Subclinical Hypothyroidism Is an Independent Risk Factor for Atherosclerosis and Myocardial Infarction in Elderly Women: The Rotterdam Study

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Background: Overt hypothyroidism has been found to be associated with cardiovascular disease. Whether subclinical hypothyroidism and thyroid autoimmunity are also risk factors for cardiovascular disease is controversial.

Objective: To investigate whether subclinical hypothyroidism and thyroid autoimmunity are associated with aortic atherosclerosis and myocardial infarction in postmenopausal women.

Design: Population-based cross-sectional study.

Setting: A district of Rotterdam, the Netherlands.

Participants: Random sample of 1149 women (mean age ± SD, 69.0 ± 7.5 years) participating in the Rotterdam Study.

Measurements: Data on thyroid status, aortic atherosclerosis, and history of myocardial infarction were obtained at baseline. Subclinical hypothyroidism was defined as an elevated thyroid-stimulating hormone level (>4.0 mU/L) and a normal serum free thyroxine level (11 to 25 pmol/L [0.9 to 1.9 ng/dL]). In tests for antibodies to thyroid peroxidase, a serum level greater than 10 IU/mL was considered a positive result.

Results: Subclinical hypothyroidism was present in 10.8% of participants and was associated with a greater age-adjusted prevalence of aortic atherosclerosis (odds ratio, 1.7 [95% CI, 1.1 to 2.6]) and myocardial infarction (odds ratio, 2.3 [CI, 1.3 to 4.0]). Additional adjustment for body mass index, total and high-density lipoprotein cholesterol level, blood pressure, and smoking status, as well as exclusion of women who took β-blockers, did not affect these estimates. Associations were slightly stronger in women who had subclinical hypothyroidism and antibodies to thyroid peroxidase (odds ratio for aortic atherosclerosis, 1.9 [CI, 1.1 to 3.6]; odds ratio for myocardial infarction, 3.1 [CI, 1.5 to 6.3]). No association was found between thyroid autoimmunity itself and cardiovascular disease. The population attributable risk percentage for subclinical hypothyroidism associated with myocardial infarction was within the range of that for known major risk factors for cardiovascular disease.

Conclusion: Subclinical hypothyroidism is a strong indicator of risk for atherosclerosis and myocardial infarction in elderly women.

Overt hypothyroidism, with its accompanying hypercholesterolemia and hypertension, has been found to be associated with cardiovascular disease (1–3). Subclinical hypothyroidism, defined as an asymptomatic state characterized by normal serum concentrations of free thyroxine and elevated serum concentrations of thyroid-stimulating hormone (TSH) (4), is highly prevalent in elderly women (5, 6). Whether subclinical hypothyroidism is related to risk for cardiovascular disease is controversial. Case–control and cross-sectional studies on the association between subclinical hypothyroidism and cardiovascular disease have been done (7–11). Results from these studies are not consistent, but many of the studies were small. The same controversy surrounds thyroid autoimmunity. In the late 1960s and early 1970s, autopsy studies (12, 13) and studies in hospital inpatients (12, 14) suggested that asymptomatic autoimmune thyroiditis was an important risk factor for coronary heart disease. These findings, however, were not confirmed by other studies (7, 8, 11, 15).

In our population-based study, we examined whether subclinical hypothyroidism and thyroid autoimmunity are associated with aortic atherosclerosis and myocardial infarction in elderly women. We conducted our study in a random sample of 1149 postmenopausal women who were participating in the Rotterdam Study.

Methods

The Rotterdam Study

The Rotterdam Study is a population-based cohort study designed to assess the occurrence and clarify the determinants of chronic diseases in an aging population (16). The cohort includes 3105 men and 4878 women at least 55 years of age (78% of the eligible population) living in a defined district in Rotterdam, the Netherlands. Baseline data were collected from August 1990 to July 1993. During a home interview, a trained research assistant gathered information on current and past health, medication, lifestyle, and risk factors for chronic diseases. Participants were subsequently invited to visit a research center for clinical examination. The study

was approved by the medical ethics committee of Erasmus University Medical School, Rotterdam, the Netherlands.

