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ORIGINAL RESEARCH

Iodine-Induced Hypothyroidism and Long-Term Risks of Incident Heart Failure

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BACKGROUND: Although most individuals can adapt to a large iodine load and remain euthyroid, hypothyroidism can develop after iodine exposure. Hypothyroidism is associated with adverse cardiovascular consequences, including heart failure. This study was performed to investigate the relationships between iodine-induced hypothyroidism and incident heart failure.

METHODS AND RESULTS: This cohort study of the US Veterans Health Administration (1998–2021) included adults aged ≥18 years with a serum thyroid-stimulating hormone (thyrotropin) <60 days of iodine contrast administration, and <1 year of a baseline normal serum thyroid-stimulating hormone. Cox proportional hazards regression ascertained risk of incident heart failure following iodine-induced hypothyroidism, adjusting for age, sex, race and ethnicity, body mass index, and history of coronary heart disease, dyslipidemia, diabetes, and hypertension. Of 45 470 veterans (mean±SD age, 61.1±14.1 years; 88% men), 3361 (7.4%) developed iodine-induced hypothyroidism. Heart failure developed in 5685 (12.5%) individuals over a median follow-up of 3.6 years (interquartile range, 1.9–7.2 years). Adjusted for risk factors, iodine-induced hypothyroidism was associated with increased risk of heart failure, compared with those who remained euthyroid after iodine exposure (adjusted hazard ratio [HR], 1.11 [95% CI, 1.01–1.22]). Women were at greater risk than men (adjusted HR: women, 1.65 [95% CI, 1.13–2.40]; men, 1.08 [95% CI, 0.98–1.19]; *P* for interaction, 0.02).

CONCLUSIONS: In the largest US study of this topic, hypothyroidism following iodine exposure was associated with an increased risk of incident heart failure, particularly in women. These findings support the need for further research to address the clinical significance of this issue, including the possible sex-specific risks of incident heart failure in more diverse data sets and study populations.

Key Words: heart failure ■ hypothyroidism ■ iodine ■ thyroid dysfunction

Iodine is an essential micronutrient that is needed for the production of thyroid hormone. Use of iodinated contrast media, which is frequently required for diagnostic computed tomography scans, coronary angiograms, and other radiologic studies, represents a common source of iodine exposure in the health care settings.[1] The iodine content in iodinated contrast media is substantial; a single dose of iodinated contrast can contain up to 13 500 μg of free iodine and 15 to 60 g of bound iodine, which equate to several hundred times the daily recommended intake of iodine.[1] Although most individuals are able to adapt to excess iodine exposure,[2] our retrospective analysis of the US Veterans Healthcare Administration from 1998 to 2021 showed a nearly 40% increased risk of thyroid dysfunction within 60 days of iodine contrast administration, compared with those who had not recently received iodine contrast (hazard ratio [HR], 1.39 [95% CI, 1.37–1.41]).[3]

The thyroid and cardiovascular system are intricately related by multiple physiological mechanisms, including thyroid hormone–mediated effects on heart

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CLINICAL PERSPECTIVE

What Is New?

- These findings propose iodine contrast administration as a novel risk factor for the development of heart failure following iodine-induced hypothyroidism.

What Are the Clinical Implications?

- The use of iodine contrast, commonly used in the medical setting with the potential to cause hypothyroidism, may require closer attention for the development of heart failure.
- These findings support the need for further research to address the clinical significance of this issue, including the possible sex-specific risks of incident heart failure in more diverse data sets and study populations.

Nonstandard Abbreviations and Acronyms

TSH	thyroid-stimulating hormone
VA	Veterans Affairs
VHA	Veterans Health Administration

rate, rhythm, myocardial contraction, risk of coronary artery disease, regulation of blood pressure via smooth muscle tone and endothelial function, and regulation of blood pressure via cardiovascular risk factors (lipid metabolism and modulation of inflammatory pathways).[4] At our institution, we reported that correction of hypothyroidism may obviate the need for lipid-lowering medications in up to 75% of patients with newly diagnosed dyslipidemia.[5]

Low thyroid hormone has been associated with various cardiovascular risk factors, including diastolic hypertension, weight gain, insulin resistance, hypercholesterolemia, and dyslipidemia.[6,7] Hypothyroidism, particularly with serum thyroid-stimulating hormone (TSH) concentrations ≥10 mIU/L, has been associated with higher risk of heart failure, as was shown in a meta-analysis of 6 prospective cohorts from the United States and Europe,[8] as well as that of 11 prospective cohorts totaling 55 287 participants (542 494 person-years of follow-up) between 1972 and 2007.[9] According to the data from the US National Health and Nutrition Examination Survey III, heart failure in individuals with hypothyroidism was associated with increased overall mortality, compared with euthyroid individuals.[10] Several other analyses have independently shown increased risks of both cardiovascular and all-cause mortality among subclinically hypothyroid individuals compared with euthyroid individuals.[9,11–13]

To address this knowledge gap and in alignment with a 2019 white paper calling for additional research on the interrelationships between thyroid and cardiovascular diseases,[14,15] we conducted a population-based study of the US Veterans Health Administration (VHA) to investigate the associations between iodine-induced hypothyroidism and the incident risks of heart failure. Given the older age and high prevalence of comorbidities among US veterans,[16] including cardiovascular disease burden,[17] this population may be particularly susceptible to the adverse effects of hypothyroidism. Further understanding of these relationships can guide the need for monitoring thyroid function and of cardiac events following iodinated contrast administration in select population subgroups.

