IODINATED CONTRAST ADMINISTRATION AND RISKS OF THYROID DYSFUNCTION: A RETROSPECTIVE COHORT ANALYSIS OF THE U.S. VETERANS HEALTH ADMINISTRATION SYSTEM

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Iodine is a micronutrient essential for thyroid hormone production, with 150 lg per day as the recommended intake for adults in the United States. Iodinated contrast media is commonly used in several types of radiologic studies. Since computed tomography (CT) scans were first introduced in the 1970s, their annual use has climbed to >70 million scans in the United States, while >1 million coronary angiograms are performed annually in the United States for cardiac catheterization procedures. A single dose of iodinated contrast administered for CT scans, coronary angiography, and other radiologic procedures can contain up to 13,500 lg of free iodine and 15–60 g of bound iodine, which is equivalent to several hundred times the recommended daily iodine intake.

- Following exposure to an iodinated contrast agent, iodine stores in the body remain raised up to several months to provide a continuous supply of iodine, thereby increasing the risk of iodine-induced serum thyroid dysfunction.

  Although most individuals are able to adapt to the high iodine load, certain susceptible subgroups (e.g., those with a history of thyroid disease and/or thyroid nodules) are at risk for thyroid dysfunction (i.e., hypothyroidism or hyperthyroidism).

This can occur after only a single exposure to an iodine-rich substance, as a result of two well-established physiologic principles in thyroidology: the failure to escape from the acute Wolff–Chaikoff effect (resulting in hypothyroidism) and the Jod–Basedow phenomenon (resulting in hyperthyroidism).5 Small series have shown that subjects exposed to high amounts of iodine have mildly low serum thyroid hormone levels and compensatory increased serum thyrotropin (TSH) to the upper limit of the normal range.

Similarly, iodine-induced hyperthyroidism might be transient or permanent, and risk factors include nontoxic or diffuse nodular goiter, latent Graves' disease, and chronic iodine deficiency. The risks of iodine-induced thyroid dysfunction are particularly pertinent in older individuals, in whom the adverse effects of hyperthyroidism and hypothyroidism may worsen underlying health conditions.

The U.S. Veteran population is at high risk for the adverse effects of thyroid dysfunction, given this group's older age and high prevalence of comorbidities; yet the association between routine medical iodine exposure and serum thyroid dysfunction has not been examined in this group. Moreover, thyroid dysfunction is an established risk factor for multiple adverse cardiovascular outcomes, including atrial fibrillation, congestive heart failure, and cardiovascular mortality10–12 potentially exacerbating the elevated cardiovascular disease burden present in the Veteran population.13 In this large population-based study of the Veterans Health Administration (VHA), we investigated the association between exposure to an iodine load and incident thyroid dysfunction employing repeated measurements of serum thyroid function.

Methods

A population-based retrospective cohort study was performed using the Veterans Affairs Corporate Data Warehouse (CDW) database, the national repository of clinical and administrative records from all U.S. VHA inpatients and outpatients, for the period from March 10, 1988 to October 20, 2021. The study sample included adults (age ‡18 years) with at least one pair of serum TSH measurements, consisting of a normal baseline TSH and a subsequent TSH within the ensuing year. Each subject was eligible to contribute ‡1 pair of TSH measurements (maximum pairs = 29) to the analyses, depending on the number and results of serum TSH levels recorded. Subjects with a history of hypothyroidism, hyperthyroidism, thyroid surgery, thyroid cancer, radioactive iodine treatment, use of thyroid hormone or anti-thyroid medications, and use of other medications that may alter serum thyroid function were excluded .

