Background: Subclinical hypothyroidism has been associated with systolic and diastolic cardiac dysfunction and an elevated cholesterol level, but data on cardiovascular outcomes and death are limited.

Methods: We studied 2730 men and women, aged 70 to 79 years, with baseline thyrotropin (TSH) measurements and 4-year follow-up data to determine whether subclinical hypothyroidism was associated with congestive heart failure (CHF), coronary heart disease, stroke, peripheral arterial disease, and cardiovascular-related and total mortality. After the exclusion of participants with abnormal thyroxine levels, subclinical hypothyroidism was defined as a TSH level of 4.5 mIU/L or greater, and was further classified according to TSH levels (4.5-6.9, 7.0-9.9, and ≥10.0 mIU/L).

Results: Subclinical hypothyroidism was present in 338 (12.4%) of the participants. Compared with euthyroid participants, CHF events occurred more frequently among those with a TSH level of 7.0 mIU/L or greater (33.0 vs 16.5 per 1000 person-years; \( P = .006 \)), but not among those with TSH levels between 4.5 and 6.9 mIU/L. In multivariate analyses, the risk of CHF was higher among those with high TSH levels (TSH of 7.0-9.9 mIU/L: hazard ratio, 2.58 [95% confidence interval, 1.19-5.60]; and TSH of ≥10.0 mIU/L: hazard ratio, 3.26 [95% confidence interval, 1.37-7.77]). Among the 2555 participants without CHF at baseline, the hazard ratio for incident CHF events was 2.33 (95% confidence interval, 1.10-4.96; \( P = .03 \)) in those with a TSH of 7.0 mIU/L or greater. Subclinical hypothyroidism was not associated with increased risk for coronary heart disease, stroke, peripheral arterial disease, or cardiovascular-related or total mortality.

Conclusions: Subclinical hypothyroidism is associated with an increased risk of CHF among older adults with a TSH level of 7.0 mIU/L or greater, but not with other cardiovascular events and mortality. Further investigation is warranted to assess whether subclinical hypothyroidism causes or worsens preexisting heart failure.

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SUBCLINICAL HYPOTHYROIDISM refers to patients who have an elevated thyrotropin (formerly thyroid-stimulating hormone) (TSH) level and a normal free thyroxine (\( T_4 \)) level.\(^1\) The prevalence of subclinical hypothyroidism increases with age, and is about 10% in women older than 70 years and is somewhat lower in men.\(^2\,\!^3\) Controversy persists as to whether screening and treatment of subclinical hypothyroidism is warranted,\(^1\,\!^3\,\!^5\,\!^6\) because evidence about the benefits and the risks is limited.\(^1\,\!^3\)

Subclinical hypothyroidism has been associated with higher levels of some cardiovascular risk factors. Despite some conflicting results,\(^8\) many studies\(^7\,\!^9\) found that subjects with subclinical hypothyroidism have higher total cholesterol and low-density lipoprotein cholesterol levels than euthyroid subjects. A cross-sectional study\(^10\) showed that subjects with subclinical hypothyroidism have increased C-reactive protein values. Subclinical hypothyroidism has been associated with increased risk for atherosclerosis.\(^11\,\!^12\) However, data on coronary heart disease (CHD) in subjects with subclinical hypothyroidism are conflicting.\(^3\) Many studies are cross-sectional\(^12\,\!^13\) or case-control\(^15\,\!^16\) studies, and some discrepancies may result from study design. Two prospective studies\(^12\,\!^17\) included fewer than 20 CHD events. To our knowledge, no randomized studies have assessed the impact of \( T_4 \) replacement on clinical cardiac endpoints.\(^3\)

See also pages 2451 and 2467

Subclinical hypothyroidism has also been associated with diastolic and systolic cardiac dysfunction, and \( T_4 \) replacement improves cardiac function in subjects with subclinical hypothyroidism.\(^18\) However, these studies are limited by the small sample size.
size (range, 8-26 subjects); the lack of important clinical end points, such as symptomatic congestive heart failure (CHF); and the uncertain clinical significance of changes in cardiac function found in intervention trials. To our knowledge, no study has directly addressed the relationship between subclinical hypothyroidism and CHF.

