Osteoporosis and Soft Tissue Disorders

Environmental Interactions

Tamara Harris, M.D., M.S.

Special Volunteer
Laboratory of Epidemiology and Population Sciences
Intramural Research Program
National Institute on Aging

harris99@mail.nih.gov
Disclosures

Current funding: None

Other financial relationships: None

Conflicts of interest: None
## Environmental Factors

### Individual Choice
- Smoking
- Exercise
- Diet (Over- and Under-Nutrition)
- Diet Quality (Essential Vitamins)
- Alcohol Intake
- Drug Intake (OTC and Prescription)
- Sleep
- Stress
- Psychosocial
- Marital Status

### Visited on the Individual
- Water Quality
- Internet Availability
- Local/Global Ecology
- Ionizing Radiation
- Poverty
- Educational Opportunity
- Employment
- Urbanicity (Overcrowding)
- Maternal Exposures (Perinatal)
- Lack of Medical Facilities

### Within the Individual
- Microbiome
- Inflammation (Acute Phase Proteins)
- Multimorbidity (Diabetes, HTN)
- Gender
- Race
- Allergic Profile
- ADL/IADL
- Strength
Interactions-think influential subgroups fooling with your results!!!!
Observed effect

Subgroup 1 - Healthy
Subgroup 2 - Frail

Mortality

Cholesterol level

Effects obscured by interaction
Interaction is all about *stratification* and occurs when an exposure has a different effect among different subgroups.

Confounding occurs when a factor is associated with both the exposure and the outcome but does not lie on the causative pathway.
As populations age, there are more distinct differences between subgroups. Interactions may become more common in old age. Lack of identification of these subgroups can lead to false results and inappropriate preventive strategies.

Example: Low cholesterol has a different effect among frail than among healthy.
Blood pressure example:

**Literature:**
Treated blood pressure in older, frailer persons has more complications and benefits are unclear.

**POLICY:**
Concern that 2014 initiation/treatment recommendations differ for persons aged 60 or older.

IS DIFFERENTIAL TREATMENT BY AGE OR FUNCTION WARRANTED?

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**SPRINT TRIAL ≥75 years old**

*Blood pressure example:*

![Restricted cubic spline (3 knots): Treated > 60 Y.O](image)

*Journal of Human Hypertension (2017). 31, 415–421*
Interaction by HIV status on gender for femoral neck BMD

Bone Mineral Density Declines Twice as Quickly Among HIV-Infected Women Compared to Men

![Graph showing bone mineral density (BMD) decline over years for females and males, highlighting a faster decline in women compared to men.](image)
Interaction by gender on SES deprivation for hip fracture

Fig. 1 Association between quintiles of deprivation and age-adjusted hip fracture incidence rates in men and women aged 50+ years residing in England, 2001–2014 (quintile 1 (Q1) (least deprived quintile)—reference category)

Conclusions: Deprivation is a stronger relative predictor of hip fracture incidence in men than in women. However, given their higher hip fracture incidence, the absolute burden of deprivation on hip fractures is greater in women. Despite pub-
Interaction of low weight over time for hip fracture among diabetics

Fig. 1 Comparisons of hip fracture risk among different BMI groups in patients with diabetes (After controlling for sex, age, urbanization of residence area, monthly salary,CCI, DCSI and weekly energy expenditure through exercise)
Interaction of age and cirrhotic status for hip fracture

In both countries the association between cirrhosis and hip fracture rate was stronger in younger age groups (aged <45 years) than in older age (p value for interaction with age <0.001).
**Figure 1** Interaction between fat mass and muscle mass on HbA1c at baseline after adjusting for age, duration of diabetes, sex, medication, dietary protein, fat, and carbohydrate intake. Data are reported as means ± standard error of the mean. There was a significant interaction effect between fat and muscle mass (P = 0.009). Bonferroni-adjusted pairwise comparison showed that participants with high fat and low muscle mass had higher HbA1c compared to high fat mass alone (P = 0.037), low muscle mass alone (P = 0.003), and low fat and high muscle mass (P = 0.007).
Interaction of weight change and age on body composition change

Trajectories of the relationships of physical activity with body composition changes in older men: the MrOS study

Ladieu et al. BMC Geriatrics (2017) 17:119
DOI 10.1186/s12877-017-0506-4
Most analytic methods can be adapted for assessment of interactions or subgroup identification.

