Response by Gutiérrez et al to Letter Regarding Article, “Hemoglobin Concentration and Risk of Incident Stroke in Community-Living Adults”

In Response:

Drs Yang, Li, and Zeng have raised several concerns about the interpretation of the association of hemoglobin with stroke risk in the REGARDS study (Reasons for Geographic and Racial Differences in Stroke). Although we appreciate their interest in our study, we think that the crux of their concerns is based on a misapplication of data from prior studies to our own study. The primary focus of our study was to examine the association of hemoglobin with future risk of incident stroke in community-dwelling adults. In contrast, the 2 comparator studies cited by Drs Yang, Li, and Zeng focused on the association of hemoglobin at the time of acute stroke hospitalization with poststroke outcomes (functional outcome, mortality, etc).1,2 We fully agree that determining the association of hemoglobin with poststroke outcomes in acutely ill, hospitalized patients would be best accomplished by using hemoglobin measurements obtained nearest to the time of the actual stroke event. However, this is a different issue from the focus of our study, which was the relationship between hemoglobin and stroke risk in a relatively healthy cohort of adults free of stroke at baseline. Because of the difference in the research questions posed, it is not surprising that the nature of the association of hemoglobin with these outcomes would differ, being equivalent to comparing apples to oranges. In fact, prior population-based studies that examined the association of hemoglobin with future risk of stroke (an apples to apples comparison) have reported J- or U-shaped relationships between hemoglobin and stroke risk, supporting the validity of our findings.3,4

Drs Yang, Li, and Zeng also raised concerns about potential residual confounding from risk factors such as alcohol consumption, hypertension, deep venous thrombosis, chronic obstructive pulmonary disease, peripheral vascular disease, and medication use (aspirin, statins, anticoagulant use). First, we would point out that the fully adjusted models presented in our published study were adjusted for chronic pulmonary disease (ie, chronic obstructive pulmonary disease), aspirin use, and systolic blood pressure. Second, when we further adjusted the model for alcohol intake, a history of peripheral vascular disease or deep venous thrombosis, statin use, and warfarin use, the magnitude and strength of the association of hemoglobin with stroke risk did not materially change in women (Quartile 2 referent; Quartile 1, hazard ratio [HR] 1.61, 95% confidence interval [CI] 1.11, 2.35; Quartile 3, HR 0.93, 95% CI 0.61, 1.41; Quartile 4, HR 1.63, 95% CI 1.10, 2.41) or men (Quartile 2 referent; Quartile 1, HR 0.98, 95% CI 0.66, 1.46; Quartile 3, HR 1.18, 95% CI 0.81, 1.73; Quartile 4, HR 0.97, 95% CI 0.65, 1.46). Next, Drs Yang, Li, and Zeng felt that the estimated glomerular filtration rate used to identify study participants with chronic kidney disease was moderately below or at a normal level. However, an estimated glomerular filtration rate <60 mL/min per 1.73 m² is a standard cutoff for chronic kidney disease and was the threshold level that was previously shown to modify the association of hemoglobin with stroke risk.5 Finally, we agree with Drs Yang, Li, and Zeng that adjusting for baseline hormone replacement therapy would have been ideal. However, we did not have complete information on hormone replacement therapy at the time of the baseline visit, and so this remains a limitation of our study. Nonetheless, it is unlikely that the use of hormone replacement therapy would completely account for the robust U-shaped association of hemoglobin with stroke risk in women.

We thank Drs Yang, Li, and Zeng for their comments. We agree with them that future studies will need to confirm the relationships between hemoglobin concentrations and incident stroke risk in community-dwelling adults.

Disclosures

None.

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