Does iodine fortification affect the risk of atrial fibrillation in incident hyperthyroidism? A national register-based cohort

Møllehave, Line T.; Knudsen, Nils; Prescott, Eva; Pedersen, Inge B.; Ravn-Haren, Gitte; Carlé, Allan; Linneberg, Allan

Published in:
Clinical Endocrinology

Link to article, DOI:
10.1111/cen.15042

Publication date:
2024

Document Version
Publisher's PDF, also known as Version of record

Received: 15 January 2024 | Revised: 20 February 2024 | Accepted: 22 February 2024

DOI: 10.1111/cen.15042

ORIGINAL ARTICLE

Thyroid

WILEY

Does iodine fortification affect the risk of atrial fibrillation in incident hyperthyroidism? A national register-based cohort

Line T. Møllehave[1] | Nils Knudsen[2] | Eva Prescott[3] | Inge B. Pedersen[4] | Gitte Ravn-Haren[5] | Allan Carlé[4] | Allan Linneberg[1,6]

[1]Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark

[2]Department of Endocrinology, Bispebjerg University Hospital, University of Copenhagen, Copenhagen, Denmark

[3]Department of Cardiology, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark

[4]Department of Endocrinology and Medicine, Aalborg University Hospital, Aalborg, Denmark

[5]Research Group for Risk Benefit, National Food Institute, Technical University of Denmark, Lyngby, Denmark

[6]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Correspondence

Line T. Møllehave, Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, Frederiksberg Hospital, Hovedvejen, Entrance 5, Nordre Fasanvej 57, DK-2000 Frederiksberg, Denmark.
Email: line.tang.moellehave@regionh.dk

Funding information

The Danish Heart Foundation, Grant/Award Number: 20-R141-A9683-22174

Abstract

Objective: Iodine fortification (IF) induces an initial increase followed by a decrease in the incidence of hyperthyroidism in the general population. Within the population of hyperthyroid patients, the sex-, age- and subtype distribution changes after IF. The risk of atrial fibrillation (AF) in hyperthyroid patients may be influenced by these factors. Therefore, we aimed to examine how the association between incident hyperthyroidism and AF was affected by IF increasing the population iodine intake from moderate-mild iodine deficiency to low adequacy.

Design, Patients and Measurements: Incident hyperthyroid patients were included at the date of first inpatient or outpatient diagnosis, and AF diagnoses within 3 months before to 6 months after the index date were identified in Danish nationwide registers, 1997–2018. The relative risk (RR) of AF each calendar year (reference: 1997; IF introduced: 2000) was analyzed in Poisson regression models adjusted for age, sex, educational level, geographic region, and comorbidities.

Results: Overall, in 62,201 patients with incident hyperthyroidism 7.9% were diagnosed with AF. There was a minor nonsignificantly increased risk of AF during the first years after IF followed by a gradual decrease to RR 0.76 (0.62–0.94) in 2017. There were no statistically significant differences in the development in the risk of AF by sex, age group, or geographic region.

Conclusions: Results indicate that IF may reduce the risk of concomitant AF in hyperthyroid patients. If these results are confirmed, IF may not only reduce the population incidence of hyperthyroidism but also reduce the burden of morbidity in the remaining hyperthyroid patients.

KEYWORDS

atrial fibrillation, epidemiology, hyperthyroidism, iodine, registries

1 | INTRODUCTION

Atrial fibrillation (AF) is a well-established consequence of hyperthyroidism.[1] The risk of AF in hyperthyroidism in previous studies varies between 8% and 28%.[2,3] This is primarily due to different causes of hyperthyroidism, sex- and age distribution of hyperthyroid patients, predisposing comorbidities, and differences in study design. An approximately linear relation between thyroid dysfunction and the risk of AF has been identified with decreased risk in hypothyroidism, a slightly increased risk in subclinical hyperthyroidism and the highest risk in overt hyperthyroidism compared with euthyroid.[4,5] This has both been indicated in single studies, meta-analyses, and in a Mendelian Randomization study.[6] Hyperthyroidism increases the risk of AF through both complex intracellular and extracellular mechanisms of thyroid hormones on cardiac electrophysiology.[7] Elevated thyroid hormones may induce paroxysmal AF followed by persistent AF if the thyroid hormone levels are not normalised.[8] Symptoms of hyperthyroidism are various but nonspecific[9] and the patient may initially seek medical attention based on cardiac symptoms. Guidelines recommend that all patients with AF are screened for hyperthyroidism, thus, some are diagnosed through this route while other hyperthyroid patients are diagnosed with AF following the diagnosis of hyperthyroidism.

AF is associated with reduced quality of life[10] and an increased risk of stroke, heart failure, and mortality.[11] Therefore, prevention of AF can have substantial public health implications. Iodine fortification (IF) is widely implemented to prevent iodine deficiency disorders and IF induces marked changes in the incidence and distribution of hyperthyroidism in the population.[12] However, it is not previously examined how IF affects the risk of concomitant AF in hyperthyroid patients.

In 2000 mandatory IF was introduced in Denmark, adding 13 ppm iodine to household salt and salt in bread and baked goods.[13] This brought the Danish iodine intake level from mild-moderate deficiency to low adequacy.[14] After introduction of IF a transient increase in incident hyperthyroidism followed by a decrease was observed.[15] This increase and decrease may directly affect the number of AF cases. Additionally, the increase in hyperthyroidism after IF was introduced was observed in all age groups,[15] and a slightly higher proportion of hyperthyroid cases was caused by toxic nodular goitre compared with Graves' disease.[16] The following decrease in hyperthyroid cases was characterised by a steeper decrease in the oldest age groups,[15] and a decrease in both main subtypes of hyperthyroidism with a steeper decrease in toxic nodular goitre than in Graves' disease.[17] The ratio between men and women remained largely unaltered after IF.[15] These changes observed after IF may affect the risk of AF in the hyperthyroid population because the risk of AF is higher in elderly persons, partly due to a higher burden of comorbidities, and higher in toxic nodular goitre compared with Graves' disease.[3] Thus, we hypothesise that IF may initially induce higher risk of AF in hyperthyroid patients, while a lower risk of AF in hyperthyroid patients will follow years after the implementation of IF.