Some additional methods include:

Stratification (a priori hypotheses versus exploratory)

Life course

Mixed models (assessment of interaction by time)

Classification trees

Major problem is power
Knowledge Gaps:

- The incidence of hip and fragility fractures by health status has been explored as well as differences in recovery rates and factors contributing to the recovery or lack thereof.

- Relatively little has been done in assessment of subgroups in relation to biomarkers contributing to fracture.

- Whether there are augmented treatment strategies for selected high risk subgroups is a knowledge gap.

Similar gaps apply to muscle and adipose interactions.
Research Opportunities:

• Thus far, primarily gene-environment or gene-risk factors interactions have been assessed. Other interactions bear assessment, particularly with relatively new biomarkers.

• Application of state-of-the-art methods for assessment of environmental interactions with bone, muscle, and adipose should be pursued.

• Exploration of race/ethnicity interactions may provide new insights especially comparisons in populations where naturally-occurring differences in risk factors occur including walking, smoking
Thank you for your attention!
What are interactions/effect modifications?

In general, the effect of one exposure may depend in some way on the presence or absence of another exposure.

Additive – the effect of two factors added together exceeds the effect of each individually (>0=positive additive interaction, <0=negative)

Multiplicative – the effect of two factors multiplied together exceeds the effect of each individually (>1=positive multiplicative interaction, <0=negative)

Any type of study, particularly genetic epidemiology
Periods of Risk Associated with Lifelong Weight Pattern

- Childhood
- Adolescence
- Young and middle adult life
- Older age
- Geriatric

Age

20 30 40 50 60 70 80
SPECIAL ISSUES IN OLD AGE:

REVERSE CAUSATION  (LOW BLOOD PRESSURE IS BAD FOR YOU AND HIGH BLOOD PRESSURE IS PROTECTIVE)  WEIGHT, CHOLESTROL

PROXIMATE EVENTS LIKE DISEASE AND DISABILITY

MULTIMORBIDITY

CRITICAL WINDOWS FOR EXPOSURES
The interactive effects of aerobic fitness and BMI on risk of IHD are shown in Table 3. Low aerobic fitness was associated with increased IHD risk among men with either normal or high BMI (IRRs, 1.87 and 1.45, respectively; Table 3, right-most column). The combination of low aerobic fitness and high BMI was associated with the highest risk of IHD, which was more than 3-fold relative to the reference group of those with high aerobic fitness and normal BMI. Low aerobic fitness and high BMI had a negative interaction on the multiplicative scale ($P_{\text{interaction}}<0.001$) (i.e., their combined effect was less than the product of their separate effects), and no interaction on the additive scale ($P_{\text{interaction}}=0.40$). Figure 1 shows the probability of IHD for the 25th, 50th, and 75th percentiles of aerobic fitness across the full distribution of BMI, from the fully adjusted model.
Biomarkers Principal components analysis to identify subgroups

FIG. 5. Diagnostic fingerprint of postmenopausal women with high (striped bars) and low/normal (white bars) bone turnover. The median fold changes in the SELDI peak intensities are shown.
Comparison of risks by age, women

<table>
<thead>
<tr>
<th>Body mass index (kg/m²)</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI at 18 yrs</td>
<td>1</td>
</tr>
<tr>
<td>BMI at 35 yrs</td>
<td>2</td>
</tr>
<tr>
<td>BMI at 50 yrs</td>
<td>3</td>
</tr>
<tr>
<td>Baseline BMI</td>
<td>4</td>
</tr>
</tbody>
</table>
Why gender differences in energy expenditure?
If not exercise, what preserves muscle and muscle function in old age?
Fig. 1. The basic instrumental variable (IV) model depicted using a directed acyclic graph. Z: the instrumental variable, X: the exposure of interest (such as a putative risk factor), Y: the outcome of interest (such as a disease), U: one or more measured or unmeasured confounders.
Fig. 1. Risk factors for the development of atrial fibrillation and heart failure in women. CRP, C-reactive protein. (Data from Refs. 12,68,69)

