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ORIGINAL ARTICLE

Thyroid Function and Dysfunction in Relation to 16 Cardiovascular Diseases

A Mendelian Randomization Study

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BACKGROUND: Subclinical thyroid dysfunction, defined as thyroid-stimulating hormone levels outside the reference range with normal free thyroxine levels in asymptomatic patients, is associated with alterations in cardiac hemodynamics. We used Mendelian randomization to assess the role of thyroid dysfunction for cardiovascular disease (CVD).

METHODS: Single-nucleotide polymorphisms associated with thyroid function were identified from a genome-wide association meta-analysis in up to 72 167 individuals. Data for genetic associations with CVD were obtained from meta-analyses of genome-wide association studies of atrial fibrillation (n=537 409 individuals), coronary artery disease (n=184 305 individuals), and ischemic stroke (n=438 847) as well as from the UK Biobank (n=367 703 individuals).

RESULTS: Genetically predicted thyroid-stimulating hormone levels and hyperthyroidism were statistically significantly associated with atrial fibrillation but no other CVDs at the Bonferroni-corrected level of significance ($P<7.8\times10^{-4}$). The odds ratios of atrial fibrillation were 1.15 (95% CI, 1.11–1.19; $P=2.4\times10^{-14}$) per genetically predicted 1 SD decrease in thyroid-stimulating hormone levels and 1.05 (95% CI, 1.03–1.08; $P=5.4\times10^{-5}$) for genetic predisposition to hyperthyroidism. Genetically predicted free thyroxin levels were not statistically significantly associated with any CVD.

CONCLUSIONS: This Mendelian randomization study supports evidence for a causal association of decreased thyroid-stimulating hormone levels in the direction of a mild form of hyperthyroidism with an increased risk of atrial fibrillation but no other CVDs.

Key Words: atrial fibrillation ■ cardiovascular disease ■ hormones ■ hyperthyroidism ■ thyrotropin

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Subclinical thyroid dysfunction, defined as serum thyroid-stimulating hormone (TSH) levels below (hyperthyroidism) or above (hypothyroidism) the reference interval with normal free thyroxine (FT4) levels in asymptomatic patients,[1] is a common condition and is particularly prevalent in older women.[2–6] Subclinical thyroid dysfunction is associated with alterations in cardiac hemodynamics, such as impaired cardiac contractility, increased heart rate, systolic hypertension, increased left ventricular mass, and diastolic dysfunction.[1,7–12]

Data from observational prospective studies on subclinical thyroid dysfunction in relation to risk of cardiovascular disease (CVD) are inconclusive. Subclinical hyperthyroidism was reported to be positively associated with risk of atrial fibrillation (AF),[4,13–18] coronary heart disease,[18,19] overall stroke,[20] and heart failure[5] in several studies. Subclinical hypothyroidism has been found to be associated with increased risk of coronary heart disease,[3,21,22] heart failure,[5] and cardiac mortality[3,21,22] but not with risk of AF or stroke.[21] However, residual confounding or reverse causality may have affected those associations and may also explain the inconsistent results.

Genetic variants with an explicit association with a potential risk factor (eg, TSH levels) can be used as unbiased proxies for the risk factor to determine causality.[23,24] This method, known as Mendelian randomization (MR), builds on Mendel's second law and the fact that genetic variants are randomly distributed at conception and thus unlikely related to possible confounders. In addition, reverse causality is avoided because disease cannot affect genotype.

Given the controversy about the role of thyroid dysfunction for CVD, we used the MR design to determine the associations of TSH levels and hyperthyroidism and hypothyroidism with CVD. Our primary aim was to assess the associations of TSH levels and hyperthyroidism and hypothyroidism with AF, coronary artery disease (CAD), and ischemic stroke using data from meta-analyses of genome-wide association studies (GWAS) of these outcomes[25–27] and data from the UK Biobank.[28] In secondary analyses, we investigated the associations of TSH levels and hyperthyroidism and hypothyroidism with other CVD outcomes in UK Biobank. Finally, we examined whether there is an association between FT4 levels and any CVD outcome.

