Subjects and Measurements

The Nuts & Bolts of Research

Optimizing Subjects & Variables

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Today's Objectives

- **Selecting the Subjects** ✓
  - **Develop systematic approach to optimize subject selection**
- **Choosing the Measurements** ✓
  - **Understand the implications of exposure & outcome variable/measurement choices**
- **Application to a Real Research Question: The Osteoporosis in Men (MrOS) Study** ✓

Subjects and Variables:
The Nuts and Bolts of the Research Question

After deciding a great research question, figuring out WHO you want to study and WHAT you want to measure are the next key steps…

Optimizing Subject Selection:
A Delicate Balancing Act

- **Generalizability**
- **Accuracy**
- **Diversity**
- **Adequate Size**

- **Feasibility**
- **Accessibility**
- **Cost**
- **Time/Efficiency**

- At the end…Will I believe the findings and will I care?

Subject Selection: The Nitty Gritty

- **Explicitly Define Inclusion Criteria**
  - Demographic features (e.g., age, gender, race)
  - Clinical criteria
  - Geographic/administrative characteristics
  - Sampling time frame
- **Explicitly Define Exclusion Criteria**
  - Minimum number necessary to be feasible yet maintain generalizability to target population

Subject Sampling Techniques:

- **Convenience Samples**
  - **True convenience** (e.g., 25 clinic patients I know well)
  - **Consecutive** (e.g., next 100 patients undergoing liposuction)
- **Probability Samples**
  - **Simple random** (e.g., using random number table)
  - **Stratified or weighted random** (e.g., by gender)
  - **Cluster** (e.g., by clinic or neighborhood)

Subject Recruitment:

- **Successful Recruitment Generally Means…**
  - **↑ response, generalizable sample, adequate size**
- **For database only studies—***Usually not a big problem*
- **For hands-on studies** (*e.g., surveys, cohorts, trials*)
  - **Expect that it will be harder than you think!**
  - **Use reasonable inclusion/exclusion criteria**
  - **Acceptable subject burden/potential benefits**
  - **Efforts to minimize subject non-response**

Applying These Principles to Answer a Real Research Question:

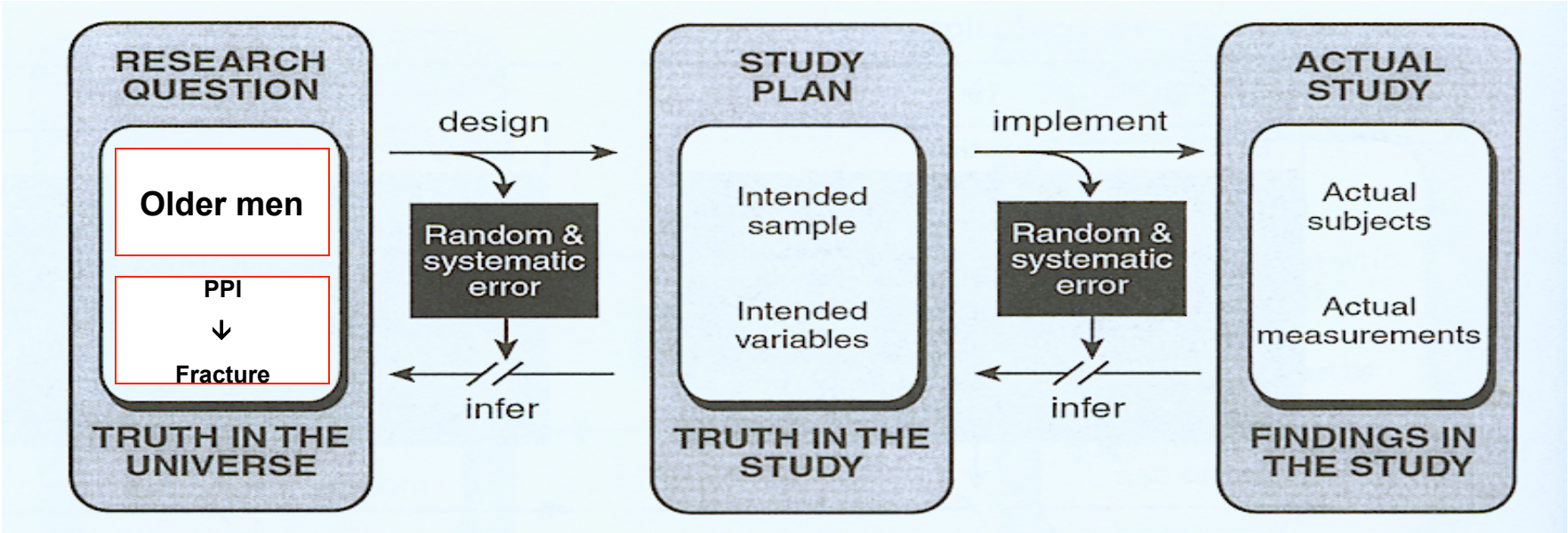
What is the association between PPI use and fracture risk in older men?

