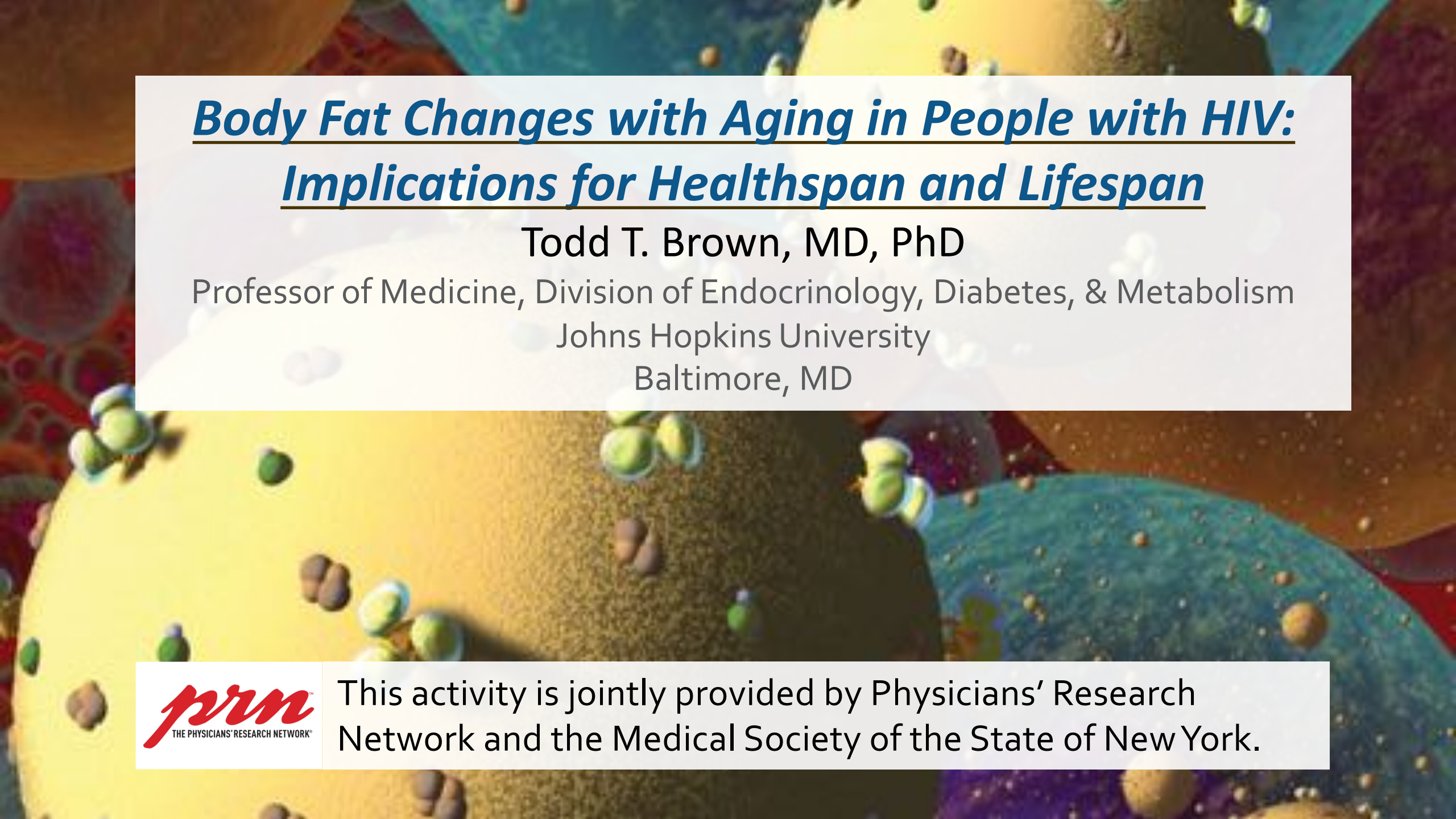


Body Fat Changes with Aging in People with HIV: Implications for Healthspan and Lifespan

Todd T. Brown, MD, PhD

Professor of Medicine, Division of Endocrinology, Diabetes, & Metabolism

Johns Hopkins University

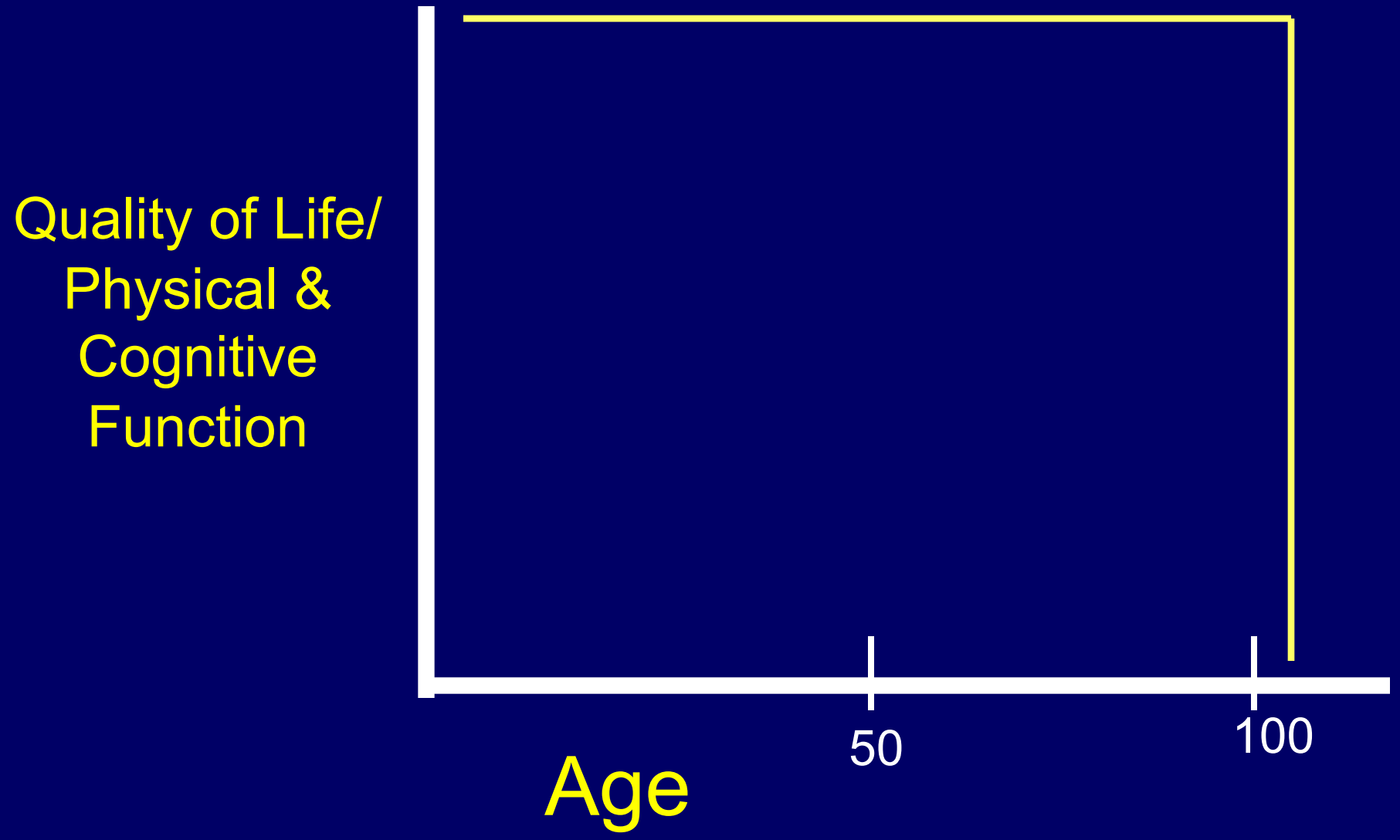
Baltimore, MD

This activity is jointly provided by Physicians' Research Network and the Medical Society of the State of New York.

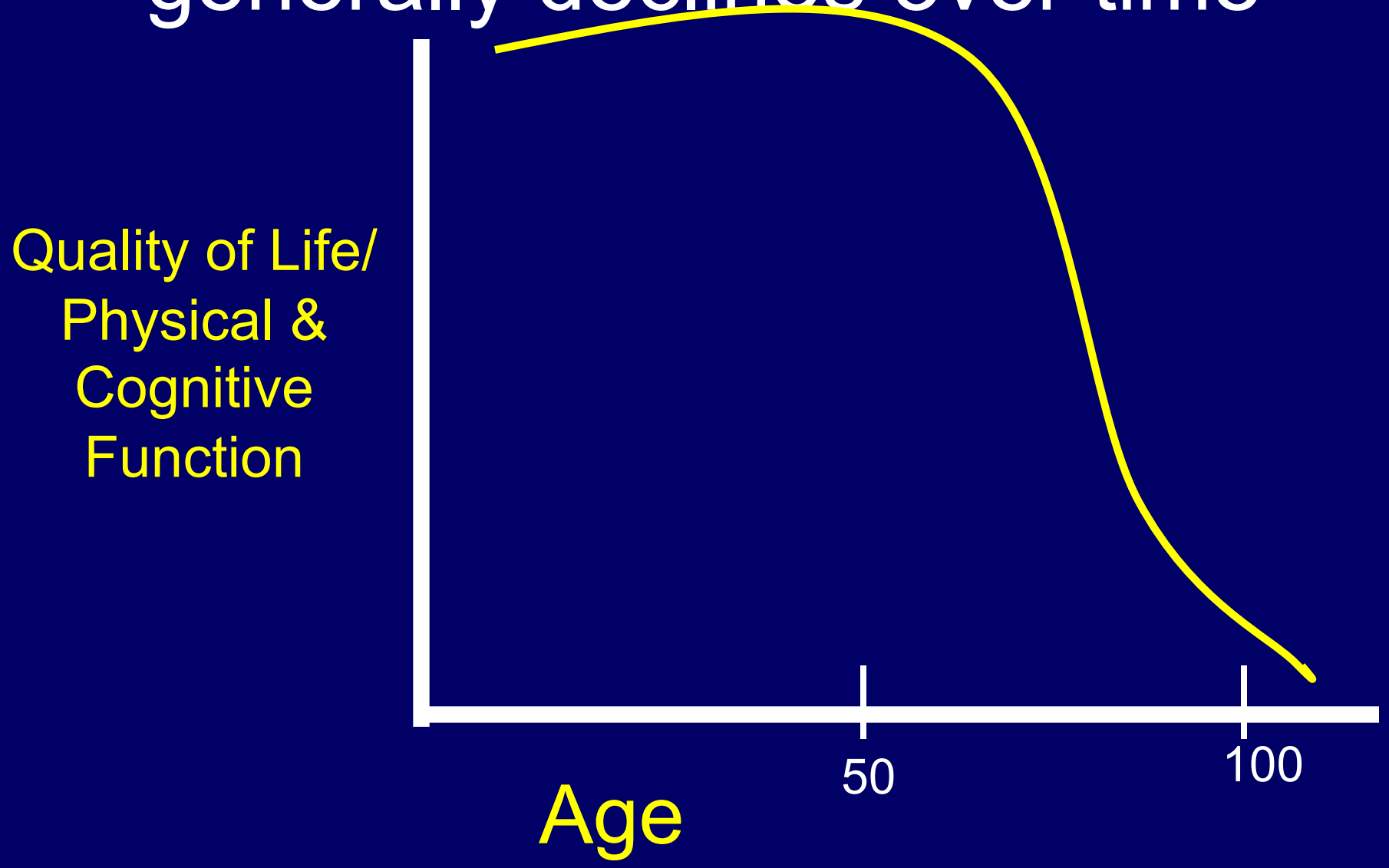
Disclosures

- Consultant: Gilead Sciences, Merck, ViiV Healthcare, BMS, EMD-Serono, Theratechnologies

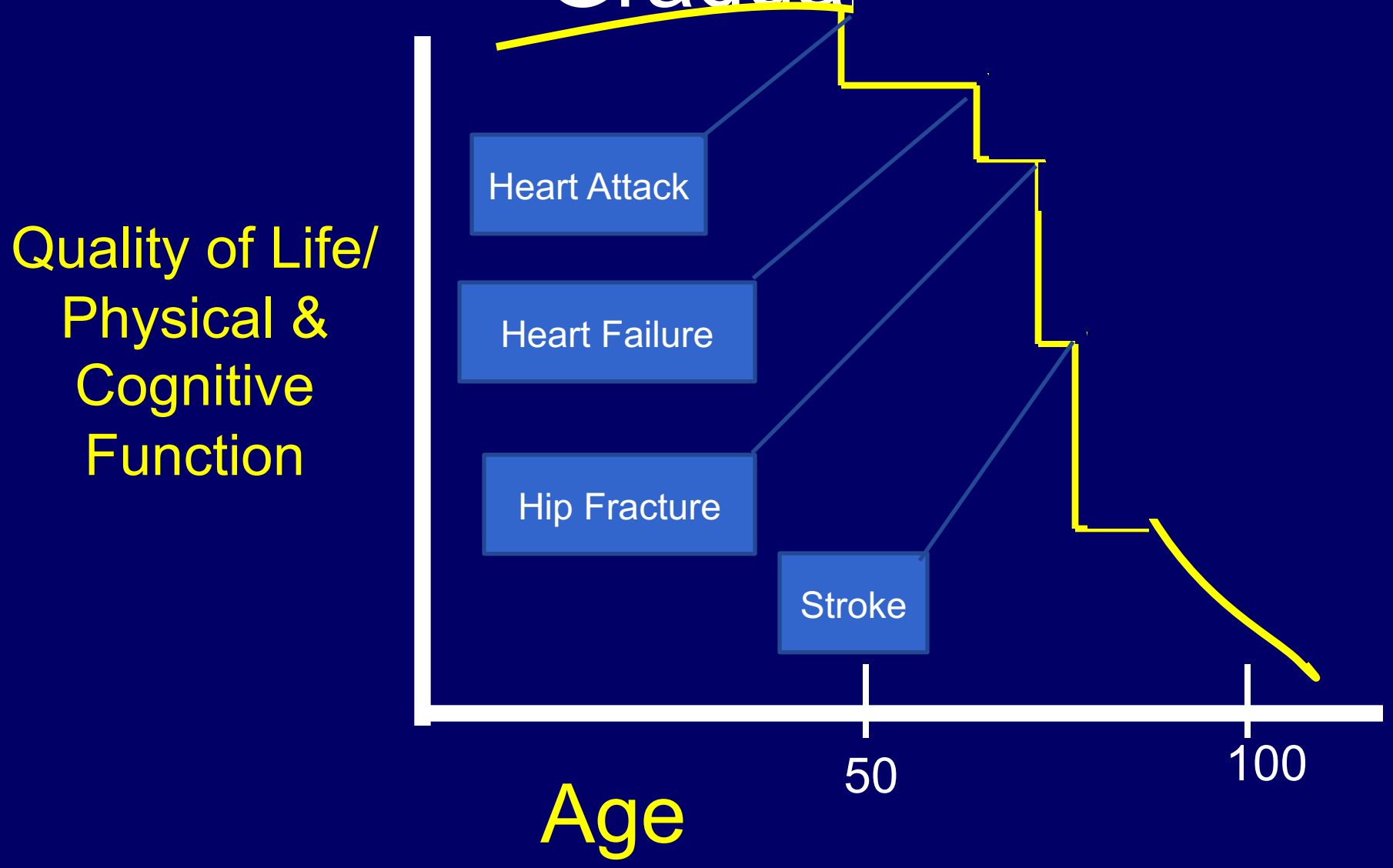
The Ideal Life: Quality x Time



Physical & cognitive function generally declines over time



Decline in Function May Not Be Gradual



Prevention of Comorbid Events is Essential and Achievable

- Good screening tests are available for comorbid conditions
- Many behavioral factors contribute to comorbid conditions and can be modified
- Early treatment is important
- Good treatments exist that can decrease the risk of events (cardiovascular disease, fracture)
- Preventing complications can alter the aging process