METHODS

Study Design and Population

This study used records from the Veterans Affairs (VA) Corporate Data Warehouse from March 10, 1988 to October 20, 2021. The Corporate Data Warehouse is the national data repository of clinical and administrative records in the US VHA system, and includes patients in both hospitalized and ambulatory settings. Subjects' informed consent was waived, and study approval was obtained by the VA Greater Los Angeles Healthcare System Institutional Review Board. The data supporting this study are available from the corresponding author on reasonable request.

Inclusion criteria were adults aged ≥18 years with an available TSH measured within 60 days of iodine contrast administration, and at least 30 days up to 1 year of a normal serum TSH level at baseline. Exclusion criteria were individuals 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, which can interfere with serum thyroid function test results (Table S1). To extract non-VA drug use and non–Corporate Data Warehouse electronic medical records,[18] we also retrieved and cross-referenced exclusion criteria against the VA Observation Medical Partnership Database.[19] The flow of the study sample selection is shown in Figure 1.

Ascertainment of Exposure and Outcome

We determined iodine contrast administration using *International Classification of Diseases, Ninth Revision* (*ICD-9*), and *International Classification of Diseases, Tenth Revision* (*ICD-10*), codes of radiologic procedures requiring iodinated contrast media (Table S2). As the primary exposure, we defined iodine-induced hypothyroidism as a serum thyrotropin (TSH) measurement

