Response to the Letter by Choy

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We have read the letter from Choy and appreciate the comment in response to our recent publication (1). In the letter, Choy discusses the importance of using newer "third-generation assays" in evaluating thyroid-stimulating hormone (TSH) concentrations in the serum of patients and rightfully notes that in a laboratory evaluation of a particular endogenous TSH serum concentration, measurements from different assays could result in differently reported TSH serum concentrations. These differences are mainly important for the functional sensitivity of detecting low TSH and are less relevant within the hypothyroid and euthyroid range for second- and third-generation assays (2). The cohorts from the Thyroid Studies Collaboration included in our study used different TSH assays (3) and, although 14 of 17 cohorts used a third-generation TSH assay, some would be expected to be more sensitive than others. However, even though we agree with Choy that "assay bias" is extremely relevant in an individual patient because it guides treatment decisions, on a population level, especially when addressing etiological questions, this is far less of an issue.

The main reason is that, by pooling data from different studies using an individual participant data meta-analysis approach, we are not comparing participants from different studies to each other. We are comparing participants with different TSH levels from the same study—ergo measured with the same assay—to each other. In other words, our study finds that irrespective of the assay used, overall, participants with higher TSH serum concentrations have lower risks of stroke. That there is no heterogeneity between the different studies ($I^2 = 0\%$) supports this notion. Besides, the TSH assay variability within each study would most probably lead to an underestimation (*i.e.*, downward bias) rather than overestimation of the association between TSH concentrations and the risk of stroke. Furthermore, we find a negative linear association of TSH (log-transformed) and the risk of stroke. This means that the decrease of the risk of stroke is similar for each increase of serum TSH, and there seems to be no threshold effect. From an etiological point of view, this is interesting and can provide insight into the pathophysiological mechanisms underlying the association in the general population.

In respect to the individual patient, we fully agree with Choy. Additionally, in an individual patient, physicians not only have to take the assay used into account, but also many other patient characteristics including age, sex, comorbidities, assay interference, and medication use (4). However, when addressing the etiological question of whether thyroid function within a particular range could be associated with the risk of disease, we respectfully disagree that "assay bias" is a major issue.

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ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 21 October 2016. Accepted 21 October 2016.

Abbreviation: TSH, thyroid-stimulating hormone.

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