Prevention of Comorbid Events is Essential and Achievable

- Good screening tests are available for comorbid conditions
- Many behavioral factors contribute to comorbid conditions and can be modified
- Early treatment is important
- Good treatments exist that can decrease the risk of events (cardiovascular disease, fracture)
- Preventing complications can alter the aging process

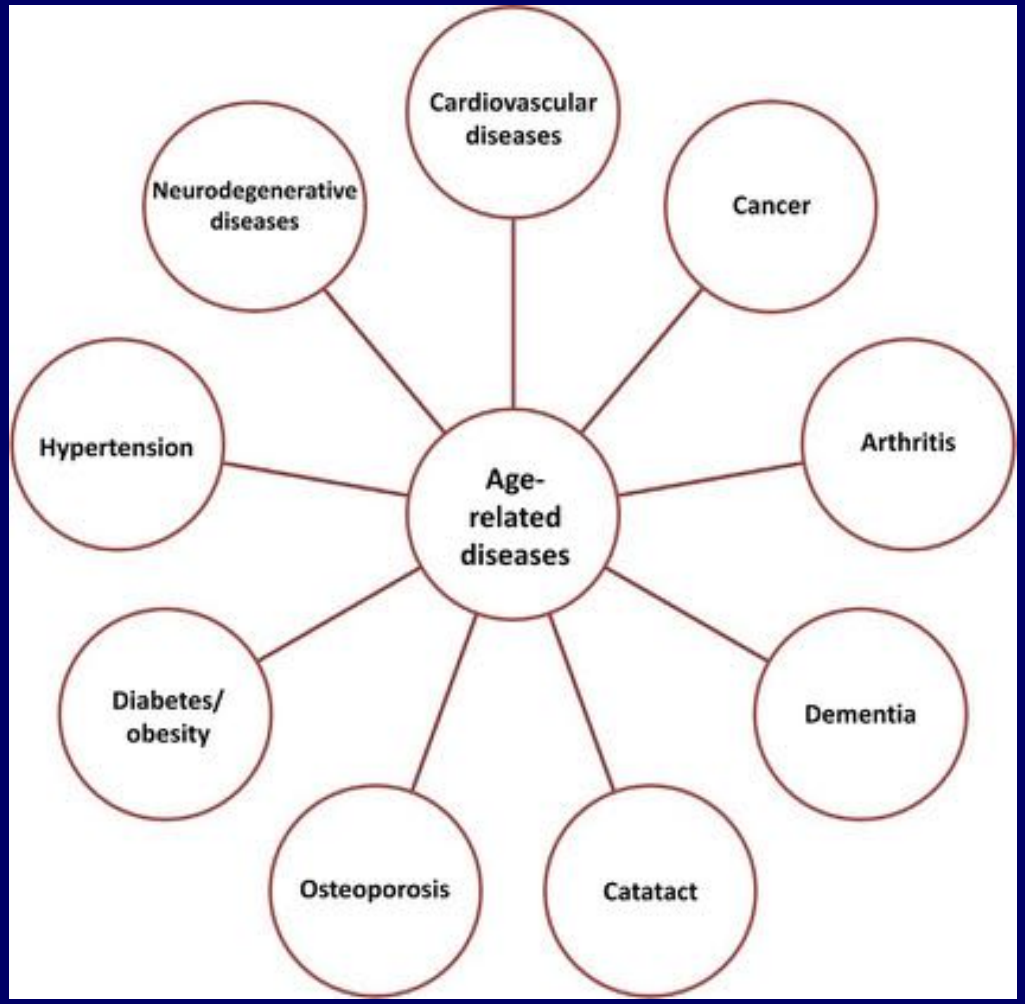
Diet
Physical Activity

Prevention of Comorbid Events is Essential and Achievable

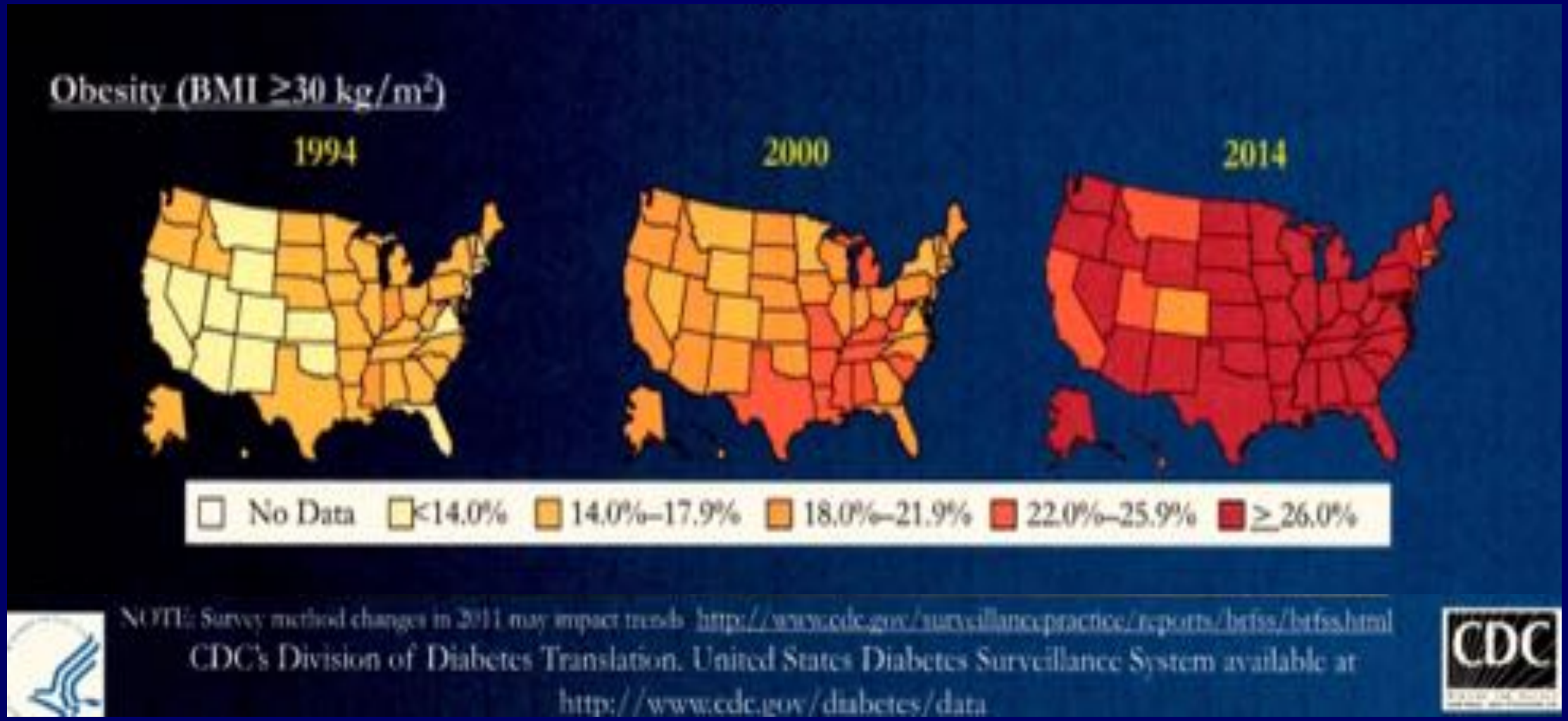
- Good screening tests are available for comorbid conditions
- Many behavioral factors contribute to comorbid conditions and can be modified
- Early treatment is important
- Good treatments exist that can decrease the risk of events (cardiovascular disease, fracture)
- Preventing complications can alter the aging process

