Subclinical Thyroid Dysfunction as a Risk Factor for Cardiovascular Disease

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Background: There have been few large epidemiological studies examining the association between thyroid dysfunction and cardiovascular disease. In particular, it is uncertain if subclinical hypothyroidism is a risk factor for cardiovascular disease.

Methods: Serum thyrotropin and free thyroxine concentrations were measured in 2108 archived serum samples from a 1981 community health survey in Busselton, Western Australia (Busselton Health Study). In a cross-sectional study, we examined the prevalence of coronary heart disease in subjects with and without subclinical thyroid dysfunction. In a longitudinal study, we examined the risk of cardiovascular mortality and coronary heart disease events (fatal and nonfatal combined) to the end of 2001 (excluding subjects who had coronary heart disease at baseline).

Results: In the cross-sectional analysis, subjects with subclinical hypothyroidism (n=119) had a significantly higher prevalence of coronary heart disease than euthyroid subjects (n=1906) (age- and sex-adjusted prevalence odds ratio, 1.8; 95% confidence interval, 1.0-3.1; P=.04). In the longitudinal analysis of subjects with subclinical hypothyroidism (n=101), there were 21 cardiovascular deaths observed compared with 9.5 expected (age- and sex-adjusted hazard ratio, 1.5; 95% confidence interval, 1.0-2.4; P= .08) and 33 coronary heart disease events observed compared with 14.7 expected (age- and sex-adjusted hazard ratio, 1.7; 95% confidence interval, 1.2-2.4; P<.01). The increased risk of coronary heart disease events remained significant after further adjustment for standard cardiovascular risk factors. Subjects with subclinical hyperthyroidism (n=39) had no adverse outcomes.

Conclusion: Subclinical hypothyroidism may be an independent risk factor for coronary heart disease.

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METHODS

The Busselton Health Study (available at: http://hsn.uwa.edu.au) includes a series of cross-sectional health surveys of adults on the electoral roll of Busselton, a rural town with a predominantly white population. Registration to vote is compulsory in Australia. Detailed descriptions of the surveys have been published previously. We used data from the 1981 community health survey, in which the response rate was 64%, comprising 3447 subjects. Briefly, subjects completed a health and lifestyle questionnaire, underwent electrocardiography, and had measurements of height, weight, and blood pressure. The questionnaire included items on smoking, diabetes mellitus, treatment for hypertension, and exercise, and a single question regarding history of thyroid disease or goiter (yes or no). The presence of coronary heart disease at baseline was determined by the Rose questionnaire for angina and myocardial infarction, the electrocardiogram results, and a self-reported confirmation of heart disease diagnosed by a physician. Venous blood was collected in the fasting state for cholesterol and triglyceride measurement, and another specimen was collected for glucose measurement 2 hours after an oral 75-g glucose load. Archived serum samples that had been stored at −70°C were available for 2108 participants in the 1981 survey, who formed the cohort. Samples had been securely stored in airtight polypropylene tubes, which were filled to capacity and had not been thawed during storage. Although the stability of free thyroxine concentrations in long-term storage has not been formally demonstrated, the stability of other analytes, including thyrotropin, antibodies, and steroid hormones, under such conditions has been shown. The proportion of men was higher among subjects for whom serum samples were available compared with those for whom serum samples were not available (50% vs 40%, P<.001), but within each sex group, the age and prevalence of previously diagnosed thyroid disease did not differ significantly between subjects with and without available serum samples. Serum thyrotropin, free thyroxine, thyroid peroxidase antibody, and thyroglobulin antibody concentrations were measured using an Immulite 2000 chemiluminescent analyzer (Diagnostic Products Corporation, Los Angeles, Calif) in 2001. For the thyrotropin assay, functional sensitivity was 0.02 mIU/L. Interassay imprecision (expressed as coefficient of variation) for each analyte was as follows: thyrotropin, 7.6%; free thyroxine, 9.6%; thyroid peroxidase antibodies, 7.2%; and thyroglobulin antibodies, 8.3%. Reference ranges (based on 95% confidence intervals [CIs] after excluding gross outliers and subjects with self-reported thyroid disease or goiter) were as follows: thyrotropin, 0.4 to 4.0 mIU/L; free thyroxine, 0.7 to 1.8 ng/dL (9-23 pmol/L); thyroid peroxidase antibodies, less than 35 kIU/L; and thyroglobulin antibodies, less than 35 kIU/L. Hypothyroidism was defined as a serum thyrotropin level of 0.4 to 4.0 mIU/L (regardless of free thyroxine concentration), subclinical hyperthyroidism as a thyrotropin level less than 0.4 mIU/L with normal free thyroxine, and subclinical hypothyroidism as a thyrotropin level greater than 4.0 mIU/L with normal free thyroxine. The subclinical hyperthyroid group was further divided into subjects with a thyrotropin level less than 0.1 mIU/L and those with a thyrotropin level between 0.1 and less than 0.4 mIU/L. The subclinical hypothyroid group was further divided into subjects with a serum thyrotropin level of 10.0 mIU/L or less and those with a thyrotropin level greater than 10.0 mIU/L. Positive thyroid antibodies were defined as an increased concentration of thyroid peroxidase antibodies or thyroglobulin antibodies.