Heart Failure Clin 15 (2019) 55–64
https://doi.org/10.1016/j.hfc.2018.08.006
Modeling life course pathways from adverse childhood experiences to adult mental health

Tiffany M. Jones*, Paula Nurius, Chiho Song, Christopher M. Fleming

School of Social Work, University of Washington, Seattle, United States

Notes. ACE = Adverse childhood experience.

https://doi.org/10.1016/j.chiabu.2018.03.005

Oval represents latent construct and squares represent measured indicators.
Why are interactions important?
SPECIAL ISSUES IN OLD AGE:

REVERSE CAUSATION (LOW BLOOD PRESSURE IS BAD FOR YOU AND HIGH BLOOD PRESSURE IS PROTECTIVE) WEIGHT, CHOLESTROL

PROXIMATE EVENTS LIKE DISEASE AND DISABILITY

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Group based trajectory method:

Trajectories of the relationships of physical activity with body composition changes in older men: the MrOS study

Trajectory Groups (Percentage of Population in Group):
- Group 1: N=305(5%)
- Group 5: N=950(16%)
- Group 2: N=1119(19%)
- Group 6: N=437(8%)
- Group 3: N=1583(26%)
- Group 7: N=151(3%)
- Group 4: N=1342(22%)
- Group 8: N=77(1%)

Trajectory Groups (Percentage of Population in Group):
- Group 1: N=464(8%)
- Group 4: N=1361(23%)
- Group 2: N=1378(23%)
- Group 5: N=763(13%)
- Group 3: N=1784(30%)
- Group 6: N=214(4%)

Trajectory Groups (Percentage of Population in Group):
- Group 1: N=2203(36%)
- Group 4: N=917(16%)
- Group 2: N=1701(28%)
- Group 5: N=286(5%)
- Group 3: N=857(15%)

Laddu et al. BMC Geriatrics (2017) 17:119
DOI 10.1186/s12877-017-0506-4
Frailty and Risk of Fractures in Patients With Type 2 Diabetes

https://doi.org/10.2337/dc18-1965
Health ABC markers that strongly predict overall mortality

Septiles of increasing value
DO YOU HAVE ANYTHING THAT STOPPS THE AGING PROCESS?

SURE, WHAT KIND OF DISEASE WOULD YOU LIKE?
Walking is a key component of physical independence
Differentiating “Age-associated” from Aging”

*Cartoon Image*
"I've had a happy childhood, a happy youth, a happy middle age. I count on a happy old age, and then I'm going straight to Heaven."
MEASUREMENT ERROR
HOW TO CAPTURE THE EXPOSURE OF INTEREST

INFLAMMATION AND MEASUREMENT OF C-REACTIVE PROTEIN AND INTERLEUKIN-6

DIET

ENVIRONMENTAL EXPOSURES

SMOKING

IN UTERO

EXERCISE

. Large-scale sequencing of bacterial genomic and metagenomic DNA indicates that the traditional, pure culture–based approach to studying bacterial natural products has provided access only to a small fraction of the diverse metabolites encoded by environmental microbiomes. Studies suggest that in most environments, uncultured bacteria outnumber their cultured counterparts by at least two orders of magnitude.
HOW DOES THE EXPOSURE RELATE TO THE OUTCOME

