University of Southampton

Bias in Bones:

Integrating sex into skeletal health and research policy to improve public health outcomes

EXECUTIVE SUMMARY

Osteoporotic fractures are a major public health concern. Fragility fractures result in serious disability, impacting quality of life, and mortality risk. Understanding fractures is important for creating successful interventions to reduce fracture risk and improve the delivery of skeletal health care. Further, as the population ages the increasing prevalence of fragility fractures is a growing economic issue.

It is well understood that women and men have anatomically and physiologically different bone structures. With age, women have a higher incidence of fragility fractures than men but men are twice as likely to die following an osteoporotic-fracture. Gender influence is also evident in other skeletal conditions including osteopenia, Paget's disease of bone, osteoarthritis and osteosarcoma. In the UK, there have been several attempts to shift from population to individual based therapeutic approaches. The aim would be to have more personalised treatments that would provide more effective treatment options for women and men.

However, the translation of personalised medicines from laboratories to the clinic is challenged at pre-clinical stage by historic sex bias, whereby laboratories favour one sex for their experiments. This bias translates to clinics where drugs studied and optimised for women with osteoporosis for example are given to men.

Relevant Sustainable Development Goals:

POLICY BRIEF AIMS

Improve understanding of **public health professionals** around the sex differences which underlie skeletal health and treatment efficacy

Prioritise the development of personalised, sex-specific medicines and **therapy for bone health**

Influence research policy to **standardise experimental design and reporting of sex** to avoid preclinical sex bias.

CONTEXT

Bone disease is a growing problem

As the UK population ages, the rising incidence of fragility fractures are a major obstacle in the quality of the lives of adults and the elderly. As a result healthcare costs are expected to exceed £6.83 billion by 2030 [1]. Further, as the age of retirement increases, fragility fractures are exerting a growing burden on our workforce and economy. Following the onset of osteoporosis, the subsequent risk of fracture bears life-changing consequences: 1 in 4 patients of working age give up work [2]; 12% of those at retirement age become institutionalised [3]. Consequently the effects of initial fracture exposes individuals to long-term effects including physical, emotional and financial strains.

Bone is different in women and men throughout life

Post puberty women and men's skeletons develop and grow to be anatomically and physiologically different. Studies carried out on women and men in military service demonstrate these health inequalities: women are more likely to suffer from fractures following military training [4]. Indeed while bone loss is typically more common in ageing women after menopause, recent studies have shown that men also account for a substantial portion of the osteoporosis burden as they are twice more likely to die following an osteoporosis-related fracture than women [5, 6]. This is of significant concern given our relatively poor understanding of the mechanisms underlying the bone loss seen in ageing men.

Development of gender based personalised therapy is constrained by pre-clinical sex bias

The approach to historical drug development assumes that all patients with a particular condition respond similarly to a given drug. Based on comprehensive diagnostic characterisation, ethnicity, age or sex can be singled out within a given condition and give us more accurate treatment. A problem in the progression of personalised medicine is that reporting of sex in pre-trials is not a requirement in the scientific literature [7]. This leads to an undetected bias when one sex is consistently selected over another. Such sex bias can translate to health inequalities. Personalised medicine is uniquely placed to address such inequality providing an individualised healthcare approach providing a more inclusive and fair therapeutic option.

KEY FINDINGS

The findings of our literature review were as follows:

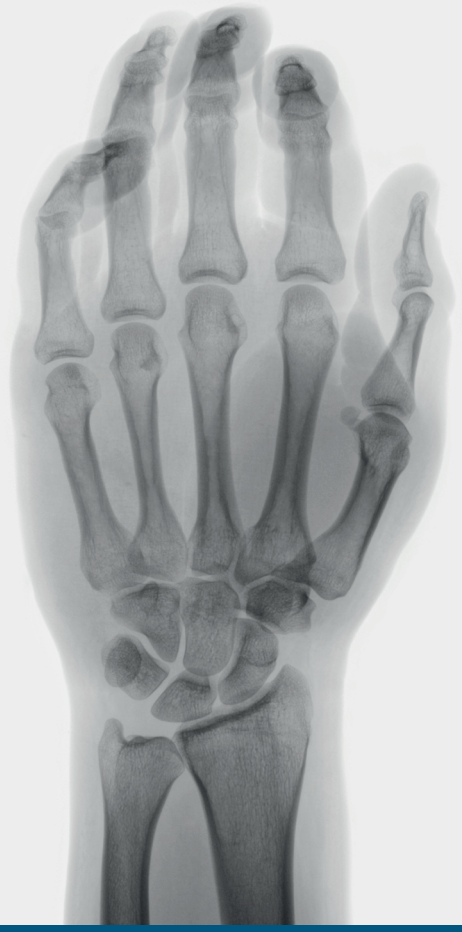
- Men and womens bones are biologically different throughout life [8]. Most skeletal diseases also impact women and men differently
- Fragility fractures are most common in women aged over 50 but also affect men, and occur as the result of age-related bone loss known as osteoporosis. **The incidence of fractures are predicted to increase by 33% in men and 23.4% in women by 2030[1].**
- An estimated 536,000 new fragility fractures are sustained in the UK each year. In 2011, fragility fractures were estimated to cost £2.3 billion in the UK, **a burden expected to increase to more than £6 billion by 2036 (9).**
- The majority of costs relate to hip fracture, which nearly always results in hospitalisation, causing around 1,100 deaths each month in the UK. **Men with hip fractures have a mortality rate two to three times higher than women (10).**
- Men receive treatments for age-related bone loss that have been developed using female preclinical models which may not be optimal for male physiology resulting in a health inequality [11-13].
- Using preclinical models, new sex-specific drug targets are being identified which could enable personalised therapies to be developed to address skeletal health inequalities evidenced with gender and intersections including age and ethnicity.

