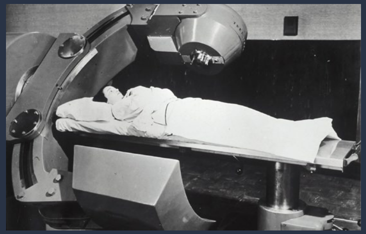
Heartland Osteoporosis Prevention Study (HOPS)

How do bone-loading exercise or bisphosphonates impact bone density and bone structure?

Nancy Waltman PhD, APRN, Laura Bilek PT, PhD, Laura Flores BA

Bone health is crucial as women move through menopause because of rapidly decreasing estrogen levels

- *43 million U.S. women have low bone mass (T-score -1 to -2.49) and are at risk for osteoporosis*
- *Experts agree that low bone mass in women requires treatment. There is some controversy about which treatment is best.*



Fracture Risk is Determined by Strength of Bones

- *Osteoporotic fractures occur when stresses from applied loads exceed the stress capacity or strength of bone tissue.*

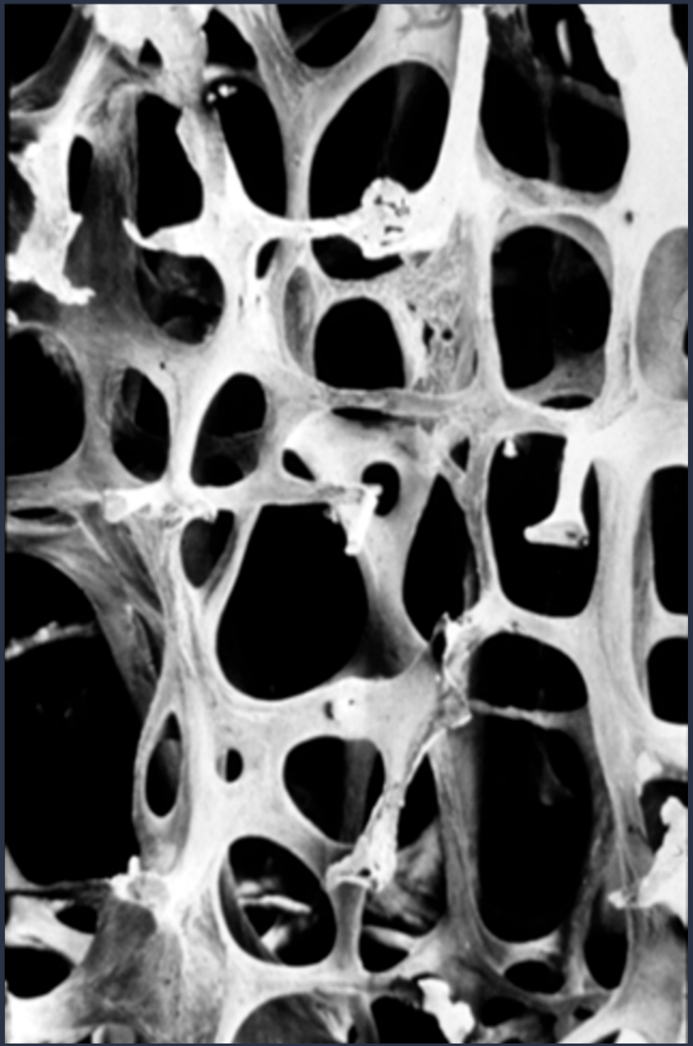
- *Stress can be from compression, bending, and tensile loads.*

- *Stress capacity or strength of bone is determined by both bone mineral density (BMD) and bone structure.*

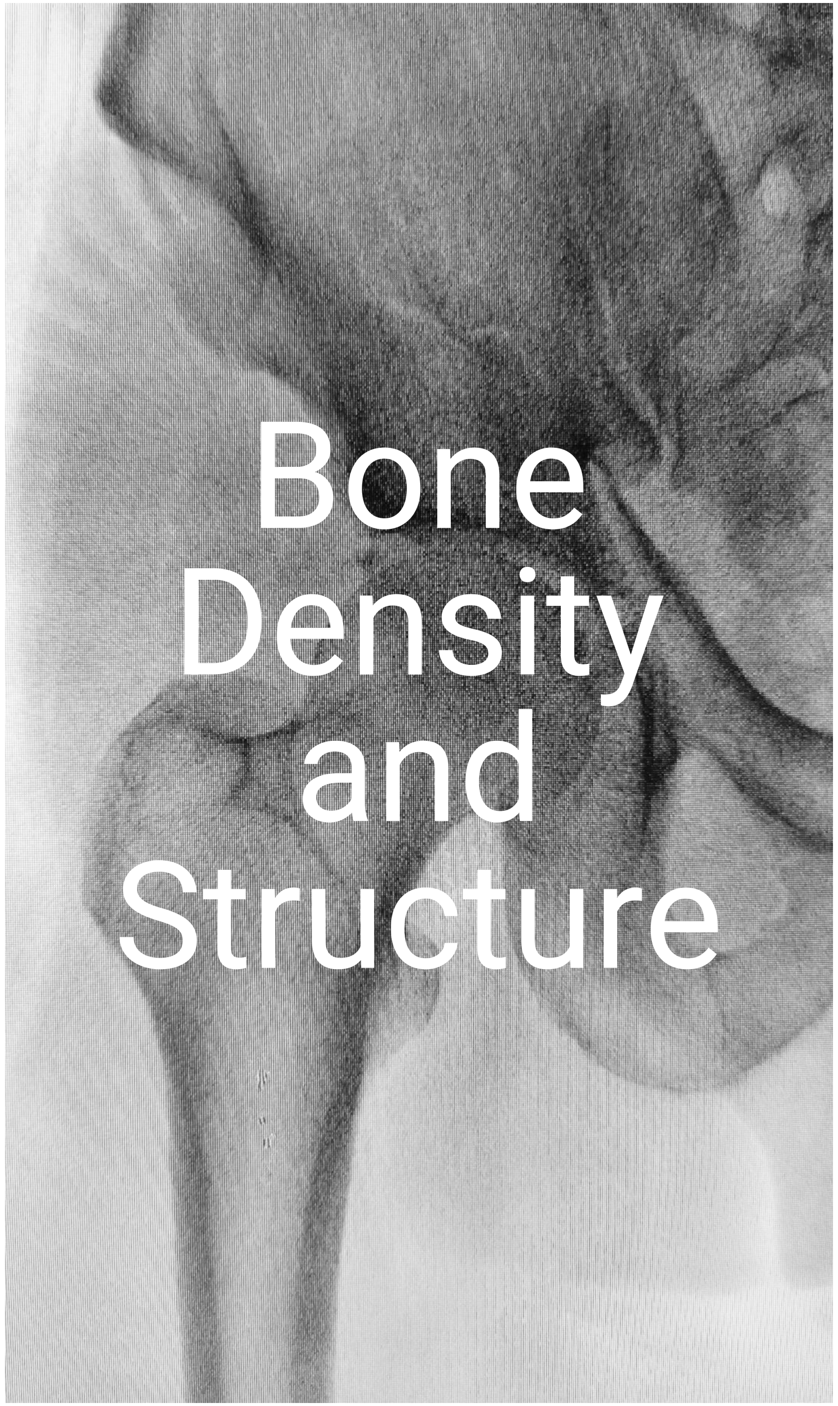
- *Women with normal BMD can still fracture due to poor bone structure. Also, strength in bone structure can improve even though no measurable change is observed in in BMD.*

Bone Density and Structure

Normal Trabecular Bone



Osteoporotic Trabecular Bone

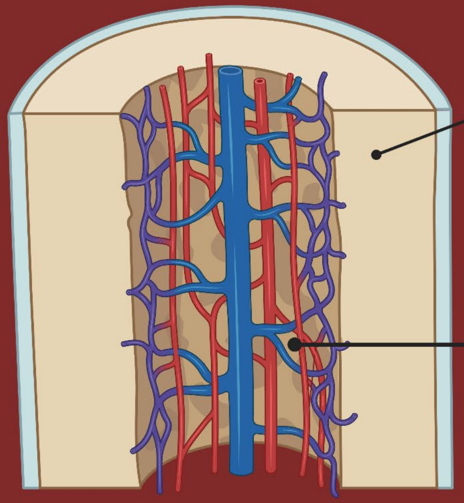


Bone Mineral Density (BMD)

- The amount of inorganic mineral in bone tissue
- The mass of mineral per volume of bone
- 65% of mineral component of bone is hydroxyapatite – an insoluble salt of calcium and phosphate
- Bone also contains small amounts of magnesium, sodium, and bicarbonate
- Minerals contribute to the strength of bone – specifically, the “hardness and rigidity of bone”