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF THE STUDY COHORT

Patient-level data	
No. of patients	4,253,119
Sex, *n* (%)	
Male	92.9%
Female	7.1%
Race/ethnicity, *n* (%)	
Hispanic	5.7%
Non-Hispanic Black	14.3%
Non-Hispanic White	65.6%
Non-Hispanic Other	3.3%
Missing	11.2%
TSH pair-level data	
No. of TSH pairs	8,729,155
Age (years), mean ± SD	63.5 ± 14.3
Male	64.5 ± 13.7
Female	48.8 ± 14.5
Baseline serum TSH (mIU/L)	1.8 ± 0.9
Duration between baseline TSH and subsequent TSH (days), *n* (%)	
30–89	8.0%
90–179	21.1%
180–269	33.0%
270–365	37.9%
eGFR ($mL \cdot min^{-1}/1.73\,m^2$), *n* (%)	
<15	0.6%
15 to 30	1.9%
30 to ≤45	1.8%
45 to ≤60	5.3%
60 to ≤90	33.8%
>90	6.2%
Missing	50.4%
Duration between iodine exposure and follow-up TSH (days)[a], mean ± SD	145.6 ± 94.4

[a]This was calculated among TSH pairs with intervening iodine contrast exposure.
TSH, thyrotropin.

Iodine exposure was determined using International Classification of Diseases, Ninth Revision (ICD-9) and ICD-10 codes of radiologic procedures requiring iodinated contrast media (Supplementary Table S2). We extracted TSH pairs, characterized by a normal baseline TSH followed by a subsequent TSH at least 30 days later and up to one year. Each patient could contribute multiple TSH pairs, but any individual with an abnormal serum TSH following iodine exposure was then censored from the ability to contribute any subsequent available TSH values (Fig. 1).

The primary outcome was serum thyroid dysfunction, as defined by an abnormal TSH following a normal baseline TSH within one year (each VHA site has its own site-specific TSH reference range used to classify values as normal or abnormal). Secondary analyses were performed to stratify the subtypes of thyroid dysfunction (overt hypothyroidism, subclinical hypothyroidism, overt hyperthyroidism, and subclinical hyperthyroidism), according to reference VA site-specific serum peripheral thyroid hormone (thyroxine [T4] and triiodothyronine [T3]) levels available < 90 days after an abnormal TSH result