Because data on cardiovascular outcomes in subjects with subclinical hypothyroidism are limited, we performed a prospective analysis in a longitudinal cohort study of older adults to examine rates of CHF, CHD, stroke, peripheral arterial disease (PAD), and cardiovascular-related and total mortality in relationship to TSH levels.

METHODS

SUBJECTS AND DESIGN

Participants were part of the Health, Aging, and Body Composition Study, a population-based cohort study that began in April 1997; the participants were 3075 healthy community-dwelling men and women aged 70 to 79 years at enrollment. Participants were identified from a random sample of white and all black Medicare-eligible adults living in designated ZIP code areas surrounding Pittsburgh and Memphis, Tenn: details of the eligibility criteria have been previously described. All participants gave written informed consent; the institutional review boards at both study sites approved the protocol.

Fasting TSH levels were measured in 2799 participants, as not all of the 3075 participants of the Health, Aging, and Body Composition Study had their fasting TSH levels measured. We excluded 2 participants who were taking antithyroid medications, 32 with a TSH level of 0.1 mIU/L or less, 23 with overt hypothyroidism, and 2 with low T4 but normal TSH levels. We also excluded participants who were taking amiodarone, because of its influence on TSH levels and its use to treat cardiovascular disease (CVD). The final sample for our analyses was 2730 participants. Participants were given their TSH results if the TSH level was 7.0 mIU/L or greater, and only those with overt thyroid abnormalities were encouraged to seek medical attention.

MEASUREMENTS

Thyroid Hormones

Thyrotropin levels were measured by immunoassay (ACS; Chiron Diagnostics Corp, Emeryville, Calif). The coefficient of variation for TSH was 4.1% at 18.94 mIU/L and 3.6% at 1.26 mIU/L. Free T4 was measured by competitive immunoassay (ACS; Chiron Diagnostics Corp) on participants with a TSH value of 7.0 mIU/L or greater or 0.1 mIU/L or less. The normal range of T4 was measured as previously described. We also excluded participants who were taking amiodarone, because of its influence on TSH levels and its use to treat cardiovascular disease (CVD). The final sample for our analyses was 2730 participants. Participants were given their TSH results if the TSH level was 7.0 mIU/L or greater, and only those with overt thyroid abnormalities were encouraged to seek medical attention.

Cardiovascular Events

During the 4-year follow-up, we assessed CHF events, CHD, stroke, PAD, and cardiovascular-related and total mortality. We included incident events among patients free of CVD at baseline and recurrent events among those with prevalent CVD at baseline. Each participant had a telephone contact every 6 months and an annual clinical visit during which health status was assessed and data about hospitalizations or major outpatient procedures were collected. Diagnoses and cause of death were adjudicated based on interview, review of all hospital records, death certificates, and other support documents by a panel of clinicians without knowledge of thyroid status. The definitions of these events were based on algorithms mirroring those of the Cardiovascular Health Study. Cardiovascular events were defined as the occurrence of death or hospitalization for the following events: CHD (acute myocardial infarction [MI], angina, angioplasty of coronary arteries, or coronary artery surgery), stroke (stroke or transient ischemic attack), PAD (hospitalization or procedures), or CHF. A panel of clinicians adjudicated CHF, based on symptoms, signs, chest x-ray film results, and echocardiographic findings, similar to the Cardiovascular Health Study. The CHF criteria required at least this diagnosis from a physician and treatment for CHF (ie, a current prescription for a diuretic agent and/or digitalis or a vasodilator). To increase our power to detect an association, we also defined an outcome of total atherosclerotic events as the first occurrence of CHD, stroke, or PAD. Follow-up time was from TSH measurement to the first onset of a cardiovascular event, loss to follow-up, or death.

