ORIGINAL INVESTIGATION

Smoking and Other Lifestyle Factors and the Risk of Graves' Hyperthyroidism

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Background: Hyperthyroidism caused by Graves' disease is common in women, yet little is known about risk factors for the disease. We sought to determine whether lifestyle factors, including smoking, alcohol consumption, physical activity level, and body mass index, are risk factors for Graves' hyperthyroidism.

Methods: This analysis was conducted using data from the Nurses' Health Study II, among 115 109 women aged 25 to 42 at entry. Incident reports of women with Graves' hyperthyroidism, confirmed to have the disorder, were included.

Results: During 1 328 270 person-years of follow-up, incident diagnoses of Graves' hyperthyroidism were confirmed in 543 women; the 12-year incidence was 4.6 per 1000 women. Cigarette smoking was a predictor of Graves' hyperthyroidism. The hazard ratio among current smokers was 1.93 (95% confidence interval [CI], 1.54-2.43), and among past smokers it was 1.27 (95% CI, 1.03-1.56), after adjusting for recent pregnancy, parity, and other variables. Among current smokers, the hazard ratio increased with the intensity of smoking and was 2.63 (95% CI, 1.71-4.04) among women who smoked 25 or more cigarettes daily. Obesity was associated with a decreased risk of Graves' hyperthyroidism. The hazard ratio for the disorder among women with a body mass index of 30 kg/m^2 or higher was 0.68 (95% CI, 0.49-0.92). Alcohol intake and physical activity level were not associated with risk of Graves' hyperthyroidism.

Conclusions: Smoking is a risk factor for Graves' hyperthyroidism in women. Obesity may be associated with a reduced risk, although weight loss as the first manifestation of hyperthyroidism cannot be excluded.

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GRAVES' DISEASE IS AN autoimmune disorder characterized by hyperthyroidism, goiter, ophthalmopathy, and dermopathy. Among women, the incidence of hyperthyroidism, the most common manifestation of the disease, has been estimated to be 0.1 to 1 per 1000 women per year.[1-3] Given this frequency, it is surprising how little is known about risk factors for the disorder. Based on family and twin studies, genetic factors are important.[4-7] Postulated environmental and lifestyle risk factors include cigarette smoking,[8-10] stress and adverse life events,[4,10,11] and high dietary iodine intake.[12] Alcohol consumption may be protective.[4,10] The evidence linking these factors to Graves' hyperthyroidism is based on small case-control studies, which are prone to recall bias. To our knowledge, no large prospective cohort studies of Graves' hyperthyroidism have been conducted.

We studied the association between lifestyle factors, including smoking, alcohol consumption, physical activity, and body mass index, and Graves' hyperthyroidism among participants in the Nurses' Health Study (NHS) II. This large cohort study allowed us to identify cases of Graves' hyperthyroidism prospectively and to identify factors associated with its development.

METHODS

STUDY SUBJECTS

The NHS II was started in 1989 among a cohort of 116 671 nurses aged 25 to 42 years (aged 37-54 at the end of the present follow-up in 2001); 92% of the women were white. Since 1989, information has been collected every 2 years. In the first questionnaire, information was collected on height, current weight, weight at age 18, race and ethnicity, age at menarche, number of pregnancies before September 1989, smoking status, and number of cigarettes smoked per day during each 5-year interval from age 15 to 35. Information was updated every 2 years. Alco-

hol intake was updated in 1991 and 1995 from the food frequency questionnaire included in the biennial surveys done in those years. In 1989, 1991, and 1997, the women were asked about time spent each week in 8 activities, including walking, jogging, running, bicycling, aerobics, calisthenics, racket sports, and swimming.

Derived variables were obtained using the information from the questionnaires. The variables included smoking status, years since cessation of smoking, pack-years of smoking, cumulative duration of oral contraceptive use, total number of pregnancies, and menopausal status. Physical activity level was assessed based on the time spent each week in each of the 8 activities listed at the end of the previous paragraph, and the weekly metabolic equivalent task score was calculated. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters, using the reported height in 1989 and the weight reported at age 18 and on each questionnaire. Grams per day of alcohol ingested was determined from the food frequency questionnaire.

The institutional review board at the Brigham and Women's Hospital approved this study.