Clinical Examination and Laboratory Methods

Height and weight were measured while each participant was wearing indoor clothing without shoes. Body mass index was computed as weight divided by height squared. A trained research assistant measured sitting systolic and diastolic blood pressure with a random-zero sphygmomanometer after 5 minutes of rest, and a standard 12-lead electrocardiogram was obtained (ACTA electrocardiogram recorder, Esoate, Florence, Italy).

Venipuncture was performed, and nonfasting serum samples were collected. The samples were immediately put on ice and were processed within 30 minutes, after which they were kept frozen at $-20\,°C$. We used an automated enzymatic procedure to determine serum total cholesterol level (17). High-density lipoprotein (HDL) cholesterol levels were measured in a similar manner after precipitation of the non-HDL cholesterol fraction. Total protein level was measured by using the biuret method, albumin level was measured by using the bromocresol-green method, and creatinine concentration was measured by using an enzymatic colorimetric method. (All products were manufactured by Boehringer Mannheim, Mannheim, Germany, currently Roche Diagnostics, Basel, Switzerland.) We assayed levels of TSH by using TSH Lumitest (Henning, Berlin, Germany, currently Brahms, Berlin, Germany) (18). When TSH concentrations were abnormal (>4.0 mU/L or <0.4 mU/L), serum free thyroxine levels were measured with an in vitro immunodiagnostic reagent (Ortho-Clinical Diagnostics, Amersham, England, United Kingdom); values between 11 and 25 pmol/L (0.9 and 1.9 ng/dL) were considered normal. Serum antibodies to thyroid peroxidase were assessed by using enzyme-linked immunosorbent assay (Milenia, DPC, Los Angeles, California); test results were considered positive if levels were greater than 10 IU/mL.

Thyroid Definitions

Subclinical hypothyroidism was defined as a TSH level greater than 4.0 mU/L in the presence of a normal free thyroxine level (11 to 25 pmol/L [0.9 to 1.9 ng/dL]). Clinical hypothyroidism was defined as a TSH level greater than 4.0 mU/L and a decreased free thyroxine level (<11 pmol/L [<0.9 ng/dL]) (4). Euthyroidism was defined as a normal TSH level (0.4 to 4.0 mU/L).

Aortic Atherosclerosis

Aortic atherosclerosis was assessed on a lateral radiographic film of the lumbar spine, which was obtained from a fixed distance while the participants were seated. A researcher who was unaware of the participants' thyroid status diagnosed atherosclerosis off-line by detecting calcified deposits in the abdominal aorta, as described elsewhere (19, 20). Calcification was considered present when linear densities were found in an area parallel and anterior to the lumbar spine (L1 to L4). We classified aortic atherosclerosis as mild, moderate, or severe, according to the length of the involved area ($\leq$1 cm, 2 to 5 cm, and >5 cm, respectively). Because of a relatively small number of participants in the categories of aortic atherosclerosis, we combined severity grades into two categories—"present" or "absent"—for analysis.

The validity of radiographic assessment of aortic atherosclerosis has been studied by comparing results of this method with data obtained at autopsy. Radiographic assessment was shown to be highly specific, and in most cases visible calcification represented advanced intima atherosclerosis (21). A comparison study involving computed tomography was performed at our department. In 56 unselected elderly persons, aortic calcifications were independently assessed by radiography and computed tomography. Calcifications were detected on abdominal radiography in 32 persons. In all but 1 person, these calcifications were shown to be located in the aorta on the corresponding computed tomography images (20).

Aortic calcification is known to be associated with risk factors for cardiovascular disease (19, 20) and with atherosclerosis at other sites (22) and predicts cardiovascular morbidity and mortality (23, 24). When aortic calcification (as detected by radiography) was compared with coronary artery calcium (as detected by electron-beam computed tomography) in 457 participants in the Rotterdam Study, aortic calcification was present in 3.9% of participants in the lowest tertile of coronary artery calcium, in 13.7% of those in the middle tertile of coronary artery calcium, and in 31.5% of those in the highest tertile of coronary artery calcium ($P < 0.001$ for trend, adjusted for age and sex). These results indicate that aortic calcification is strongly related to coronary calcification.

