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

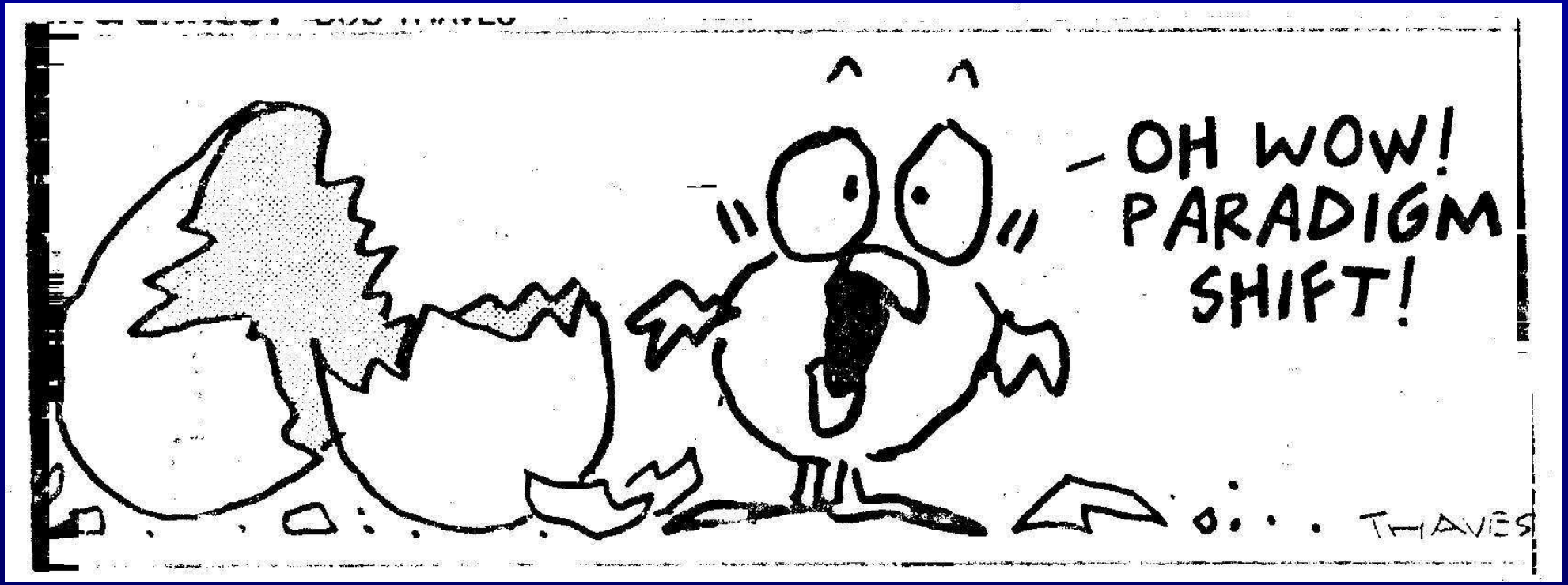
SMOKING
EXERCISE
DIET (OVER- AND UNDER-NUTRITION)
DIET QUALITY (ESSENTIAL VITAMINS)
ALCOHOL INTAKE
DRUG INTAKE (OTC AND PRESCRIPTION)
SLEEP
STRESS
PSYCHOSOCIAL
MARITAL STATUS

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

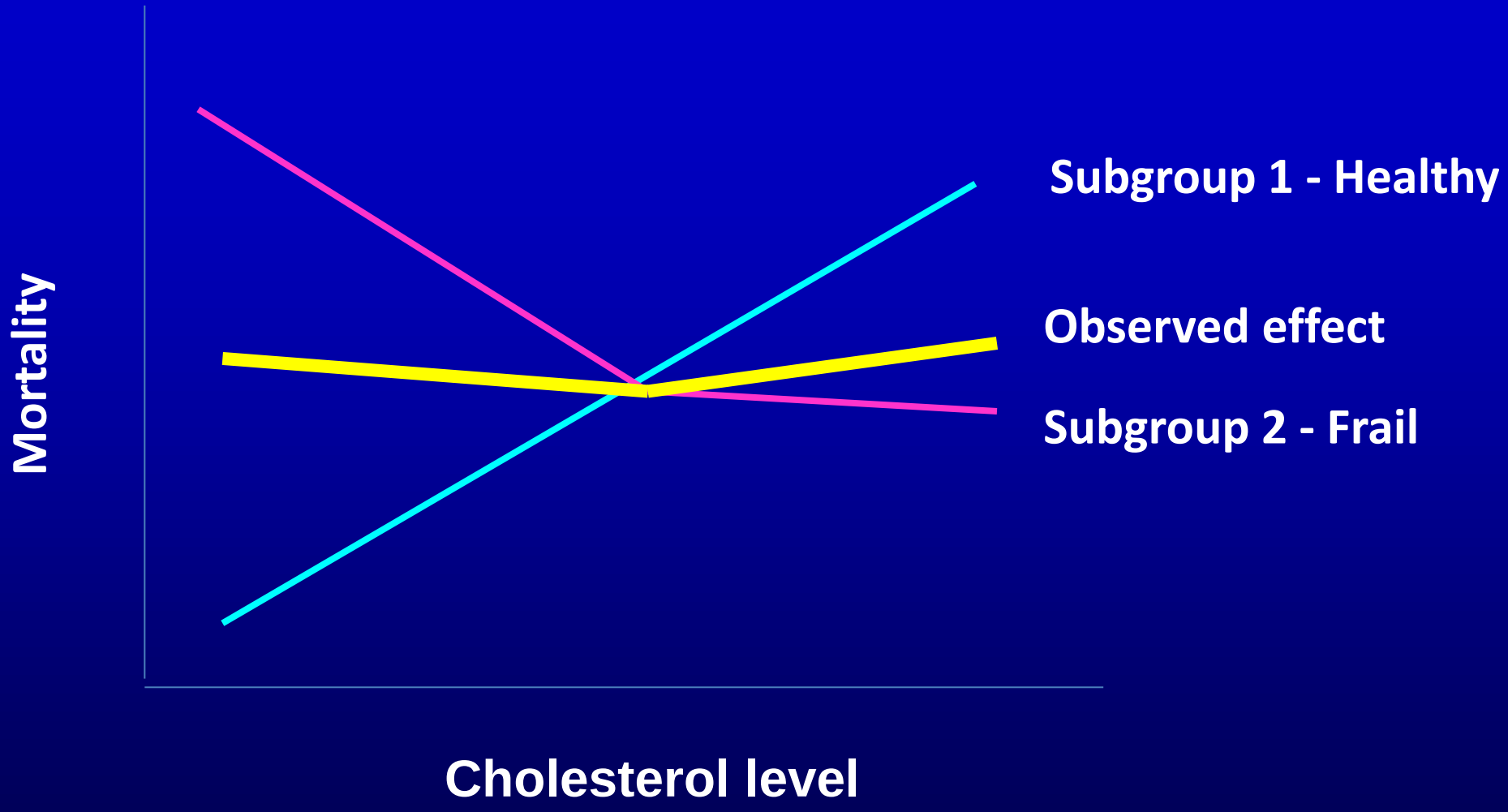
WITHIN THE INDIVIDUAL

MICROBIOME
INFLAMMATION (ACUTE PHASE PROTEINS)
MULTIMORBIDITY (DIABETES, HTN)
GENDER
RACE
ALLERGIC PROFILE
ADL/IADL
STRENGTH



Interactions-think influential subgroups fooling with your results!!!!

Effects obscured by interaction



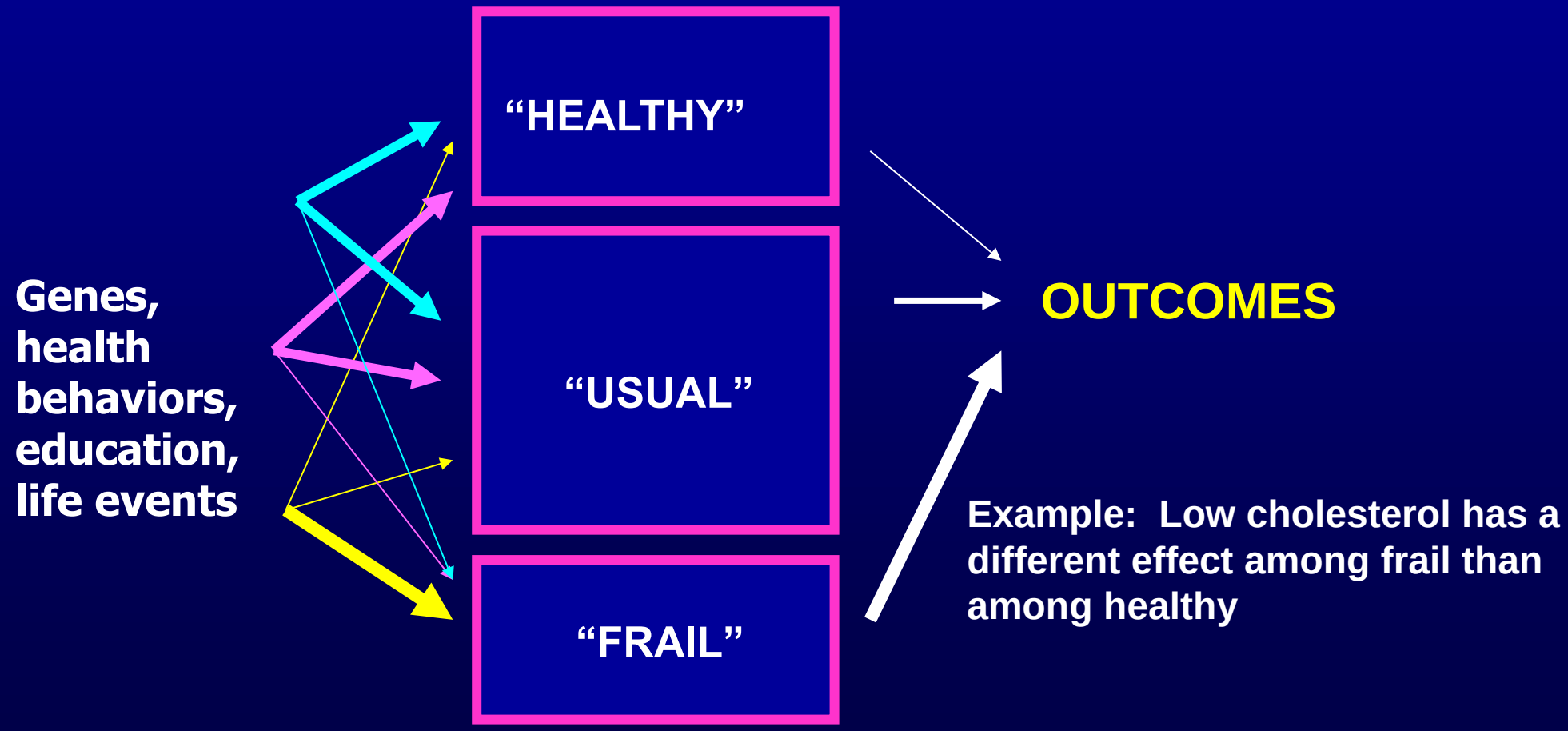
Does adjustment for confounders address this problem?

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.

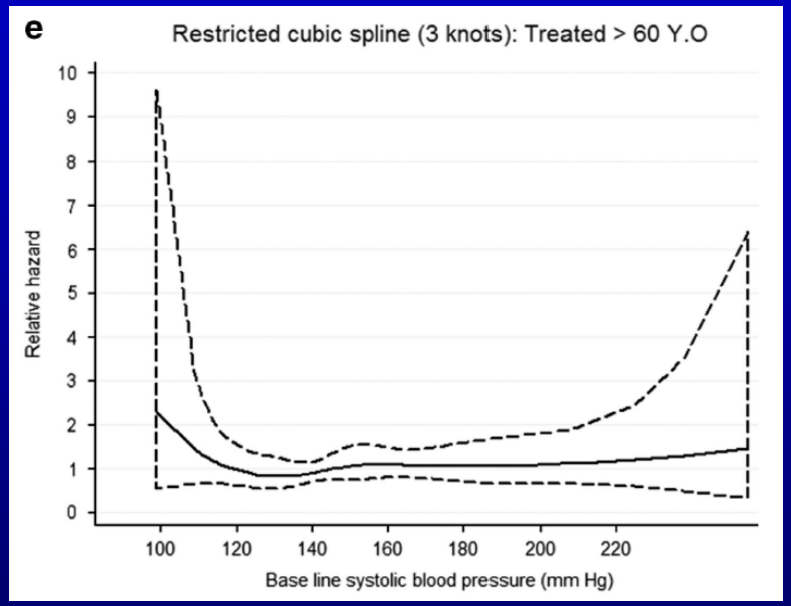
As populations age, there are more distinct differences between subgroups.

Interactions may become more common in old age. Lack of identification of these subgroups can lead to false results and inappropriate preventive strategies.



Blood pressure example:

Literature:

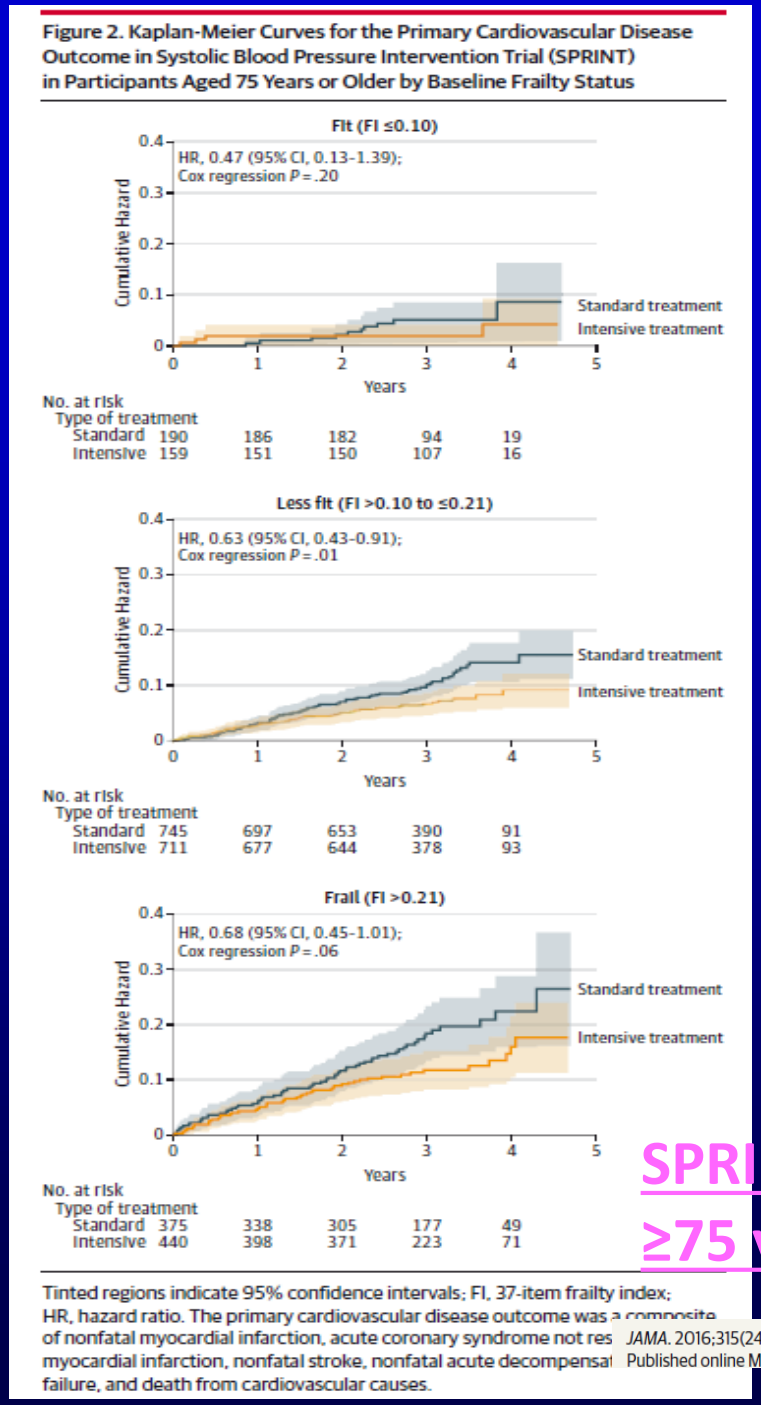


Journal of Human Hypertension (2017) **31,** 415–421

POLICY:

Concern that 2014 initiation/treatment recommendations differ for persons aged 60 or older

IS DIFFERENTIAL TREATMENT BY AGE OR FUNCTION WARRANTED?

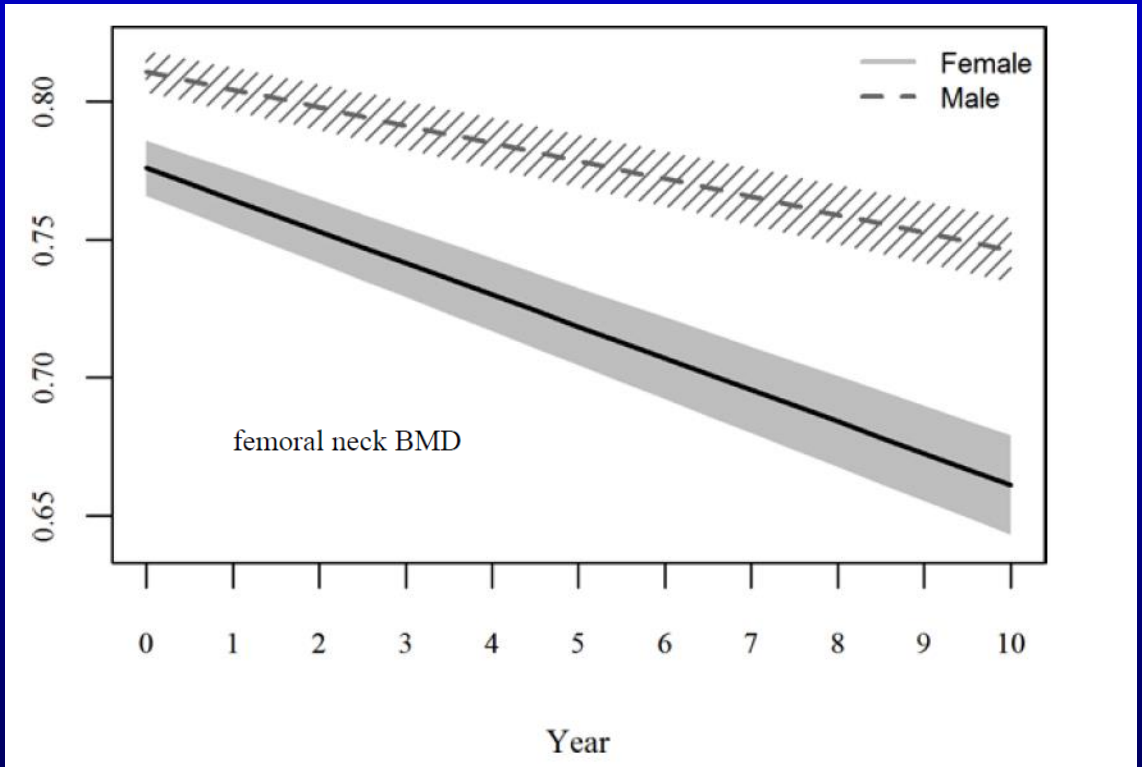


JAMA. 2016;315(24):2673-2682. doi:10.1001/jama.2016.7050
Published online May 19, 2016.

