



# Iodine-Induced Hyperthyroidism and Long-term Risks of Incident Atrial Fibrillation and Flutter

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## Abstract

**Context:** Although iodine-induced hyperthyroidism is a potential consequence of iodinated radiologic contrast administration, its association with long-term cardiovascular outcomes has not been previously studied.

**Objective:** To investigate the relationships between hyperthyroidism observed after iodine contrast administration and incident atrial fibrillation/flutter.

**Methods:** Retrospective cohort study of the U.S. Veterans Health Administration (1998-2021) of patients age  $\geq 18$  years with a normal baseline serum thyrotropin (TSH) concentration, subsequent TSH  $< 1$  year, and receipt of iodine contrast  $< 60$  days before the subsequent TSH. Cox proportional hazards regression was employed to ascertain the adjusted hazard ratio (HR) with 95% CI of incident atrial fibrillation/flutter

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- Iodine is a micronutrient essential for thyroid hormone production, for which the recommended intake for US adults is 150  $\mu\text{g}$  daily.
  - Iodine is present in contrast medium that is commonly required for radiologic studies
  - a single dose of iodine contrast administered for CTscans, coronary angiography, and other radiologic procedures may contain up to 13 500  $\mu\text{g}$  of free iodine and 15 to 60g of bound iodine, amounts that equate to several hundred times the recommended daily requirement for iodine
  - Iodine-induced hyperthyroidism is a well-recognized clinical entity that results from the **Jöd-Basedow** phenomenon



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- The risks of hyperthyroidism may be particularly concerning among older individuals
  - Atrial fibrillation may be seen in up to 60% of individuals with hyperthyroidism
  - we conducted a cohort study of the U.S. Veterans Health Administration to investigate the associations between iodine-induced hyperthyroidism and the incident risks of atrial fibrillation/flutter.
  - Given the older age and high prevalence of comorbidities in U.S. Veterans , including cardiovascular disease burden this population may be particularly vulnerable to the adverse effects of hyperthyroidism.
  - A better understanding of these relationships would help clinicians consider the importance of monitoring for hyperthyroidism following iodinated contrast use in select population subgroups.

# MATERIALS AND METHODS

## STUDY DESIGN AND POPULATION

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- study population was extracted from the Veterans Affairs (VA) Corporate Data Warehouse database, from all U.S. Veterans Health Administration patients in both hospitalized and ambulatory settings, from March 10, 1988, to October 20, 2021.
- eligible sample included adults aged  $\geq 18$  years with a follow-up TSH measurement within 60 days after iodine contrast administration, and up to 1 year of a normal baseline serum TSH concentration.
- We then excluded subjects with a history of hypothyroidism, hyperthyroidism, atrial fibrillation/flutter, heart failure, thyroid surgery, thyroid cancer, radioactive iodine treatment, use of thyroid hormone or antithyroid medications, and use of other medications that may alter serum thyroid function
- The study was approved by the VA Greater Los Angeles Healthcare System Institutional Review Board.

# ASCERTAINMENT OF IODINE-INDUCED HYPERTHYROIDISM

## AND ATRIAL FIBRILLATION/FLUTTER

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- Our exposure was defined by a follow-up serum TSH measurement less than the lower limit of each VA site-specific reference range within 60 days after iodine contrast administration, and restricted to only those TSH values available up to 1 year after a normal baseline serum TSH level.
- Hyperthyroid individuals with available T3 and/or T4 concentrations were further categorized into overt hyperthyroidism (decreased TSH and elevated T3 and/or T4 levels) and subclinical hyperthyroidism (decreased TSH and normal T3 and/or T4 levels).
- Iodine contrast administration was determined using ICD-9 and ICD-10 codes of radiologic procedures that employed iodinated contrast media (Table 1B (11)).
- The outcome was atrial fibrillation/flutter identified using ICD-9 and ICD-10 codes