Myocardial Infarction at Baseline

The presence of myocardial infarction was assessed by self-report and by analysis of the standard 12-lead electrocardiograms, which were stored digitally and were analyzed by using the Modular Electrocardiogram Analysis System (MEANS) (25, 26). For participants who reported myocardial infarction but had no electrocardiographic evidence of it, we collected additional information from their general practitioners or cardiologists. Myocardial infarction
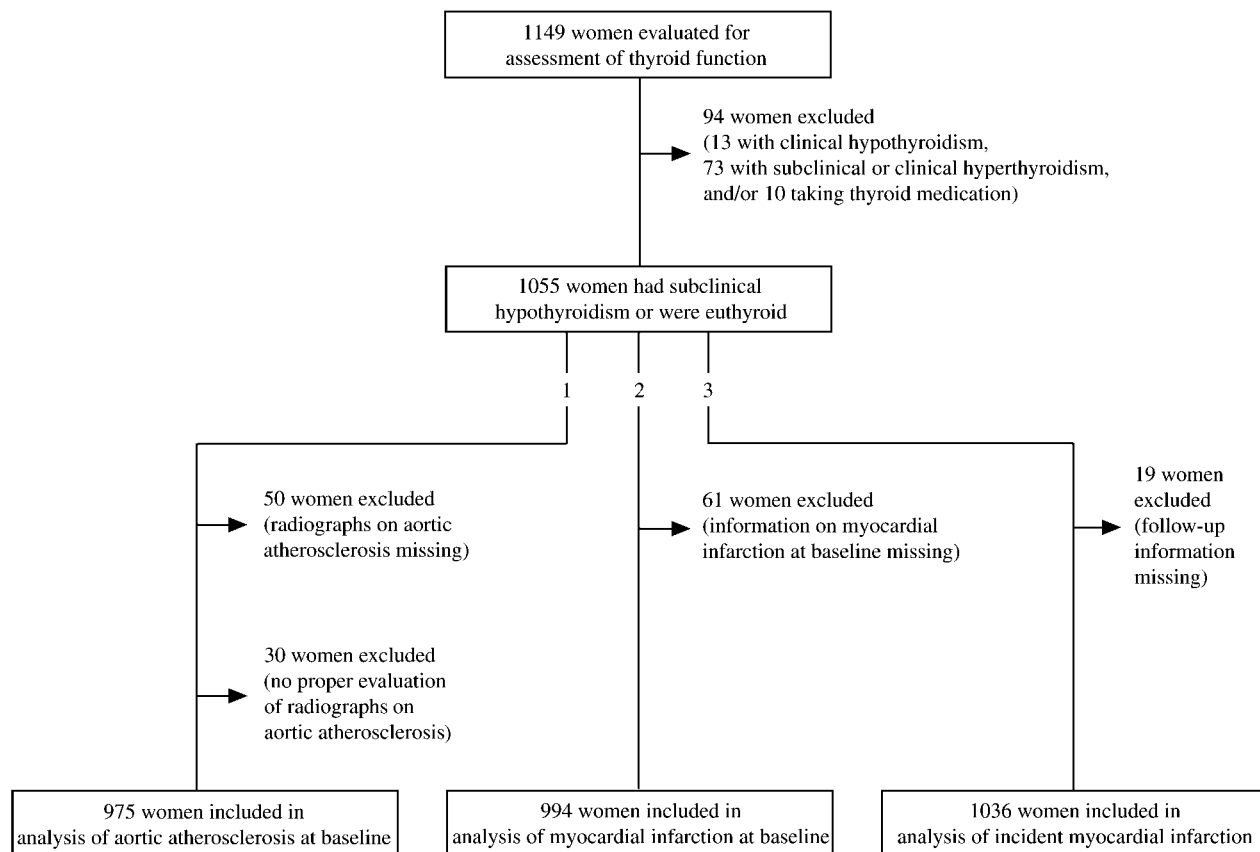
Figure. Selection of sample for analysis. 1 = selection of women for analysis of aortic atherosclerosis at baseline; 2 = selection of women for analysis of history of myocardial infarction at baseline; 3 = selection of women for analysis of incident myocardial infarction.

was confirmed if the information in the medical records met standard diagnostic criteria. An experienced cardiologist reviewed the electrocardiograms of participants who had not reported myocardial infarction but had electrocardiographic evidence of it. In these participants, absence of symptoms was confirmed by medical records review. When the cardiologist confirmed myocardial infarction (silent myocardial infarction), it was considered present. We combined both types of myocardial infarction into one variable for analysis. No information on the thyroid status of participants was available at assessment for myocardial infarction.