Baseline characteristics of the study subjects in each category of thyroid dysfunction were compared with those of euthyroid subjects using linear and logistic regression models, and multivariate models were used to determine the significance of differences between thyroid categories after adjustment for age and sex. Thyrotropin and triglyceride values were log transformed for analysis. In the cross-sectional analysis, logistic regression was used to assess the association of thyroid dysfunction with the presence of coronary heart disease. Prevalence odds ratios (ORs) and 95% CIs were calculated for the categories of thyroid dysfunction. Results were adjusted for age and sex, as well as for self-reported history of thyroid disease or goiter. The following cardiovascular risk factors were included as covariates in the statistical model: diabetes mellitus (defined as a history of diabetes mellitus, treatment for diabetes mellitus, or a glucose level ≥200 mg/dL [≥11.1 mmol/L] 2 hours after the glucose load), body mass index, cholesterol, triglycerides, exercise (number of days per week), mean arterial blood pressure, treatment for hypertension, and smoking status (never smoked, ex-smoker, current smoker of <15 cigarettes daily, current smoker of ≥15 cigarettes daily, or pipe or cigar smoker).

In the longitudinal analysis, morbidity and mortality outcomes up to December 31, 2001, were obtained by record linkage to the Registrar General’s list of deaths in Western Australia and the statewide Hospital Morbidity Data System, which records all admissions to public and private hospitals in Western Australia. Vital status at December 31, 2001, was ascertained for 95% of the cohort. The survival times for the remaining 5% were censored at the last time they were known to be alive. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes were used for events up to June 30, 1999, and ICD-10 codes were used for subsequent events. Cardiovascular mortality was defined as death from cardiovascular disease (ICD-9-CM codes 390-459). Coronary heart disease events were defined as death from coronary heart disease or hospital admission with a diagnosis of coronary heart disease (ICD-9-CM codes 410-414). A Cox proportional hazards regression model was used to analyze the association between thyroid dysfunction and the time from the 1981 survey until the first event. Hazard ratios and 95% CIs were calculated for the categories of thyroid dysfunction after adjustment for age and sex (by including these as covariates in the statistical model) and after further adjustment for the covariates listed at the end of the previous paragraph.

In the Whickham Survey, a serum thyrotropin level greater than 2.0 mIU/L at baseline was associated with an increased risk of subsequent hypothyroidism, and some authorities suggest that the upper limit of the thyrotropin reference range should be lowered from approximately 4 to 2.5 mIU/L. We therefore examined whether serum thyrotropin in the upper reference range (2.0-4.0 mIU/L) was associated with cardiovascular end points in the cross-sectional and longitudinal analyses, using subjects with a serum thyrotropin level of 0.4 to 2.0 mIU/L as the comparator group.

Statistical analyses were performed using S-PLUS 2000 (Insightful Corporation, Seattle, Wash). Significance was set at P<.05. The study was approved by the Royal Perth Hospital Ethics Committee.