SPRINT TRIAL
≥75 years old

Interaction by HIV status on gender for femoral neck BMD

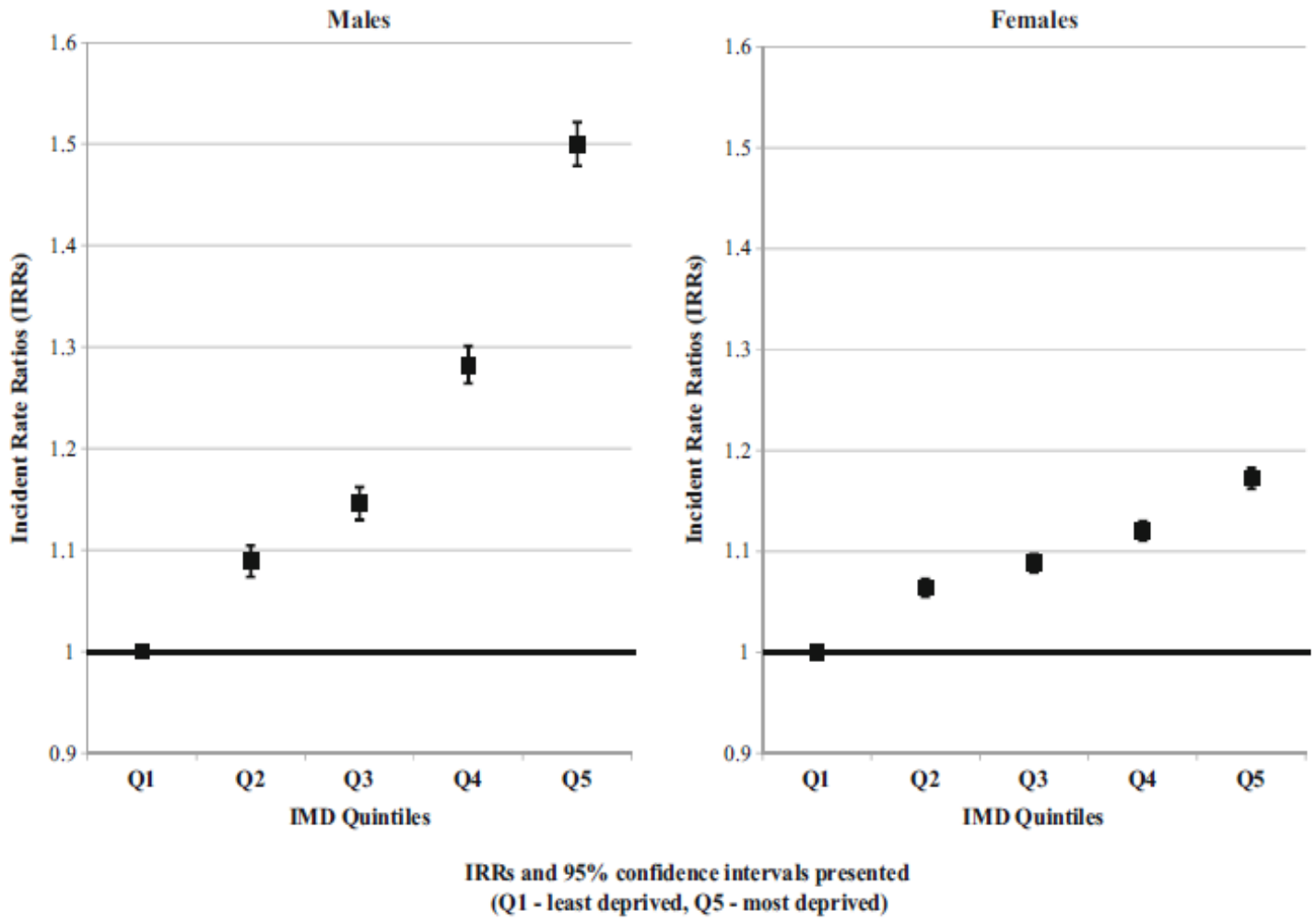
Bone Mineral Density Declines Twice as Quickly Among HIV-Infected Women Compared to Men



J Acquir Immune Defic Syndr. 2018 March 01; 77(3): 288–294

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

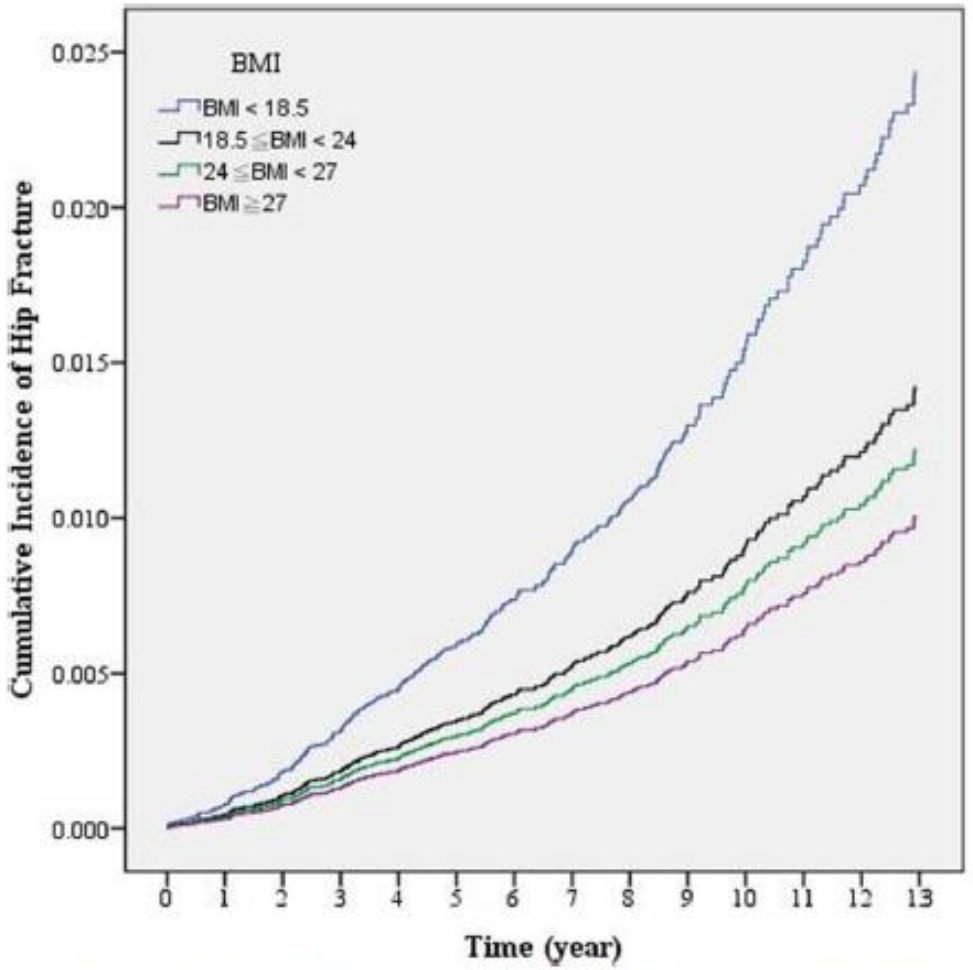
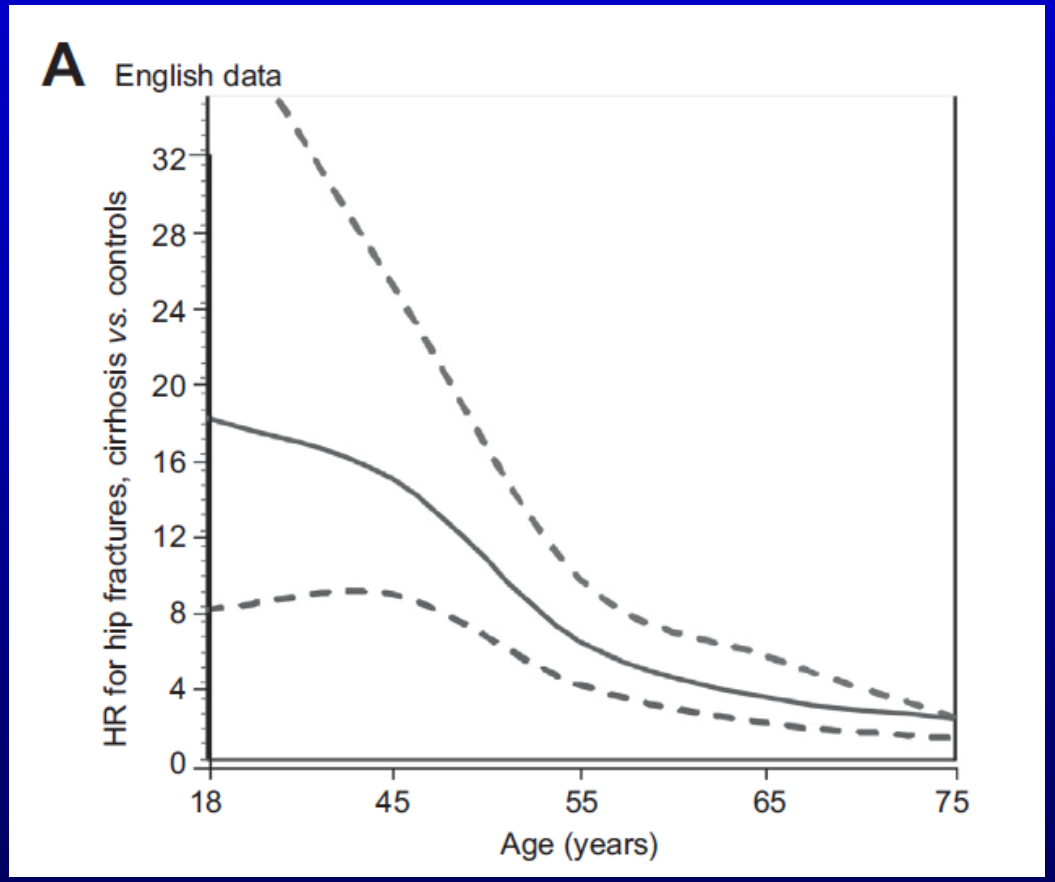
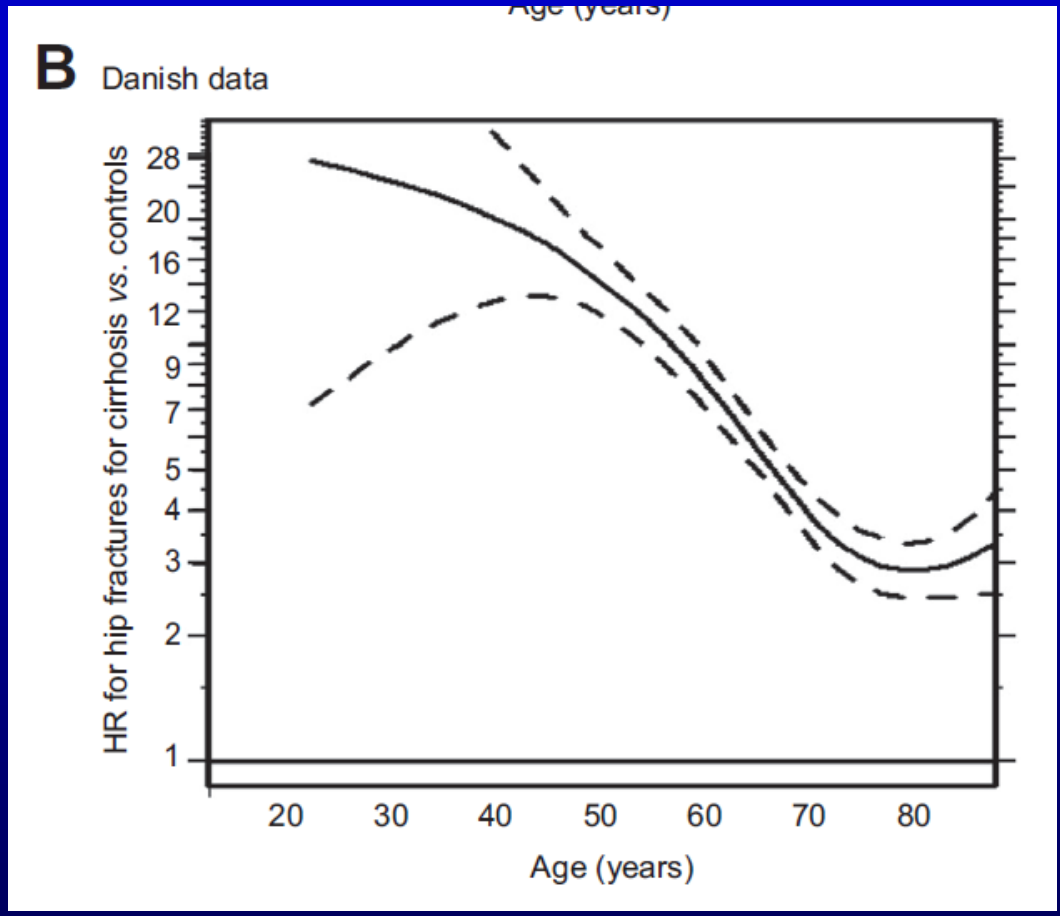


Fig. 1 Comparisons of hip fracture risk among different BMI groups in patients with diabetes (After controlling for sex, age, urbanization of residence area, monthly salary, CCI, DCSI and weekly energy expenditure through exercise)

Interaction of age and cirrhotic status for hip fracture





Journal of Hepatology **2018** vol. 69 | 697–704

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).

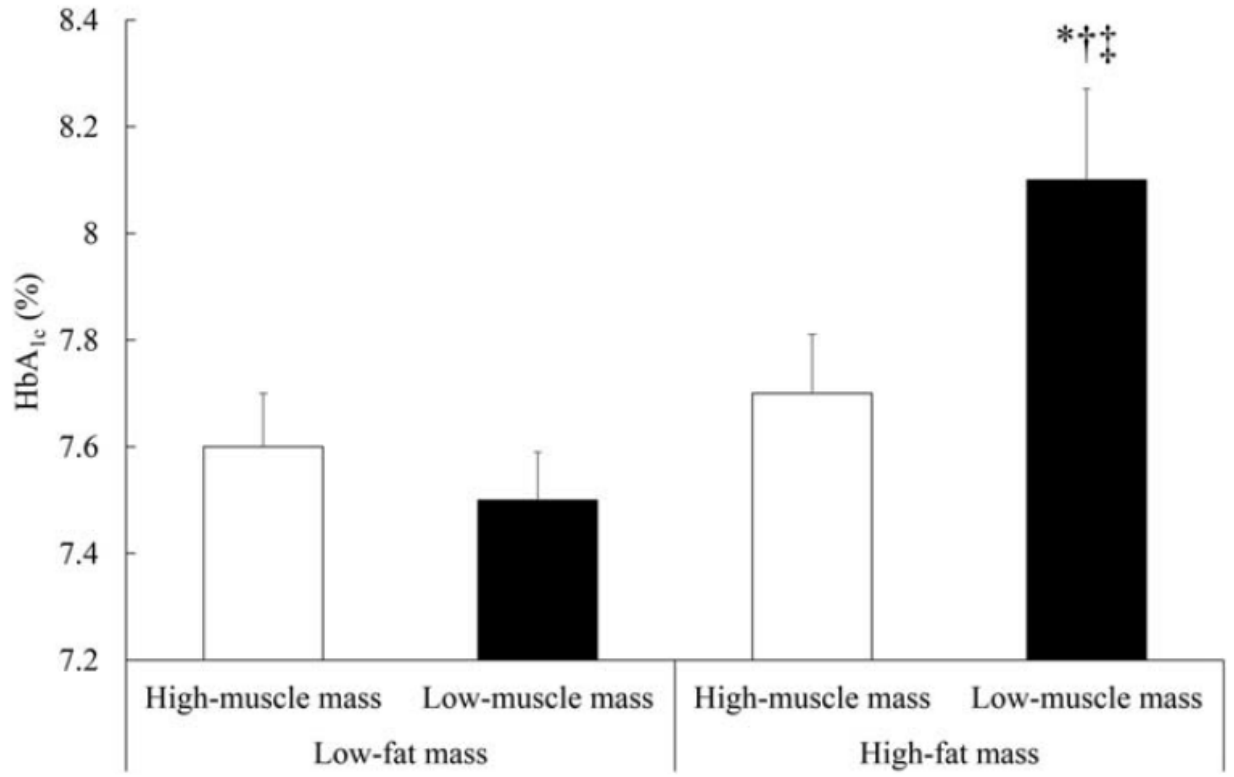
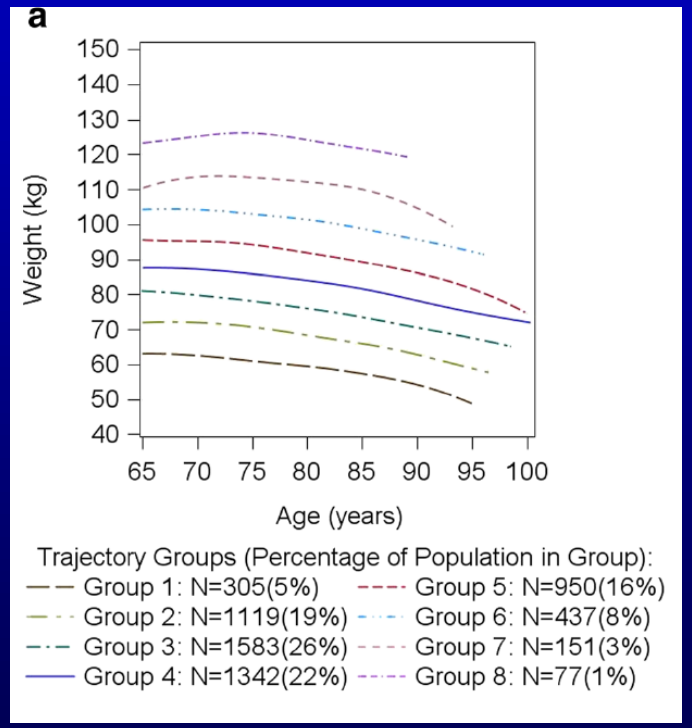
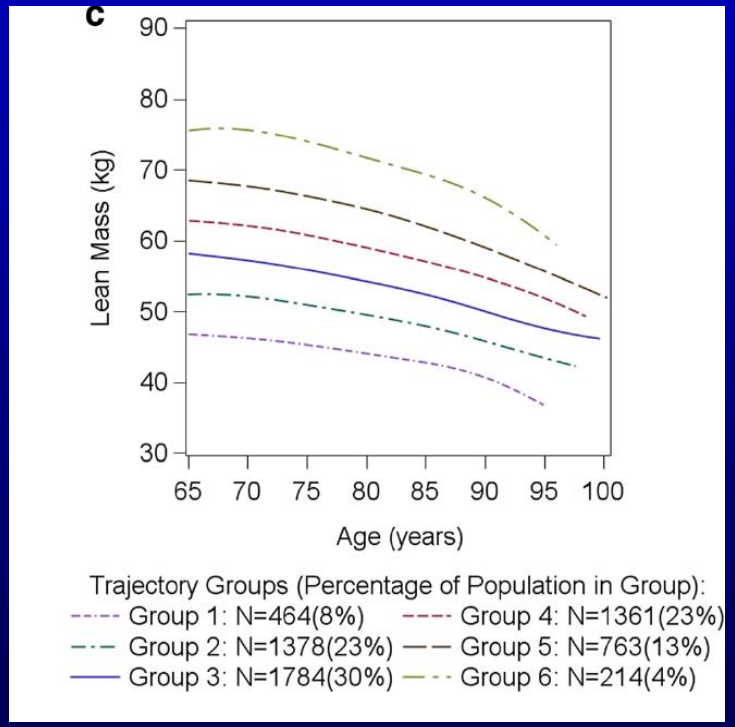


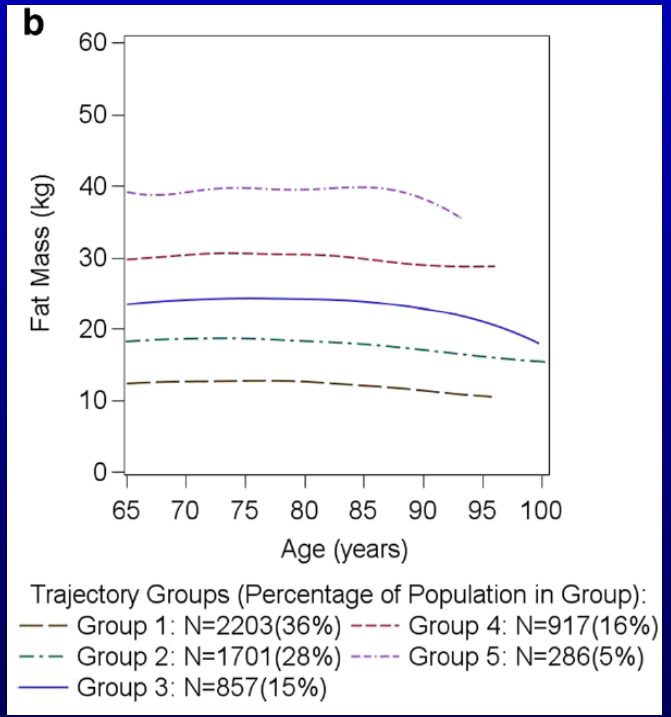
Figure 1 Interaction between fat mass and muscle mass on HbA_{1c} at baseline after adjusting for age, duration of diabetes, sex, medication, dietary protein, fat, and carbohydrate intake. Data are reported as means ± standard error of the mean. There was a significant interaction effect between fat and muscle mass ($P = 0.009$). Bonferroni-adjusted pairwise comparison showed that participants with high fat and low muscle mass had higher HbA_{1c} 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







Laddu *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.