Covariates

We collected data on self-reported race, level of education completed, family income, alcohol consumption, and self-reported health. We defined smoking status as never, current, or former (if the participants had smoked ≥100 cigarettes in their lives but were not currently smoking). Physical activity was assessed by questionnaire about all types of walking and exercise performed in the prior week. Diabetes mellitus was defined as a self-reported medical diagnosis and/or the use of any hypoglycemic medication at baseline. Medications taken in the previous 2 weeks were brought in and coded according to the Iowa Drug Information System.

We defined prevalent CVD as a diagnosis of CHD, stroke, PAD, or CHF at baseline. The presence of clinical disease at baseline was based on self-reported history, the use of selected drugs, and 5-year review of Medicare data. By using standardized protocols, we measured blood pressure, weight, and height. Total cholesterol, creatinine, and glucose levels were measured as previously described.

STATISTICAL ANALYSES

We used Kaplan-Meier curves and Cox proportional hazards models to assess the associations between subclinical hypothyroidism, TSH levels, and cardiovascular events. We calculated event rates per 1000 person-years of follow-up, and compared them with log-rank tests. The multivariate model included factors based on clinical plausibility (eg, diabetes mellitus and blood pressure) or an association (P<.05) with cardiovascular events (eg, income). We hypothesized some interactions a priori: the relation between subclinical hypothyroidism and cardiovascular events might differ by race, sex, thyroid hormone use, prevalent CVD, or prevalent CHF. We also performed sensitivity analyses excluding participants who used thyroid hormone, similar to previous studies.
variables were used as appropriate). To convert glucose to millimoles per liter, multiply by 0.0555; and to convert total cholesterol to millimoles per liter, multiply by 88.4; to convert glucose to millimoles per liter, multiply by 88.4.

Abbreviations: ACE, angiotensin-converting enzyme; CHF, congestive heart failure; CVD, cardiovascular disease.

§Percentages do not total 100 because of rounding.
‡Data are given as mean ± SD.
†Based on \( \chi^2 \) tests and t tests (\( \chi^2 \) tests for trend for multilevel categorical variables were used as appropriate).

FIGURE. Cumulative congestive heart failure (CHF) events in older subjects according to thyrotropin (TSH) levels. The rate of CHF events increased with higher TSH levels (\( P = .03 \) for trend). Participants with a TSH level of 7.0 mIU/L or greater had a higher rate of CHF events compared with euthyroid participants (\( P = .006 \)); this was not the case for those with a TSH level between 4.5 and 6.9 mIU/L.

We checked the proportional hazard assumption using graphical methods and Schoenfeld tests (\( P > .10 \) for all). To check the sensitivity of our results to the selection of covariates, we assessed models that included potential confounders with \( P < .20 \) after adjustment using backward deletion, and obtained similar results. Results are reported as hazard ratios (HRs), with 95% confidence intervals (CIs). We conducted analyses using Stata 8.0 (Stata Corp, College Station, Tex).

RESULTS

BASELINE CHARACTERISTICS

The mean age of the participants was 74.7 years; 51.0% were women, and 39.9% were black. The mean (SD) TSH level was 2.1 (2.3) mIU/L, and subclinical hypothyroidism was present in 338 participants (12.4%) at baseline. Subclinical hypothyroidism was less common in black subjects, and was associated with higher levels of education, physical activity, total cholesterol, and thyroid hormone use (Table 1). Prevalent CVD did not differ by thyroid status. The relative prevalence of CHF was 30% higher in participants with subclinical hypothyroidism compared with euthyroid participants, but this difference was not statistically significant.

