2013 DECADAL STUDY

The Impact of Sex & Gender on Adaptation to Space

A Joint Study by the National Aeronautics and Space Administration and the National Space Biomedical Research Institute

Musculoskeletal Working Group Report

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Working Group Members and Affiliations

- Debra Bemben, PhD – Professor Health and Exercise Science, University of Oklahoma, Norman OK.
  - Expertise: Bone metabolism, exercise, loading and endocrine responses to exercise in humans
- Susan Bloomfield, PhD – Professor Kinesiology and Assistant Provost of Graduate Studies, Texas A&M University, College Station, TX
  - Expertise: Skeletal response to exercise, the microgravity environment, and caloric restriction in animals
- Sandra Hunter, PhD – Associate Professor Exercise Science, Marquette University, Milwaukee, WI
  - Expertise: Sex and age differences in muscle function
- Lori Ploutz-Snyder, PhD – Lead Scientist Exercise Physiology and Countermeasures, USRA, NASA Johnson Space Center, Houston, TX
  - Expertise: Skeletal muscle adaptation to disuse, integrative exercise physiology and countermeasures
- Scott M Smith, PhD – Nutritionist, Manager for Nutritional Biochemistry, NASA Johnson Space Center, Houston, TX
  - Expertise: Nutritional requirements for spaceflight, calcium, vitamin D and bone metabolism
- Kim Templeton, MD – Professor, Orthopedic Surgery, University of Kansas Medical Center, Kansas City, KS and President, US Bone and Joint Initiative
  - Expertise: Orthopedic surgery, women's musculoskeletal health, bone and joint disorders
- The working group gratefully acknowledges the assistance of Andrea Hanson, PhD, Wyle, NASA Johnson Space Center

Terrestrial Medicine-Based Consensus of the Impact of Sex on Musculoskeletal Health

- Well-established: men and women differ in many aspects of the musculoskeletal system, men generally having greater muscle and bone mass.
- Important questions for spaceflight application
  - Does the initial start point for muscle mass/function or bone density/ architecture influence the *rate of loss*?
  - What is the pattern of loss over a ~ 3 year period for men and women?
    - Linear decline over entire period?
- If there are large sex differences in the pattern or rate of loss, this would present a compelling argument for sex-specific crew selection and/or countermeasure development for very long exploration missions.
- Do the losses in bone and muscle impact other tissues such as cartilage?
- No studies have directly addressed these questions for either sex.
  - Resource demands of spaceflight and bed rest protocols, number of subjects required for proper sex comparisons are challenging.
  - Most sex comparisons quoted herein derive from very similar protocols performed separately on male and female subjects.

Terrestrial Medicine-Based Consensus of the Impact of Sex on Muscle

- Unloading induces **marked reductions in muscle strength and power** (~0.8%/d) **exceeding relative loss in muscle cross sectional area** (~0.4%/d), with considerable individual variability and muscle group dependency.

