Risk of Coronary Heart Disease and Mortality for Adults With Subclinical Hypothyroidism Reply

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To the Editor: In their study, Dr Rodondi and colleagues[1] addressed the issue of the relationship between subclinical hypothyroidism and coronary heart disease (CHD) or mortality. Previous large prospective cohort studies have provided conflicting results about this extensively studied association. In the study by Rodondi et al, an attempt to reduce the effects of several confounders (including age, sex, degree of thyroid stimulating hormone [TSH] elevation, and pre-existing cardiovascular disease) was performed.[1] However, the finding of no association of risk with subclinical hypothyroidism for TSH concentration up to 10.0 mIU/L may be flawed because it did not provide information about the body mass index (BMI) of the patients diagnosed with subclinical hypothyroidism.

This might be a problem because subclinical hypothyroidism, especially when characterized by minor increases in serum TSH levels, is frequently observed among obese patients.[2-4] The elevated serum TSH found in obese (and particularly in morbidly obese) patients may be a mere consequence of the excess body weight rather than a condition of primary thyroid failure.[2-4] This concept would imply that obese patients with a moderate elevation in serum TSH would not experience increased systemic vascular resistance, altered endothelial function, increased atherosclerosis, altered coagulability, and lipid abnormalities, which account for the increased risk of CHD associated with subclinical hypothyroidism.[5]

Positive tests for thyroid autoantibodies are the only parameters able to discriminate between true subclinical hypothyroidism and obesity-induced hyperthyrotropinemia.[3] Because thyroid antibodies were not taken into account in diagnosing subclinical hypothyroidism in the study by Rodondi et al, the conclusions may have been biased. Indeed, obese patients with a moderately increased TSH (up to 10 mIU/L) may include a subgroup of patients who are not truly hypothyroid, thus underestimating the real CHD risk associations of subclinical hypothyroidism (defined as high serum level of TSH with normal free thyroxine levels and positive test results for thyroid antibodies).

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To the Editor: Dr Rodondi and colleagues[1] assessed the risk of CHD and total mortality for adults with subclinical hypothyroidism. In this study, the hazard ratio (HR) for CHD events was 1.00 (95% confidence interval [CI], 0.86-1.18) for a TSH level of 4.5 to 6.9 mIU/L, 1.17 (95% CI, 0.96-1.43) for a TSH level of 7.0 to 9.9 mIU/L, and 1.89 (95% CI, 1.28-2.80) for a TSH level of 10.0 to 19.9 mIU/L. They concluded that subclinical hypothyroidism was associated with an increased risk of CHD events and CHD mortality in persons with higher TSH levels, particularly in those with a TSH concentration of 10 mIU/L or greater, and that minimal TSH elevations were not associated with an increased risk of CHD events and CHD mortality. However, they did not verify the CHD events and CHD mortality among those within the reference range of TSH levels.

TSH levels within the reference range may be positively associated with BMI[2] and inversely associated with insulin sensitivity.[3] We investigated the relationship between thyroid function and carotid intima-media thickness (CIMT) in 643 participants with euthyroid status and demonstrated that CIMT was independently associated with thyroid function within the normal reference range, which suggests increased cardiovascular risk in persons with low-normal thyroid function.[4] Furthermore, in a population-based prospective cohort study, TSH levels even within the reference range were positively and linearly associated with CHD mortality in women.[5]

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One possible explanation for the difference in findings is the effect of confounding factors. In the study by Åsvold et al,[5] a modest attenuation of the association of TSH level with CHD mortality was observed after adjustment for blood pressure and serum lipids, suggesting that the effect of TSH may be at least partially mediated by these factors. Further analysis should be conducted with a similar strategy in the study by Rodondi et al, aimed at those within the reference range of TSH.

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In Reply: We agree with Dr Rotondi and colleagues and Dr Takamura and colleagues that the mediating factors between subclinical hypothyroidism and CHD remain to be determined, since in our study the associations between subclinical hypothyroidism and CHD remained of similar magnitude after adjustment for traditional cardiovascular risk factors. Rotondi et al hypothesized that inclusion of obese individuals might explain the lack of the significant association with CHD among adults with minimal TSH elevations. We disagree with this hypothesis for several reasons.

First, TSH level in most obese individuals is usually in the normal or upper normal range (2.5-4.5 mIU/L),[1] even in severe obesity,[2] so misclassification should be uncommon. Second, further adjustment for BMI (available in 10 of the 11 cohort studies) yielded similar risk estimates, as shown in Table 3 of our article. Third, we have performed a further sensitivity analysis excluding obese participants with a BMI of 30 or more (calculated as weight in kilograms divided by height in meters squared) and found similar results: the age and sex-adjusted HR for CHD events was 1.04 for a TSH level of 4.5 to 6.9 mIU/L (95% CI, 0.91-1.20), 1.18 for a TSH level of 7.0 to 9.9 mIU/L (95% CI, 0.93-1.49), and 1.95 for a TSH level of 10 mIU/L or more (95% CI, 1.27-2.99; $P=.002$ for trend), with corresponding HRs for CHD mortality of 1.07 (95% CI, 0.87-1.32), 1.45 (95% CI, 1.04-2.03), and 1.78 (95% CI, 1.21-2.62; $P=.001$ for trend), respectively. However, as mentioned in our limitations, some participants might have had spontaneous resolution of subclinical hypothyroidism (normalization of TSH without treatment), which might be particularly common in participants with TSH levels of 4.5 to 6.9 mIU/L. Further studies among adults with persistent subclinical hypothyroidism are needed.

Regarding the lack of data on thyroid autoantibodies, the commonly accepted definition of subclinical hypothyroidism[3,4] is a serum TSH concentration above the statistically defined upper limit of the reference range with normal serum free T4 concentration and does not include thyroid autoantibodies. Differences in risks of subclinical hypothyroidism with and without thyroid autoantibodies should be examined in future studies.

We agree with Takamura et al that the issue of CHD risks related to TSH within the euthyroid range is very interesting, but this question was outside the scope of this specific study.

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Well-being of Patients With Dementia and Their Caregivers After a Biobehavioral Home-Based Intervention

To the Editor: Dr Gitlin and colleagues[1] reported the results of the Care of Persons with Dementia in their Environments (COPE) randomized controlled trial, assessing a biobehavioral home-based intervention to support physical function and quality of life for patients with dementia and the well-being of their caregivers. The authors