SUBCLINICAL HYPOTHYROIDISM AND THE RISK OF CHF EVENTS

During the 4-year follow-up, 178 participants had CHF events. The rate of CHF events increased with higher TSH levels (\( P = .03 \) for trend), particularly among participants with a TSH levels of 7.0 mIU/L or greater (Figure). Participants with a TSH level of 7.0 mIU/L or greater had a higher rate of CHF events compared with euthyroid participants (35.0 vs 16.5 per 1000 person-years; \( P = .006 \)), but rates were similar among those with TSH levels between 4.5 and 6.9 mIU/L (\( P = .71 \)) (Table 2). In multivariate analyses, the risk of CHF events was higher among those with high TSH levels. By using TSH as a continuous variable, each standard deviation increase of 4.0 mIU/L was associated with a 30% increase in CHF events (95% CI, 8%-55%; \( P = .004 \)). The results were similar after...
logarithmic transformation of TSH. After excluding thyroid hormone users, the adjusted HR for CHF was 2.49 (95% CI, 1.20-5.18; \( P = .006 \)) among those with a TSH level of 7.0 mIU/L or greater. Among the 2555 participants without prevalent CHF at baseline, 127 had incident CHF events; the adjusted HR was 2.33 (95% CI, 1.10-4.96; \( P = .03 \)) in those with a TSH level of 7.0 mIU/L or greater. Among the 175 participants with prevalent CHF, 51 had recurrent CHF events; the adjusted HR was 7.62 (95% CI, 2.25-25.77; \( P = .001 \)) in those with a TSH level of 7.0 mIU/L or greater. The relationship between subclinical hypothyroidism and CHF did not differ by prevalent CHF, prevalent CVD, race, sex, or thyroid hormone use (\( P > .20 \) for each interaction).

In multivariate analyses, current smoking, prevalent CVD, poor or fair health, creatinine level, and marginal diabetes mellitus were also significantly associated with a higher risk of CHF events (Table 2).

### Table 2. Subclinical Hypothyroidism and the Risk of Congestive Heart Failure–Related Events

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%) of Events*</th>
<th>Rate, per 1000 Person-Years</th>
<th>Adjusted HR (95% CI)†</th>
<th>( P ) Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euthyroid subjects (n = 2392)</td>
<td>151 (6.3)</td>
<td>16.5</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Subjects with subclinical hypothyroidism (n = 338)</td>
<td>27 (8.0)</td>
<td>21.2</td>
<td>1.61 (1.02-2.52)</td>
<td>.04</td>
</tr>
<tr>
<td>TSH level, mIU/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \geq 4.5-6.9 ) (n = 230)</td>
<td>13 (5.7)</td>
<td>14.8</td>
<td>1.07 (0.57-2.01)</td>
<td></td>
</tr>
<tr>
<td>( \geq 7.0-9.9 ) (n = 64)</td>
<td>8 (12.5)</td>
<td>33.8</td>
<td>2.58 (1.19-5.60)</td>
<td>.002§</td>
</tr>
<tr>
<td>( \geq 10.0 ) (n = 44)</td>
<td>6 (13.6)</td>
<td>36.9</td>
<td>3.26 (1.37-7.77)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CHF, congestive heart failure; CI, confidence interval; HR, hazard ratio; NA, data not applicable; TSH, thyrotropin.

*The denominators for these percentages are given in parentheses in the first column.
†Adjusted for covariates in this table, age, sex, race, education, income, and use of thyroid hormone and angiotensin-converting enzyme inhibitors.
‡The HRs are adjusted for age, sex, race, smoking status, diabetes mellitus, prevalent cardiovascular disease, poor or fair health, blood pressure, total cholesterol, creatinine level, education, income, and use of thyroid hormone and angiotensin-converting enzyme inhibitors.
§Defined as coronary heart disease, stroke, peripheral disease, or congestive heart failure.