Follow-up Procedures

We collected data on incident myocardial infarction from baseline (1990 to 1993) until 1 April 1996. Fatal and nonfatal events were reported by general practitioners in the research area (in which 85% of the study cohort resides) who cooperate with the Rotterdam Study and provide information through a computerized system. Research physicians verified all information by checking participants' medical records at the general practitioners' offices. In addition, we obtained letters from medical specialists and discharge reports for hospitalized patients. Two

research physicians coded events independently according to the International Classification of Diseases, 10th Revision (27). If the two physicians disagreed, they reached consensus in a separate session. Subsequently, a medical expert in the field reviewed all events coded by the research physicians and verified that all coding rules had been applied correctly. When discrepancies were found between the coding of the medical expert and that of the research physicians, the expert's judgment was considered final. Myocardial infarction was defined as a nonfatal or fatal myocardial infarction (ICD-10 codes I21–I23). When we compared our results with data registered by the nationwide morbidity registry of hospitals, we found that 98% of all incident myocardial infarctions that occurred in Rotterdam Study participants before 1 April 1996 had been detected by our follow-up data collection system.

Selection of the Sample for Analysis

The selection of the sample for analysis is shown in the **Figure**. We determined thyroid status in a random sample of 1149 women after excluding those who took amiodarone, which may nonsystematically alter TSH levels (28). To obtain a reference category that included only euthyroid women (those

Table 1. Baseline Characteristics of the Study Sample

Variable	Euthyroid Women (n = 931)*	Women with Subclinical Hypothyroidism (n = 124)†
Mean age ± SD, y	68.9 ± 7.4	69.0 ± 7.9
Mean body mass index ± SD, kg/m²	26.7 ± 4.1	27.1 ± 3.8
Mean systolic blood pressure ± SD, mm Hg	138 ± 21	137 ± 22
Mean diastolic blood pressure ± SD, mm Hg	73 ± 11	73 ± 11
Mean total cholesterol level ± SD, mmol/L (mg/dL)	7.0 ± 1.2 (271 ± 46)	6.7 ± 1.0 (259 ± 39)‡
Mean high-density lipoprotein cholesterol level ± SD, mmol/L (mg/dL)	1.5 ± 0.4 (58 ± 15)	1.4 ± 0.4 (54 ± 15)§
Mean total protein level ± SD, g/L	71.0 ± 4.9	71.7 ± 4.7
Mean albumin level ± SD, g/L	42.7 ± 2.4	43.0 ± 2.5
Mean creatinine concentration ± SD, μmol/L (mg/dL)	77.6 ± 13.9 (0.9 ± 0.2)	77.4 ± 14.7 (0.9 ± 0.2)
Smoking status, % (n)		
Never	50 (466)	51 (63)
Past	29 (272)	30 (37)
Current	19 (176)	19 (23)

* For some euthyroid women, data were missing on body mass index (n = 7), blood pressure and HDL cholesterol level (n = 4), albumin level (n = 2), creatinine concentration (n = 1), and smoking habits (n = 17).
† Data on body mass index, blood pressure, and smoking habits were each missing for 1 woman.
‡ P < 0.05, adjusted for age.
§ P = 0.07, adjusted for age.

whose TSH levels were within the normal range), we excluded women with clinical hypothyroidism (n = 13); those with a decreased TSH level (<0.4 m U/L), which indicated clinical hyperthyroidism (free thyroxine level > 25 pmol/L [>1.9 ng/dL]) or subclinical hyperthyroidism (free thyroxine level, 11 to 25 pmol/L [0.9 to 1.9 ng/dL]) (n = 73); and/or those taking thyroid medication (L-thyroxine or thyrostatic medication [propylthiouracil, carbimazole, or thiamazole]) (n = 10).

Of the 1055 women remaining, we excluded those for whom data were missing (n = 50) or improper (n = 30); therefore, 975 were included in our analysis of aortic atherosclerosis (**Figure**, *selection 1*). Data on myocardial infarction at baseline were available for 994 women (**Figure**, *selection 2*). At the time of analysis, 19 women had not been completely followed because of linking problems between their general practitioners' medical records and our computerized registration system. Therefore, until 1 April 1996, completed follow-up for analysis of incident myocardial infarction was available for 1036 women, covering an average period (±SD) of 4.6 ± 0.7 years (**Figure**, *selection 3*).

