Thyroid dysfunction is not linked with a significantly increased risk for coronary heart disease

Boekholdt MS, Titan SM, Wiersinga WM, Chatterjee K, Basart DC, Luben R, Wareham NJ, Khaw KT. Initial thyroid status and cardiovascular risk factors: The EPIC-Norfolk prospective population study. Clin Endocrinol (Oxf) 2009 doi: 10.1111/j.1365-2265.2009.03640.x

SUMMARY

BACKGROUND

Overt hypothyroidism is associated with cardiovascular risk factors; however, whether subclinical hypothyroidism alters cardiac risk factors, especially, dyslipidemia and coronary heart disease (CHD) remains uncertain. The aim of this study was to explore the relationship between subclinical thyroid status, cardiovascular risk factors, and the risk for CHD and mortality.

METHODS

The Study Population

The European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk study is a population-based study of 25,633 men and women, 45 through 79 years of age residing in Norfolk, United Kingdom. Participants were recruited by mail from age-sex registries of primary care practices in Norfolk as part of a 10-country collaborative study designed to investigate dietary and other causes of cancer. Data were also obtained to facilitate assessment of the causes of other diseases. Eligible participants completed a baseline study conducted from 1993 through 1997 during which a detailed health and lifestyle questionnaire was completed and nonfasting fresh blood specimens were obtained to measure high-density lipoprotein cholesterol (HDL-C) and triglyceride levels and to calculate low-density lipoprotein cholesterol (LDL-C) levels with the Friedewald formula. Thyroid-function tests were measured on stored (–80°C) baseline samples for thyrotropin (TSH) and free thyroxine (FT4). For TSH, the sensitivity was 0.03 µIU/ml (normal range, 0.4 to 4.0); for FT_4, the sensitivity was 2.0 pmol/L (normal range, 8.0 to 20). Thyroid-function tests were randomly measured in approximately half the participants, a choice made as the result of limited funding. Vital statistics were ascertained for the entire cohort, and death certificates from the Office of National Statistics were evaluated and coded by trained nosologists. Participants with CHD were identified during follow-up if they had a hospital admission and died of CHD or had this diagnosis as an underlying cause of death.

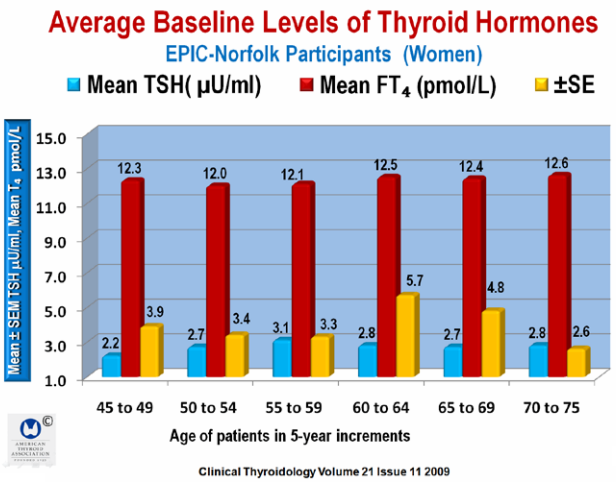
Definitions of Thyroid Dysfunction

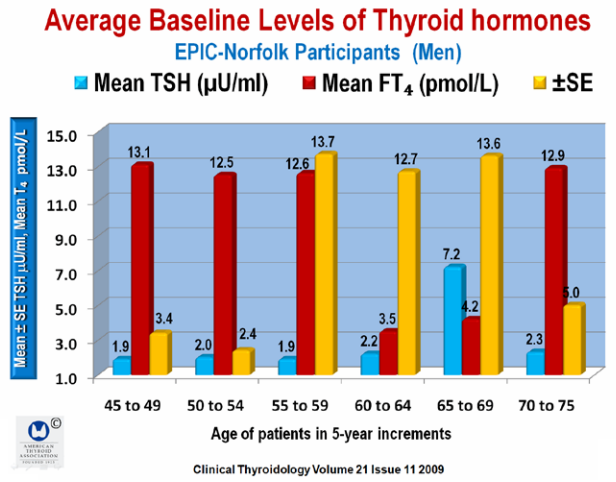
Hyperthyroidism was defined as a serum TSH <0.1 µIU/ml with a free thyroxine (FT_4) >20 pmol/L. Subclinical hyperthyroidism was defined as a serum TSH ranging from 0.1 through 0.4 µIU/ml or a TSH <0.1 µIU/ml with FT_4 in the normal range. Euthyroidism was defined as a TSH in the normal range. Subclinical hypothyroidism was defined as a TSH >4.0 µIU/ml with an FT_4 ranging from 9.0 through 20.0 pmol/L. Hypothyroidism was defined as a TSH >4.0 µIU/ml with an FT_4 <9 pmol/L.