### Table 3. Subclinical Hypothyroidism and the Risk of Atherosclerotic Events*

<table>
<thead>
<tr>
<th>Variable</th>
<th>CHD Events (n = 334)</th>
<th>Stroke Events (n = 153)</th>
<th>PAD Events (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euthyroid subjects (n = 2392)</td>
<td>439 (50.9)</td>
<td>298 (33.5)</td>
<td>110 (13.6)</td>
</tr>
<tr>
<td>Subjects with subclinical hypothyroidism (n = 338)</td>
<td>60 (49.7)</td>
<td>36 (28.7)</td>
<td>22 (17.5)</td>
</tr>
<tr>
<td>TSH level, mIU/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \geq 4.5-6.9 ) (n = 230)</td>
<td>37 (45.0)</td>
<td>24 (28.3)</td>
<td>12 (14.1)</td>
</tr>
<tr>
<td>( \geq 7.0-9.9 ) (n = 64)</td>
<td>15 (68.2)</td>
<td>7 (29.3)</td>
<td>7 (29.3)</td>
</tr>
<tr>
<td>( \geq 10.0 ) (n = 44)</td>
<td>8 (48.5)</td>
<td>5 (29.6)</td>
<td>3 (17.7)</td>
</tr>
</tbody>
</table>

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; NA, data not applicable; PAD, peripheral arterial disease; TSH, thyrotropin.

*There were no significant (\( P < .05 \)) differences noted.
†Per 1000 person-years.
‡The HRs are adjusted for age, sex, race, smoking status, diabetes mellitus, prevalent cardiovascular disease, poor or fair health, blood pressure, total cholesterol level, creatinine level, education, income, and use of thyroid hormone and angiotensin-converting enzyme inhibitors.

**SUBCLINICAL HYPOTHYROIDISM AND THE RISK OF ATHEROSCLEROTIC EVENTS**

During the 4-year follow-up, 334 participants had CHD events (including 98 with an MI), 153 strokes, and 83 PAD events, for a total of 499 atherosclerotic events. The rate of each of these events did not significantly differ by thyroid status or TSH level (Table 3). In multivariate analyses, neither subclinical hypothyroidism nor TSH level independently predicted the risk of CHD, stroke, or PAD events.
Because cholesterol may be on the causal pathway between subclinical hypothyroidism and atherosclerotic events, we repeated our multivariate models omitting cholesterol levels, and obtained similar results. In this older population, total cholesterol level was not associated with a higher risk of atherosclerotic events (HR per 10 mg/dL [0.26 mmol/L], 0.98; 95% CI, 0.96-1.01). The results for subclinical hypothyroidism and atherosclerotic events did not differ by race, sex, thyroid hormone use, or prevalent CVD (P >.20 for each interaction). Excluding participants who used thyroid hormone or those with prevalent CVD yielded similar results. The only exception was an increased risk of MI for a TSH level of 10.0 mIU/L or greater compared with euthyroid participants. This association persisted after adjustment for cardiovascular risk factors. We found no consistent evidence that subclinical hypothyroidism was associated with CHD events, stroke, PAD, cardiovascular-related mortality, or total mortality.

Because cholesterol may be on the causal pathway between subclinical hypothyroidism and atherosclerotic events, we repeated our multivariate models omitting cholesterol levels, and obtained similar results. In this older population, total cholesterol level was not associated with a higher risk of atherosclerotic events (HR per 10 mg/dL [0.26 mmol/L], 0.98; 95% CI, 0.96-1.01). The results for subclinical hypothyroidism and atherosclerotic events did not differ by race, sex, thyroid hormone use, or prevalent CVD (P >.20 for each interaction). Excluding participants who used thyroid hormone or those with prevalent CVD yielded similar results. The only exception was an increased risk of MI for a TSH level of 10.0 mIU/L or greater compared with euthyroid participants. This association persisted after adjustment for cardiovascular risk factors. We found no consistent evidence that subclinical hypothyroidism was associated with CHD events, stroke, PAD, cardiovascular-related mortality, or total mortality.