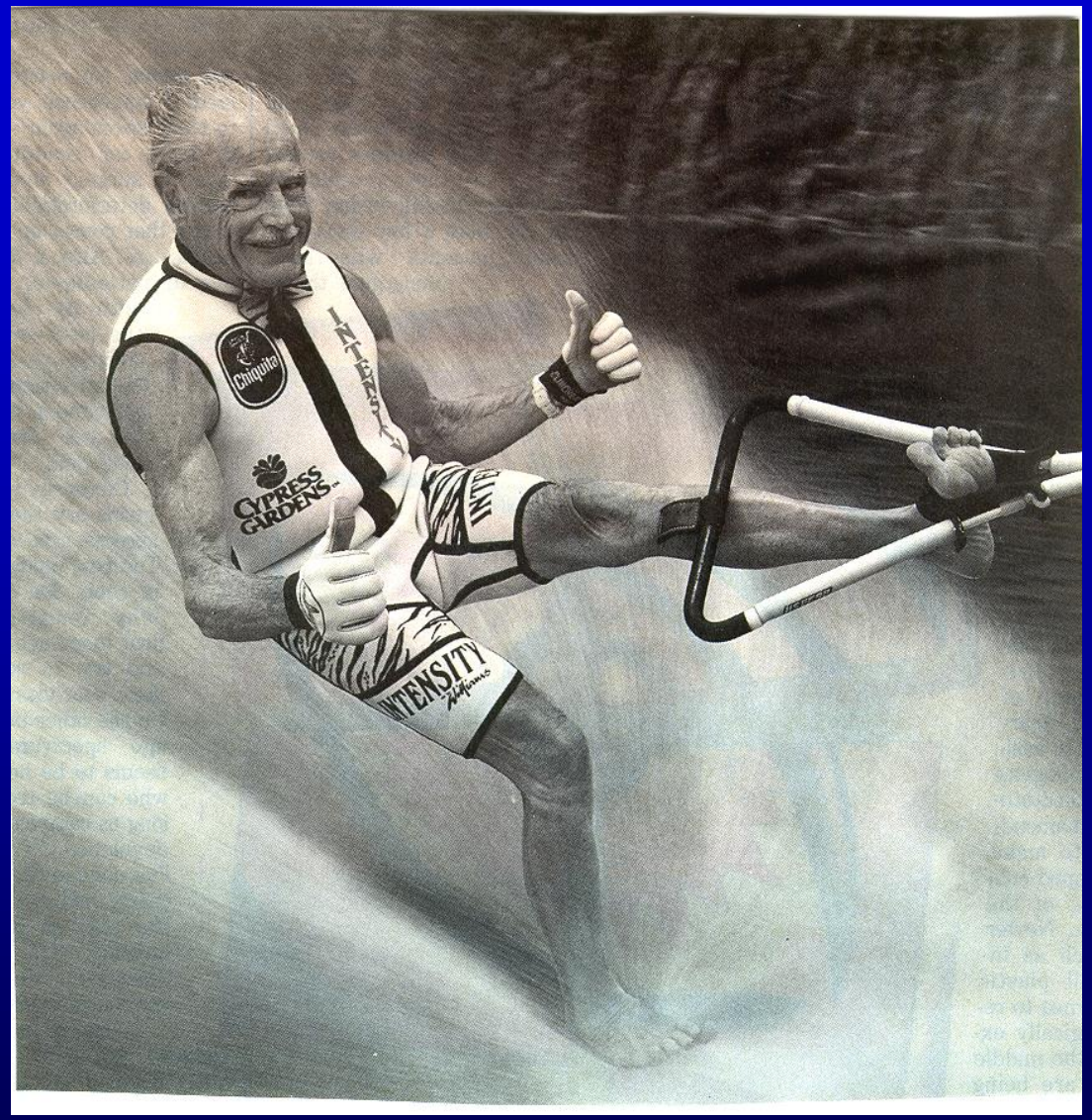
Similar gaps apply to muscle and adipose interactions.

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?

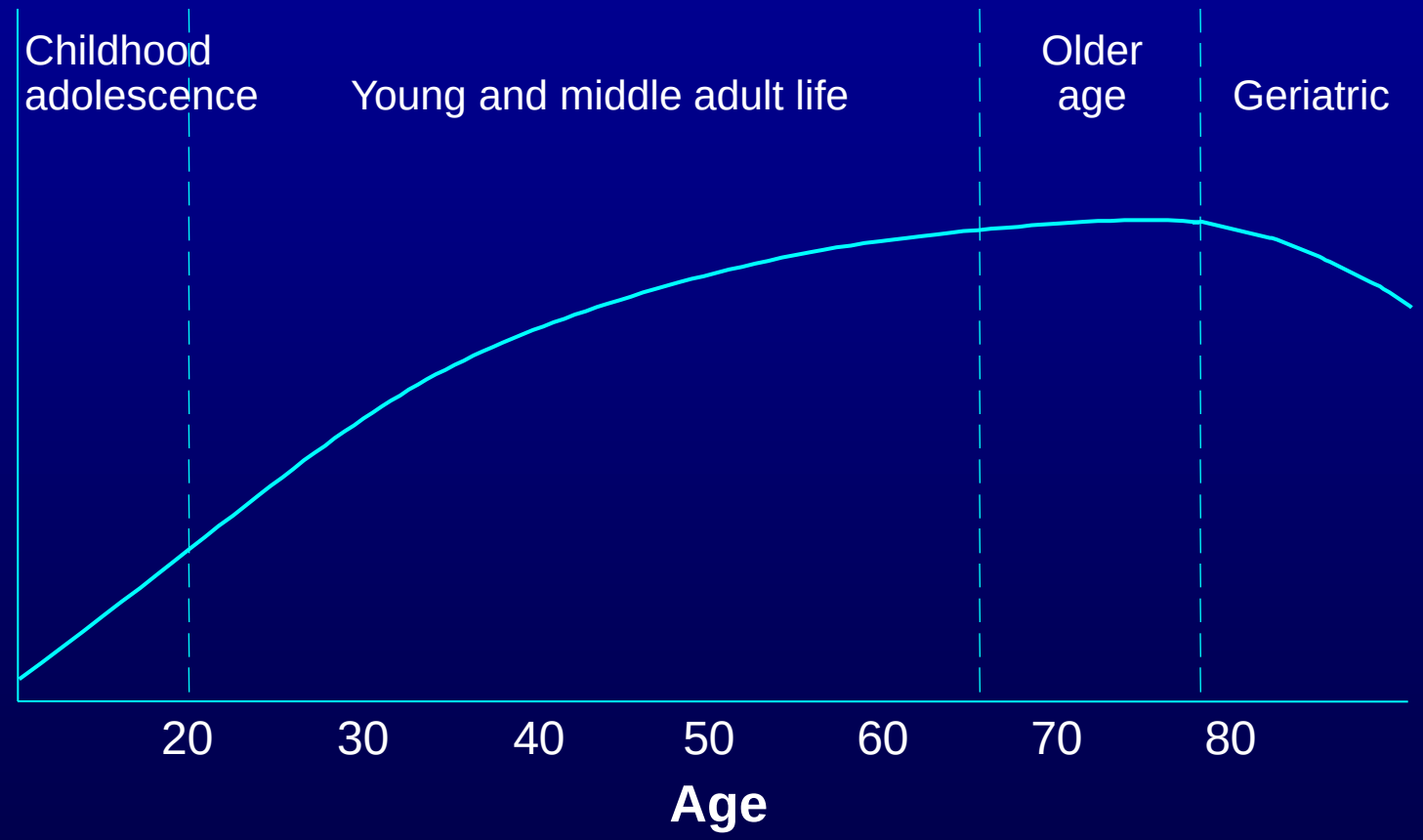
In general, the effect of one exposure may depend in some way on the presence or absence of another exposure.

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



SPECIAL ISSUES IN OLD AGE:

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

PROXIMATE EVENTS LIKE DISEASE AND DISABILITY

MULTIMORBIDITY

CRITICAL WINDOWS FOR EXPOSURES

Int J Obes (Lond). 2017 February ; 41(2): 255–261. doi:10.1038/ijo.2016.209.

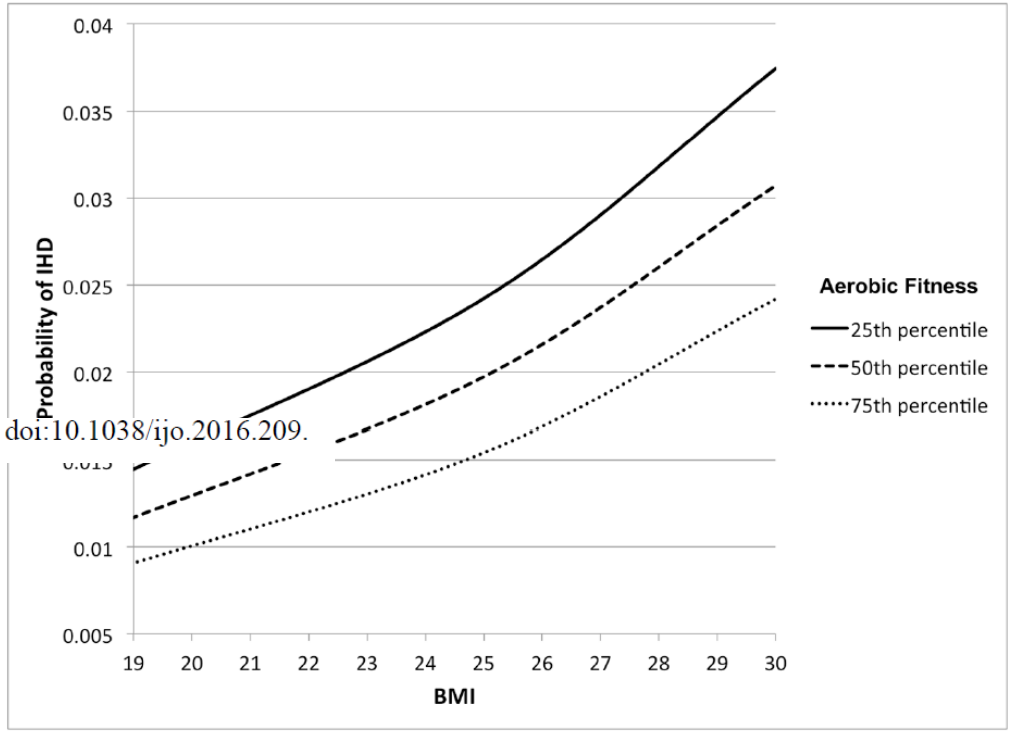


Figure 1.
Probability of IHD by aerobic fitness and BMI in 18-year-old men with mean follow-up of 25.7 years (maximum age 62 years).

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 ($P_{interaction}<0.001$) (i.e., their combined effect was less than the product of their separate effects), and no interaction on the additive scale ($P_{interaction}=0.40$). 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.

normal BMI. Low aerobic fitness and high BMI had a negative interaction on the multiplicative scale ($P_{interaction}<0.001$) (i.e., their combined effect was less than the product of their separate effects), and no interaction on the additive scale ($P_{interaction}=0.40$). Figure 1

Biomarkers Principal components analysis to identify subgroups

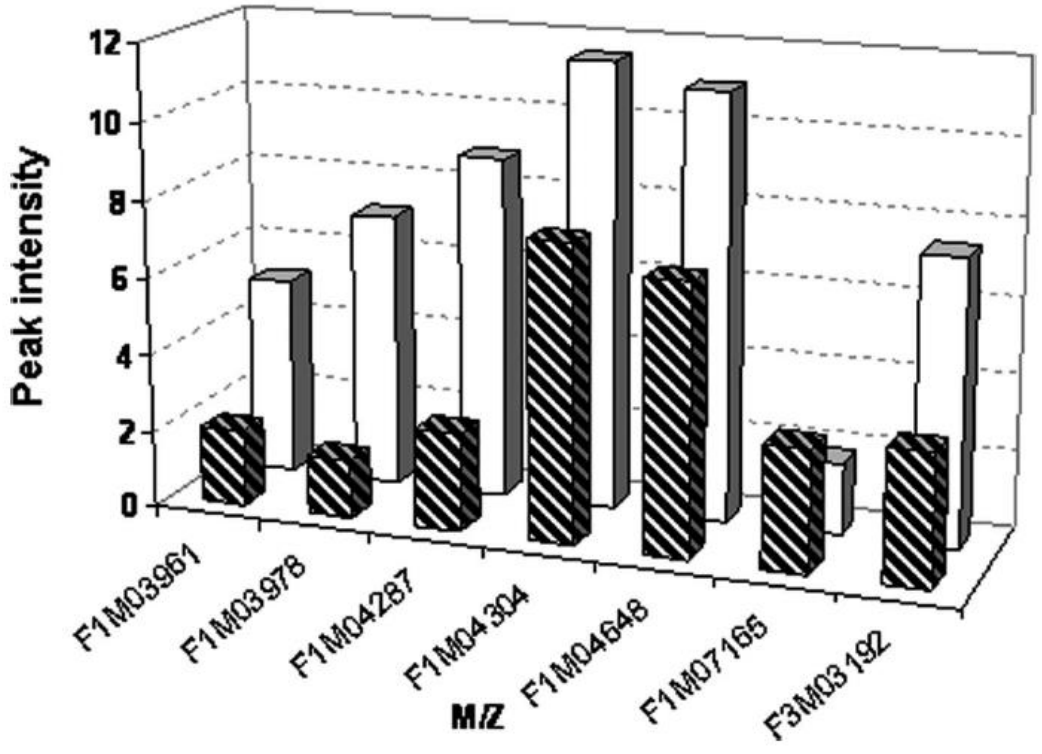
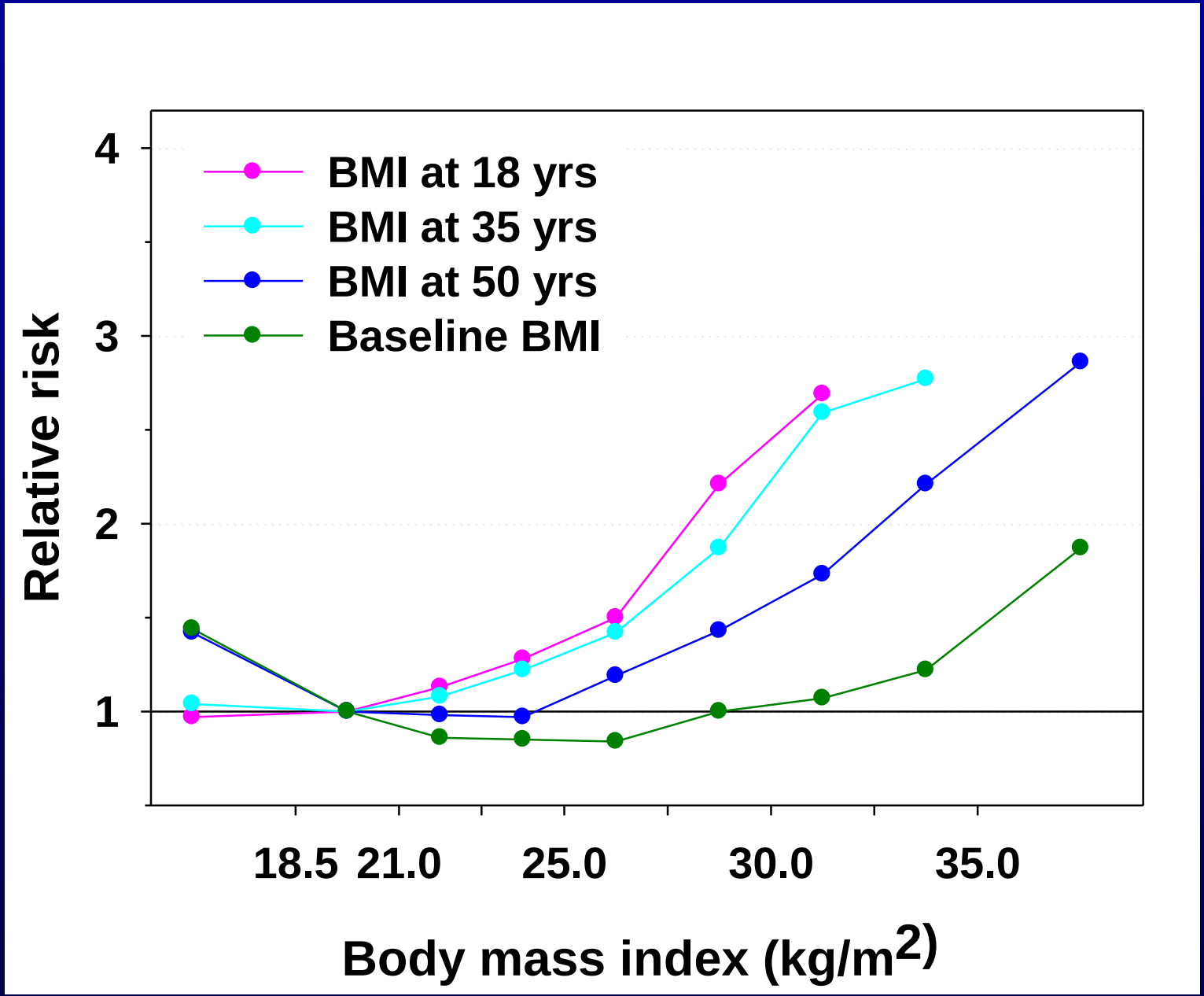


FIG. 5. Diagnostic fingerprint of postmenopausal women with high (striped bars) and low/normal (white bars) bone turnover. The median fold changes in the SELDI peak intensities are shown.

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 23, Number 7, 2008
Published online on February 25, 2008; doi: 10.1359/JBMR.080235

Comparison of risks by age, women



Why gender differences in energy expenditure?
If not exercise, what preserves muscle and muscle function in old age?

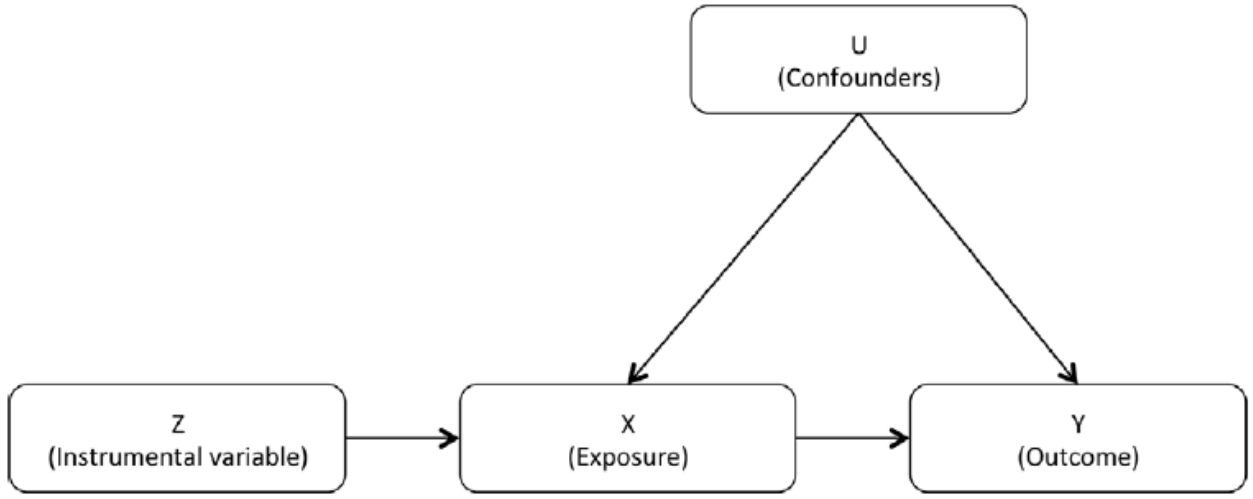


Fig. 1. The basic instrumental variable (IV) model depicted using a directed acyclic graph. Z: the instrumental variable, X: the exposure of interest (such as a putative risk factor), Y: the outcome of interest (such as a disease), U: one or more measured or unmeasured confounders.

