



Editor's Spotlight/Take 5

Editor's Spotlight/Take 5: Sex-specific Analysis of Data in High-impact Orthopaedic Journals: How Are We Doing?

Seth S. Leopold MD

Medical conditions affect men and women differently, a fact one can easily miss when reading scientific journals. Most federally funded randomized trials do not report outcomes separately for men and women [2], and the research supporting many treatments

administered more commonly to women—such as the prescription of COX-II antiinflammatories [7]—has been performed disproportionately on men [1].

A recent report from Brigham and Women's Hospital found severe gender disparities in the diagnosis and treatment of conditions that cause disproportionate harm to women, including lung cancer, Alzheimer's disease, and depression [3]—all of which have important orthopaedic implications (bone metastases, falls causing injury, and poorer outcomes scores after surgery, respectively).

For these reasons, *Clinical Orthopaedics and Related Research*® has taken a number of steps to level the field where we can. For example, we instituted reporting standards for sex and gender [6], and we have highlighted those studies in our Journal that we believe can help identify and minimize gender-driven disparities in care [4, 5]. In August of this year, we

published an important symposium on sex differences in musculoskeletal disease and science. We are especially proud of our affiliation with the Ruth Jackson Orthopaedic Society, an organization that supports women orthopaedic professionals through education, mentoring, research and outreach, and that promotes issues related to sex and gender differences in musculoskeletal health.

However, there is only so much a journal can do; ultimately, it is up to scientists to design clinical trials that appropriately enroll women and report results separately by sex and gender. So how are scientists doing with respect to these key obligations? According to a multiinstitutional collaborative lead by Dr. Jo A. Hannafin from the Hospital for Special Surgery, published in a cannot-miss article in this month's *CORR*®, the answer is that musculoskeletal investigators were doing somewhat better in 2010 than they were doing in 2000. But even in 2010 (the latest year Dr. Hannafin's team surveyed), seven in 10 articles from five leading orthopaedic surgery journals did not provide sex- or gender-specific analyses. And rather

Note from the Editor-In-Chief: In "Editor's Spotlight," one of our editors provides brief commentary on a paper we believe is especially important and worthy of general interest. Following the explanation of our choice, we present "Take Five," in which the editor goes behind the discovery with a one-on-one interview with an author of the article featured in "Editor's Spotlight."

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disconcertingly, the uptick in the proportion of studies reporting results by gender actually occurred between 2000 and 2005; the proportion of studies stratifying by sex or gender did not increase between 2005 and 2010.

This is a challenging topic: On one hand, it is essential that biomedical research enroll and evaluate women to whatever degree the conditions being studied affect them; on the other, it is not possible to tell from papers like Dr. Hannafin's what proportion of studies in fact should stratify or analyze by gender. Some conditions affect only men, and some affect men and women in vastly different proportions. Undoubtedly, the solution to this problem should come from many sources: Funding agencies and institutional review boards need to ensure that new research enrolls women in sufficient numbers, investigators must analyze thoughtfully by sex and gender, and journals ought to articulate and apply appropriate standards to the work they publish. But how best to do all of this? Please join me for a deeper dive into this critically important topic with Dr. Hannafin in the Take 5 interview that follows.

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I would like to thank Clare M. Rimnac PhD for her thoughtful suggestions on this Spotlight feature.

Take Five Interview with Jo A Hannafin MD, PhD, senior author of "Sex-specific Analysis of Data in High-impact Orthopaedic Journals: How Are We Doing?"

Seth S. Leopold MD: *Congratulations on this fascinating work. As with so many areas of research, quantifying a finding is only the first step; interpreting it comes next, and this is not always so easy. You found that 70% of studies did not provide subanalyses by gender or sex. I suspect readers are wondering what the "right" proportion should have been. What do you think, and on what do you base your estimation?*

Jo A. Hannafin MD, PhD: First, we would like to thank *CORR*® for recognizing the importance of this topic and publishing this manuscript. As we were working on the study, it was suggested that we "had an agenda" as a group of female orthopaedic surgeons reporting on this issue. We do have an agenda, which is providing the best care for our patients of both sexes. Both men and women may respond differently to pharmacologic or surgical treatments, and it is important to understand this. We feel strongly that all studies should report results based on sex or gender (whichever applies), and should present sex- or gender-specific data in addition to aggregate data. During the

process of reviewing the published manuscripts in preparation of this paper, it was clear that authors were careful to report the numbers of men and women in the study, but only a limited number of studies reported sex or gender as an independent variable. Since stratification by sex or gender creates smaller groups of patients, it clearly can limit the ability for a group to reach a statistical threshold, thus many authors choose to report aggregate data. Nevertheless, it remains important to report the sex- or gender-specific data in addition to the aggregate data. This may prompt the reader to question the potential role of sex in outcome. If we only choose to stratify when we think the results may be meaningful we may never uncover important differences.