In the present study, we aimed to examine the risk of AF among patients with incident hyperthyroidism and how the risk of AF was affected over time by the introduction of IF. We hypothesised that the increased iodine status following IF would decrease the risk of AF associated with hyperthyroidism.

2 | MATERIALS AND METHODS

2.1 | Data sources

We utilized data from Danish nationwide healthcare and administrative registers. All Danish citizens are registered with a unique personal-identification number allowing individual-level linkage between registers.[18] The Danish National Patient Register (NPR) contains diagnoses for all in- and outpatient hospital contacts since 1977,[19] we utilized primary and secondary diagnoses. The Danish National Prescription Registry (DNPR) contains records of all redeemed prescriptions since 1995.[20] Administrative registers contain information on date of birth, sex, educational level, and municipality of residence.[21,22]

2.2 | Population: Incident hyperthyroidism

We included all incident hyperthyroid patients during 1997–2017 aged 25–79 years. Hyperthyroidism was defined as a first-time in- or outpatient diagnosis of hyperthyroidism (ICD-10: E05.0-E05.9) in the NPR. The date of first hospital contact with the diagnosis was defined as the index date.

Hyperthyroid patients were excluded if there was (a) a previous diagnosis of hypothyroidism (ICD-10: E03), thyroid cancer (ICD-10: C73.9), or pituitary disease (ICD-10: E23.0–9), (b) within 2 years before the index date a redeemed prescription of amiodarone (ATC: C01BD01) or lithium (ATC: N05AN01), (c) within 6 months before the index date a redeemed prescription of monoclonal antibodies (ATC: L01XC), protein kinase inhibitors (ATC: L01XE), interferon alpha (ATC: L03AB), levothyroxine (ATC: H03AA), or (d) within 12 months before or until 12 months after the index date a birth or abortion (ICD-10: Z338 and O03).

In- and exclusions to the population are illustrated in Figure 1.

2.3 | AF

AF was defined as a diagnosis of AF (ICD-10: I48) within 3 months before or until 6 months after the index date for hyperthyroidism. For sensitivity analyses AF was also defined within 3 months before until index date, 1 month before to 3 months after, and 6 months before to 12 months after the index date for hyperthyroidism.

2.4 | Covariables

Age was defined at index date. Region of residence was divided into the regions with moderate iodine deficiency before IF (western Denmark) and mild iodine deficiency before IF (eastern Denmark).

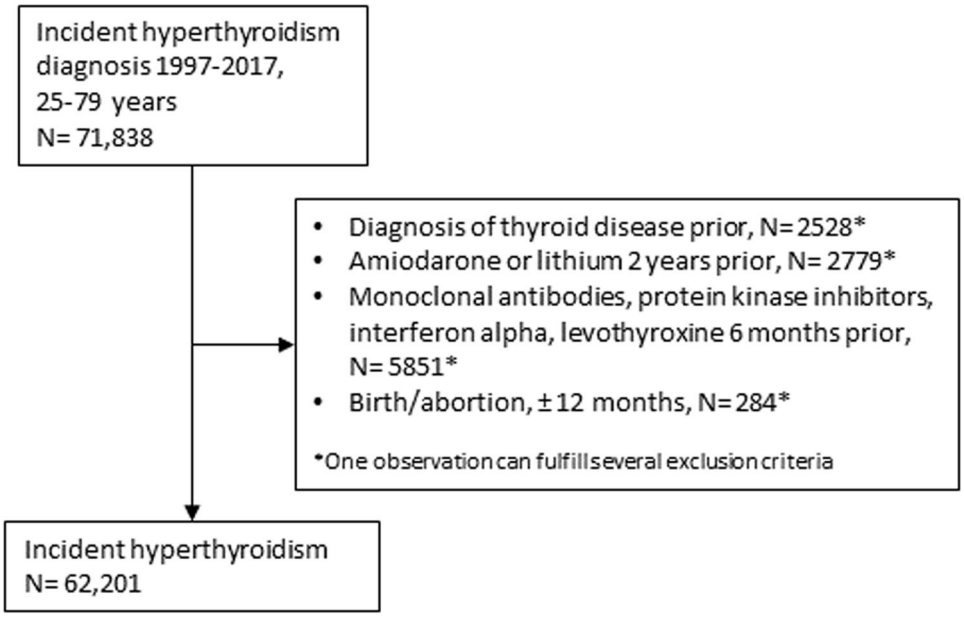

FIGURE 1 In- and exclusions to the study population.

Highest attained educational level was classified according to the International Standard Classification of Education (ICSED) levels: short education (primary or upper secondary education), medium education (>4 years; vocational education) and long education (≥4 years: bachelor's or master's degree or short-cycle higher education).

The Charlson comorbidity index (CCI) as updated in 2011 by Quan et al.[23,24] was calculated for each observation as a cumulative weighted score (maximum 24) from the number and severity of comorbid conditions. The CCI was calculated using a SAS macro (developed by Ken Turner and Charles Burchill).[25] The CCI was classified as a score of 0, 1, 2, and ≥3.

Specific comorbidities defined were congestive heart failure, diabetes, hypertension, ischaemic heart disease, heart valve disease and chronic obstructive pulmonary disease (see definitions in Supporting Information S1: Table S1).

Both the CCI and specific comorbidities were defined from diagnoses derived from the NPR during the 5 years before the index date.

