Reply. We appreciate the letter from Dr Smith et al.[1] regarding our recent publication. We agree that the most significant histologic feature of nonalcoholic fatty liver disease (NAFLD) is the degree of fibrosis, which predicts long-term clinical outcome in patients with NAFLD[2–4] We also agree that the NAFLD activity score (NAS), although useful for clinical research in nonalcoholic steatohepatitis, is not an ideal prognosticator of outcomes for patients with NAFLD.[2–4] The NAS was developed in 2005 to provide a standardized scoring system for clinical trials, and was created to encompass the full spectrum of NAFLD histology in both adults and children.[5] The scoring system permits steatosis and inflammation severity to be graded from 0 to 3, whereas it has a more restricted grading range for severity of hepatocyte injury (ie, ballooning) (0–2). Fibrosis is not scored in the NAS. With the wealth of knowledge gained in the past decade, the role of NAS for clinical research may warrant reappraisal.

Natural history studies have now demonstrated that the severity of steatosis neither correlates with the severity of liver inflammation, hepatocyte ballooning, or fibrosis nor predicts subsequent liver-related morbidity or mortality.[2,4] On the other hand, strong associations between histologic features of hepatocyte damage and inflammation and fibrosis severity have been demonstrated by cross sectional analyses of NAFLD cohorts.[6,7] These findings are not surprising because inflammation and fibrosis are dynamic components of the wound healing response that is triggered by tissue injury. Repetitive bouts of injury or defective repair perpetuates attempts at tissue regeneration, leading to progressive accumulation of fibrous scar.

In our recent study, we investigated the association between histologic severity of hepatocyte injury and inflammation and sex, menopause status, and synthetic hormone use in patients with NAFLD. We used the grades of the individual histologic features of nonalcoholic steatohepatitis, as opposed to the composite NAS score. The results showed that premenopausal status or use of synthetic hormones for women is associated with increased histologic severity of hepatocyte injury and inflammation among patients with NAFLD at a given level of metabolic stress. Interestingly, we found that premenopausal women have lower hepatic fibrosis stage as compared with postmenopausal women and men, despite having enhanced hepatocyte injury and inflammation. This finding suggests that female hormones "uncouple" the severity of liver injury and inflammation from the intensity of the associated fibrotic response, justifying further research to clarify mechanisms that might be involved.

Consistent with previous studies,[8–10] our findings suggest that female hormones mitigate fibrosis progression. This antifibrotic activity cannot be easily explained by reduction of liver injury or inflammation, important profibrogenic forces. Further research is needed to evaluate the role of female hormones on stellate cells and their regulators and immune responses. Also, the multifaceted aspects of liver repair, along with gender differences in NAFLD pathobiology, should be considered in analyzing a longitudinal cohort data or trial designs.

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Conflicts of interest
The authors disclose no conflicts. Q3

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