Statistical Analysis

We used linear regression analysis to compare the age-adjusted continuous baseline characteristics of euthyroid women and women with subclinical hypothyroidism. The chi-square test was used to compare proportions of women who smoked in both groups and to compare proportions of women who had subclinical hypothyroidism and antibodies to thyroid peroxidase according to vascular disease status.

Multivariate logistic regression analysis was used to evaluate the association of aortic atherosclerosis and myocardial infarction as assessed at baseline (history of myocardial infarction) with subclinical hypothyroidism. For women with subclinical hypo-

thyroidism, we computed the risk for incident myocardial infarction (both fatal and nonfatal) during follow-up by using Cox proportional hazards regression analysis. In this analysis, we excluded women with a history of myocardial infarction (n = 79). We adjusted all analyses for age by entering age as a continuous variable in the regression model; we subsequently adjusted analyses for body mass index, cholesterol and HDL cholesterol level, systolic and diastolic blood pressure, and smoking status (never, past, or current). To ensure that comparisons between models were valid, the age-adjusted models included the number of participants for whom information was available on all of the covariates for which the multivariate model was adjusted.

We performed additional analyses after excluding women who took β-blockers (alprenolol, oxprenolol, pindolol, propranolol, timolol, and sotalol) (n = 37) because these drugs may influence TSH levels (29). In addition, we used logistic regression analysis to compare the associations of aortic atherosclerosis and history of myocardial infarction with subclinical hypothyroidism in women who had subclinical hypothyroidism and antibodies to thyroid peroxidase relative to those in euthyroid women who did not have antibodies to thyroid peroxidase. We also used logistic regression analysis to compare the frequency of aortic atherosclerosis and history of myocardial infarction in women with antibodies to thyroid peroxidase and women without antibodies to thyroid peroxidase, independent of thyroid status.

The attributable risk percentage, or etiologic fraction, and the population attributable risk percentage for subclinical hypothyroidism associated with incident myocardial infarction were calculated (30). For purposes of comparison, we calculated the attributable risk percentage and the population attributable risk percentage for the four major, classic risk factors for cardiovascular disease—hypercholes-

terolemia (total cholesterol level ≥ 8.0 mmol/L [≥309 mg/dL]), hypertension (systolic blood pressure ≥ 160 mm Hg and/or diastolic blood pressure ≥ 95 mm Hg, and/or antihypertensive medication use), smoking status (current and past compared with never), and diabetes mellitus (use of antidiabetic medication or a random postload glucose level >11.1 mmol/L [200 mg/dL])—associated with incident myocardial infarction in all female participants of the Rotterdam Study ($n = 4878$).

All measures of association are presented with 95% CIs. A P value less than 0.05 was considered statistically significant. We used SPSS 8.0 for Windows (SPSS, Inc., Chicago, Illinois) for all analyses.

Results

Before exclusion of clinically hypothyroid women, women with a decreased TSH level, and women using thyroid medication, the prevalence of subclinical hypothyroidism in the study sample was 10.8%. The baseline characteristics of the study sample are shown in **Table 1**. Women with subclinical hypothyroidism did not differ from euthyroid women with regard to age, body mass index, blood pressure, total protein level, albumin level, creatinine concentration, or smoking status but had significantly lower levels of total cholesterol and borderline significantly lower levels of HDL cholesterol in age-adjusted comparisons.

Table 2 shows the characteristics of participants according to vascular disease status. Fifty-three percent of participants ($n = 560$) had aortic atherosclerosis at baseline, and 7.5% ($n = 79$) had a history of myocardial infarction. Subclinical hypothyroidism was present in 11.8% of women in our sample for analysis. Women who had aortic atherosclerosis and a history of myocardial infarction had a higher prevalence of subclinical hypothyroidism and subclinical hypothyroidism accompanied by antibodies to thyroid peroxidase than those who did not have these diseases. The prevalence of thyroid autoimmunity independent of thyroid status itself did not differ

significantly among the specific subgroups. Among women with subclinical hypothyroidism, concentrations of TSH were higher in those with antibodies to thyroid peroxidase than in those without such antibodies (age-adjusted geometric means, 6.6 mU/L [CI, 6.1 to 7.1 mU/L] and 5.4 mU/L [CI, 5.0 to 5.8 mU/L], respectively; $P = 0.001$). Independent of thyroid status, TSH levels were also higher in women who had antibodies to thyroid peroxidase than in those who did not (geometric means, 2.4 mU/L [CI, 2.2 to 2.6 mU/L] and 1.6 mU/L [CI, 1.5 to 1.7 mU/L], respectively; $P < 0.001$).