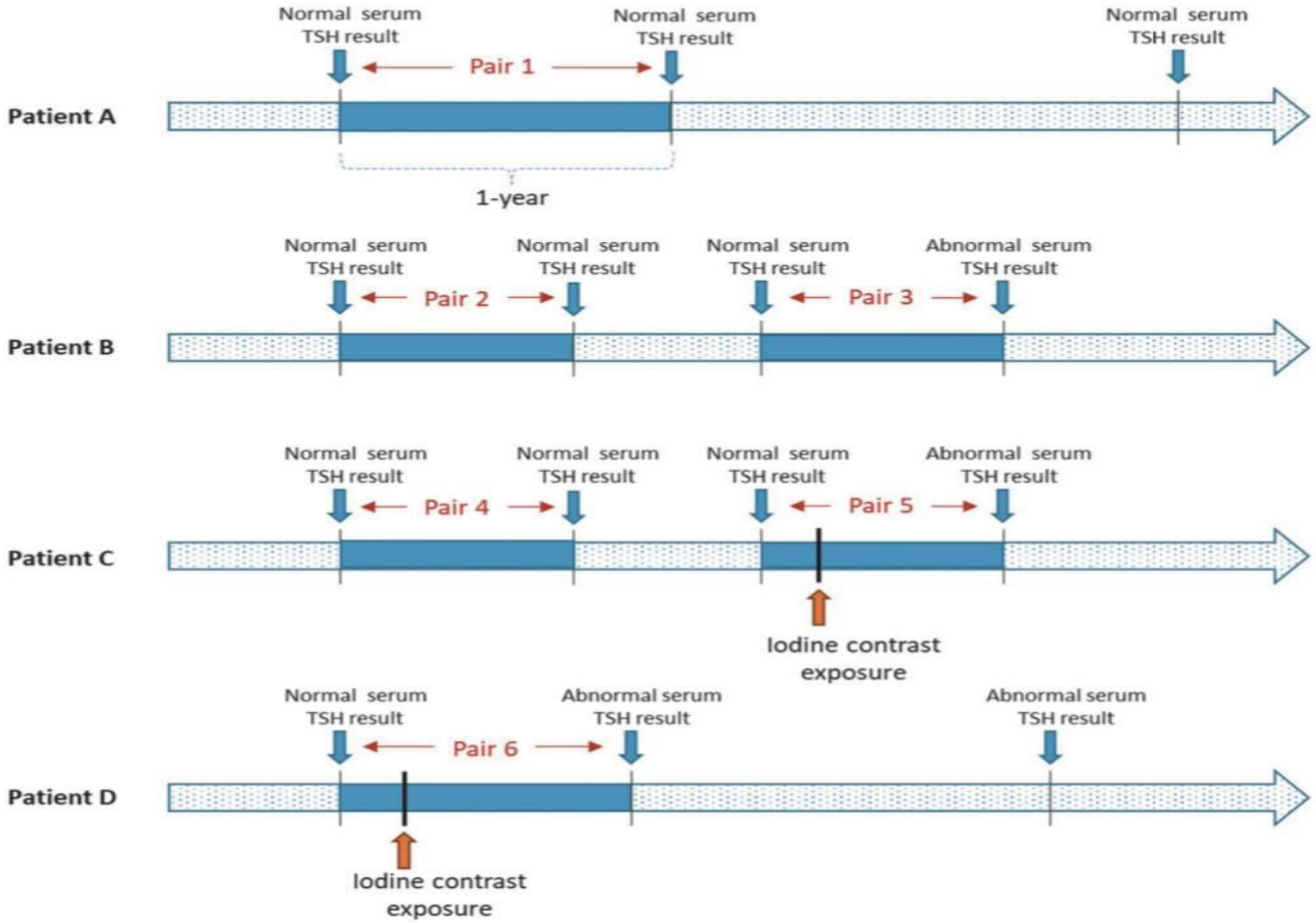

FIG. 1. Extraction of TSH pairs using four patient examples. TSH pairs were defined by any normal baseline TSH and a subsequent TSH within one year. As given in the examples in this figure, each patient can have ≥1 TSH pairs based on the number of TSH measurements and incident thyroid dysfunction. For Patient A, one pair was extracted because they had one follow-up TSH measurement within a year. For Patient B, two pairs were extracted, and the second pair had an event (i.e., thyroid dysfunction) under the absence of iodine contrast exposure. For Patient C, two pairs were also extracted, and the second pair had an event under the presence of iodine contrast exposure. For Patient D, one pair was extracted of the two possible follow-up TSH measurements within a year, as the first pair had an event. TSH, thyrotropin.

Statistical analyses

Summary statistics were generated to describe the study cohort. To estimate the adjusted odds ratio (OR) or relative risk ratio (RRR) with 95% confidence interval (CI) of the association between iodinated contrast exposure and incident thyroid dysfunction (including all subtypes of overt and subclinical thyroid dysfunction), we used multivariable binary and polytomous logistic regression models using generalized estimating equations.

The model covariates included sex, race/ethnicity, age, and baseline TSH (Model 1). In Model 2, we additionally included the duration between the baseline and subsequent serum TSH (our primary model).

We computed the E-value to identify the minimum strength of the association between an unmeasured confounder and both the treatment and the outcome, conditional on the measured covariates, to explain away the observed association between iodinated contrast use and increased risk of thyroid dysfunction.

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). In these stratified analyses,we combined subclinical and overt thyroid dysfunction (i.e., hypothyroidism and hyperthyroidism) to ensure a sufficient number of events in each analysis.