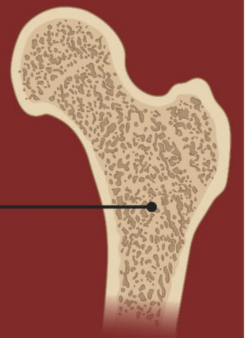
Cortical and Cancellous Bone

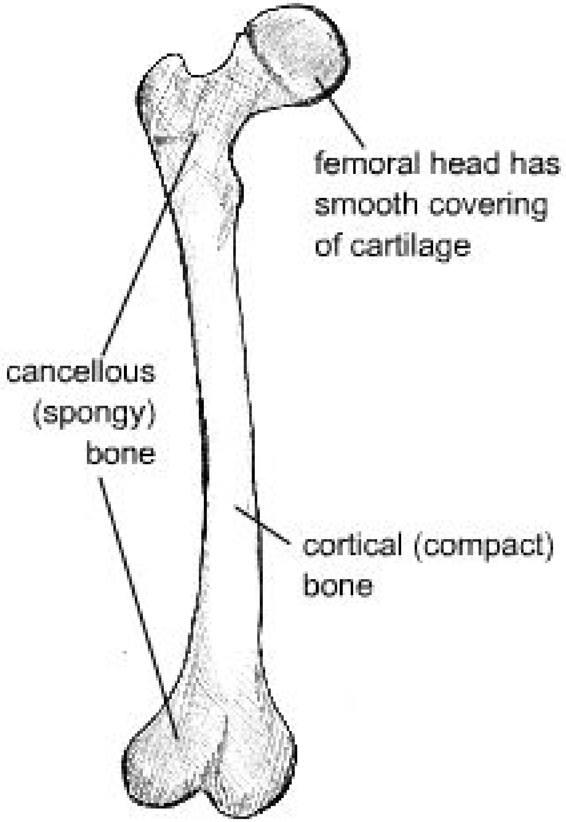
Two Types of Bony Tissue



Cortical- Consist of closely packed haversian canal systems. About 80% of the bone mass is housed in the compact bone

Cancellous- Consists of plates and rods (trabeculae), and small networks of cavities that contain bone marrow, fat, and vasculature



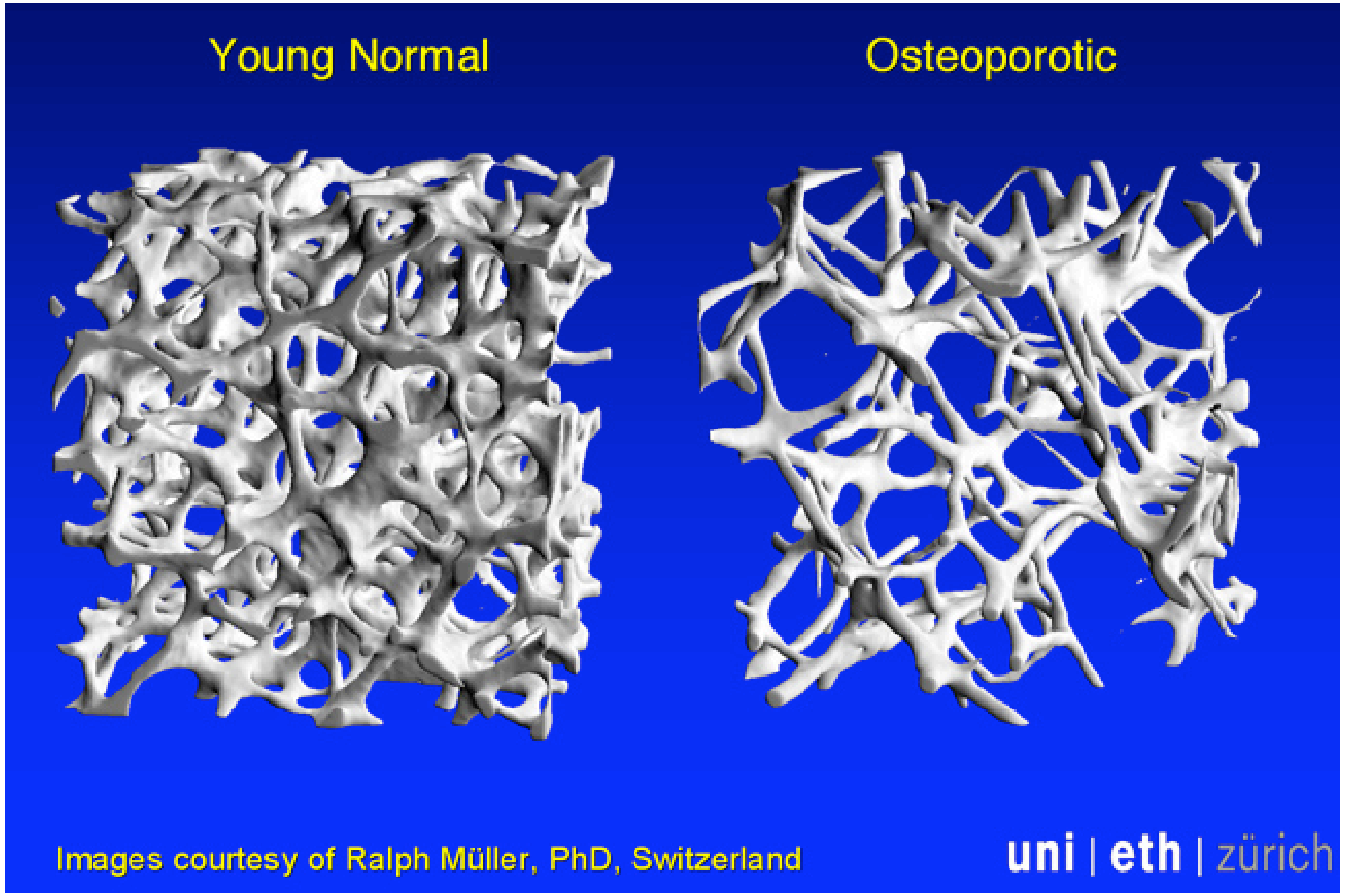


Bones with a greater percentage of cortical bone are less likely to fracture

Bone Structure

- The complex internal and external geometric configuration of bone including its distribution of minerals
- The macroarchitecture and microarchitecture of bone
- The macroarchitecture of bone consists of its size, shape, length and width at specific sites.
- The microarchitecture of bone is a honeylike matrix consisting mostly of trabecular rods and plates (fibers contain type 1 collagen protein, bone cells [osteocytes, osteoblasts, and osteoclasts] and the inorganic minerals), bone marrow, nerves , blood vessels, and cartilage.

Trabecular Rods When Bone Structure is Poor – Fewer Vertical and Horizontal Cross Links



Principles of Architecture

Trabeculae (the fibrous collagen rods) are the Structure of Bone – The Steel Beams.

When trabeculae are damaged, bones become weaker

Heartland Osteoporosis Prevention Study (HOPS)

Bone Loading Exercises Versus Risedronate for the Prevention of Osteoporosis in Postmenopausal Women with Low Bone Mass

Bone-loading Exercises versus Risedronate for the Prevention of Osteoporosis in Postmenopausal Women with Low Bone Mass

Heartland Osteoporosis Prevention Study (HOPS)

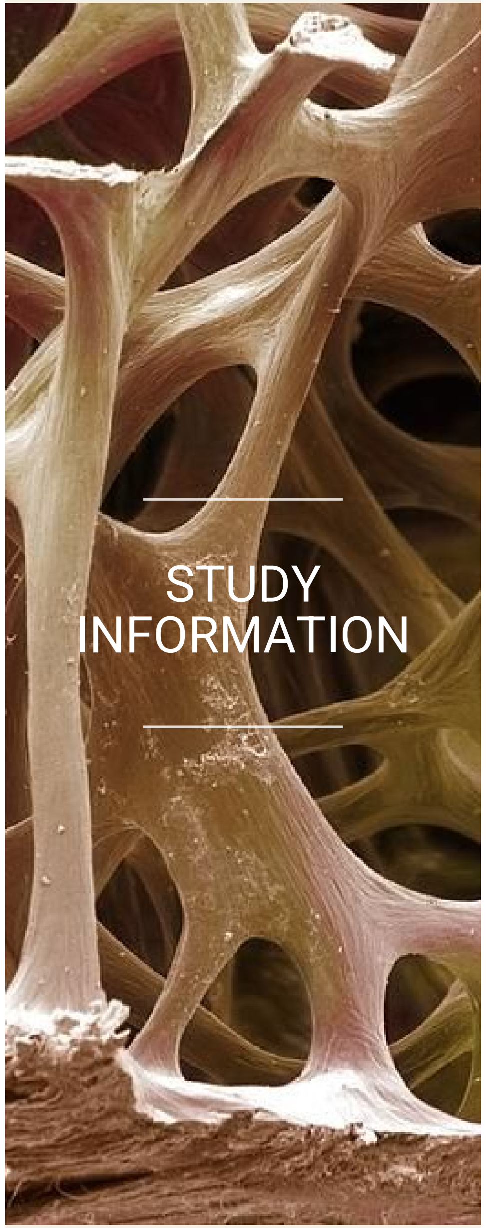
Aims of HOPS

Bone Mineral Density

How is bone mineral density (BMD) impacted by one of three treatments: exercise, risedronate, or control?

Bone Structure

How is bone structure impacted by one of three treatments: exercise, risedronate, or control?



