The Impacts of Sex on Osteoarthritis: Role for Regenerative Medicine?

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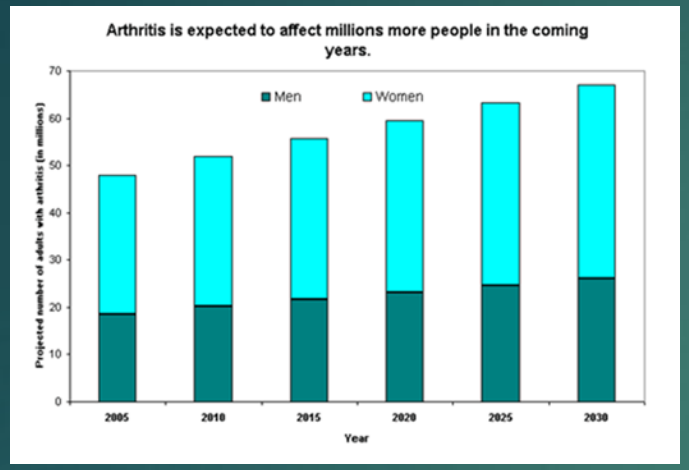
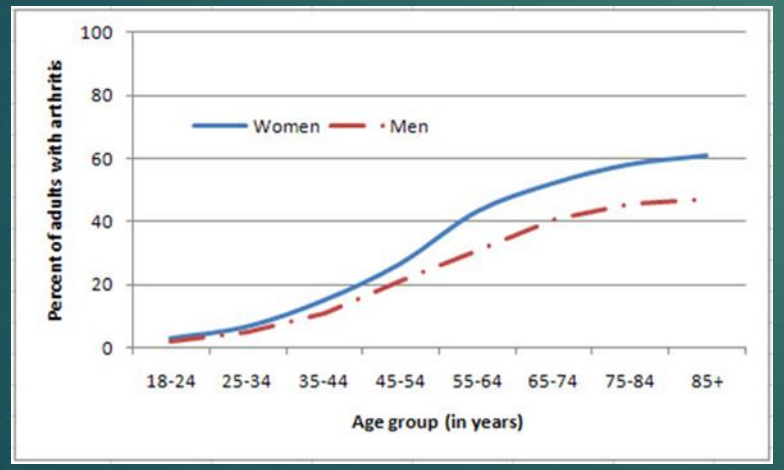
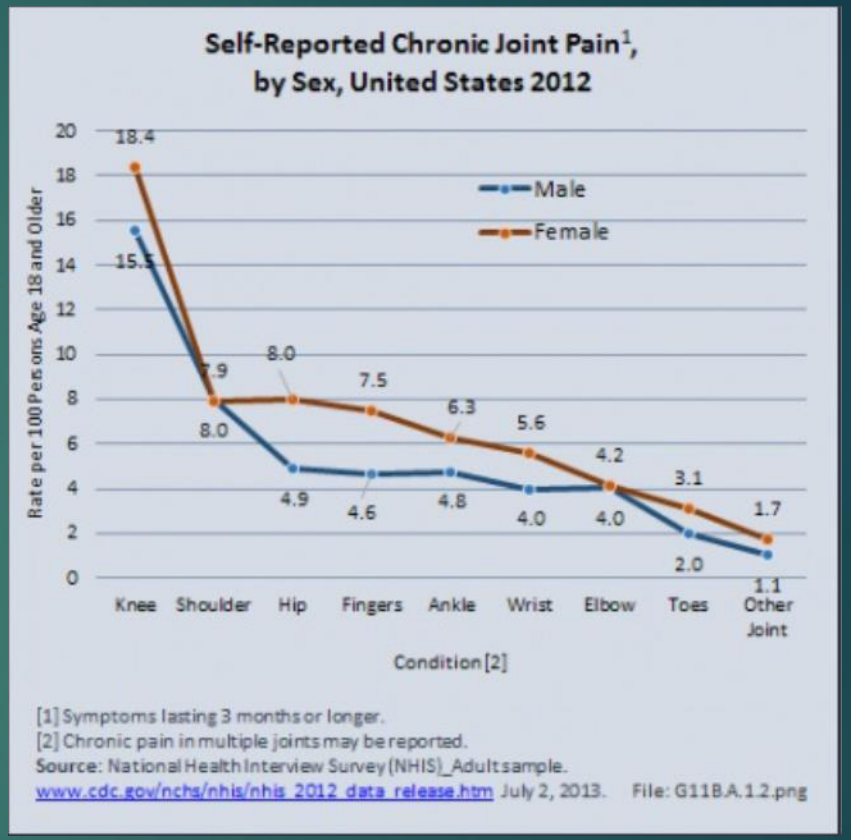
OCTOBER 1, 2024