RESULTS

Baseline Characteristics of Study Subjects (Figures 1 and 2)

Serum TSH and FT_4 was measured in 13,076 participants. After excluding participants with self-reported thyroid disease and those taking thyroid hormone, complete data were available for 11,554 participants, 5206 men (45%) and 6348 women (55%). The association between age and FT_4 was not very strong, and





Figures 1 and 2. These figures show means, standard errors, and percentages of abnormal values of TSH and FT_4 in 5-year age groups in women (Figure 1) and men (Figure 2) 45 to 75 years of age in the EPIC-Norfolk cohort. Although mean TSH levels increase with age, median levels (not shown in this figure) show only a slight increase, which is a consequence of the skewed distribution of TSH in both sexes. Data for these figures are derived from Table 1 in Boekholdt et al.

although TSH increased with age, the median TSH was only slightly increased. (Figure 1 for women; Figure 2 for men). All percentages in the text are reduced to the nearest integer; however, the figures show the exact percentages.

The Prevalence of Thyroid Dysfunction in the Study Group (Figure 3)

Of the entire study group, 10,301 were euthyroid (89%). Subclinical hypothyroidism was present in 800 persons, of whom 238 were men (5%) and 562 were women (9%). Undiagnosed hypothyroidism was found in only 47 men (1%) and 158 women (2.5%). The rate of subclinical hyperthyroidism was relatively low, at 2% in both women and men, and overt hyperthyroidism was present in less than 1% of the entire group. The prevalence of subclinical and clinical thyroid disease in the population without self-reported thyroid disease or the use of thyroid medication is shown in Figure 3.

Baseline Characteristics of Cardiovascular Status in Men and Women According to Thyroid Function (Figures 4 to 6)

Men with subclinical hypothyroidism were older and had higher waist circumference and body-mass index (BMI) than did the euthyroid group; those with overt hypothyroidism were also older and had higher LDL-C levels and glycated hemoglobin

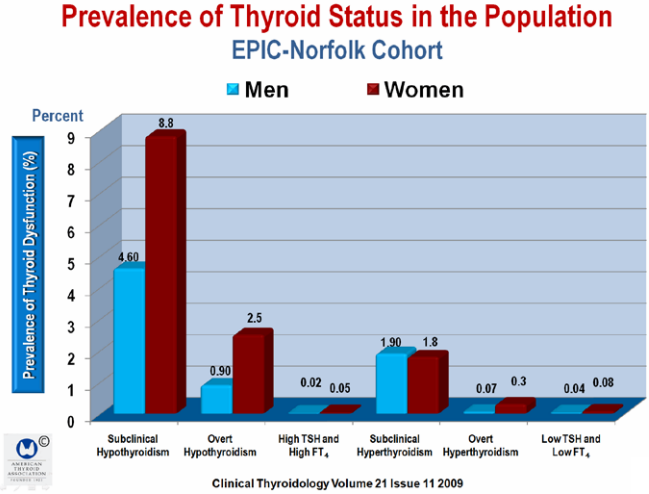


Figure 3. This figure shows the prevalence of thyroid dysfunction in men and women in the EPIC-Norfolk Cohort. Data for this figure are derived from Table 2 in Boekholdt et al.