Cornish, A.J., Molecular Aspects of Medicine, https://doi.org/10.1016/j.mam.2019.01.002

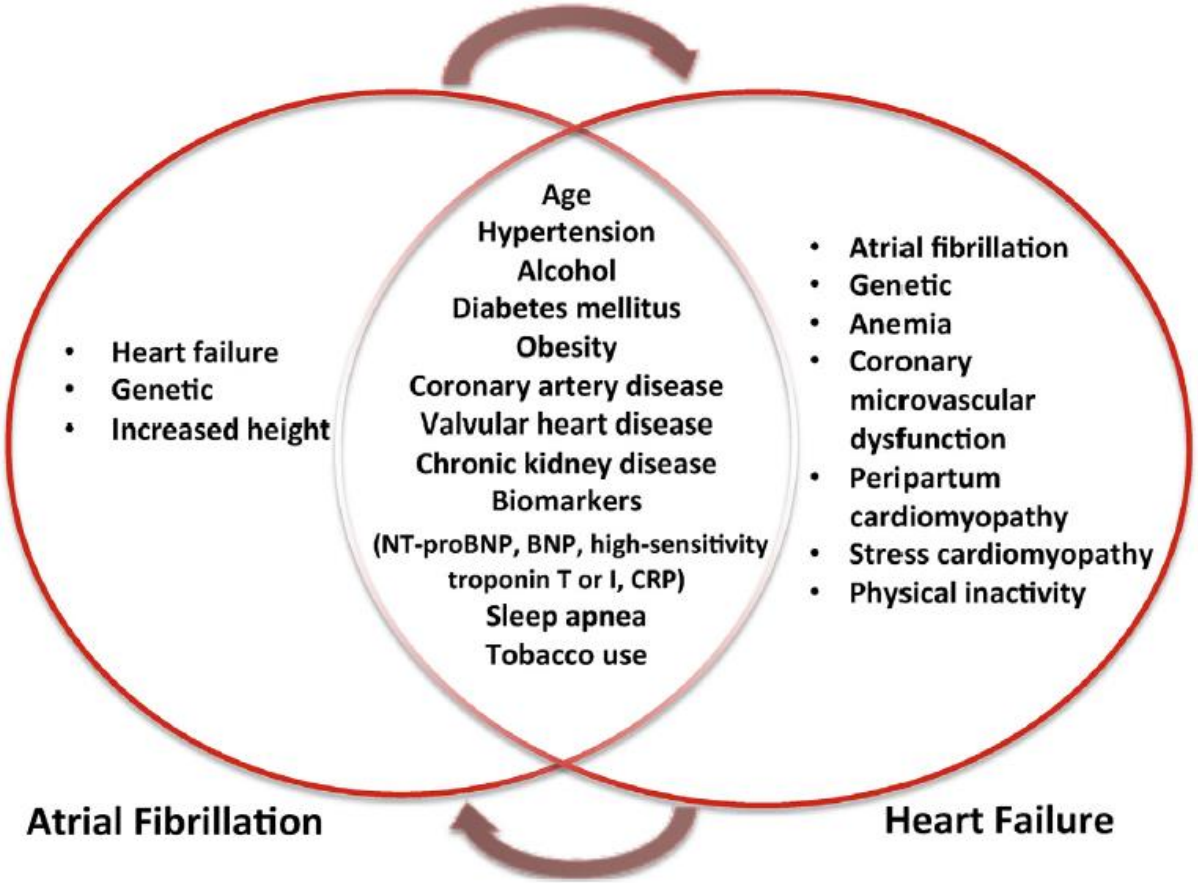


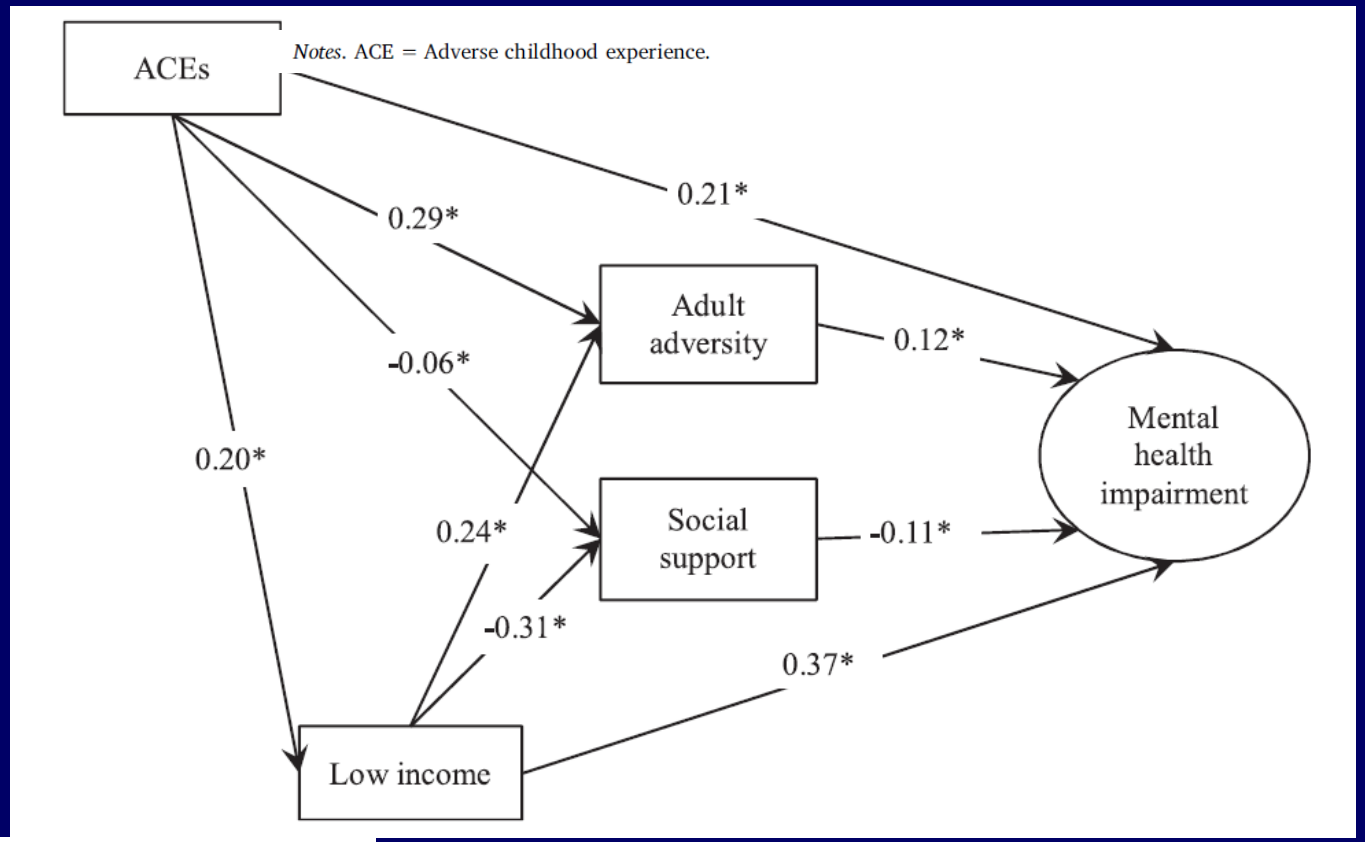
Fig. 1. Risk factors for the development of atrial fibrillation and heart failure in women. CRP, C-reactive protein. (*Data from* Refs.[12,68,69])

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

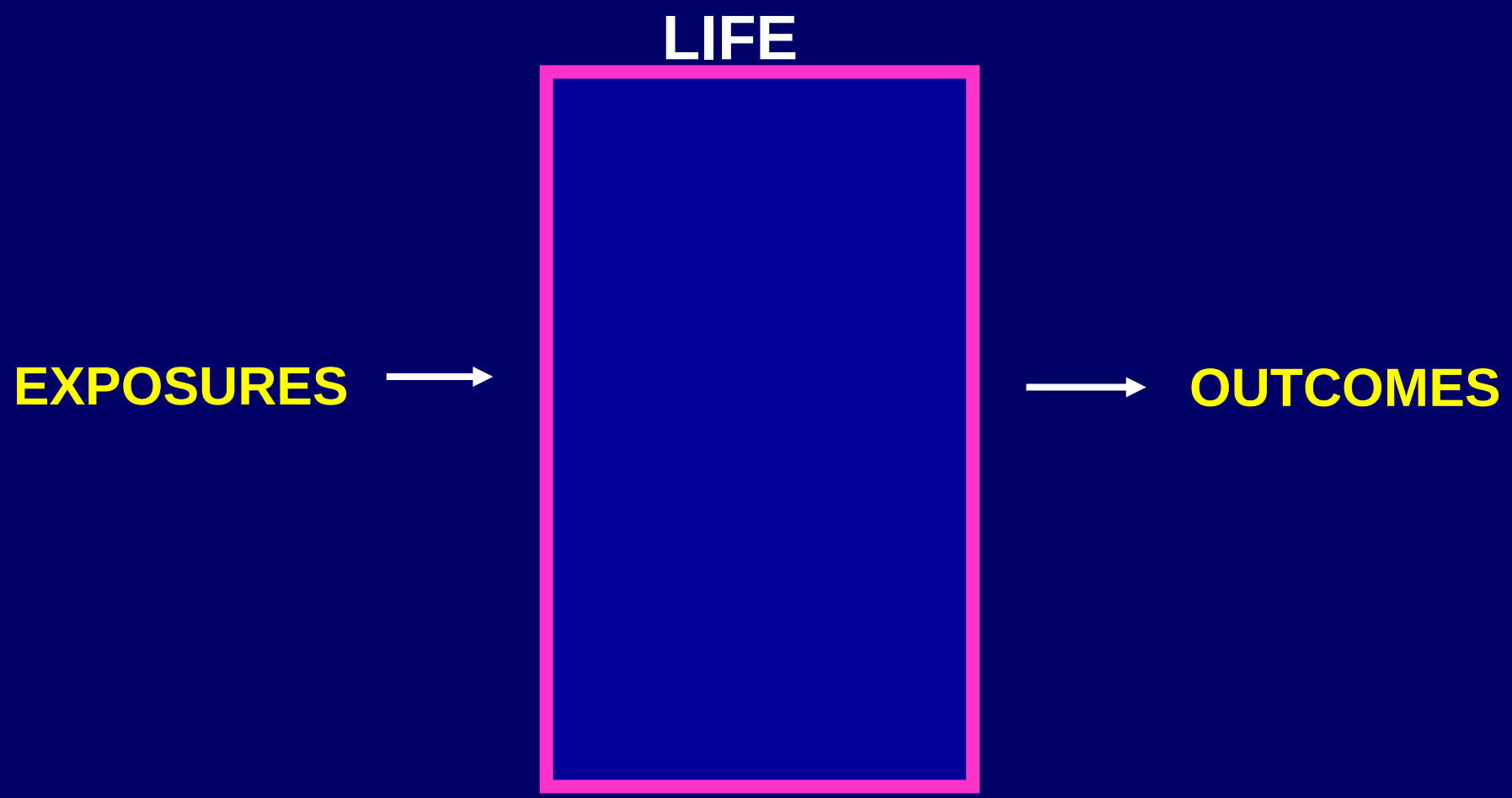


Notes. ACE = Adverse childhood experience.

Oval represents latent construct and squares represent measured indicators.

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

Why are interactions important?



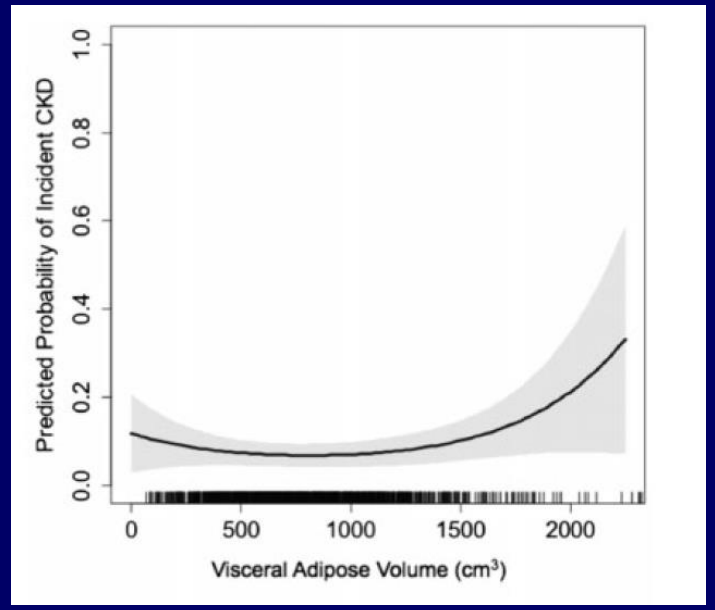
SPECIAL ISSUES IN OLD AGE:

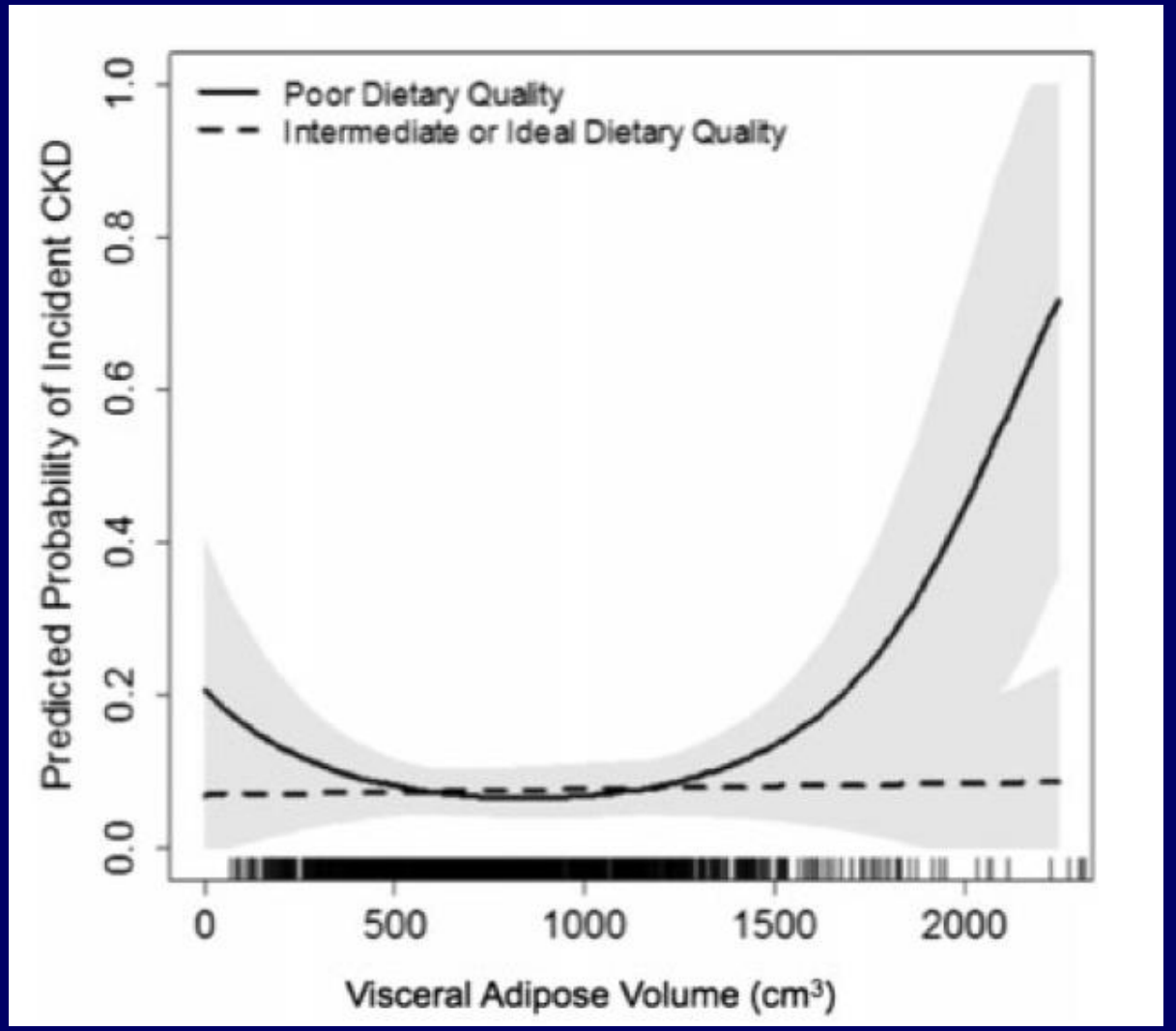
REVERSE CAUSATION (LOW BLOOD PRESSURE IS BAD FOR YOU AND HIGH BLOOR PRESSURE IS PROTECTIVE) WEIGHT, CHOLESTROL

PROXIMATE EVENTS LIKE DISEASE AND DISABILITY

MULTIMORBIDITY

CRITICAL WINDOWS FOR EXPOSURES





Nephrol Dial Transplant (2018) 33: 992–1001
doi: 10.1093/ndt/gfx230

Int J Obes (Lond). 2017 February ; 41(2): 255–261. doi:10.1038/ijo.2016.209.

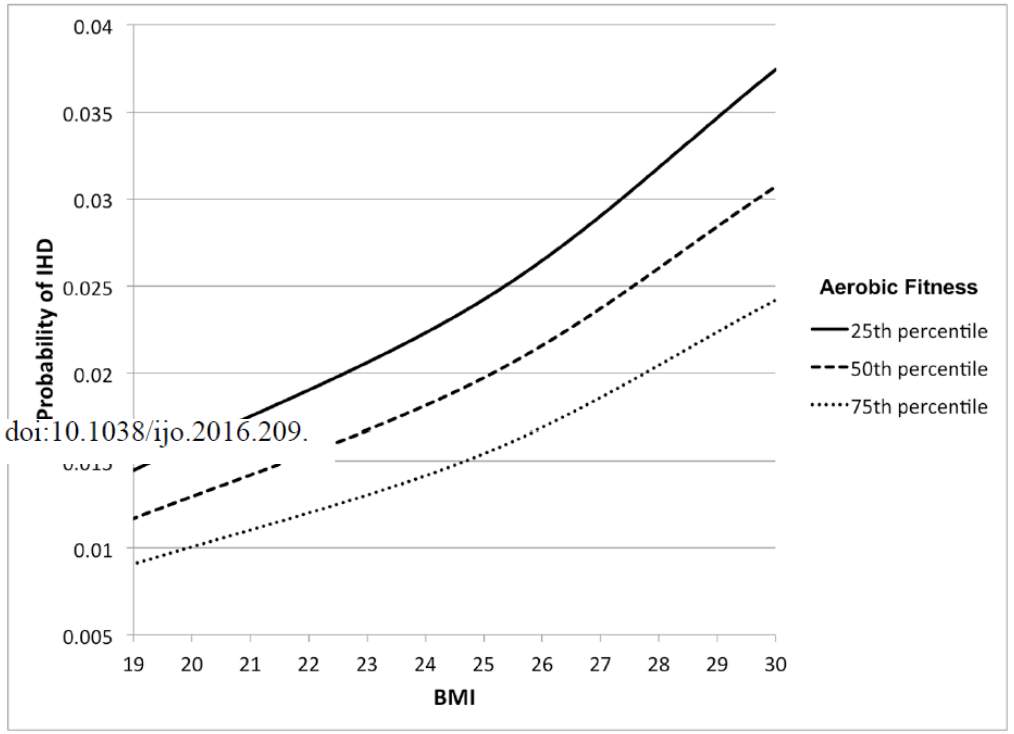


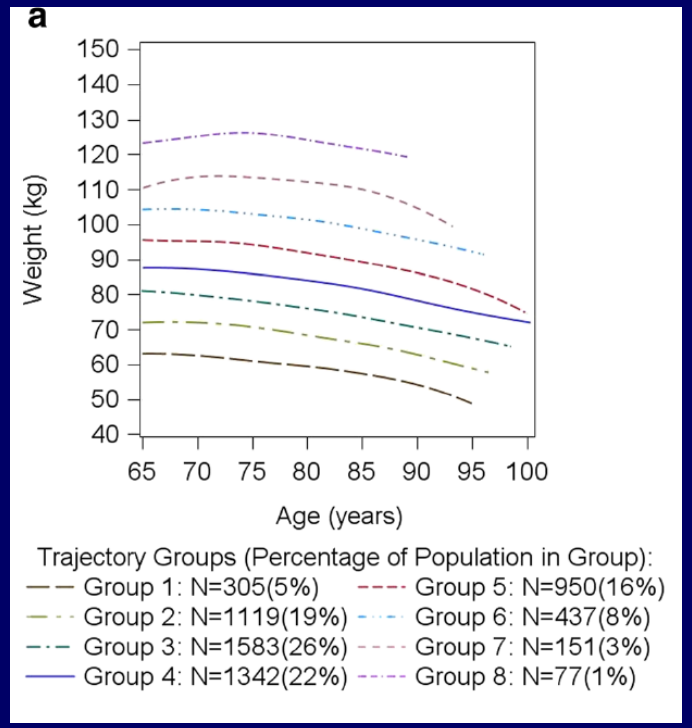
Figure 1.
Probability of IHD by aerobic fitness and BMI in 18-year-old men with mean follow-up of 25.7 years (maximum age 62 years).

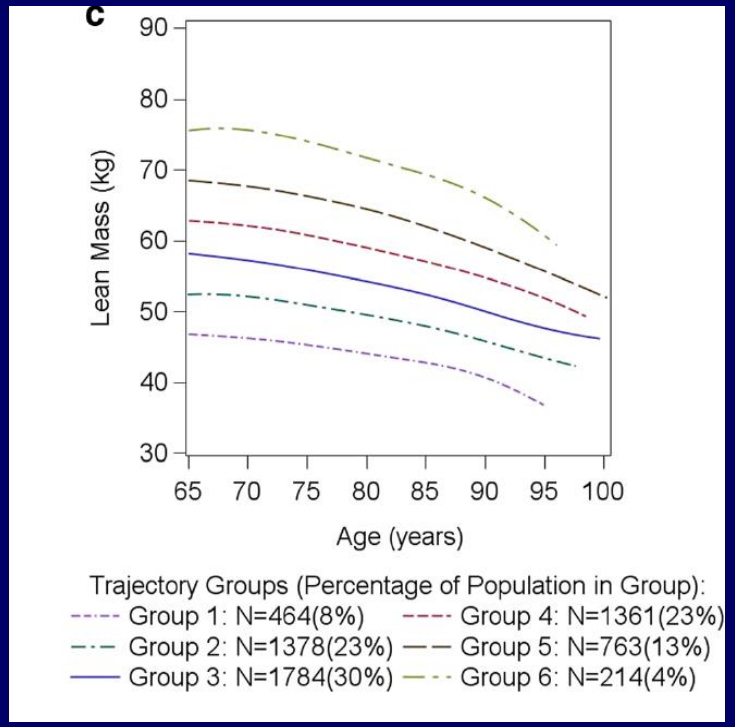
The interactive effects of aerobic fitness and BMI on risk of IHD are shown in Table 3. Low aerobic fitness was associated with increased IHD risk among men with either normal or high BMI (IRRs, 1.87 and 1.45, respectively; Table 3, right-most column). The combination of low aerobic fitness and high 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 ($P_{interaction}<0.001$) (i.e., their combined effect was less than the product of their separate effects), and no interaction on the additive scale ($P_{interaction}=0.40$). 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.