276 Postmenopausal Women with Low Bone Mass enrolled

Inclusion Criteria

- Low bone mass
  (-1 to -2.49 T scores)
- Within 6 years of menopause
- 19 years of age and older

Exclusion Criteria

- Osteoporosis (T score < -2.5) or normal BMD (T score > -1)
- FRAX score indicating increased risk of major or hip fracture
- Currently on estrogen, tamoxifen, aromatase inhibitors
- Serum vitamin D level <10 or >100 mg/ml
- Over 300 lbs

Study Design

Calcium / Vitamin D (**Control or CaD**):

1200 mg of calcium daily (diet or supplements) + 1000 to 3000 IU vitamin D daily

Risedronate

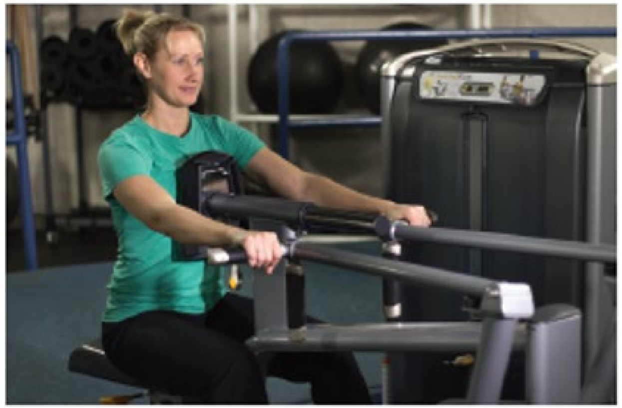
150 mg oral risedronate monthly + CaD

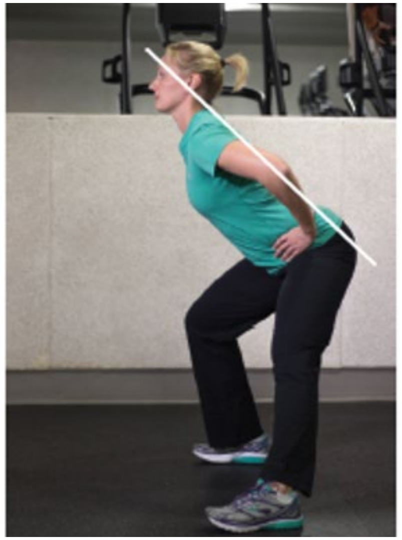
Exercise

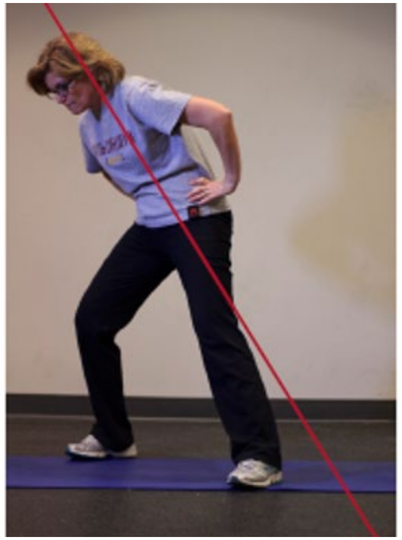
Three times weekly exercise for 12 months including **impact** (jogging using weighted vest) and **resistance exercises** of major muscle groups + CaD

Bone-Loading Exercise Intervention Conducted at Community Fitness Centers

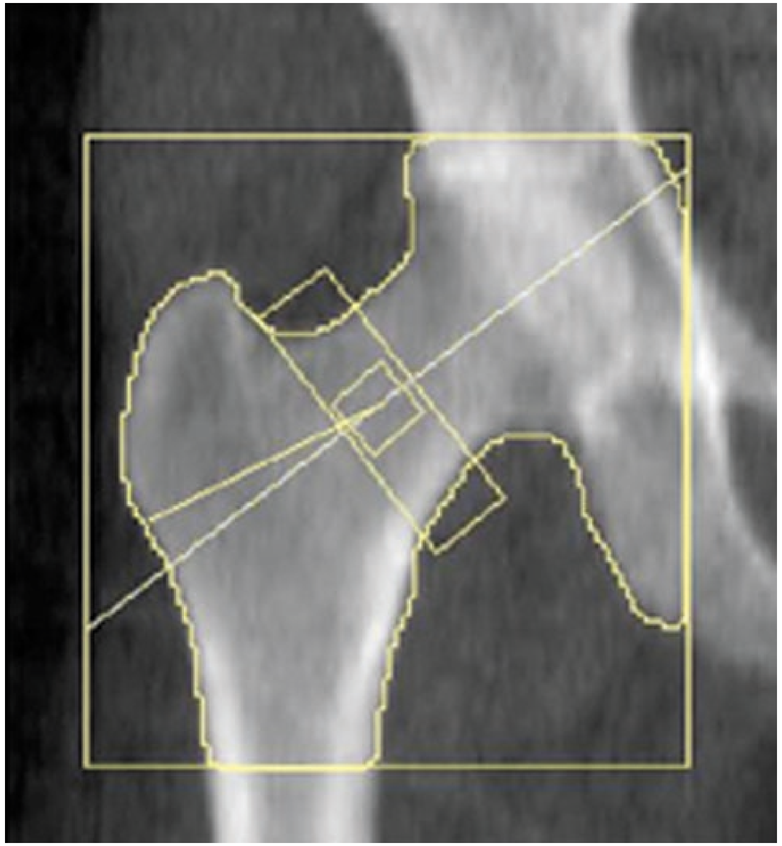
Jogging with a weighted vest





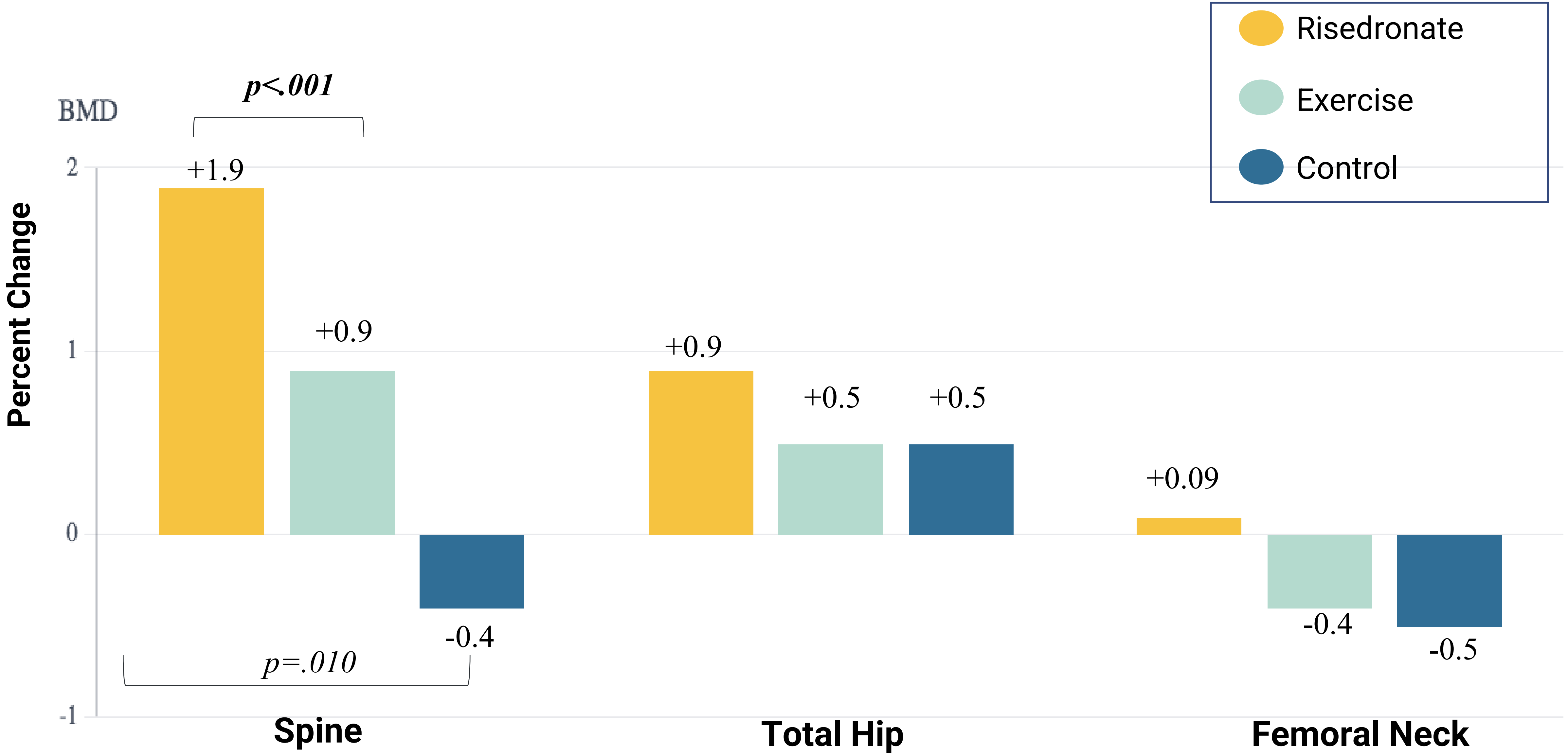


HSA & BMD measures obtained using Dual Energy X-ray Absorptiometry (DXA)



Percent Changes in BMD at 12 Months Per Group

Waltman, et al. Osteoporosis International (2021).