Osteoarthritis Prevalence





CDC data



Burden of Musculoskeletal Conditions in the US, 2015

Sex-Specific Knee OA Risk Factors

- Acquired
  - injury
  - patterns of overuse?
- Inherent
  - anatomy
  - gait pattern
  - impact of estrogen
  - muscle strength
- Inflammatory response (to injuries, obesity, OA)

Joint Injuries

- Higher risk in women (especially ACL)
- Significantly higher risk of OA in younger people after knee injury-even with reconstruction
- Earlier among women than men with ACL injuries (even with reconstruction)

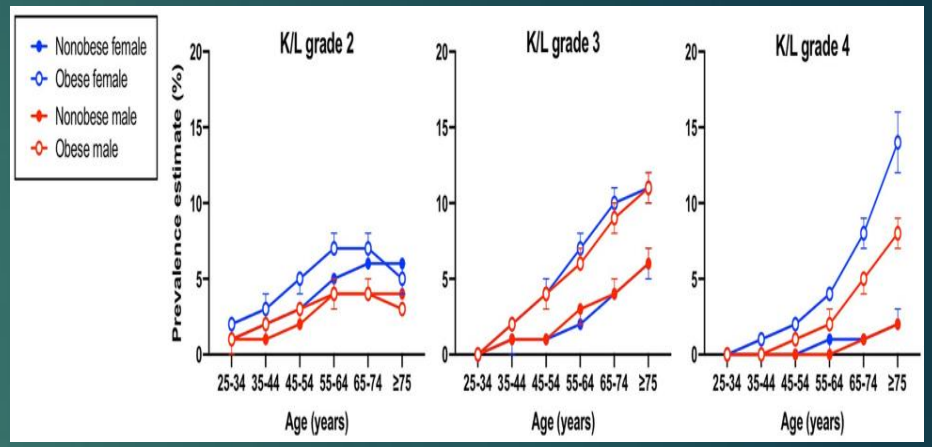
Roos *Current Opinion in Rheumatology* 2005

Related to articular cartilage damage at the time of injury?

Sex-based differences in immune response at time of injury?

Impact of/Response to Obesity

- Women more likely to demonstrate association between metabolic syndrome and symptomatic OA
- Effect of obesity was greater in women than men for more severe knee OA (K/L grade 2 and 4)
- More than only increased cartilage loads (increased risk of hand OA)
- Link between obesity and OA may be mediated by leptin/ chronic low-grade inflammation, especially for women