We also conducted the following four sensitivity analyses. First, given the relationship of renal function with urinary iodine excretion and therefore thyroid dysfunction, we further adjusted for calculated eGFR among patients with available component data (n = 4,333,072 pairs [50%];mean – SD = 72.3 – 19.1 mL.min-1 /1.73 m2). Second, to assess whether the association differs by the duration between iodine exposure and thyroid hormone measurement, we reanalyzed the data using the two shorter thresholds of the duration (i.e., up to 3 months and up to 6 months) instead of 12 months defined in our main analysis. Third, to minimize the influence of multiple iodine contrast exposures within a short time frame, we reanalyzed the data restricting samples to the first TSH pair for each individual (i.e., only one TSH pair per person). Finally, we reanalyzed the data further excluding the participants with other drugs that might alter thyroid function (i.e., multikinase inhibitors, immune checkpoint inhibitors, and immunomodulators) and those with eGFR <30 mL.min-1 /1.73 m2 who are not generally recommended to receive iodinated contrast media.

Results

There were N = 4,253,119 patients (mean – SD age at baseline TSH measurement is 63.5 – 14.3 years; 92.9% men, 65.6% non-Hispanic White) in the study to provide 8,729,155 pairs of serum TSH (mean number of pairs of TSH measurements per patient is 2.1; Table 1), from which 499,681 pairs of TSH had intervening iodine exposure (iodine received at 145.6 – 94.4 days [mean – SD] from the baseline TSH). Following a normal baseline serum TSH, thyroid dysfunction developed within one year in 4.8% of those pairs who had received iodine contrast, compared with 3.6% in those who had not.

In primary analysis, iodinated contrast use was associated with an increased risk of thyroid dysfunction (adjusted OR = 1.39, 95% CI = 1.37–1.41, $p < 0.001$) (Table 2; Model 1). The increased risk of iodine-induced thyroid dysfunction remained significant (OR= 1.38, 95% CI = 1.36–1.40, $p < 0.001$) after additionally adjusting for the duration between the baseline and subsequent serum TSH (Table 2; Model 2). The predictive probabilities of thyroid dysfunction among iodine exposed group and unexposed group were 4.6% and 3.4%, respectively (Supplementary Table S3). For the secondary outcomes, iodinated contrast use was associated with increased risk of all types of serum thyroid dysfunction: overt hypothyroidism, RRR = 1.71, 95% CI = 1.56–1.89, $p < 0.001$; subclinical hypothyroidism, RRR =1.40, 95% CI = 1.35–1.45, $p < 0.001$; overt hyperthyroidism,RRR = 1.65, 95% CI = 1.40–1.95, $p < 0.001$; and subclinical hyperthyroidism, RRR = 1.71, 95% CI = 1.64–1.79, $p < 0.001$

TABLE 2. ASSOCIATIONS OF IODINATED CONTRAST EXPOSURE AND RISK OF THYROID DYSFUNCTION

	TSH pairs[a] with intervening iodine exposure	*TSH pairs[a] without intervening iodine exposure*	*Model 1[b] (ref = normal thyroid function)*			*Model 2[c] (ref = normal thyroid function)*			
Primary outcome	*No. of events/ total pairs*	*No. of events/ total pairs*	*Adjusted odds ratio*	*95% CI*	p-*Value*	*Adjusted odds ratio*	*95% CI*	p-*Value*	E-*value (Lower bound of 95% CI)[d]*
Overall thyroid dysfunction	23,901/499,681	294,339/8,229,474	1.39	1.37–1.41	<0.0001	1.38	1.36–1.40	<0.0001	2.13 (2.08)
Secondary outcomes[e]	*No. of events/ total pairs*	*No. of events/ total pairs*	*Adjusted relative risk ratio*	*95% CI*	p-*Value*	*Adjusted relative risk ratio*	*95% CI*	p-*Value*	E-*value (CI)[d]*
Overt hypothyroidism	187/263,589	1836/4,068,595	1.70	1.54–1.88	<0.0001	1.70	1.54–1.88	<0.0001	2.81 (2.49)
Subclinical hypothyroidism	1713/263,589	20,231/4,068,595	1.38	1.33–1.44	<0.0001	1.38	1.33–1.44	<0.0001	2.15 (2.04)
Overt hyperthyroidism	73/263,589	725/4,068,595	1.65	1.39–1.94	<0.0001	1.64	139–1.96	<0.0001	2.69 (2.15)
Subclinical hyperthyroidism	1189/263,589	10,343/4,068,595	1.70	1.63–1.78	<0.0001	1.70	1.63–1.78	<0.0001	2.81 (2.66)