Elaine Wu, MD, Medicine R3

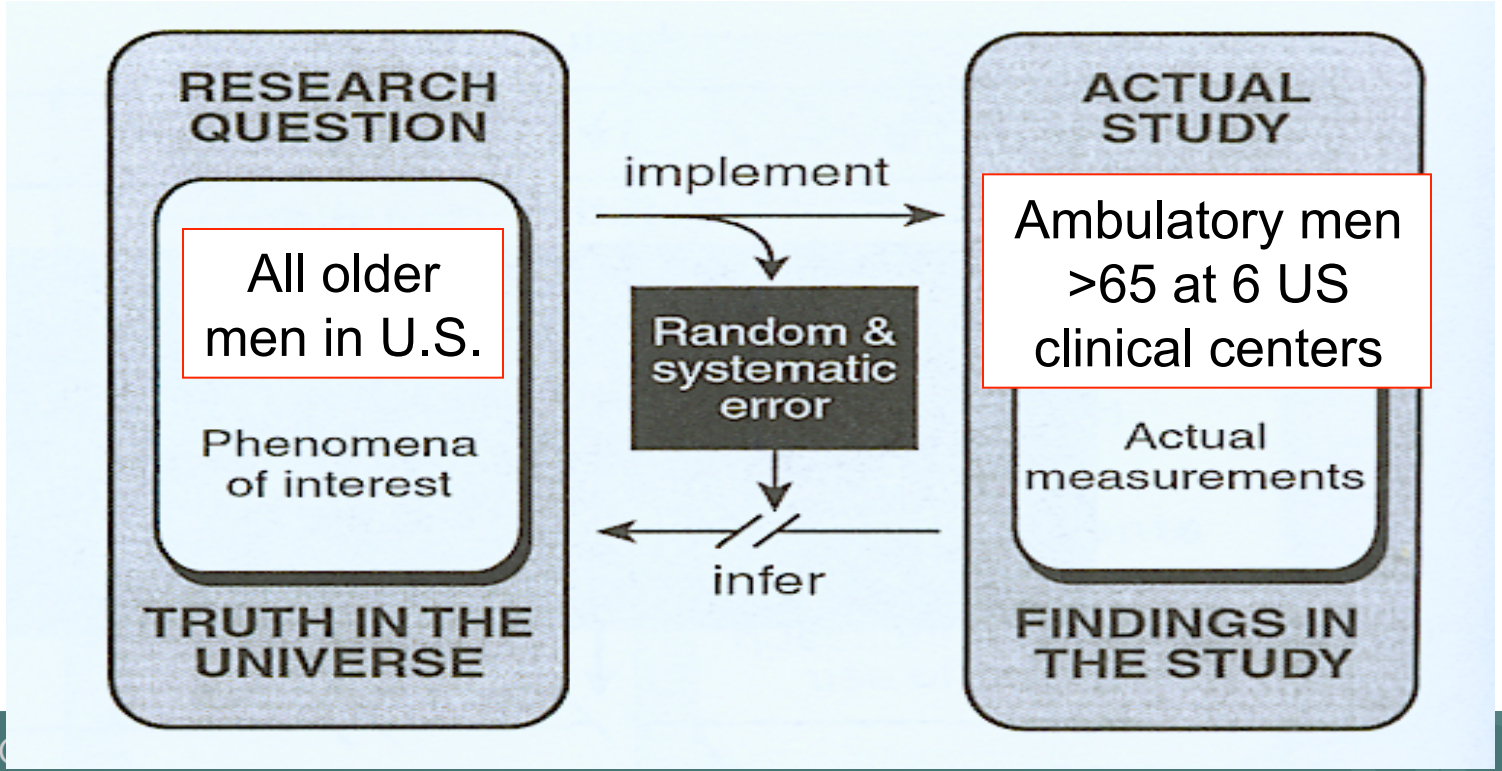
PPI Use and Osteoporosis

- **Proton pump inhibitors (PPIs) are commonly used to reduce gastric acid secretion**
- **Over 82 million PPI prescriptions written in 2004**
  - PPI over-the-counter since 2003
- **A cross-over trial of 18 postmenopausal women found that short-term PPI use (omeprazole, 20 mg/d) was associated with a 41% reduction in intestinal absorption of calcium (O'Connell, 2005)**
- **MrOS: prospective study of risk factors for osteoporosis among 5,595 men >65**

MrOS Study


RESEARCH QUESTION
Older men
PPI
↓
Fracture
TRUTH IN THE UNIVERSE
design
Random & systematic error
infer
STUDY PLAN
Intended sample
Intended variables
TRUTH IN THE STUDY
implement
Random & systematic error
infer
ACTUAL STUDY
Actual subjects
Actual measurements
FINDINGS IN THE STUDY

MrOS Study: Subjects



MrOS Study: Inclusion Criteria

- **Sampling Frame**: All ambulatory, independently living men