METHODS

The methods are available in the Material in the Data Supplement. This study is based on publicly available summary level data, which are available in the Material in the Data Supplement. All studies included in the analyses received ethics approval from a relevant institutional review board, and all participants had provided informed consent.

RESULTS

Genetic Consortia

Analyses using data from 3 large-scale genetic consortia (Atrial Fibrillation Consortium 2018 GWAS dataset, Coronary Artery Disease Genome-wide Replication and Meta-analysis plus The Coronary Artery Disease consortium's 1000 Genomes-based GWAS, and MEGASTROKE) revealed a statistical significant association between genetically decreased TSH levels and higher odds of AF (odds ratio [OR] 1.15; 95% CI, 1.11–1.19; $P=2.4\times10^{-14}$) but not CAD or ischemic stroke as a whole (Figure). Among ischemic stroke subtypes, genetically decreased TSH levels were associated with higher odds of cardioembolic stroke (OR, 1.11; 95% CI, 1.02–1.22; $P=0.02$; Figure) but the association did not achieve statistical significance at the Bonferroni-corrected threshold. Hyperthyroidism was associated with higher odds of AF (OR, 1.05; 95% CI, 1.03–1.08; $P=5.4\times10^{-5}$), whereas hypothyroidism was associated with lower odds of AF (OR, 0.95; 95% CI, 0.92–0.98; $P=8.0\times10^{-4}$; Figure). Genetically higher FT4 levels were not associated with any outcome (Figure).

Results for AF were similar when using data from the Atrial Fibrillation Consortium 2017 GWAS dataset. In these analyses, the ORs were 1.16 (95% CI, 1.10–1.23, $P=7.1\times10^{-7}$) per 1 SD decrease of TSH levels, 1.05 (95% CI, 1.01–1.09; $P=0.02$) for hyperthyroidism, 0.94 (95% CI, 0.89–0.99; $P=0.01$) for hypothyroidism, and 1.00 (95% CI, 0.92–1.09; $P=0.93$) per 1 SD increase of FT4 levels.

UK Biobank

In the UK Biobank, genetically decreased TSH levels were statistically significantly associated with higher odds of AF (OR, 1.20; 95% CI, 1.13–1.27; $P=1.4\times10^{-9}$) but not the other outcomes (Table). There was suggestive evidence of associations between hyperthyroidism and higher odds of AF and lower odds of thoracic aortic aneurysm; hypothyroidism and higher odds of CAD and hypertension; and increased FT4 levels and lower odds of peripheral arterial disease (Table).

Sensitivity Analyses

The associations of TSH and FT4 levels with the outcomes were robust when limiting the analysis to the lead single-nucleotide polymorphism (SNP) of each locus (Table V in the Data Supplement). When excluding the 3 loci associated with both hyperthyroidism and hypothyroidism, the ORs of AF (using data from Atrial Fibrillation Consortium 2018 GWAS dataset) were 1.07 (95% CI, 1.04–1.11; $P=3.6\times10^{-5}$) for hyperthyroidism and 0.99 (95% CI, 0.95–1.03; $P=0.59$) for hypothyroidism. The results for TSH levels using the