ASSESSMENT OF GRAVES' HYPERTHYROIDISM

In 1993, the women were asked if they had developed Graves' disease before or after September 1989, and, starting in 1995, they were asked if they had developed Graves' disease or Graves' hyperthyroidism in the preceding 2 years. Women reporting a diagnosis before 1989 were excluded. Hereafter, we use the term *Graves' hyperthyroidism* to describe the diagnosis of women who met the criteria for hyperthyroidism caused by Graves' disease, as described herein.

A validation study was performed in 1995 to assess the reliability of self-reports of Graves' disease or Graves' hyperthyroidism. A supplemental questionnaire and request for permission to obtain medical records from the treating physician were sent to women who had reported this outcome on the NHS II questionnaire. On the supplemental questionnaire, the women were asked about the following: if they had been diagnosed as having Graves' disease or Graves' hyperthyroidism and the year of diagnosis; symptoms and signs of hyperthyroidism; whether they had goiter or eye changes; tests done to confirm the diagnosis (thyroid function tests, thyroid scan and uptake, and ophthalmologic examination); antithyroid drug, radioiodine, or surgical treatment; and diagnosis of other thyroid disorders (hyperfunctioning nodule, multinodular goiter, hypothyroidism, or thyroid cancer). If permission was granted to contact the physician, the physician was asked to send copies of medical records confirming the diagnosis and treatment or to complete a questionnaire similar to the questionnaire sent to the women. The supplemental questionnaires and medical records were reviewed for 72 women who had reported having Graves' hyperthyroidism on the questionnaire to determine if the supplemental questionnaire alone was reliable or if the medical record was needed to confirm the diagnosis. Criteria for the diagnosis of Graves' hyperthyroidism included test results consistent with hyperthyroidism, institution of treatment for hyperthyroidism, and absence of other thyroid disorders. Based on review of the supplemental questionnaire alone, the investigators corroborated the diagnosis of Graves' hyperthyroidism in 61 (85%) of the 72 women. Subsequently, the physicians' reports for these 61 women were reviewed, and in 59 (97%) of the cases, the physicians' reports confirmed the diagnosis of Graves' hyperthyroidism. This finding demonstrated that the supplemental questionnaire alone provided sufficient information to confirm the diagnosis in most cases. However, permission to obtain the medical record was always requested to ensure the most accurate data possible.

Since 1993, supplemental questionnaires and requests to contact the treating physician have been sent to 1637 women who responded affirmatively to having Graves' disease or Graves' hyperthyroidism on the NHS II questionnaire. The following women were excluded: 352 women denied the diagnosis of Graves' disease or Graves' hyperthyroidism on the supplemental questionnaire, 258 women gave a date of diagnosis before September 1989, 125 women could not be contacted, 3 women declined to participate, and 2 women had died. In addition, 93 questionnaires were returned after the analysis was performed; the physicians' records are still missing for 17 women; and 63 women declined to give permission to contact their physician. Therefore, 724 supplemental questionnaires were reviewed.

We designed a coding scheme to identify women with documented Graves' hyperthyroidism. We based the coding on the following information gathered from the supplemental questionnaire and, if available, from the medical record: symptoms and signs of hyperthyroidism; results of thyroid function tests; results of a thyroid radioiodine uptake or scan study; treatment with an antithyroid drug, radioactive iodine, or surgery; and absence of other thyroid disorders.

Women were assigned a "definite" diagnosis of Graves' hyperthyroidism if they had high serum thyroxine and low serum thyrotropin concentrations, and a high thyroid radioiodine uptake or diffuse pattern of uptake on scan; were treated for hyperthyroidism with an antithyroid drug, radioactive iodine, or thyroidectomy; and did not have another thyroid disorder. The presence of symptoms or signs was not required for a definite diagnosis of Graves' hyperthyroidism. Women were assigned a "probable" diagnosis of Graves' hyperthyroidism if they had at least 1 symptom of hyperthyroidism or 1 of 2 signs (goiter or eye changes); high serum thyroxine and low serum thyrotropin concentrations, or a high thyroid radioiodine uptake or diffuse pattern of uptake on scan (but not both); were treated for hyperthyroidism; and did not have another thyroid disorder. Women who had all of the clinical signs of Graves' hyperthyroidism (goiter, eye changes, and at least 1 symptom) and had laboratory test results consistent with Graves' hyperthyroidism, but were not treated, were also categorized as probable case subjects.