Physical Activity Decreases Probability of Any Hip Fracture

Probability of Any Hip Fracture

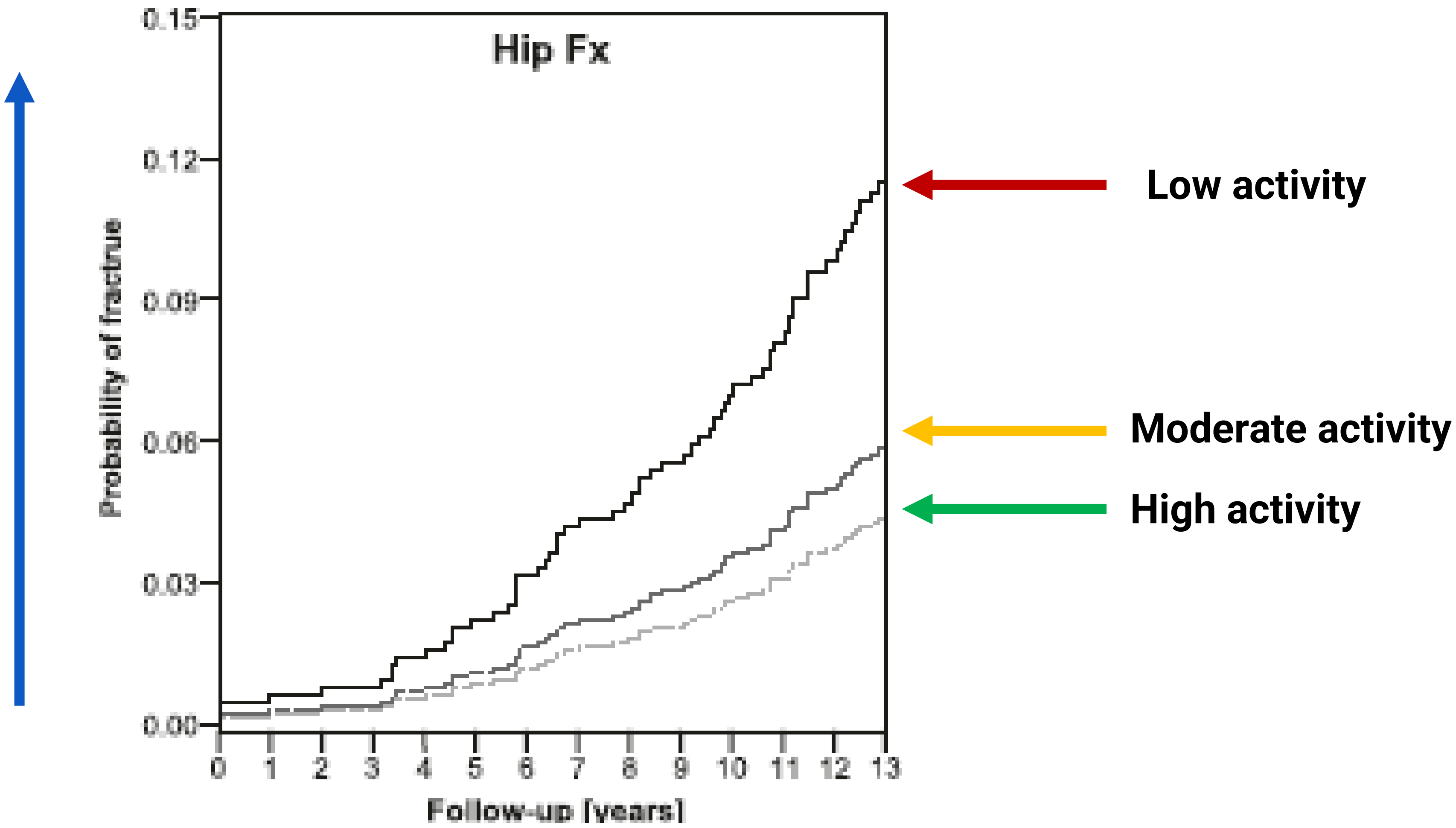


Figure 2 Probability of (A) any hip fracture and (B) cervical fracture with different baseline physical activity indices (very low or low, moderate, and high) adjusted by age and body mass index at baseline, and of (C) cervical fracture after adjustment for age and change in body weight between baseline and 2004 (NF n = 488, Neck Fx n = 17).

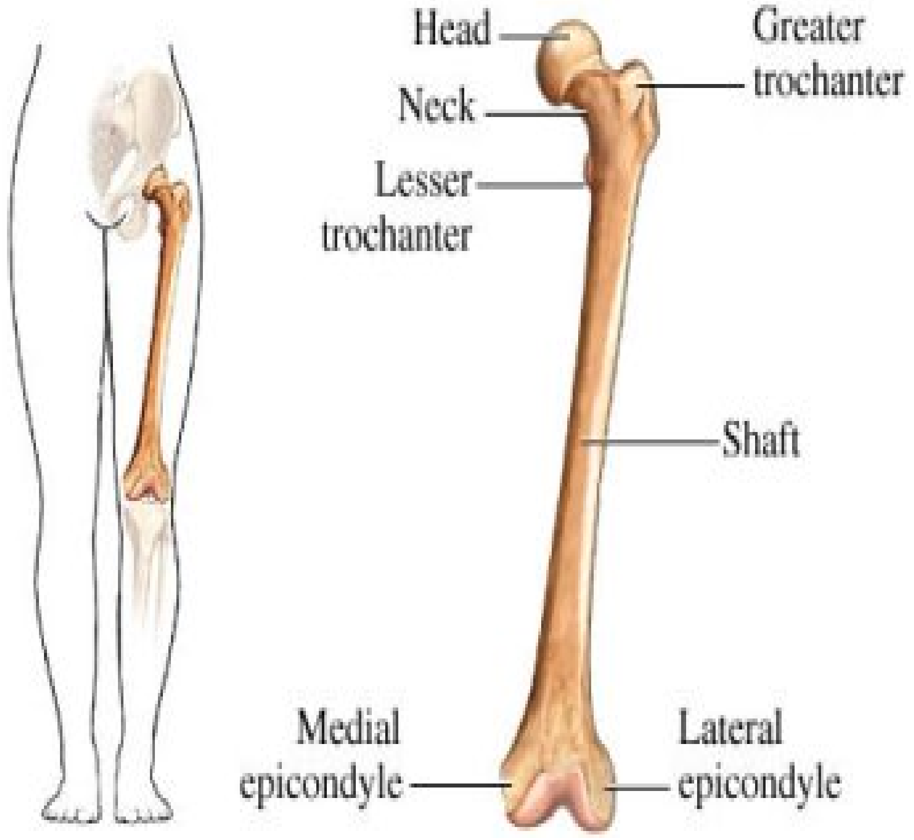
Physical Activity and Hip Fracture Risk. Määttä et al. BMC Musculoskeletal Disorders 2012, 13:173

Hip Structural Analysis (HSA)

- Structure at hip measured using Dual Energy Absorptiometry (DXA) and Hip Structural Analysis (HSA) software for geometrical calculations

- Both BMD and HSA related to increased hip fractures.

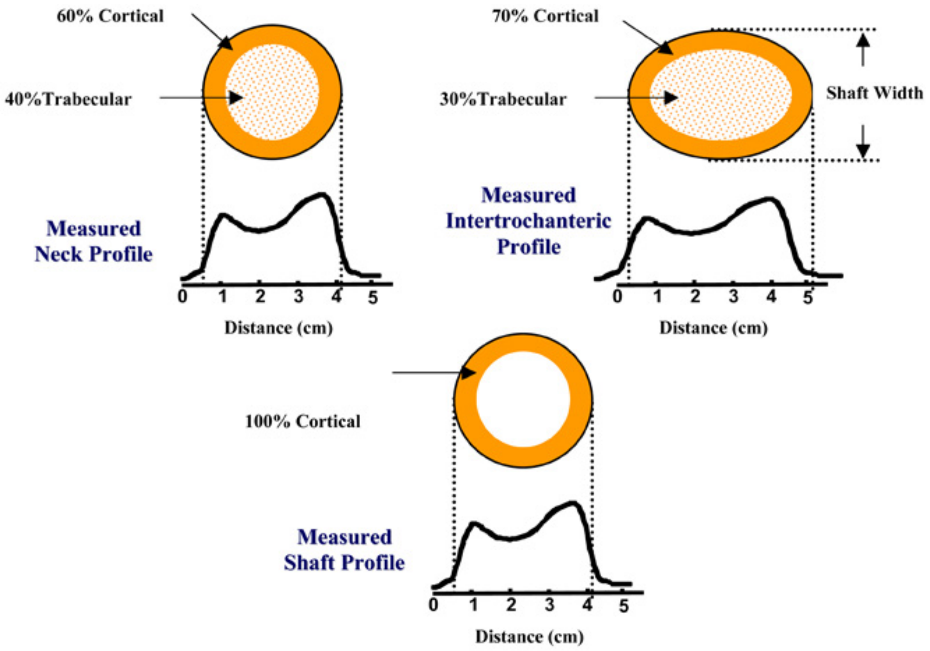
- HSA measures include cross sectional area (CSA), cross sectional moment of inertia (CSMI). section modulus (SM), and buckling ratio (BR) at the narrow neck (NN), intertrochanter (IT), and femoral shaft (FS) sites of the proximal femur