# STATISTICAL ANALYSES

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- Inverse propensity score–weighted cumulative incidence curves for incident atrial fibrillation were generated according to thyroid status, with weight adjusting for age, sex, race/ethnicity, body mass index, and history of coronary heart disease, dyslipidemia, diabetes, and hypertension.
- We then employed Cox proportional hazards regression models to estimate the adjusted hazard ratio (HR) with 95% CI of the association between iodine-induced hyperthyroidism and incident atrial fibrillation/flutter, adjusting for age, sex, race/ethnicity, body mass index, and history of coronary heart disease, dyslipidemia, diabetes, and hypertension.
- The date of the follow-up TSH result was designated as time 0 relative to incident atrial fibrillation/flutter.
- To evaluate the heterogeneity in the association by demographic characteristics, we also stratified the analyses by sex (male, female), age (<65 years, ≥ 65 years), and race/ethnicity (Hispanic, non-Hispanic White, non-Hispanic Black, and non-Hispanic others). Statistical significance was defined as 2-sided  $\alpha < .05$ .

# STATISTICAL ANALYSES

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- We also conducted the following 3 sensitivity analyses.
- First, we reanalyzed the data using 2 shorter thresholds of the duration (ie, up to 12 and up to 24 months), in addition to our main analysis performed without time restriction, of the date of atrial fibrillation/flutter during long-term follow-up.
- Second, we assessed the strength of the association according to the type of radiologic study requiring iodinated contrast (ie, iodinated CT scans, angiograms, venograms, cystograms, hysterosalpingograms, urograms, and other iodinated radiologic procedures).
- Third, we calculated the E value to quantify association between an unmeasured confounder and both the exposure (iodine-induced hyperthyroidism) and the outcome (atrial fibrillation/flutter), conditional on the measured covariates, to determine whether or not this could explain the observed overall exposure–outcome association (14).
- All analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC).

