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The diabetes-atrial fibrillation paradox

To the Editor We appreciate the editorial by Burden and Timpson¹ highlighting collider bias as a potential explanation for our findings of a differential association between diabetes and atrial fibrillation (AF) by ethnicity as well as by heart failure (HF) type.² Collider bias applies in aetiologic research where causal associations between two independent variables are spuriously created due to stratification by a causally related health outcome. First we point out that ours was *not* aetiologic research, and we specifically acknowledged that our observational study design does not allow ascertainment of causality. We nonetheless agree that the diabetes–AF paradox was one of our most intriguing observations, raising questions that, while not answered by our data, are worthy of further study.

To fully address collider bias, however, data from non-HF populations are needed. In non-HF cohorts, there have been inconsistent reports on the association between diabetes and AF, and although in recent meta-analyses diabetes was associated with increased risk of AF, body mass index (BMI) was acknowledged as a residual confounding factor.³ Schoen *et al* found an increased association with AF only among obese patients but not with normal weight,⁴ while two separate Japanese studies did not demonstrate an association, both with mean BMI (22–25 kg/m²) within normal ranges.^{5,6} Stratifying rather than adjusting for BMI in AF studies would be helpful in providing clarity on the confounding effects of BMI.³ In Asia-Pacific, we further investigated a population-based non-HF cohort from Western Australia (7435 with diabetes, 29 005 without diabetes) and found decreased incident AF with diabetes (age-adjusted /sex-adjusted odds for AF was 0.77 [95% CI 0.71 to 0.84] in diabetes versus no diabetes; personal communication: Dr Frank Sanfilippo and Dr Xiwen Qin from School of Population and Global Health, University of Western Australia. The date of communication is 15 Jan 2019).

Is there biological plausibility for the diabetes–AF paradox? We found smaller indexed left atrial volumes in diabetes with and without AF, and in both HF with reduced and preserved ejection fraction.² Interestingly, diabetes has been shown to be associated with similar negative/inward remodelling in coronary atherosclerosis, aortic disease (paradoxical

protection against aortic aneurysms), left ventricular (LV) remodelling (smaller indexed LV volumes in STICH, less LV enlargement postmyocardial infarction in SAVE, more concentric LV remodelling in I-PRESERVE). The ‘protection’ from outward remodelling has been attributed to advanced glycation endproduct cross-links in diabetes, and indeed the cross-link breakage with alagebrium resulted in a trend towards LV dilation in HF in the BENEFICIAL trial. ‘Diabetic protection’ from left atrial outward remodelling would plausibly be related to a lower risk of AF.

We fully acknowledge that despite adjusting for known confounders, sampling bias and unmeasurable genotypically driven effects could not be accounted for in our study. If collider bias from HF-only selection explains the diabetes–AF paradox, it is difficult to understand why collider bias would apply to Asians but not NZ-Europeans, or to preserved but not reduced ejection fraction HF (regardless of ethnicity), in cohorts simultaneously recruited using identical protocols. Also difficult to explain is why collider bias would not similarly impact hypertension and other HF risk factors. The diabetes–AF paradox clearly needs confirmation to establish whether it derives from collider bias or other sources.

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