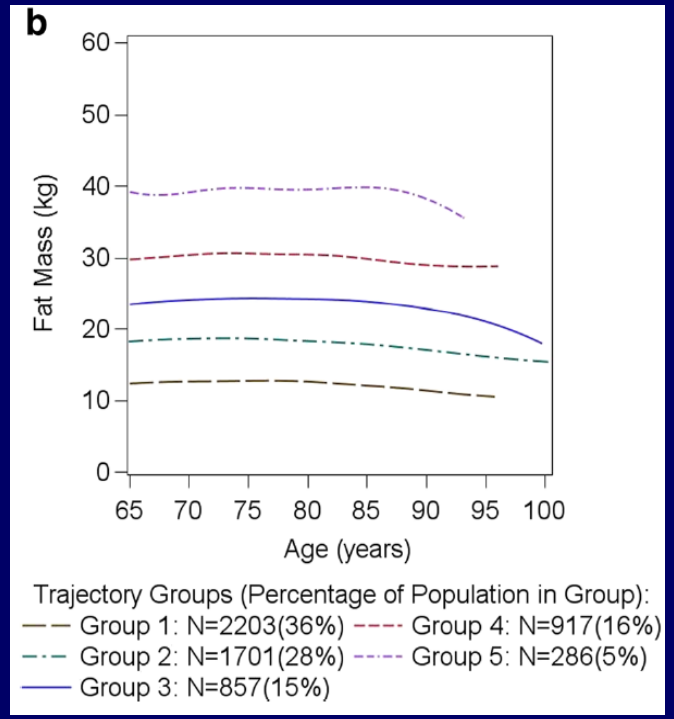
normal BMI. Low aerobic fitness and high BMI had a negative interaction on the multiplicative scale ($P_{interaction}<0.001$) (i.e., their combined effect was less than the product of their separate effects), and no interaction on the additive scale ($P_{interaction}=0.40$). Figure 1

Group based trajectory method:

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







Laddu *et al. BMC Geriatrics* (2017) 17:119
DOI 10.1186/s12877-017-0506-4

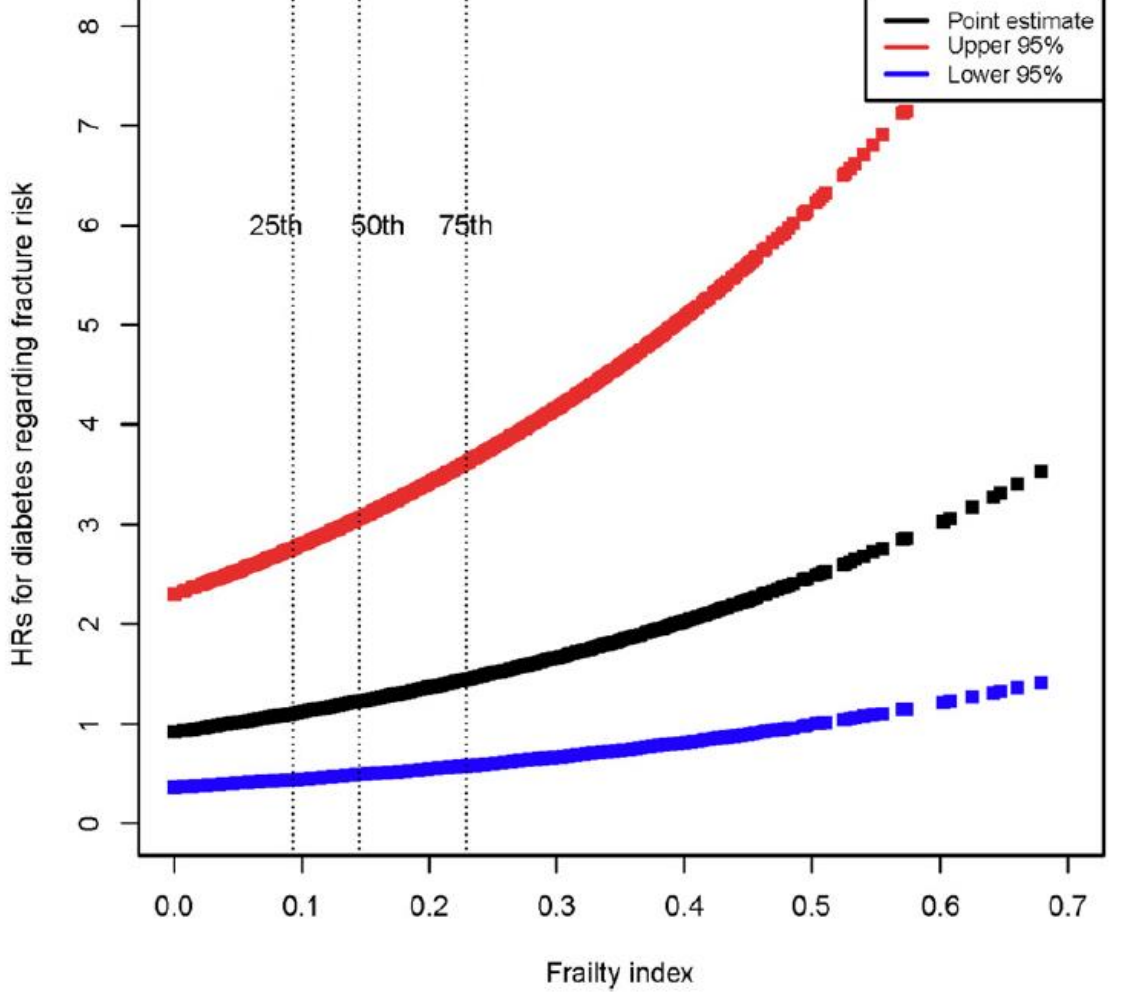
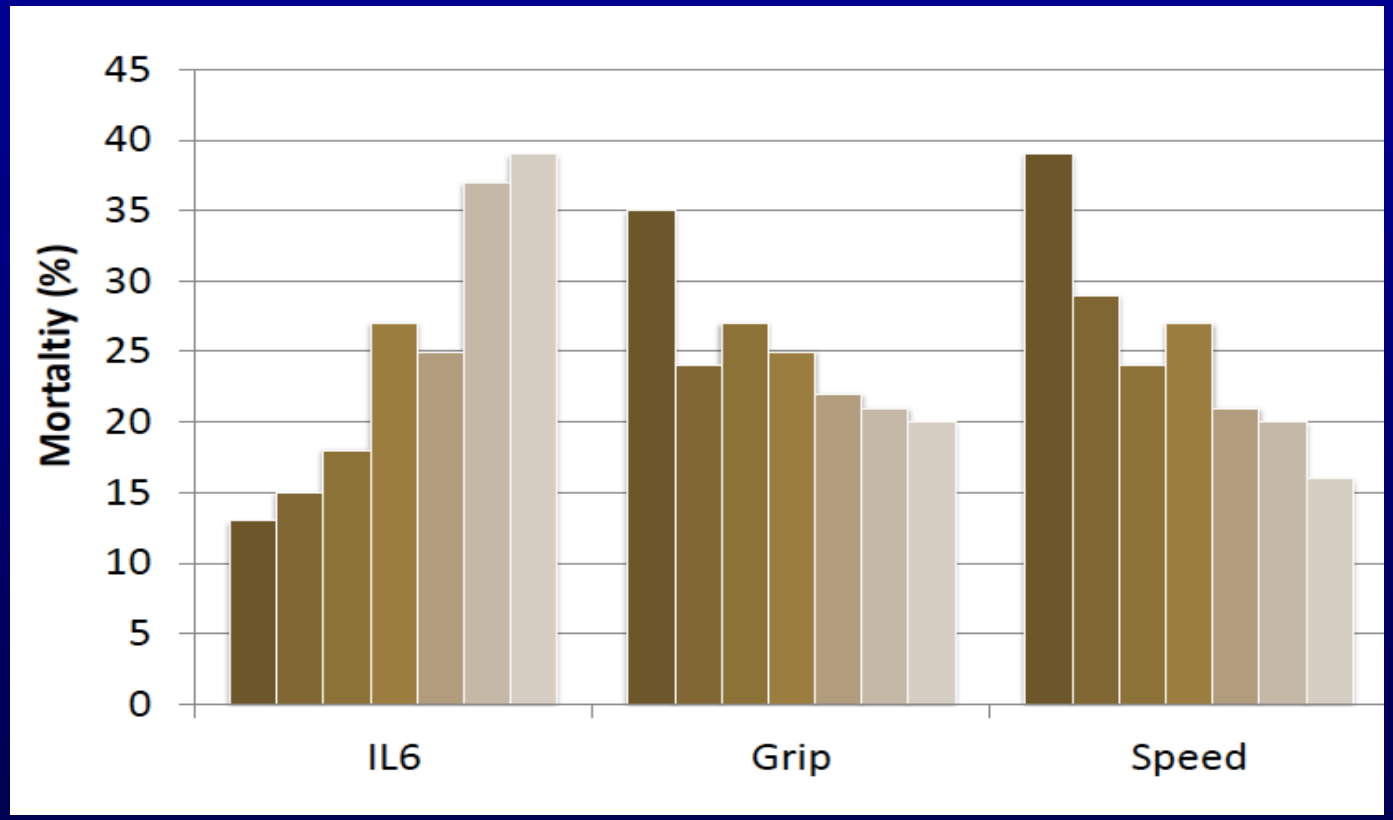


Figure 1—Different HRs for diabetes regarding the fracture risk at different levels of the FI (25th, 50th, 75th denoting quartiles of the FI). (A high-quality color representation of this figure is available in the online issue.)

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

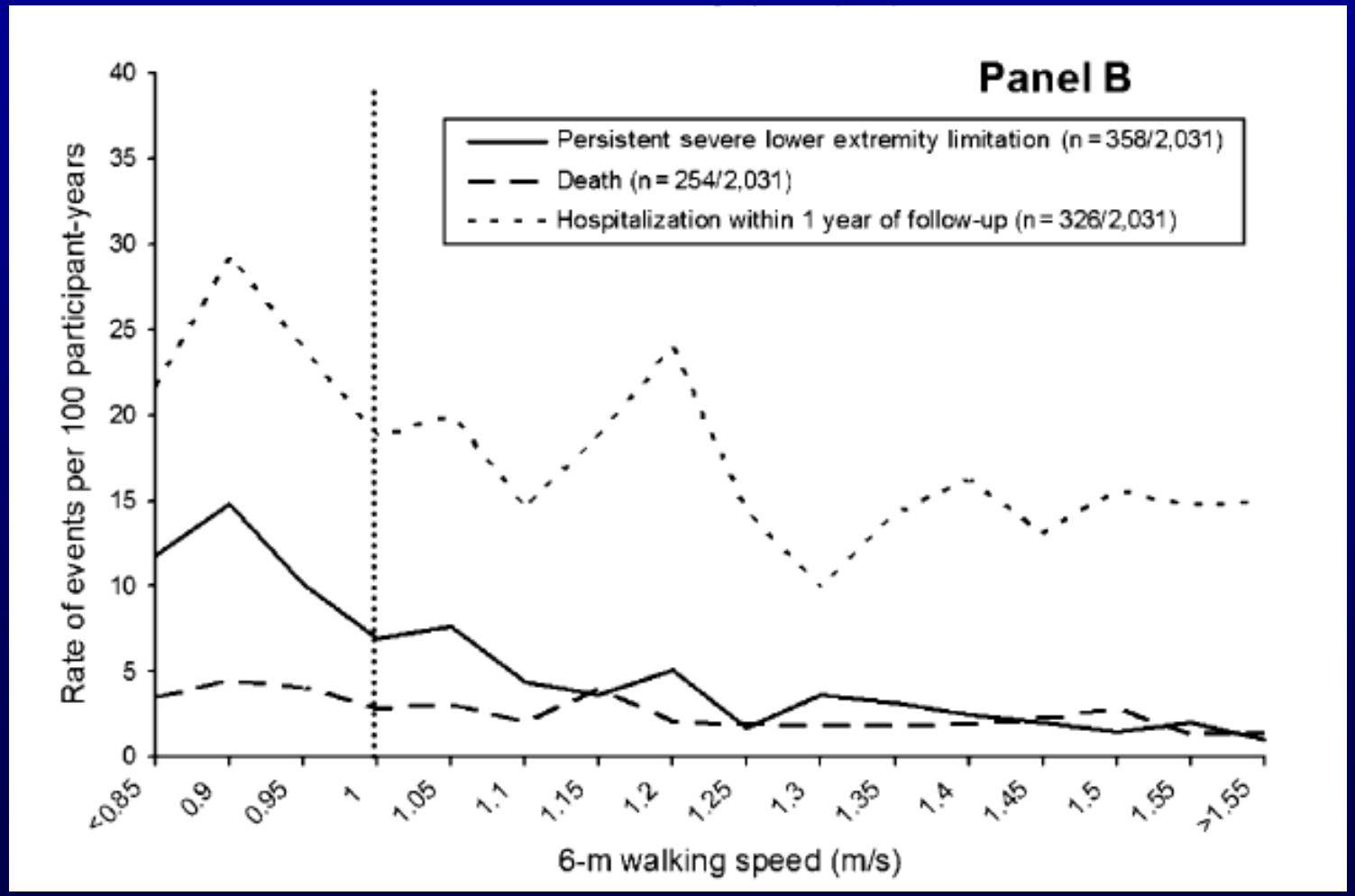


Septiles of increasing value

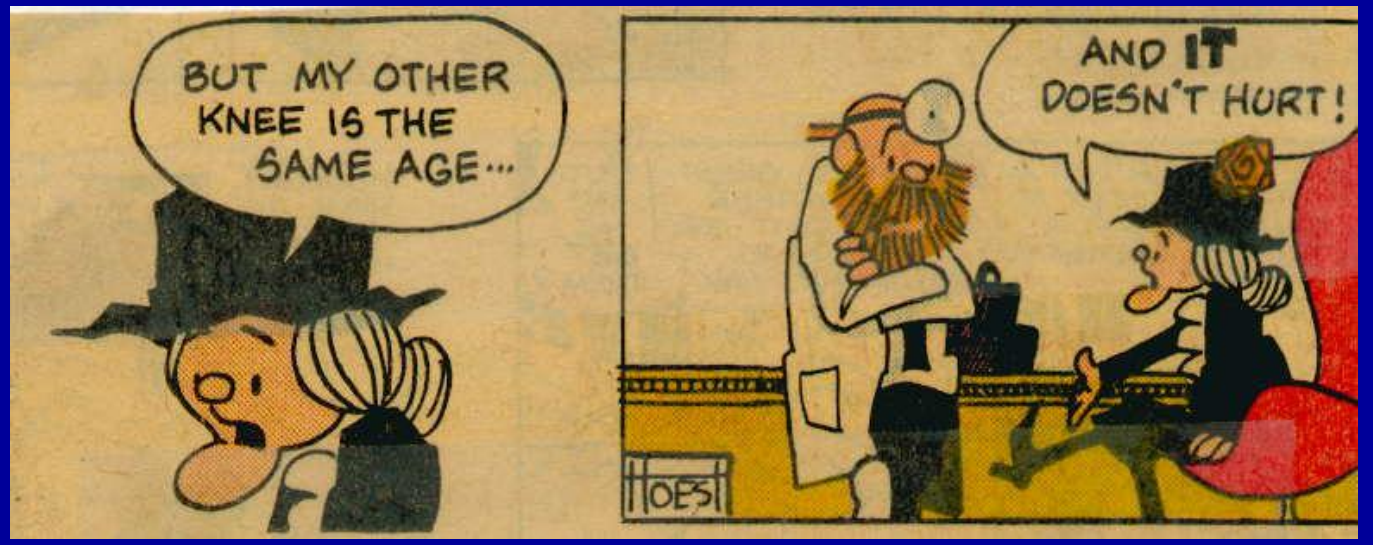
Kritchevsky S

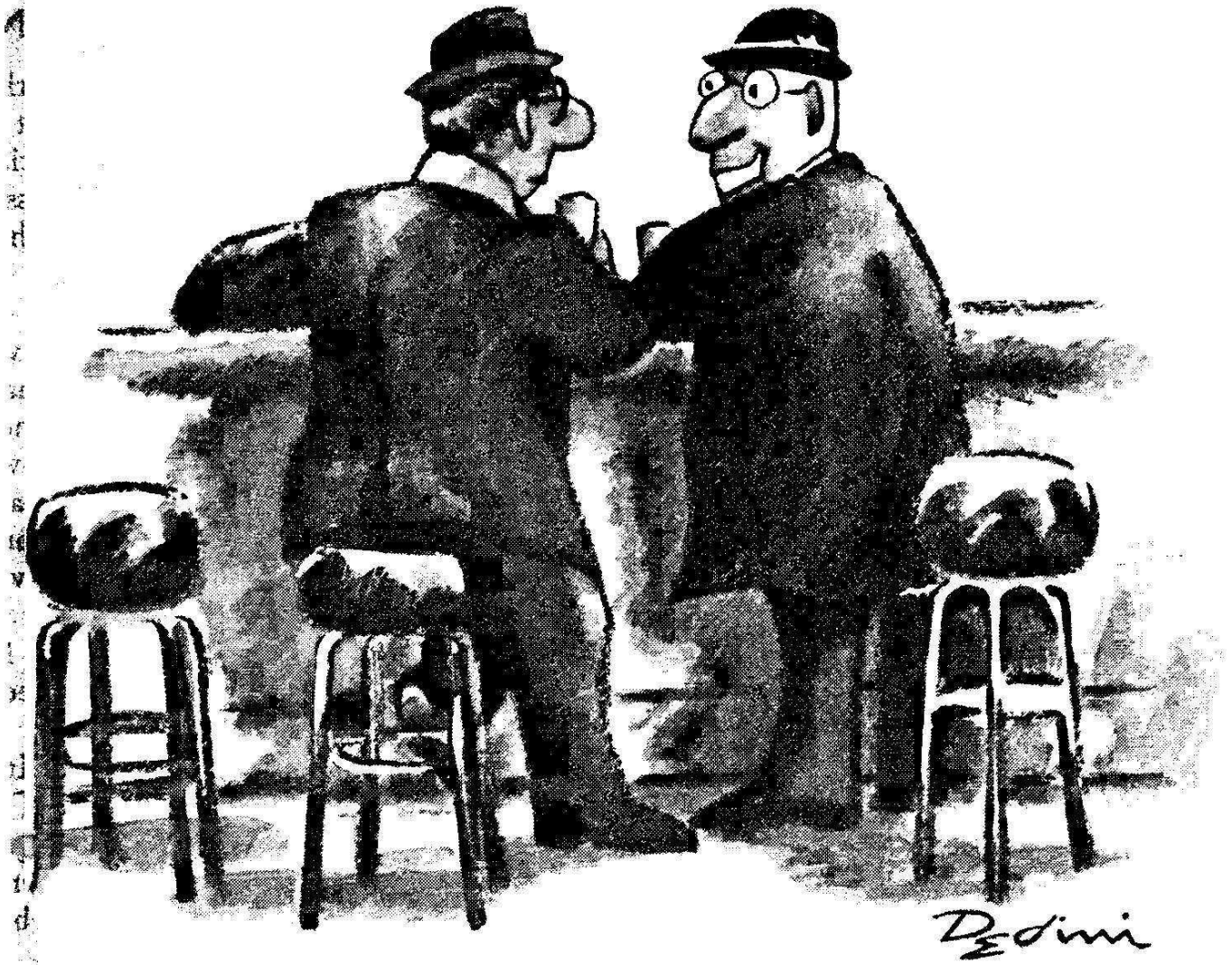
THE WIZARD OF ID PARKER & HART
DO YOU HAVE ANYTHING THAT STOPS THE AGING PROCESS?
SURE, WHAT KIND OF DISEASE WOULD YOU LIKE?
11-8
©2001 CREATORS SYNDICATE, INC. WWW.CREATORS.COM
PARKER

Walking is a key component of physical independence



Differentiating "Age-associated" from Aging"