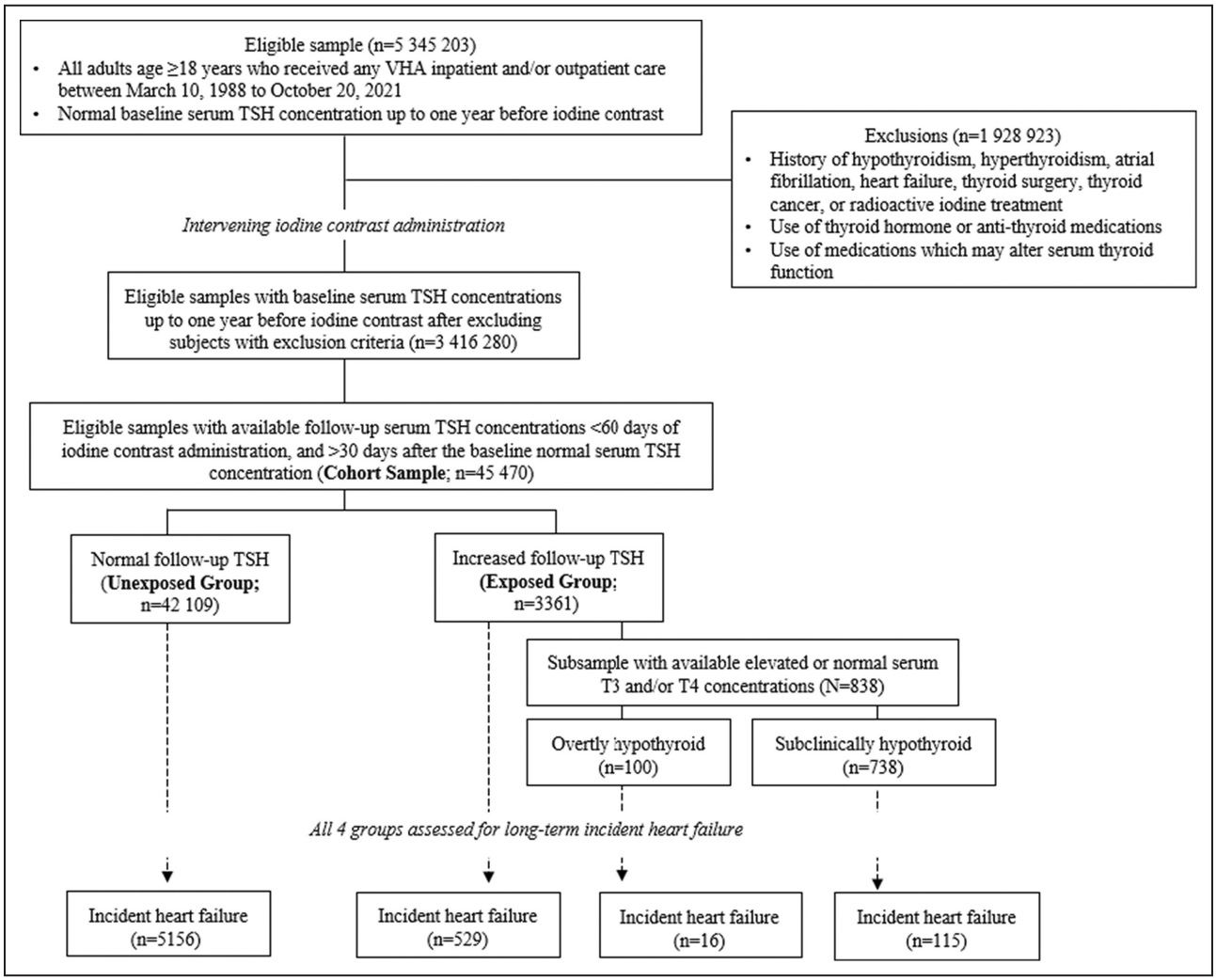

Figure 1. Flow of study sample selection.
T3 indicates triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; and VHA, Veterans Health Administration.

higher than the upper limit of VA site-specific reference ranges within 60 days after iodine contrast administration, and at least 30 days up to 1 year of a normal baseline serum TSH level. We also subclassified those with hypothyroidism in 2 ways: (1) by serum peripheral thyroid hormone thyroxine and triiodothyronine within 90 days after an abnormal TSH result, according to their VA site-specific reference ranges, to distinguish between overt hypothyroidism and subclinical hypothyroidism; and (2) by TSH levels (<7.5 and ≥7.5 mIU/L).

Similarly, we defined the outcome of heart failure using the *ICD-9* and *ICD-10* codes 428.X and I50.X, respectively, where X denotes any number.

Other Covariates

Covariates, including age, sex, self-reported race and ethnicity (adults of Hispanic, non-Hispanic White, non-Hispanic Black, and non-Hispanic other races and ethnicities [composed of Alaska Native, American Indian or Native American, Asian, or multiracial]), and body mass index, were extracted, with body mass index recorded as the most proximal value to the TSH measurement (up to 1 year before or after). Reporting race and ethnicity in this study was mandated by the US Department of Veterans Affairs, consistent with its Inclusion of Women, Minorities, and Children policy. The following comorbidities were also extracted for each subject using *ICD-10* codes: coronary heart disease (I21, I22, I23, I24, and I25), dyslipidemia (E78), diabetes (E08, E09, E11, and E13), and hypertension (I10, I11, I12, I13, I15, and I16).

Statistical Analysis

After providing the summary statistics of the study sample, we created inverse probability-weighted cumulative incidence curves for incident heart failure based on thyroid status, with the inverse probability weights adjusted for age, sex, race and ethnicity, body mass index, and

a history of coronary heart disease, dyslipidemia, diabetes, and hypertension. Then, using multivariate Cox proportional hazards regression models, we calculated the adjusted HR (aHR) with 95% CIs to examine the relationship between iodine-induced hypothyroidism and incident heart failure. We also examined the risk of incident heart failure of the following subtypes of thyroid dysfunction by calculating their aHRs with euthyroidism as the reference: (1) subclinical hypothyroidism and overt hypothyroidism; and (2) TSH <7.5 mIU/L and TSH ≥7.5 mIU/L. All aHRs were adjusted for age, sex, race and ethnicity, body mass index, and history of coronary heart disease, dyslipidemia, diabetes, and hypertension. We also computed the *E*-value to quantify the minimum strength of the association of an unmeasured confounder with both iodine-induced hypothyroidism (the exposure) and heart failure (the outcome) conditional on the measured covariates, to explain away the observed exposure-outcome association.[20]

Last, we conducted the stratified analyses for the association between overall hypothyroidism following iodine contrast exposure and incident heart failure by sex (men and women), age (<65 and ≥65 years), and race and ethnicity (Hispanic, non-Hispanic White, non-Hispanic Black, and non-Hispanic other race and ethnicity). All analyses were performed with SAS, version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Among 45 470 veterans included in this study (mean±SD age, 61.1±14.1 years; 88% men), 3361 (7.4%) developed hypothyroidism (mean TSH, 6.73±6.81 mIU/L) after a previously normal baseline serum TSH and within 60 days after iodine contrast administration. Compared with those who remained euthyroid, those who developed hypothyroidism were more likely to be older and non-Hispanic White adults, and showed a slightly higher prevalence of comorbidities (Table 1). This pattern was also observed among subjects with subclinical hypothyroidism or TSH levels <7.5 mIU/L, but not among those with overt hypothyroidism or TSH levels ≥7.5 mIU/L (Tables S3 and S4).

Iodine-Induced Hypothyroidism and Incident Heart Failure

Over a median follow-up period of 3.6 years (interquartile range, 1.9–7.2 years), new-onset heart failure was observed in 5685 (12.5%) subjects. After adjusting for sociodemographic and cardiovascular risk factors in the multivariate Cox regression models, overall hypothyroidism after a previously normal baseline TSH and iodine administration was associated with an increased risk of heart failure (aHR, 1.11 [95% CI, 1.01–1.22]; Figure 2). The *E*-value was 1.46, showing that an unmeasured confounder would need to be associated with both hypothyroidism and incident heart failure, with a risk ratio >1.46 conditional on measured covariates to explain away this observed association.