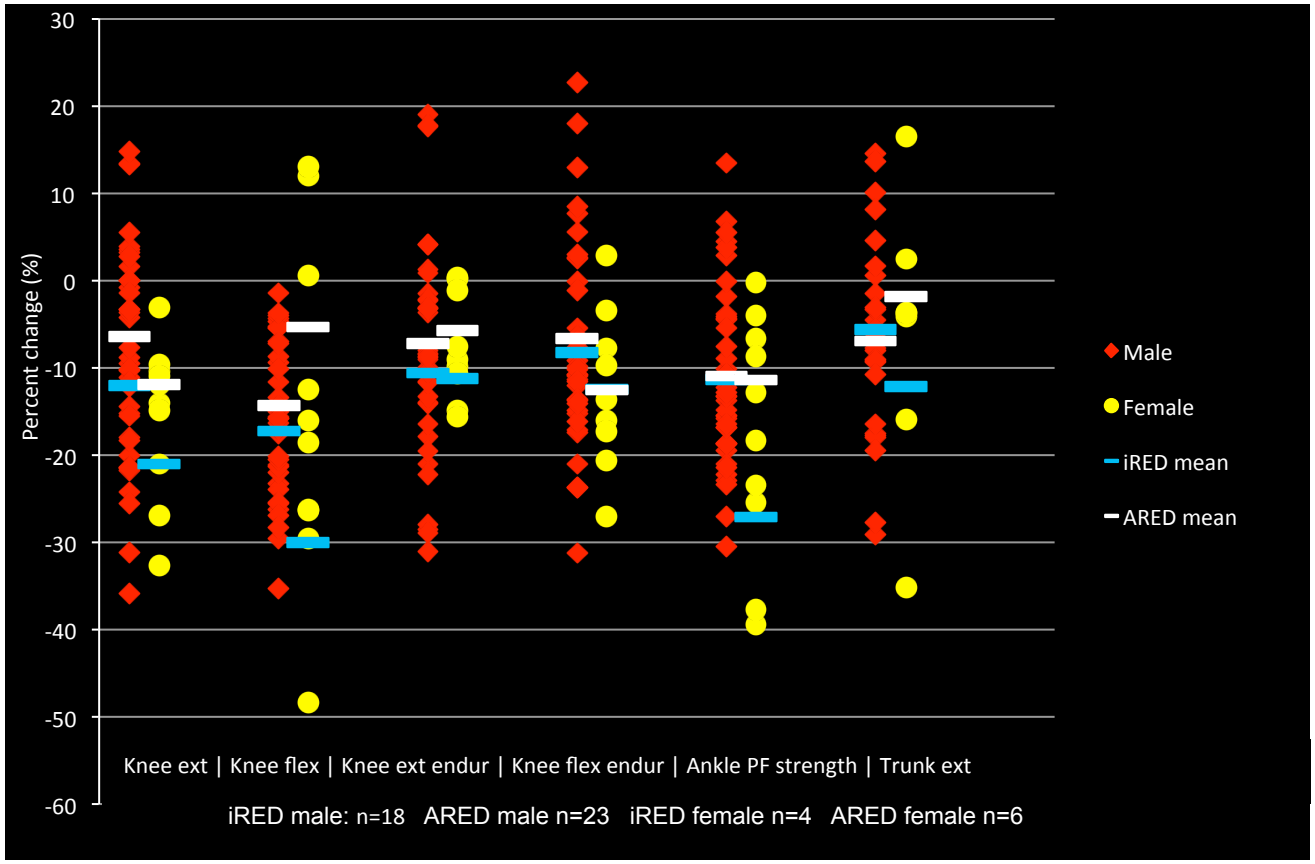
- **No studies with adequately powered sex comparisons**. Many studies include both males and females (but low n's) or similar protocols, but with only males or females.
  - Some evidence that women are less fatigable (greater endurance). Women's fatigability may increase less with unloading than men's (1 study).
  - Mean change muscle size in women may be larger (more atrophy) than men, though this difference is less than the individual variability.
  - Recovery of muscle size following unloading is slower in women (1 study).
  - No sex difference in altered sprint performance following bed rest (1 study).

- Muscle strength/body weight will influence mission task performance; **minimum strength for mission-specific tasks should be defined.**

Terrestrial and Space Medicine-Based Consensus of the Impact of Sex on Muscle

Human muscle response to 6 mo microgravity is highly variable

- ISS long duration crew using iRED or aRED still show considerable variability in muscle strength
- No clear sex differences



Unpublished data, courtesy of Johnson Space Center Exercise Physiology and Countermeasures Laboratory and LSAH

Terrestrial Medicine-Based Consensus of the Impact of Sex on Bone

- **Unloading induces rapid bone loss** (~10-fold faster than post-menopausal loss); rate of loss highly variable across individuals even within gender.