Based on these definitions, women with a definite or probable diagnosis of Graves' hyperthyroidism were considered to be "confirmed" case subjects with Graves' hyperthyroidism. The diagnosis of Graves' hyperthyroidism was coded as "unconfirmed" in women who were not treated (with the exception noted in the previous paragraph), did not fulfill the criteria outlined in the previous paragraph, or had another thyroid disorder. Two reviewers (I.A.H. and R.D.U.) coded all of the questionnaires.

STATISTICAL ANALYSIS

We calculated person-time from the date of return of the 1989 baseline questionnaire to the date of diagnosis of Graves' hyperthyroidism, or June 2001, whichever came first. Hazard ratios and 95% confidence intervals (CIs) for developing Graves' hyperthyroidism were determined using Cox proportional hazards regression analysis. The exposures and covariates were updated biennially, except for age at menarche and BMI at age 18. The updated exposures and covariates were assessed from the questionnaire completed 2 years before the questionnaire indicating the diagnosis of Graves' hyperthyroidism. For one analysis of BMI, we used the BMI from 4 years before the diagnosis of Graves' hyperthyroidism (2 questionnaires before the questionnaire indicating the diagnosis).

Table 1. Hazard Ratios (HRs) for Graves' Hyperthyroidism Associated With Smoking Status Among Participants of the Nurses' Health Study II Assessed From 1989 to 2001

Smoking Status	No. of Cases	Person-Years of Follow-up	Age-Adjusted HR (95% CI)	Covariate-Adjusted HR (95% CI)*
Never smoker	299	859 338	1.00	1.00
Past smoker†	137	302 682	1.28 (1.05-1.57)‡	1.27 (1.03-1.56)§
1-14 Cigarettes/d	71	167 639	1.21 (0.93-1.56)	1.19 (0.91-1.54)
15-24 Cigarettes/d	41	87 025	1.34 (0.96-1.85)	1.33 (0.95-1.84)
≥25 Cigarettes/d	23	43 504	1.47 (0.96-2.25)	1.47 (0.96-2.26)
Current smoker†	105	150 203	1.96 (1.57-2.45)‖	1.93 (1.54-2.43)¶
1-14 Cigarettes/d	45	66 024	1.93 (1.41-2.64)	1.88 (1.37-2.58)
15-24 Cigarettes/d	35	56 077	1.74 (1.23-2.48)	1.73 (1.21-2.46)
≥25 Cigarettes/d	23	24 002	2.63 (1.72-4.03)	2.63 (1.71-4.04)

Abbreviation: CI, confidence interval.
*Model adjusted for age, duration of oral contraceptive use, age at menarche, parity, recent pregnancy, menopausal status, body mass index, alcohol intake, and physical activity level.
†Numbers do not sum to total numbers of cases because of missing data.
‡P=.38 for trend among past smokers only; P=.01 for trend among never and past smokers.
§P=.35 for trend among past smokers only; P=.02 for trend among never and past smokers.
‖P=.49 for trend among current smokers only; P<.001 for trend among never and current smokers.
¶P=.40 for trend among current smokers only; P<.001 for trend among never and current smokers.

For the smoking variables, the reference group was "never smokers." Smoking status was categorized as never, past, or current. The number of cigarettes per day for past and current smokers was categorized as 1 to 14, 15 to 24, or 25 or more. Years since a smoker quit smoking was classified in 5-year intervals. Pack-years of smoking were categorized as 1 to 5, 6 to 10, 11 to 15, 16 to 20, 21 to 25, or more than 25. Body mass index was included in the analysis in the categories of less than 21 (reference group), 21 to 22.9, 23 to 24.9, 25 to 29.9, or 30 or higher. Physical activity scores (metabolic equivalent tasks per week) were categorized as less than 3 (reference group), 3 to less than 9, 9 to less than 18, 18 to less than 27, 27 to less than 42, or 42 or higher. Alcohol intake (from the 1991 and 1995 food frequency questionnaires) was categorized as none (reference group), 0 to less than 5 g/d, 5 to less than 10 g/d, 10 to less than 15 g/d, or 15 g/d or more. Age was categorized as a continuous variable. Menopausal status was categorized as premenopausal or postmenopausal. Duration of oral contraceptive use was listed as never (reference group), 1 to 23 months, 24 to 47 months, 48 to 71 months, 72 to 95 months, 96 to 119 months, or 120 months or longer. Parity (defined as the number of pregnancies lasting ≥6 months) was categorized as nulliparous (reference group), 1, 2, 3, or 4 or more. Women were asked if they were pregnant at the time the questionnaire was completed (yes or no). Age at menarche was categorized as 10 or younger, 11, 12, 13 (reference group), 14, 15, or 16 or older.