Excess Adiposity

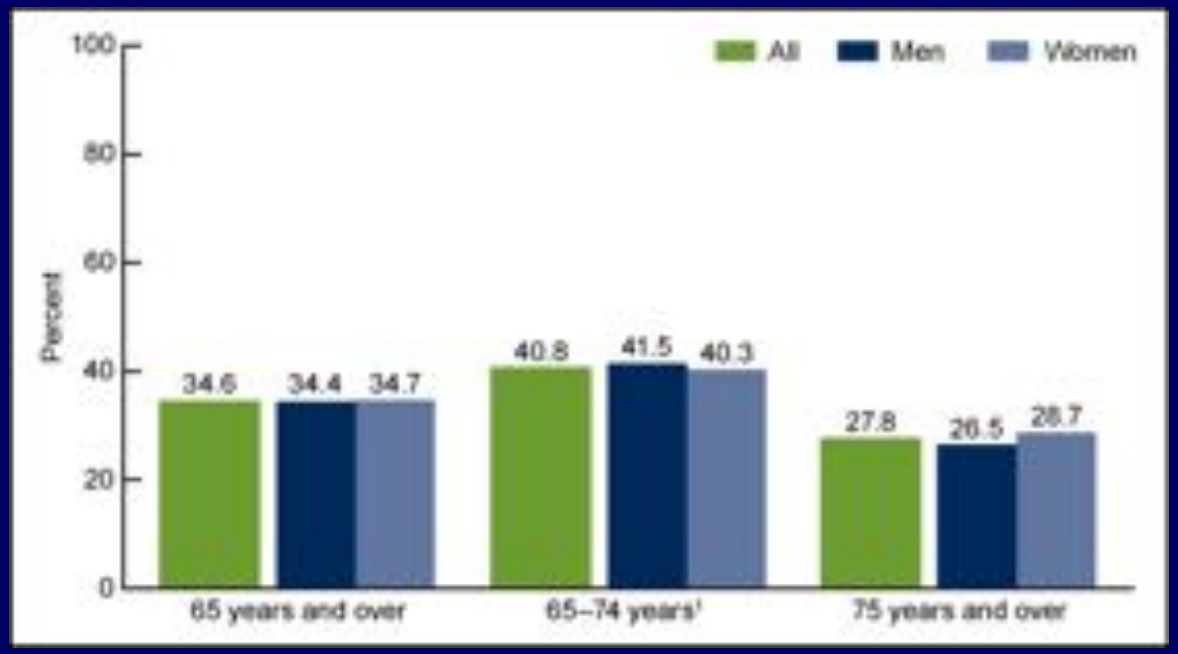
Obesity and Aging Related Diseases



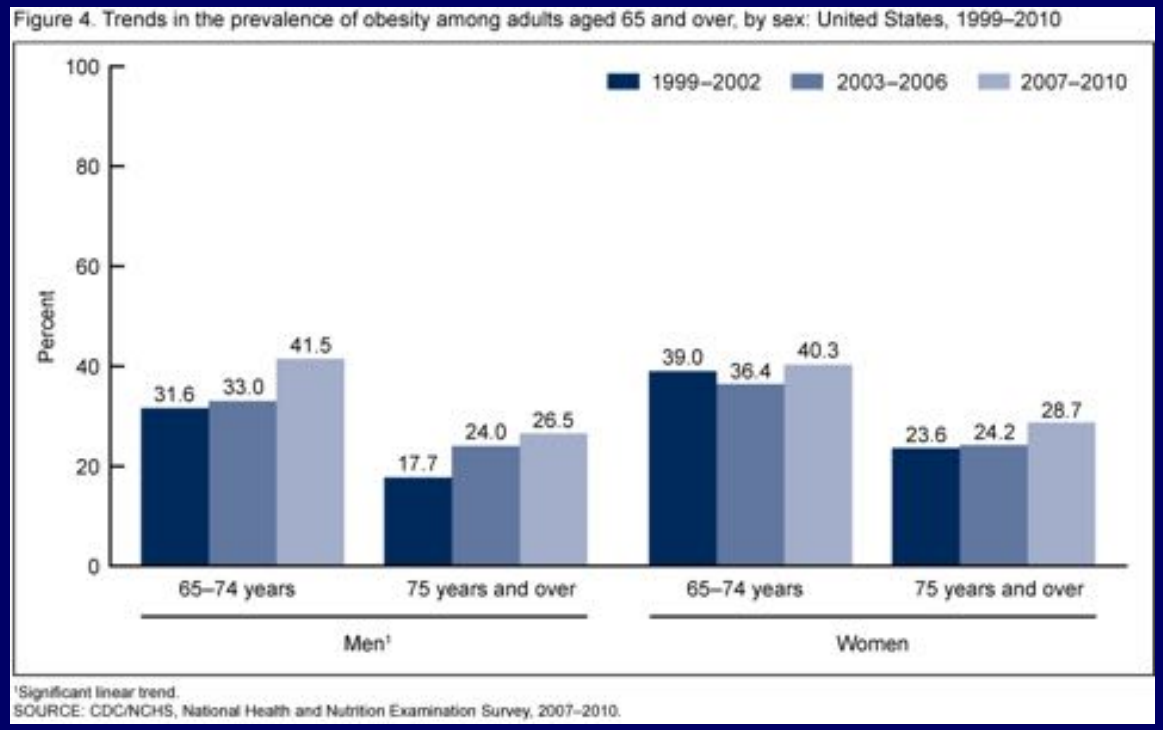
Increasing Prevalence of Obesity in US



Obesity Prevalence is Lower Among Older Adults, But Has Increased Over Time

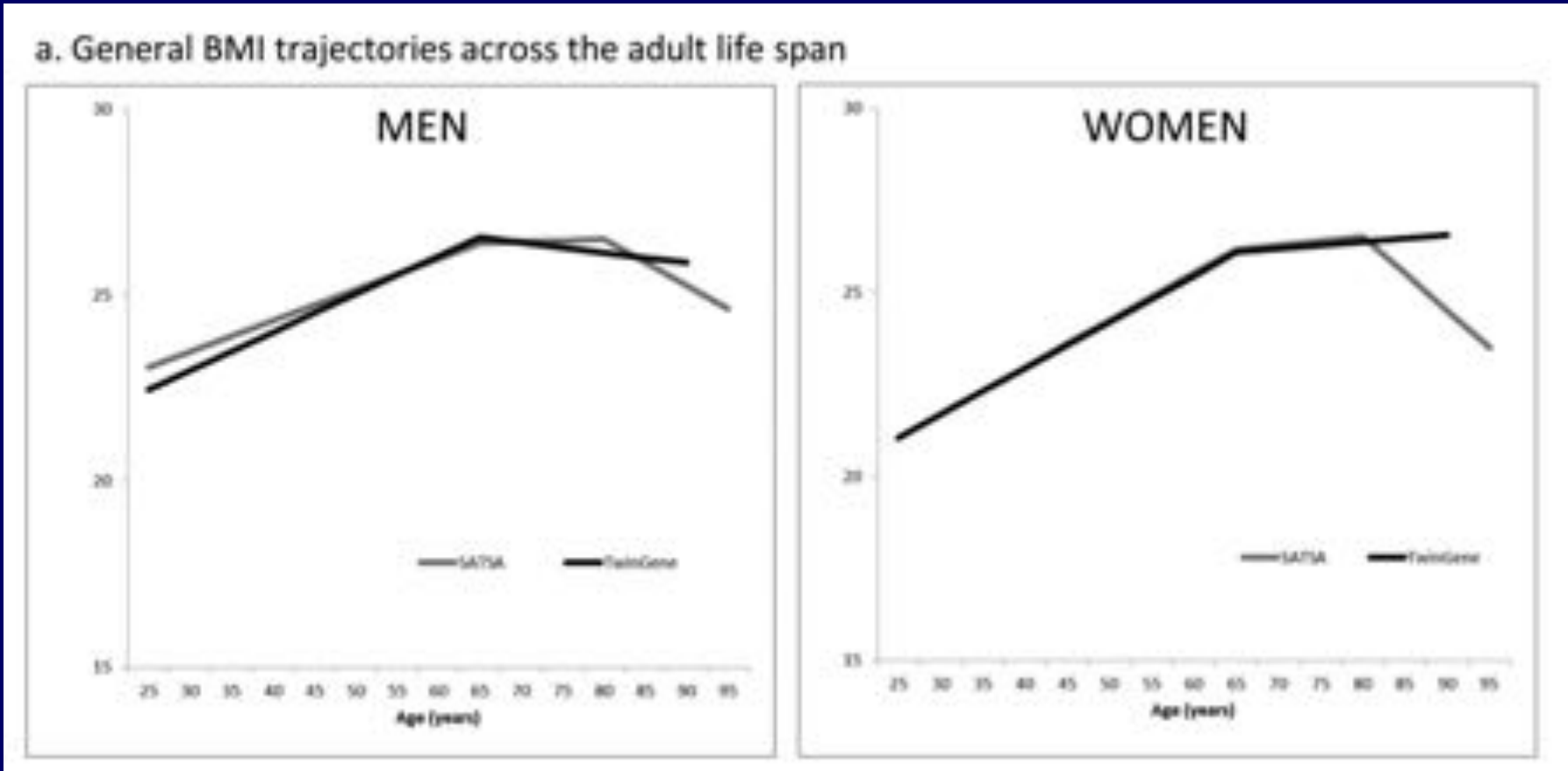


NHANES Survey 2007–2010



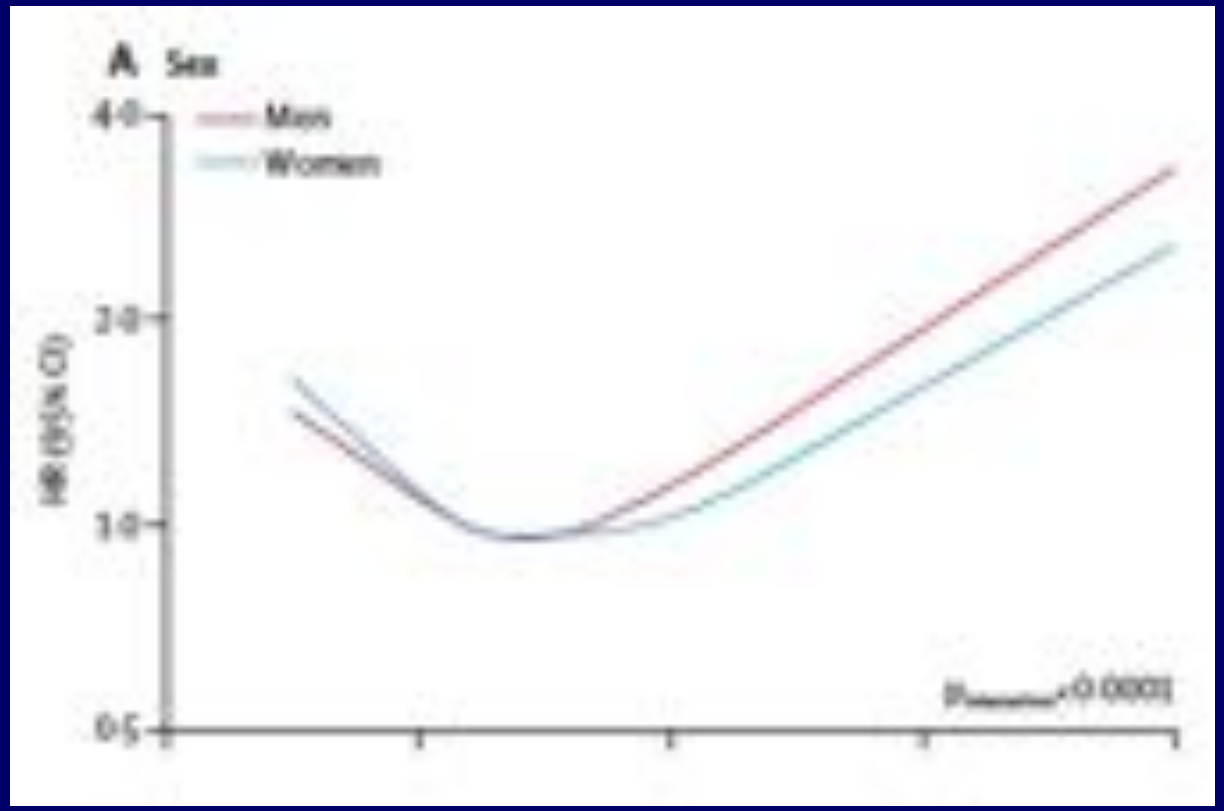
https://www.cdc.gov/nchs

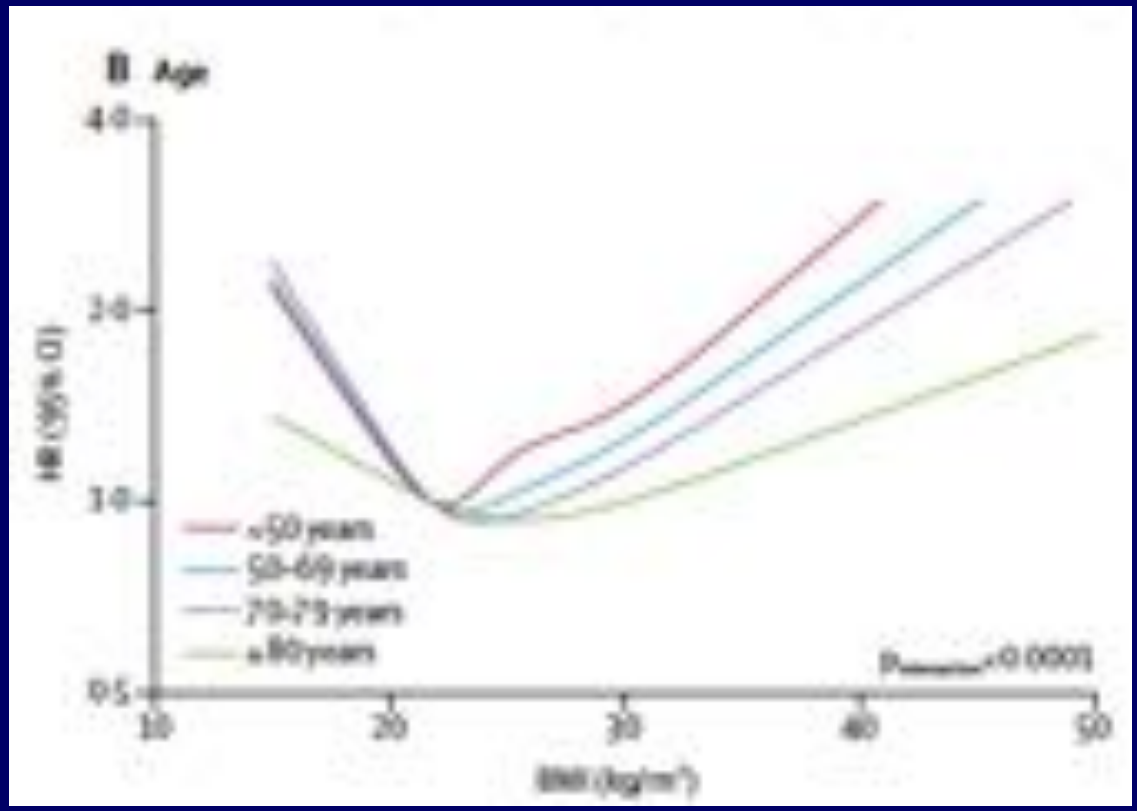
Longitudinal Changes in BMI in General Population: Sweden



Dahl AK, et al. Int J Obes (Lond) 2014;38:1133–41

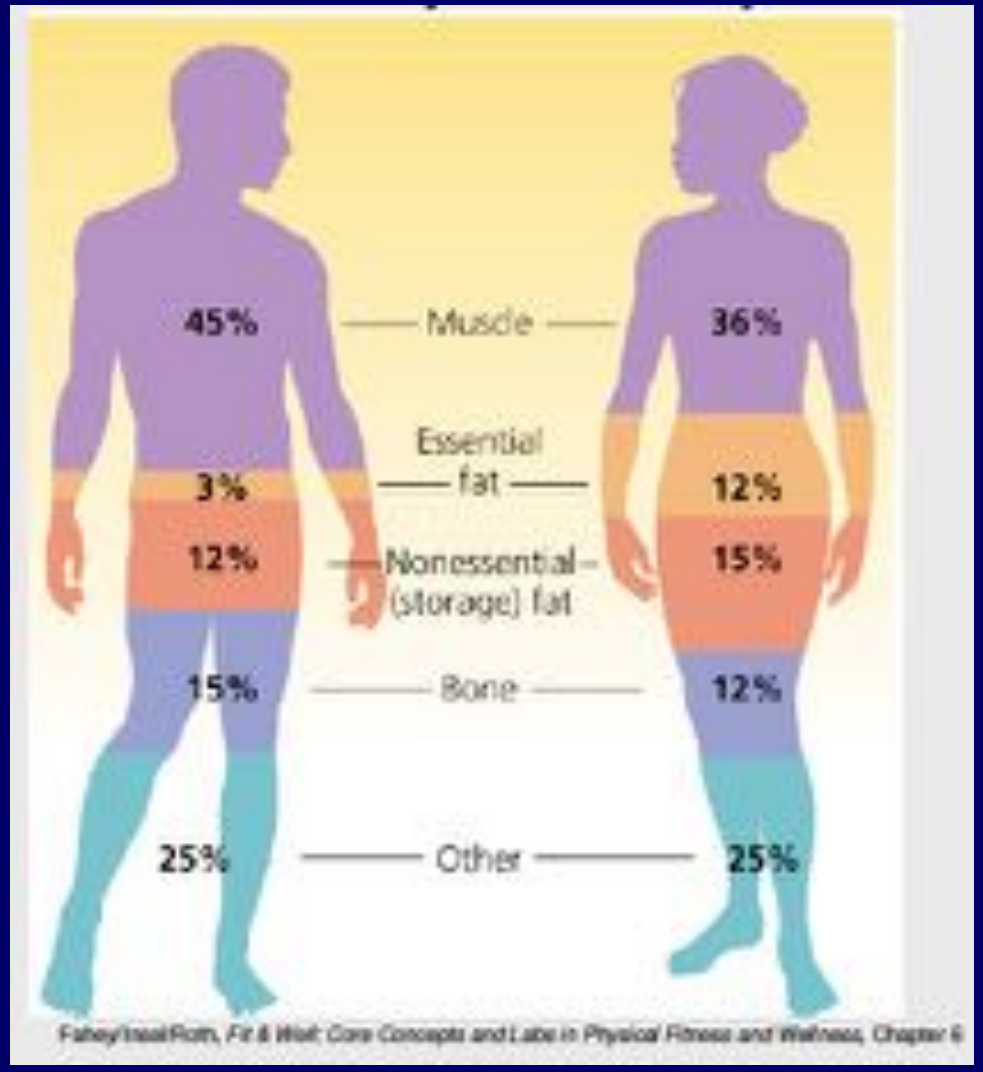
Limitations of BMI as Risk Predictor: J-Shape Relationship with Mortality