2.5 | Statistical methods

Population characteristics are presented stratified into groups of 3 calendar years and trends in characteristics during the study period were tested. Poisson regression with robust standard errors was applied to assess the relative risk (RR) and 95% confidence intervals (95% CI) for the associations between AF and calendar year with year 1997 as the reference. The association was examined in a series of models, first adjusting for sex and age (continuous), second, including educational level and region of residence (moderate vs. mild iodine deficiency before IF) and lastly including the specific comorbidities that may affect the risk of AF. A nonlinear (quadratic) effect of age was identified and included in the model. In the final model effect measure modifications were assessed by testing the interaction terms of calendar year with sex, three age groups, and region of residence, one interaction pair at the time. The estimates of the interactions are derived from the joint model and presented graphically. From the final model we also derived the mutually adjusted effect of sex, three age groups, and region. Analyses were performed in SAS, version 9.4 (SAS Institute Inc.) and statistical significance defined as $p < 0.05$.

2.6 | Sensitivity analyses

The primary analyses were repeated with AF 3 months before the index date, 1 month before to 6 after and 6 months before to 12 months after the index date for hyperthyroidism. The effect of initiation of antithyroid medication before the index date was evaluated. Finally, the analyses were replicated in a population with incident goitre (ICD-10: DE04) and no medication or diagnosis of hyperthyroidism.

2.7 | Ethics

According to Danish legislation ethical approval is not required for studies based solely on registers. Approval from the Danish Data Protection Agency (journal number p-2021-43), Statistics Denmark, and the Health Data Authorities (FSEID-00005629) was obtained for handling the data. All analyses were performed at servers at Statistics Denmark with pseudonymized personal identification numbers.

3 | RESULTS

3.1 | Population and characteristics

During the study period 71,838 patients with incident hyperthyroidism were identified and 62,201 were available after exclusions (Figure 1). The crude annual number of incident hyperthyroid patients was higher in the years immediately after IF and decreased again. There were statistically significant but minor changes in the distribution of most patient characteristics during the study period (Table 1).

3.2 | Development in the association between hyperthyroidism and AF

The overall risk of AF was 7.88% (95% CI: 7.66–8.09). During the first years of the study period, in 1998–2002, there was a nonsignificant indication of an elevated risk of AF compared with the risk in 1997. From 2001 until the end of the study period the risk of AF fell gradually and was statistically significantly below the baseline risk in 2006, 2011, 2013 and 2015–2017 with RR 0.76 (95% CI: 0.62–0.94) in 2017 compared with 1997. This pattern

TABLE 1 Characteristics of patients with incident hyperthyroidism throughout the study period.

	1997–1999	2000–2002	2003–2005	2006–2008	2009–2011	2012–2014	2015–2017
Total *n*	8367	10,020	9699	8566	7890	8548	9111
Female, % (*n*)	83.3 (6972)	83.0 (8318)	82.6 (8010)	80.6 (6904)	80.2 (6326)	78.9 (6745)	79.4 (7232)
Age							
25–34, % (*n*)	4.7 (391)	5.0 (502)	5.8 (562)	5.2 (448)	5.0 (392)	5.5 (468)	0.9 (536)
35-44, % (*n*)	12.5 (1049)	12.9 (1293)	14.4 (1393)	14.2 (1214)	14.5 (1145)	13.9 (1188)	13.8 (1253)
45–54, % (*n*)	16.00 (1338)	16.5 (1649)	16.6 (1607)	17.3 (1480)	16.2 (1275)	16.4 (1398)	14.9 (1360)
55–64, % (*n*)	20.1 (1681)	22.1 (2214)	22.6 (2187)	21.7 (1861)	19.9 (1572)	19.8 (1688)	19.8 (1801)
65–74, % (*n*)	21.0 (1756)	19.7 (1974)	20.0 (1943)	21.8 (1870)	24.1 (1905)	24.2 (2070)	22.4 (2043)
75–79, % (*n*)	25.7 (2152)	23.8 (2388)	20.7 (2007)	19.8 (1693)	20.3 (1601)	20.3 (1736)	23.3 (2118)
Educational level							
Short, % (*n*)	51.7 (4324)	50.4 (5050)	45.9 (4447)	41.6 (3564)	39.4 (3105)	35.3 (3014)	33.8 (3082)
Medium, % (*n*)	27.2 (2272)	30.7 (3079)	32.8 (3178)	34.4 (2946)	35.3 (2786)	36.4 (3111)	35.8 (3260)
Long, % (*n*)	14.1 (1183)	16.6 (1661)	19.6 (1904)	22.3 (1910)	23.5 (1853)	26.3 (2245)	28.5 (2594)
Unknown, % (*n*)	7.0 (588)	2.3 (230)	1.8 (170)	1.7 (146)	1.9 (146)	2.1 (178)	1.9 (175)
Region							
Moderate ID before IF, % (*n*)	60.5 (5061)	63.8 (6390)	63.3 (6135)	60.9 (5220)	60.7 (4789)	59.3 (5064)	53.8 (4901)
Mild ID before IF, % (*n*)	39.5 (3306)	36.2 (3630)	36.8 (3564)	39.1 (3346)	39.3 (3100)	40.8 (3483)	46.2 (4208)
CCI							
0, % (*n*)	81.8 (6844)	83.2 (8332)	83.6 (8110)	83.6 (7160)	82.2 (6489)	82.2 (7024)	82.2 (7491)
1, % (*n*)	8.2 (689)	7.4 (740)	7.5 (727)	7.1 (605)	7.5 (593)	0.7 (660)	6.7 (612)
2, % (*n*)	7.2 (600)	6.7 (669)	6.0 (586)	6.3 (542)	6.8 (536)	0.8 (582)	7.4 (676)
≥3, % (*n*)	2.8 (234)	2.8 (279)	2.9 (276)	3.0 (259)	3.5 (272)	3.3 (282)	3.6 (332)
Hypertension, % (*n*)	6.3 (526)	7.6 (759)	10.3 (998)	12.2 (1047)	14.1 (1110)	13.6 (1165)	13.5 (1226)
IHD, % (*n*)	6.4 (535)	6.9 (686)	6.5 (627)	5.4 (466)	6.0 (470)	6.0 (511)	5.5 (499)
HF, % (*n*)	4.3 (362)	4.3 (426)	3.0 (290)	3.2 (275)	2.9 (227)	2.5 (212)	2.9 (264)
Heart valve disease, % (*n*)	1.0 (83)	1.1 (114)	1.3 (123)	1.2 (104)	1.6 (127)	1.6 (139)	1.7 (152)
Diabetes, % (*n*)	5.8 (485)	5.8 (581)	5.8 (560)	6.0 (515)	6.5 (516)	5.9 (503)	5.4 (493)
COPD, % (*n*)	4.6 (382)	4.8 (480)	4.3 (416)	4.5 (387)	5.0 (391)	4.6 (389)	4.5 (407)