In our study, a TSH level of 7.0 mIU/L or greater was predictive of incident and recurrent CHF events in those without and with a prevalent diagnosis of CHF. We did not have baseline echocardiographic data in the Health, Aging, and Body Composition Study, but this association was stronger for recurrent CHF, with a 7-fold increase in CHF events. Similarly, overt hypothyroidism may exacerbate underlying cardiac disease, but cardiomyopathy severe enough to cause heart failure is rare. Impaired myocardial relaxation and decreased myo-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cardiovascular-Related Mortality (n = 104)</th>
<th>Total Mortality (n = 324)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Events (Rate*)</td>
<td>Adjusted HR (95% CI)†</td>
</tr>
<tr>
<td>Euthyroid subjects (n = 2392)</td>
<td>94 (10.6)</td>
<td>1.00</td>
</tr>
<tr>
<td>Subjects with subclinical hypothyroidism (n = 338)</td>
<td>10 (8.0)</td>
<td>0.74 (0.34-1.61)</td>
</tr>
<tr>
<td>TSH level, mIU/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥4.5-6.9 (n = 230)</td>
<td>4 (4.7)</td>
<td>0.44 (0.14-1.39)</td>
</tr>
<tr>
<td>≥7.0-9.9 (n = 64)</td>
<td>3 (12.6)</td>
<td>1.30 (0.32-5.35)</td>
</tr>
<tr>
<td>≥10.0 (n = 44)</td>
<td>3 (17.7)</td>
<td>2.26 (0.54-9.45)</td>
</tr>
</tbody>
</table>

Abbreviations: See Table 3.
†The HRs are adjusted for age, sex, race, smoking status, diabetes mellitus, prevalent cardiovascular disease, poor or fair health, blood pressure, total cholesterol level, creatinine level, education, income, and use of thyroid hormone and angiotensin-converting enzyme inhibitors.
‡Per 1000 person-years.
§Tests for trend were used for multilevel categorical variables, and the Wald test from the Cox proportional hazards model was used for other variables.

In this population-based study of older adults, subclinical hypothyroidism was associated with a higher rate of incident and recurrent CHF among participants with a TSH level of 7.0 mIU/L or greater compared with euthyroid participants. This association persisted after adjustment for cardiovascular risk factors. We found no consistent evidence that subclinical hypothyroidism was associated with CHD events, stroke, PAD, cardiovascular-related mortality, or total mortality.

Previous studies have found that subjects with subclinical hypothyroidism had diastolic dysfunction at rest and systolic dysfunction with effort, and that these abnormalities were reversed by restoration of euthyroidism. Restoration of euthyroidism normalized cardiac function, with a shortening of isovolumic relaxation time and an increase of early diastolic/late diastolic mitral flow velocity ratio, and increased left ventricular ejection fraction during exercise. One randomized, double-blind, placebo-controlled trial confirmed the normalization of diastolic function and the decrease in prejection/ejection time ratio and increased left ventricular ejection fraction during exercise.

During the 4-year follow-up, 324 participants (11.9%) died, 32.1% of cardiovascular causes. The rates of cardiovascular-related and total mortality did not significantly differ by thyroid status or TSH level (Table 4). In multivariate analyses, neither subclinical hypothyroidism nor TSH level was associated with cardiovascular-related and total mortality. Total mortality was increased in those without prevalent CVD for a TSH level of 10.0 mIU/L or greater (HR, 3.13; 95% CI, 1.11-8.79), but did not reach statistical significance in the overall population (HR, 2.05; 95% CI, 0.90-4.68).
mechanisms leading to cardiac dysfunction in those with overt hypothyroidism.