[a]A TSH pair was defined as a normal baseline TSH followed by a subsequent TSH within one year. Each patient could have had ≥2 TSH pairs.
[b]Multivariable binominal and polytomous logistic regression models using generalized estimating equations were used to account for the correlations between repeated measures within each patient (i.e., adjusting for time-invariant individual-level characteristics). Model 1 included sex, race/ethnicity, age, and baseline TSH within each TSH pair.
[c]Model 2 additionally included the duration between the baseline serum TSH and subsequent TSH following iodine exposure (our primary model).
[d]*E*-value represents the minimum strength of association of an unmeasured confounder with both the treatment and outcome, conditional on the measured covariates, to explain away the observed associations between iodinated contrast use and thyroid dysfunction. Numbers in the parenthesis represent the *E*-value for the lower bound of 95% CI.
[e]Secondary outcomes were defined based on the reference VA site-specific serum peripheral thyroid hormone T4 and T3 levels among patients with T4 and T3 available ≤90 days after a TSH result.
CI, confidence interval; T3, triiodothyronine; T4, thyroxine; VA, Veterans Affairs.

In the stratified analyses, the association between iodinated contrast use and increased risk of overall thyroid dysfunction was stronger among older Veterans (age > 65 years, OR= 1.44, 95% CI = 1.41–1.47; age <65 years, OR= 1.37, 95% CI = 1.34–1.40; p-value for the interaction between age and thyroid dysfunction is 0.049) and men (men: OR= 1.42, 95% CI = 1.40–1.44; women: OR = 1.16, 95% CI = 1.11–1.21; p-value for the interaction between sex and thyroid dysfunction is <0.001; Fig. 2). The age difference was most prominent for hyperthyroidism (age > 65 years, RRR = 2.04, 95% CI = 1.90–2.18; age <65 years, RRR = 1.53, 95% CI = 1.46–1.62; p-value for the interaction between age and hyperthyroidism is <0.001; Fig. 3).