"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

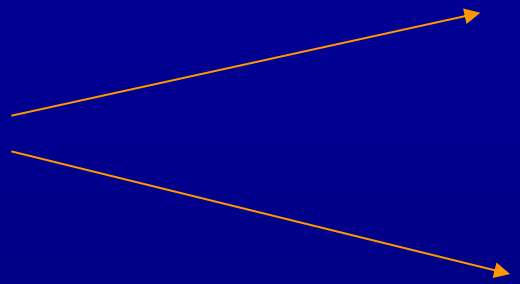
TIME-COURSE

RADIATION AND INCIDENCE OF BREAST CANCER IN JAPAN

CHILDHOOD AND MENTAL ILLNESS

CHILDHOOD AND ADULT OUTCOMES OF OBESITY

TRUTH



Assay range
Timing of assessment
Processing

Recall and other biases

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

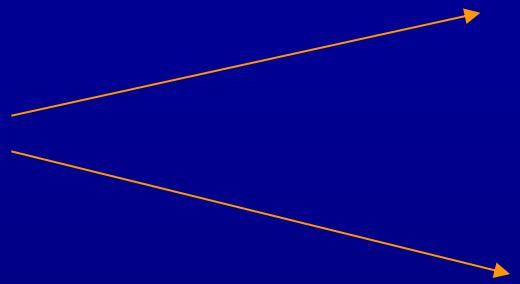
TIME-COURSE

RADIATION AND INCIDENCE OF BREAST CANCER IN JAPAN

CHILDHOOD AND MENTAL ILLNESS

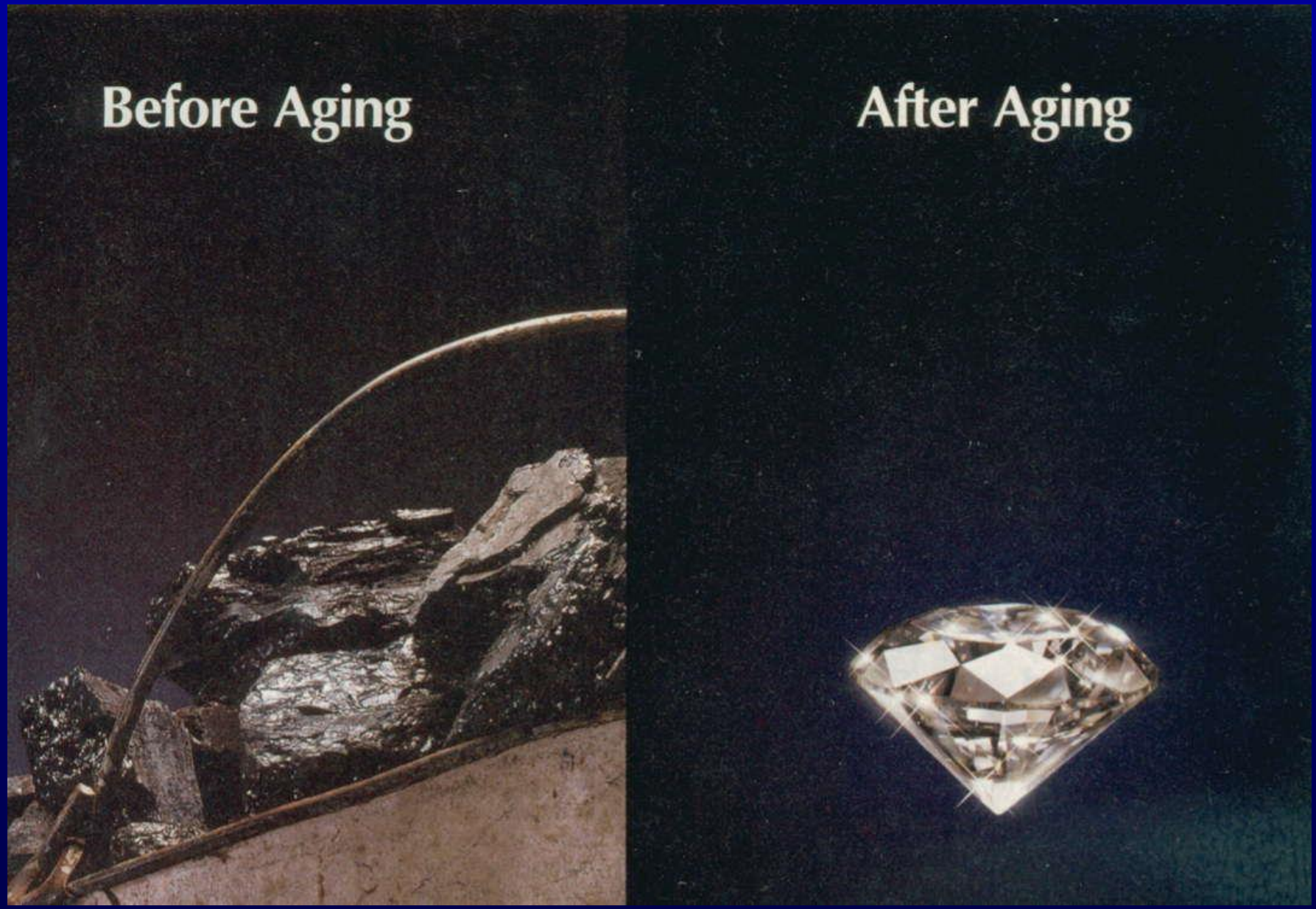
CHILDHOOD AND ADULT OUTCOMES OF OBESITY

TRUTH



Assay range
Timing of assessment
Processing

Recall and other biases



Thank you for your attention!

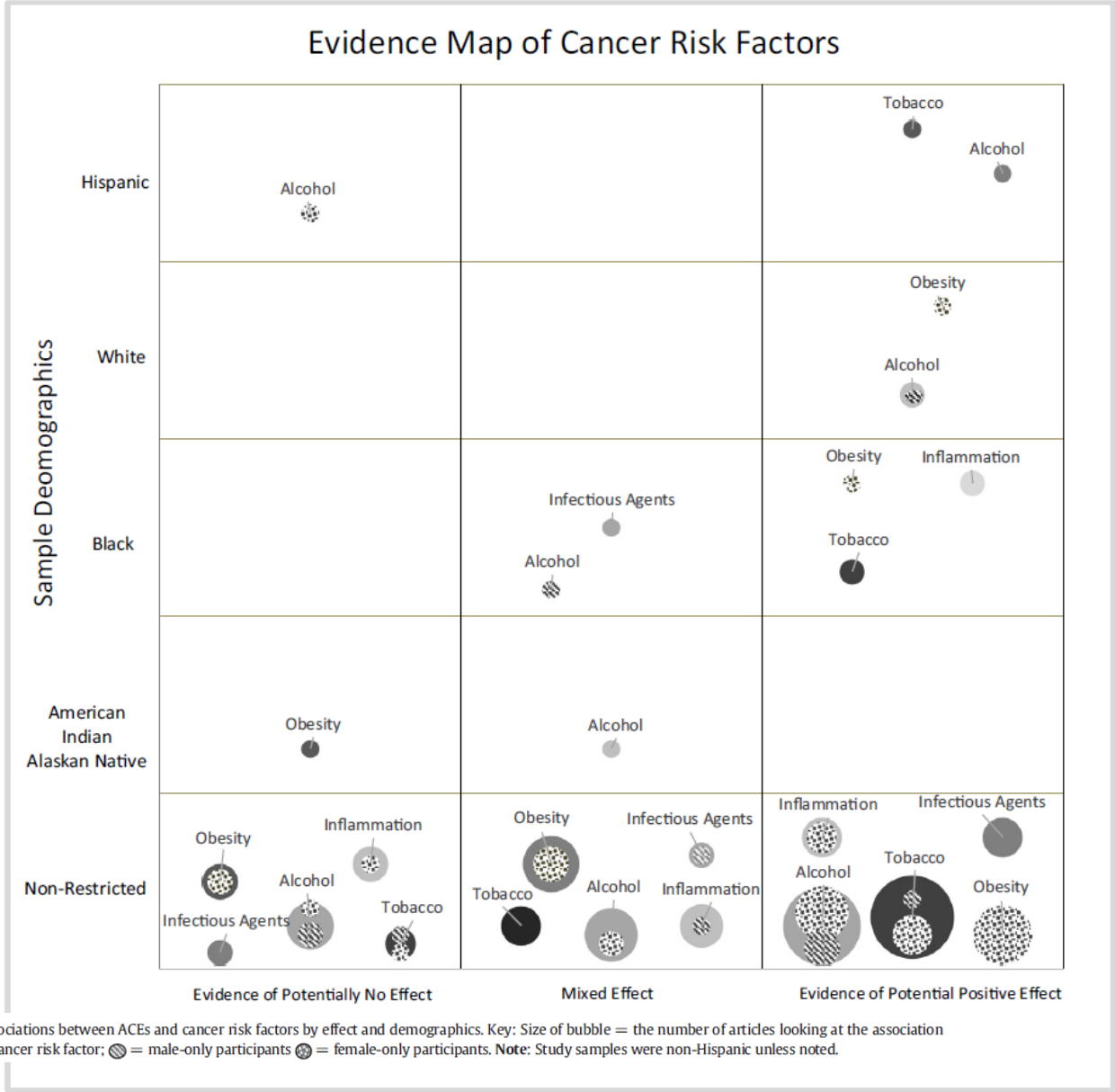


Fig. 3. Bubble plot of reported associations between ACEs and cancer risk factors by effect and demographics. Key: Size of bubble = the number of articles looking at the association between ACEs and the identified cancer risk factor; ⦸ = male-only participants ⦸ = female-only participants. **Note**: Study samples were non-Hispanic unless noted.

Table 3
Domains of potentially modifiable determinants.

Domain name	Included determinants (n = 30)
Oral	1. Dental status
	2. Chewing
	3. Mouth pain
	4. Gum issues
	5. Swallowing
Psychosocial	6. Cognitive function
	7. Depression/depressive symptomology
	8. Psychological distress
	9. Anxiety
	10. Social support
	11. Residential status
	12. Transport
	13. Loneliness
	14. Wellbeing
	15. Meals on wheels
Medication and care	16. Medication and polypharmacy
	17. Hospitalisation
Health	18. Co-morbidities
	19. Functional health status
	20. Eating dependency/difficulty feeding
	21. Self-perceived health
Physical function	22. Activities of daily living, performance or strength
Lifestyle	23. Smoking
	24. Alcohol
	25. Physical activity
Eating	26. Appetite/leaves food on plate
	27. Complaints about taste of food
	28. Dietary factors – nutrient intake and modified texture diets
	29. Hunger

Please cite this article as: O'Keeffe 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

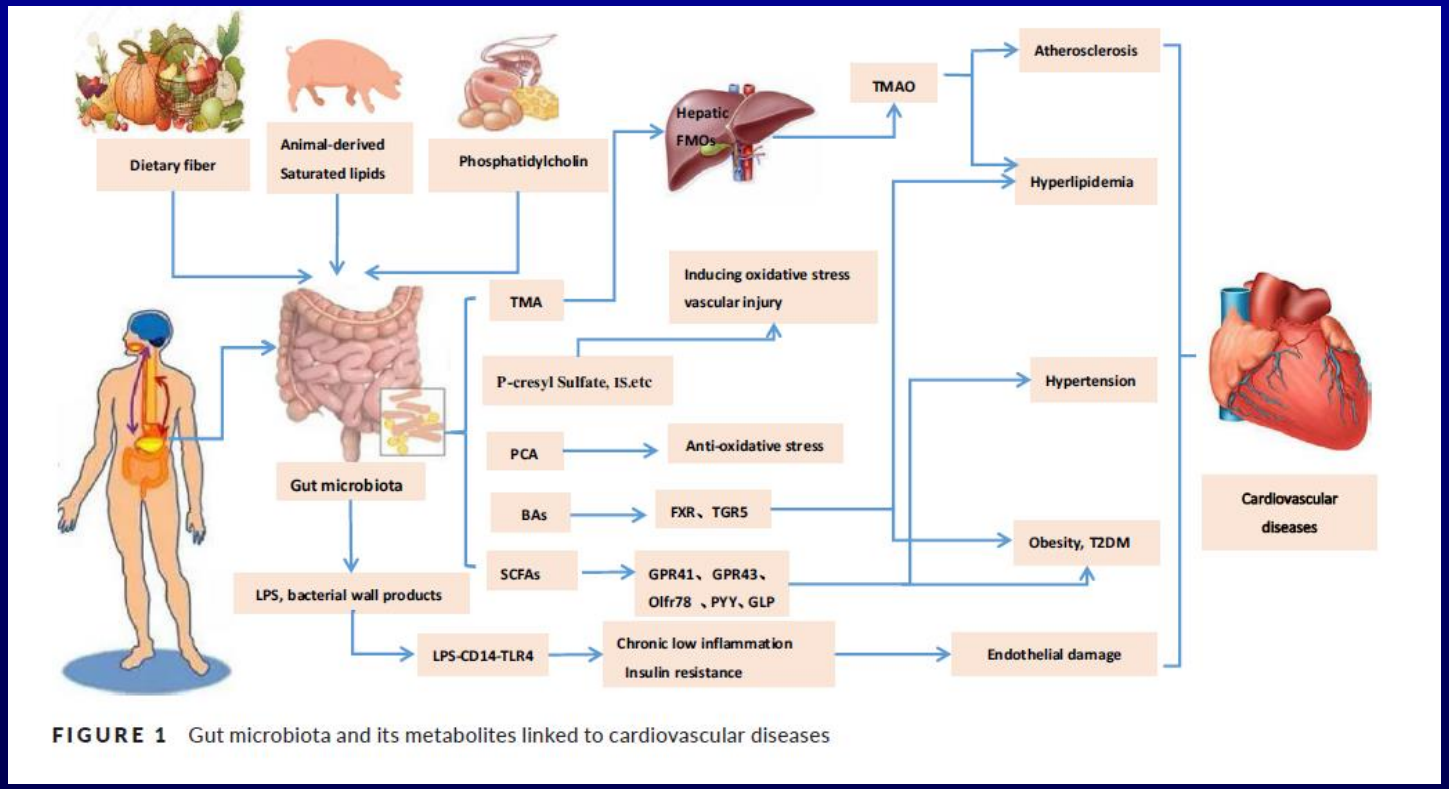
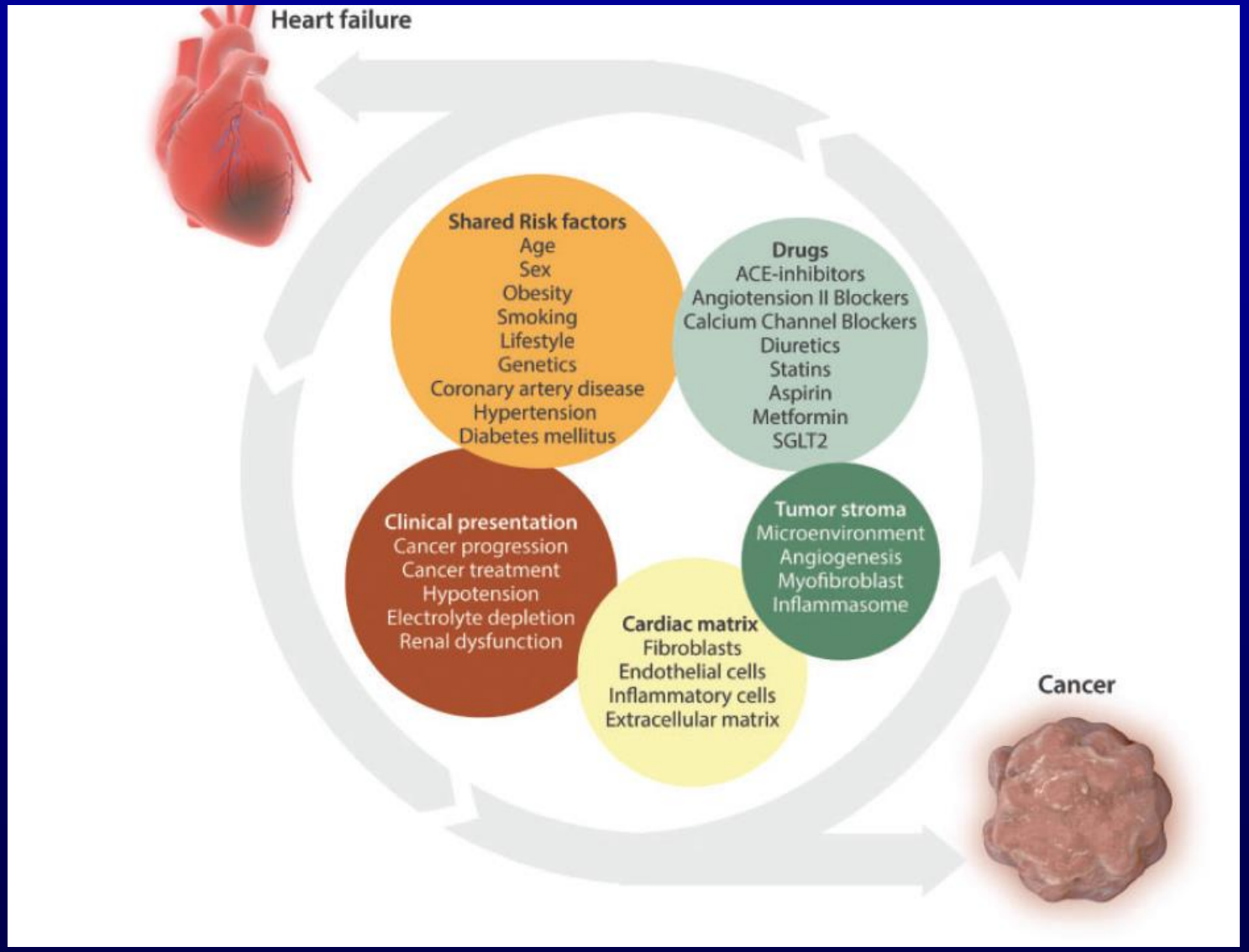


FIGURE 1 Gut microbiota and its metabolites linked to cardiovascular diseases

© 2019 The Authors. Journal of Cellular and Molecular Medicine published by John Wiley & Sons Ltd and Foundation for Cellular and Molecular Medicine.



Cardiovascular Research
doi:10.1093/cvr/cvz035

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

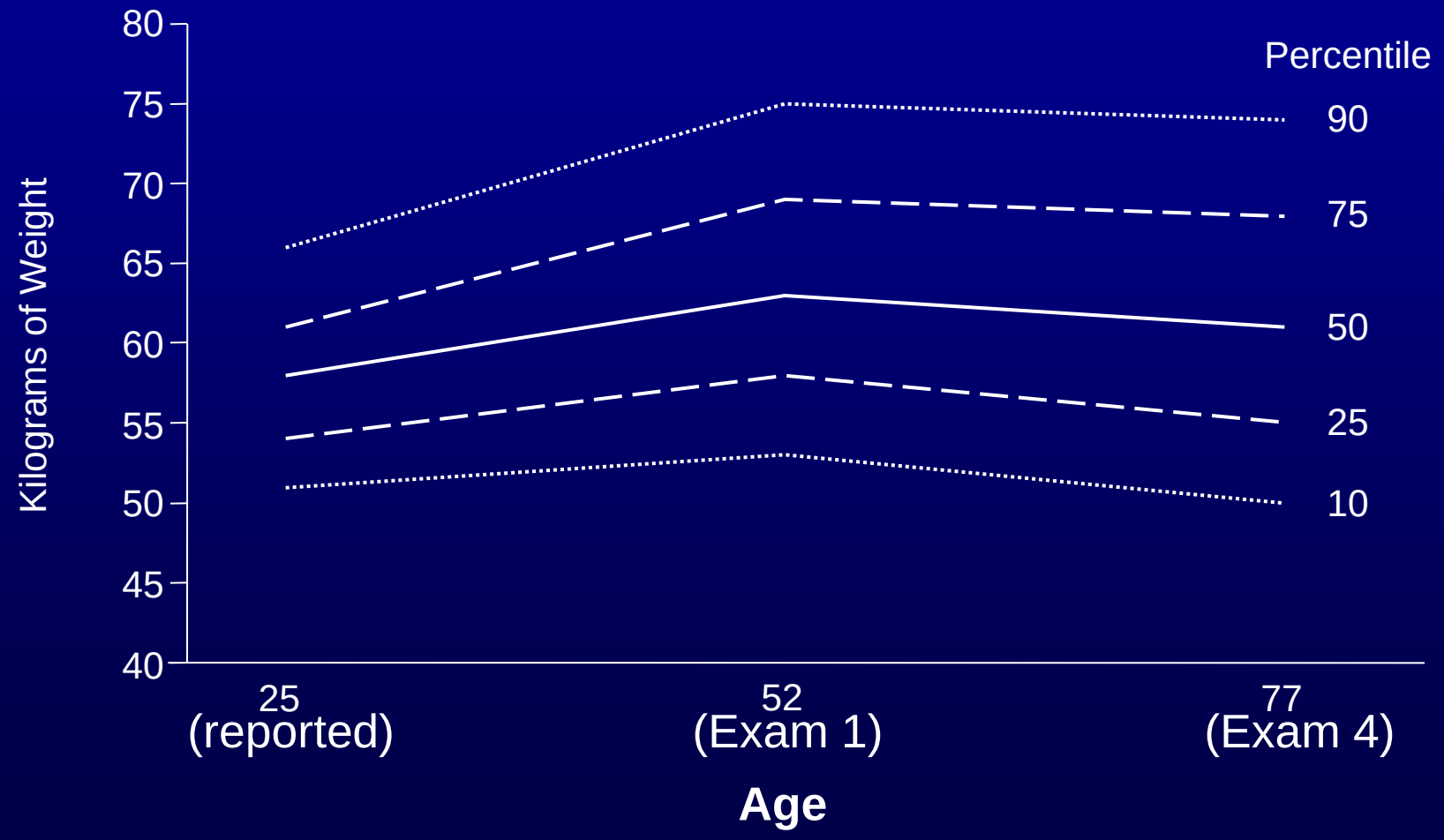
	Diabetes	High blood pressure	Heart attack	Fair/poor health
Stable	1.0	1.0	1.0	1.0
Continuous weight gain	6.6*	3.2*	2.0*	2.1*
Weight gain maintenance	3.8*	1.8*	1.6*	1.3*
Weight loss regain	2.3*	1.8*	1.9*	1.7*
Weight loss maintenance	0.6	0.8	1.3	1.1

* $p<.01$

French, Jeffery, Folsom et al. *Inter J Obesity* 1996;303.

