
Stroke							
No	436	355 653	1.23	1.00	–		
Yes	34	30 197	1.13	0.90	(0.64 to 1.28)		
Hypertension							
No	380	285 810	1.33	1.00	–	1.00	–
Yes	90	100 040	0.90	0.67	(0.53 to 0.84)***	0.79	(0.60 to 1.03)
Hyperlipidaemia							
No	374	318 869	1.17	1.00	–		
Yes	96	66 981	1.43	1.19	(0.95 to 1.49)		
CKD							
No	450	367 610	1.22	1.00	–		
Yes	20	18 240	1.10	0.88	(0.56 to 1.37)		
Constipation							
No	354	304 702	1.16	1.00	–		
Yes	116	81 148	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.

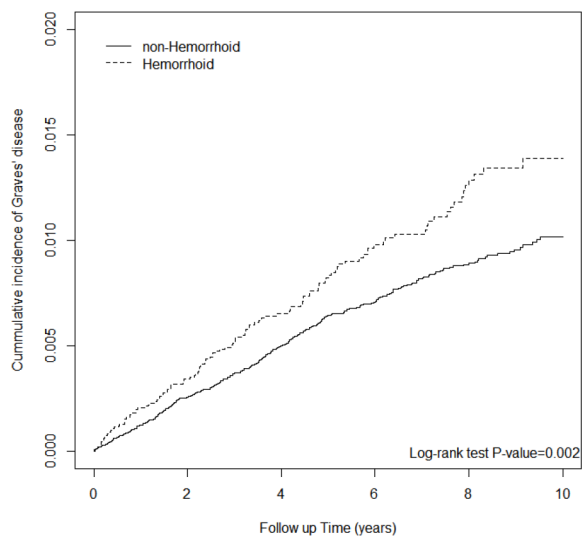


Figure 1 Cumulative incidence of Graves' disease between individuals with and without haemorrhoids.

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.⁸ 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.^{15 16} 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.^{4 17} Population-based studies have indicated that haemorrhoids are also associated with peripheral arterial occlusive disease and coronary heart disease.^{18 19} By considering these findings and those of our previous study,¹⁴ 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.¹⁴ 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.²⁰ The genetic–environmental interaction involved in AITD remains unknown.²¹ 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.²² 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

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	133 785	1.90	91	33 063	2.75	1.45	(1.14 to 1.84)**	1.44	(1.13 to 1.83)**
Male	95	174 780	0.54	30	44 222	0.68	1.25	(0.83 to 1.88)	1.25	(0.83 to 1.88)
Age, year										
18–29	65	45 340	1.43	20	11 296	1.77	1.23	(0.75 to 2.04)	1.24	(0.75 to 2.04)
30–39	85	65 215	1.30	37	16 445	2.25	1.73	(1.18 to 2.55)**	1.73	(1.18 to 2.55)**
40–49	85	71 986	1.18	31	18 245	1.70	1.44	(0.95 to 2.17)	1.44	(0.95 to 2.17)
≥50	114	126 023	0.90	33	31 301	1.05	1.17	(0.79 to 1.72)	1.16	(0.79 to 1.71)
Comorbidities										
CAD										
No	345	301 668	1.14	119	75 098	1.58	1.39	(1.13 to 1.71)**	1.39	(1.13 to 1.71)**
Yes	4	6 897	0.58	2	2 187	0.91	1.55	(0.28 to 8.47)	1.35	(0.24 to 7.47)
Heart failure										
No	341	299 400	1.14	118	74 619	1.58	1.39	(1.13 to 1.71)**	1.39	(1.13 to 1.71)**
Yes	8	9 164	0.87	3	2 667	1.13	1.27	(0.34 to 4.80)	1.23	(0.33 to 4.65)
DM										
No	305	273 427	1.12	109	68 100	1.60	1.44	(1.15 to 1.79)**	1.44	(1.16 to 1.79)**
Yes	44	35 137	1.25	12	9 185	1.31	1.05	(0.55 to 1.98)	1.01	(0.53 to 1.91)
Depression										
No	302	289 116	1.04	106	72 045	1.47	1.41	(1.13 to 1.76)**	1.42	(1.14 to 1.77)**
Yes	47	19 449	2.42	15	5 240	2.86	1.19	(0.66 to 2.12)	1.19	(0.67 to 2.13)
Stroke										
No	324	284 909	1.14	112	70 744	1.58	1.39	(1.12 to 1.73)**	1.40	(1.13 to 1.73)**
Yes	25	23 656	1.06	9	6 541	1.38	1.31	(0.61 to 2.80)	1.21	(0.56 to 2.60)
Hypertension										
No	277	228 657	1.21	103	57 153	1.80	1.49	(1.19 to 1.87)***	1.49	(1.19 to 1.87)***
Yes	72	79 907	0.90	18	20 133	0.89	0.99	(0.59 to 1.66)	0.98	(0.58 to 1.64)
Hyperlipidaemia										
No	276	255 176	1.08	98	63 693	1.54	1.42	(1.13 to 1.79)**	1.43	(1.13 to 1.80)**
Yes	73	53 389	1.37	23	13 593	1.69	1.24	(0.78 to 1.98)	1.21	(0.76 to 1.94)
CKD										
No	334	294 382	1.13	116	73 228	1.58	1.40	(1.13 to 1.73)**	1.40	(1.13 to 1.73)**
Yes	15	14 182	1.06	5	4 057	1.23	1.16	(0.42 to 3.18)	1.07	(0.39 to 2.97)
Constipation										
No	258	243 731	1.06	96	60 970	1.57	1.49	(1.18 to 1.88)***	1.49	(1.18 to 1.89)***
Yes	91	64 833	1.40	25	16 315	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.

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 4 Relationship between haemorrhoid treatments and Graves' disease

Haemorrhoids	Drug	Graves' disease			cHR	(95% CI)	aHR†	(95% CI)
		N	PY	IR				
No	No	349	308 565	1.13	1.00	–	1.00	–
Yes	No	86	56 304	1.53	1.35	(1.06 to 1.70)*	1.35	(1.06 to 1.71)*
Yes	Yes	35	20 982	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, or 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.

Provenance and peer review Not commissioned; externally peer reviewed.

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: stcarolwu@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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