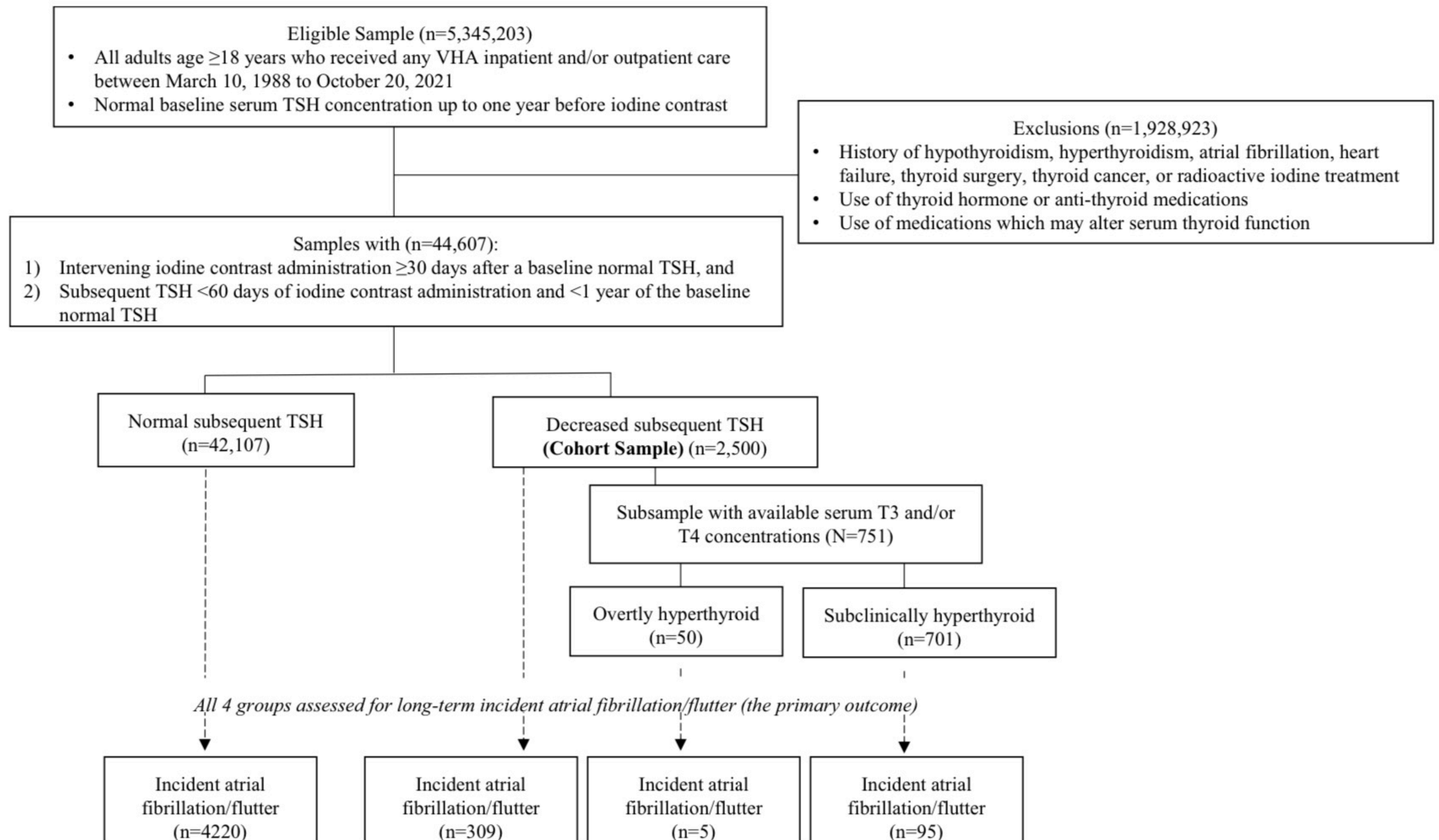
# RESULTS

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Among 44 607 Veterans defined as our cohort sample (mean  $\pm$  SD age,  $60.9 \pm 14.1$  years; 88% men), there were 2500 (5.6%) individuals found to be hyperthyroid (mean  $\pm$  SD TSH,  $0.30 \pm 0.18$  mIU/L) within 60 days after iodine contrast exposure and a previously normal baseline serum TSH (Fig. 1).

Hyperthyroid individuals were more likely to be female and non-Hispanic Black than those who were euthyroid