TIME-COURSE

RADIATION AND INCIDENCE OF BREAST CANCER IN JAPAN

CHILDHOOD AND MENTAL ILLNESS

CHILDHOOD AND ADULT OUTCOMES OF OBESITY
MEASUREMENT ERROR
HOW TO CAPTURE THE EXPOSURE OF INTEREST

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IN UTERO

EXERCISE
HOW DOES THE EXPOSURE RELATE TO THE OUTCOME

TIME-COURSE

RADIATION AND INCIDENCE OF BREAST CANCER IN JAPAN

CHILDHOOD AND MENTAL ILLNESS

CHILDHOOD AND ADULT OUTCOMES OF OBESITY
Thank you for your attention!
Fig. 3. Bubble plot of reported associations between ACIs and cancer risk factors by effect and demographics. Key: Size of bubble = the number of articles looking at the association between ACIs and the identified cancer risk factor; ♂ = male-only participants ■ = female-only participants. Note: Study samples were non-Hispanic unless noted.
<table>
<thead>
<tr>
<th>Domain name</th>
<th>Included determinants (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>1. Dental status</td>
</tr>
<tr>
<td></td>
<td>2. Chewing</td>
</tr>
<tr>
<td></td>
<td>3. Mouth pain</td>
</tr>
<tr>
<td></td>
<td>4. Gum issues</td>
</tr>
<tr>
<td></td>
<td>5. Swallowing</td>
</tr>
<tr>
<td>Psychosocial</td>
<td>6. Cognitive function</td>
</tr>
<tr>
<td></td>
<td>7. Depression/depressive symptomology</td>
</tr>
<tr>
<td></td>
<td>8. Psychological distress</td>
</tr>
<tr>
<td></td>
<td>9. Anxiety</td>
</tr>
<tr>
<td></td>
<td>10. Social support</td>
</tr>
<tr>
<td></td>
<td>11. Residential status</td>
</tr>
<tr>
<td></td>
<td>12. Transport</td>
</tr>
<tr>
<td></td>
<td>13. Loneliness</td>
</tr>
<tr>
<td></td>
<td>14. Wellbeing</td>
</tr>
<tr>
<td></td>
<td>15. Meals on wheels</td>
</tr>
<tr>
<td>Medication and care</td>
<td>16. Medication and polypharmacy</td>
</tr>
<tr>
<td></td>
<td>17. Hospitalisation</td>
</tr>
<tr>
<td>Health</td>
<td>18. Co-morbidities</td>
</tr>
<tr>
<td></td>
<td>19. Functional health status</td>
</tr>
<tr>
<td></td>
<td>20. Eating dependency/difficulty feeding</td>
</tr>
<tr>
<td></td>
<td>21. Self-perceived health</td>
</tr>
<tr>
<td>Physical function</td>
<td>22. Activities of daily living, performance or strength</td>
</tr>
<tr>
<td>Lifestyle</td>
<td>23. Smoking</td>
</tr>
<tr>
<td></td>
<td>24. Alcohol</td>
</tr>
<tr>
<td></td>
<td>25. Physical activity</td>
</tr>
<tr>
<td>Eating</td>
<td>26. Appetite/leaves food on plate</td>
</tr>
<tr>
<td></td>
<td>27. Complaints about taste of food</td>
</tr>
<tr>
<td></td>
<td>28. Dietary factors – nutrient intake and modified texture diets</td>
</tr>
<tr>
<td></td>
<td>29. Hunger</td>
</tr>
</tbody>
</table>

Please cite this article as: O’Keefe M et al., Potentially modifiable determinants of malnutrition in older adults: A systematic review, Clinical Nutrition, https://doi.org/10.1016/j.clnu.2018.12.007
Figure 1: Gut microbiota and its metabolites linked to cardiovascular diseases.
INDIVIDUAL CHOICE

SMOKING
EXERCISE
DIET (OVER- AND CALORIC RESTRICTION)
DIET QUALITY (ESSENTIAL VITAMINS)
ALCOHOL INTAKE
DRUG INTAKE (OTHERWISE AND
PRESCRIPTION)
SLEEP
STRESS
PSYCHOSOCIAL
MARITAL STATUS
VISITED ON THE INDIVIDUAL