We found no evidence that subclinical hypothyroidism was associated with risk of CHD, except for incident MI in participants with a TSH level of 10.0 mIU/L or greater. Previous studies of subclinical hypothyroidism and CHD have been conflicting. A 10-year cohort study of 1191 individuals found no association between subclinical hypothyroidism and cardiovascular-related mortality. A large prospective study from Whickham, England, found no association between autoimmune thyroid disease, the most frequent cause of subclinical hypothyroidism, and CHD. However, 2 prospective studies found a pattern of an increased risk of CHD with a TSH level of 2.5 (95% CI, 0.7-9.1) and 4.8 (95% CI, 0.8-29.3). Low power in our data is unlikely, because our study included 20 times more CHD events than each of these 2 previous studies. One important difference was that these 2 studies mainly included younger subjects, who were otherwise at low risk of CHD. A cross-sectional study of 1212 subjects in Denmark found that the risk of CHD associated with subclinical hypothyroidism was higher and statistically significant only in subjects younger than 30 years. One potential explanation for these age differences might be competing mortality among older subjects (eg, due to cancer). However, excluding participants who died during follow-up in our study did not change the results. An association between subclinical hypothyroidism and CHD might also weaken with age if this risk was mediated primarily by elevated cholesterol levels. Total and low-density lipoprotein cholesterol levels are strong cardiovascular risk factors in middle-aged adults, but not in older adults. Accordingly, in our data, participants with subclinical hypothyroidism had no increase in CHD despite significantly higher cholesterol levels, and cholesterol itself was not associated with an increased risk of atherosclerotic events. To our knowledge, no prospective study has assessed the risk of stroke or PAD in subjects with subclinical hypothyroidism, except one in Japan that did not find an association with cerebrovascular disease (HR, 1.9; 95% CI, 0.5-7.3).

Similar to previous studies, our data did not show a higher total mortality in participants with subclinical hypothyroidism. The only exception in our data was a higher risk of total mortality for a TSH level of 10.0 mIU/L or greater in participants without prevalent CVD. Conversely, one prospective study in Japan found that men, but not women, with subclinical hypothyroidism (mean age, 63 years) had an increased total mortality for the first 6 years of follow-up (HR, 1.9; 95% CI, 1.1-3.2). These conflicting results are difficult to interpret, but the relative youth of the study population in Japan compared with other studies is a potential explanation.

Our study has several limitations. Because we did not have T4 measured in participants with a TSH level between 4.5 and 6.9 mIU/L, we could have included some participants with overt instead of subclinical hypothyroidism. Although unlikely, the inclusion of participants with overt hypothyroidism might bias the results toward an increased risk of CHF, but we found a significant association with CHF only in participants with a TSH level of 7.0 mIU/L or greater who all had a T4 measurement. We did not measure thyroid autoantibodies and, therefore, may have overlooked more specific associations with pure thyroid autoimmunity. The CHF events studied were also limited to those requiring hospitalization. Because some patients may have developed CHF without hospitalization, our rates of CHF are likely underestimated. Possible misclassification of CHF events might have occurred, because diagnostic criteria for CHF are difficult to define. Different criteria have produced different incidence estimates, but no significant survival difference. We had limited power to perform subgroup analyses, because the number of outcome events in each TSH stratum was small. Our data are also limited to older adults who have a high prevalence of CVD and subclinical hypothyroidism.

In summary, our study suggests that subclinical hypothyroidism is associated with an increased risk of incident and recurrent CHF events among older adults with a TSH level of 7.0 mIU/L or greater, but not with other cardiovascular events and mortality. Because no other prospective study has assessed the risk of CHF events in subjects with subclinical hypothyroidism, to our knowledge, our results should be confirmed in other large prospective studies, including those in younger populations. Further investigation is also warranted to assess whether subclinical hypothyroidism causes or worsens preexisting heart failure.

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Correspondence: Nicolas Rodondi, MD, MAS, Department of Community Medicine and Public Health, University of Lausanne, Bugnon 44, 1011, Lausanne, Switzerland (Nicolas.Rodondi@hospvd.ch).
Author Contributions: Dr Vittinghoff reviewed the statistical analyses of this article. Dr Rodondi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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