For the association between the subtypes of iodine-induced hypothyroidism (ie, subclinical or overt hypothyroidism, based on triiodothyronine and thyroxine values) and incident heart failure, subclinical hypothyroidism was associated with an increased risk of heart failure

Table 1. Demographic Characteristics of the Study Cohort

Demographic characteristics	Total (N=45 470)	Euthyroidism (N=42 109)	Overall hypothyroidism (N=3361)
Age, mean±SD, y	61.1±14.1	61.0±14.2	62.7±13.1
Sex, n (%)			
Women	5583 (12)	5211 (12)	372 (11)
Men	39 887 (88)	36 898 (88)	2989 (89)
Race and ethnicity, n (%)			
Hispanic	2906 (6)	2689 (6)	217 (6)
Non-Hispanic White	28 629 (63)	26 245 (62)	2384 (71)
Non-Hispanic Black	7944 (17)	7625 (18)	319 (9)
Non-Hispanic other*	1495 (3)	1402 (3)	93 (3)
Missing	4496 (10)	4148 (10)	348 (10)
BMI, mean±SD, mg/kg^2	28.6±6.4	28.6±6.4	28.8±6.7
Serum TSH, mean±SD, mIU/L	2.13±2.38	1.78±0.93	6.73±6.81
History of coronary heart disease, n (%)	11 656 (26)	10 727 (25)	929 (28)
History of diabetes, n (%)	16 175 (36)	14 896 (35)	1279 (38)
History of hypertension, n (%)	31 041 (68)	28 688 (68)	2353 (70)
History of dyslipidemia, n (%)	28 289 (62)	26 111 (62)	2178 (65)

BMI indicates body mass index; and TSH, thyroid-stimulating hormone.
*Non-Hispanic other race is composed of Alaska Native, American Indian or Native American, Asian, or multiracial adults.

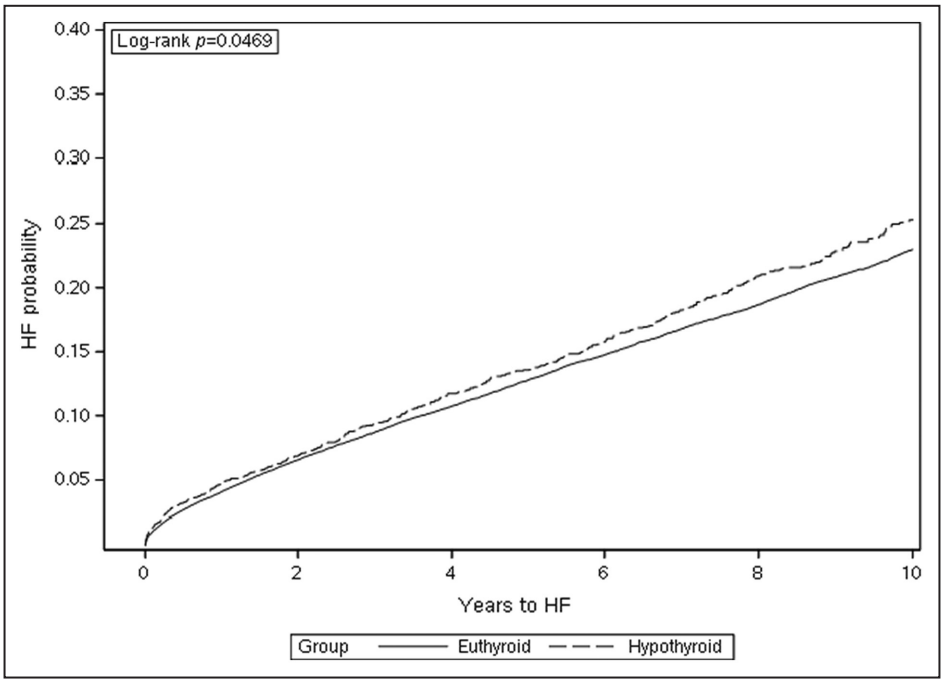

Figure 2. Cumulative incidence of heart failure (HF) according to thyroid function (euthyroid vs hypothyroid) following iodine exposure.
The adjusted hazard ratio (aHR) was calculated by Cox proportional hazard models adjusting for age, sex, race and ethnicity, body mass index, and history of coronary heart disease, diabetes, dyslipidemia, and hypertension. Inverse probability weight obtained used these variables was applied to draw the adjusted incidence curve. Overall hypothyroidism after a previously normal baseline thyroid-stimulating hormone and iodine administration was associated with an increased risk of heart failure (aHR, 1.11 [95% CI, 1.01–1.22]). The *E*-value for the point estimate (and the lower bound of 95% CI) was 1.46 (1.11).