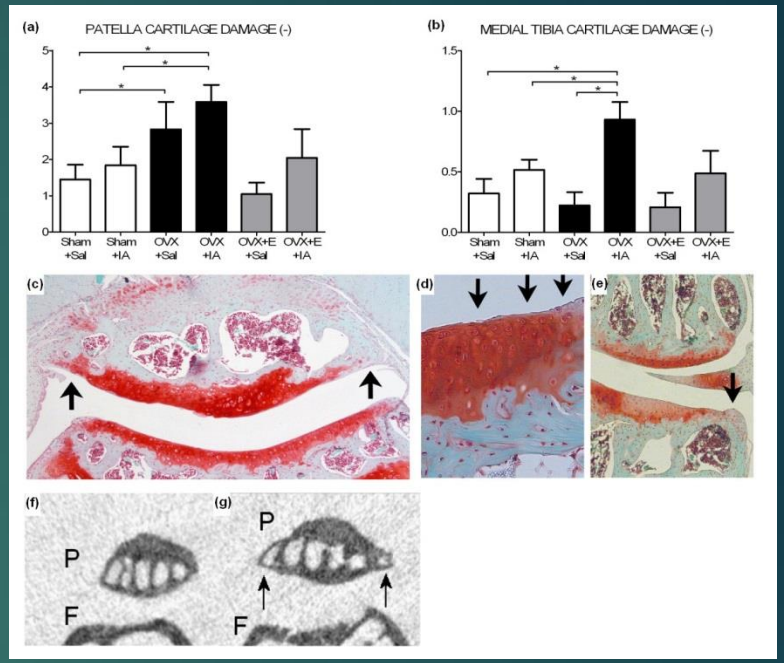


Batushansky et al *Arthritis and Cartilage* 2021

- Other differences in inflammatory responses?
- Role of estrogen in inflammatory response?

Effects of Estrogen

- Mice with model of induced OA
- Ovariectomy increased degree of cartilage injury
- Due to loss of bone or direct effect on cartilage?
- Does this translate to joint issues for women after menopause?

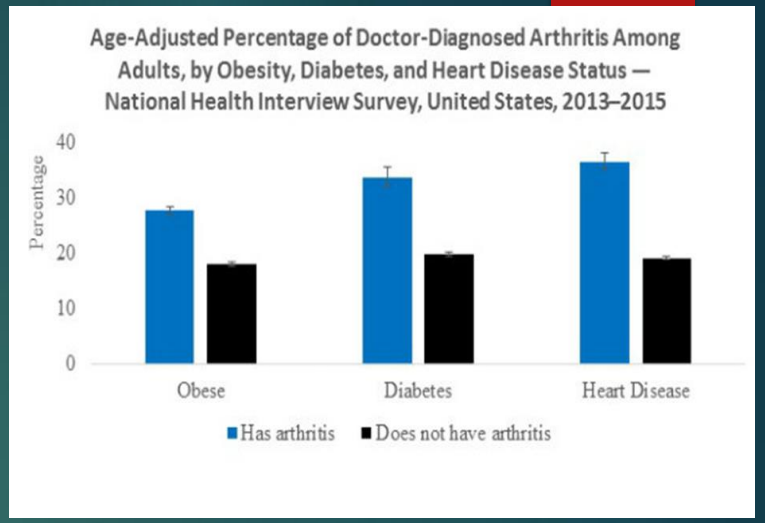


Sniekers et al *Arthritis Res Ther* 2010

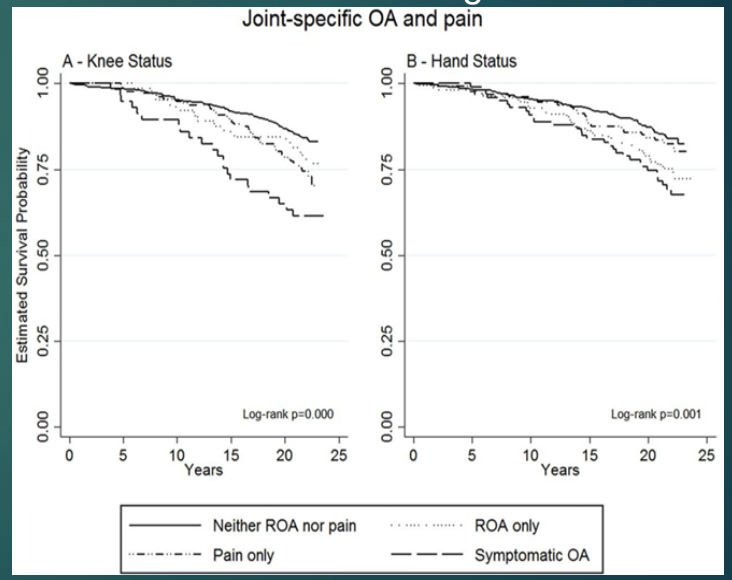
OA and Co-morbidities

- HTN, depression, COPD most common co-morbidities for women and men with OA
- Prevalence of each additional condition more common among women
- Women had higher number of co-morbidities