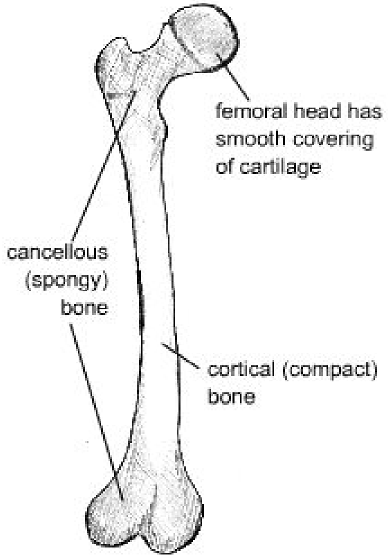


Cross sectional area (CSA):

Total surface area of bone in a cross-sectional slice, excluding marrow and soft tissue

- Greater CSA = greater cortical thickness
- Cortical - solid outer bone
- Trabecular-cancellous or spongy interior of bone
- Cortical thickness in post-menopausal women reduced.
- Uusi-Rasi, 2006 documented mean increase of 3.7% in cortical thickening after 12 months of exercise.



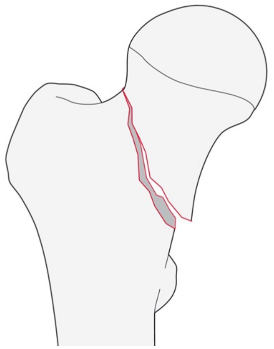


Cross Sectional Moment of Inertia (CSMI)

CSMI is a geometric formula describing the tendency to resist angular acceleration in a cross section of bone.

Low CSMI measures indicate patients have a greater risk for basicervical hip fractures. (Cha & Yoo, 2021)

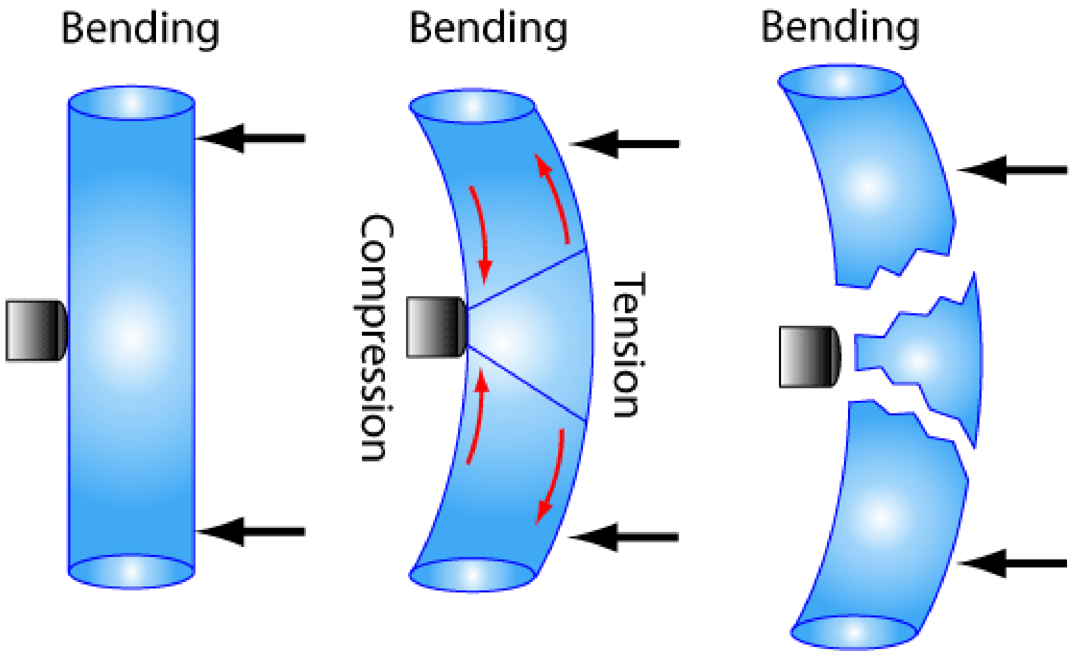
Basicervical fractures are at the junction of the femoral neck and intertrochanteric bone.



AO

Section modulus (SM): A geometric formula used as an indicator of bending strength of bone – ability to withstand bending stress

- Increased SM = Stronger bones - better resistance to bending stress
- Increased CSA = Stronger bones - better resistance to compression stress
- Result is **reduced fracture risk.**



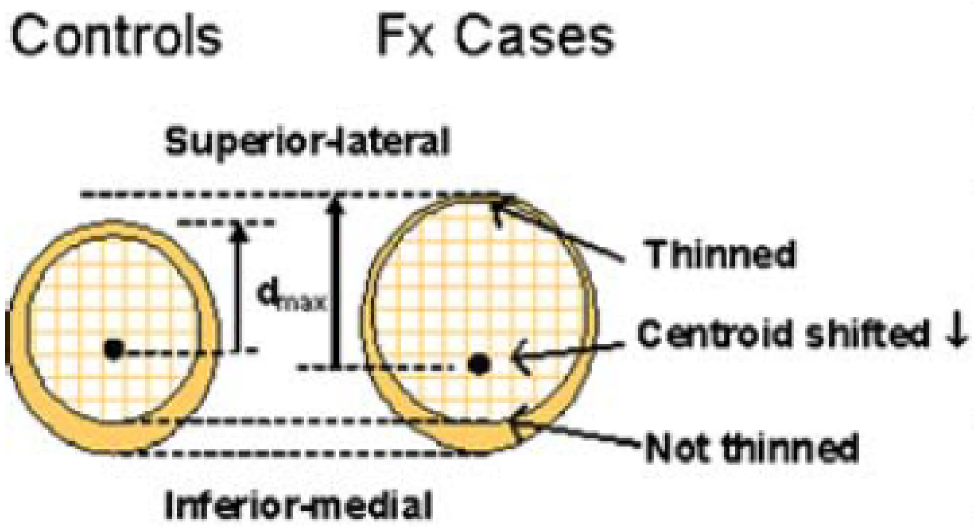
Buckling Ratio

- Buckling refers to the tendency of bone to bend or collapse under pressure. Buckling ratio is an index of cortical stability.

- Buckling ratio (BR) estimates cortical thickness relative to the width of the entire cross-section of bone. The formula for BR is the following: the radius (1/2 the diameter) of the subperiosteal bone divided by the cortical thickness of the bone. Generally, when cortical bone is wider compared to the width of the trabecular bone a wider cortical bone is less likely to bend or buckle.

- Thus, **higher** buckling ratios are related to a **greater fracture rate**, and this has been documented in numerous studies..

What do we know about normal changes to prevent fracture?