Note: Test for trend: sex $p < 0.001$, age class $p < 0.001$, educational level $p < 0.001$, region $p < 0.001$, CCI $p < 0.001$, hypertension $p < 0.001$, IHD $p < 0.001$, HF $p < 0.001$, heart valve disease $p < 0.001$, diabetes $p = 0.812$, COPD $p = 0.875$.

Abbreviations: CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; HF, heart failure; ID, iodine deficiency, IF, iodine deficiency, IHD, ischaemic heart disease; *N*, number of observations, SD, standard deviation.

was minimally affected by adjustment for confounding factors (Table 2).

There were no statistically significant interactions between calendar year and sex ($p = 0.240$), three age groups ($p = 0.552$), or geographic region ($p = 0.907$); meaning that the development in the risk of AF did not differ between these groups during the study period. The results are presented graphically in Figures 2–4.

In the mutually adjusted model, the risk of AF was higher in men compared with women [RR: 1.688 (95% CI: 1.585–1.797)], higher with higher age [RR: 5.944 (95% CI: 4.945–7.144) in 45–64 years and RR: 14.828 (95% CI: 12.366–17.781) in 65–79 years compared with 25–44 years] and higher in the region with moderate compared with mild iodine deficiency before IF [RR: 1.138 (95% CI: 1.068–1.208)]. Most comorbidities were associated with an increased risk of AF: heart faliure [RR: 2.672 (95% CI: 2.451–2.914)], hypertension [RR: 1.376 (95% CI: 1.281–1.477)], ischaemic heart disease [RR: 1.039 (95% CI: 0.952–1.133)], heart valve disease [RR: 1.579 (95% CI: 1.382–1.798)], but not diabetes [RR: 1.042 (95% CI: 0.949–1.145)] or chronic obstructive lung disease [RR: 0.999 (95% CI: 0.906–1.101)].

3.3 | Sensitivity analyses

The overall risk of AF was 6.61% (95% 6.41–6.80) from 3 months before until index date, and the development in the risk of AF during 1997–2017 was close to that for the primary analyses (Supporting Information S1: Table S2). The overall risk of AF was 6.89% (95% CI: 6.69–7.08) within 1 month before to 3 months after the index date and 8.73% (95% CI: 8.51–8.95) within 6 months before to 12 months after the index date. The gradual decrease in the risk of AF during

TABLE 2 Development in the risk of atrial fibrillation in incident hyperthyroid patients during 1997–2017.

	% (*n* AF/*n* hyperthyroid)	Model 1[a] RR (95% CI)	Model 2[b] RR (95% CI)	Model 3[c] RR (95% CI)
1997	8.8 (231/2618)	1 (ref)	1 (ref)	1 (ref)
1998	8.9 (249/2788)	1.011 (0.845–1.209)	1.056 (0.868–1.285)	1.040 (0.855–1.266)
1999	10.0 (297/2961)	1.119 (0.942–1.328)	1.131 (0.937–1.366)	1.112 (0.921–1.343)
2000	9.3 (291/3142)	1.069 (0.898–1.268)	1.071 (0.889–1.292)	1.069 (0.887–1.289)
2001	9.9 (333/3372)	1.132 (0.957–1.339)	1.138 (0.950–1.365)	1.110 (0.926–1.331)
2002	8.8 (311/3506)	1.066 (0.899–1.264)	1.068 (0.889–1.284)	1.032 (0.858–1.240)
2003	8.0 (278/3495)	0.993 (0.834–1.182)	1.003 (0.831–1.210)	1.000 (0.829–1.207)
2004	7.5 (239/3187)	0.942 (0.786–1.129)	0.957 (0.789–1.161)	0.933 (0.769–1.132)
2005	7.5 (227/3017)	0.932 (0.776–1.120)	0.954 (0.784–1.159)	0.941 (0.774–1.144)
2006	6.2 (186/2995)	0.773 (0.637–0.937)*	0.784 (0.638–0.962)*	0.768 (0.625–0.943)*
2007	8.3 (236/2836)	1.020 (0.850–1.222)	1.039 (0.855–1.261)	0.990 (0.815–1.202)
2008	7.8 (213/2735)	0.940 (0.780–1.132)	0.957 (0.784–1.168)	0.907 (0.743–1.108)
2009	7.2 (188/2631)	0.885 (0.730–1.073)	0.902 (0.735–1.106)	0.871 (0.709–1.069)
2010	7.8 (202/2578)	0.916 (0.758–1.106)	0.943 (0.771–1.153)	0.896 (0.732–1.096)
2011	7.0 (187/2681)	0.817 (0.673–0.990)*	0.835 (0.680–1.025)	0.807 (0.657–0.991)*
2012	7.5 (206/2750)	0.905 (0.750–1.092)	0.930 (0.761–1.136)	0.901 (0.737–1.102)
2013	6.9 (201/2908)	0.813 (0.673–0.983)*	0.828 (0.676–1.013)	0.810 (0.661–0.992)*
2014	8.3 (241/2890)	0.951 (0.794–1.139)	0.960 (0.790–1.166)	0.945 (0.777–1.148)
2015	6.5 (203/3114)	0.751 (0.622–0.907)*	0.776 (0.635–0.949)*	0.751 (0.613–0.919)*
2016	5.9 (198/3351)	0.671 (0.555–0.811)*	0.687 (0.561–0.841)*	0.674 (0.550–0.826)*
2017	6.8 (182/2646)	0.759 (0.625–0.921)*	0.789 (0.642–0.971)*	0.760 (0.617–0.935)*

Note: Asterix (*) indicates relative risk estimates statistically significantly different from the level in 1997 (reference).