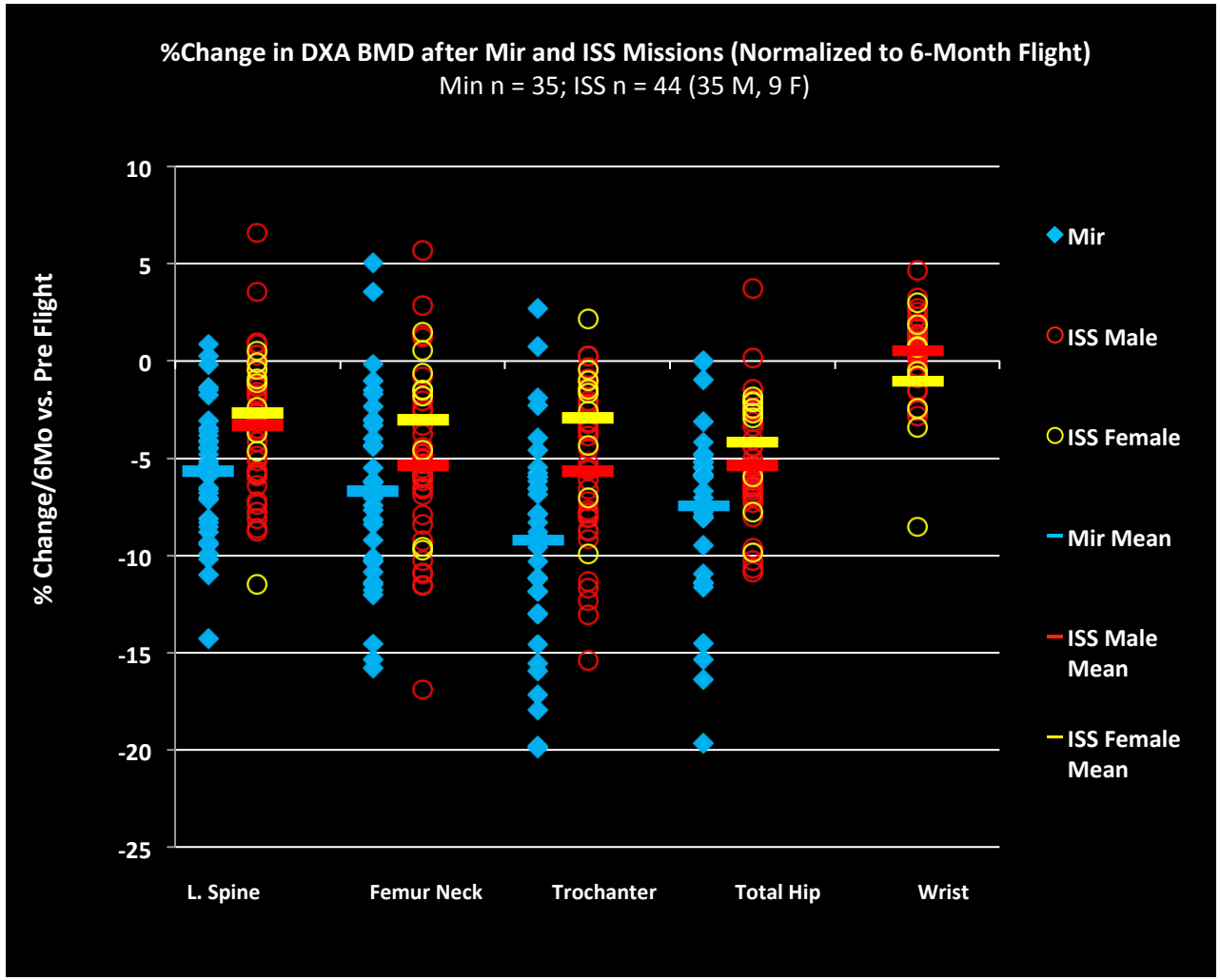
- **No human studies with adequately powered sex comparisons**. Many studies include both males and females (but low n's) or there are separate sex studies, using similar protocols. No data found on sex differences for recovery of bone mass following spaceflight or bed rest.
  - Women on 17 wks bed rest experienced smaller % loss in BMD at 7 of 10 sites than men in same study (low n's in one study) as measured by DXA
  - Newer technologies report small cancellous deficits at distal tibia (pQCT in men over 60 days, high resolution pQCT in women over 90 days), but the sex difference in magnitude of loss is within reported precision of the method.

- **Live animal studies: Some evidence for greater loss in female vs male mice,** but studies in mature rats indicate few sex differences.

Current Understanding of the Impact of Sex on Bone Health in Space

Human bone response to 6 mo microgravity is highly variable

- ISS long duration crew using resistance exercise still exhibit large variability in BMD loss
- Mir crew, using only aerobic exercise, lost considerably more BMD at 4 sites
- No clear sex differences



Unpublished data, courtesy of Johnson Space Center Bone Laboratory and LSAH

Current Understanding of the Impact of Sex on Musculoskeletal Health

- **Negative energy balance can aggravate bone and muscle loss in 0-g**
  - Sex-specific comparisons have not been made within the same study
  - The weight loss (non-obese) literature may be a useful analog
  - Studies that used both males and females have other confounding factors (age, body size, diet, exercise, rate of weight loss).
  - No major sex differences apparent, but cannot be completely ruled out.

- **Sex differences exist in joint health in 1-g; unknown in 0-g**
  - Incidence of osteoarthritis (OA) higher in women, may be exacerbated by osteoporotic changes in bone underlying cartilage and sarcopenia
  - Loss of stabilizing muscle around a joint predisposes to joint injury and development of OA
  - In 1-g, prolonged non-weight bearing can induce cartilage degeneration that may predispose to OA

Recommended Research Priorities

- **Understand the factors contributing to the large individual variability** in bone and muscle loss associated with spaceflight – bed rest analog. Sample factors to consider:
  - Sex-specific or stress hormones
  - Energy balance
  - Genetic factors specific to muscle and bone
  - Responsiveness to exercise countermeasures
  - Individualized countermeasures

- **Assess risk for articular cartilage injury** imposed by reduced/ 0-g
  - Since cartilage health is affected by the quality of underlying bone and strength of adjacent muscles, all 4 tissues –subchondral bone, muscle, tendon and cartilage—should be tracked in tandem.

- **Infrastructure:** Bed rest facility with exercise capability, 3T MRI, qCT

Summary

- **Primary areas of concern for the musculoskeletal system**
  - Time course/magnitude of muscle/bone loss with unloading
  - Influence of negative energy balance on loss of muscle and bone
  - Susceptibility to joint, especially articular cartilage injury; role of sex-specific biomechanics

- **No published human studies directly assessing sex differences.**
  - Apparent sex differences derived from separate studies' data are overwhelmed by the individual variation

- **Central question – do sex differences make a significant contribution to large (10-fold) individual variability?**
  - Useful for crew selection and/or countermeasure development for very long duration missions.
  - Earth benefits for predicting who is most at risk from hospital-based deconditioning or age-related loss of independence as a result of insufficient muscle strength/function.