(aHR, 1.26 [95% CI, 1.04–1.52]), whereas no association was observed for overt hypothyroidism attributable to a limited number of events (16 cases of new-onset heart failure) (Table 2). When we subclassified hypothyroidism according to TSH levels, those with a mildly elevated TSH level (<7.5 mIU/L) showed increased risk of incident heart failure (aHR, 1.24 [95% CI, 1.02–1.52]), whereas those with TSH ≥7.5 mIU/L showed an increased risk but was not statistically significant (aHR, 1.26 [95% CI, 0.84–1.88]; 23 cases of new-onset heart failure).

Table 2. Cumulative Incidence of Heart Failure According to Iodine-Induced Hypothyroidism Subtypes

Exposure	No. of events/ total samples	Adjusted hazard ratio (95% CI)*	*P* value	*E*-value (lower bound of 95% CI)†
Hypothyroidism				
Euthyroidism	5156/42 109	Reference	Reference	Reference
Subclinical hypothyroidism	115/738	1.26 (1.04–1.52)	0.0161	1.83 (1.24)
Overt hypothyroidism	16/100	0.92 (0.53–1.59)	0.7597	NA
TSH categories				
Reference range TSH	5156/42 109	Reference	Reference	Reference
Increased TSH levels <7.5 mIU/L	104/634	1.24 (1.02–1.52)	0.0327	1.79 (1.16)
Increased TSH levels ≥7.5 mIU/L	23/179	1.26 (0.84–1.88)	0.2670	1.83 (NA)

NA indicates not applicable; and TSH, thyroid-stimulating hormone.
*The adjusted hazard ratio was calculated by Cox hazard models adjusting for age, sex, race and ethnicity, body mass index, and history of coronary heart disease, diabetes, dyslipidemia, and hypertension.
†The *E*-value is a measure of how strongly an unmeasured confounder is associated with both the treatment and the result, conditional on the measured covariates, to explain away the observed associations between iodine-induced hypothyroidism and heart failure. The *E*-value for the lower bound of 95% CI is shown in parentheses.

Stratified Analyses by Age, Sex, and Race and Ethnicity

In stratified analyses, we found that the association between iodine-induced hypothyroidism and heart failure was stronger among women than men (aHR: women, 1.65 [95% CI, 1.13–2.40]; men, 1.08 [95% CI, 0.98–1.19]; *P* for interaction between hypothyroidism and sex, 0.02; Figure 3). We found no evidence of heterogeneity in the association by age (*P* for interaction between hypothyroidism and age, 0.77). When stratified by race and ethnicity, the association remained among non-Hispanic Black adults (aHR, 1.38 [95% CI, 1.11–1.70]) but not among Hispanic adults (aHR, 0.92 [95% CI, 0.61–1.38]) and non-Hispanic White adults (aHR, 1.05 [95% CI, 0.93–1.18]; *P* for interaction between hypothyroidism and race and ethnicity, 0.05).

DISCUSSION

This epidemiologic study of the largest integrated health care system in the United States demonstrates that hypothyroidism observed after a normal baseline serum TSH and within 60 days of iodine contrast administration was associated with an 11% overall increased risk of heart failure in veterans, as observed over a median follow-up of 3.6 years.

The findings refine our understanding of the long-term risks of an iodine load. Our recent longitudinal analysis of the VHA data set reported an increased