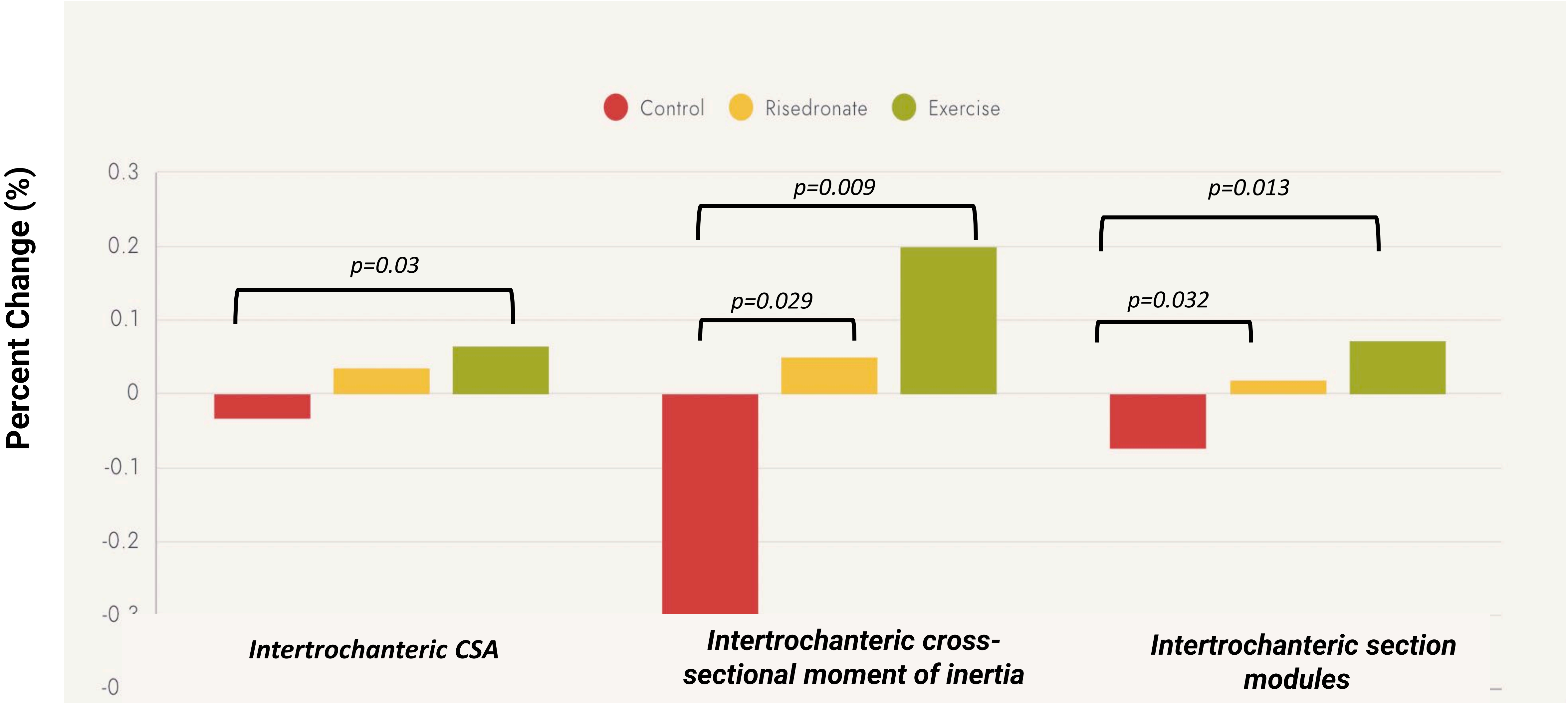


Differences vs. Controls*	
DXA BMD	13% ↓
vBMD	15% ↓
CSA	11% ↓
CSM	5% ↓
SM	9% ↓
OD	3% ↑
BR	20% ↑
d_{max}	4% ↑
Centroid position	2% ↓

Fig. 2 Typical geometric differences in a femoral neck cross-section between hip fracture cases (*n*=635) and unfractured controls (*n*=6839); right, average differences between unfractured controls and hip fracture controls from Table 1 in Kaptoge et al. [24]

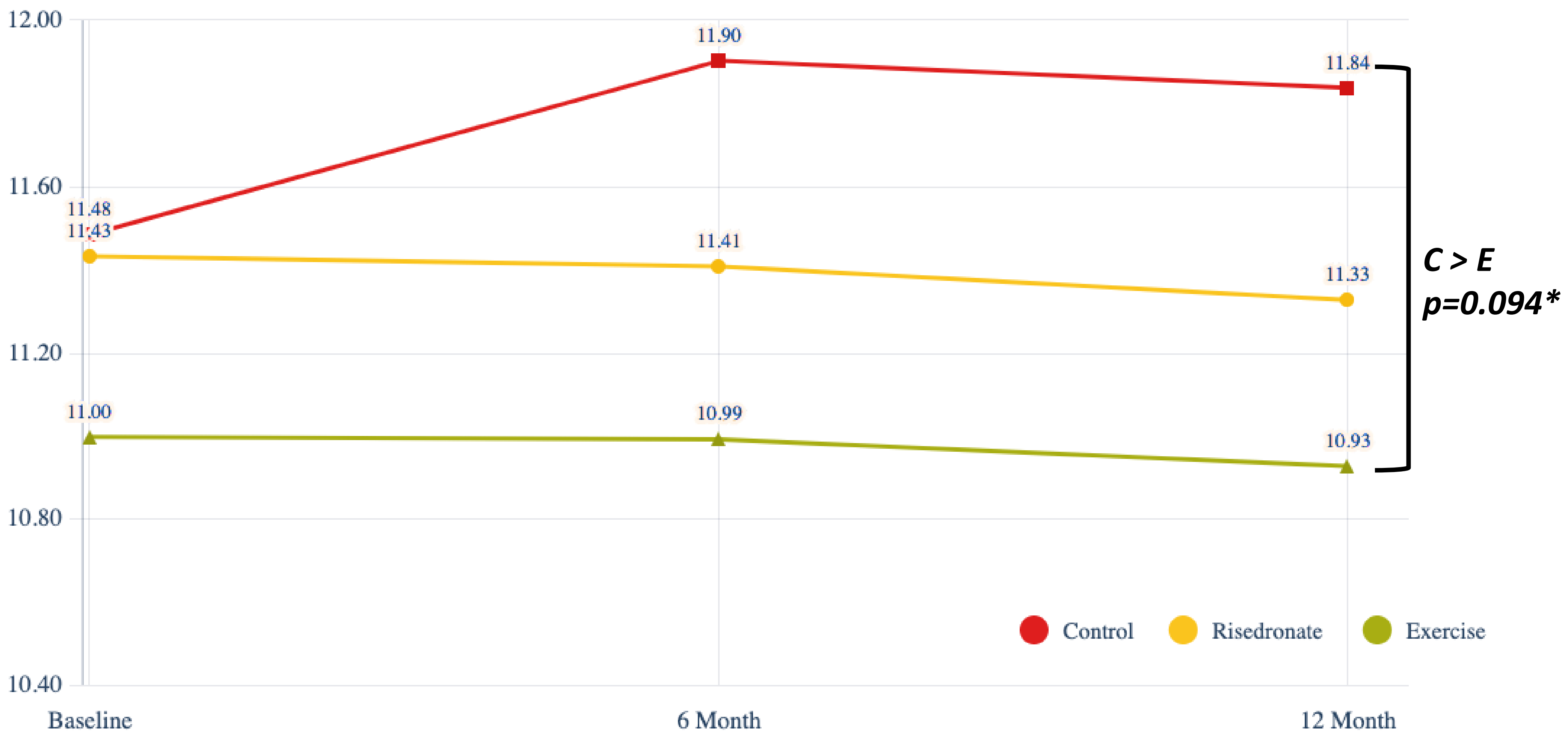
Bonnick and Beck, et al Osteoporos Int (2009) 20:911–921

Changes in Intertrochanteric Hip Structural Analysis Measures from Baseline to 12-Months



Decreased buckling ratio is associated with **stronger** bones. Exercise resulted in a decreased buckling ratio compared to control.

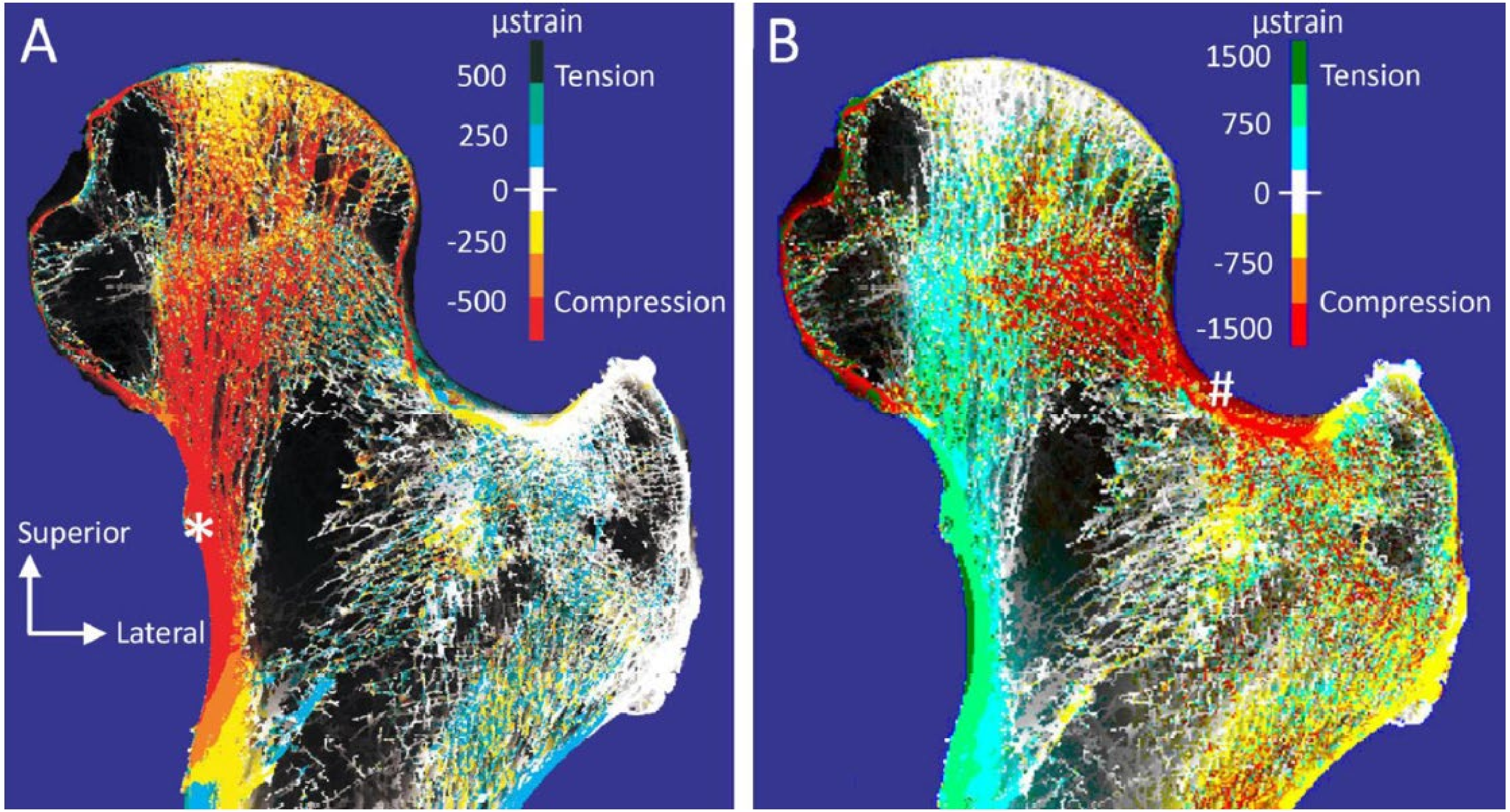
Change in Buckling Ratio By Group



Narrow neck buckling ratio				
Control	11.484 (1.67)	11.902 (1.69)	11.837 (1.72)	
Risedronate	11.432 (2.22)	11.407 (2.3)	11.326 (2.09)	
Exercise	10.997 (2.06)	10.991 (2.25)	10.926 (1.95)	*C < E p=0.094**

How is strain distributed throughout the hip?