Subclinical hypothyroidism was associated with a greater prevalence of aortic atherosclerosis. The odds ratio for aortic atherosclerosis (1.7 [CI, 1.1 to 2.6]) was increased in women with subclinical hypothyroidism (**Table 3**). Women with subclinical hypothyroidism also had a greater prevalence of myocardial infarction than euthyroid women (odds ratio, 2.3 [CI, 1.3 to 4.0]) (**Table 3**). Additional adjustment for body mass index, total cholesterol and HDL cholesterol levels, systolic and diastolic blood pressure, and smoking status did not affect these associations, nor did exclusion of participants who used β-blockers (data not shown). During an average follow-up of 4.6 years, 16 women had a first incident myocardial infarction. When we used a Cox proportional hazards regression analysis in women with subclinical hypothyroidism, a statistically nonsignificant adjusted relative risk of 2.5 (CI, 0.7 to 9.1) was observed for myocardial infarction.

Women with subclinical hypothyroidism and antibodies to thyroid peroxidase had a greater prevalence of aortic atherosclerosis than euthyroid women without antibodies to thyroid peroxidase (odds ratio, 1.9 [CI, 1.1 to 3.6]) (**Table 3**). The presence of antibodies to thyroid peroxidase increased the odds ratio for a history of myocardial infarction to 3.1 (CI, 1.5 to 6.3) in women who had subclinical hypothyroidism compared with euthyroid women who did not have antibodies to thyroid peroxidase (**Table 3**). Because only one woman with subclinical hypothyroidism and antibodies to thyroid peroxidase had myocardial infarction during follow-up, we were not

Table 2. Characteristics of Women according to Vascular Disease Status

Characteristic	All Women ($n = 1055$)	Women with Aortic Atherosclerosis ($n = 560$)	Women with a History of Myocardial Infarction ($n = 79$)
Mean age ± SD, *y*	68.9 ± 7.5	70.7 ± 7.4	71.1 ± 6.9
Median thyroid-stimulating hormone level (25th, 75th percentile), *mU/L*	1.7 (1.1, 2.7)	1.7 (1.1, 2.8)	2.0 (1.2, 3.4)
Women with subclinical hypothyroidism, % *(n)*	11.8 (124)	13.9 (78)*	21.5 (17)†
Women with subclinical hypothyroidism and antibodies to thyroid peroxidase, % *(n)*	5.8 (61)	7.1 (40)*	13.9 (11)†
Women with antibodies to thyroid peroxidase, % *(n)*	21.6 (228)	21.4 (120)	26.6 (21)

* $P < 0.05$ compared with women without the specific vascular disease status (chi-square test).
† $P < 0.01$ compared with women without the specific vascular disease status (chi-square test).

Table 3. Odds Ratios for Aortic Atherosclerosis and Myocardial Infarction*

Variable	Condition Present	Condition Absent	Odds Ratio (95% CI)†	Odds Ratio (95% CI)‡
		n		
Aortic atherosclerosis				
Women with subclinical hypothyroidism	77	37	1.7 (1.1–2.6)	1.9 (1.2–3.1)
Euthyroid women	474	376	1§	1§
Women with subclinical hypothyroidism and antibodies to thyroid peroxidase	39	16	1.9 (1.1–3.6)	2.2 (1.1–4.3)
Euthyroid women without antibodies to thyroid peroxidase	398	301	1§	1§
Myocardial infarction				
Women with subclinical hypothyroidism	17	99	2.3 (1.3–4.0)	2.3 (1.3–4.2)
Euthyroid women	61	806	1§	1§
Women with subclinical hypothyroidism and antibodies to thyroid peroxidase	11	46	3.1 (1.5–6.3)	3.5 (1.7–7.4)
Euthyroid women without antibodies to thyroid peroxidase	52	660	1§	1§

* The number of women may not be exactly the same as in Table 2 because data on some covariates were missing.
† Adjusted for present age.
‡ Adjusted for present age, body mass index, cholesterol level, high-density lipoprotein cholesterol level, systolic and diastolic blood pressure, and smoking status (current, past, or never).
§ Reference risk.

able to compute the corresponding risk for incident myocardial infarction. No association was found between the presence of antibodies to thyroid peroxidase and history of myocardial infarction or between aortic atherosclerosis and history of myocardial infarction when thyroid status was not altered (data not shown).