WATER QUALITY
INTERNET AVAILABILITY
LOCAL ECOLOGY
GLOBAL ECOLOGY
IONIZING RADIATION
POVERTY
EDUCATIONAL OPPORTUNITY
EMPLOYMENT
URBANICITY (OVERCROWDING)
MATERNAL EXPOSURES (PERINATAL)
LACK OF MEDICAL FACILITIES
WITHIN THE INDIVIDUAL

GUT MICROBIOME
INFLAMMATION (ACUTE PHASE PROTEINS)
MULTIMORBIDITY (DIABETES, CYSTIC FIBROSIS, HTN)
GENDER
RACE
ALLERGIC PROFILE
ADL/IADL
STRENGTH
Fig. 1. Types of adverse childhood experiences included in studies. Note: The size of the word reflects its frequency of measurement in studies. The adversity type may have been measured as an individual item, included as part of a summary or score, or both. The shade of the word has no meaning.
### Weight Change and Health in Women not Overweight at Age 18

**Iowa Women’s Study**

<table>
<thead>
<tr>
<th></th>
<th>Diabetes</th>
<th>High blood pressure</th>
<th>Heart attack</th>
<th>Fair/poor health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Continuous weight gain</td>
<td>6.6*</td>
<td>3.2*</td>
<td>2.0*</td>
<td>2.1*</td>
</tr>
<tr>
<td>Weight gain maintenance</td>
<td>3.8*</td>
<td>1.8*</td>
<td>1.6*</td>
<td>1.3*</td>
</tr>
<tr>
<td>Weight loss regain</td>
<td>2.3*</td>
<td>1.8*</td>
<td>1.9*</td>
<td>1.7*</td>
</tr>
<tr>
<td>Weight loss maintenance</td>
<td>0.6</td>
<td>0.8</td>
<td>1.3</td>
<td>1.1</td>
</tr>
</tbody>
</table>

* p<.01

Lifetime average weight from longitudinal data

Lifetime Weight Patterns Based on Percentile Distributions in 3,611 Japanese-American Men

Kilograms of Weight

Age

Percentile

10
25
50
75
90

25 (reported)
52 (Exam 1)
77 (Exam 4)
Heterogeneity of weight patterns in the population

YOUTH- from 25 to midlife: **61% gain**, 27% stable, 12% lose

From midlife to old age: 19% gain, 27% stable, **44% lose**

Honolulu Heart Study – Honolulu Asia Aging Study
Use of midlife weight to predict old age outcomes gives estimates that are less affected by health status in old age.
Aging-Prevention Paradigm

Among healthy → prevent disease
Among ‘at risk’ → stabilize disease, prevent disability
Among frail → prevent progression of disability

Holistic gerontological perspective expressed in the Health ABC Study
Increasingly anabolic hormonal milieu

Health, Aging and Body Composition Study

Hypothetical Trajectory for Weight in Relation to Illness and Risk of Disability

Weight

Younger age

Older age

Time

Increasingly anabolic hormonal milieu

Vellas; Kottler, Grunfeld
## Baseline Characteristics of the Health ABC cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White</td>
<td>Black</td>
</tr>
<tr>
<td>BMI</td>
<td>27.0</td>
<td>27.2</td>
</tr>
<tr>
<td>Percent fat</td>
<td>29.9</td>
<td>28.0</td>
</tr>
<tr>
<td>Lean mass in cm²</td>
<td>127</td>
<td>139</td>
</tr>
<tr>
<td>Days hospitalized (mean)</td>
<td>3.8</td>
<td>4.9</td>
</tr>
<tr>
<td>Percent hypertensive</td>
<td>69</td>
<td>82</td>
</tr>
<tr>
<td>&lt; HS education</td>
<td>14</td>
<td>49*</td>
</tr>
<tr>
<td>Good/F/P</td>
<td>47</td>
<td>65*</td>
</tr>
</tbody>
</table>
**Functional limitation:** Difficulty walking ¼ mile or up 10 steps reported consistently over a 6-month period