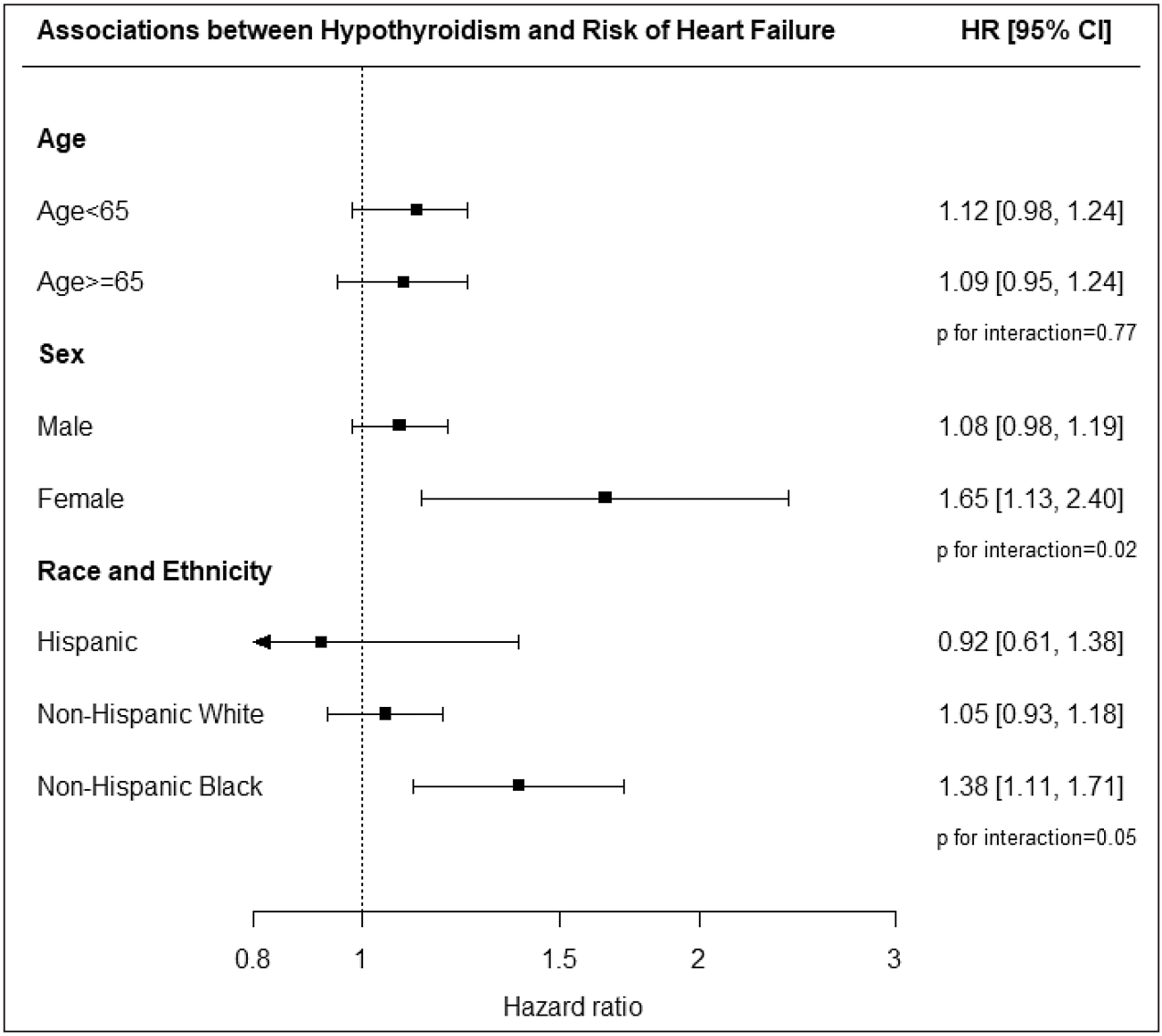

Figure 3. Associations between hypothyroidism and risk of heart failure by age, sex, and race and ethnicity.
Model adjusted for age, sex, race and ethnicity, body mass index, and history of coronary heart disease, diabetes, dyslipidemia, and hypertension. HR indicates hazard ratio.

risk of overall thyroid dysfunction (both hypothyroidism and hyperthyroidism) following iodine contrast administration, compared with individuals who had not received an iodine load (odds ratio, 1.39 [95% CI, 1.37–1.41]; $P<0.001$).[3] The United States currently does not have recommendations supporting the general screening for thyroid dysfunction after iodinated contrast administration in the general adult population (only in young infants),[21,22] and the European Thyroid Association has only recently recommended an individualized, selected approach toward such screening in adults,[23] following guidance from the European Society of Urogenital Radiology.[24] Furthermore, the long-term risk of heart failure seen in select individuals with iodine-induced hypothyroidism suggests the benefit of monitoring.

In 2017, a multidisciplinary working group convened by the National Heart, Lung, and Blood Institute at the US National Institutes of Health called for data on the intersection of thyroid status and cardiovascular disease, including sex-specific analyses.[14,15] Previous data show that women are 2 times more likely than men to develop heart failure with preserved ejection fraction.[25] It is notable that the association between iodine-induced hypothyroidism and heart failure in the current study was stronger among women than men, and there was a significant interaction between hypothyroidism and sex. One potential mechanism for these findings is the higher prevalence of thyroid autoimmunity in women[26]; the associations between cardiovascular burden and autoimmune disease in women are thought to be in part attributable to sex-specific differences in altered microvasculature and dysfunctional endothelium.[27] Because of the established low frequency of positive serum thyroid autoantibodies in men,[26] it is rarely checked in the male-predominant VHA clinical setting (this study contained 88% men), thus preventing its analysis in the current study. As such, rigorous, adequately powered studies in more sex-diverse populations focusing on sex as a biological variable are needed. It is notable that female veterans are less likely to have traditional cardiovascular risk factors, compared with male veterans.[28] A further understanding of the differential risks of iodine-induced thyroid dysfunction between women and men will allow tailored sex-based strategies for the use of iodinated contrast in health care settings.

This study represents the largest sample size available on this topic in the United States. In addition, the VHA is the largest integrated health care system in the United States and is supported by highly detailed demographic, medical/surgical, laboratory, radiologic, and pharmacy data, thereby allowing for the long-term capture of incident heart failure. Furthermore, the rigor of the study is enhanced by the criterion that iodine-induced hypothyroidism was recorded only in individuals with a previously normal baseline serum TSH concentration within the past year. These data are the first to establish the risks of heart failure following iodine-induced thyroid dysfunction.