From our data, we calculated an attributable risk percentage of 60 and a population attributable risk percentage of 14 for subclinical hypothyroidism associated with myocardial infarction (**Table 4**). If subclinical hypothyroidism is assumed to be causally related to myocardial infarction, our findings suggest that it contributed to 60% of cases of myocardial infarction among women affected by subclinical hypothyroidism and that it was involved in the pathogenesis of 14% of all myocardial infarctions in the study sample. For purposes of comparison, the attributable risk percentages and the population attributable risk percentages for hypercholesterolemia, hypertension, smoking, and diabetes associated with myocardial infarction in all female participants in the Rotterdam Study are presented in **Table 4**.

Discussion

Our results show that subclinical hypothyroidism is highly prevalent among elderly women and is associated with a greater frequency of aortic atherosclerosis and myocardial infarction. Among women with subclinical hypothyroidism, these associations are slightly stronger in those who have antibodies to thyroid peroxidase. Thyroid autoimmunity itself is not associated with aortic atherosclerosis or myocardial infarction.

One limitation of our study is the cross-sectional nature of the design, which necessitates careful in-terpretation of the results. The relative risk for myocardial infarction in women with subclinical hypothyroidism in the prospective part of our study was similar to the point estimate in the cross-sectional part of our study. However, the CI was wide and included 1.0. Furthermore, we must consider the fact that elevated TSH levels may be caused by nonthyroidal illness (31, 32). However, we excluded women with a low free thyroxine level and observed that women with subclinical hypothyroidism did not differ from euthyroid women in levels of total protein, albumin, and creatinine. Therefore, it is highly unlikely that nonthyroidal illness affected the validity of our results. Serum samples were obtained only from women who visited the research center. We assume that the nonresponse for the visit to the research center will not depend on subclinical hypothyroidism differently among persons with or without the presence of cardiovascular disease, making selection bias unlikely. Furthermore, follow-up information was not available for all study participants as a result of logistic reasons. Because we have no reason to assume that the relation between subclinical hypothyroidism and myocardial infarction in women with complete follow-up data differs from this association in those without follow-up data, we do not believe that this lack of information influenced the validity of our results.

Approximately 11% of women in our sample had a TSH level greater than 4 mU/L. This prevalence closely resembles that reported in women in the Wickham survey (5), the Framingham Study (6), and a study in community-dwelling elderly persons (33). Among all women in our sample for analysis, 13 (1.1%) had unrecognized overt thyroid failure characterized by an elevated TSH level (>4.0 mU/L) and an abnormal free thyroxine level (<11 pmol/L [0.9 ng/dL]), which is in agreement with reports of prevalence found during screening (4).

These data suggest that our sample is representative of the general population.

Several studies on the association between coronary heart disease and subclinical hypothyroidism have been done. Our results agree with those of previous case–control studies that also showed an association between subclinical hypothyroidism and coronary heart disease in elderly women (9, 10). However, a Finnish study that presented results of men and women together provided no evidence that latent thyroid failure is associated with coronary heart disease (7). Female patients with coronary heart disease were shown to have significantly lower serum levels of TSH than controls; however, subclinical hypothyroidism did not seem to be related to the presence of coronary heart disease (11). In the Wickham survey, no cross-sectional association with ischemic heart disease was observed, but a weak association between minor electrocardiographic changes and minor degrees of hypothyroidism was found in women (8).

Data on atherosclerosis and subclinical hypothyroidism are scarce. A case–control study in elderly women suggested an association between subclinical hypothyroidism and peripheral arterial disease (34). We are the first to describe an association between subclinical hypothyroidism and atherosclerosis as assessed by a noninvasive measurement in a general population sample. Aortic atherosclerosis was diagnosed by radiographic detection of calcified deposits in the abdominal aorta, which has been shown to be a highly specific technique for the measurement of aortic intima atherosclerosis (21). False-negative misclassification may have occurred in our study, but it was probably independent of thyroid status and therefore may have affected our results only by causing us to underestimate the association. Because we found that subclinical hypothyroidism was associated with both atherosclerosis and myocardial infarction, our data may indicate that atherosclerosis is involved in the mechanism by which subclinical hypothyroidism and myocardial infarction are associated.