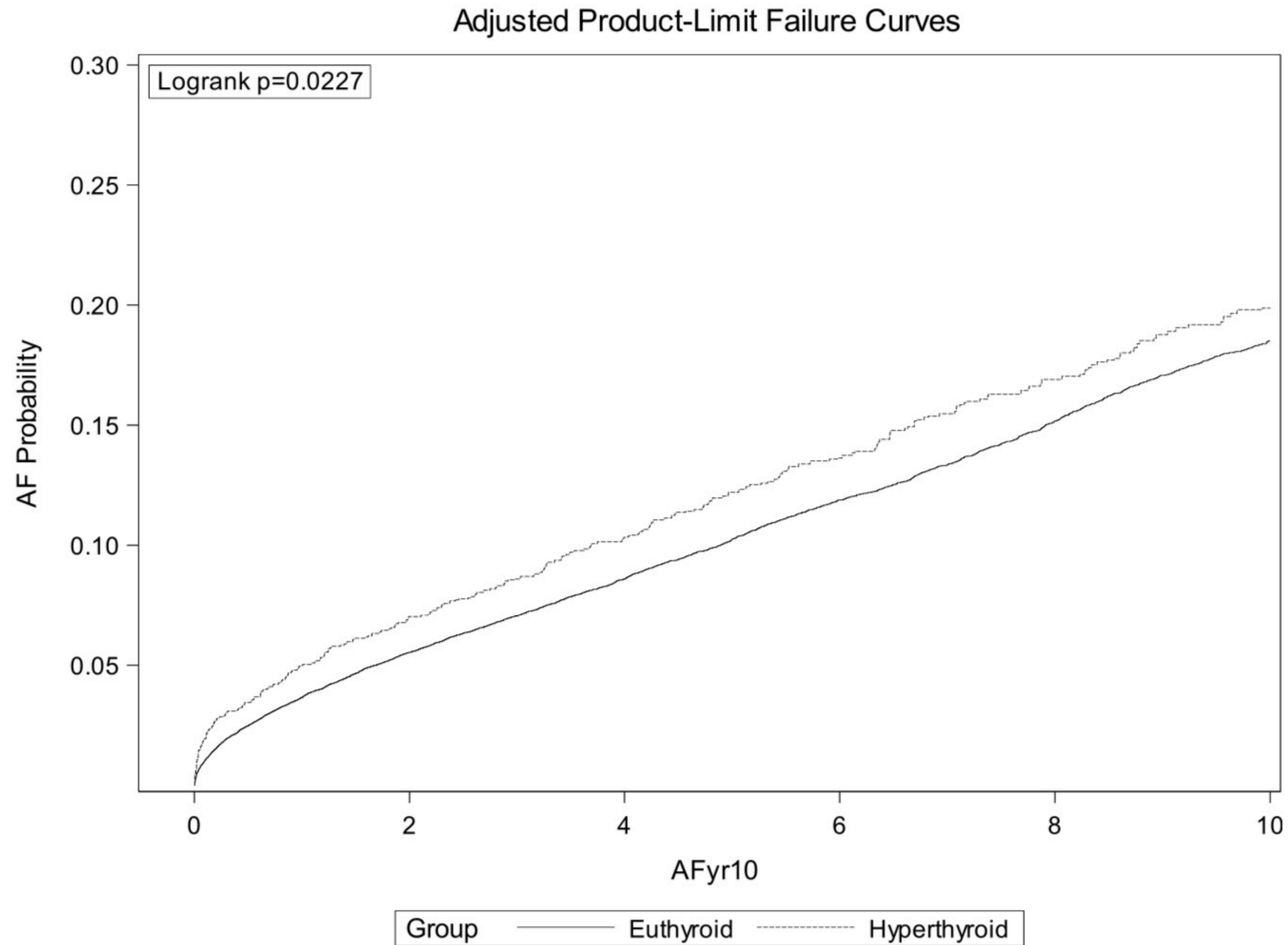
**Figure 1.** Flow chart of study sample selection.

# HYPERTHYROIDISM FOLLOWING IODINE EXPOSURE AND

## INCIDENT ATRIAL FIBRILLATION

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- Over a median follow-up period of 3.7 years (IQR 1.9-7.4), **atrial fibrillation/flutter** was observed in 4629 (10.4%) individuals, composed of 409 individuals who had developed **hyperthyroidism** following iodine exposure and 4220 who had remained **euthyroid** following iodine exposure (Fig. 1).
- In Cox regression models adjusting for sociodemographic and cardiovascular risk factors, hyperthyroidism after iodine exposure in the setting of a previously normal baseline TSH was associated with an **increased risk of atrial fibrillation** (HR 1.19, 95% CI 1.06-1.33; Fig. 2);



**Figure 2.** Cumulative incidence of atrial fibrillation according to thyroid function (euthyroid vs hyperthyroid) following iodine exposure.