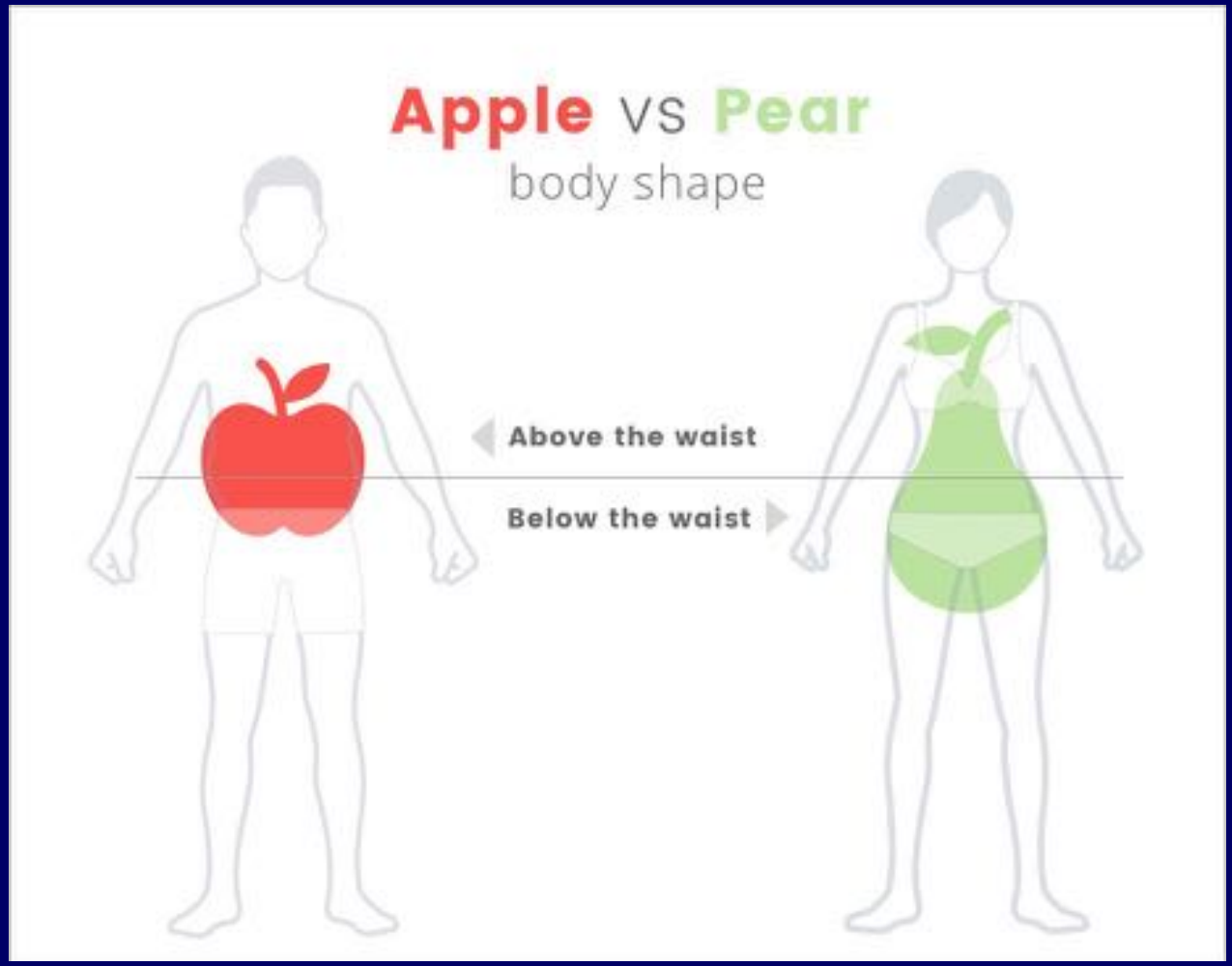




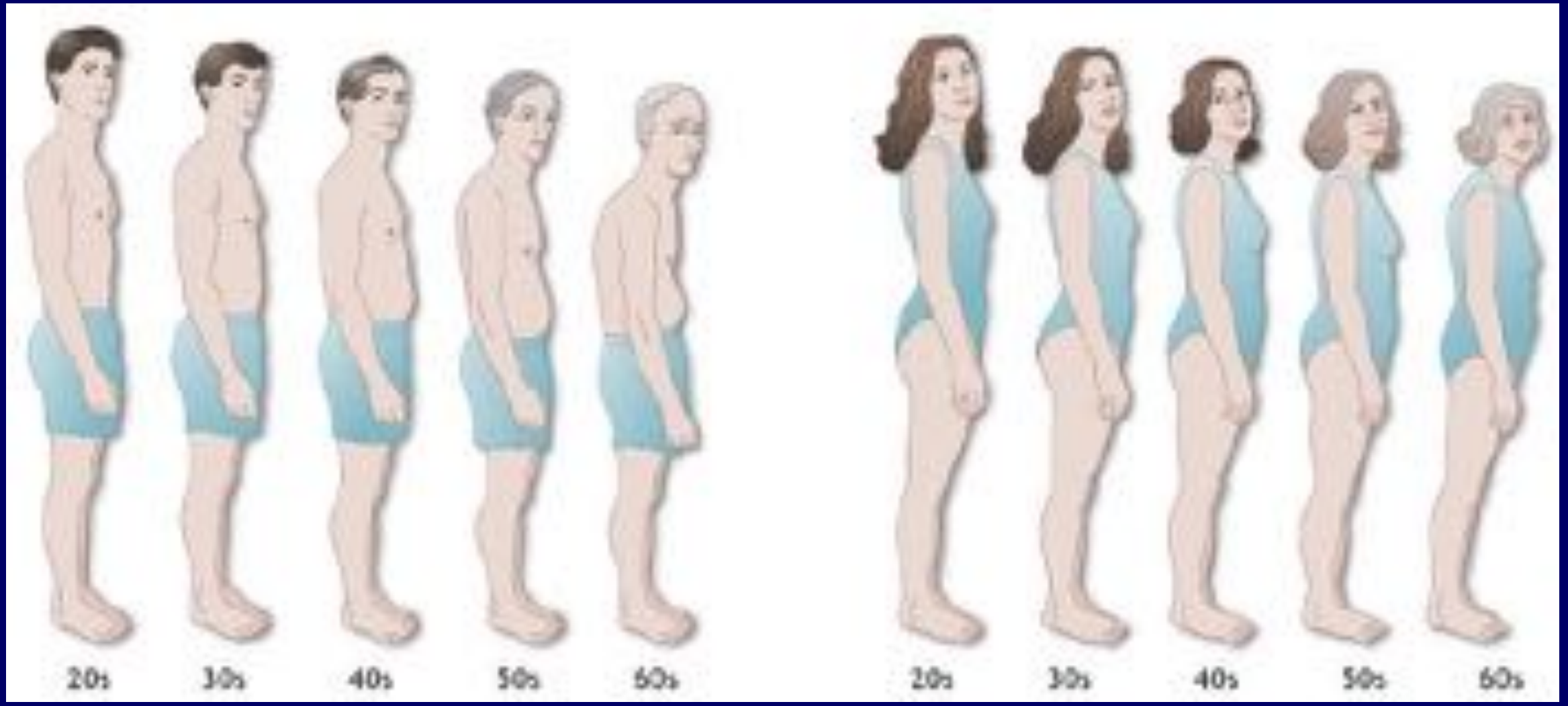
Bhaskaran, Lancet Diab Endo, 2018

Weight vs Body Composition

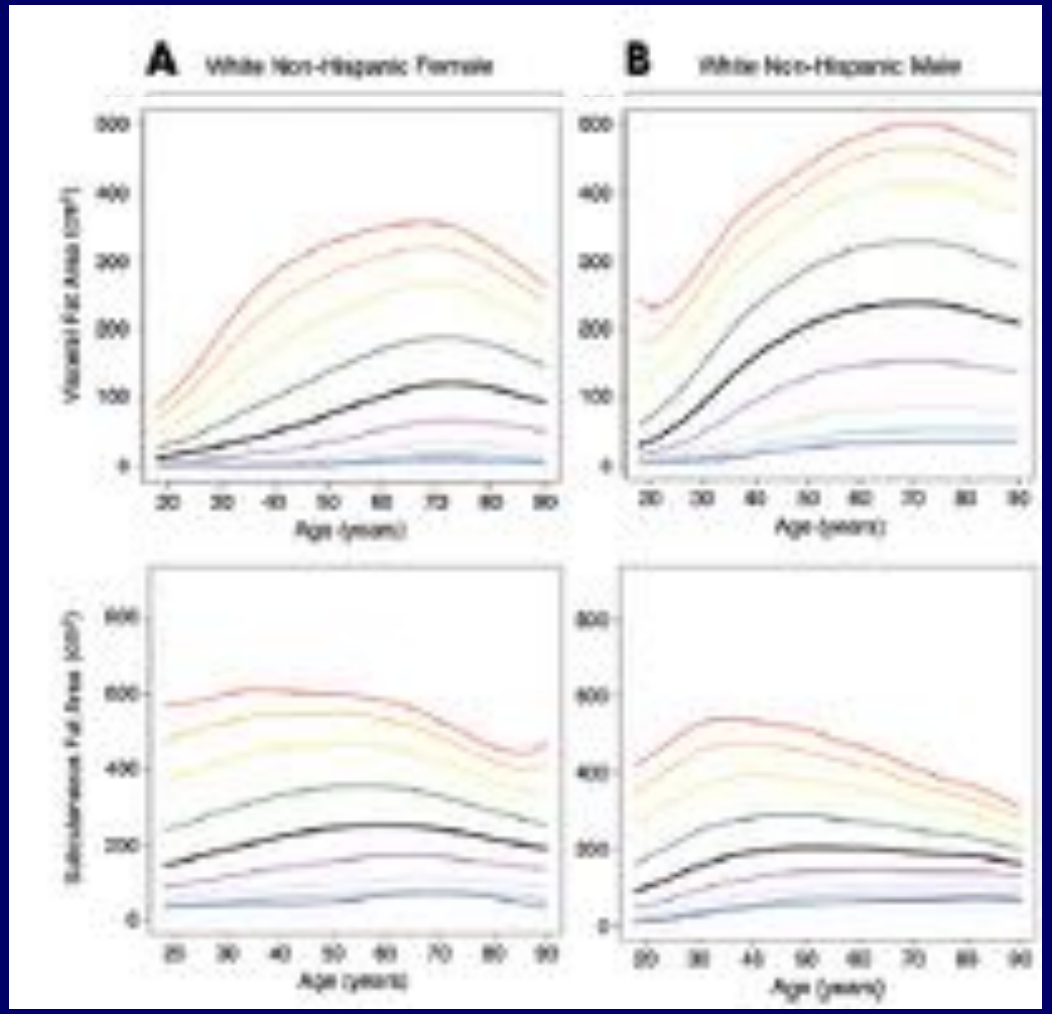


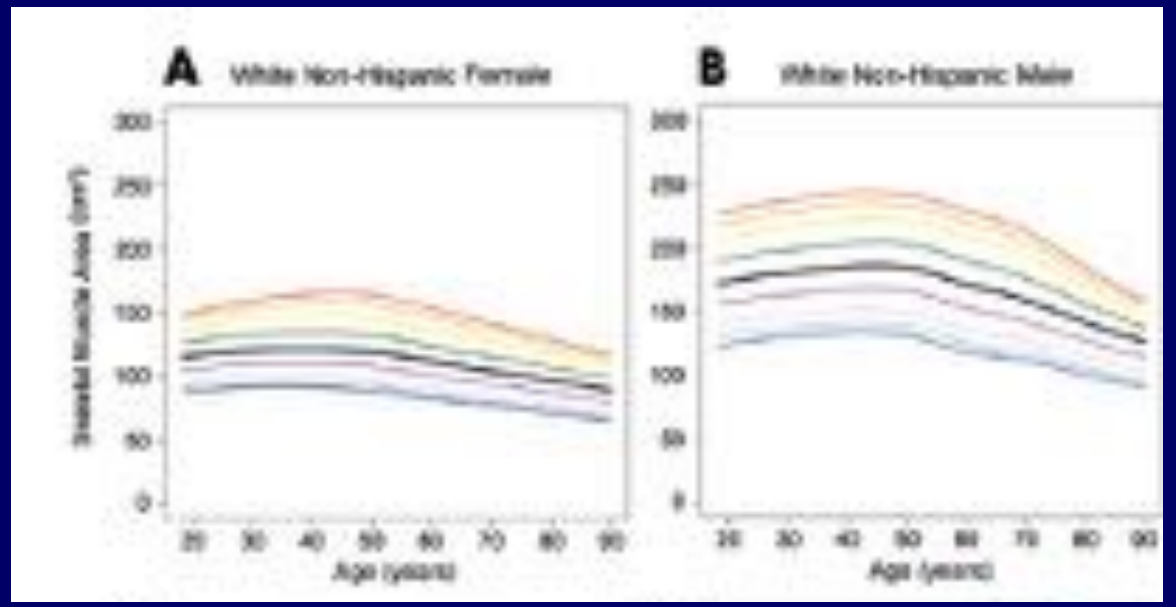


Changes in Body Composition and Fat Distribution with Aging



CT-measured Body Composition with Age

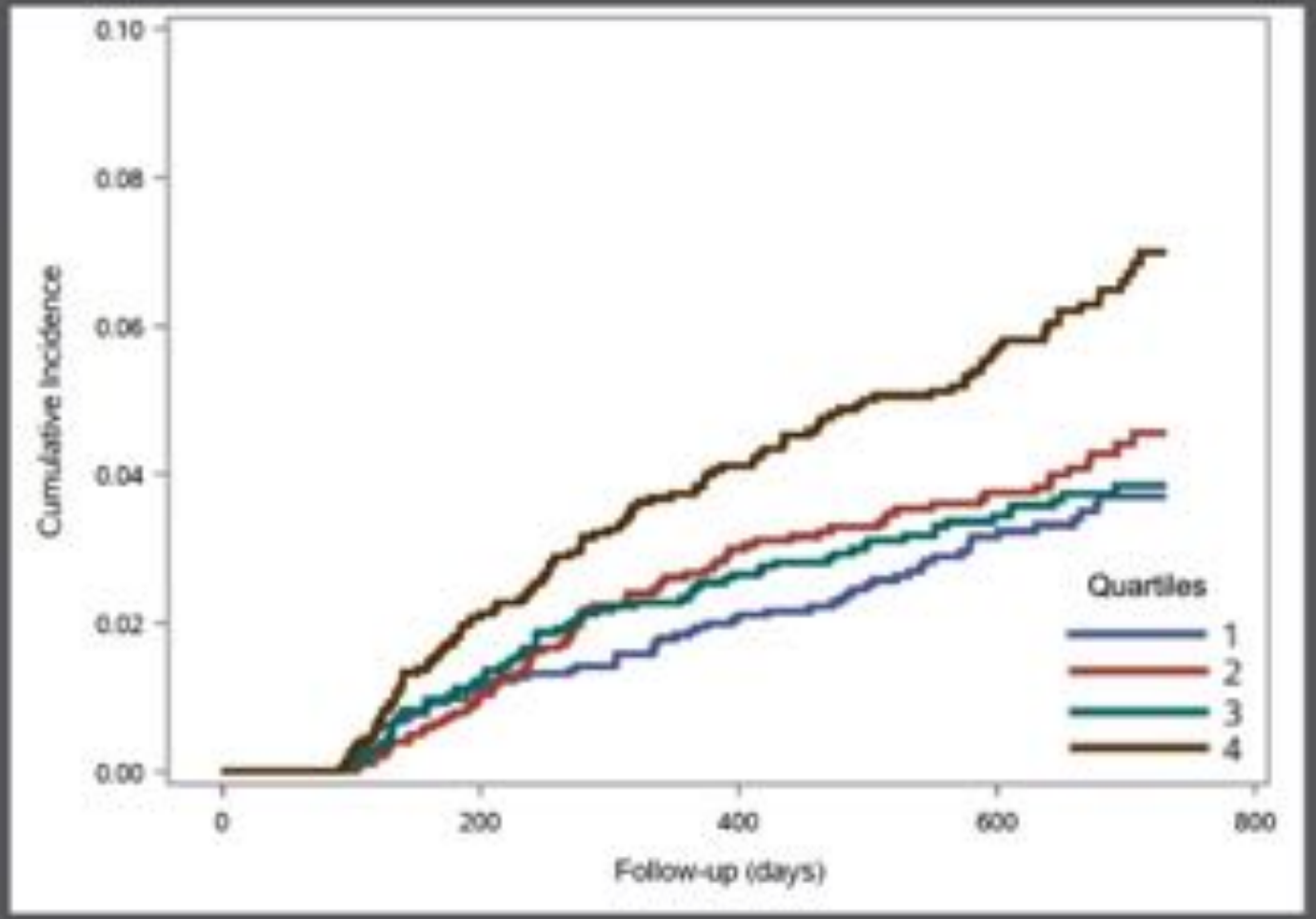




Women, n=4971; Men, n=3963

Magudia, Radiology, 2020

Heart Attack and Visceral Fat Area