Our study has some limitations. First, as with any database analysis, there may be bias attributable to unmeasured confounding on the relationship between iodine-induced hypothyroidism and heart failure. The *E*-value in our sensitivity analysis showed that such unmeasured confounders need to be associated with both hypothyroidism and incident heart failure, with a risk ratio >1.46 conditional on measured covariates to fully explain away the observed overall association. Second, the possibility of potential misclassifications attributable to miscoding of inclusion and exclusion criteria, iodinated contrast use, and incident heart failure is possible in any secondary analysis of an existing data set. In future analyses, it would also be important to consider heart failure diagnoses that are not solely captured by *ICD-9* or *ICD-10* coding, that, for example, include patients with heart failure associated with both reduced and preserved left ventricular ejection fractions. Third, thyroid dysfunction was ascertained by an abnormal serum TSH, which may be an imperfect measure, although all included subjects were required to have a baseline normal serum TSH before iodine exposure. In addition, the lack of association between hypothyroidism and heart failure in those with TSH levels >7.5 mIU/L may have been limited by the low event rate in this subgroup. Fourth, serum thyroid hormone levels may have been measured selectively, given the possibility that clinicians obtain such testing particularly when they suspect thyroid dysfunction; thus, it is possible that our findings may contain some selection bias. Furthermore, in this study, we also did not assess for a possible sustained nature of the thyroid dysfunction, which requires further research. Future analyses should also investigate the potential reversibility of these findings, including whether the correction of hypothyroidism with thyroid hormone replacement may mitigate the heart failure risk. Finally, caution is needed to extrapolate the study's results to other populations, given that the VA population is primarily composed of older, non-Hispanic, and White men.

In summary, this study demonstrates that in a predominantly male population of US adults, hypothyroidism following routine iodine contrast administration was associated with an 11% increased risk of incident heart failure over a median follow-up of 3.6 years. Although the results are statistically and plausibly clinically significant, the cost-benefit analysis of such long-term monitoring requires further investigation. We urge for further research to robustly study the clinical significance of this issue, including the investigation of this topic in more sex-diverse populations.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S4