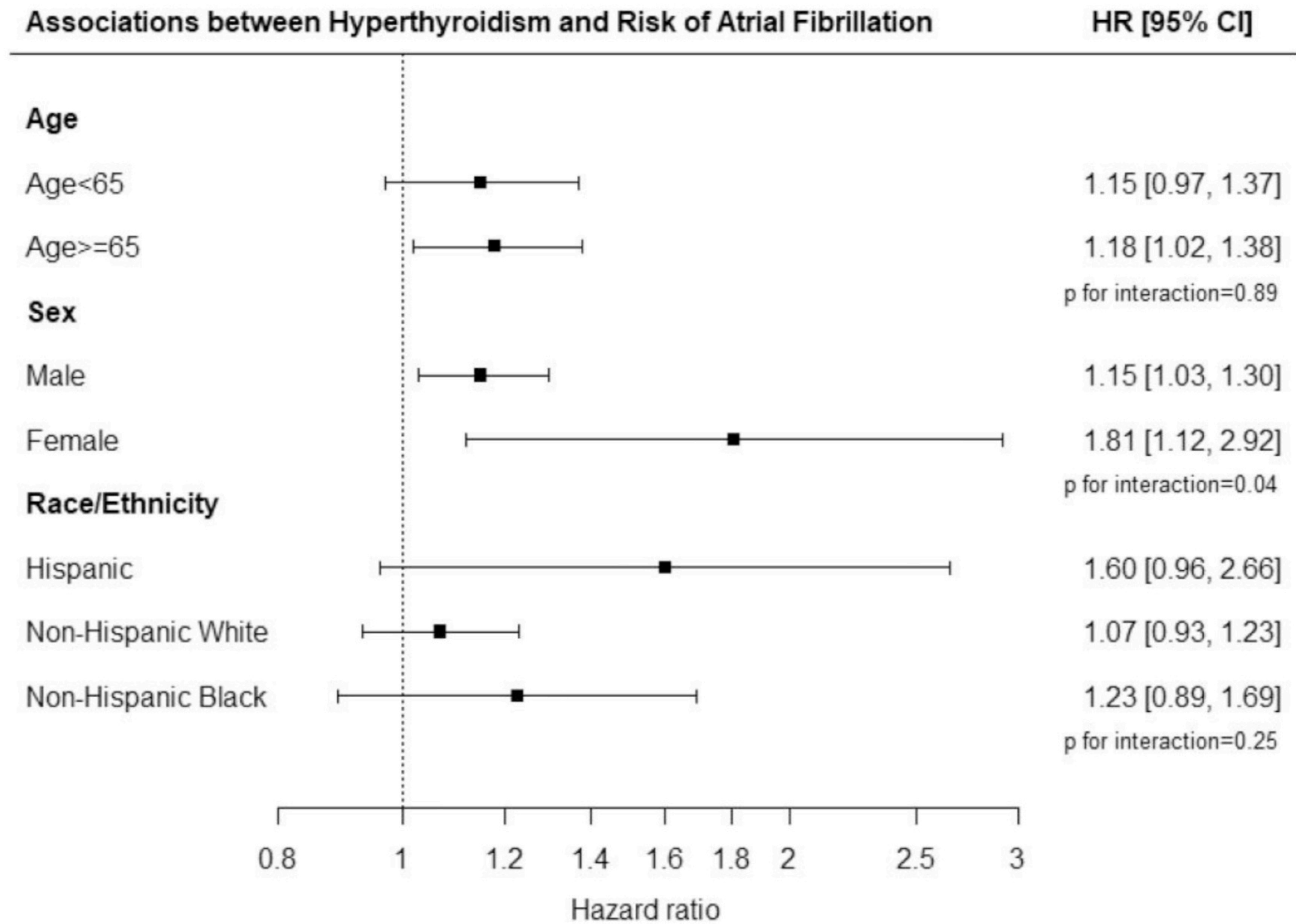
# STRATIFIED ANALYSES BY AGE, SEX, AND RACE/ETHNICITY

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- we found **no** evidence of heterogeneity in the **association** between hyperthyroidism following an iodine load and atrial fibrillation/flutter by **age** (Fig. 3).
- The association was stronger among **females** than males (females, HR 1.81, 95% CI 1.12-2.92; males, HR 1.15, 95% CI 1.03-1.30; P for interaction between hyperthyroidism and sex = .04).
- Across race/ethnicity, the association was the strongest among **Hispanic** (HR 1.60, 95% CI 0.96-2.66) followed by non-Hispanic Black (HR 1.23, 95% CI 0.89-1.69) and non-Hispanic White (HR 1.07, 95% CI 0.93-1.23), although the estimates did not have enough statistical power to detect heterogeneity due to limited sample size.