Marshall et al *BMJ Open* 2019



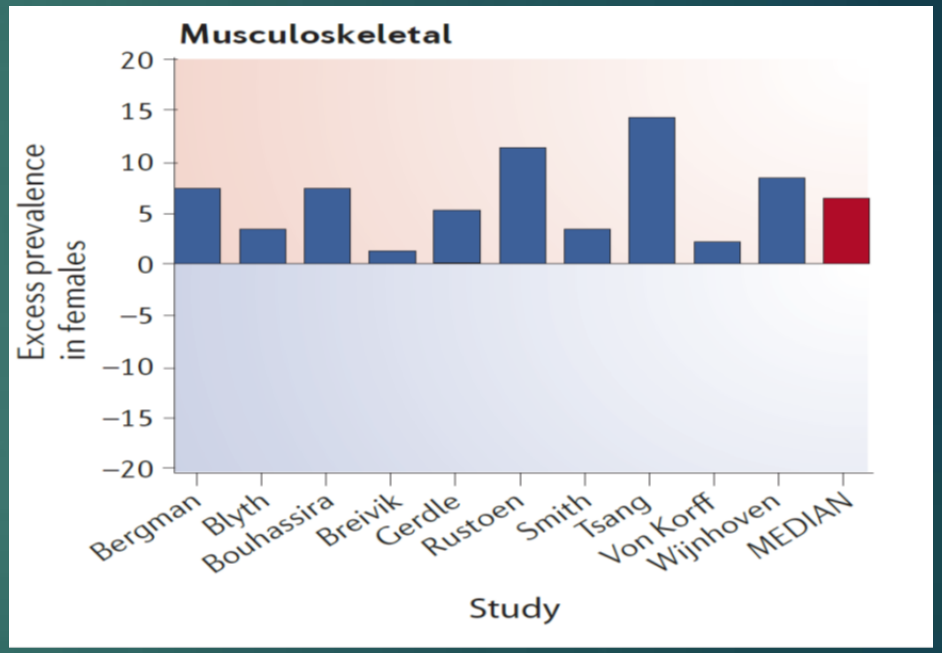
www.CDC.gov



Kluzek et al *Ann Rheum Dis* 2015

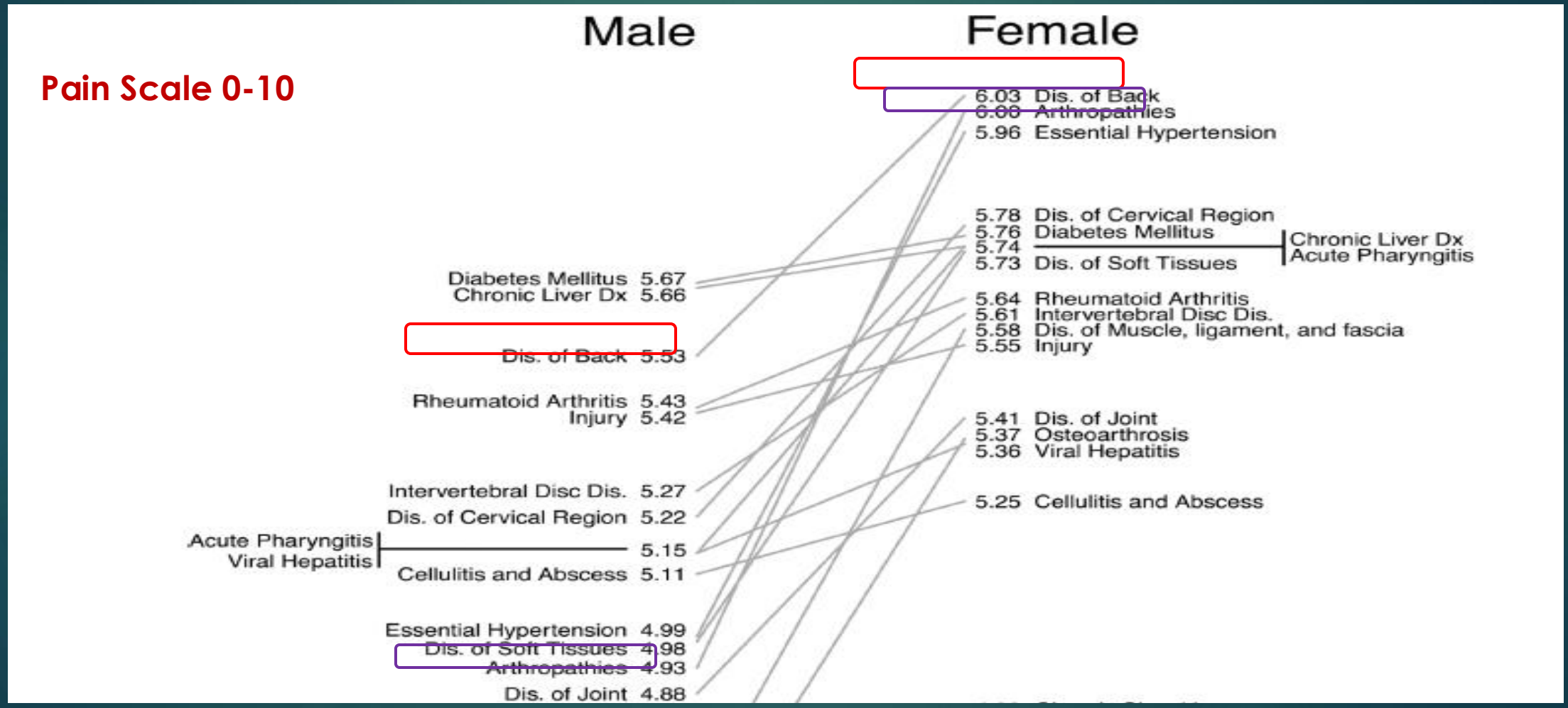
Chronic pain

- More common among women than men
- Most common reason that patients with OA present for care
- Significant impact on function, quality of life, independence