Tests for trend for the smoking variables were carried out using the midpoint of the interval as the value for that interval. Tests for trend for the BMI variables were carried out using the continuous variables for all of the BMI variables.

Cases that were unconfirmed were excluded from the statistical analysis. After the exclusions, 115 109 women formed the study population for this analysis.

RESULTS

During 1 328 270 person-years of follow-up, the diagnosis of Graves' hyperthyroidism was confirmed in 543 women, including 424 definite and 119 probable cases. The incidence was 4.6 per 1000 women during the 12-year period (1989-2001). The mean age of women who developed Graves' hyperthyroidism was 38.8 years, which was similar to that of those who did not (mean age, 39.2 years).

Smoking status was available for 114 963 women, including 541 of the 543 women who had Graves' hyperthyroidism. Smoking was associated with risk of Graves' hyperthyroidism. The risk of Graves' hyperthyroidism among past and current smokers was increased above that of never smokers, with the highest risk among current smokers (**Table 1**). When only the 424 definite cases were included, the results for past and current smokers were similar (data not shown). When women who never smoked were included in the trend test, the risk of Graves' hyperthyroidism increased as the number of cigarettes smoked per day increased for past and current smokers (Table 1). Women currently smoking 25 or more cigarettes daily had the highest risk among all of the groups (hazard ratio, 2.63; 95% CI, 1.71-4.04). In addition, the greater the number of pack-years smoked, the greater the risk (P<.001 for trend) (**Table 2**). Finally, among past smokers, the risk decreased as the time since smoking cessation increased (**Table 3**).

Body mass index was available for 114 848 women, including 500 of the 543 women who had Graves' hyperthyroidism. In addition to BMI (updated biennially), we assessed BMI in 1989 and BMI at age 18 as exposures. A BMI of 30 or higher was associated with a decreased risk of Graves' hyperthyroidism (**Table 4**), and as BMI increased, the risk of Graves' hyperthyroidism decreased (P=.02 for trend). A BMI in 1989 of 30 or higher was also associated with a decreased risk (hazard ratio, 0.68; 95% CI, 0.49-0.96), and as BMI in 1989 increased, the risk decreased (P=.03 for trend) (data not shown). A BMI at age 18 of 25 to 29.9 (but not a BMI at age 18 of ≥30) was associated with a decreased risk (hazard ratio, 0.69; 95% CI, 0.48-1.00) (data not shown). However, an increasing BMI at age 18 was not associated with a decreasing risk (P=.11 for trend) (data not shown). Because the exposures and covariates were assessed from the questionnaire preceding the questionnaire indicat-

Table 2. Hazard Ratios (HRs) for Graves' Hyperthyroidism Associated With Pack-Years of Smoking Among Participants of the Nurses' Health Study II Assessed From 1989 to 2001

Smoking Status	No. of Cases	Person-Years of Follow-up	Age-Adjusted HR (95% CI)	Covariate-Adjusted HR (95% CI)*
Never smoker	299	859 338	1.00	1.00
Ever smoker†	242	452 885	1.51 (1.27-1.79)‡	1.49 (1.25-1.78)‡
1-5 Pack-year	43	134 757	0.92 (0.67-1.27)	0.91 (0.66-1.26)
6-10 Pack-year	55	105 474	1.49 (1.12-1.99)	1.47 (1.10-1.97)
11-15 Pack-year	49	79 249	1.78 (1.32-2.42)	1.77 (1.31-2.41)
16-20 Pack-year	35	58 153	1.76 (1.24-2.51)	1.76 (1.24-2.51)
21-25 Pack-year	27	39 788	1.98 (1.33-2.95)	1.97 (1.32-2.95)
>25 Pack-year	30	44 877	1.97 (1.34-2.89)	1.96 (1.33-2.90)

Abbreviation: CI, confidence interval.
*Model adjusted for age, duration of oral contraceptive use, age at menarche, parity, recent pregnancy, menopausal status, body mass index, alcohol intake, and physical activity level.
†Numbers do not sum to total number of cases because of missing data.
‡$P<.001$ for trend excluding and including those who never smoked.