- **Inclusion criteria**:
  - Demography: ≥65 years, all race/ethnic groups
  - Geography/Administrative: Recruited from population-based listing (e.g. DMV records) at 6 US clinical centers
  - Time Period: Enrolled 2000-2006, one follow-up visit after 4.6 yr

MrOS Study: Exclusion Criteria

- **Exclusion criteria:**
  - Bilateral hip replacement (precludes DXA)
  - Life-threatening malignancy, dementia
  - Planning to move within 2 years

MrOS: Baseline Characteristics

Mean age (yr)	73.5
BMI	27.3
Dietary calcium (mg/d)	797
Calcium supplements	35%
Hypertension	50%
Diabetes mellitus	18%
Hip BMD (g/cm^2)	0.958
PPI use at baseline	8%
PPI use at follow-up	15%

Making the Measurements:

Implications for Exposure & Outcome Variable Choices

"The most elegant design of a clinical study will not overcome the damage caused by unreliable or imprecise measurement."

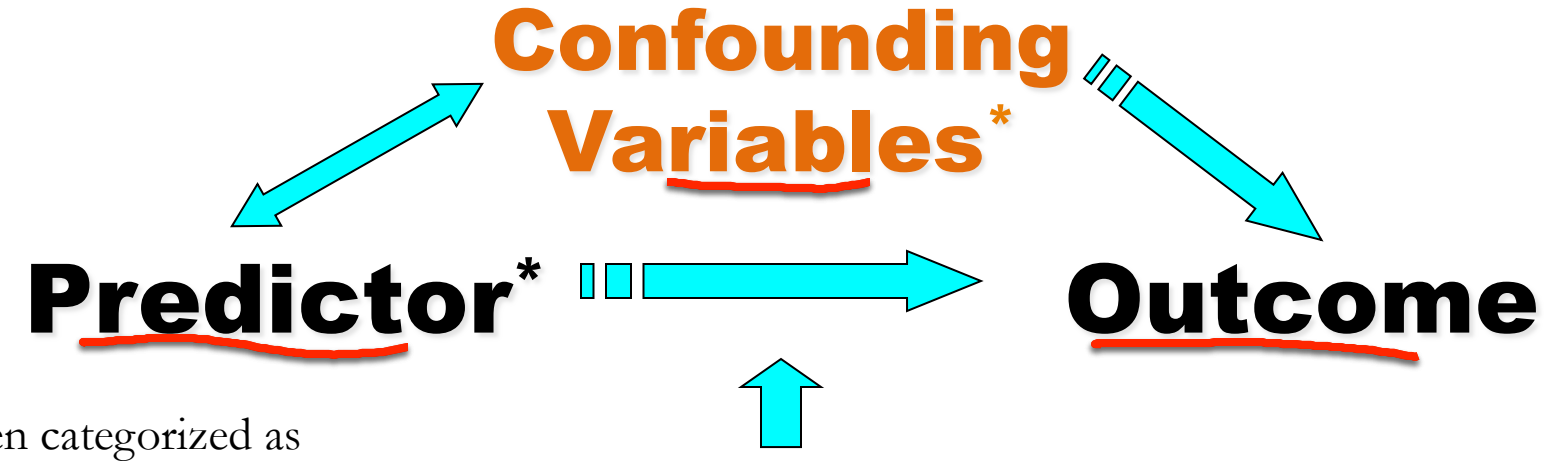
J.L. Fleiss (1986)