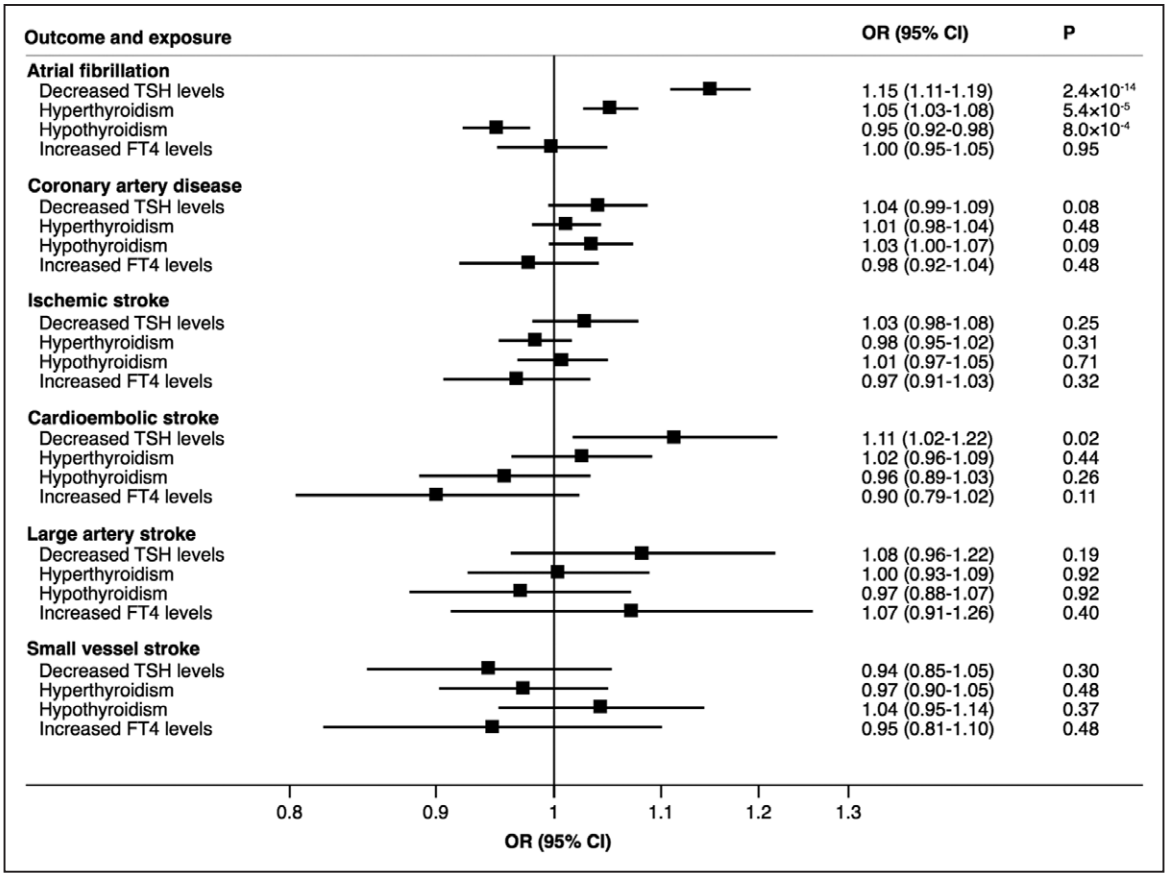

Figure. Associations of genetically decreased thyroid-stimulating hormone (TSH) levels, hyperthyroidism, hypothyroidism, and increased FT4 levels with odds ratio (OR) of atrial fibrillation (AF), coronary artery disease (CAD), and ischemic stroke and its subtypes based on data from the Atrial Fibrillation Consortium (AFGen), Coronary Artery Disease Genome-wide Replication and Meta-analysis plus The Coronary Artery Disease consortium's 1000 Genomes-based GWAS (CARDIoGRAMplusC4D), and MEGASTROKE consortia.

ORs are expressed per 1 SD decrease of TSH levels, per one unit higher log-odds of hyperthyroidism and hypothyroidism and per 1 SD increase of FT4 levels. Hyperthyroidism: TSH levels below the reference range in the population and hypothyroidism: TSH levels above the reference range in the population.

weighted median and MR-Egger approaches were similar to those of the primary analysis (inverse-variance weighted method), but the precision of the estimates was as expected lower (Table VI in the Data Supplement). The MR-Egger analysis provided no evidence of directional pleiotropy (Table VI in the Data Supplement). The MR-PRESSO (Mendelian Randomization Pleiotropy RESidual Sum and Outlier) analysis identified no outlying SNPs in the analysis of TSH levels and AF. However, there was one outlying SNP in the analyses of TSH levels in relation to CAD and aortic valve stenosis and 3 outlying SNPs in the analyses of TSH and hypertension (Table VII in the Data Supplement). Exclusion of those SNPs did not change the results appreciably (Table VII in the Data Supplement). Likewise, the inclusion of the pleiotropic SNP in the *ABO* gene did not change the interpretation of the results for TSH levels and any CVD outcome (Table VIII in the Data Supplement).

