# Letter to the Editor

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## Letter by Zhao and Schooling Regarding Article, "Thyroid Function and the Risk of Atherosclerotic Cardiovascular Morbidity and Mortality: The Rotterdam Study"

*To the Editor:*

We read with great interest the recent study by Bano et al,[1] which shows that thyroid function, indicated by thyroid-stimulating hormone, free thyroxine, and thyroid peroxidase antibodies, is associated with higher risk of atherosclerosis throughout its spectrum, from subclinical atherosclerosis, incident atherosclerotic cardiovascular events to cardiovascular mortality. This novel study could indicate a role of thyroid function in ischemic heart disease (IHD). However, these observed associations have not been corroborated by a randomized controlled trial of exogenous dextrothyroxine in secondary prevention of IHD[2] and an MR (Mendelian randomization) study of prevalent IHD.[3] Both study designs take advantage of randomization, of the treatment for randomized controlled trial, and of the random assortment of genetic endowment at conception for MR, to generate unconfounded estimates. Specifically, the study of Zhao and Schooling[3] showed no association of genetically predicted endogenous thyroid-stimulating hormone, free thyroxine, or thyroid peroxidase antibodies with IHD.

Findings may differ between study designs because of study or population-specific attributes, but can also occur because observation studies, as reported by Bano et al,[1] can be confounded by a common driver of both thyroid function and IHD. Many biological processes could underlie such an association, one of these increasingly gaining attention is androgens. The hypothalamic–pituitary–thyroid axis interacts with the hypothalamic–pituitary–gonadal axis.[4] Gonadotropin-releasing hormone treatment has been shown to moderately increase thyroid-stimulating hormone secretion in animal experiments, suggesting that gonadotropin-releasing hormone may modulate thyroid function at the pituitary level.[4] At the same time, agents that modulate gonadotropin-releasing hormone, such as tachykinin neurokinin 3 receptor antagonists, have recently been proposed as a way of reducing cardiovascular disease.[5] Although the role of testosterone remains controversial, both Health Canada and the Food and Drug Administration in the United States have warned of the cardiovascular risk of testosterone in men,[5] supported by the evidence from a recent randomized controlled trial showing that testosterone increases coronary artery plaque volume, the hallmark of atherosclerosis.[6] Evidence from and meta-analysis of randomized controlled trials also suggests that testosterone increases venous thrombosis and that the effect on cardiovascular events is usually in the direction of harm.[5] As such, to exclude the potential confounding by androgens, it would be worthwhile to examine the sex-specific associations of thyroid function with cardiovascular risk after controlling for testosterone. Replication using MR, if available, in the same study, would also provide more evidence to clarify the role of thyroid function in IHD.

Notably, the authors also pointed out that these associations are independent of cardiovascular disease risk factors and stressed the importance of identifying modifiable mediators underlying these observed associations. Androgens might act as mediators based on these known effects. However, in that case, the association of thyroid function with cardiovascular disease risk would be expected to be more obvious in men than in women, which is not consistent with the findings of no differences by sex.[1] Examining and interpreting observations within the context of known causal effects may provide a guide to interpretation and identification of the potentially modifiable targets and would be beneficial, before further investigation of proposed pathways.

## Disclosures

None.

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## References

1. Bano A, Chaker L, Mattace-Raso FUS, van der Lugt A, Ikram MA, Franco OH, Peeters RP, Kavousi M. Thyroid function and the risk of atherosclerotic cardiovascular morbidity and mortality: the Rotterdam Study. *Circ Res*. 2017;121:1392–1400. doi: 10.1161/CIRCRESAHA.117.311603.
2. Coronary Drug Project Research Group. The coronary drug project. Findings leading to further modifications of its protocol with respect to dextrothyroxine. *JAMA*. 1972;220:996–1008. doi: 10.1001/jama.1972.03200070084015.
3. Zhao JV, Schooling CM. Thyroid function and ischemic heart disease: a Mendelian randomization study. *Sci Rep*. 2017;7:8515. doi: 10.1038/s41598-017-07592-z.
4. Castañeda Cortés DC, Langlois VS, Fernandino JI. Crossover of the hypothalamic pituitary-adrenal/interrenal, -thyroid, and -gonadal axes in testicular development. *Front Endocrinol (Lausanne)*. 2014;5:139. doi: 10.3389/fendo.2014.00139.
5. Schooling CM. Tachykinin neurokinin 3 receptor antagonists: a new treatment for cardiovascular disease? *Lancet*. 2017;390:709–711. doi: 10.1016/S0140-6736(16)31648-8.
6. Budoff MJ, Ellenberg SS, Lewis CE, et al. Testosterone treatment and coronary artery plaque volume in older men with low testosterone. *JAMA*. 2017;317:708–716. doi: 10.1001/jama.2016.21043.

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