Fleiss, JL. *The design and analysis of clinical experiments*. pp. 1-5. 1986. John Wiley and Sons, New York.

"Accuracy must be balanced against practical considerations, and that method chosen which will provide the maximal accuracy within the bounds of the investigator's resources and other practical limitations." ***J.H. Abramson (1984)***

Abramson, JH. *Survey methods in community medicine* (3rd Ed.), p. 121. 1984. Churchill Livingstone, Edinburgh.

Planning the Measurements



*Often categorized as "exposures"

Additional "Exposure" Considerations

	Medication Examples
Dose Issues	
Cumulative exposure	Total # of pills
Exposure rate	# pills/day
Time Issues	
Start of exposure	Date of first use
When it ended	Date of last use
Exposure distribution	Daily vs. intermittent

Note: MrOS did not collect medication dose or duration of use

General Variable Types

Continuous

- Quantitative intervals with typical ranking
- Examples:
  - Cholesterol level
  - Number of drinks
  - Day supply of drug
  - Waist size
  - BMD

Categorical

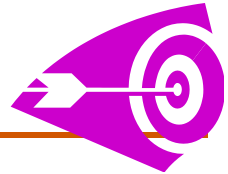
- Dichotomous (yes/no)
  (e.g., death, fracture, DM)
- Nominal (no order)
  (e.g., ethnicity, occupation)
- Ordinal (ordered rank)
  (e.g., NYHA HF Class I-IV)

Typical Data Sources

Goal: choose the source that gives data closest to the "gold standard" while being feasible to collect

- Survey/questionnaire
- Interviews
- Diaries
- Direct observation
- Environmental measurements
- Databases/registries
- Medical records
- Physiologic measures
- Biomarkers (e.g., DNA, sera)
- Imaging tests
- Pathology

General Measurement Goals…



- **You get the same result when measured repeatedly (i.e., maximize precision)—within the same subject, between subjects, and over time**
- **It represents what it's really supposed to be (i.e., maximize accuracy/validity) + high sensitivity & specificity**

The Measurement Spectrum

- **After deciding the exposure/outcome of interest, "measurement" includes:**
  - **Preparing written instructions for applying the method for measuring the variable**
  - **Actually doing the measurement method itself**
  - **Delineation of steps of preparing the collected data for analysis**
  - **Implementing quality control procedures throughout (i.e., making sure you get what you meant to get)**