Table 3. Hazard Ratios (HRs) for Graves' Hyperthyroidism Associated With Number of Years Since a Past Smoker Stopped Smoking Among Participants of the Nurses' Health Study II Assessed From 1989 to 2001

Smoking Status	No. of Cases*	Person-Years of Follow-up	Age-Adjusted HR (95% CI)	Covariate-Adjusted HR (95% CI)†
Current smoker	105	150 203	1.00	1.00
Past smoker, y since quit			‡	§
5	39	65 597	0.84 (0.58-1.21)	0.83 (0.58-1.21)
>5-10	32	59 905	0.75 (0.50-1.12)	0.75 (0.51-1.12)
>10-15	30	70 126	0.58 (0.38-0.87)	0.58 (0.39-0.87)
>15	35	105 954	0.52 (0.35-0.76)	0.52 (0.35-0.77)
Never smoker	299	859 338	0.51 (0.41-0.64)	0.52 (0.41-0.65)

*Among 540 women for whom information on years since smoking cessation was available.
†Model adjusted for age, duration of oral contraceptive use, age at menarche, parity, recent pregnancy, menopausal status, body mass index, alcohol intake, and physical activity level.
‡$P=.001$ for trend excluding current smokers; $P<.001$ for trend including current smokers.
§$P=.002$ for trend excluding current smokers; $P<.001$ for trend including current smokers.

ing the diagnosis of Graves' hyperthyroidism, we increased the lag time and assessed the BMI as reported on the questionnaire 4 years (2 cycles) before the questionnaire on which Graves' hyperthyroidism was reported. In this model, BMI was not associated with risk of Graves' hyperthyroidism (Table 4).

Height and physical activity level were not associated with risk of Graves' hyperthyroidism. Alcohol intake was also not associated with risk of Graves' hyperthyroidism, in the unadjusted model or in the model adjusted for smoking status (data not shown).

COMMENT

In this large cohort of women, smoking was a predictor of the risk of Graves' hyperthyroidism. The relationship was time dependent; current smokers had a higher risk than past smokers; and among the women who quit smoking, the risk decreased progressively with time. The relationship was also dose dependent; those with the highest risk of Graves' hyperthyroidism were women with the greatest number of pack-years of smoking and current smokers who smoked the most cigarettes per day. The results among women without ophthalmopathy were similar to the results among all case subjects. However, the data collected on Graves' ophthalmopathy were not optimal; therefore, results of that analysis are not presented herein.

Case-control studies[4,10,13-15] have assessed smoking as a risk factor for Graves' hyperthyroidism. In a meta-analysis[16] of 25 studies of the association between smoking and thyroid diseases (8 of which assessed the risk of Graves' hyperthyroidism alone), compared with never smokers, the odds ratio was 3.30 (95% CI, 2.09-5.22) among current smokers, and it was 1.41 (95% CI, 0.77-2.58) among previous smokers. The numbers of cases in these studies ranged from 62 to 208. To our knowledge, our study of 543 cases is the largest study of Graves' hyperthyroidism reported to date and the first with a prospective design.

We found a dose-response relationship between smoking and Graves' hyperthyroidism, with increasing numbers of cigarettes smoked and increasing pack-years of smoking associated with an increased risk of the disorder. Two retrospective studies assessed the risk of Graves' hyperthyroidism and the number of cigarettes smoked. In a study[15] of 13 twin pairs who smoked but were discordant for Graves' hyperthyroidism, pack-years of smoking was higher in the affected twin. In another study[10] of 228 women who were smokers, the risk was increased

Table 4. Hazard Ratios (HRs) for Graves' Hyperthyroidism Associated With Body Mass Index (BMI) Among Participants of the Nurses' Health Study II Assessed From 1989 to 2001