Mogil, JS *Nature Reviews Neuroscience*, 2012

Differences in pain scores between men and women for similar conditions



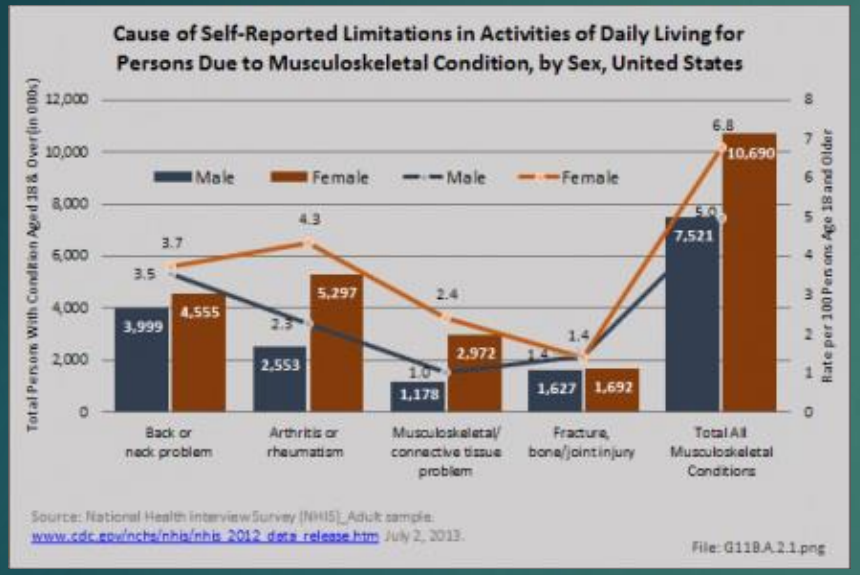
Ruau D et al *J Pain*, 2012

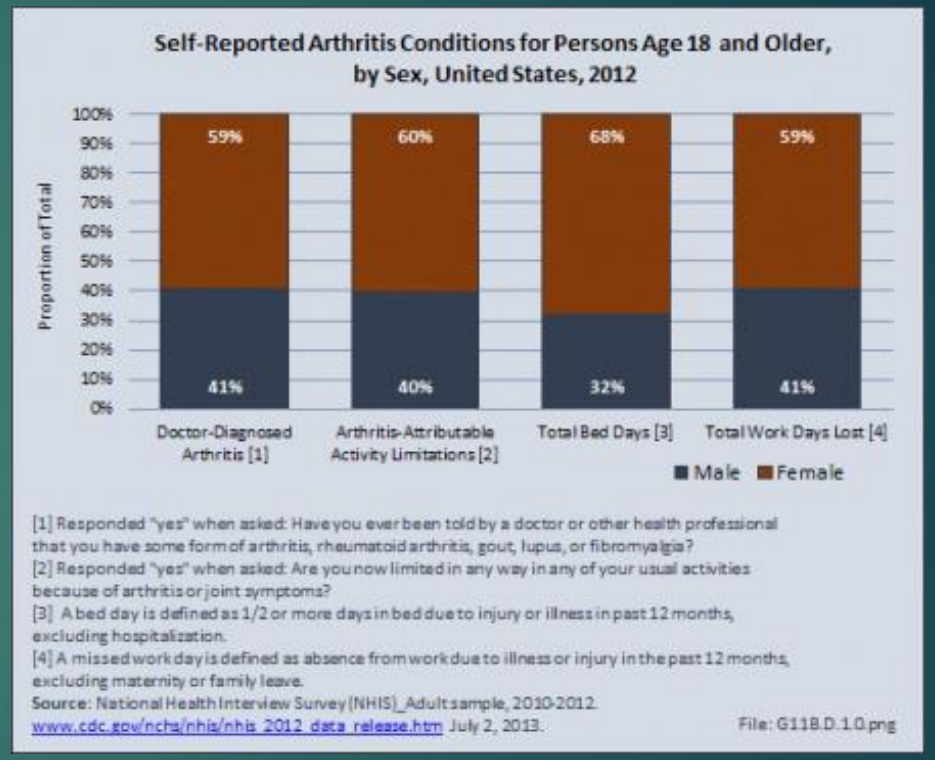
Perception of Pain

- Likely different between the sexes
- Anatomic differences (in rat models) in organization of brain circuits that process pain signals
- fMRI and PET imaging of brains different between men and women with chronic pain
- Are these differences primary, leading to increased risk of developing chronic pain or are they changes that occur as a result of chronic pain?