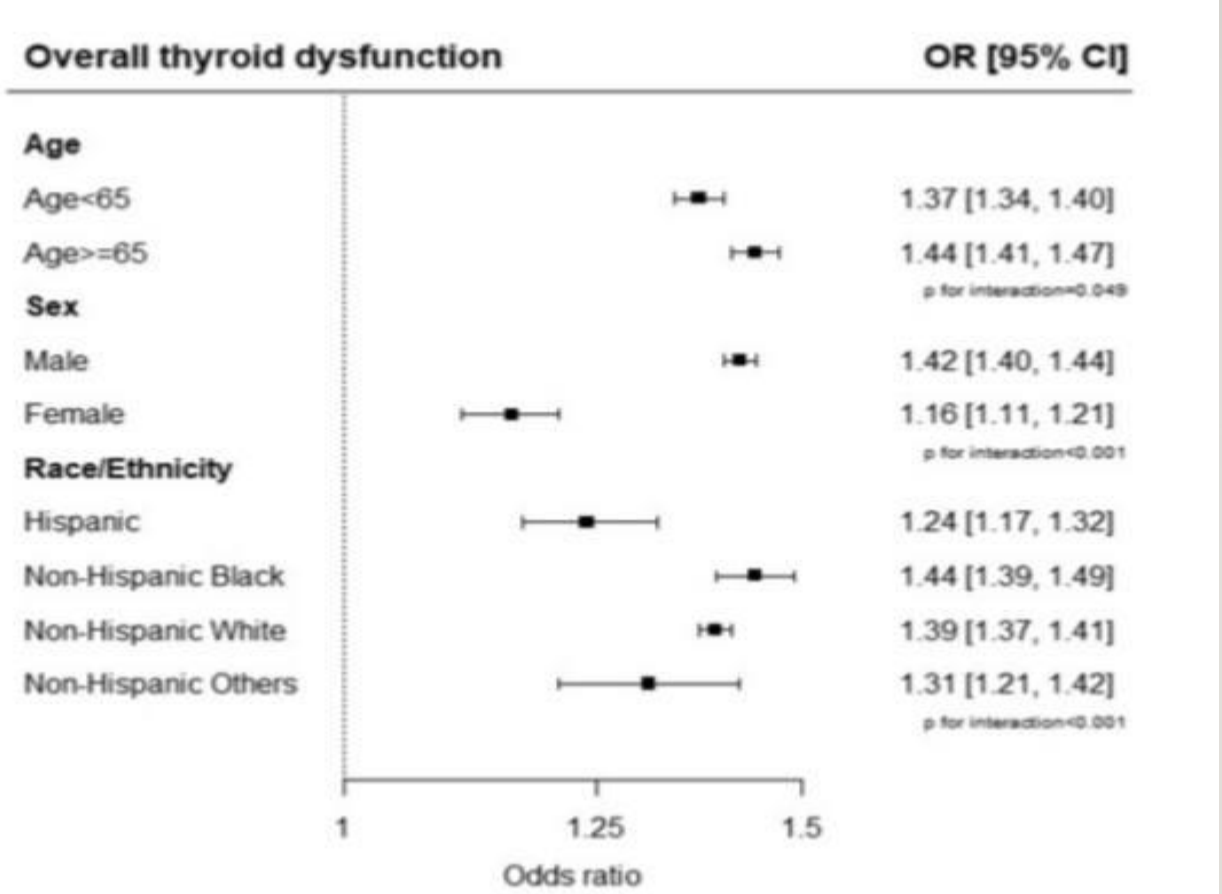

FIG. 2. Association of iodinated contrast exposure and risk of overall thyroid dysfunction by age, sex, and race/ethnicity. Multivariable binary logistic regression models using a generalized estimating equation approach and adjusted for sex, race/ethnicity, age, baseline TSH within each TSH pair, and the duration between the baseline serum TSH and subsequent TSH following iodine exposure. OR, odds ratio.

