Letters to the Editor will be published, if suitable, as space permits. They should not exceed 1000 words (typed double-spaced) in length and may be subject to editing or abridgment.

Response by Bano et al to Letter Regarding Article, "Thyroid Function and the Risk of Atherosclerotic Cardiovascular Morbidity and Mortality: The Rotterdam Study"

In Response:

We appreciate the comments by Drs Zhao and Schooling on our recent publication.[1] In this study, we showed that higher circulating free thyroxine levels are associated with an increased risk of atherosclerosis throughout its full spectrum.

Zhao and Schooling[2] argue that our observed associations are not supported by an MR study (Mendelian Randomization), which found no evidence of an association between thyroid function and ischemic heart disease. The following considerations need to be taken into account with regard to this study. First, the MR study focused on coronary artery disease. However, there are no MR studies, to our knowledge, on thyroid function and atherosclerotic cardiovascular disease. Second, the MR approach assumes that genetic variants determine the exposure. Still, only a limited number of genetic variants for free thyroxine have been identified, whereas a large proportion of thyroid function heritability remains unexplained. Third, the possibility of developmental compensation (ie, canalization) and pleiotropic effects of genetic variants cannot be excluded. Taken together, the current lack of genetic evidence does not rule out a potential effect of thyroid function on atherosclerotic cardiovascular disease.

We agree with the authors that we cannot prove a causal relationship because of the observational character of our study. However, the biological plausibility of our findings, the temporal relationship of the exposure with atherosclerotic events, and the various sensitivity analyses accounting for reverse causation strongly suggest an effect of thyroid function on atherosclerotic cardiovascular morbidity and mortality.[1] Moreover, our findings are consistent with the results of the randomized controlled trial cited by Zhao and Schooling.[2,3] This trial investigated the effects of dextrothyroxine treatment in patients with a history of myocardial infarction. The proportions of all-cause deaths, deaths from cardiovascular disease, deaths from coronary heart disease, and nonfatal recurrent myocardial infarctions were higher in the treatment arm than in the placebo arm of the trial, leading to a discontinuation of the trial after 36 months. In line, our study shows that higher free thyroxine levels are associated with an increased risk of atherosclerotic cardiovascular mortality, particularly among subjects with preexisting atherosclerotic cardiovascular disease.

Furthermore, Zhao and Schooling[2] hypothesize that androgens can confound or mediate the association of thyroid function with atherosclerotic cardiovascular outcomes. This is an intriguing hypothesis, though the association of testosterone with atherosclerotic cardiovascular outcomes remains largely unclear.[4] To date, randomized controlled trials investigating the effects of testosterone treatment on major cardiovascular events have yielded conflicting results.[4] We had data available on testosterone concentrations in >99% of participants. After adding testosterone to our models, the association of thyroid function with atherosclerotic cardiovascular outcomes remained unchanged or became slightly stronger. Sex-specific analyses provided consistent findings before and after additional adjustments for testosterone. These data suggest that the association of thyroid function with atherosclerosis is independent of testosterone concentrations.

In the future, large MR studies are warranted to examine the association of genetically predicted thyroid function with atherosclerotic cardiovascular outcomes. Further investigations are also needed to elucidate the exact mechanisms linking thyroid function to atherosclerosis.

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Disclosures

None.

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