RESULTS

The 2108 study subjects comprised 1063 men and 1045 women, with a mean age of 50 years (age range, 17-89 years). The baseline characteristics of the study subjects are given in Table 1. The prevalence of subclinical hyperthyroidism was 1.8%, and that of subclinical hypothyroidism was 5.6%. Serum cholesterol was higher in subjects with subclinical hypothyroidism than in euthyroid subjects (mean±SD, 244±50 mg/dL [6.3±1.3 10021]
but the difference was not significant after adjustment for age and sex ($P = .06$). Serum triglycerides were also higher in subjects with subclinical hypothyroidism than in euthyroid subjects (mean±SD, 151±124 mg/dL [1.7±1.4 mmol/L] vs 124±89 mg/dL [1.4±1.0 mmol/L]; $P = .02$), but the difference was not significant after adjustment for age and sex ($P = .11$).

### CROSS-SECTIONAL ANALYSIS

In the cross-sectional analysis, the prevalence OR for coronary heart disease was significantly increased (after adjustment for age and sex) in subjects with subclinical hypothyroidism compared with euthyroid subjects (OR, 1.8; 95% CI, 1.0-3.1; $P = .04$) (Table 2). The association remained significant after further adjustment for standard cardiovascular risk factors and self-reported thyroid disease or goiter (OR, 2.2; 95% CI, 1.2-4.0; $P = .01$). When subjects with subclinical hypothyroidism were divided into those with a serum thyrotropin level of 10.0 mIU/L or less and those with a serum thyrotropin level greater than 10.0 mIU/L, the association with coronary heart disease was significant only in the latter subgroup. No significant association was found between subclinical hyperthyroidism and coronary heart disease.

The analysis was repeated after excluding subjects with a history of thyroid disease or goiter at baseline (n=75). In this analysis, the ORs for coronary heart disease in...
jects with subclinical hypothyroidism (n=105) were 1.7 (95% CI, 0.9-3.0; P=.09) after adjustment for age and sex and 2.0 (95% CI, 1.1-3.8; P=.03) after adjustment for multiple covariates.

The prevalence of coronary heart disease was not significantly increased among subjects with a serum thyrotropin level in the upper reference range (>2.0 mIU/L) compared with those with a serum thyrotropin level of 0.4 to 2.0 mIU/L. It also did not differ significantly between subjects with positive thyroid antibodies and antibody-negative subjects (data not shown).

LONGITUDINAL ANALYSIS

In 1926 subjects who were free of coronary heart disease at baseline cardiovascular mortality was not significantly increased in any of the groups with thyroid dysfunction (ie, 1890 subjects who were categorized as having subclinical hyperthyroidism, euthyroidism, or subclinical hypothyroidism) (Table 3). In subjects with subclinical hypothyroidism at baseline, the hazard ratio (HR) for death from cardiovascular disease (after adjustment for age and sex) was 1.5 (95% CI, 1.0-2.4; P=.08). The risk of coronary heart disease events (fatal and nonfatal combined) was significantly increased in subjects with subclinical hypothyroidism after adjustment for age and sex (HR, 1.7; 95% CI, 1.2-2.4; P<.01) and after further adjustment for cardiovascular risk factors and self-reported thyroid disease or goiter (HR, 1.8; 95% CI, 1.2-2.7; P<.01) (Table 4 and the Figure). The increased risk associated with subclinical hypothyroidism was apparent in subjects with a serum thyrotropin level of 10.0 mIU/L or less and in those with a serum thyrotropin level greater than 10.0 mIU/L. There was no significant increase in risk of coronary heart disease events in subjects with subclinical hypothyroidism as a group or in the subgroups with a serum thyrotropin level less than 0.1 mIU/L or a serum thyrotropin level between 0.1 and 0.4 mIU/L.

When subjects with self-reported thyroid disease or goiter at baseline were excluded from the analysis, subjects with subclinical hypothyroidism (n=90) still had a significantly increased risk of coronary heart disease events (28 events observed and 13 expected; HR after adjustment for age and sex, 1.6; 95% CI, 1.1-2.3; P=.02; and HR after adjustment for multiple covariates, 1.7; 95% CI, 1.1-2.5; P=.02).