Quartile 4

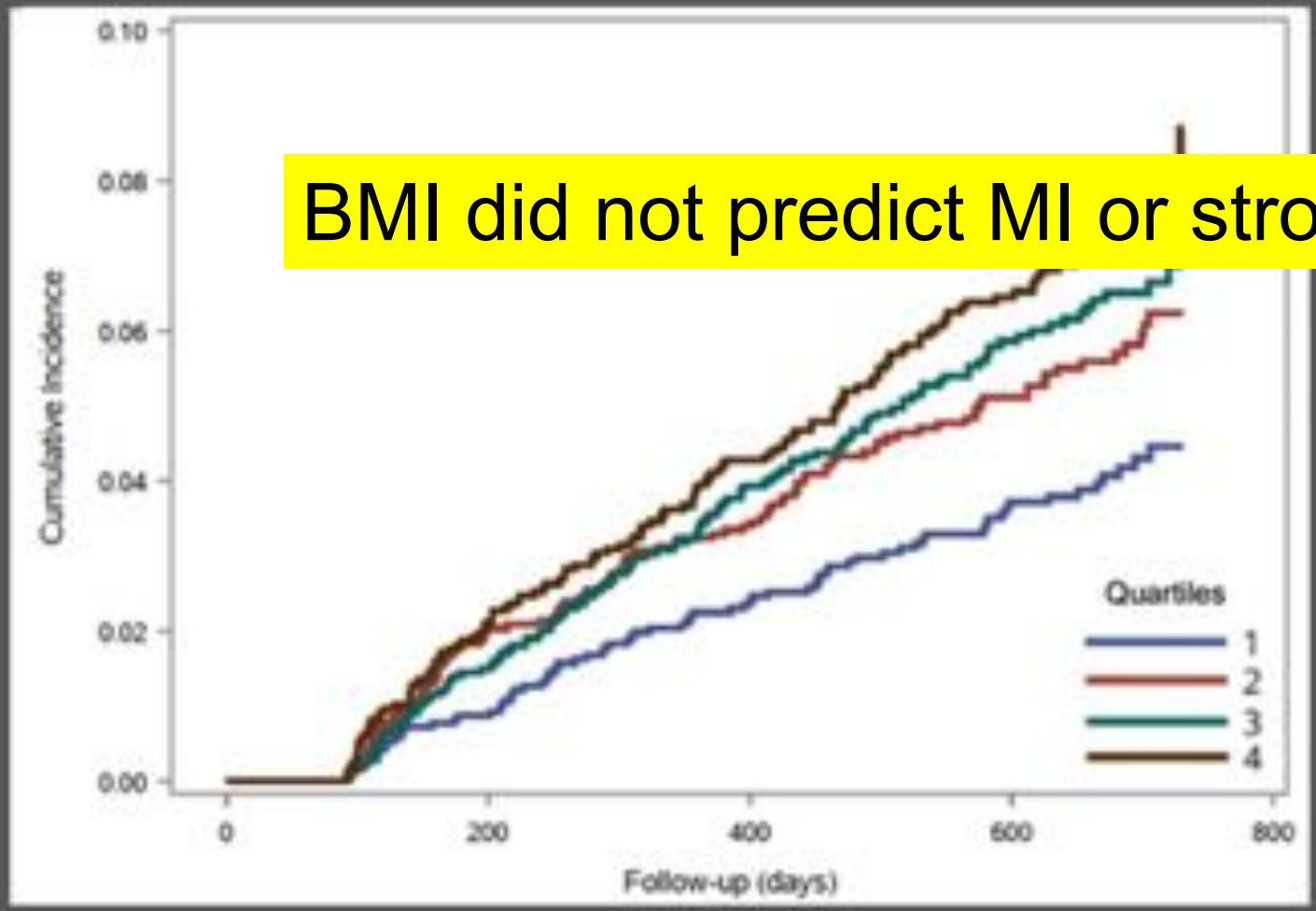
Quartile 3
Quartile 2
Quartile 1

Univariate
p<0.0001

Multivariate
p=0.04

Magudia, AJR, 2023

Stroke and Visceral Fat Area



BMI did not predict MI or stroke

Quartile 4

3

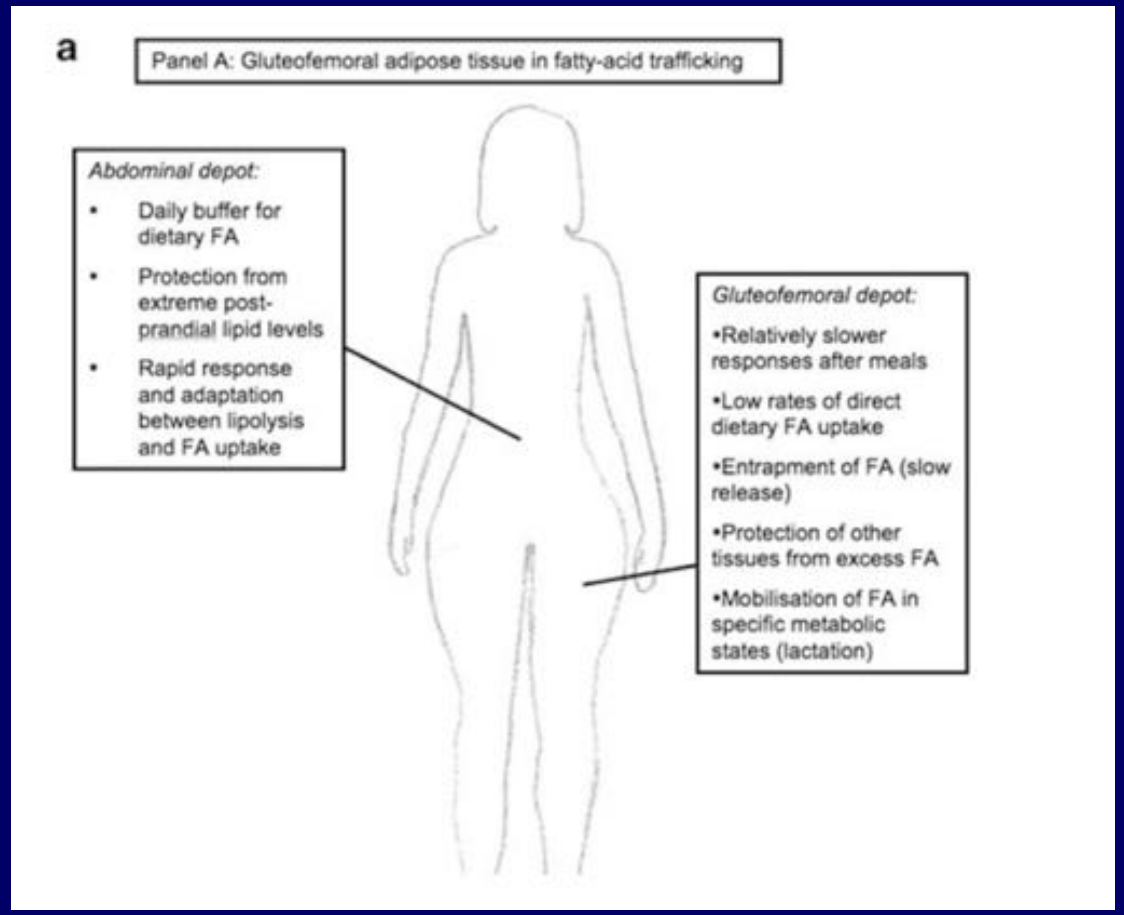
Quartile 2

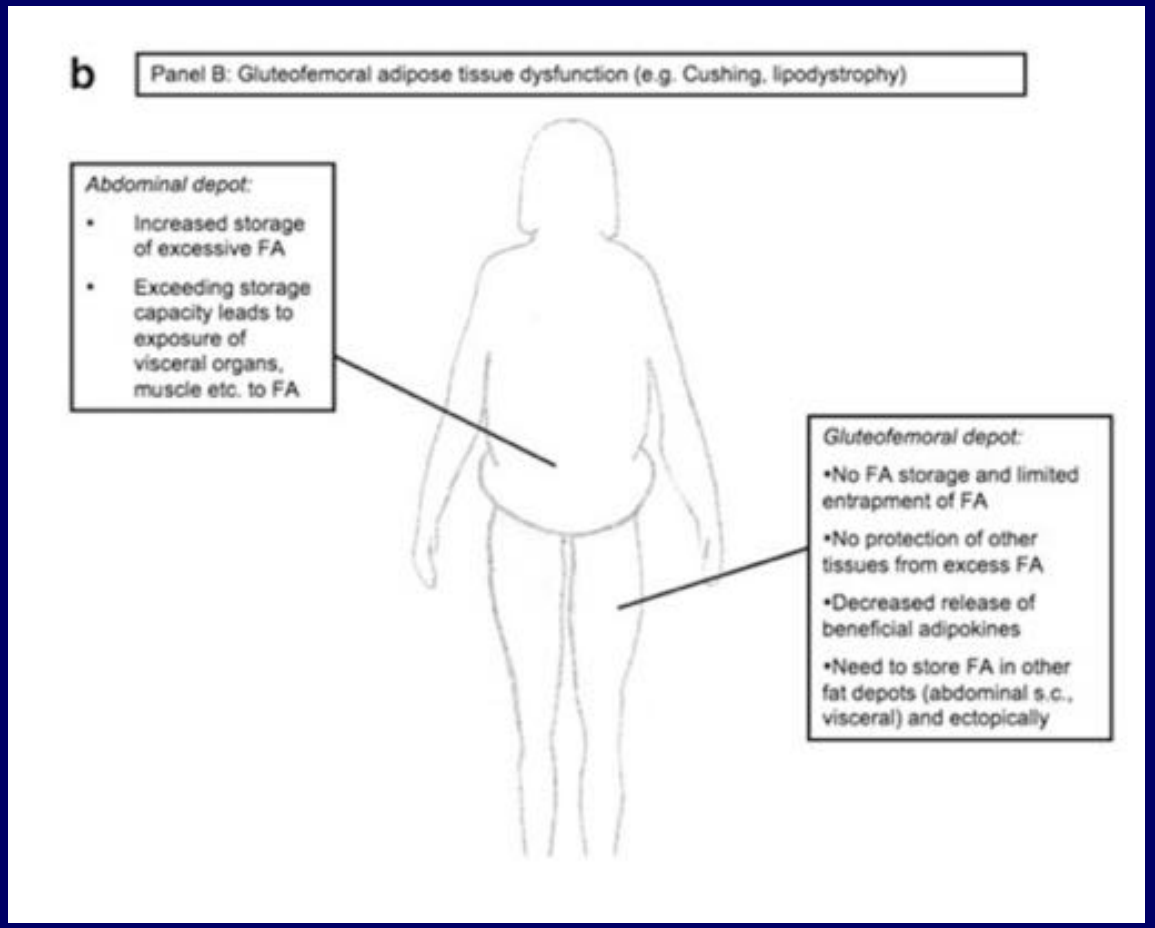
Quartile 1

Univariate
p<0.0001

Multivariate
p=0.04

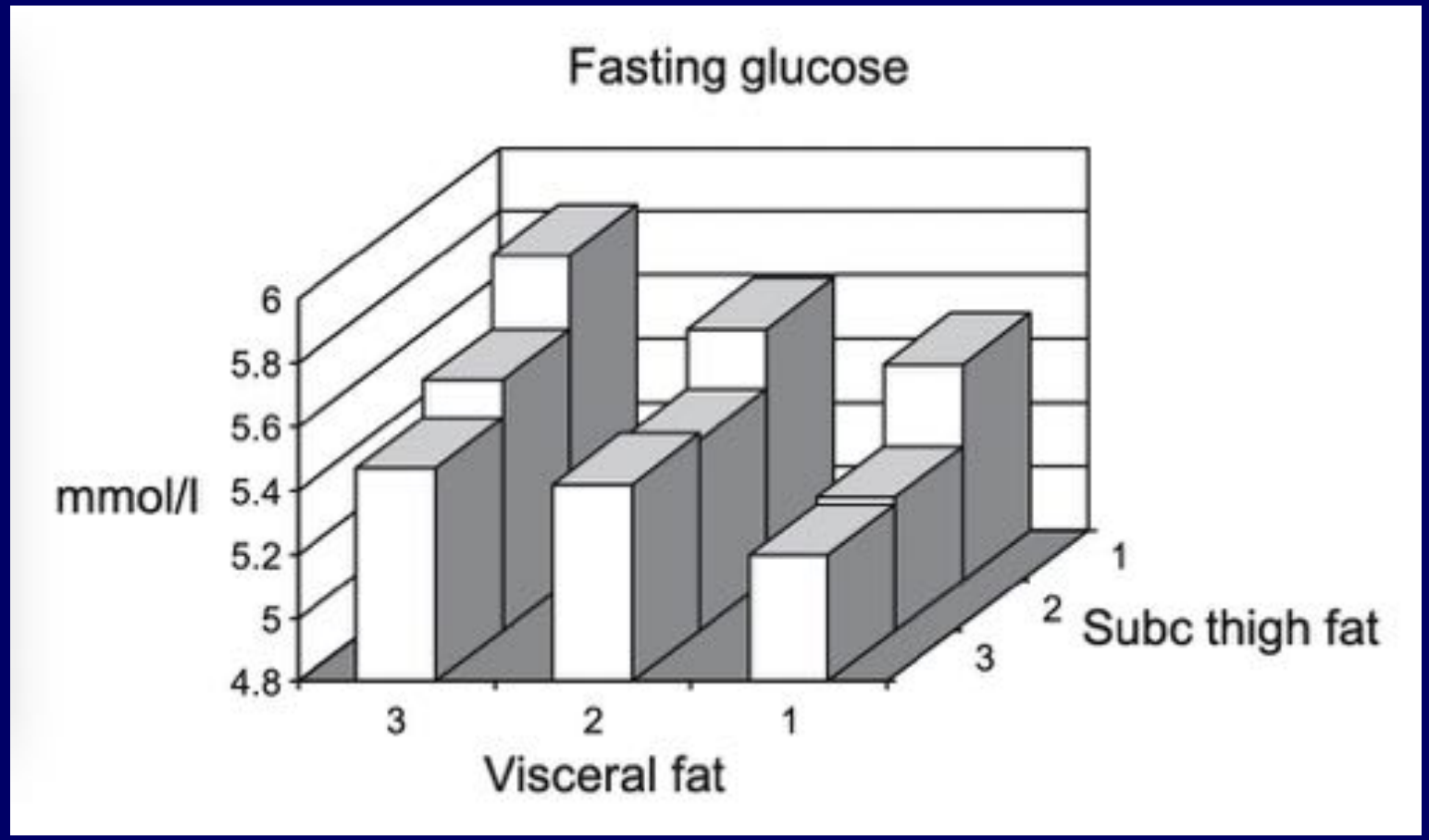
Lower body fat has a different function than central fat