Several mechanisms that may be involved with the association of subclinical hypothyroidism with atherosclerosis and myocardial infarction can be considered. A common cause of thyroid failure in elderly women is autoimmune thyroiditis (6, 35). It has been suggested that pathologic immune reactivity (for example, immune complex–mediated vascular damage) may be important in the association of autoimmune thyroiditis with coronary heart disease (36). However, the literature on this association is controversial. Some studies have described an association between thyroid autoimmunity and coronary heart disease (9, 10, 12, 14, 37), and other studies have not (7, 8, 11, 15). Different uses of various

Table 4. Attributable Risk Percentages and Population Attributable Risk Percentages for Subclinical Hypothyroidism and Classic Risk Factors for Cardiovascular Disease Associated with Incident Myocardial Infarction in Women in the Rotterdam Study

Risk Factor	Age-Adjusted Relative Risk*	Attributable Risk	Population Attributable Risk
		%	
Subclinical hypothyroidism	2.5	60	14
Hypercholesterolemia	2.4	58	18
Hypertension	1.6	38	14
Smoking	2.0/1.2†	50/17‡	15
Diabetes mellitus	2.4	58	14

* Determined by using Cox proportional hazards regression analysis.
† Age-adjusted relative risk and attributable risk percentage for current compared with never smokers.
‡ Age-adjusted relative risk and attributable risk percentage for past compared with never smokers.

generations of antibody assays and different definitions of thyroid autoimmunity may have played a role in these discrepant findings. We found no association between the presence of antibodies to thyroid peroxidase itself and aortic atherosclerosis or myocardial infarction, which weakens the notion that a pathologic immune reactivity is important. We found that associations between subclinical hypothyroidism and aortic atherosclerosis or myocardial infarction were slightly stronger when subclinical hypothyroidism was accompanied by antibodies to thyroid peroxidase. This suggests that subclinical hypothyroidism, which is thought to be more severe and lasting in the presence of thyroid antibodies, contributes to the pathogenesis of cardiovascular disease.

Some authors found a disturbance in the atherogenic lipid metabolism in patients with subclinical hypothyroidism (38–42), whereas other studies did not (43–45). Although in our study the total cholesterol level was higher in women with overt hypothyroidism than in euthyroid women (data not shown), we did not find that total cholesterol level was higher in women with subclinical hypothyroidism than in euthyroid women. High-density lipoprotein and total cholesterol levels provided no pathophysiologic explanation for the association of subclinical hypothyroidism with aortic atherosclerosis and myocardial infarction. Other lipids—such as low-density lipoprotein cholesterol level, enhanced low-density lipoprotein oxidation (46), triglyceride level, and lipoprotein(a) level (42)—may be responsible for the association between subclinical hypothyroidism and cardiovascular disease, but we did not measure these factors.

Other mechanisms that may be involved in the association between subclinical hypothyroidism and cardiovascular disease can be derived from experimental data. In vitro, thyroid hormones inhibit

collagen-induced platelet aggregation (47, 48) and directly relax smooth muscle (49). These effects may be important if thyroid hormones have the same effects in adult humans, although in subclinical hypothyroidism, by definition, levels of thyroid hormones are not decreased. Hypothyroidism is accompanied by a hypercoagulable state (50), increased blood viscosity (51), and a greater plasma concentration of total homocysteine (52); if these factors are also seen in subclinical hypothyroidism, they may account for atherosclerotic and ischemic disorders.

In conclusion, we found that subclinical hypothyroidism is highly prevalent in elderly women and is strongly and independently associated with aortic atherosclerosis and myocardial infarction. The population attributable risk percentage for subclinical hypothyroidism associated with myocardial infarction was within the range of that for known major risk factors for cardiovascular disease. Additional research should be done to determine whether this association can be confirmed in a prospective study. If not, subsequent studies may focus on the effectiveness of possible therapies for subclinical hypothyroidism in elderly women and the desirability of screening such women for this disorder.

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