Abbreviations: AF, atrial fibrillation; CI, confidence interval AF within 3 months before to 6 months after diagnosis of incident hyperthyroidism; *N*, number of observations; RR, relative risk.

[a]adjusted for age and sex.

[b]adjusted for age, sex, educational level, geographic area.

[c]adjusted for age, sex, educational level, geographic area and comorbidities (congestive heart failure, diabetes, hypertension, ischaemic heart disease, heart valve disease and chronic obstructive pulmonary disease).

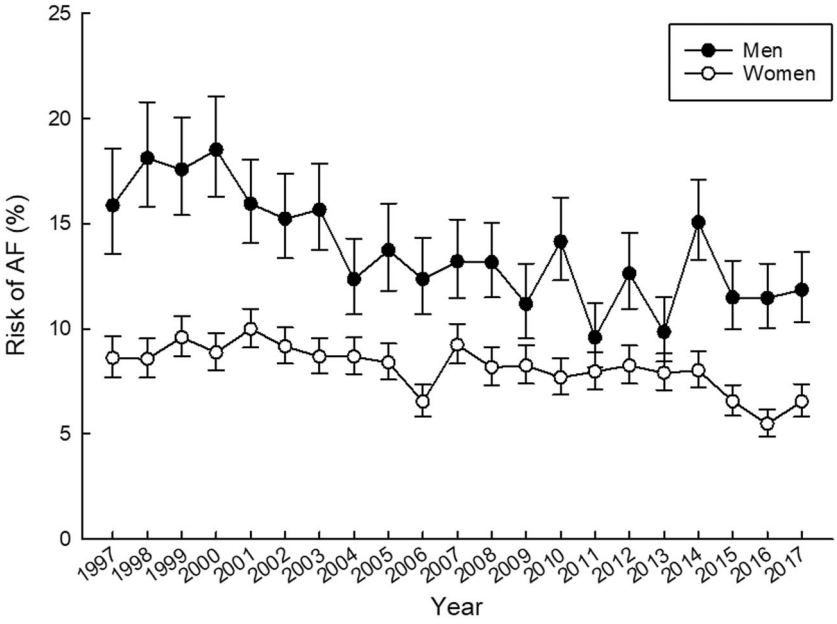

FIGURE 2 Risk of atrial fibrillation in incident hyperthyroid patients during 1997–2017 by sex. Circles illustrates the estimated risk and error bars illustrate the 95% confidence intervals each calendar year for men (black circles) and women (white circles).

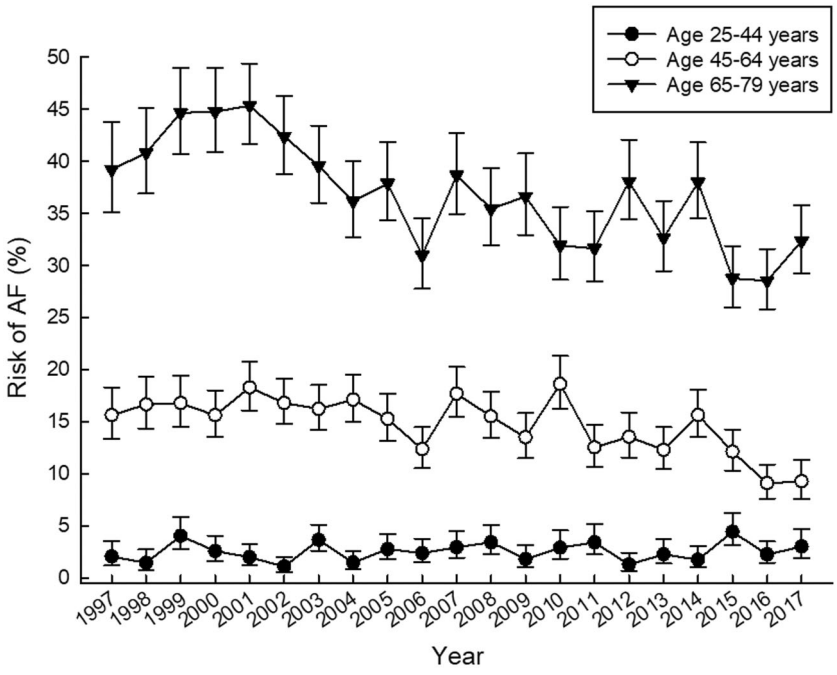

FIGURE 3 Risk of atrial fibrillation in incident hyperthyroid patients during 1997–2017 by age groups. Symbols illustrate the estimated risk and error bars illustrate the 95% confidence intervals each calendar year for patients aged 25–44 years (black circles), 45–64 years (white circles) and 65–79 years (black triangles).

1997–2017 was slightly stronger when AF was defined within 1 month before to 3 months after the index date (Supporting Information S1: Table S3 and S4).

Overall, 37.4% of the hyperthyroid population started antithyroid medication before the first hospital contact, which marks the index date. Medication initiation before index was associated with a lower risk of AF [RR: 0.789 (95% CI: 0.752–0.838)], but additional adjustment for medication in the final model did not affect development in the risk of AF (results not shown).

