Age and sex are among the most frequently studied preinjury health and demographic factors thought to be related to outcome after mild traumatic brain injury (mTBI). Indeed, the current body of literature supports the observation that women have more postconcussive symptoms and take longer to recover than men. Moreover, a reasonable amount of evidence substantiates the notion that women of reproductive age have worse outcomes after mTBI compared with premenarchal or postmenopausal women. An emerging hypothesis is that hormonal fluctuations during the reproductive years underlie this age and sex interaction, leading to a burgeoning line of investigation into whether the observed age-sex interaction could provide clues not only to the pathophysiology of mTBI but also to putative therapeutics to hasten recovery. However, the literature to date has been hampered by the lack of appropriate control groups in these studies, leaving considerable room for speculation that age and sex differences in these prior studies reflected a nonspecific response to injury in general, and not mTBI specifically, reducing enthusiasm for this line of research investigation as a path forward.

The current study by Levin et al\(^6\) in JAMA Network Open has gone a long way to put that speculation to rest. Among 2000 adult emergency department patients with mTBI accrued from 16 level 1 trauma centers in the US and followed prospectively for 12 months, women were found to have worse cognitive and somatic postconcussion symptoms than men, and somatic symptoms were worse in women aged 35 to 49 years compared with those between the ages of 17 and 34 years and women aged 50 years and older. The key methodologic innovation of this study was the inclusion of 299 patients with orthopedic trauma who served as a comparison control group. This large and well-chosen control group allowed the authors to demonstrate 2 important points. First, in contradistinction to the sex differences observed in the mTBI cohort, there were no sex differences in symptom-based recovery after orthopedic injury. Second, the fact that the orthopedic control group reported significantly fewer cognitive and somatic symptoms than the mTBI cohort suggests that these postconcussive symptoms, traditionally thought to be a nonspecific response to injury, are in fact specific to mTBI. Taken together, these findings support the contention that the observed age-sex interaction in symptom-based recovery is likely rooted in mTBI pathophysiology.

However, when it comes to shedding light on the mechanisms underlying the age-sex interaction, this study raises more questions than it answers. Levin et al\(^6\) showed that women in the group aged 35 to 49 years had worse cognitive, somatic, and emotional symptoms than women aged 17 to 34 years as well as those 50 years and older. Although the differences in emotional and cognitive symptom domains were not statistically significant, the trajectories of the 3 symptom domains were strikingly similar, as shown in Figure 2 of the study. Why would only the subset of reproductive-aged women aged 35 to 49 years experience worse post-mTBI symptoms? Why were their outcomes dissimilar from those in the 17- to 34-year reproductive age group, who were also presumably premenopausal? Why do women aged 17 to 34 years have nearly identical recovery trajectories as those aged 50 years and older? What is happening across the female reproductive age span to explain such unique findings?

These age- and sex-specific findings are novel and beg for a better understanding of the role played by female sex hormones in mTBI pathophysiology. As the authors acknowledge, age is not a surrogate for reproductive status, and assessing women’s reproductive status at the time of injury...
could have greatly strengthened the study, while providing answers to some of the questions raised by the results. The authors did not account for use of hormonal contraception and hormone replacement therapy, menstrual phase at the time of injury, and menopause status in the study population. These are important covariates to consider in sex differences research. Was there a lower prevalence of hormonal contraception use in the 35- to 49-year age group leaving them more susceptible to adverse mTBI outcome than their peers? What was the prevalence of hormone replacement therapy use in the group aged 50 years and older? Was this protective? Moreover, if luteal phase at the time of injury is associated with worse outcome as has been suggested by others, were women in the 35- to 49-year age group more likely to be in this phase of the menstrual cycle than those in the aged 17 to 34 years? These and many other questions could have been answered if hormonal biomarkers or assessments of reproductive status had been included in the analyses. Attributing these unique findings to work and family stress, as the authors do, is somewhat speculative, as women across the entire reproductive age span have various levels of work and family stress. These stressors are not unique to those between the ages of 35 and 49 years. The authors failed to account for the complex interactions between sex hormones and neuroendocrine stress mechanisms that may mediate the influence of stress on outcomes after mTBI but not orthopedic injuries.

Perhaps the most important message to emerge from this study is that efforts to examine the age-sex interaction in mTBI outcomes with objective biomarkers of women’s reproductive or hormonal function are not only needed but are now clearly justified. These efforts will require robustly designed cohort studies that consider the additions that Levine et al6 have made to the literature as well as several of the points raised in this commentary. These biomarkers will not only help us to identify those at greatest risk for poor mTBI outcomes but may provide a window into potential targeted therapies for improving post-mTBI outcomes in women.

ARTICLE INFORMATION
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