The risk of coronary heart disease events in euthyroid subjects with serum thyrotropin levels in the upper reference range (>2.0 mIU/L) (n=432) did not differ from that in those with serum thyrotropin levels in the lower reference range (≤2.0 mIU/L) (n=1474) after adjustment for age and sex (age- and sex-adjusted HR, 0.9; 95% CI, 0.7-1.2; P=.70). After adjustment for age and sex, positive thyroid antibodies at baseline were not associated with increased cardiovascular mortality (HR, 1.0; 95% CI, 0.7-1.4; P=.97) or increased risk of coronary heart disease events (HR, 1.3; 95% CI, 0.8-2.0; P=.30) compared with antibody-negative subjects. Among subjects with subclinical hypothyroidism, the risk of coronary heart disease events did not differ significantly between subjects with positive thyroid antibodies (age- and sex-adjusted HR, 0.6; 95% CI, 0.3-1.2; P=.18) compared with antibody-negative subjects.

Table 3. Hazard Ratios for Cardiovascular Mortality in the Longitudinal Analysis of Subjects Free of Coronary Heart Disease at Baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subclinical Hypothyroid Group</th>
<th>Euthyroid Group</th>
<th>Subclinical Hypothyroid Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 37)</td>
<td>(n = 1752)</td>
<td>(n = 101)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>Observed</td>
<td>3</td>
<td>170</td>
</tr>
<tr>
<td>Hazard ratio (95% confidence interval)</td>
<td>Age and sex adjusted</td>
<td>1.1 (0.3-3.4)</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Further adjusted†</td>
<td>1.0 (0.2-4.3)</td>
<td>1.0</td>
</tr>
<tr>
<td>Data are given as number of subjects unless otherwise indicated.</td>
<td>Adjusted for age, sex, coronary heart disease at baseline, body mass index, smoking status, diabetes mellitus, cholesterol, triglycerides, mean arterial blood pressure, hypertension treatment, exercise, and self-reported thyroid disease or goiter at baseline.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Hazard Ratios for Coronary Heart Disease Events (Fatal and Nonfatal) in the Longitudinal Analysis of Subjects Free of Coronary Heart Disease at Baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subclinical Hyperthyroid Group</th>
<th>Euthyroid Group</th>
<th>Subclinical Hypothyroid Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 37)</td>
<td>(n = 1752)</td>
<td>(n = 101)</td>
</tr>
<tr>
<td></td>
<td>Thyrotrhopin ≤10.0 mIU/L (n = 77)</td>
<td>Thyrotrhopin &gt;10.0 mIU/L (n = 24)</td>
<td></td>
</tr>
<tr>
<td>Coronary heart disease events</td>
<td>Observed</td>
<td>5</td>
<td>229</td>
</tr>
<tr>
<td>Hazard ratio (95% confidence interval)</td>
<td>Age and sex adjusted</td>
<td>1.0 (0.4-2.5)</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>.79</td>
<td>. . .</td>
</tr>
<tr>
<td></td>
<td>Further adjusted†</td>
<td>1.3 (0.6-3.3)</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>.51</td>
<td>. . .</td>
</tr>
<tr>
<td>Data are given as number of events unless otherwise indicated.</td>
<td>Adjusted for age, sex, body mass index, smoking status, diabetes mellitus, cholesterol, triglycerides, mean arterial blood pressure, hypertension treatment, exercise, and self-reported thyroid disease or goiter at baseline.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In this community-based study, subclinical hypothyroidism was an independent predictor of coronary heart disease (after adjustment for age and sex) in the cross-sectional and longitudinal analyses. These results are in agreement with previous cross-sectional studies showing an association between subclinical hypothyroidism and coronary heart disease in selected groups, namely, women 55 years or older,5 Japanese atomic bomb survivors,10 nursing home residents,17 men younger than 50 years,18 and older community-dwelling subjects.19 Our findings go beyond these studies, first, because we studied an unselected population and, second, because the increased cardiac risk was apparent in the cross-sectional and longitudinal components of our study. To our knowledge, this is the first cohort study to demonstrate an association between subclinical hypothyroidism and coronary heart disease. It is generally recognized that cohort studies provide stronger evidence than cross-sectional studies for a causal association.20