Dr. Leopold: *To what degree is this a problem at the investigator or institutional review board level (not enrolling enough patients of both genders when doing so was possible, and so not having the necessary data to analyze), and to what degree is this an editorial problem (where journals should have asked for stratification or analysis of data that the authors collected but neglected to present)?*

Dr. Hannafin: The problem exists at multiple levels. To my knowledge, most institutional review boards do not mandate the inclusion of men and

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Jo A. Hannafin MD, PhD

women in all studies. Many investigators do not recognize the need to analyze sex as an independent variable or may be reluctant to report such data if there is not enough power for such an analysis. Journal editors and reviewers do not mandate that this topic be addressed. The field of cardiology provides an excellent example for us. The current analyses and study of sex-specific presentation and response to treatment in cardiac disease has changed the clinical care of men and women in our country. We can do the same for

common orthopaedic conditions that impact both sexes including trauma, arthritis, joint reconstruction and back pain to name a few.

Dr. Leopold: *What topics in orthopaedic surgery do you think are most likely to benefit from added attention to gender differences? In particular, if you could, what topics would you advocate to the NIH or other funding bodies as being of the highest priority?*

Dr. Hannafin: Almost all areas of orthopaedic research can benefit from

increased attention to sex- or gender-specific reporting and analysis, including epidemiology of injury or disease, response to pharmacologic treatment, role of physical therapy in recovery and sex differences in patient-reported outcomes. Areas that might particularly benefit from this kind of attention include the immune response to material debris, osteolysis and implant loosening in arthroplasty; the study of mechanisms of development of arthritis on a cellular, translational clinical level; outcomes of ACL reconstruction and analysis of whether a patient's sex may increase an athlete's risk of the development of posttraumatic arthritis; and the efficacy of sports-injury-prevention programs.

But it is not just women who are at risk from research that fails to analyze by sex or gender. There has been an enormous amount of research focused on prevention of ACL injuries in girls and women; it seems to us that boys and men may deserve more attention in studies about these programs. An additional male-specific issue to be addressed relates to increased mortality in men following hip fracture. The focus should be on common conditions that affect both sexes and have the capacity to affect long-term quality of life.

Dr. Leopold: *Your paper's conclusion ("... studies should be designed with*

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sufficient sample size to allow for subgroup analysis by sex to be performed, and they should include sex-specific differences among the a priori research questions”) is, in a sense, not tremendously different from the NIH’s 20-year-old policy on the matter, nor from the 2001 Institute of Medicine (IOM) recommendation. Despite those longstanding regulations, your paper suggests that investigators and journals fall short more often than we would like. What is needed, in addition to (or in place of) the NIH and IOM policies, to bring about sustained and more broadly embraced change?

Dr. Hannafin: Funding through the NIH requires that both sexes be included in any proposed study unless there is clear justification for the study of only one. Basic science and translational studies should be designed and powered to analyze the potential role of sex of the animal or cells utilized as required by the NIH. Continued exposure of the role of sex in orthopaedic conditions through vehicles such as the “Sex Matters” column in *AAOS Now* should be encouraged and supported. Journal editors and reviewers have the potential to play an enormous role in this effort. All papers that are published should include data stratified by sex unless there is a preponderance of patients of a single sex who have undergone a specific treatment. For prospective studies on the

treatment of common diseases such as arthritis, ACL reconstruction, orthopaedic trauma, and joint replacement, analysis by sex should not be difficult. For Level 2, 3, and 4 studies, the data available may not permit statistical analysis based on sex or gender, but the data should be reported based on sex or gender in addition to the aggregate. This will strengthen the power of future systematic reviews.

Dr. Leopold: *Might there be some tradeoffs here? For example, if funding agencies increase the funding to each study so that each can recruit enough patients to stratify properly by gender, might this reduce the overall number of projects—and so the number of avenues of inquiry—that can be explored in each funding cycle? How do you see this, and are there other tradeoffs we should be concerned about?*

Dr. Hannafin: There may be tradeoffs, but the NIH has clearly defined the importance of analysis of sex. Funding of prospective registries or clinical outcomes studies by the NIH will be restricted if the role of sex is not addressed. There will be areas of research where the epidemiology is well known and it will be justifiable to study one sex, or if a condition is so rare that collecting more patients would not be possible. But the bottom line is if we do not ask these questions we will never

obtain the answers. It is also important to recognize that this initiative is to encourage and support the study of both men and women in order to improve clinical care and surgical results for men and women alike.

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