Lifetime average weight from longitudinal data

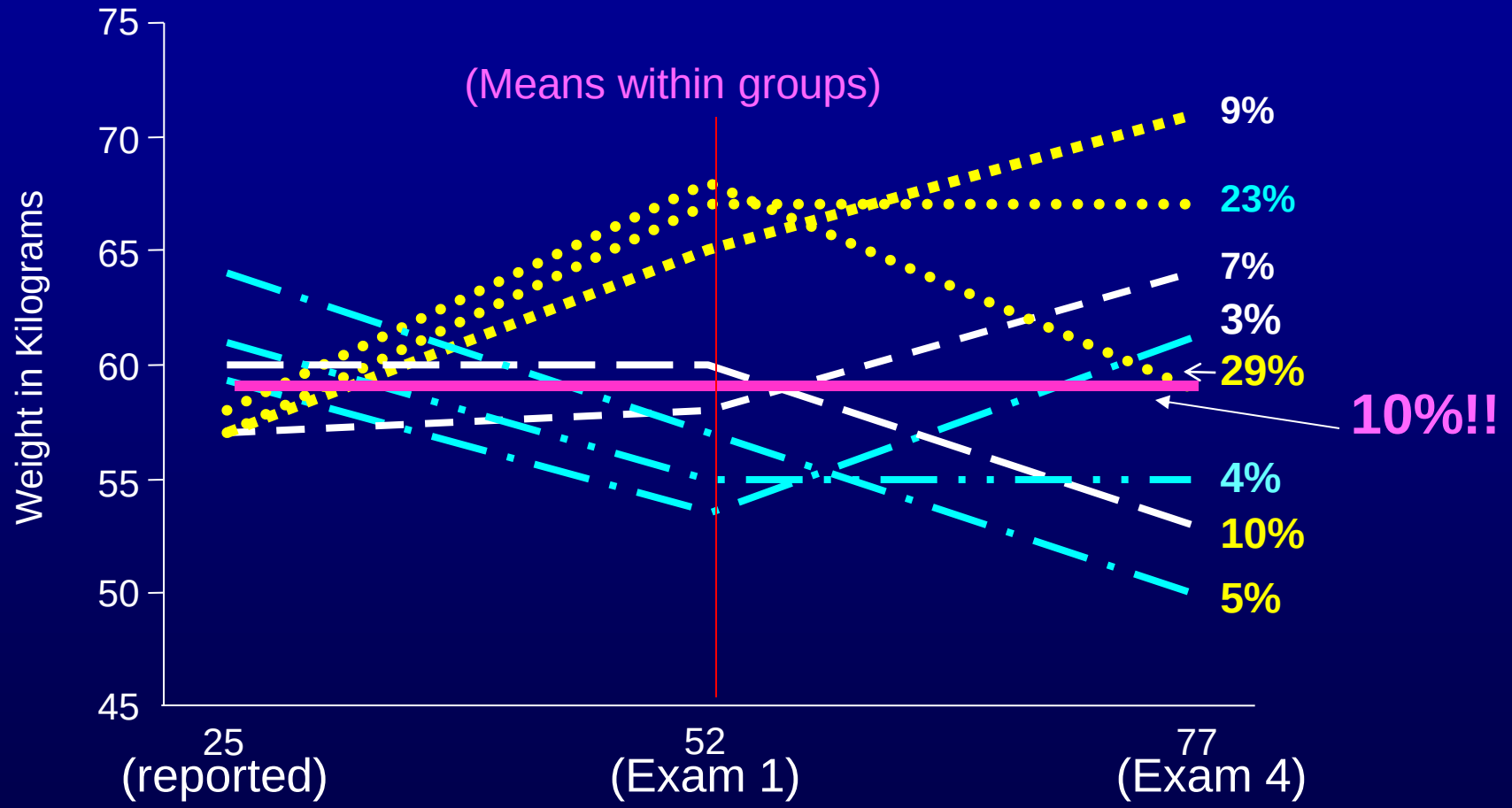
Lifetime Weight Patterns Based on Percentile Distributions in 3,611 Japanese-American Men



Heterogeneity of weight patterns in the population

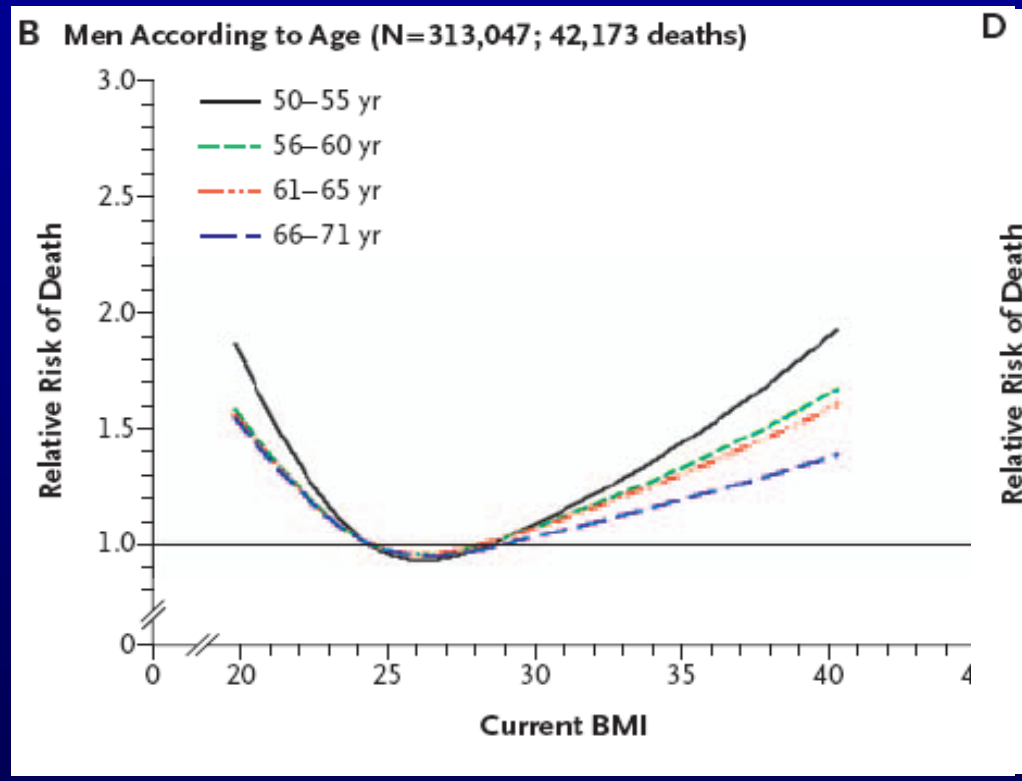
YOUTH- from 25 to midlife: 61% gain, 27% stable, 12% lose

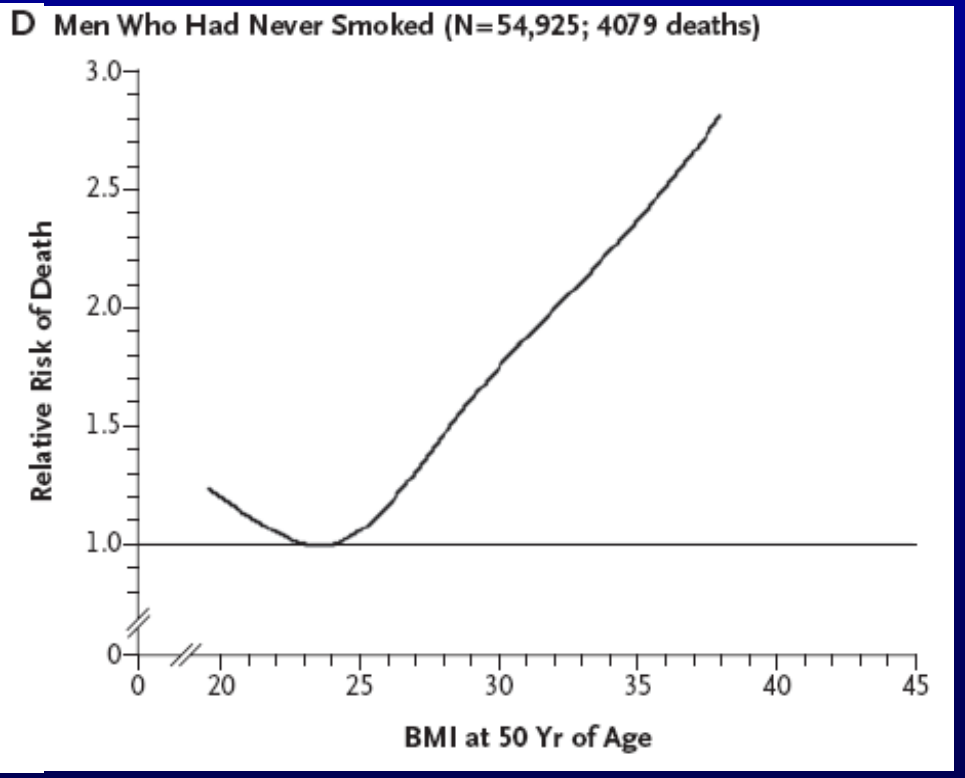
From midlife to old age: 19% gain, 27% stable, 44% lose



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





Adams et al. NEJM 2006; 763

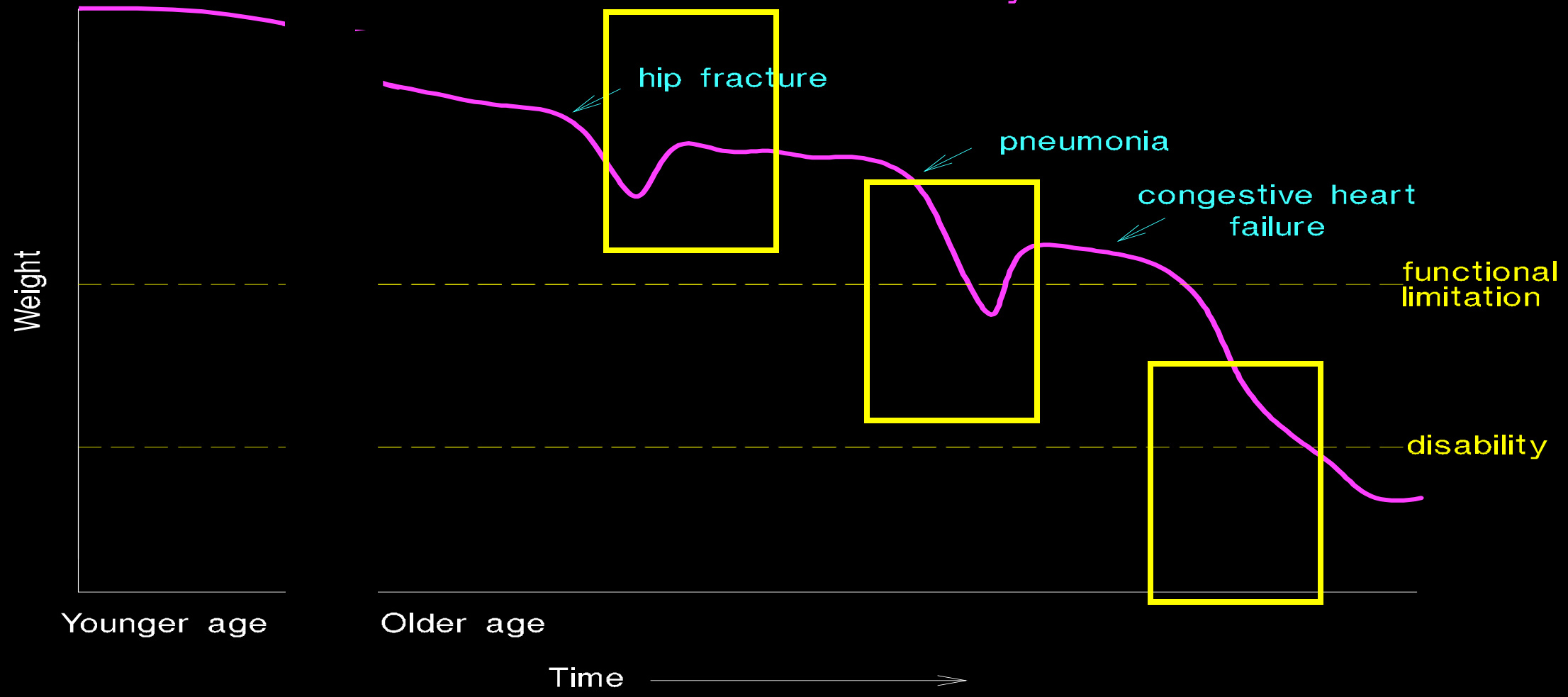
Aging-Prevention Paradigm

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

Health, Aging and Body Composition Study

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



Vellas; Kottler, Grunfeld

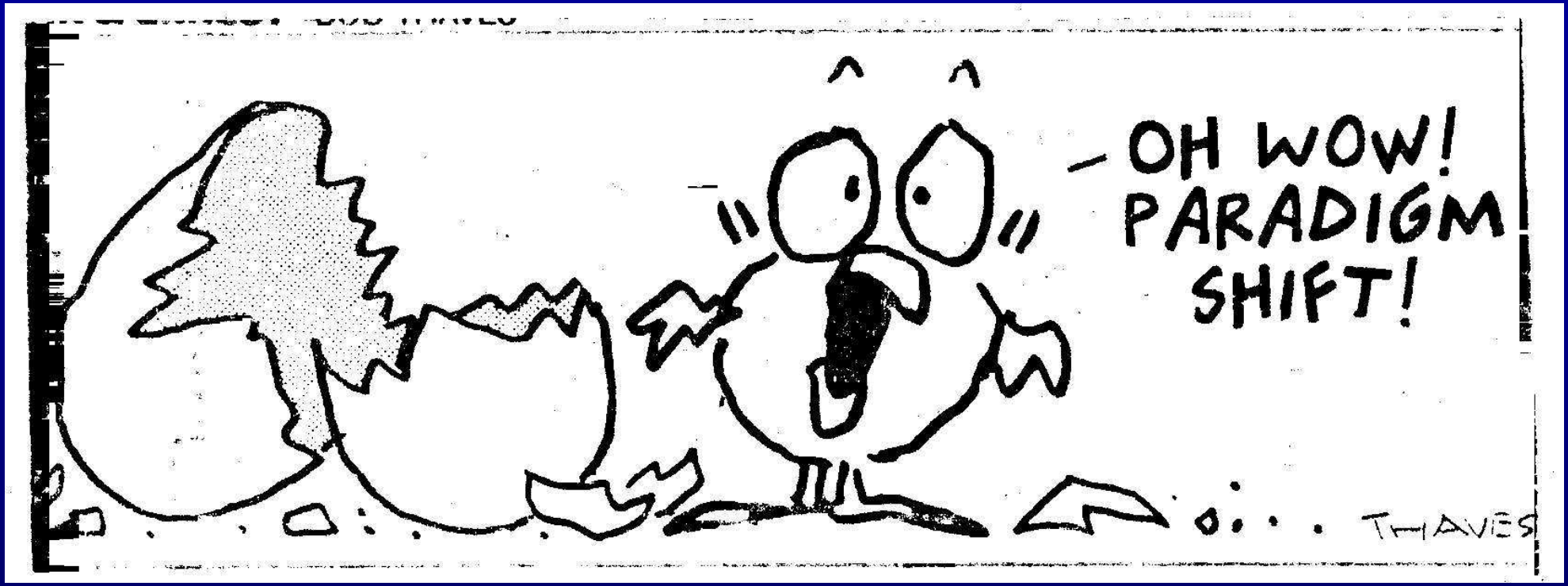
Baseline Characteristics of the Health ABC cohort

	Men		Women	
Characteristic	White (939)	Black (552)	White (855)	Black (729)
BMI	27.0	27.2	26.0	29.7
Percent fat	29.9	28.0	40.0	41.0
Lean mass in cm^2	127	139	85	101
Days hospitalized (mean)	3.8	4.9	3.8	4.8
Percent hypertensive	69	82	70	86
< HS education	14	49*	10	38*
Good/F/P	47	65*	50	67*

Functional limitation: Difficulty walking ¼ mile or up 10 steps reported consistently over a 6-month period

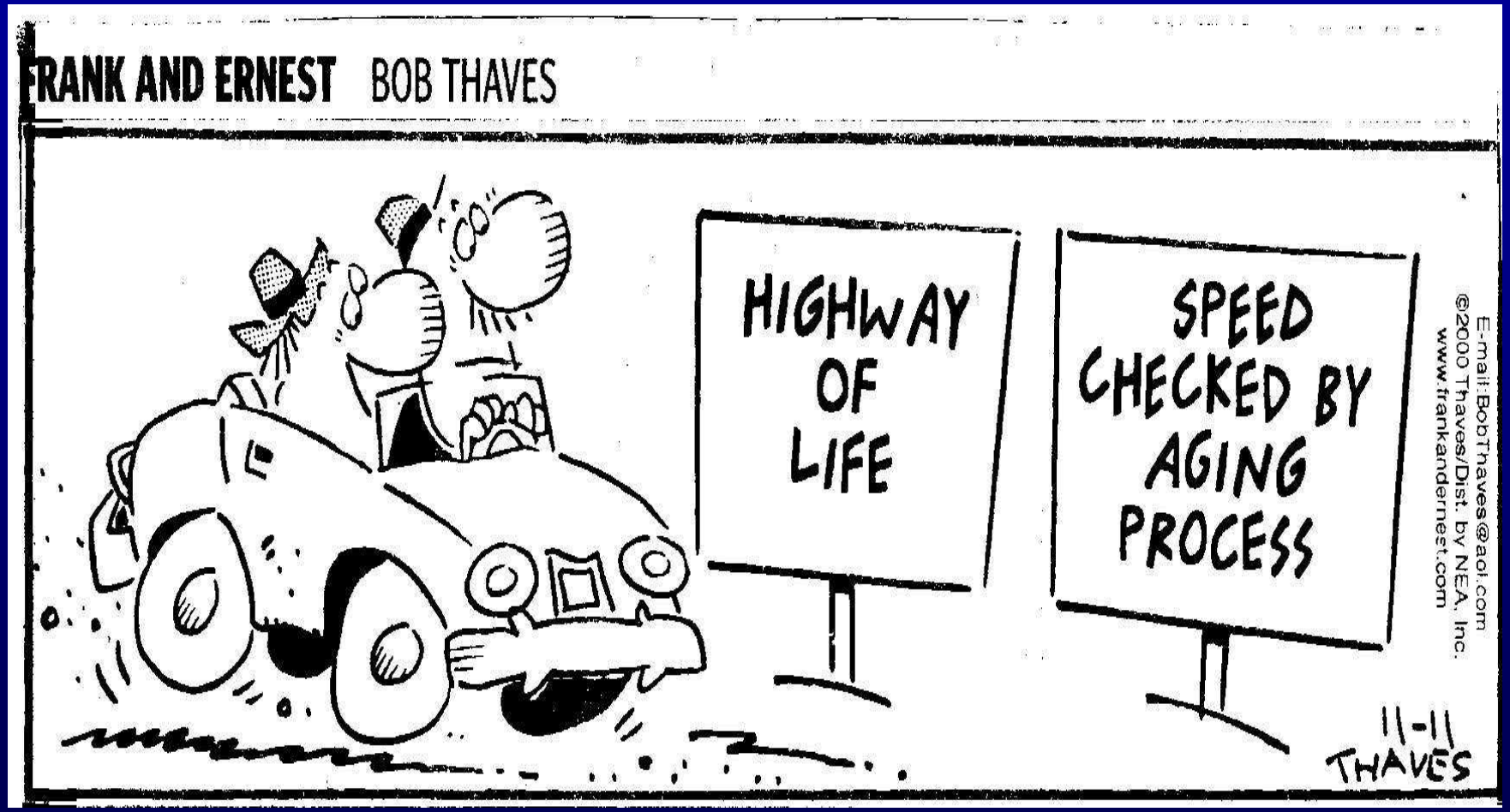
Over 13 years of follow-up, percent incident functional limitation