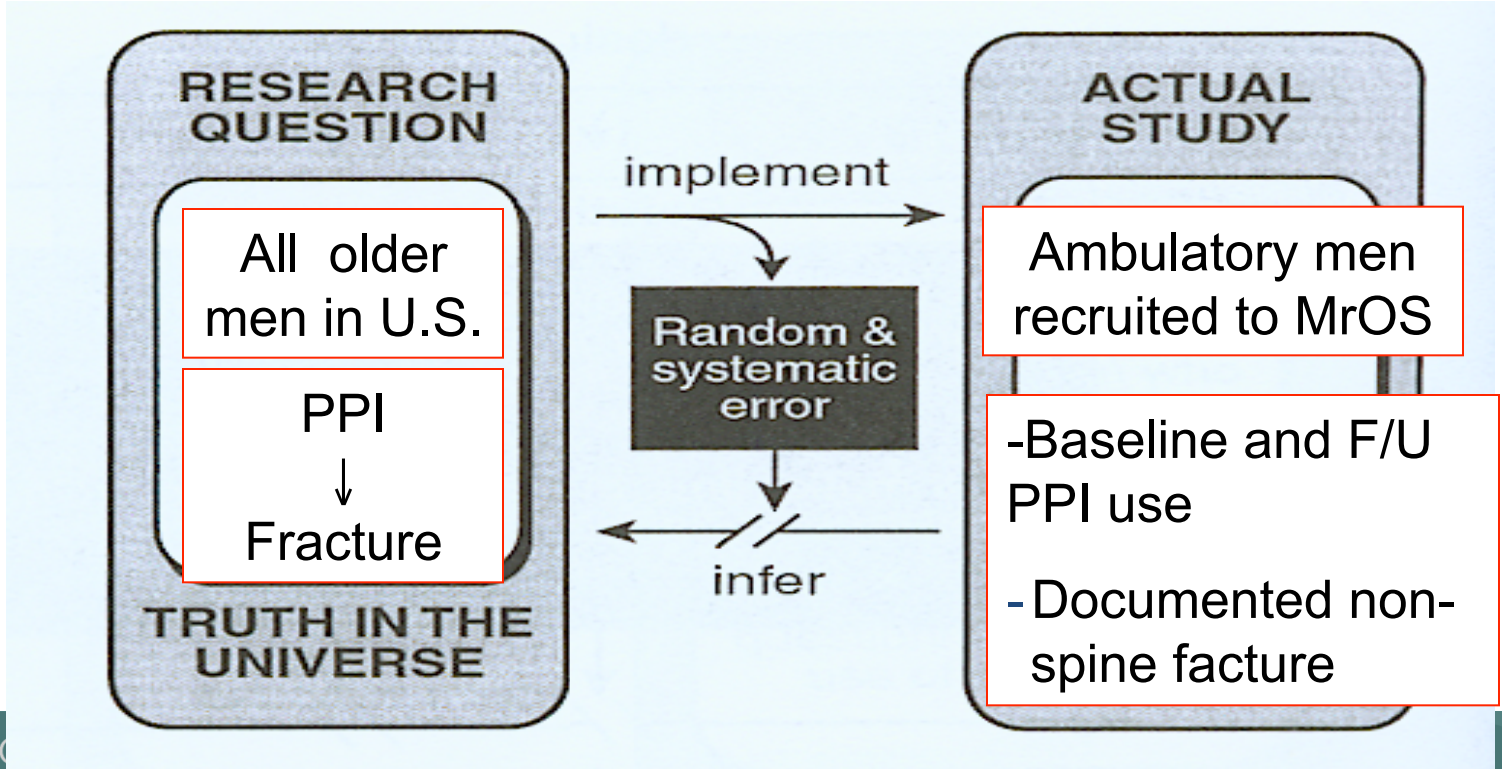
Improving Precision and Accuracy of Variables & Reducing Bias

- Standardize methods
- Pretest, pretest, pretest
- Refine/automate instrument
- Train & evaluate staff
- Timely editing, coding & correcting of forms
- Multiple measurements
- Use or validate against "gold standard"
- Less obtrusive measures
- For outcomes, blinding to exposure status
- Institute quality control measures during data collection, processing, and analysis