BMI Before Diagnosis of Graves' Hyperthyroidism*	No. of Cases	Person-Years of Follow-up	Age-Adjusted HR (95% CI)	Covariate-Adjusted HR (95% CI)†
Assessed 2 y before			‡	§
<21	117	245 426	1.00	1.00
21-22.9	113	247 133	0.96 (0.74-1.24)	0.96 (0.74-1.24)
23-24.9	88	205 758	0.90 (0.68-1.19)	0.89 (0.67-1.18)
25-29.9	114	271 126	0.89 (0.68-1.15)	0.87 (0.66-1.13)
≥30	68	204 753	0.71 (0.52-0.96)	0.68 (0.49-0.92)
Assessed 4 y before‖			¶	#
<21	102	220 929	1.00	1.00
21-22.9	117	217 060	1.20 (0.92-1.56)	1.20 (0.92-1.56)
23-24.9	69	177 311	0.89 (0.66-1.21)	0.88 (0.65-1.20)
25-29.9	97	228 141	1.00 (0.76-1.32)	0.98 (0.74-1.31)
≥30	59	167 915	0.85 (0.61-1.17)	0.81 (0.58-1.14)

*BMI calculated as weight in kilograms divided by the square of height in meters.
†Model adjusted for age, duration of oral contraceptive use, age at menarche, parity, recent pregnancy, menopausal status, smoking status, alcohol intake, and physical activity level.
‡P=.03 for trend.
§P=.02 for trend.
‖Among 444 women, as the analysis was restricted to women reporting the diagnosis on the 1993 questionnaire and beyond. In addition, BMI data are missing for 25 women.
¶P=.22 for trend.
#P=.15 for trend.

(odds ratio, 5.1; 95% CI, 1.0-27) among the 8 women who smoked 21 to 40 cigarettes per day. This compares with the hazard ratio of 2.63 for the 23 women who were the heaviest smokers (≥25 cigarettes/d) in our study. We also found that the risk of Graves' hyperthyroidism diminishes with time after smoking cessation, and by 10 to 15 years after cessation, the risk significantly decreases. To our knowledge, previous studies have not assessed the relationship with smoking cessation.

The mechanism by which smoking increases the risk of Graves' hyperthyroidism is not known. Smokers have higher serum thiocyanate concentrations than nonsmokers. Thiocyanate inhibits iodide transport into thyroid cells,[17,18] which may decrease thyroid hormone synthesis. Benzpyrene, another component of cigarette smoke, may stimulate thyroid secretion by stimulating the sympathetic nervous system.[9] Smoking also has effects on the immune system. It increases the production of the proinflammatory cytokines from mononuclear cells.[19,20] Although smoking decreases serum immunoglobulin concentrations overall, smokers tend to have higher serum concentrations of autoantibodies than nonsmokers.[21] How these changes might affect the risk of Graves' hyperthyroidism is not known.

We found that a high BMI in the interval 2 years before the diagnosis and in 1989 (at the beginning of the study) was associated with a lower risk of Graves' hyperthyroidism. However, this finding must be interpreted with caution, because the association could be explained by reverse causality. When we assessed the exposure 4 years before the diagnosis, the association was no longer significant. Therefore, we cannot rule out the possibility that Graves' hyperthyroidism was present for more than 2 years before the diagnosis, led to weight loss, and thus was the first sign of hyperthyroidism, rather than low weight being protective. In addition, an increasing BMI at age 18, well before the onset of Graves' hyperthyroidism, was not associated with a decreasing risk of Graves' hyperthyroidism.

A limitation of this study is that we might have misclassified some women, particularly in our probable category, as having Graves' hyperthyroidism who did not have the disorder. We were as stringent as possible in our classification to avoid this problem. Another limitation is that the exposure data were gathered by self-report. However, the women were all nurses, who would be expected to report health-related behaviors more accurately than the general population. In addition, one would expect underreporting of smoking, especially by nurses, given the stigma against smoking, which might bias the results toward the null hypothesis. The facts that the subjects were all nurses, nearly all were white, and all were women may limit the generalizability of the results. Finally, another limitation is that we have little data on other environmental factors, such as iodine intake, stress, negative life events, and infections.

In conclusion, this prospective study confirms and expands on the work of earlier studies that demonstrate that smoking is a risk factor for Graves' hyperthyroidism. The finding of an inverse relationship between BMI 2 years before diagnosis and the risk of Graves' hyperthyroidism is intriguing but should be interpreted with caution, as this may be related to preclinical weight loss associated with the disease.

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