To the Editor,

We read with interest the recent Scientific Statement from the American Heart Association on sex differences in cardiovascular consequences among persons with diabetes.[1] The authors informed us of the loss of the usual female protection against cardiovascular disease (CVD) in diabetes, stating that women experience higher risk, provided a review of some of the literature regarding a loss of CVD protection among women with diabetes, and suggested biological and potential clinical and health-care related explanations for this "long recognized fact." The Statement also noted the differential burden of diabetes borne by racial and ethnic minorities, and the heavy impact of diabetes on CVD, acknowledging the limited amount of data on these populations.

We thus found it surprising the authors did not mention data from the Southern Community Cohort Study (SCCS), a cohort of ~86,000 adults, two-thirds African American, where diabetes is common.[2] In the SCCS, among approximately 9,000 African Americans and 3,000 Whites who entered the cohort with diabetes diagnosed at age ≥30, we have documented a nearly two-fold excess all-cause mortality compared to their race-specific, non-diabetic counterparts and a lower-all cause-mortality in African Americans compared with Whites,[3] findings consistent with the Statement.[1] However, contrary to the Statement's claim of elevated coronary heart disease (CHD) and heart failure risks in women with diabetes, we found lower hazard ratios (HR) of both ischemic heart disease (HR=0.57, 95% CI=0.44-0.73) and heart failure (HR=0.61, 0.44-0.84) mortality in women than men, deficits which were seen among both African Americans and Whites with diabetes.[4]

The Statement[1] notes "It has also been recognized for years that DM confers greater risk for CHD death in women compared with men", citing a 1991 reference from the Rancho Bernardo Study. The text also cites cohort studies in Finland regarding higher CHD risk among diabetic females, but a meta-analysis[5] cited elsewhere in the article concluded that there were no significant sex differences in diabetes-

associated risks for CVD or all-cause mortality and that absolute CHD rates were in fact higher for men than women in all but the very oldest age strata. In commenting on the higher heart failure risk among females, the Statement cites a 1974 report from the Framingham cohort, a cohort in Portland Oregon and a recent Italian study, but the latter two reported no significant female excess. Hence the evidence presented supporting the Statement's premise of worse outcomes for women with diabetes seems not convincing.

This is not to say that there are no sex differences in outcomes among diabetes patients. However, given that Scientific Statements offer the appearance of scientific consensus and conclusiveness, we suggest that the existing data do not fully support poorer outcomes among women, especially among African Americans. We agree with the authors of the Statement that more information is needed on the cardiovascular consequences in general, and sex differences in particular, of diabetes in ethnic and racial minorities, for whom diabetes prevalence is highest.

Sincerely,

Baqiyyah Conway, PhD and William Blot, PhD

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Response to: Southern Community Cohort Study

Judith G. Regensteiner, PhD, FAHA; Sherita Golden, MD, MHS, FAHA; and Amy G. Huebschmann, MD, MSc; on behalf of the Writing Group

We appreciate Dr. Conway and colleagues' critiques regarding our recent scientific statement in *Circulation*[1]*.* We will address the 2 major issues raised: 1) that our data regarding the sex differences in cardiovascular (CV) mortality among minority populations did not include findings from a large community-based cohort and 2) that the authors disagree with our literature assessment about whether there is disproportionate CV mortality and heart failure among women with type 2 diabetes (T2D) as compared to male T2D counterparts.

1) We appreciate Dr. Conway bringing the Southern Community Cohort Study to our attention as it sheds light on contributors to mortality in low-income African Americans and Whites with similar health care access. Data from this important cohort, published following completion of our manuscript, showed that while ischemic heart disease was the leading cause of death in African Americans and Whites with T2D, African Americans had a lower risk of death from heart disease compared to Whites[2]. An earlier analysis from the Southern Community Cohort Study showed that mortality among African Americans with diabetes and prevalent cardiovascular disease (CVD) was higher than among Whites, despite a lower prevalence of CVD among African Americans[3]. In this cohort, in contrast to others, CVD mortality did not differ by sex in the two racial groups. We agree that further research is needed to determine whether CVD and CVD mortality in association with T2D differs between men and women among racial/ethnic minority groups.

2) The other critique by Dr. Conway and colleagues regards data we presented supporting higher mortality from coronary heart disease in women with T2D than in T2D men. Many reports support the idea that CVD mortality is greater in women with T2D than men (for example,[4-9]). They also cited our use of a meta-analysis that reported no sex differences in CV mortality for people with T2D after adjustment for several CV risk factors[10]. However, this meta-analysis sought to understand the mechanisms of sex differences in CV mortality in adults with T2D **rather than to disprove this phenomenon.** In fact, using 8 prospective studies, Kanaya et al. found that the age-adjusted odds ratio of coronary heart disease mortality was indeed significantly higher in women with T2D than their nondiabetic female counterparts (OR = 3.42) as compared to men with T2D compared to nondiabetic male counterparts (OR = 2.07), p = 0.05 for comparison of OR between men and women. After adjusting for differences in CV risk factors, the sex difference in CV mortality was explained and no longer significant. In addition, since the publication of the manuscript in *Circulation*, new data in very large studies continue to strongly support the finding that women with diabetes have greater CVD mortality than T2D men[11,12]. Similar issues pertain to heart failure. Seghieri et al.[13] showed that although there was not a difference in the overall heart failure risk between hospitalized male and female patients with diabetes, there was a difference in heart failure risk in perimenopausal women compared to age-similar men with T2D. The Framingham

study was the first to show that risk of developing heart failure in women with diabetes was greater than the risk in men[14]. We agree with Dr. Conway and colleagues that there is a need for more research in this area; but available data do support the likelihood that sex differences are present in CHD mortality and heart failure among those with T2D.

Finally, Dr. Conway and colleagues state, "Hence the evidence base presented supporting the Statement's premise of worse outcomes for women than men with diabetes seems not convincing". There are many instances of sex differences in CV outcomes discussed in the manuscript supported by existing literature and these should also be considered as an integral part of building the evidence-base for sex differences.

Both our article and that of Dr. Conway and colleagues, call for additional studies to evaluate sex differences in CV mortality among men and women with T2D. We strongly support this conclusion and hope that our scientific statement will serve as a call for more research into contributors to sex differences in CV outcomes in T2DM.

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