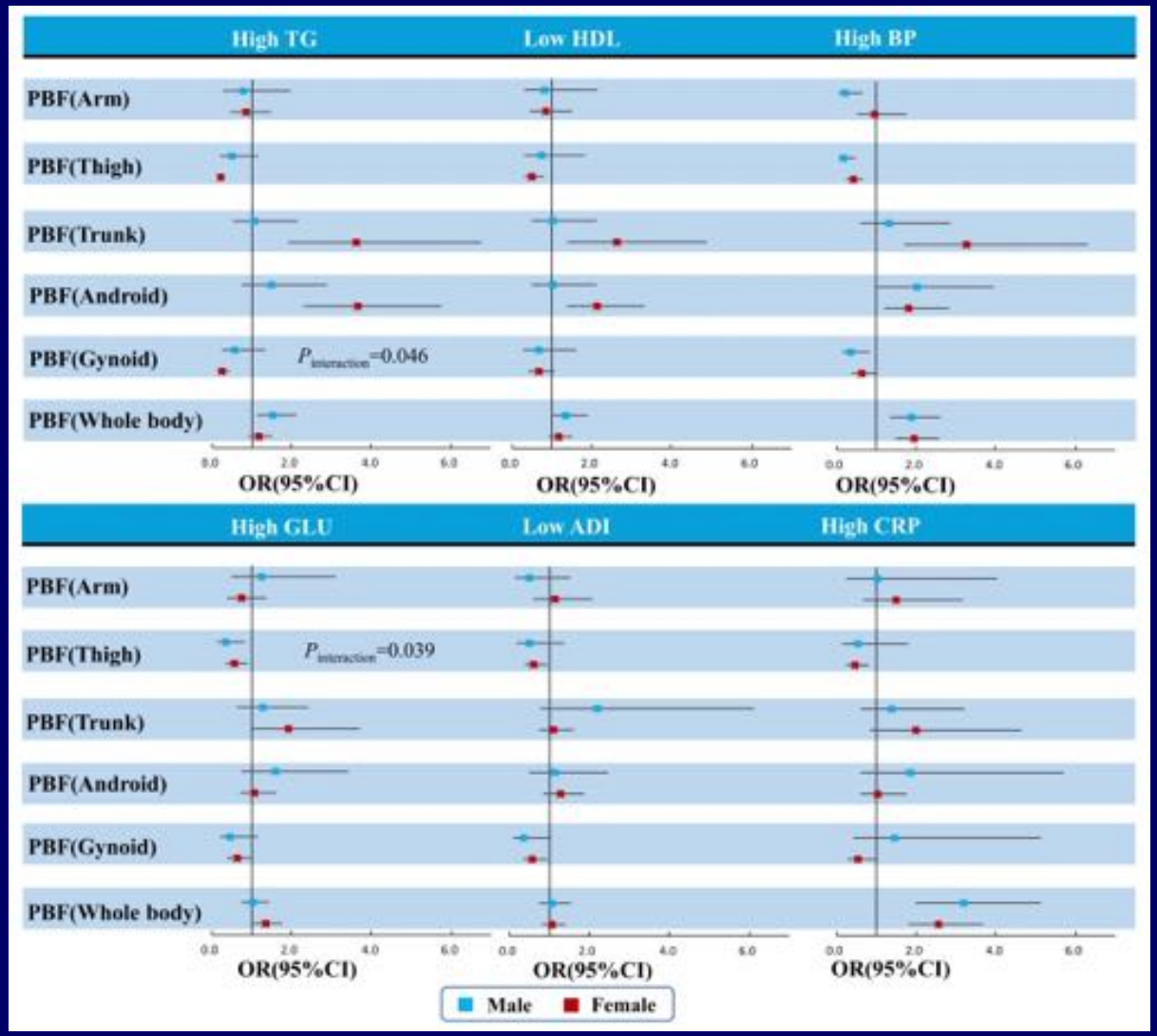
Manolopoulos, Int J Obesity, 2010

Opposite associations between visceral and subcutaneous thigh fat on fasting glucose: Health ABC Study



Snijder, Diabetologia, 2004

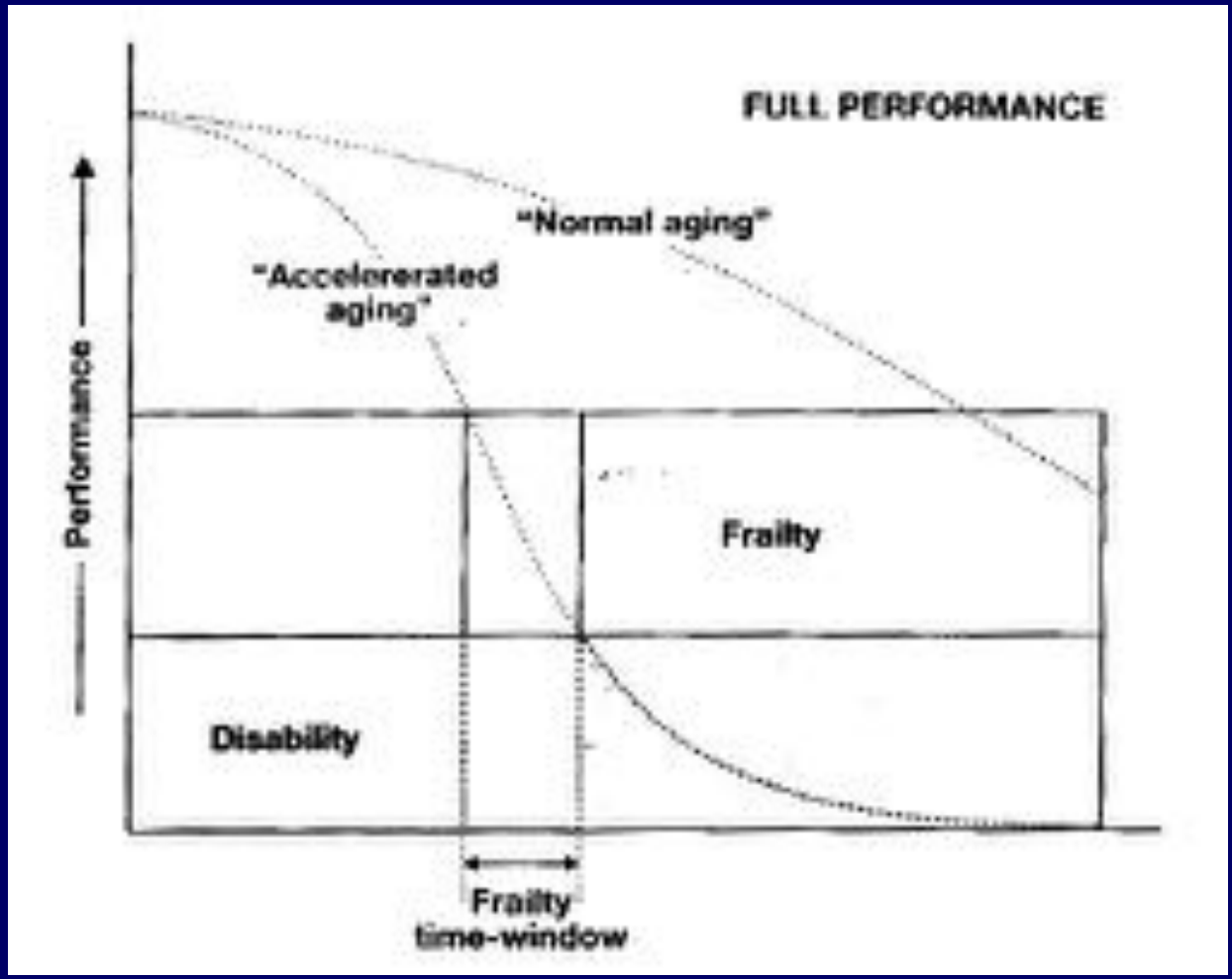
Lower body fat is protective for CV risk factors



Yang, BMC Public Health, 2021

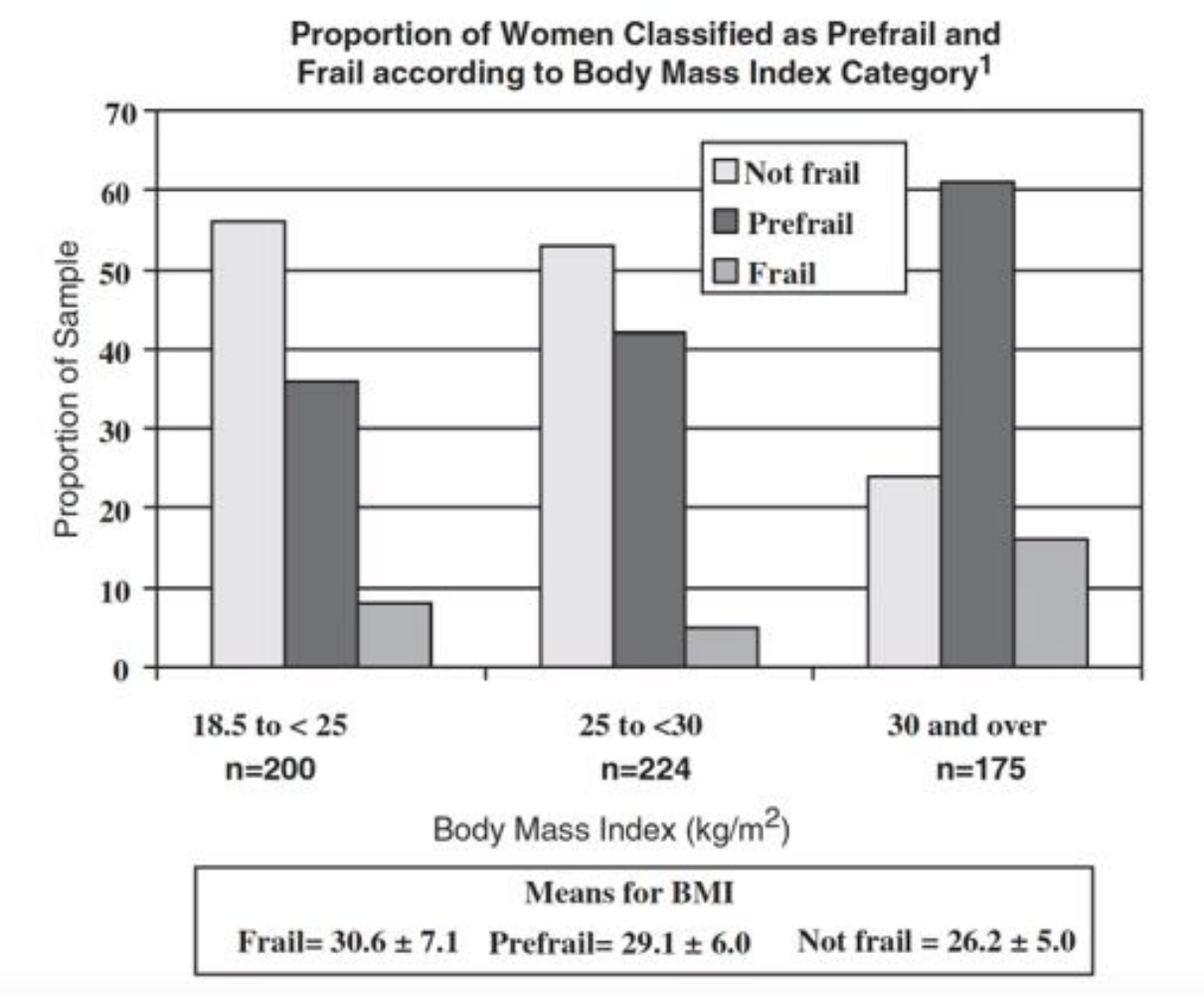
Frailty: A Brief Overview

- Weight loss
- Weakness
- Exhaustion
- Slowness
- ↓ Physical Activity



[1] Fried LP, *et al.* 2005

Higher BMI is associated with a higher prevalence of pre-frailty/frailty:WHAS



Blaum, JAGS, 2005

Adiposity is associated with cognitive dysfunction

PeerJ. 2018; 6: e5624.
Published online 2018 Sep 7. doi: 10.7717/peerj.5624
PMCID: PMC6130234
PMID: 30210946