In a control population of patients with incident goitre and no hyperthyroidism ever before or up to 12 months after the index date (Supporting Information S1: Figure S1 and Table S5) we found an overall risk of AF of 1.12% (95% CI: 1.04–1.21). In patients with incident goitre there was no statistically significant change in the risk of AF during the study period (Supporting Information S1: Table S6).

4 | DISCUSSION

4.1 | Summing up results

This is the first study to examine how IF affects the risk of AF in hyperthyroid patients. We found a nonsignificant indication of an increase in the risk of AF in hyperthyroid patients in the first years

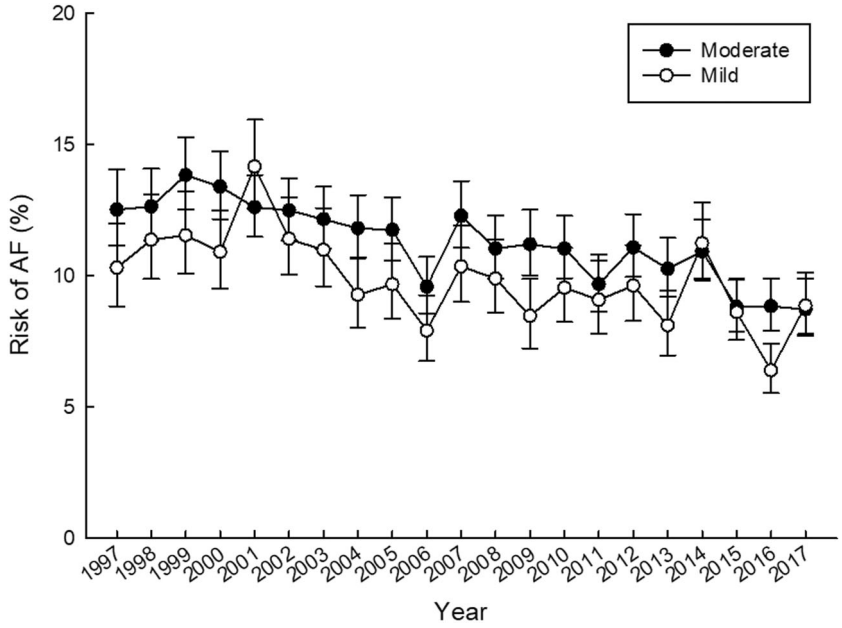

FIGURE 4 Risk of atrial fibrillation in incident hyperthyroid patients during 1997–2017 by region. Circles illustrate the estimated risk and error bars illustrate the 95% confidence intervals each calendar year in the region with moderate iodine deficiency before iodine fortification (black circles) and the region with mild iodine deficiency before iodine fortification (white circles).

after introduction of IF, and thereafter a gradual reduction in the risk of AF which was statistically significant from approximately 2011–2013. The overall risk but not the development in risk differed by sex, age groups, and region of residence. Sensitivity analyses did not markedly affect the results.

4.2 | Comparison with previous studies

To our knowledge, no studies have previously examined how the risk of AF in the hyperthyroid population is affected by IF. Aminorroaya et al examined the prevalence of thyrotoxicosis in 100 AF patients immediately before and 100 patients 8–10 years after introduction of IF in Iran increasing the iodine intake from iodine deficiency to sufficiency. The prevalence of hyperthyroidism in AF patients increased from 3.7% to 8%.[26] It is difficult to directly compare the risk of hyperthyroidism in the AF population with the risk if AF in the hyperthyroid population, however, in our study the risk of AF identified in the 3 months before the incident diagnosis of hyperthyroidism mirrored the overall trend with an initial minor increase followed by a decrease in the risk of AF. It made little difference to the overall results of the present study whether AF was defined within 1–3 months or 6–12 months of the index date, indicating that hyperthyroidism and AF are concomitantly diagnosed. Similar to previous studies, we found an increased risk of AF in men, with higher age, and with specific comorbidities.[27] The proportion of men and comorbidities in the study population increased slightly during the study period but the decline in risk of AF was observed before adjustment for these variables and adjustment changed the results minimally.

Contrary to the decline in the risk of AF in the hyperthyroid population observed in the current study, in the total Danish population the incidence of AF increased by mean 1.4% annually between 2000 and 2012.[11] The awareness of AF and prevalence of diagnostic procedures in the general population is lower than in hyperthyroid patients and may have changed differently during the study period. Therefore, we examined the development in the risk of AF in patients with an incident diagnosis of goitre who are typically followed in endocrinology departments and therefore have a risk of detection bias closer to that of hyperthyroid patients. In these patients we found no change in the risk of AF during the study period, thus supporting that the decline in the risk of AF in hyperthyroid patients may not be solely ascribed to detection bias and might be linked with IF.

4.3 | Possible mechanisms: Biologic

The risk of AF in hyperthyroid patients is associated with the severity of disease as indicated by the level of thyroid hormones[6] and with the duration of disease.[27,28] During the first years after IF the incidence of hyperthyroidism increases[15] and the severity of hyperthyroidism in the patient population may also be aggravated especially in the elderly patients where nontoxic thyroid nodules may become slightly hyperfunctioning, and slightly hyperfunctioning thyroid nodules may develop into overt hyperthyroidism when an increased level of iodine is available,[16] leading to a somewhat elevated risk of AF in the hyperthyroid population. Approximately 5–10 years after introduction of IF the risk of AF in the hyperthyroid population gradually decreased. After IF the subtypes of thyroid disease in the hyperthyroid population also changed; between 1997 and 2014–2016 multinodular toxic goitre and Graves' disease had decreased by 82% (95% CI: 77–85) and 33% (95% CI: 21–44), respectively, in the Northwestern part of Denmark. Hereby, the proportion of multinodular toxic goitre made up a smaller proportion of the hyperthyroid population after IF.[17] The risk of AF is indicated to be higher in multinodular toxic goitre compared with

Graves' disease,[3,29,30] which may be explained by increased age and longer durations of subclinical hyperthyroidism,[3] despite higher levels of thyroid hormones at diagnosis in Graves' disease.[31] Thus, the shift in subtype of hyperthyroidism towards a lower proportion of multinodular toxic goitre may explain part of the decreased risk of AF. In a sample of incident hyperthyroid patients in Northwestern Denmark in 2006–2019 the thyroid hormone tests identifying overt disease showed that total T4 but not total T3 had decreased during the study period (Supporting Information S7). This mirrors the changes in subtypes because T4 is especially elevated in multinodular toxic goitre and T3 is especially elevated in younger persons and Graves' disease. The decrease in thyroid hormone levels might explain some of the decrease in the risk of AF. However, in this study, we are unable to distinguish if this is due to the IF, changes in referral, or both.

