Editorial

The Need for SPACE to Plan the Future for Spondyloarthritis

Mark Hwang¹ and Michael H. Weisman²

“Lifestyle Factors and Disease Activity Over Time in Early Axial Spondyloarthritis: The SPondyloArthritis Caught Early (SPACE) Cohort” by Exarchou et al aimed at looking at the importance of baseline lifestyle factors of BMI, smoking, and alcohol consumption (AC) on disease activity in recent-onset axial spondyloarthritis (axSpA).¹ Does this study add to our knowledge of the natural history of axSpA? Does it help us design a potential intervention strategy that, in addition to pharmacologic management, could make a difference? We think it does, and here we explain our reasoning.

First, was this cohort really axSpA as we know it in the clinic? The answer is a resounding yes. The patients in the SPACE cohort had chronic lower back pain of ≥ 3 months to ≤ 2 years in duration and were < 45 years of age.² They had a probably of a definitive diagnosis of axSpA (≥ 6 on a 0–10 scale of confidence) by expert opinion at baseline in this multicenter, multinational study. Disease activity, defined by the Ankylosing Spondylitis Disease Activity Score–C-reactive protein (ASDAS-CRP), was calculated over a 1-year period with observation timepoints of baseline, 3 months, and 12 months as their primary outcome. The individual ASDAS components studies in secondary analyses were assessed in similar fashion.³ Three hundred forty-four patients were included in the study.

The SPACE cohort was recently critically examined for its “fit” as more nearly matching a diagnostic cohort rather than a research collection, based on inappropriate circular reasoning from expert opinion. In utilizing a technique that circumvents expert opinion (latent class analysis), this SPACE cohort clearly represents a real-world collection of patients with axial and peripheral SpA, seen early, with an equal distribution of male

vs female sex.⁴ Moreover, and to support the relevance of this cohort to what we are seeing in the clinic today, the equal sex representation of “early” cases of SpA in SPACE corresponds to our recently published data on the similarity for both sexes in AS incidence in a US military healthcare setting.⁵

This cohort study was well designed.¹ To account for their longitudinal dataset/outcome, the authors chose random coefficient analysis. The strengths of this type of longitudinal modeling over other analytic techniques allowed them to account for patient-level effects and how these might vary in their relationship to the risk factors chosen. The authors specifically stratified a priori on sex. The previously published differences in disease manifestations between the sexes do justify these analyses.^{6,7,8,9,10}

The results showed sex-specific associations for women and not men, although these associations were modest. Women were found to have statistically significant associations in the multivariable modeling: higher ASDAS was associated with obesity and previous history of smoking, whereas lower ASDAS was associated only in the women with the highest AC. In their secondary analyses, however, obesity in women was not associated with any of the patient-reported components of ASDAS when they were broken down, except for CRP. The general population literature does show that increased adipose tissue is associated with increased proinflammatory cytokines such as CRP,^{11,12} and this association of elevated CRP is perhaps stronger in women compared to men.¹³

Although, as the authors pointed out in their discussion, alcohol and smoking have long been associated with divergent directions for health outcomes in the general population, the sex-specific findings noted in this cohort remain unexplained. It is unlikely that study design (mostly power, or baseline imbalance) issues provide the entire reason. In addition, this early-stage cohort should eliminate the possibility of any bidirectional effects from the chronic disease itself causing lifestyle choices to occur. Nevertheless, we do not truly know why this effect of sex on BMI, smoking, and AC does occur.

There were limitations in this study. Data were not available on known factors that are associated with disease activity—

¹M. Hwang, MD, MS, Internal Medicine, Division of Rheumatology and Clinical Immunogenetics, University of Texas John P. and Katherine G. McGovern Medical School, Houston, Texas; ²M.H. Weisman, MD, Stanford University School of Medicine, Stanford, California, USA.

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Address correspondence to Dr. M.H. Weisman, Cedars-Sinai Medical Center, 8700 Beverly Bl, #B-131, Los Angeles, CA 90048, USA.
Email: Michael.Weisman@csbs.org.

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including exercise—that may be independently associated with these risk factors and/or obfuscate the true effects of baseline lifestyle factors. Sixty-nine (20.1%) of the patients had a confidence level of 10 (out of 10) of having axSpA, creating some potential heterogeneity in the patient population of SpA-related symptoms vs other chronic lower back pain. Last, given the time of follow-up, it is unclear if these lifestyle factors will have an effect over longer-term disease activity.

We do feel this well-designed study is important for patients and clinicians, given that it shows potential for nonpharmacological management in addressing SpA disease activity. Patients, especially recently diagnosed patients, can feel helpless given their symptoms. Tangible, self-directed lifestyle targets can empower patients and hopefully help improve their disease activity long term. How should this come about? We need more information to embark on such a lifestyle intervention. The study by Exarchou et al¹ is important because it provides justification to encourage investigators to seek funding for obtaining information to develop or validate objective biomarkers or subjective outcome measures. These future observation studies would identify the stages of disease during which patients are most likely to respond to an intervention. That is the take-home message of this study.¹

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