- Gender-based differences in expression of pain?

Nasser et al *Life Sciences*, 2019

Why this matters: Quality of Life/Disability





Burden of Musculoskeletal Conditions in the US 2015

How are sex or gender differences in pain manifested?

Women more likely (than men) to be treated in the 12 months prior to joint replacement surgery with

- opioids
- non-opioids
- injections (steroids, viscosupplementation)
- physical therapy

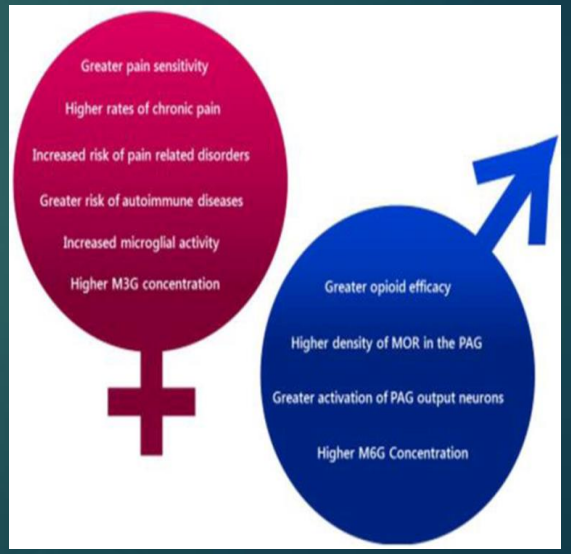
Bawa et al *J of Arthroplasty,* 2016

Sex-Based Differences in Opioid Response?