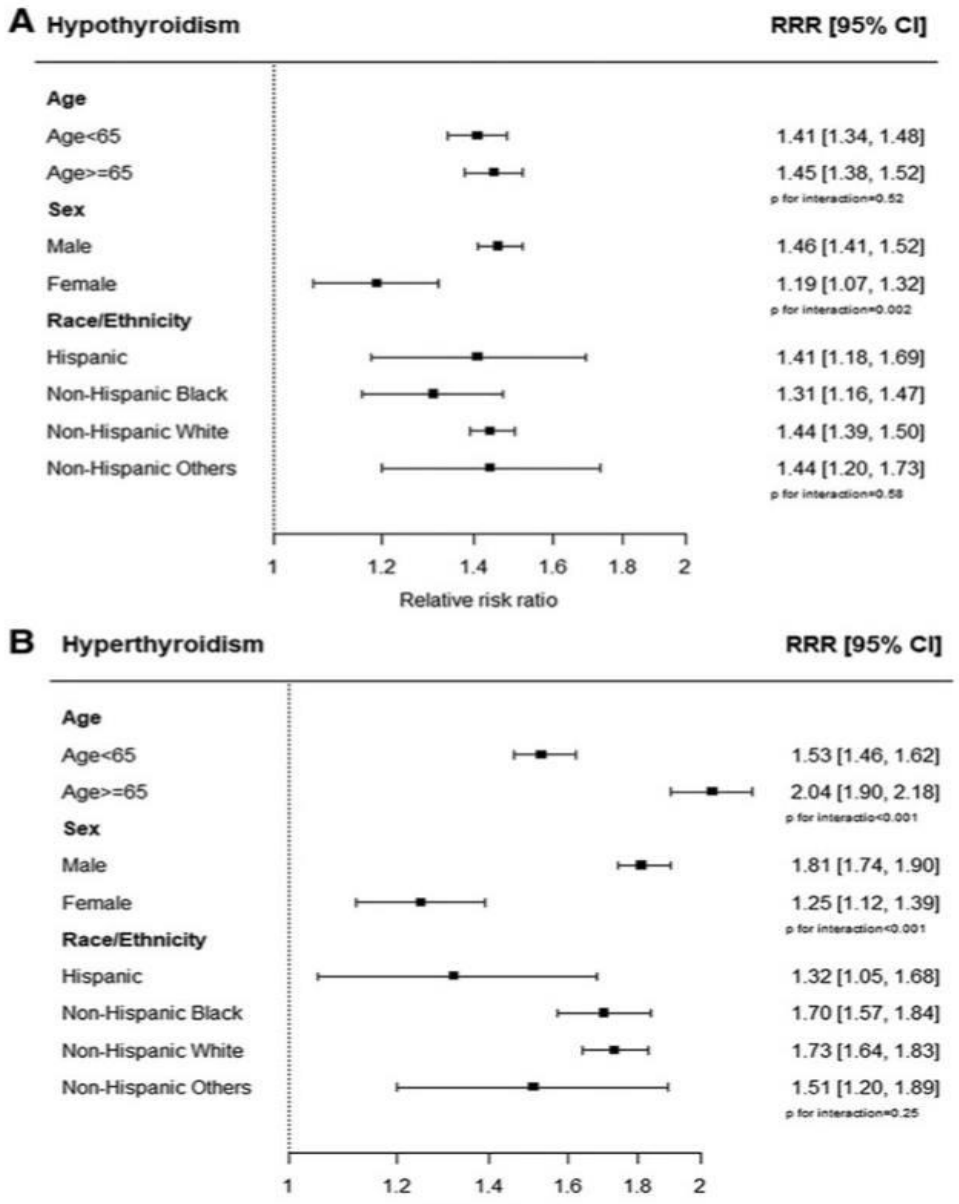

FIG. 3. Association of iodinated contrast exposure and risk of hypothyroidism and hyperthyroidism by age, sex, and race/ethnicity. Hypothyroidism included both subclinical or overt hypothyroidism, and hyperthyroidism included both subclinical or overt hyperthyroidism. Multivariable polytomous logistic regression models using a generalized estimating equation approach and adjusted for sex, race/ethnicity, age, baseline TSH within each TSH pair, and the duration between the baseline serum TSH and subsequent TSH following iodine exposure. RRR, relative risk ratio.

Discussion

Findings from this study of the largest integrated health care system in the United States showed that iodinated contrast media exposure was associated with only a clinically small absolute increased risk of incident thyroid dysfunction.

In this cohort of primarily older non-Hispanic White men, risks were highest in male Veterans. Although the difference in the overall risk of iodine-induced thyroid dysfunction was clinically small between sex, older Veterans were more likely to develop hyperthyroidism after the iodine exposure than younger Veterans. Given that radiologic iodine contrast is necessary for diagnosis and follow-up of several diseases, our findings suggest that monitoring thyroid function following its administration may be beneficial only in those at highest risk.

One of the largest studies in the United States was a case–control study of medical records from two hospitals in Boston over a 20-year period.22 In that study, Rhee et al reported that patients without preexisting known hypothyroidism or hyperthyroidism had two- to three-fold increased risks of developing either incident hyperthyroidism (including overt hyperthyroidism) or overt hypothyroidism at a median of 9 months following iodinated contrast administration, compared with patients who did not receive the high iodine load.

In summary, these findings suggest that excess iodine exposure in routine clinical settings represents a potentially modifiable risk, and the risks of thyroid dysfunction and its associated comorbidities should be weighed against the need for iodinated contrast use that is commonly obtained. Furthermore, should radiologic iodine contrast use be necessary, serum thyroid function should be selectively monitored in the one year following its administration highly susceptible patients, particularly men.

با تشکر از توجه شما