<table>
<thead>
<tr>
<th></th>
<th>Functional limitation: Difficulty walking ¼ mile or up 10 steps reported consistently over a 6-month period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Over 13 years of follow-up, percent incident functional limitation</td>
</tr>
<tr>
<td>White men</td>
<td>67</td>
</tr>
<tr>
<td>White women</td>
<td>72</td>
</tr>
<tr>
<td>Black men</td>
<td>73</td>
</tr>
<tr>
<td>Black women</td>
<td>80</td>
</tr>
</tbody>
</table>
CT properties of muscle - a combination of science and serendipity
Reciprocity between muscle and adipose
Contribution to performance measures
Measuring fitness in older adults: The Health ABC Long Distance Corridor Walk

Association of Long-Distance Corridor Walk Performance With Mortality, Cardiovascular Disease, Mobility Limitation, and Disability

Figure 3. Kaplan-Meier Plots of Mobility Limitation and Disability Event Rates

- Men:
  - Excluded (dotted line)
  - Stopped (dashed line)
  - Quartile 1 (dotted-dashed line)
  - Quartile 2 (dash-dotted line)
  - Quartile 3 (dashed line)
  - Quartile 4 (solid line)

- Women:
  - Excluded (dotted line)
  - Stopped (dashed line)
  - Quartile 1 (dotted-dashed line)
  - Quartile 2 (dash-dotted line)
  - Quartile 3 (dashed line)
  - Quartile 4 (solid line)

P < .001
Lower daily free-living activity energy expenditure increases risk of death—doubly labeled water

Adjusting for Age, Sex, Race & Site

- >770 kcal/d  HR=1.00
- 521-770 kcal/d  HR=0.74 (0.49-1.13)
- <521 kcal/d  HR=0.59 (0.37-0.95)

Manini et al. 2006
“How dangerous are those extra pounds? A new study shows that being pleasantly plump may actually be good for you.”

Gina Kolata  AARP Bulletin, June 21, 2005
Stevens J NEJM 1998

Analysis in a healthier population-American Cancer Society cohort

Risk of death associated with thinner BMI increases with age.

Risk of death associated with heavier BMI flattens with age.
Osteoporosis Self-assessment Tool

Score = [weight (kg) – age (years)] × 0.2
FRAX Clinical Risk Factors

- Age
- Sex
- Weight
- Height
- Previous fracture
- Parental history of hip fracture
- Smoking status
- Glucocorticoid use
- Rheumatoid arthritis
- Secondary osteoporosis
- ≥3 units of alcohol per day†
- Femoral neck BMD (g/cm²)

BMD = bone mineral density.
* Calculator freely available at www.shef.ac.uk/FRAX.
† The quantity of alcohol that constitutes 1 unit varies slightly by country. For FRAX, 1 unit of alcohol is equivalent to 9–10 oz of beer, 4 oz of wine, 1 oz of spirits, or 2 oz of aperitif.
Figure 1: Effects of antiresorptive and anabolic drugs on bone remodelling and modelling.
Age-related bone loss is associated with an increase in remodelling and a negative remodelling balance in individual bone remodelling units. Antiresorptive agents act predominantly by reducing remodelling rate. Anabolic agents produce their effects by increasing remodelling in combination with a positive remodelling balance, or stimulating bone modelling.
<table>
<thead>
<tr>
<th>Risk factor inputs</th>
<th>Fracture risk assessment tool(^2)</th>
<th>Garvan Fracture risk calculator(^4)</th>
<th>QFractureScores-2016(^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture risk assessment tool(^2)</td>
<td>Age, sex, body-mass index, previous fragility fracture, glucocorticoid use ≥3 months, secondary osteoporosis, rheumatoid arthritis, parental hip fracture, current cigarette smoking, alcohol intake of ≥3 units per day, femoral neck bone mineral density or T score (optional)</td>
<td>Age, sex, fractures after age 50 years (none, 0, 1, 2, ≥3), history of falls in the previous 12 months (none, 0, 1, 2, ≥3), femoral neck bone mineral density or T score, weight</td>
<td>Age, sex, height, weight, smoking, alcohol, diabetes, previous fracture, parental osteoporosis or hip fracture, living in a nursing or care home, history of falls, dementia, cancer, asthma or COPD, cardiovascular disease, chronic liver disease, advanced chronic kidney disease, Parkinson's disease, rheumatoid arthritis, systemic lupus erythematosus, malabsorption, endocrine problems, epilepsy or anticoagulant use, antidepressant use, steroid use, hormone replacement therapy</td>
</tr>
</tbody>
</table>

COPD=chronic obstructive pulmonary disease.