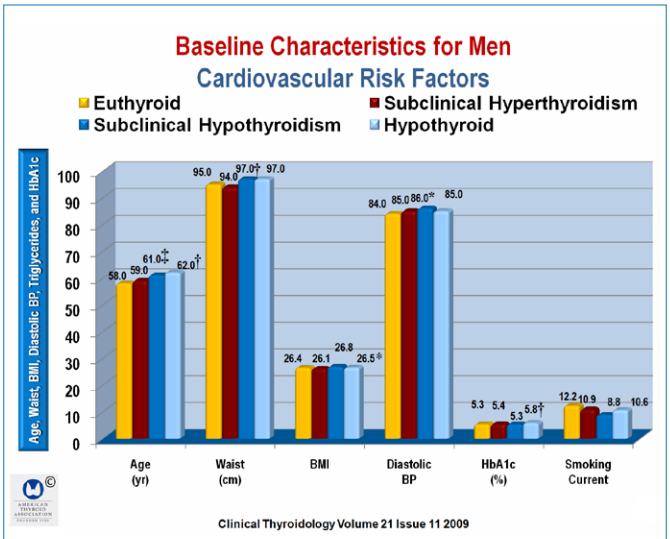


Figure 4. This figure shows the baseline cardiovascular characteristics of thyroid dysfunction in men as compared with euthyroid participants. Data for this figure are derived from Table 3 in Boekholdt et al. *P<0.05.†P<0.01. ‡P = 0.001. BMI = body-mass index (the weight in kilograms divided by the square of the height in meters); BP = blood pressure; HbA1c = glycated hemoglobin.

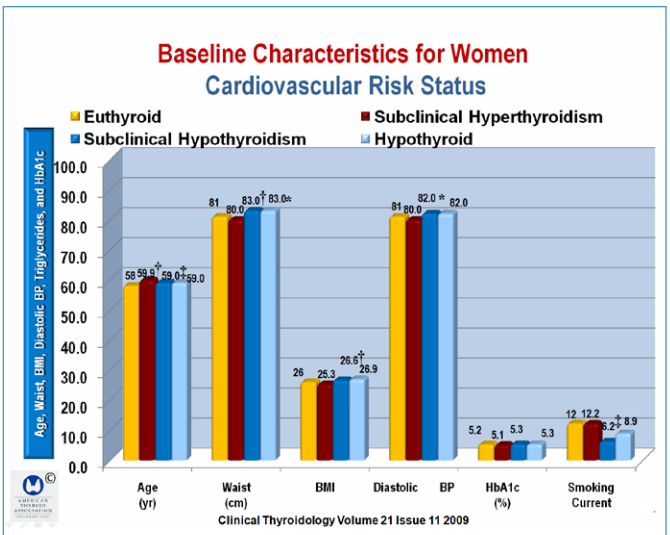


Figure 5. This figure shows the baseline characteristics cardiovascular of thyroid dysfunction in women as compared with euthyroid participants. Data for this figure are derived from Table 3 in Boekholdt et al. *P<0.05. †P<0.01. ‡P = 0.001. BMI = body-mass index (the weight in kilograms divided by the square of the height in meters); BP = blood pressure; HbA1c = glycated hemoglobin.

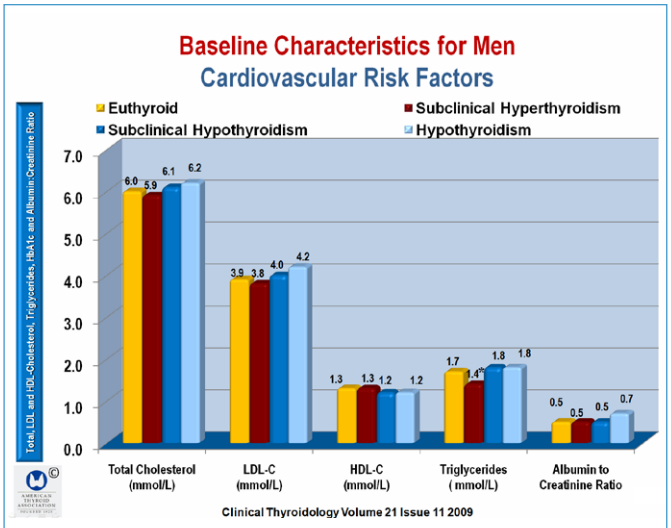


Figure 6. This figure shows the lipid characteristics in men as they relate to thyroid status and as compared with healthy euthyroid participants*P<0.05. †P<0.01. ‡P = 0.001. Data are derived from Table 3 in Boekholdt et al. HbA1c = glycated hemoglobin.

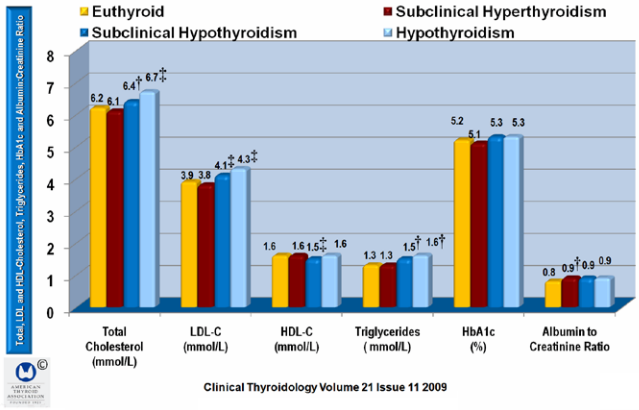


Figure 7. This figure shows the lipid characteristics in women as they relate to thyroid status and as compared with healthy euthyroid participants. *P<0.05. †P<0.01. ‡P = 0.001. Data are derived from Table 3 in Boekholdt et al. HbA1c = glycated hemoglobin.