Our results differ from those of the longitudinal component of the Rotterdam Study9 and the cohort study by Parle et al.,3 in which subclinical hypothyroidism was not associated with a significant increase in cardiovascular risk. This is probably explained by the shorter follow-up in those studies (4.6 years in the Rotterdam Study and 10 years in the study by Parle et al., compared with 20 years in our study), because in our Kaplan-Meier plots, the divergence of the disease-free survival curves is most obvious from 10 years onward. Our results appear to differ from those of a 20-year cohort study4 that reported no association between autoimmune thyroid disease and coronary heart disease. In that study, however, subjects with subclinical hypothyroidism were combined with antibody-positive, euthyroid subjects for analysis and not analyzed as a separate group. Our findings also differ from a cohort study16 from Japan, in which subclinical hypothyroidism was associated with increased all-cause mortality. In that study, however, the excess mortality was limited to years 3 through 6 of follow-up and was observed only in men, making the data difficult to interpret. In addition, that cohort was highly selected (atomic bomb survivors). Those results and ours differ from a recent cohort study21 of subjects aged 85 years at baseline in which subclinical hypothyroidism was associated with greater longevity. The reason for this is not clear, but it may be that subclinical hypothyroidism has different implications in very old subjects compared with the general population.

In contrast to the study by Parle et al.,5 we found no evidence of increased cardiovascular risk associated with subclinical hyperthyroidism. This may be because our cohort was younger, with a lower prevalence of subclinical hyperthyroidism and fewer cardiovascular events, than the subjects in the study by Parle et al., who were 60 years or older at baseline.

The strengths of our study include a large sample size, its community-based design (avoiding biases present in studies of selected smaller groups), and the comprehensive follow-up, with only 5% of subjects being lost to follow-up during a 20-year period. Only one previous cohort study (the Whickham Survey14) has examined the association between thyroid dysfunction and cardiovascular disease in an unselected community-based sample. Our study also has weaknesses. First, although participants in the 1981 survey were asked if they had a history of thyroid disease or goiter, details of diagnosis and treatment were not recorded. It is therefore possible that some subjects in the subclinical hypothyroid group had inadequately treated overt hypothyroidism or overtreated hyperthyroidism. However, excluding subjects with self-reported thyroid disease or goiter at baseline made little difference in the results, suggesting that this is not a major confounder. Second, thyroid function was measured only at baseline, and we have no data on progression or treatment of thyroid dysfunction among the members of the cohort. The natural history of subclinical hypothyroidism is variable; thyroid function normalizes spontaneously in some subjects, whereas it progresses to overt hypothyroidism in others.14,22,23 It is therefore possible that the increase in cardiac events observed in the subclinical hypothyroid group arose not because of subclinical hypothyroidism per se but because of progression to overt hypothyroidism, which is associated with atherosclerosis.24 This, however, would not explain the association between subclinical hypothyroidism and coronary heart disease in the cross-sectional analysis, and the consistency between the cross-sectional and longitudinal components of our study constitutes strong evidence that subclinical hypothyroidism is indeed a risk factor for coronary heart disease. Third, ascertainment of cardiovascular events was based on population-based linkage of health records rather than on clinical follow-up of the cohort; however, previous findings have shown that diagnostic codes obtained using these methods are reliable.15 Fourth, although we adjusted for serum total cholesterol concentrations, high-density lipoprotein and low-density lipoprotein cholesterol concentrations were not available and could not be included in the analysis.

A causal relationship between subclinical hypothyroidism and cardiovascular disease is biologically plausible. Subclinical hypothyroidism is associated with hy-
percholesterolemia (although the evidence for this is convincing only for subjects with a serum thyrotropin level >10.0 mIU/L), left ventricular diastolic dysfunction that is reversible with thyroxine therapy,25-27 and impaired endothelium-dependent vasodilatation, a marker of atherosclerosis.20,26,28

Our study is observational, and it does not necessarily follow that treatment of subclinical hypothyroidism will reduce the risk of cardiovascular disease. To demonstrate such a benefit would require a large clinical trial with a long follow-up period. Until such a trial is conducted, evidence-based management of subclinical hypothyroidism will be based on epidemiological studies such as this and on clinical trials with surrogate cardiovascular end points.

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Author Contributions: Dr Walsh had full access to all the data in this study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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