- Opioids act through mu and kappa receptors (almost all opioids in current rely on mu receptor)
- Estrogen increases or decreases density of mu receptors (hormonal status? Pain status?)
- Kappa may be more significant for women
- Differences in response to opioids not clear
- Studies (including in animals) indicate that morphine produces more and longer lasting analgesia in males (women consume ~30% more morphine than men to attain the same extent of analgesia- Nasser et al *Life Sciences*, 2019)
- Onset of pain relief may be faster in males

BUT

- Females may be more sensitive to respiratory depression



Fullerton et al *Curr Opin Behav Sci*, 2018

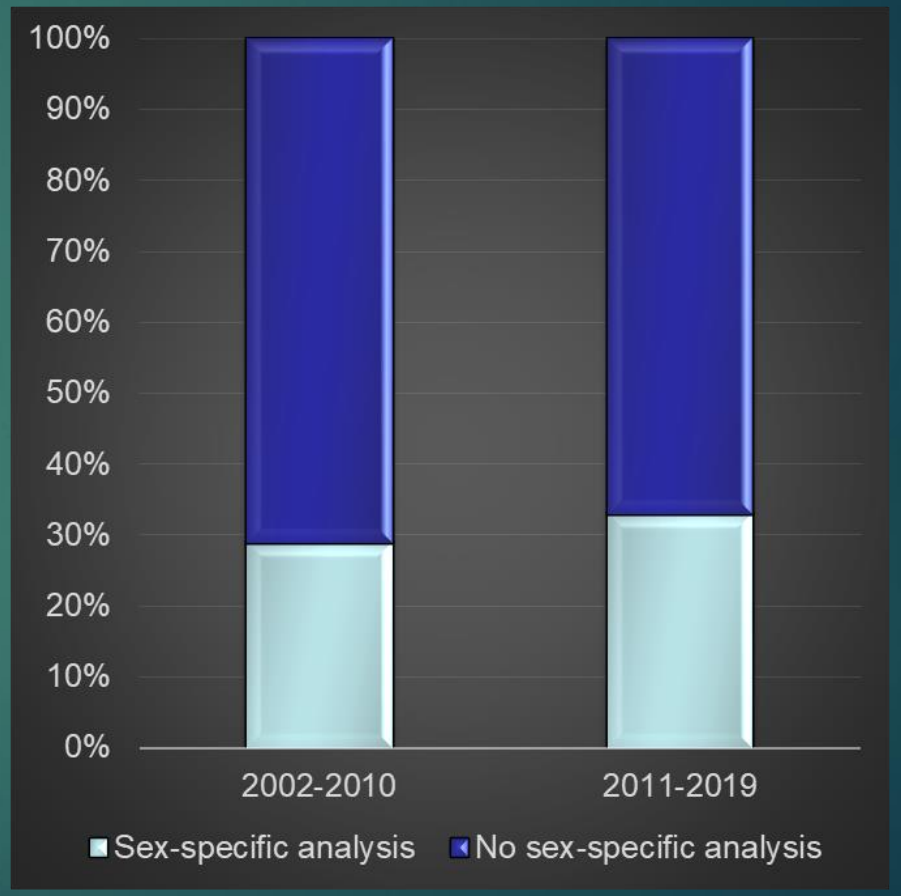
Complexities of OA Pain: Surgery Isn't Always the Answer