Table 1: Fracture risk prediction tools with at least one independent validation cohort
Figure 2: UK National Osteoporosis Guidelines Group assessment and treatment thresholds

Green denotes that an individual's risk lies below the intervention threshold—i.e., pharmacological intervention is not required. Red denotes that the fracture probability is consistently above the upper assessment threshold, and pharmacological intervention is strongly recommended in most cases. Patients with fracture probabilities in the intermediate category (yellow) should be considered for BMD assessment using dual energy x-ray absorptiometry, and fracture probability should then be recomputed using the Fracture Risk Assessment Tool. Pharmacological intervention would be recommended if the recomputed fracture probability exceeds the intervention threshold (dashed line). BMD = bone mineral density.
Mendelian Randomization (MR), an approach that uses genetic variants as instrumental variables (IV) for assessing the causal effect of a risk factor on an outcome from observational data [38]. Under certain assumptions, an un-confounded estimate of the causal effect of an exposure on an outcome can be made using the observed IV-exposure and IV-outcome associations [39]. Although the assumptions underlying the validity of MR estimates are often unverifiable, a series of recent papers have proposed sensitivity analyses to test the robustness of MR results when the assumptions fail [40].

Despite the well-established role of vitamin D deficiency in bone health, current MR analyses have not provided any evidence for a genetically predicted level of 25(OH)D to be associated with neither bone mineral density (BMD) nor bone metabolism markers [41–43]. One of the largest studies, used GWAS summary statistics based on 32,965 individuals from the Genetic Factors for Osteoporosis Consortium, and 142,487 individuals from the UK Biobank, and used the previous identified 4 loci as IVs, found that genetically predicted 1 standard deviation increment of 25(OH)D was not associated with higher femoral neck BMD (change per SD = 0.02, p = 0.37) or lumbar spine BMD (0.02, p = 0.49), and only suggestively with estimated BMD (−0.03, p = 0.02), which did not pass multiple correction [42]. It is
### Randomized controlled trial

**Participants**
- Estrogen therapy
- Placebo group
  - Serum estradiol increased
  - Serum estradiol unchanged
- Random assignment of treatment
- BMD increased
- BMD unchanged

### Mendelian randomization study

**Population**
- Random allocation of alleles
- CYP19A1 rs727479-AA
  - Serum estradiol higher
  - BMD higher
- CYP19A1 rs727479-CC
  - Serum estradiol lower
  - BMD lower

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**Assumption 1**
The genetic variant is reliably associated with the exposure

**Assumption 2**
The genetic variant is not associated with confounding factors

**Assumption 3**
The genetic variant affects the outcome only through the exposure and not through any other causal pathway

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**Fig. 2.** Assumptions underlying a Mendelian randomization study. BMD, bone mineral density; BMI, body mass index.
Similarities and differences between muscle fat and bone fat

Response to treatment

Resistance exercise
Impact exercise
1,25 Dihydroxy Vitamin D3
Estrogen/ more specific Rx
Alendronate
Resveratrol
Endocannabinoid receptor antagonists
Vibration (mechanical signals)
Where to in the future?

Key events that might alter muscle mass, strength and attenuation:

- Periods of bed rest – hospitalizations
- Sprains, strains and fractures
- Unsupervised weight loss (maximum weight)
- Elective surgery
- Retirement

Interventions – Create “noise” in muscle

Non-pharmacologic – Electrical stimulation
  - Low oscillation, high frequency vibration
  - Exercise - Tai Chi, resistance exercise, impact

Pharmacologic
“Everything that was bad for you is now good for you.”