4.4 | Possible mechanisms: Bias

Changes in referral, diagnosis, and treatments during the study period may have affected the results. First, the annual number of thyroid function tests by general practitioners increased by over 250% during 2000–2015 in the Copenhagen area.[32] Second, during the study period, a larger proportion of hyperthyroid patients were referred to treatment in hospital departments and fewer patients are managed only by general practitioners (results not shown). We speculate that more mild cases of hyperthyroidism (with subsequently lower risk of AF) were identified and referred to treatment in hospital departments which may affect our results towards a lower risk of AF in the study population. Third, the use of routine electrocardiograms has declined in endocrinology departments, while home monitoring devices have become more common in patients where AF is suspected. Simultaneously, the recognition and awareness of the cardiological effects of hyperthyroidism have increased and all AF patients are screened for thyroid disease. Therefore, we consider it implausible that the reduction observed in the risk of AF can be attributed to detection bias.

4.5 | Strengths and limitations

The main strength of this study is the use of register data which provides a large sample size through 21 years and long follow-up after implementation of IF. Furthermore, the nationwide registers cover all patients treated in the tax-funded public hospitals and thus carries no risk of self-selection into the study and no loss to follow-up. Register diagnoses of hyperthyroidism[33] and AF[34] have been found to be of high validity. There is a risk that the index date is not precise for all hyperthyroid cases because of diagnostic delay. In 2013 and 2016 laws were passed securing the right to, respectively, diagnostic examinations within 1 month[35] and treatment within 1 month,[36] which can have reduced waiting times.

Despite the availability of information on several key confounders we acknowledge that there may be residual confounding. Smoking and alcohol can increase the risk of AF[37] and also affects thyroid function,[12] but individual-level information on this was not available. Also, increasing BMI is associated with AF,[38] but was not available. We attempted to define the subtype of hyperthyroidism from the diagnosis codes, but despite good validity of the overall diagnosis the validity of the subtype classification was found to be too poor. Therefore, we did not apply this variable.

4.6 | Conclusion and perspectives

A mandatory IF programme increasing the iodine status of the population from mild-moderate deficiency to low-adequacy might be associated with an initial small increase followed by a marked decrease in the risk of AF in patients with incident hyperthyroidism. This needs to be confirmed in future studies and more research is needed to elucidate the effect of IF on subtype and severity of hyperthyroidism in the patient population. If these results are confirmed, IF may not only reduce the population incidence of hyperthyroidism but may also lower the burden of morbidity in the remaining hyperthyroid patients.

ACKNOWLEDGEMENTS

The authors would like to thank Dorthe Corfitzen Pedersen for graphical assistance. The study received financial support from The Danish Heart Foundation grant no. 20-R141-A9683-22174. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ORCID

Line T. Møllehave http://orcid.org/0000-0001-7116-9346

REFERENCES

1. Benjamin EJ. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA*. 1994;271(11):840-844.
2. Frost L, Vestergaard P, Mosekilde L. Hyperthyroidism and risk of atrial fibrillation or flutter: a population-based study. *Arch Intern Med*. 2004;164(15):1675-1678.
3. Biondi B, Kahaly GJ. Cardiovascular involvement in patients with different causes of hyperthyroidism. *Nat Rev Endocrinol*. 2010;6(8):431-443.
4. Selmer C, Olesen JB, Hansen ML, et al. The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. *BMJ (Clinical research ed)*. 2012;345:e7895.
5. Huang M, Yang S, Ge G, Zhi H, Wang L. Effects of thyroid dysfunction and the thyroid-stimulating hormone levels on the risk of atrial fibrillation: a systematic review and dose-response meta-analysis from cohort studies. *Endocrine Pract*. 2022;28(8):822-831.
6. Ellervik C, Roselli C, Christophersen IE, et al. Assessment of the relationship between genetic determinants of thyroid function and atrial fibrillation: A Mendelian Randomization Study. *JAMA Cardiol*. 2019;4(2):144-152.