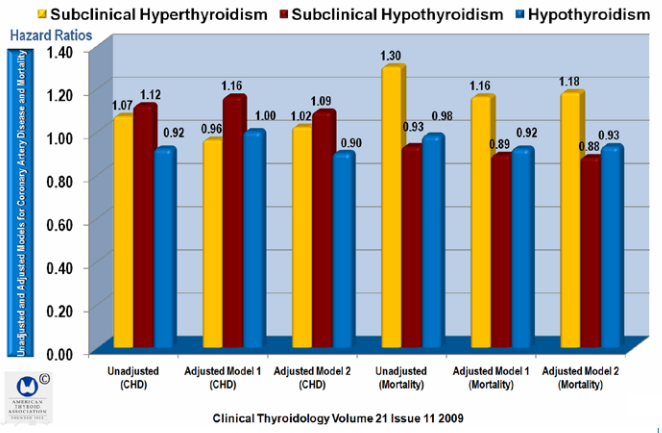


Figure 8. This figure shows the hazard ratios (the corresponding 95% confidence intervals are not shown). Model 1 is adjusted for sex, age and smoking; model 2 is adjusted for sex, age, smoking, diabetes mellitus, waist: hip ratio, systolic blood pressure, LDL-C and HDL-C. Euthyroid participants were the reference group. This figure shows that despite the association between thyroid hormone levels and cardiovascular risk factors, thyroid status was not significantly associated with the risk for future CHD or all-cause mortality. Euthyroid people comprised the reference group.

(HbA1c) levels than the euthyroid group (Figure 4). Among men with normal TSH and FT_4 levels, the TSH levels were significantly associated with total cholesterol, LDL-C, and HDL-C levels and diastolic blood pressure, whereas FT_4 levels were inversely associated only with BMI.

Baseline Characteristics of thyroid hormone levels and cardiovascular status in Women

Among women, TSH levels were associated with HDL-C levels, BMI, and systolic blood pressure, whereas FT_4 levels were associated only with HDL-C levels. There was no evidence for an important interaction between thyroid hormone levels and lipid levels, blood pressure, or smoking, nor was there a significant interaction between TSH and age with lipids, BMI, and diastolic blood pressure (Figure 5). The interaction between TSH and sex was statistically significant with total cholesterol and LDL-C, suggesting that the association between TSH and lipids differs between the sexes (Figure 6. The interaction between FT_4 and sex was statistically significant for total cholesterol, LDL-C, HDL-C, BMI, and systolic blood pressure (Figure 7).

Moreover, the interaction between FT_4 and age was statistically significant for LDL-C, HDL-C, BMI, and diastolic blood pressure. However, neither subclinical hyperthyroidism nor subclinical hypothyroidism nor overt hypothyroidism was associated with a statistically significantly increased risk for coronary heart disease, as compared with euthyroid people (Figures 4, 7 and 8). Women with subclinical hypothyroidism and overt hypothyroidism had substantially worse cardiovascular risk profiles and lipid levels than did euthyroid women (Figure 5).

CONCLUSION

Although there is an association between thyroid hormone levels and cardiovascular risk factors, the thyroid dysfunction is not linked with a significantly increased risk for coronary heart disease.

COMMENTARY

Considerable controversy surrounds the notion that subclinical hypothyroidism (SCH) has a significant effect on the risk profile of cardiovascular disease. The study by Boekholdt and associates provides important information that addresses this issue in a large cohort of participants. The study found that participants with thyroid dysfunction had an altered cardiovascular risk profile. Specifically, women with SCH and overt hypothyroidism had elevated LDL-C levels and higher systolic blood pressure. TSH levels, even in the normal range, were independently associated with LDL-C and HDL-C, BMI, and systolic blood pressure in both men and women. Finally, the participants in the EPIC-Norfolk cohort with thyroid abnormalities did not have a statistically significantly increased risk for future cardiovascular heart disease (CHD), which was comparable to that in other studies of people younger than 65 years of age (1).