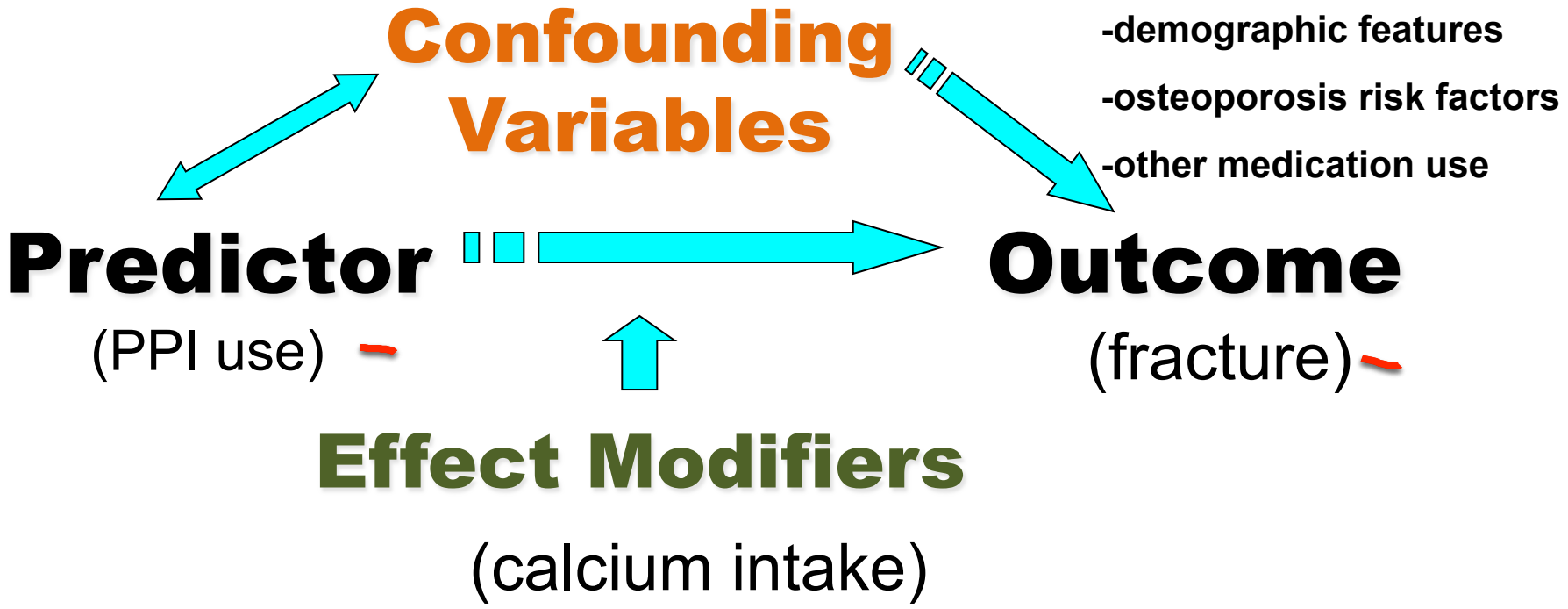
Applying These Principles to Answer a Real Research Question:

What is the association between PPI use and fracture risk in older men?

MrOS Study: Measurements



MrOS Measurements



Exposure: PPI Use

- **PPI Use (main predictor)**
  - **Baseline "PPI use"—**
    - **Self-reported use (any) in preceding 1 month**
  - **Longitudinal "PPI use"—time-dependent exposure based on PPI at follow-up visit**
- **Validation study of method for baseline use**
  - **Chart review of random sample of "users" & "non-users": 94% raw agreement (κ=0.90)**

Outcome: Fracture

- **Non-spine fracture (primary outcome)**
  - **Identification method: self-report**
    - Post card reporting of falls and fracture every 4 months
  - **Validation method: masked review and adjudication of objective documentation**
    - Obtain pre-operative radiology reports, medical records
    - Central MD and/or radiologist review
    - Obtain original radiographs if needed
    - Questionable or uncertain events reviewed by Endpoints Committee
- **Hip BMD using DXA (secondary outcome)**

What Did We Find?

- **Among 5,595 ambulatory men, longitudinal use of PPI therapy was associated with…**
  - Lower BMD among PPI users (0.946 vs. 0.958, p=0.04)
  - Trend towards increased fracture risk among PPI users (RH=1.26, 95% CI: 0.88, 1.75)
  - Increased in fracture risk (RH=1.78, CI: 1.16, 2.73) among men with low calcium intake (interaction between calcium intake and effect of PPI use on fracture risk, $p<0.05$)
- **Similar findings in WHI, other cohorts. Lead to FDA warning about fracture risk with long term PPI use…**

Thanks for Listening!