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<7.8×10⁻⁴). The odds ratios of atrial fibrillation were 1.15 (95% CI, 1.11–1.19; P=2.4×10⁻¹⁴) per genetically predicted 1 SD decrease in thyroid-stimulating hormone levels and 1.05 (95% CI, 1.03–1.08; P=5.4×10⁻⁵) 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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Section studies (GWAS) of these outcomes and data from meta-analyses of genome-wide association studies (GWAS) of coronary artery disease (CAD), and ischemic stroke using the Atrial Fibrillation Consortium 2018 GWAS dataset.

Our primary aim was to assess the associations of TSH levels and hyperthyroidism with CAD, and ischemic stroke using data from meta-analyses of genome-wide association studies (GWAS) of these outcomes and data from the UK Biobank. 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.

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 MEGA-STROKE) 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=2.4×10^{-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=5.4×10^{-5}), whereas hypothyroidism was associated with lower odds of AF (OR, 0.95; 95% CI, 0.92–0.98; P=8.0×10^{-4}; Figure). Genetically higher FT4 levels were not associated with any outcome (Figure).

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=1.4×10^{-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=3.6×10^{-5}) for hyperthyroidism and 0.99 (95% CI, 0.95–1.03; P=0.59) for hypothyroidism. The results for TSH levels using the
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 of 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, coronary artery disease 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.
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 and AF was not detected in the present MR analysis. 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 thyroid dysfunction and CVD.

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cases*</th>
<th>TSH Levels OR (95% CI)†</th>
<th>P Value</th>
<th>Hyperthyroidism P Value</th>
<th>Hypothyroidism P Value</th>
<th>FT4 Levels OR (95% CI)†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>13538</td>
<td>1.20 (1.13–1.27)</td>
<td>1.4×10^-4</td>
<td>1.06 (1.02–1.10)</td>
<td>0.005</td>
<td>0.95 (0.90–1.01)</td>
<td>0.11</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>24531</td>
<td>1.00 (0.96–1.05)</td>
<td>0.91</td>
<td>0.99 (0.96–1.02)</td>
<td>0.40</td>
<td>1.06 (1.02–1.11)</td>
<td>0.008</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>3554</td>
<td>1.02 (0.91–1.14)</td>
<td>0.75</td>
<td>1.03 (0.95–1.11)</td>
<td>0.51</td>
<td>1.10 (0.99–1.22)</td>
<td>0.09</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>1655</td>
<td>0.99 (0.84–1.17)</td>
<td>0.91</td>
<td>1.04 (0.93–1.17)</td>
<td>0.47</td>
<td>0.99 (0.84–1.16)</td>
<td>0.89</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>1834</td>
<td>1.06 (0.91–1.24)</td>
<td>0.44</td>
<td>1.08 (0.97–1.20)</td>
<td>0.17</td>
<td>0.92 (0.79–1.07)</td>
<td>0.28</td>
</tr>
<tr>
<td>Heart failure</td>
<td>4803</td>
<td>1.02 (0.92–1.12)</td>
<td>0.71</td>
<td>0.98 (0.91–1.04)</td>
<td>0.46</td>
<td>1.04 (0.95–1.14)</td>
<td>0.41</td>
</tr>
<tr>
<td>Aortic valve stenosis</td>
<td>1252</td>
<td>1.01 (0.99–1.04)</td>
<td>0.35</td>
<td>1.01 (0.99–1.03)</td>
<td>0.18</td>
<td>1.00 (0.97–1.02)</td>
<td>0.84</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
<td>758</td>
<td>0.90 (0.71–1.15)</td>
<td>0.41</td>
<td>1.02 (0.86–1.20)</td>
<td>0.84</td>
<td>0.86 (0.68–1.08)</td>
<td>0.20</td>
</tr>
<tr>
<td>Thoracic aortic aneurysm</td>
<td>231</td>
<td>0.65 (0.42–0.91)</td>
<td>0.06</td>
<td>0.60 (0.44–0.81)</td>
<td>0.001</td>
<td>1.47 (0.97–2.23)</td>
<td>0.07</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>3514</td>
<td>1.07 (1.00–1.15)</td>
<td>0.05</td>
<td>1.00 (0.95–1.05)</td>
<td>0.93</td>
<td>1.04 (0.97–1.11)</td>
<td>0.28</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>8891</td>
<td>1.09 (0.99–1.20)</td>
<td>0.07</td>
<td>1.03 (0.96–1.10)</td>
<td>0.39</td>
<td>1.06 (0.96–1.16)</td>
<td>0.23</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>5097</td>
<td>1.06 (0.94–1.18)</td>
<td>0.34</td>
<td>0.99 (0.92–1.07)</td>
<td>0.86</td>
<td>1.06 (0.95–1.18)</td>
<td>0.33</td>
</tr>
<tr>
<td>Hypertension</td>
<td>119500</td>
<td>1.01 (0.98–1.03)</td>
<td>0.66</td>
<td>1.01 (1.00–1.03)</td>
<td>0.14</td>
<td>1.04 (1.01–1.06)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

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.
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.  

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Disclosures

None.

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