It is distributed based on the type of force



All Exercise is Not Created Equal: Specificity of Exercise

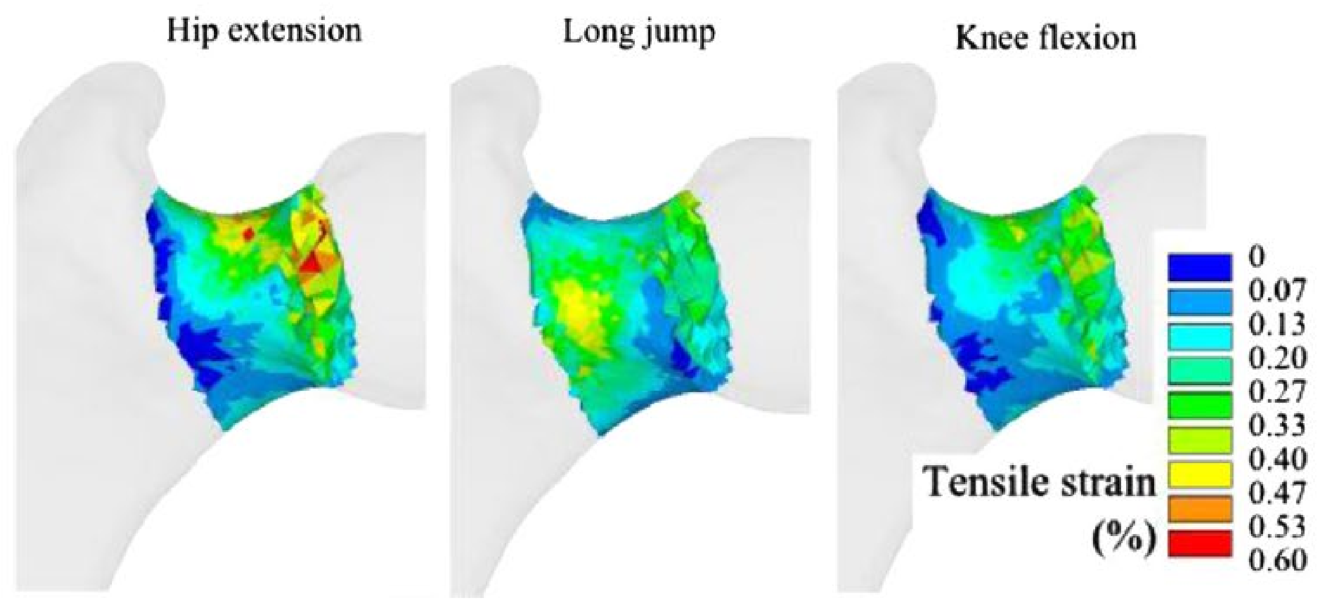


Fig. 4. Tensile strain distribution in the femoral neck during isokinetic maximal hip extensions, isokinetic knee flexion and one-legged long jumps at the instant of the peak strain energy and tensile strain.

Martelli, Journal of Biomechanics47(2014)1784–1791

Physical Activity Decreases Probability of Any Hip Fracture

Probability of Any Hip Fracture

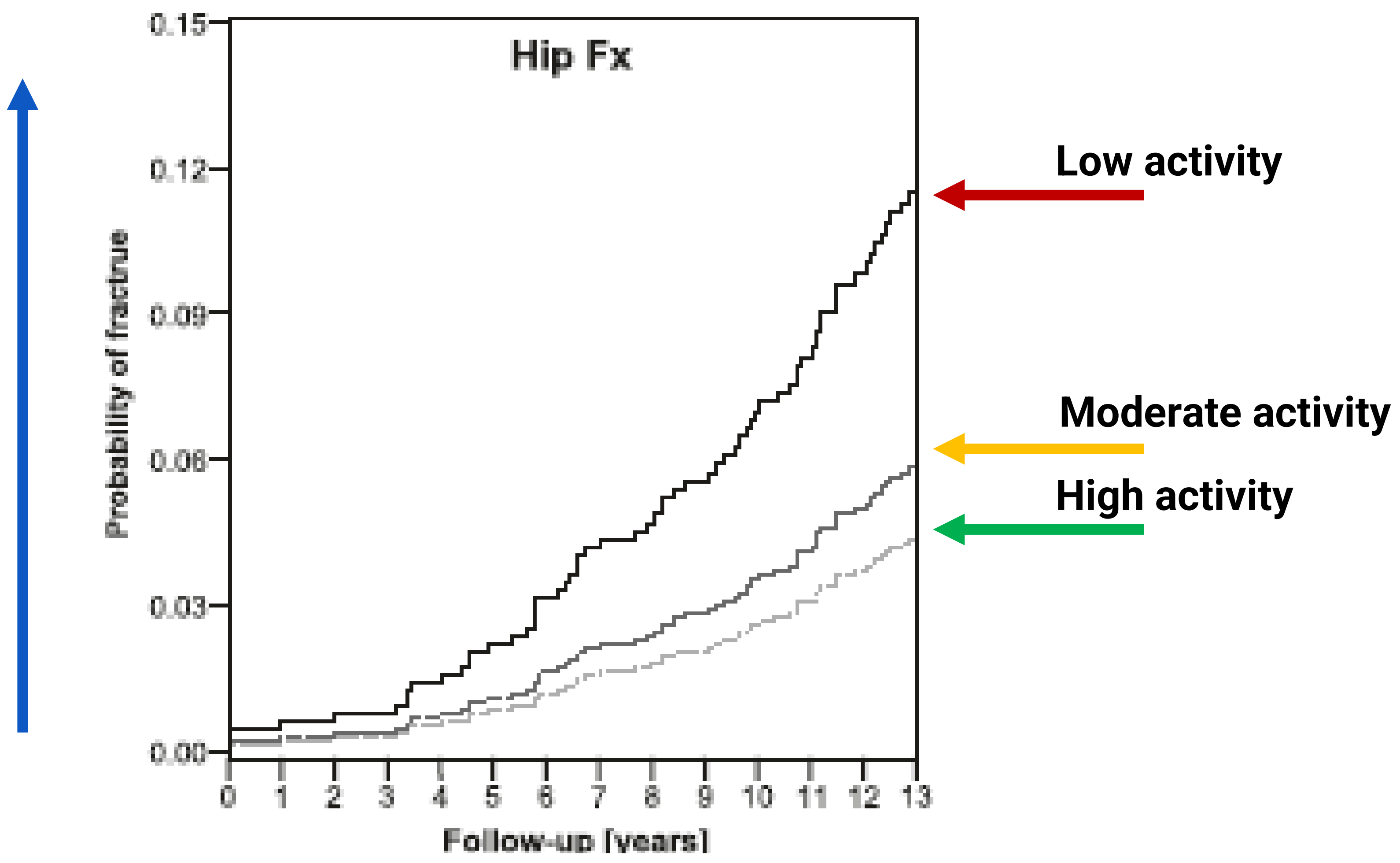


Figure 2 Probability of (A) any hip fracture and (B) cervical fracture with different baseline physical activity indices (very low or low, moderate, and high) adjusted by age and body mass index at baseline, and of (C) cervical fracture after adjustment for age and change in body weight between baseline and 2004 (NF n = 488, Neck Fx n = 17).

Physical Activity and Hip Fracture Risk. Määttä et al. BMC Musculoskeletal Disorders 2012, 13:173

Factors influencing hip fracture:

- **Lean mass**
- **Strength**
- **Balance**

Conclusions

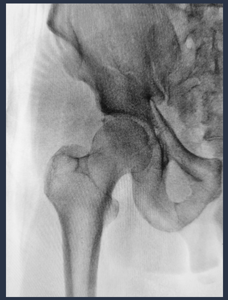
Findings from this Study and Others

Both Bisphosphonates (BPs) and bone-loading exercises reduce fracture risk.

BPs improve bone strength by increasing BMD at the spine, hip, and femoral neck, and to some extent, can also improve bone structure.