White men	67	White women	72
Black men	73	Black women	80



CT properties of muscle- a combination of science and serendipity

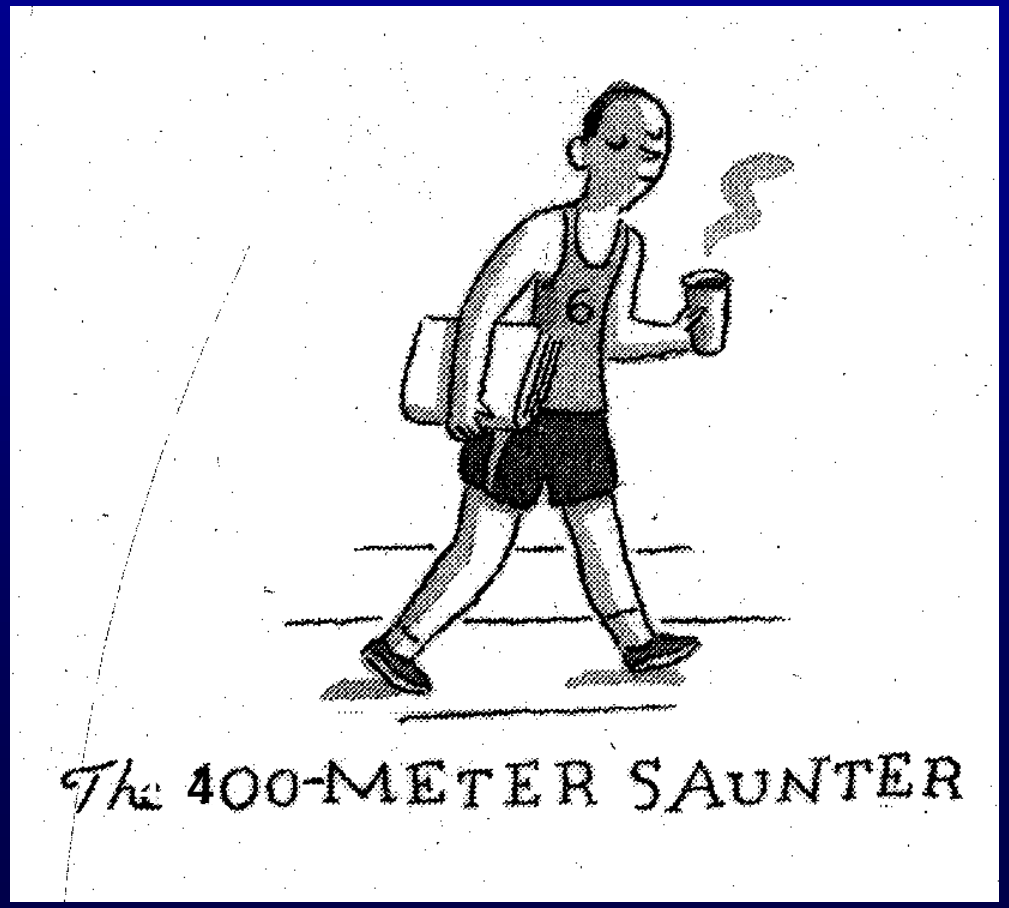
Reciprocity between muscle and adipose



Contribution to performance measures

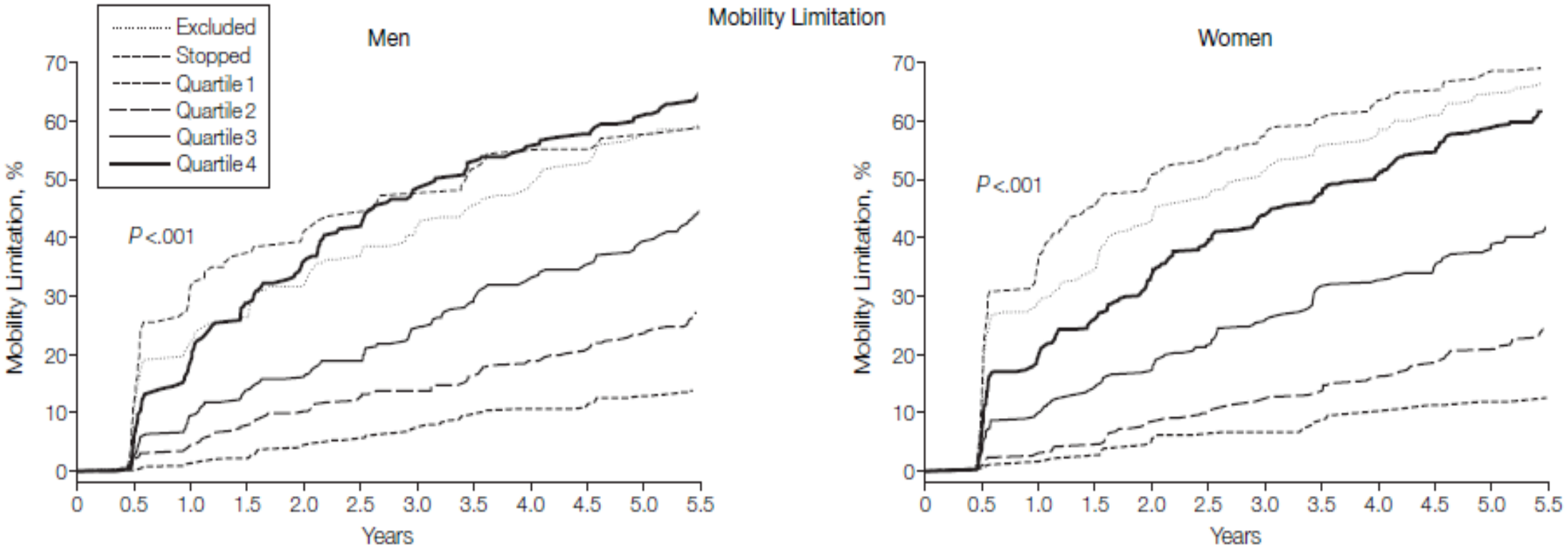
Measuring fitness in older adults: The Health ABC Long Distance Corridor Walk

Simsonick, Montgomery, Newman, Bauer, and Harris. JAGS 49:1544, 2001.



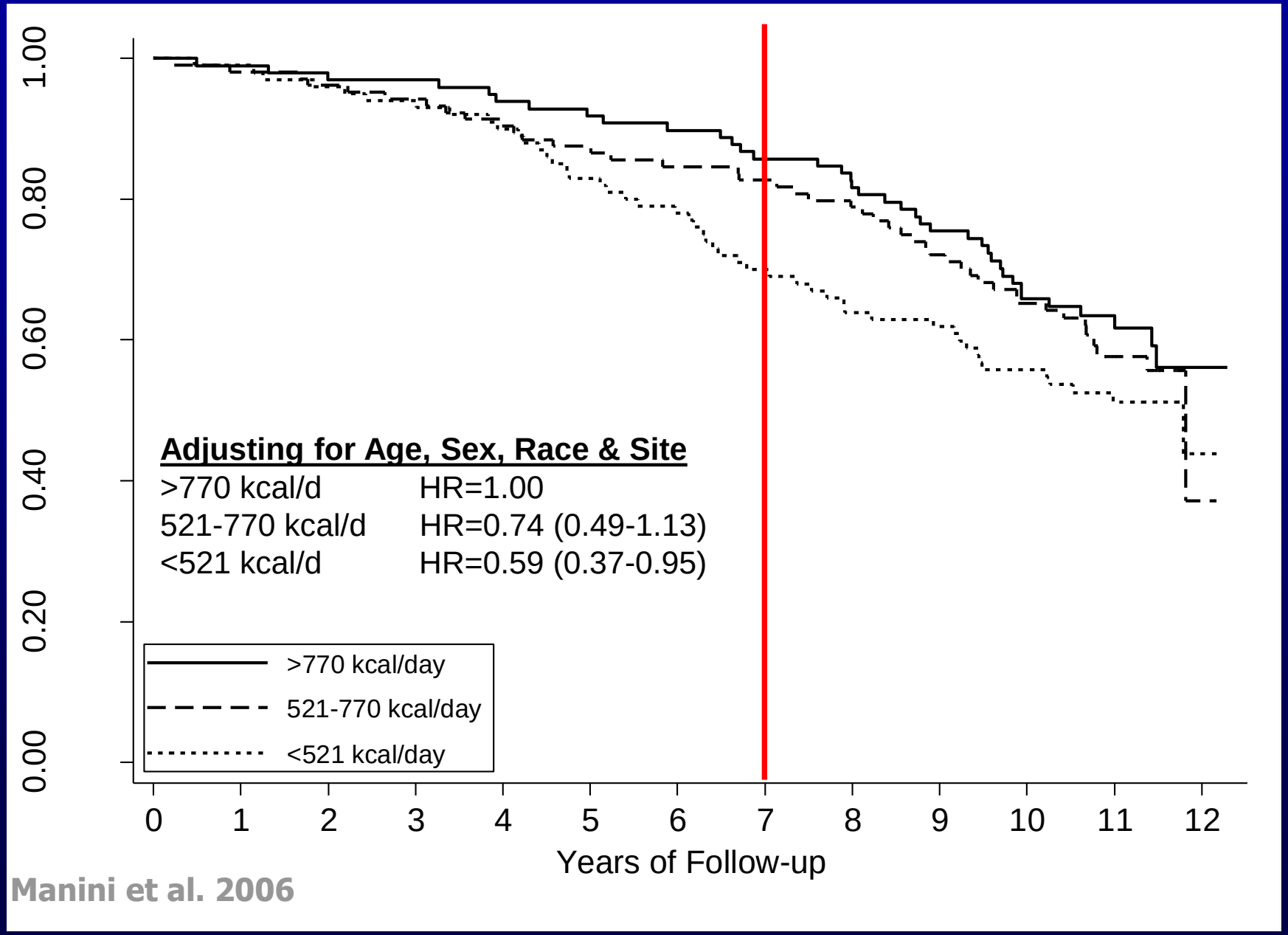
Association of Long-Distance Corridor Walk Performance With Mortality, Cardiovascular Disease, Mobility Limitation, and Disability

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



JAMA. 2006;295:2018-2026

Lower daily free-living activity energy expenditure increases risk of death- doubly labeled water



Manini et al. 2006

Paradoxical Risk Factors in Old Age

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

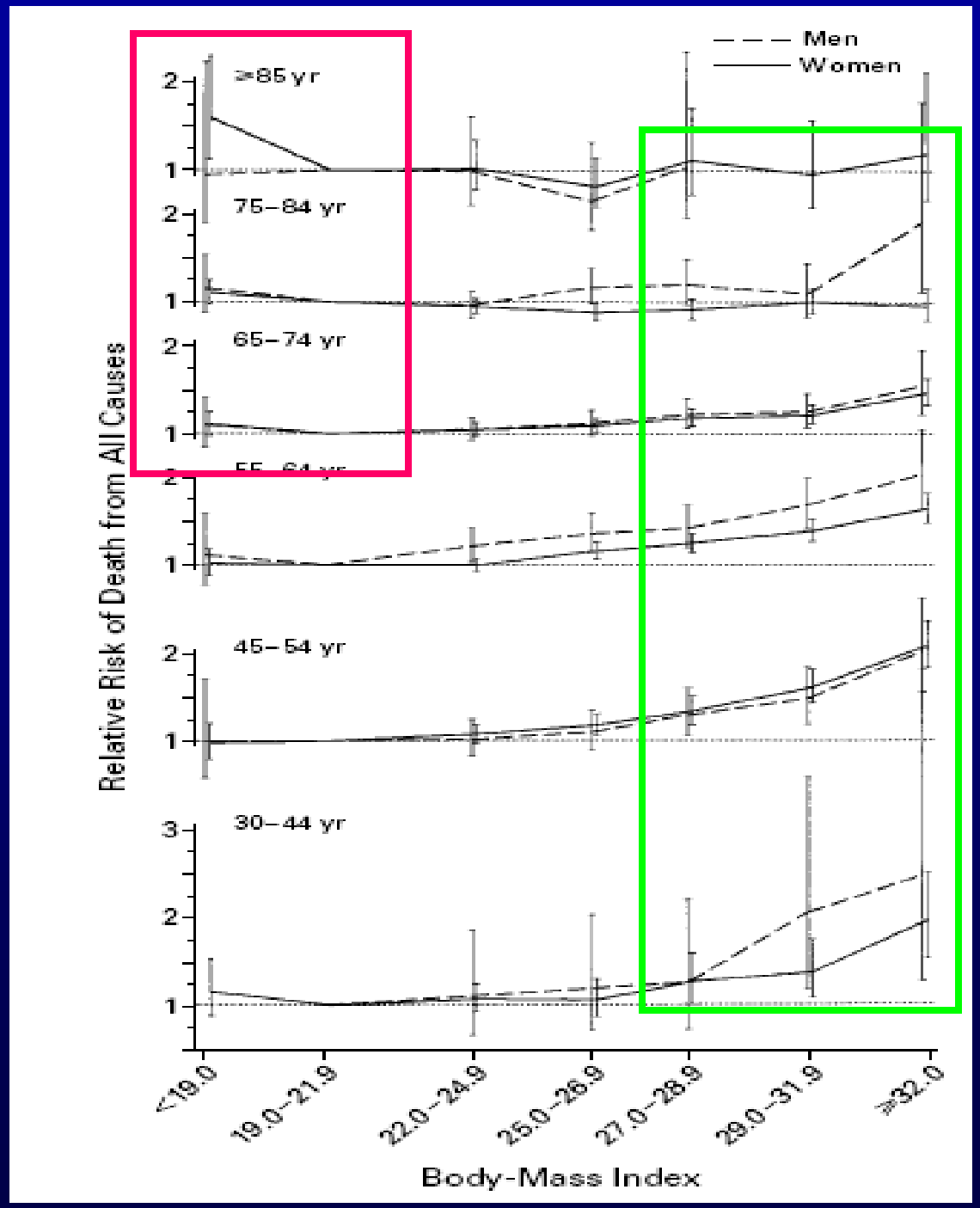
Gina Kolata AARP Bulletin, June 21, 2005

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

doi:10.7326/AITC201708010

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/cm^2)

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 apéritif.*

doi:10.7326/AITC201708010

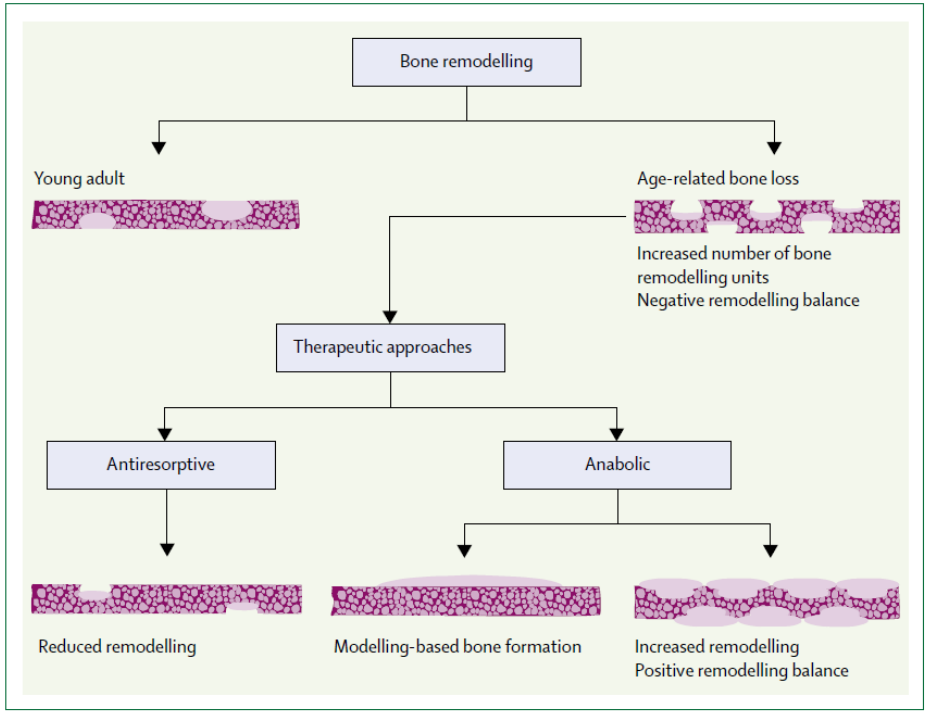


Figure 1: **Effects of antiresorptive and anabolic drugs on bone remodelling and modelling**
Age-related bone loss is associated with an increase in remodelling and a negative remodelling balance in individual bone remodelling units. Antiresorptive agents act predominantly by reducing remodelling rate. Anabolic agents produce their effects by increasing remodelling in combination with a positive remodelling balance, or stimulating bone modelling.

	Risk factor inputs
Fracture risk assessment tool[53]	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)
Garvan Fracture risk calculator[54]	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
QFractureScores-2016[55]	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 anticonvulsant use, antidepressant use, steroid use, hormone replacement therapy

COPD=chronic obstructive pulmonary disease.

Table 1: **Fracture risk prediction tools with at least one independent validation cohort**

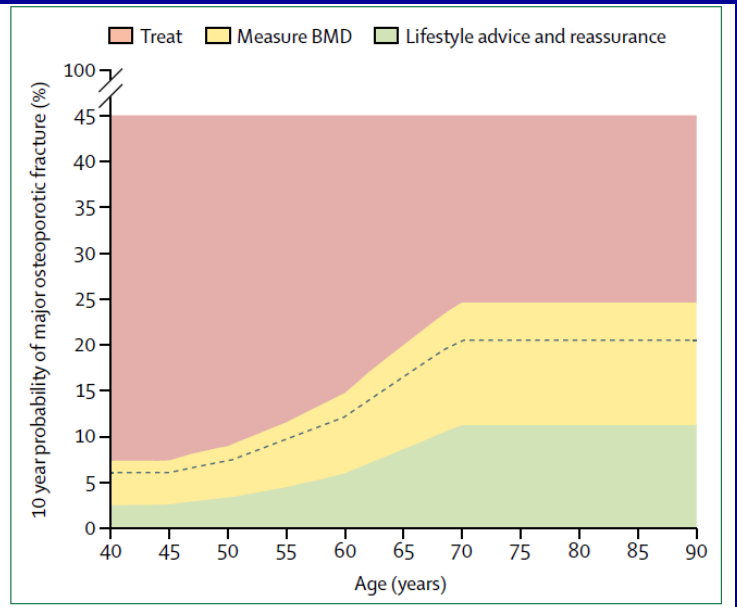


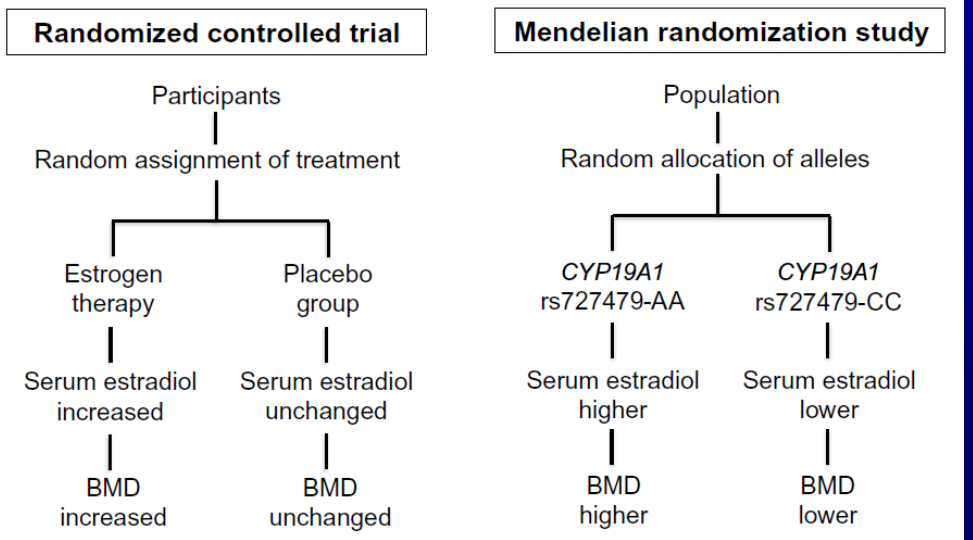
Figure 2: **UK National Osteoporosis Guidelines Group assessment and treatment thresholds**

Green denotes that an individual's risk lies below the intervention threshold—ie, 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 lumber 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

S.C. Larsson et al.



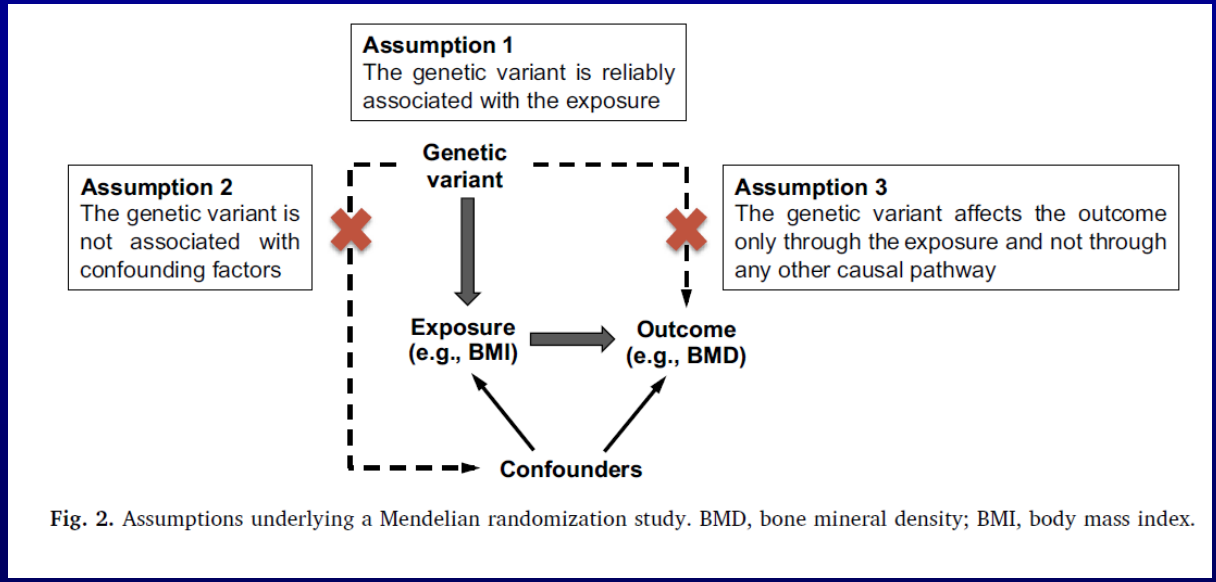


Fig. 2. Assumptions underlying a Mendelian randomization study. BMD, bone mineral density; BMI, body mass index.

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."