POLICY RECOMMENDATIONS

The overall aim of our project is to highlight sex bias in skeletal research, in order to eliminate gender inequality in treatment and ultimately provide more effective treatments for bone disease.

The project team's vision is

1. **Educate** public health professionals and increase awareness of growing incidence of fracture, the emerging sex differences and to address limitations in potential treatments to better maintain societal skeletal health.
   Department of Health and Social Care. Royal Society for the Prevention of Accidents. Royal College of Physicians.
2. **Improve** participation of men and women in research studies and trials to better understand sex-based differences clinically.
   Royal College of Physicians, National Osteoporosis Society, Paget's Association, Royal Society of Biology
3. **Investment** in the development of novel personalised therapies specific to sex for skeletal disease.
   Department of Health and Social Care.
4. **Address** bias which exists in preclinical and clinical skeletal study design by funding research where both sexes are investigated and appropriately reported.
   National Institute for Health and Research, UK Research and Innovation Medical Research Council.
5. **Prioritise** funding of research institutions which specialise in sex and gender and health equality.
   National Institute for Health and Research, UK Research and Innovation Medical Research Council.



Authors

Dr Claire Clarkin School of Biological Sciences, University of Southampton
Dr Valentina Cardo Winchester School of Art, University of Southampton
Dr Aikta Sharma School of Biological Sciences, University of Southampton
Professor Julie Greeves Army Health and Performance Research, Ministry of Defence

To Cite: Clarkin, C., Cardo, V., Sharma, A. (2022) Bias in Bones: Integrating sex into skeletal health and research policy to improve public health outcomes, Policy Brief, University of Southampton, DOI: 10.5258/SOTON/PP0004

References

1. International Osteoporosis Foundation. Broken Bones, Broken Lives: A roadmap to solve the fragility fracture crisis in the United Kingdom. 2018.
2. Royal Osteoporosis Society . Life with Osteoporosis: the untold story. 2021.
3. Royal College of Physicians. Falls and Fragility Fracture Audit Programme. 2021.
4. Wentz L, Liu PY, Haymes E, Ilich JZ. Females have a greater incidenceof stress fractures than males in both military and athletic popula-tions: a systemic review. Mil Med. 2011;176(4):420-430
5. Kannegaard PN, van der Mark S, Eiken P, Abrahamsen B. Excess mortality in men compared with women following a hip fracture. National analysis of comedications, comorbidity and survival. Age and ageing. 2010;39(2):203-9.
6. Frost SA, Nguyen ND, Center JR, Eisman JA, Nguyen TV. Excess mortality attributable to hip-fracture: A relative survival analysis. Bone. 2013;56(1):23-9.
7. Sharma A, Michels, L.V., Pitsillides, A.A., Greeves, J., Plotkin, L.I., Cardo, V., Sims, N.A., Clarkin, C.E. Sexing bones: Improving transparancy of sex reporting to address bias within preclinical studies. [Unpublished Research]. In press 2022.
8. Seeman E. Sexual Dimorphism in Skeletal Size, Density, and Strength Volume 86, Issue 10, 1 October 2001, The Journal of Clinical Endocrinology & Metabolism, Pages 4576–4584.
9. National Osteoporosis Guideline Group (NOGG UK clinical guideline for the prevention and treatment of osteoporosis Arch Osteoporos (2017) 12: 43 DOI 10.1007/s11657-017-0324-5
10. Alder RA (2014) Osteoporosis in men:a review. Bone Research 2, Article number: 1400.
11. Ominsky MS, Vlasseros F, Jolette J, Smith SY, Stouch B, Doellgast G, et al. Two doses of sclerostin antibody in cynomolgus monkeys increases bone formation, bone mineral density, and bone strength. J Bone Miner Res. 2010;25(5):948-59
12. Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T, et al. Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis. New England Journal of Medicine. 2017;377(15):1417-27.
13. Cosman F, Crittenden DB, Ferrari S, Khan A, Lane NE, Lippuner K, et al. FRAME Study: The Foundation Effect of Building Bone With 1 Year of Romosozumab Leads to Continued Lower Fracture Risk After Transition to Denosumab. J Bone Miner Res. 2018;33(7):1219-26