Bone-loading exercises improve bone strength and reduce fractures by maintaining BMD, improving bone structure, muscle strength, balance, and gait, and by reducing fractures.

(Hurley & Armstrong, 2012 and others)



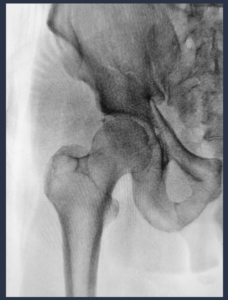
Clinical Implications

Why should I exercise?

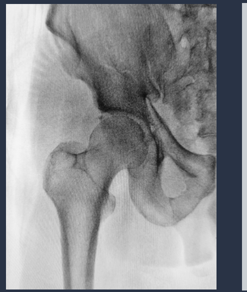
- *Exercise promotes structural changes in bone associated with lower fracture risk.*
- *Exercise has additional benefits of maintenance of muscle and improved balance which are also associate with decreased fracture risk*

Clinical Implications

How should I exercise?



- Dose/Intensity
  - Resistance training for muscle STRENGTH (~70% 1 RM)
  - Volitional fatigue 8-12 reps
  - 1, 2 or 3 sets ?
- Frequency
  - Goal is 3 days/week



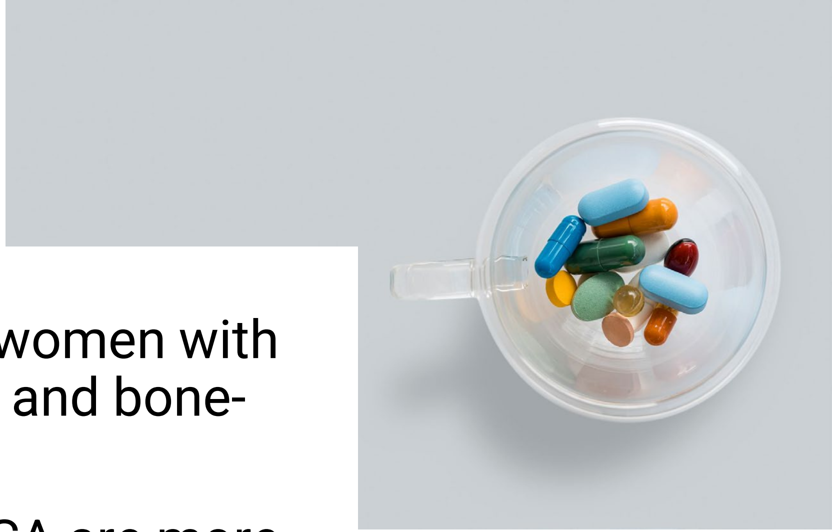
Clinical Implications

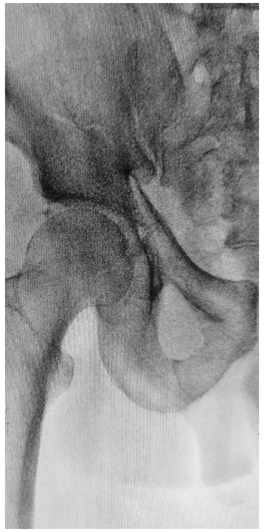
When should I start thinking about medication?

- Always with a diagnosis of osteoporosis
- Medications are also FDA approved for women with low bone mass or osteopenia
- Medications should be considered when women with low bone mass have noticeable decreases in BMD- especially at the spine
- Treatment plan should be based on collaboration between patient and provider.

Clinical Implications

- Clinicians should be aggressive in treating postmenopausal women with increased risk of bone loss with both bone-loading exercises and bone-loading medications.
- While currently, bone structure testing using tools such as HSA are more commonly used in clinical research than in clinical practice, patients should recognize that bone strength is determined by both BMD and bone structure.
- The importance of bone-loading exercises are often under-estimated because bone strength and fracture risk are determined only by BMD measures.
- All postmenopausal women should be encouraged to obtain sufficient calcium and vitamin D daily and to participate in bone-loading exercises
- Women with low BMD (especially at the spine) may also require bone-building medications such as bisphosphonates.





Additional Publications and Resources

Osteoporosis International
https://doi.org/10.1007/s00198-021-06083-2

ORIGINAL ARTICLE

Bone-loading exercises versus risedronate for the prevention of osteoporosis in postmenopausal women with low bone mass: a randomized controlled trial

Nancy Waltman[1] · Kevin A. Kupzyk[2] · Laura E. Flores[3] · Lynn R. Mack[4] · Joan M. Lappe[5] · Laura D. Bilek[3]

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Abstract

Purpose This randomized controlled trial compared changes in bone mineral density (BMD) and bone turnover in postmenopausal women with low bone mass randomized to 12 months of either risedronate, exercise, or a control group.
Methods Two hundred seventy-six women with low bone mass, within 6 years of menopause, were included in analysis. Treatment groups were 12 months of (a) calcium and vitamin D supplements (CaD) (control), (b) risedronate + CaD (risedronate), or (c) bone-loading exercises + CaD (exercise). BMD and serum markers for bone formation (Alkphase B) and resorption (Serum Ntx) were analyzed at baseline, 6, and 12 months.
Results Using hierarchical linear modeling, a group by time interaction was found for BMD at the spine, indicating a greater improvement in the risedronate group compared to exercise ($p \leq .010$) or control groups ($p \leq .001$). At 12 months, for women prescribed risedronate, changes in BMD at the spine, hip, and femoral neck from baseline were + 1.9%, + 0.9%, and + .09%; in exercise group women, + 0.2%, + 0.5%, and − 0.4%; and in control group women, − 0.7%, + 0.5%, and − 0.5%. There were also significant differences in reductions in Alkphase B (RvsE, $p < .001$, RvsC, $p < .001$) and Serum Ntx (RvsE, $p = .004$, RvsC, $p = .007$) in risedronate women compared to exercise and control groups. For risedronate, 12-month changes in Alkphase B and Serum Ntx were − 20.3% and − 19.0%; for exercise, − 6.7% and − 7.0%; and for control, − 6.3% and − 9.0%.
Conclusion Postmenopausal women with low bone mass should obtain adequate calcium and vitamin D and participate in bone-loading exercises. Additional use of BPs will increase BMD, especially at the spine.

Keywords Postmenopausal women · Low bone mass · Risedronate · Bone-loading exercises · Bone mineral density (BMD) · Bone formation and resorption

Waltman, N., Kupzyk, K.A., Flores, L.E. *et al.* Bone-loading exercises versus risedronate for the prevention of osteoporosis in postmenopausal women with low bone mass: a randomized controlled trial . *Osteoporos Int* (2021). https://doi.org/10.1007/s00198-021-06083-2

Osteoporosis International
https://doi.org/10.1007/s00198-021-06146-4

ORIGINAL ARTICLE

Examining effects of habitual physical activity and body composition on bone structure in early post-menopausal women: a pQCT analysis

L. E. Flores[1] · S. Nelson[1] · N. Waltman[2] · K. Kupzyk[3] · J. Lappe[4] · L. Mack[5] · L. D. Bilek[1]

Received: 19 May 2021 / Accepted: 2 September 2021

Abstract

Summary After menopause, bones decline in structure and can break more easily. Physical activity can strengthen bones. This study investigated how activity and body composition can impact bone structure in post-menopausal women. Higher levels of physical activity were positively associated with bone structure at the lower leg.
Purpose The menopausal transition is characterized by dramatic bone loss, leading to an increased risk of fracture. Few studies have examined how modifiable risk factors influence bone structure. Thus, the objective of this cross-sectional study was to examine the relationship between habitual physical activity (PA), body composition, and bone structure in post-menopausal women with low bone mass.
Methods Data was analyzed from 276 post-menopausal women with low bone mass enrolled in the Heartland Osteoporosis Prevention Study. Body composition and bone structure measures were collected using dual X-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT) at the tibia. Habitual PA was collected using the Human Activity Profile questionnaire. Multiple regression analysis was used to determine the relative impact of habitual PA and body composition on bone structure measures (density, area, and strength). Direct and/or indirect effects of PA on bone outcomes were assessed by path analysis.
Results Mean (± SD) age of participants was 54.5 (± 3.2) years and average BMI was 25.7 (± 4.7). Mean T-score of the total lumber spine and hip were − 1.5 (± .6) and − 0.8 (± .59), respectively, with all women classified with low bone mass. Habitual PA had a significant positive effect on bone area and strength measures at the 66% site, and trend effects at the 4% site. Lean mass had a significant positive effect on area and strength at the 66% site and 4% site. Fat mass showed no effect at the 66% site, with a positive effect on density and strength at the 4% site.
Conclusion Increased habitual activity was related to improved bone structure of the tibia. Our results in post-menopausal women emphasize that PA and lean mass preservation are important for maintaining bone structure in the years following menopause.

Keywords Osteoporosis · Menopause · Exercise · Bone Structure · Osteopenia

Flores, L.E., Nelson, S., Waltman, N. *et al.* Examining effects of habitual physical activity and body composition on bone structure in early post-menopausal women: a pQCT analysis. *Osteoporos Int* (2021). https://doi.org/10.1007/s00198-021-06146-4