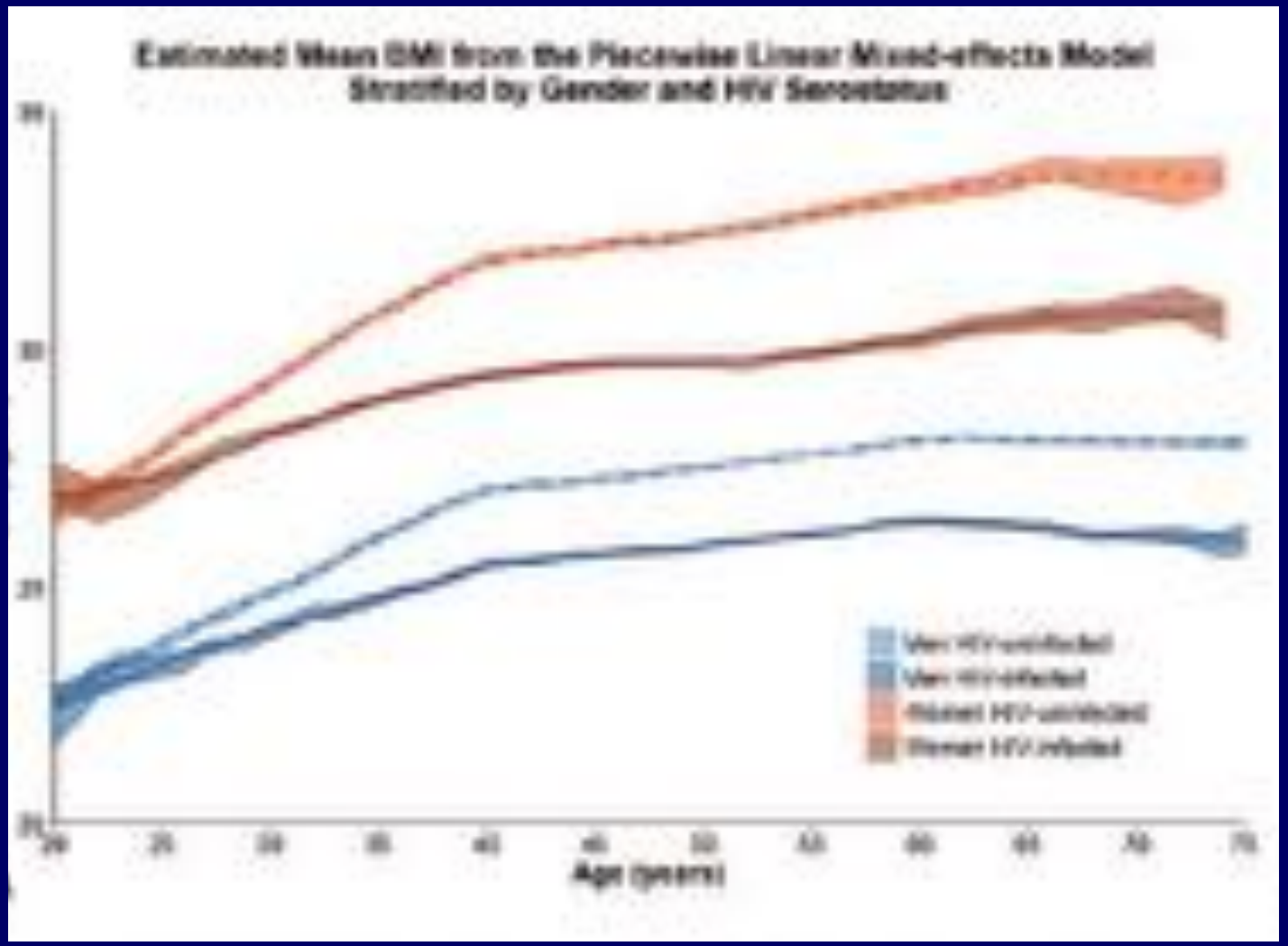
Measurement matters: higher waist-to-hip ratio but not body mass index is associated with deficits in executive functions and episodic memory

Andree Hartanto[✉1] and Jose C. Yong[1,2]

Summary in General Population

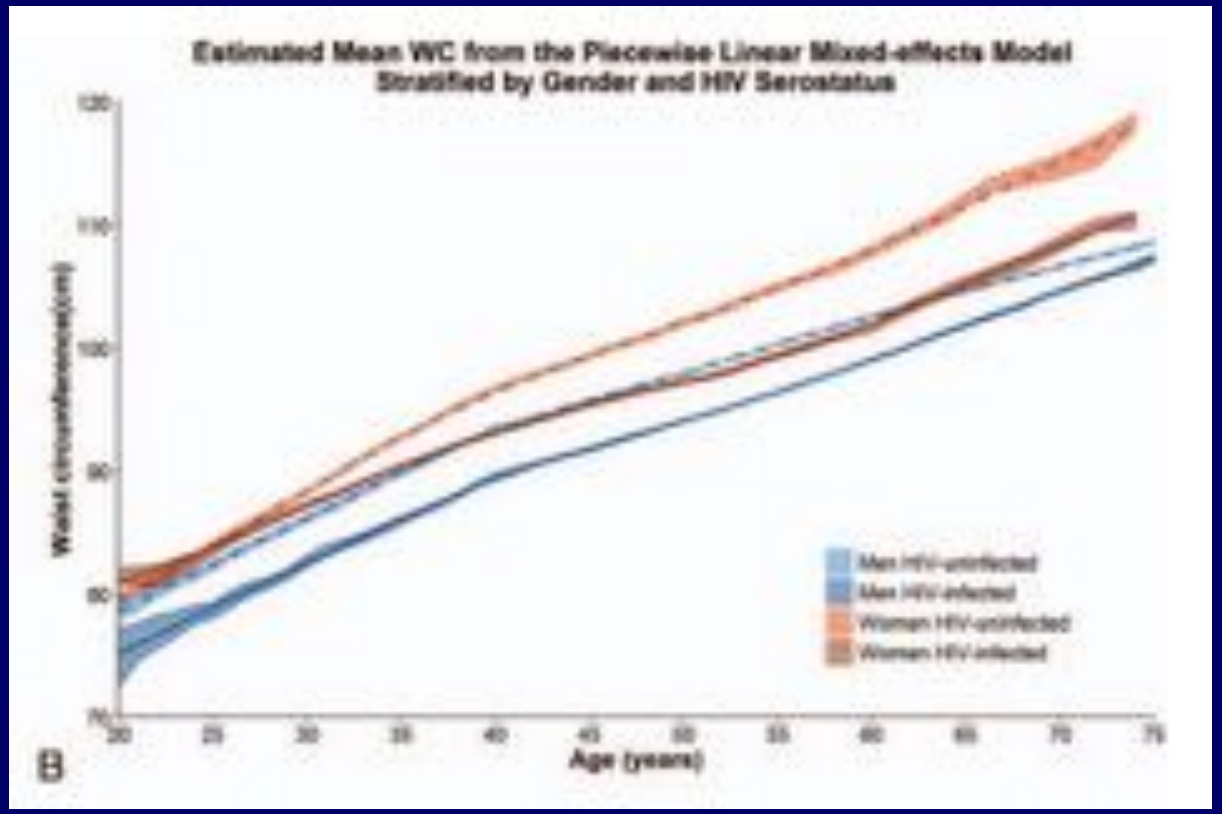
- Weight increases with age and then levels out
- Central adiposity increases with age which is associated with negative health outcomes
- Subcutaneous fat decreases with age, which is also associated with negative health outcomes
- In addition to cardiometabolic risk, excess adiposity is associated with declines in physical and cognitive function