- 323 women and 171 men assessed after total knee arthroplasty
- *Women* had worse outcomes for pain and function at 6 and 12 months after surgery
- Women were significantly *worse on pre-surgery, pain, function, depression, obesity, symptomatic joint count*
- Effect of sex was lessened if pre-op pain/function was considered
- Pre-surgery pain, low back pain, and worse depression scores significantly associated with worse *pain* scores at 6 months for women and men (but all greater among women)
- Worse pre-surgery function, low back pain, worse depression scores, and presence of *comorbidities* were significantly associated with worse *functional* outcome at 6 months and 12 months (all more common among women)

Mehta et al, *Osteoarthritis and Cartilage* 2015

Part of the issue: Are Results Reported Based on Sex?

- Evaluation of musculoskeletal literature (2 general, 2 specialty journals) for rotator cuff injuries and OA of the knee
- 31% reported sex-specific analysis
- 30-40% reported based on sex for knee OA studies
- No change over time
- Similar to findings in other fields
- Increased odds if woman first and/or last author



Stumpff et al *JWH* 2020

Moving forward....

Editorial

Improving How Orthopaedic Journals Report Research Outcomes Based on Sex and Gender*

Sex-based differences in cell biology, tissue function, and anatomy impact disease risk, presentation, and treatment outcomes[1], including in musculoskeletal care[2-4]. As such, these differences should influence how orthopaedic surgeons and other healthcare professionals conduct research and provide care for patients who have musculoskeletal disease and injury. In addition, gender roles influence interactions with people who conduct research and with healthcare professionals as well as the likelihood that patients will seek care and how they will respond to treatment[1,5,6].

Musculoskeletal research, similar to research in other areas of healthcare, does not always disaggregate results based on a patient's sex or gender[7]. Although some orthopaedic surgery journals have explicit editorial standards on the topic of sex and gender in scientific reporting, and although international entities have published sensible guidelines about it[8], we have observed that these standards are inconsistently applied[7].

Inattention to high-quality standards of scientific reporting can harm patients[9,10]. Women have been underrepresented in medical research[11], and this trend continues to varying degrees even today, despite mandates to remedy this disparity, at least in federally funded research[12,13]. However, these mandates include no guidance about how data should be analyzed or reported, thereby limiting the impact of including more women in clinical studies. The care of women has been substantially compromised as a result[14-18]; not getting this right has sometimes harmed men with certain diagnoses as well[19]. As such, it is no stretch to say that doing better research—and improving how that research is reported in journals—would benefit our patients regardless of their sex or gender.

With this background in mind, leaders of the editorial boards of 6 orthopaedic journals, along with leaders of funding agencies as well as National Institutes of Health officials, met in November 2023 to discuss these issues. Following that meeting, those editors reached out to the Editors-in-Chief of all indexed orthopaedic surgery journals, seeking concurrence on a few key

Scan here to go to Proceedings from the Sex and Gender Research in Orthopaedics Symposium.

*The authors of this editorial are the Editors-in-Chief of *Clinical Orthopaedics and Related Research*, *Journal of Pediatric Orthopaedics*, *Spine*, and *The Journal of Bone and Joint Surgery*; the Assistant Editor-in-Chief of *Arthroscopy: The Journal of Arthroscopic & Related Surgery*; an Associate Editor of *JBJS Case Connector*; and the members of the Sex and Gender Research in Orthopaedic Journals Group. This editorial is being published concurrently in the first 5 journals listed above. The articles are identical except for minor stylistic and spelling differences in keeping with each journal's style. Citation of any

Summary

- Osteoarthritis is a common condition more common among women that can lead to pain, disability, and increased risk for co-morbidities
- Once injured, cartilage does not have the capacity to repair itself
- Current interventions (e.g., medications, injections, physical therapy) are intended to decrease symptoms but do not reverse (or slow) the cartilage degradation process
- Joint replacement surgery is the ultimate answer, but there are differences between women and men in final outcomes (including issues with metal hypersensitivity) and is not always feasible (e.g., age)
- New modalities are needed for 1) earlier diagnosis and 2) interventions that result in cartilage repair