**Table 1. Demographic characteristics of the study cohort**

Demographic characteristics	Total (n = 44 607)	Euthyroid after iodine exposure (n = 42 107)	Hyperthyroid after iodine exposure (n = 2500)
Age (years, mean $\pm$ SD)	60.9 $\pm$ 14.1	61.0 $\pm$ 14.2	60.3 $\pm$ 13.4
Sex, n (%)			
Female	5550 (12)	5211 (12)	339 (14)
Age (years, mean $\pm$ SD)	45.1 $\pm$ 13.4	45.0 $\pm$ 13.4	46.3 $\pm$ 13.9
Male	39 057 (88)	36 896 (88)	2161 (86)
Age (years, mean $\pm$ SD)	63.2 $\pm$ 12.7	63.2 $\pm$ 12.8	62.5 $\pm$ 11.9
Race/Ethnicity, n (%)			
Hispanic	2804 (6)	2689 (6)	115 (5)
Non-Hispanic Black	8322 (19)	7625 (18)	697 (28)
Non-Hispanic Other	1490 (3)	1402 (3)	88 (4)
Non-Hispanic White	27 594 (62)	26 244 (62)	1350 (54)
Missing	4397 (10)	4147 (10)	250 (10)
Body mass index (mg/kg <sup>2</sup> ), mean $\pm$ SD	28.5 $\pm$ 6.3	28.6 $\pm$ 6.4	27.6 $\pm$ 6.2
Serum thyrotropin (mIU/L), mean $\pm$ SD	1.7 $\pm$ 1.0	1.8 $\pm$ 0.9	0.3 $\pm$ 0.2
History of coronary heart disease, n (%)	11 351 (25)	10 726 (25)	625 (25)
History of diabetes, n (%)	15 750 (35)	14 895 (35)	855 (34)
History of hypertension, n (%)	30 417 (68)	28 686 (68)	1731 (69)
History of dyslipidemia, n (%)	27 629 (62)	26 109 (62)	1520 (61)



**Figure 3.** Associations between hyperthyroidism and risk of atrial fibrillation by age, sex, and race/ethnicity.



# SENSITIVITY ANALYSES

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- The risks remained significant in the sensitivity analysis restricting the detection of incident atrial fibrillation/flutter to shorter durations;
- HR was 1.44 (1.19-1.75, P = .0002) for incident atrial fibrillation/flutter <12 months, and HR was 1.35 (1.15-1.59, P = .0003) for incident atrial fibrillation/flutter <24 months.

# SENSITIVITY ANALYSES

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- The sensitivity analysis examining incident atrial fibrillation/flutter by **type of radiologic study** requiring iodinated contrast **showed similar results**
- **Iodine-induced hyperthyroidism** was associated with a greater risk of atrial fibrillation/flutter compared with **those who remained euthyroid** after iodine administration, both in those who had received iodine contrast for a **CT scan** (iodine-induced hyperthyroidism, 281/2252 [12.5%]) vs iodine-induced euthyroidism, 3786/36 705 [10.3%]; HR 1.15, 95% CI 1.02-1.3, P = .0239) and in those who had received iodine contrast for all **other types of radiologic imaging** (iodine-induced hyperthyroidism, 28/248 [11.3%] vs iodine-induced euthyroidism, 434/5401 [8.0%]; HR 1.76, 95% CI 1.24-2.49, P = .0017).
- Finally, examination of the E value showed that an unmeasured confounder would need to be associated with both hyperthyroidism and incident atrial fibrillation/flutter with an HR >1.67 to explain away the observed overall association conditional on measured covariates

# DISCUSSION

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- In this cohort study of the largest integrated health care system in the United States, hyperthyroidism observed within 60 days of an acute iodine load was associated with a significantly increased risk of incident atrial fibrillation/flutter over a median follow-up of 3.7 years.
- The association was stronger among females than males. The sex-specific differences seen are notable, as women are more likely to die from atrial fibrillation-related stroke than men (15), which may be related to different thresholds of membrane potential and action potential duration between the sexes (16).