Most studies have confirmed that an association exists between dyslipidemia and hypertension. A meta-analysis by Danese et al. (2) aimed at estimating the expected change in serum lipoprotein concentrations after levothyroxine ($L\text{-}T_4$) treatment found that all 13 studies in the analysis reported changes in serum total cholesterol concentration during $L\text{-}T_4$ treatment, 12 reported triglyceride changes, 10 reported HDL-C changes, and 9 reported LDL-C changes. Furthermore, they found that a decline in serum total cholesterol was directly proportional to its baseline concentration, and that studies enrolling

hypothyroid participants on suboptimal doses of L-T_4 reported significantly larger decreases in serum total cholesterol after TSH normalization than studies enrolling previously untreated individuals with mild thyroid failure. The results, although based on fewer than 250 patients, suggested that L-T_4 therapy in individuals with mild thyroid failure lowers mean serum total and LDL-C concentrations.

Boekholdt and associates found that even in a completely euthyroid population, there is an association between serum TSH and lipid levels, suggesting to the authors that a physiological mechanism may underlie this relationship. On the other hand, this study did not confirm the previously reported interaction between thyroid dysfunction and the metabolic effects of smoking. The study also found significant interactions between serum TSH and sex for lipid outcomes, suggesting to the authors that these lipid levels differ between men and women. Perhaps of most importance, the results of this study did not support an association between SCH and a substantial increase in CHD.

Still, a recent meta-analysis (3) found that SCH may be associated with a modest increase in cardiovascular risk. Ten of the 12 studies in the analysis, which included 14,449 participants, examined risks associated with SCH (2134 CHD events and 2822 deaths). The relative risk (RR) for CHD in patients with SCH was 1.20 (95% confidence interval [CI], 0.97 to 1.49; P for heterogeneity = 0.14). The estimates of risk were lower when higher-quality studies were pooled (RR, 1.02 to 1.08) and were higher among participants with a mean age of <65 years (RR, 1.51; 95% CI, 1.09 to 2.09), as compared with participants ≥65 years (RR, 1.05; 95% CI, 0.90 to 1.22). The RR was 1.18 (95% CI, 0.98 to 1.42) for CVD mortality and 1.12 (95% CI, 0.99 to 1.26) for total mortality. For subclinical hyperthyroidism, the RR was 1.21 (95% CI, 0.88 to 1.68) for CHD, 1.19 (CI, 0.81 to 1.76) for cardiovascular mortality, and 1.12 (95% CI, 0.89 to 1.42) for total mortality (P for heterogeneity >0.50.

Another relatively recent meta-analysis by Razvi et al. (4) was aimed at investigating whether age and sex influence the prevalence, incidence, and mortality of CHD in people with SCH. Fifteen studies were included in the analysis of 2531 participants with SCH and 26491 euthyroid individuals. The incidence and prevalence of CHD were higher in SCH subjects compared with euthyroid participants from studies including those less than 65 years but not studies of subjects aged more than 65 years [Odds Ratio (95% CI)]: 1.57 (1.19 to 2.06) vs. 1.01 (0.87 to 1.18) and 1.68 (1.27 to 2.23) verses. 1.02 (0.85 to 1.22), respectively. All-cause mortality from CHD was also significantly higher in participants <65 years of age as compared with older people (OR, 1.37; 95% CI, 1.04 to 1.79 vs. OR, 0.85; 95% CI, 0.56 to 1.29). The prevalence of coronary artery disease was higher in both men and women with SCH, although this was statistically significant only in women. The conclusion of the study was that both the incidence and prevalence of SCH is associated with increased, CHD mortality, but only in younger subjects.

Boekholdt and associates suggest that the Razvi study is consistent with the Boekholdt study insofar as both found no statistically significant increased risk for CHD in patients with SCH. Boekholdt and associates point out that the results of their study cannot be applied to the general population because people with thyroid disease were excluded from the study, and their results are based on a single TSH and FT_4 measurement and cannot exclude the possibility that limited statistical power may have prevented identifying a moderately increased risk for SCH. Nonetheless, the Boekholdt study does not support an association between SCH and a substantial increase in the risk for CHD, although this has been reported in several small cross-sectional studies (5;6).

In conclusion, SCH is a common condition that has been associated with coronary artery disease in some, but not all studies, which may be due to differences in study design and the characteristics of the study participants. The study by Boekholdt offers important new information in a large study cohort.

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