7. Bekiaridou A, Kartas A, Moysidis DV, et al. The bidirectional relationship of thyroid disease and atrial fibrillation: established knowledge and future considerations. *Rev Endocr Metab Disord*. 2022;23(3):621-630.
8. Bielecka-Dabrowa A, Mikhailidis DP, Rysz J, Banach M. The mechanisms of atrial fibrillation in hyperthyroidism. *Thyroid Res*. 2009;2(1):4.
9. De Leo S, Lee SY, Braverman LE. Hyperthyroidism. *Lancet*. 2016;388(10047):906-918.
10. Dorian P, Jung W, Newman D, et al. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. *J Am Coll Cardiol*. 2000;36(4):1303-1309.
11. Schmidt M, Ulrichsen SP, Pedersen L, Bøtker HE, Nielsen JC, Sørensen HT. 30-year nationwide trends in incidence of atrial fibrillation in Denmark and associated 5-year risk of heart failure, stroke, and death. *Int J Cardiol*. 2016;225:30-36.
12. Taylor PN, Albrecht D, Scholz A, et al. Global epidemiology of hyperthyroidism and hypothyroidism. *Nat Rev Endocrinol*. 2018;14(5):301-316.
13. Bekendtgørelse om tilsætning af jod til husholdningssalt og salt i brød og almindeligt bagværk m.v. In. Fødevareministeriets bekendtgørelse nr. 6272000.
14. Rasmussen LB, Carlé A, Jørgensen T, et al. Iodine intake before and after mandatory iodization in Denmark: results from the Danish investigation of iodine intake and thyroid diseases (DanThyr) study. *Br J Nutr*. 2008;100(1):166-173.
15. Petersen M, Knudsen N, Carlé A, et al. Thyrotoxicosis after iodine fortification. A 21-year Danish population-based study. *Clin Endocrinol*. 2018;89(3):360-366.
16. Zimmermann MB, Boelaert K. Iodine deficiency and thyroid disorders. *Lancet Diabetes Endocrinol*. 2015;3(4):286-295.
17. Petersen M, Bülow Pedersen I, Knudsen N, et al. Changes in subtypes of overt thyrotoxicosis and hypothyroidism following iodine fortification. *Clin Endocrinol*. 2019;91(5):652-659.
18. Erlangsen A, Fedyszyn I. Danish nationwide registers for public health and health-related research. *Scand J Public Health*. 2015;43(4):333-339.
19. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449-490.
20. Wallach Kildemoes H, Toft Sørensen H, Hallas J. The Danish National Prescription Registry. *Scand J Public Health*. 2011;39(7 suppl):38-41.
21. Pedersen CB. The Danish civil registration system. *Scand J Public Health*. 2011;39(7 suppl):22-25.
22. Jensen VM, Rasmussen AW. Danish education registers. *Scand J Public Health*. 2011;39(7 suppl):91-94.
23. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.
24. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173(6):676-682.
25. Haupt T, Petersen J, Ellekilde G, et al. Plasma suPAR levels are associated with mortality, admission time, and Charlson Comorbidity Index in the acutely admitted medical patient: a prospective observational study. *Crit Care*. 2012;16(4):R130.
26. Aminorroaya A, Rohani S, Sattari G, Haghighi S, Amini M. Iodine repletion, thyrotoxicosis and atrial fibrillation in Isfahan, Iran. *Ann Saudi Med*. 2004;24(1):13-17.
27. Ponomartseva DA, Derevitskii IV, Kovalchuk SV, Babenko AY. Prediction model for thyrotoxic atrial fibrillation: a retrospective study. *BMC Endocr Disord*. 2021;21(1):150.
28. Lillevang-Johansen M, Abrahamsen B, Jørgensen HL, Brix TH, Hegedüs L. Duration of hyperthyroidism and lack of sufficient treatment are associated with increased cardiovascular risk. *Thyroid*. 2019;29(3):332-340.
29. Agner T, Almdal T, Thorsteinsson B, Agner E. A reevaluation of atrial fibrillation in thyrotoxicosis. *Dan Med Bull*. 1984;31(2):157-159.
30. Turan E. Comparison of cardiac arrhythmia types between hyperthyroid patients with Graves' disease and toxic nodular goiter. *Acta Endocrinol (Bucharest)*. 2018;14(3):324-329.
31. Carlé A, Knudsen N, Pedersen IB, et al. Determinants of serum T4 and T3 at the time of diagnosis in nosological types of thyrotoxicosis: a population-based study. *Eur J Endocrinol*. 2013;169(5):537-545.
32. Medici BB, Nygaard B, La Cour JL, et al. Changes in prescription routines for treating hypothyroidism between 2001 and 2015: An observational study of 929,684 primary care patients in Copenhagen. *Thyroid*. 2019;29(7):910-919.
33. Vestergaard P, Mosekilde L. Fractures in patients with hyperthyroidism and hypothyroidism: a nationwide follow-up study in 16,249 patients. *Thyroid*. 2002;12(5):411-419.
34. Rix TA, Riahi S, Overvad K, Lundbye-Christensen S, Schmidt EB, Joensen AM. Validity of the diagnoses atrial fibrillation and atrial flutter in a Danish patient registry. *Scand Cardiovasc J*. 2012;46(3):149-153.
35. Lov om ændring af sundhedsloven og lov om klage og erstatningsadgang inden for sundhedsvæsenet (Ret til hurtig udredning i sygehusvæsenet og differentieret ret til udvidet frit sygehusvalg m.v.). LOV nr 1401 af 23/12/2012 (Historisk). In: Indenrigs- og Sundhedsministeriet; 2012. In English: Act amending the Health Act and the Act on Complaint and Compensation Access within the Healthcare System (Right to rapid assessment in the hospital system and differentiated right to extended free choice of hospital, etc.). Act no. 1401 of December 23, 2012 (Historical). In: Ministry of the Interior and Health; 2012.
36. Lov om ændring af sundhedsloven (Reel ret til hurtig udredning og udvidet frit sygehusvalg ved 30 dages ventetid på behandling m.v.). LOV nr 653 af 08/06/2016 (Historisk). In: Indenrigs- og Sundhedsministeriet; 2016. In English: Act amending the Health Act (Actual right to rapid assessment and extended free choice of hospital at 30-day waiting period for treatment, etc.). Act no. 653 of June 8, 2016 (Historical). In: Ministry of the Interior and Health; 2016.
37. Dong XJ, Wang BB, Hou FF, et al. Global burden of atrial fibrillation/atrial flutter and its attributable risk factors from 1990 to 2019. *EP Europace*. 2023;25(3):793-803.
38. Kim MS, Kim WJ, Khera AV, et al. Association between adiposity and cardiovascular outcomes: an umbrella review and meta-analysis of observational and Mendelian randomization studies. *Eur Heart J*. 2021;42(34):3388-3403.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Møllehave LT, Knudsen N, Prescott E, et al. Does iodine fortification affect the risk of atrial fibrillation in incident hyperthyroidism? A national register-based cohort. *Clin Endocrinol (Oxf)*. 2024;100:502-510. doi:10.1111/cen.15042