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- hyperthyroidism-related atrial fibrillation is thought to confer higher risks of ischemic stroke and systemic embolism than atrial fibrillation resulting from nonthyroidal causes (23).
  - In longitudinal epidemiologic studies, abnormally low serum TSH concentration (such as in inadequately treated Graves disease or in hypothyroidism that is over-replaced with thyroid hormone) is associated with both cardiovascular morbidity and mortality (24, 25).
  - A recent meta-analysis of 13 studies that included 649 293 participants showed that both subclinical and overt hyperthyroidism was associated with a risk of incident atrial fibrillation over a mean follow-up period of 7.1 years

- Our previous longitudinal analysis of the U.S. Veterans Health Administration system reported that there is **only a small increased risk of thyroid dysfunction following iodine contrast administration**, with **males** in particular having a higher risk (1.4-fold) than unexposed individuals (27), findings which support only targeted screening of thyroid dysfunction after iodine exposure.
- In accordance with those findings, the European Thyroid Association recommends an **individualized approach** toward whether or not to ascertain iodine-induced thyroid dysfunction after iodine administration on the basis of the **patient's age, clinical symptoms, the presence of any pre-existing thyroid diseases, coexisting morbidities, and iodine intake** (28, 29).
- In the United States, there are currently **no** clinical recommendations for the generalized screening or monitoring of at-risk patients receiving iodinated contrast radiologic scans, with the **exception of infants aged <3 years** in whom the developing thyroid gland remains immature.

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- In March 2022, the U.S. Food and Drug Administration issued guidance to screen for thyroid dysfunction within 3 weeks of intravascular iodinated contrast medium administration in **this** particularly vulnerable subgroup
  - **The present study** suggests that in the **select individuals** who are found to have iodine-induced hyperthyroidism, poses a long-term risk of atrial fibrillation/flutter, and such patients should be considered for increased monitoring.
  - At present, the mechanism for a **long- lasting effect is unknown** but may be related to alternations in cardiovascular hemodynamics following thyroid dysfunction.



# STRENGTHS

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- large sample size, use of a highly detailed demographic, medical/surgical, laboratory, radiologic, and pharmacy database, and the use of the largest integrated health care system in the United States

# LIMITATIONS

- thyroid dysfunction was denoted by an abnormal serum TSH that may not always reflect hyperthyroidism (ie, nonthyroidal acute illness)
- we cannot rule out the possibility of unmeasured confounding between iodine-induced hyperthyroidism and atrial fibrillation, including smoking status, that we felt reflected substantial missing and/or potentially inaccurate capture in this dataset.
- However, the E value in our sensitivity analysis (1.67) indicated that it is unlikely for such unmeasured confounders to fully explain away the observed overall association between iodine-induced hyperthyroidism and atrial fibrillation.
- caution is needed when extrapolating our results to external populations, given that VA data are composed primarily of older, non-Hispanic, White men.

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- In summary,
  - among US adults, **hyperthyroidism** following iodine exposure was associated with a **significantly increased risk** of incident atrial **fibrillation/flutter** over a median follow-up of 3.7 years.
  - Given the high prevalence of asymptomatic atrial fibrillation/flutter in elderly people, and increased risk of stroke and systemic embolism in patients with atrial fibrillation/flutter, the **European, Canadian, and Australian** guidelines currently advocate for the **universal screening of atrial fibrillation in those age  $\geq 65$  years**
  - Regarding the population analyzed in the current study, we believe the present data support the need for further research to refine the clinical significance of this issue.



# CONCLUSION

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- **Hyperthyroidism** following a **high iodine load** was associated with an **increased risk of incident atrial fibrillation/flutter**, particularly among **females**.
- The observed sex-based differences should be confirmed in a more sex-diverse study sample,
- and the cost–benefit analysis of long-term monitoring for cardiac arrhythmias following iodine-induced hyperthyroidism should be evaluated.