REFERENCES

1. Lee SY, Rhee CM, Leung AM, Braverman LE, Brent GA, Pearce EN. A review: radiographic iodinated contrast media-induced thyroid dysfunction. *J Clin Endocrinol Metab*. 2015;100:376–383. doi: 10.1210/jc.2014-3292
2. Leung AM, Braverman LE. Consequences of excess iodine. *Nat Rev Endocrinol*. 2014;10:136–142. doi: 10.1038/nrendo.2013.251
3. Inoue K, Guo R, Lee ML, Ebrahimi R, Neverova NV, Currier JW, Bashir MT, Leung AM. Iodinated contrast administration and risks of thyroid dysfunction: a retrospective cohort analysis of the U.S. Veterans Health Administration system. *Thyroid*. 2023;33:230–238. doi: 10.1089/thy.2022.0393
4. Klein I, Danzi S. Thyroid disease and the heart. *Curr Probl Cardiol*. 2016;41:65–92. doi: 10.1016/j.cpcardiol.2015.04.002
5. Willard DL, Leung AM, Pearce EN. Thyroid function testing in patients with newly diagnosed hyperlipidemia. *JAMA Int Med*. 2014;174:287–289. doi: 10.1001/jamainternmed.2013.12188
6. Andersen MN, Olsen AM, Madsen JC, Faber J, Torp-Pedersen C, Gislason GH, Selmer C. Levothyroxine substitution in patients with subclinical hypothyroidism and the risk of myocardial infarction and mortality. *PLoS One*. 2015;10:e0129793. doi: 10.1371/journal.pone.0129793
7. Rodondi N, Newman AB, Vittinghoff E, de Rekeneire N, Satterfield S, Harris TB, Bauer DC. Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. *Arch Intern Med*. 2005;165:2460–2466. doi: 10.1001/archinte.165.21.2460
8. Gencer B, Collet TH, Virgini V, Bauer DC, Gussekloo J, Cappola AR, Nanchen D, den Elzen WP, Balmer P, Luben RN, et al. Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from 6 prospective cohorts. *Circulation*. 2012;126:1040–1049. doi: 10.1161/CIRCULATIONAHA.112.096024
9. Rodondi N, den Elzen WP, Bauer DC, Cappola AR, Razvi S, Walsh JP, Asvold BO, Iervasi G, Imaizumi M, Collet TH, et al. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA*. 2010;304:1365–1374. doi: 10.1001/jama.2010.1361
10. Rhee CM, Curhan GC, Alexander EK, Bhan I, Brunelli SM. Subclinical hypothyroidism and survival: the effects of heart failure and race. *J Clin Endocrinol Metab*. 2013;98:2326–2336. doi: 10.1210/jc.2013-1039
11. Collet TH, Bauer DC, Cappola AR, Asvold BO, Weiler S, Vittinghoff E, Gussekloo J, Bremner A, den Elzen WP, Maciel RM, et al. Thyroid antibody status, subclinical hypothyroidism, and the risk of coronary heart disease: an individual participant data analysis. *J Clin Endocrinol Metab*. 2014;99:3353–3362. doi: 10.1210/jc.2014-1250
12. Tseng FY, Lin WY, Lin CC, Lee LT, Li TC, Sung PK, Huang KC. Subclinical hypothyroidism is associated with increased risk for all-cause and cardiovascular mortality in adults. *J Am Coll Cardiol*. 2012;60:730–737. doi: 10.1016/j.jacc.2012.03.047
13. Inoue K, Ritz B, Brent GA, Ebrahimi R, Rhee CM, Leung AM. Association of subclinical hypothyroidism and cardiovascular disease with mortality. *JAMA Netw Open*. 2020;3:e1920745. doi: 10.1001/jamanetworkopen.2019.20745
14. Cappola AR, Desai AS, Medici M, Cooper LS, Egan D, Sopko G, Fishman GI, Goldman S, Cooper DS, Mora S, et al. Thyroid and cardiovascular disease research agenda for enhancing knowledge, prevention, and treatment. *Circulation*. 2019;139:2892–2909. doi: 10.1161/CIRCULATIONAHA.118.036859
15. Cappola AR, Desai AS, Medici M, Cooper LS, Egan D, Sopko G, Fishman GI, Goldman S, Cooper DS, Mora S, et al. Thyroid and cardiovascular disease: research agenda for enhancing knowledge, prevention, and treatment. *Thyroid*. 2019;29:760–777. doi: 10.1089/thy.2018.0416
16. Bloomfield H, Linsky A, Bolduc J, Greer N, Naidl T, Vardeny O, MacDonald R, McKenzie L, Wilt TJ. *Deprescribing for Older Veterans: A Systematic Review*. U.S. Department of Veterans Affairs; 2019. Accessed September 26, 2023. https://www.ncbi.nlm.nih.gov/books/NBK561691/
17. Al Rifai M, Blumenthal RS, Stone NJ, Schofield RS, Orringer CE, Michos ED, Heidenreich PA, Braun L, Birtcher KK, Smith SC, et al. Department of Veterans Affairs (VA) and U.S. Department of Defense (DoD) guidelines for management of dyslipidemia and cardiovascular disease risk reduction: putting evidence in context. *Prog Cardiovasc Dis*. 2021;68:2–6. doi: 10.1016/j.pcad.2021.08.001
18. Lynch K. The VA OMOP common data model: the basics. US Department of Veterans Affairs. 2019. Accessed March 24, 2023. https://www.hsrd.research.va.gov/for_researchers/cyber_seminars/archives/video_archive.cfm?SessionID=3632
19. Viernes B, Lynch KE, South B, Coronado G, DuVall SL. Characterizing VA users with the OMOP common data model. *Stud Health Technol Inform*. 2019;264:1614–1615. doi: 10.3233/SHTI190561
20. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the *E*-value. *Ann Intern Med*. 2017;167:268–274. doi: 10.7326/M16-2607
21. Callahan MJ, Iyer RS, Wassner AJ. Is thyroid monitoring warranted in infants and young children after intravascular administration of iodine-based contrast media? *AJR Am J Roentgenol*. 2023;220:144–145. doi: 10.2214/AJR.22.28007
22. FDA recommends thyroid monitoring in babies and young children who receive injections of iodine-containing contrast media for medical imaging. US Food and Drug Administration. 2022. Accessed March 24, 2023. https://www.fda.gov/drugs/drug-safety-and-availability/fda-recommends-thyroid-monitoring-babies-and-young-children-who-receive-injections-iodine-containing
23. Bednarczuk T, Brix TH, Schima W, Zettinig G, Kahaly GJ. 2021 European thyroid association guidelines for the management of iodine-based contrast media-induced thyroid dysfunction. *Eur Thyroid J*. 2021;10:269–284. doi: 10.1159/000517175
24. van der Molen AJ, Thomsen HS, Morcos SK; Contrast Media Safety Committee, European Society of Urogenital Radiology. Effect of iodinated contrast media on thyroid function in adults. *Eur Radiol*. 2004;14:902–907. doi: 10.1007/s00330-004-2238-z
25. Scantlebury DC, Borlaug BA. Why are women more likely than men to develop heart failure with preserved ejection fraction? *Curr Opin Cardiol*. 2011;26:562–568. doi: 10.1097/HCO.0b013e32834b7faf
26. Prummel MF, Wiersinga WM. Thyroid peroxidase autoantibodies in euthyroid subjects. *Best Pract Res Clin Endocrinol Metab*. 2005;19:1–15. doi: 10.1016/j.beem.2004.11.003
27. Gianturco L, Bodini BD, Atzeni F, Colombo C, Stella D, Sarzi-Puttini P, Drago L, Galaverna S, Turiel M. Cardiovascular and autoimmune diseases in females: the role of microvasculature and dysfunctional endothelium. *Atherosclerosis*. 2015;241:259–263. doi: 10.1016/j.atherosclerosis.2015.03.044
28. Whitehead AM, Maher NH, Goldstein K, Bean-Mayberry B, Duvernoy C, Davis M, Safdar B, Saechao F, Lee J, Frayne SM, et al. Sex differences in veterans' cardiovascular health. *J Womens Health (Larchmt)*. 2019;28:1418–1427. doi: 10.1089/jwh.2018.7228