Letters to the Editor

RE: “HEPATITIS C VIRUS INFECTION AND THE DEVELOPMENT OF TYPE 2 DIABETES IN A COMMUNITY-BASED LONGITUDINAL STUDY”

With their 7-year, prospective study of incident type 2 diabetes in a community with high prevalence of hepatitis C virus (HCV), Wang et al. (1) have generated valuable data for studying the contribution of HCV to the development of diabetes. However, I believe that the statistical methodology was inappropriate and that two of the three stated conclusions are erroneous.

Because of baseline characteristics (age ≥65 years in 24.7 percent, hepatitis B virus in 13.3 percent, HCV in 18.7 percent), the cohort studied by Wang et al. was at risk of not only diabetes but also death without prior diabetes. The number of such deaths during follow-up was not reported but was likely substantial. Standard methods of survival analysis assume that event types are independent, in which case it is appropriate to censor events other than the event of interest (2). This assumption is violated when subjects are at risk of event types that are dependent (“competing risks”), where one type of event precludes the other (i.e., diabetes and death without diabetes) or the two are alternate manifestations of one phenomenon (i.e., toxicity and lack of efficacy). When death is a competing outcome, censoring deaths limits the analysis to describing the risk of event in imaginary persons who can never die, not in persons who could fail from either the event or death (3). Because the probabilities of survival, death, and the event of interest together equal 1, censoring deaths has the effect of overestimating the survival probability, the cumulative incidence of the event of interest, or both (2). Most importantly, if both competing outcomes are associated with the risk factor of interest, censoring deaths can distort the association between the risk factor and the event of interest (i.e., HCV and diabetes) (4). To avoid biased results, appropriate methodologies and statistical programs have been developed (4–6).

The current study and prior cross-sectional studies that stratified by age have found that the association between HCV and diabetes is significant only in persons below the age of 60 or 65 years (1, 7, 8). Wang et al. (1) attribute this finding to effect modification by age, concluding that “the younger the persons . . . the greater the risk [that HCV will cause diabetes]” (1, p. 200). However, a likelier interpretation is that the finding is an artifact of survival bias against older persons with advanced HCV disease, who may have been disproportionately removed by death both before and during the study.

By concluding that “HCV infection and overweight or obesity showed a synergic effect on the development of diabetes” (1, p. 200), the authors misinterpret the simple additive effect of two risk factors (overweight or obesity and HCV) as a synergistic interaction. On the contrary, as shown in table 4 of their paper (1), HCV confers a similar hazard of diabetes in each category of body mass index; thus, no interaction between body mass index and HCV is evident. Moreover, no term for such an interaction appears in their final multivariate model (table 5).

ACKNOWLEDGMENTS
Conflict of interest: none declared.

REFERENCES

Carolyne E. Behrendt (e-mail: cbehrendt@coh.org)
From the Department of Biostatistics and Epidemiology, City of Hope National Medical Center, Duarte, CA 91010

DOI: 10.1093/aje/kwm399; Advance Access publication January 27, 2008