DISCUSSION

For the first time, this study uses an MR approach to systematically investigate the relationship of thyroid function and dysfunction with a wide range of CVD outcomes. Our results showed that genetically decreased TSH levels and hyperthyroidism were robustly associated with higher odds of AF. We found no statistically significant and consistent associations of TSH levels, hyperthyroidism or hypothyroidism, or FT4 levels with the other CVD outcomes, though there was suggestive evidence of possible associations between decreased TSH levels and higher odds of cardioembolic stroke, hyperthyroidism and lower odds of thoracic aortic aneurysm, hypothyroidism and higher odds AF, CAD and hypertension, and increased FT4 levels and lower odds of peripheral arterial disease. However, those suggestive associations were only observed in one dataset (one of the genetic consortia or UK Biobank) or were not consistent in sensitivity analyses.

Our findings support prior observational studies associating decreased TSH levels and hyperthyroidism to increased risk of AF[4,13–17] as well as results from 2 recent MR studies associating genetically higher TSH levels to decreased risk of AF.[29,30] However, an individual patient data analysis of 30 085 participants (including 2574 AF cases) from 11 cohorts showed only a suggestive association of lower TSH levels within the reference range

Table. Associations of Genetically Predicted Decreased TSH Levels, Hyperthyroidism, Hypothyroidism, and Increased FT4 Levels With OR of 13 Cardiovascular Diseases in UK Biobank

Outcome	Cases*	TSH Levels		Hyperthyroidism		Hypothyroidism		FT4 Levels	
		OR (95% CI)†	*P* Value	OR (95% CI)†	*P* Value	OR (95% CI)†	*P* Value	OR (95% CI)†	*P* Value
Atrial fibrillation	13 538	1.20 (1.13–1.27)	1.4×10^{-9}	1.06 (1.02–1.10)	0.005	0.95 (0.90–1.01)	0.11	0.97 (0.90–1.05)	0.47
Coronary artery disease	24 531	1.00 (0.96–1.05)	0.91	0.99 (0.96–1.02)	0.40	1.06 (1.02–1.11)	0.008	0.99 (0.93–1.05)	0.63
Ischemic stroke	3554	1.02 (0.91–1.14)	0.75	1.03 (0.95–1.11)	0.51	1.10 (0.99–1.22)	0.09	1.01 (0.87–1.17)	0.91
Intracerebral hemorrhage	1655	0.99 (0.84–1.17)	0.91	1.04 (0.93–1.17)	0.47	0.99 (0.84–1.16)	0.89	1.03 (0.83–1.28)	0.81
Subarachnoid hemorrhage	1834	1.06 (0.91–1.24)	0.44	1.08 (0.97–1.20)	0.17	0.92 (0.79–1.07)	0.28	1.10 (0.89–1.36)	0.36
Heart failure	4803	1.02 (0.92–1.12)	0.71	0.98 (0.91–1.04)	0.46	1.04 (0.95–1.14)	0.41	1.01 (0.89–1.15)	0.91
Aortic valve stenosis	1252	1.01 (0.99–1.04)	0.35	1.01 (0.99–1.03)	0.18	1.00 (0.97–1.02)	0.84	1.01 (0.98–1.05)	0.51
Abdominal aortic aneurysm	758	0.90 (0.71–1.15)	0.41	1.02 (0.86–1.20)	0.84	0.86 (0.68–1.08)	0.20	1.05 (0.76–1.46)	0.75
Thoracic aortic aneurysm	231	0.65 (0.42–1.01)	0.06	0.60 (0.44–0.81)	0.001	1.47 (0.97–2.23)	0.07	0.64 (0.36–1.13)	0.13
Deep vein thrombosis	3514	1.07 (1.00–1.15)	0.05	1.00 (0.95–1.05)	0.93	1.04 (0.97–1.11)	0.28	0.98 (0.89–1.08)	0.65
Pulmonary embolism	8891	1.09 (0.99–1.20)	0.07	1.03 (0.96–1.10)	0.39	1.06 (0.96–1.16)	0.23	0.94 (0.83–1.06)	0.31
Peripheral arterial disease	5097	1.06 (0.94–1.18)	0.34	0.99 (0.92–1.07)	0.86	1.06 (0.95–1.18)	0.33	0.83 (0.71–0.96)	0.01
Hypertension	119 500	1.01 (0.98–1.03)	0.66	1.01 (1.00–1.03)	0.14	1.04 (1.01–1.06)	0.003	0.99 (0.96–1.02)	0.65

