Response to Comments on: Selvin et al. sRAGE and Risk of Diabetes, Cardiovascular Disease, and Death. Diabetes 2013;62:2116–2121

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We thank Drs. Schalkwijk and Stehouwer (1) and Dr. Yamagishi (2) for their interest in our recent article (3). We agree with the authors that it is interesting that some studies in populations with preexisting conditions (i.e., type 1 or type 2 diabetes) have shown positive associations of soluble circulating receptor for advanced glycation end products (sRAGEs) with clinical outcomes. These results are in contrast to our community-based study of middle-aged adults in which sRAGE was inversely associated with incident coronary heart disease, diabetes, and all-cause mortality. It may be that as a marker of disease risk sRAGE acts differently in populations with long-standing chronic disease. In addition to our study, other reports in general ("healthy") populations have shown that lower sRAGE was associated with a higher prevalence of cardiovascular risk factors and subclinical cardiovascular disease (4–6). Indeed, there is evidence that sRAGE has properties of an acute-phase reactant, rising rapidly with acute injury (7,8). Much remains unknown about the biology of sRAGE, and the contradictory associations with clinical outcomes are puzzling. We strongly agree that the substantial differences in the distribution of sRAGE by race/ethnicity and genetic determinants of sRAGE deserve further consideration.

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