Hyperthyroidism: TSH levels below the reference range in the population and hypothyroidism: TSH levels above the reference range in the population. FT4 indicates free thyroxine; and TSH, thyroid-stimulating hormone.

*Total number of participants is 367 703.

†Odds ratios are expressed per 1 SD decrease of TSH levels, per one unit higher log-odds of hyperthyroidism and hypothyroidism, and per 1 SD increase of FT4 levels.

with increased risk of AF (*P* for linear trend =0.054).[31] That analysis further showed that FT4 levels were positively associated with AF risk in euthyroid individuals.[31] A positive association between genetically higher FT4 levels and AF was not detected in the present MR analysis, but we were unable to simultaneously control for TSH levels. In addition, these MR results reflect the association between lifelong higher FT4 levels on AF risk and it is unknown whether high FT4 levels during different periods in the life course differently affect the risk of developing AF.

An association between decreased TSH levels and increased risk of AF may in part be mediated by increased left ventricular mass[8,10–12] and diastolic dysfunction,[7] both of which are associated with an increased risk of AF,[32,33] though the causal relationships remain unclear. Findings from an experimental study in mice showed that hyperthyroidism, with suppression of circulating TSH levels, leads to impaired Pitx2>Wnt>microRNA signaling,[34] thus providing a molecular link between hyperthyroidism and AF since *PITX2* is one of the strongest genetic locus related to AF.[25]

A chief strength of this study is the MR approach, which reduces systematic biases (eg, confounding and reverse causality) that can distort the results of conventional observational studies. Another major strength is that we examined the associations of thyroid function and dysfunction with AF, CAD, and ischemic stroke using data from large-scale genetic consortia, which included a large number of cases. Hence, we had high statistical power to detect weak associations of the examined exposures and those outcomes. However, the power was low in the analyses of several CVD outcomes measured in UK Biobank, in particular intracerebral and subarachnoid hemorrhage, abdominal and thoracic aortic aneurysm, and aortic valve stenosis. We thus cannot rule out that the lack of association with those outcomes are because of insufficient power. We could restrict the study populations (except in the Coronary Artery Disease Genome-wide Replication and Meta-analysis plus The Coronary Artery Disease consortium's 1000 Genomes-based GWAS consortium) to individuals of European ancestry, a constraint that reduced bias from population stratification. A limitation of any MR analysis is that pleiotropy cannot be ruled out as an explanation for an observed association. Nevertheless, we found no evidence that directional pleiotropy may have influenced the results. A further shortcoming is that we could not examine U-shaped associations or effects of very low or high TSH and FT4 levels or different combinations of TSH and FT4 levels on CVD risk.

CONCLUSIONS

This MR study supports evidence for a causal association between decreased TSH levels in the direction of a mild form of hyperthyroidism and increased risk of AF. Suggestive evidence of possible associations was found between thyroid dysfunction and some other CVD outcomes, including cardioembolic stroke. These findings may have clinical implications because they suggest that treatment of subclinical hyperthyroidism may be a complement to other possible prevention strategies for

AF, such as reducing excessive alcohol consumption, tobacco control, reducing blood pressure, blood glucose, and body mass, and therapy for myocardial infarction and heart failure.[35]

ARTICLE INFORMATION

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Disclosures

None.

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