Changes in BMI with Age: MACS and WIHS

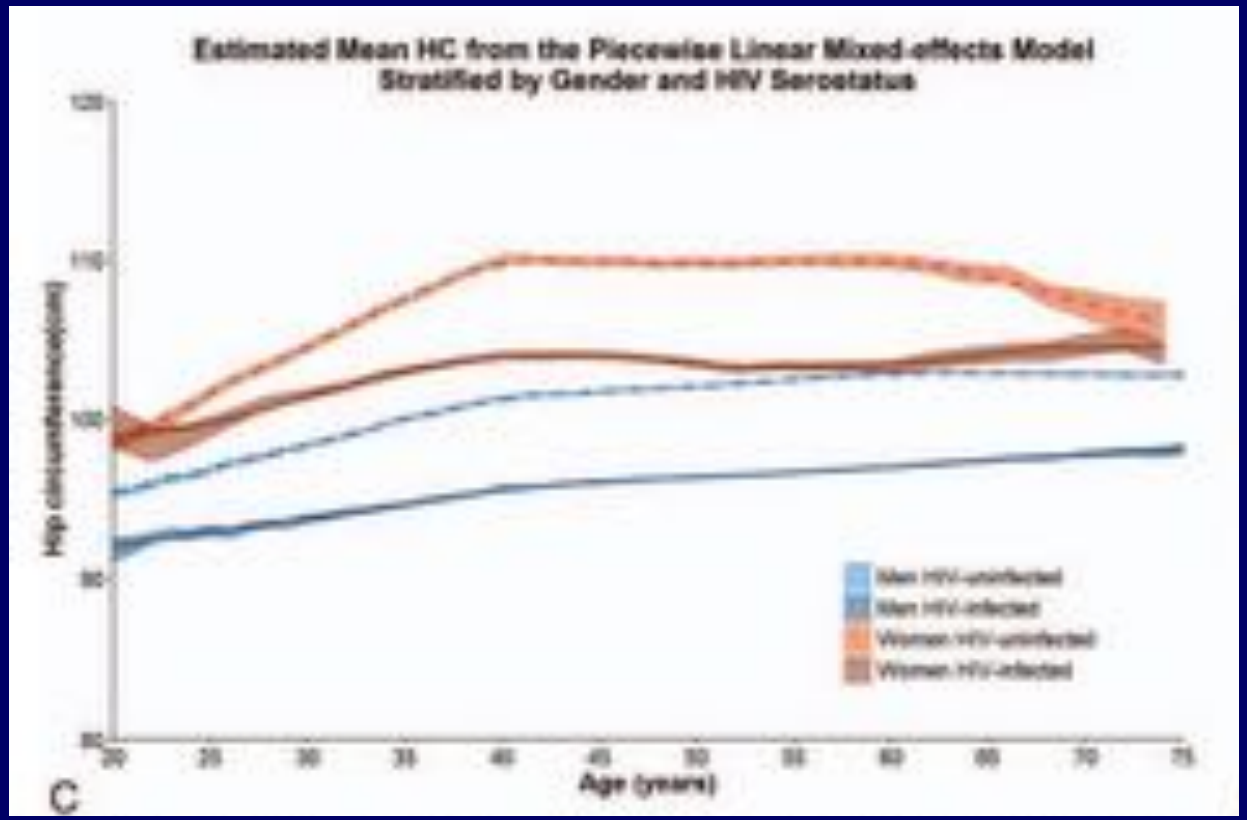


Erlandson, Medicine, 2016

Waist & Hip Circumference Changes in MACS/WIHS: 1999–2004



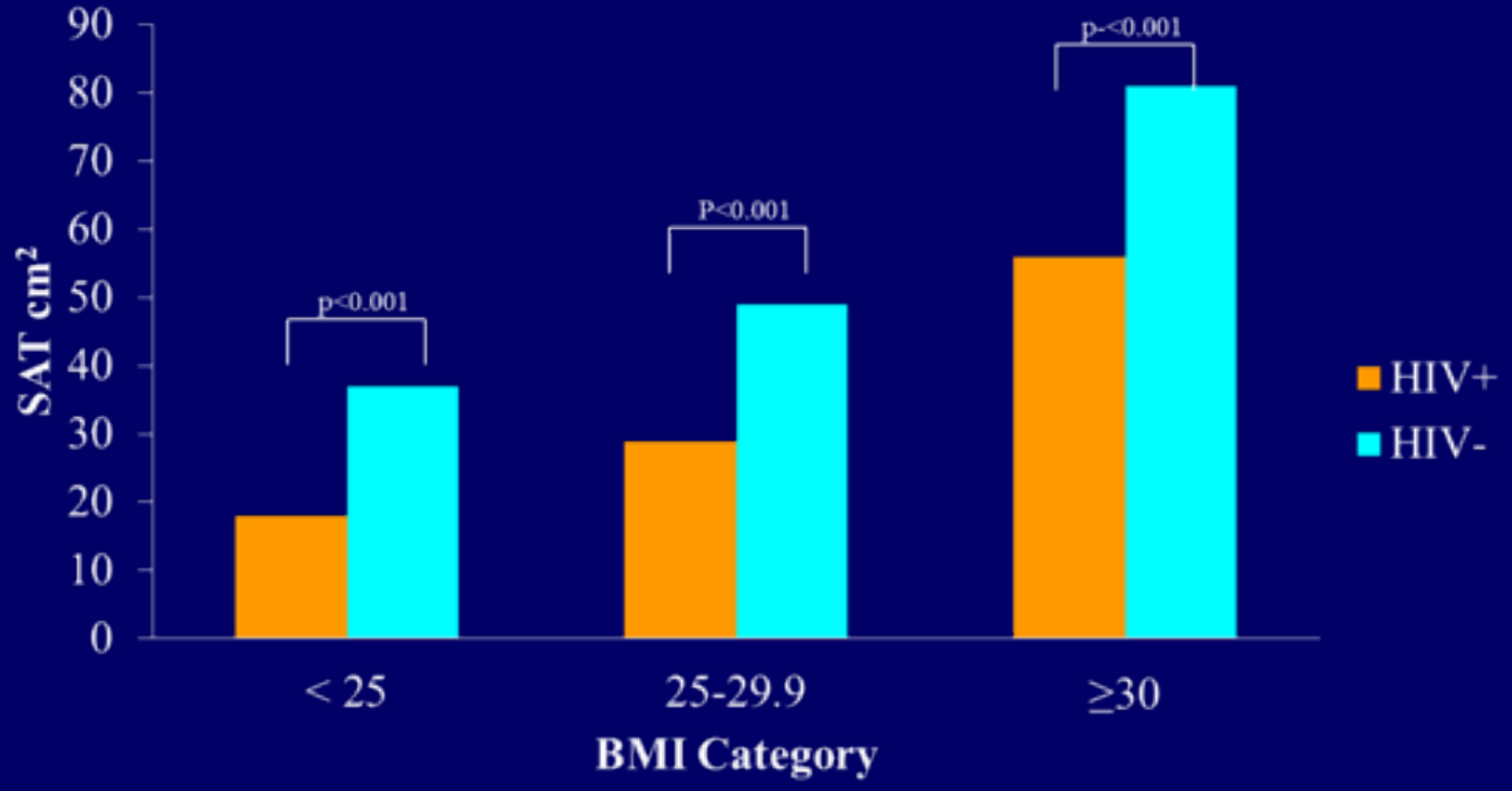
Waist Circumference



Hip Circumference

Erlandson KM, et al. Medicine (Baltimore) 2016;95:e5399

Legacy Effects of Previous ART: Thigh SAT in the MACS CVD Substudy 2010-2012



Palella, OFID, 2016

n=940

Lipoatrophic Fat is Sick Fat

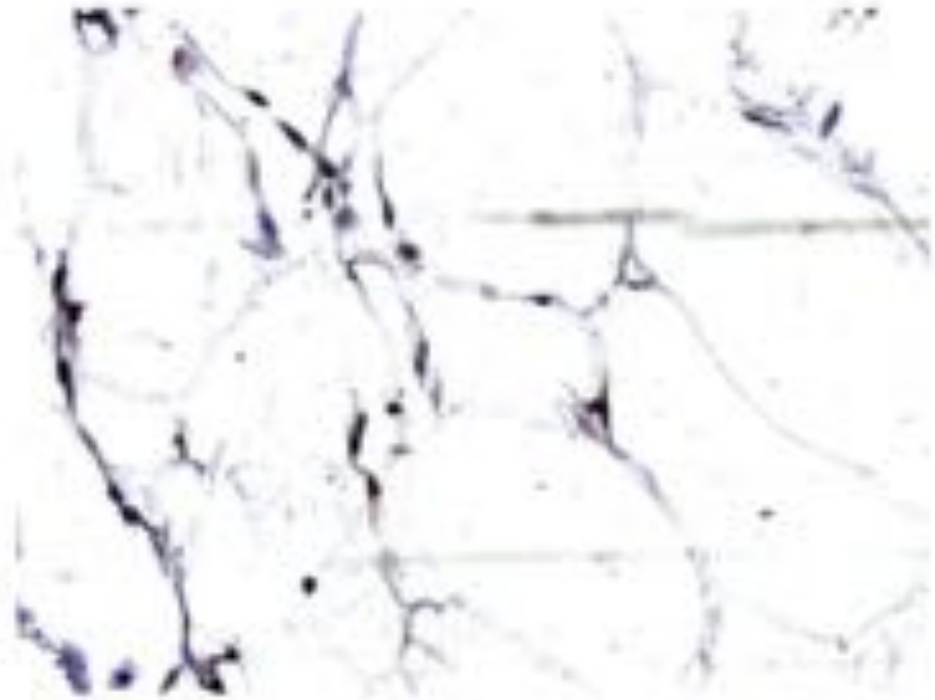


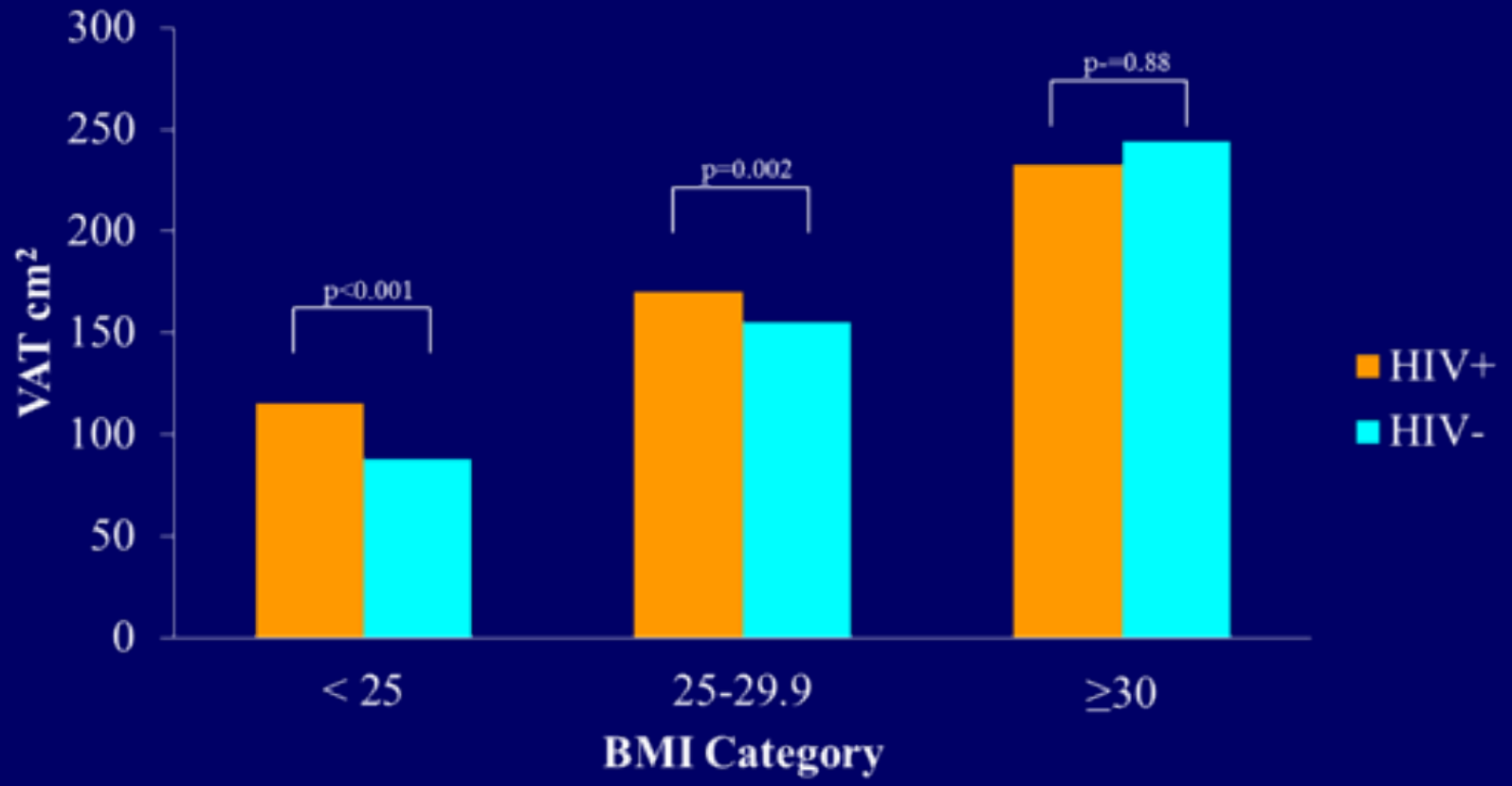
Fig. 1. Immunohistochemical staining of caspase-3 under optical microscopy, indicating apoptosis of adipocytes in subcutaneous tissue of lipodystrophic patients (400× magnification). Source: Data from the authors.

Fig. 2. Immunohistochemical staining of TNF-α under optical microscopy, indicating inflammatory activity in subcutaneous tissue of lipodystrophic patients (400× magnification). Source: Data from the authors.

SAT and Coronary Plaque: Effects May Go in Opposite Directions in People With and Without HIV

	Abdominal Subcutaneous Adipose Tissue		
Plaque Type, Analytic Model	All Estimate (SE)	HIV+ Estimate (SE)	HIV− Estimate (SE)
CAC	N = 486	N = 314	N = 172
Model 1	−0.001 (0.01)	0.003 (0.01)	−0.001 (0.01)
Model 2	−0.01 (0.01)	−0.0001 (0.01)	−0.01 (0.02)
Noncalcified Plaque (NCP)	N = 423	N = 277	N = 146
Model 1	−0.002 (0.003)	−0.004 (0.003)	0.003 (0.01)
Model 2	−0.01 (0.01)	−0.01 (0.01)	−0.004 (0.01)
Calcified Plaque (CP)	N = 251	N = 148	N = 103
Model 1	0.001 (0.004)	0.01 (0.01)	−0.003 (0.01)
Model 2	−0.002 (0.01)	0.01 (0.01)	−0.01 (0.01)
Mixed Plaque (MP)	N = 234	N = 151	N = 83
Model 1	−0.002[b] (0.004)	−0.01 (0.01)	0.01 (0.01)
Model 2	−0.01[b] (0.01)	−0.02 (0.01)	0.002 (0.01)
Total Plaque Score	N = 538	N = 337	N = 201
Model 1	**−0.01* (0.003)**	**−0.01* (0.004)**	0.001 (0.01)
Model 2	**−0.01** (0.004)**	**−0.02** (0.01)**	−0.01 (0.01)

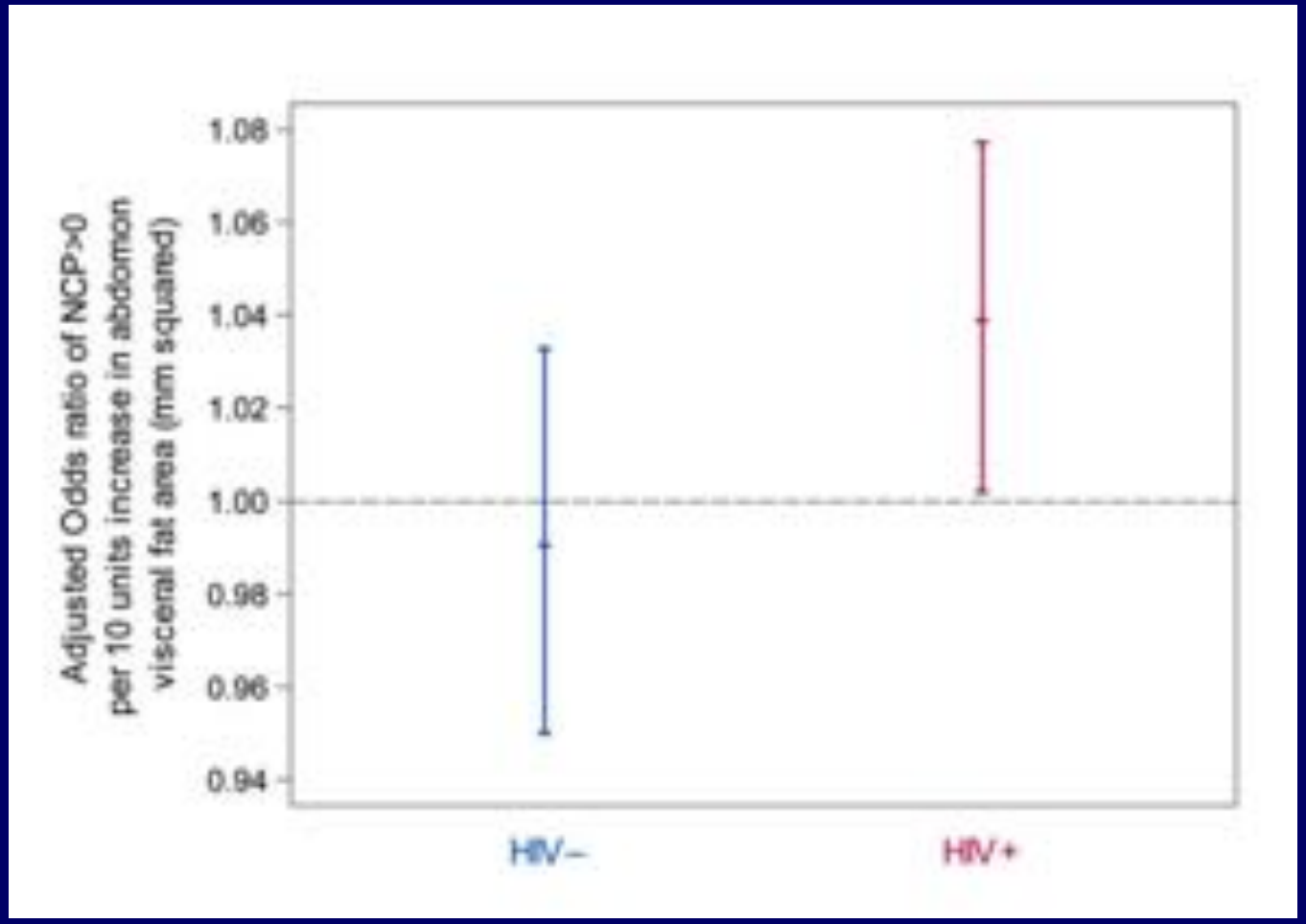
VAT in the MACS CVD Substudy 2010-2012



Palella, OFID, 2016

n=940

Associations With Adiposity Can be HIV Specific: VAT and the Presence of Non-calcified Plaque in the MACS CVD Substudy

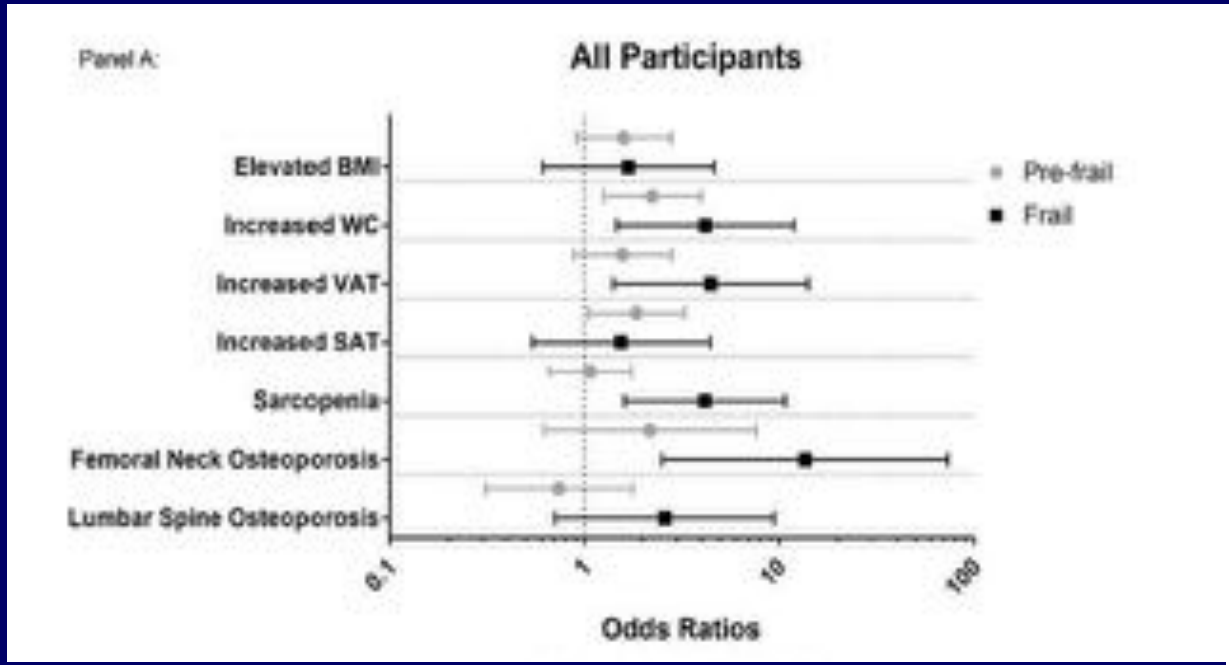


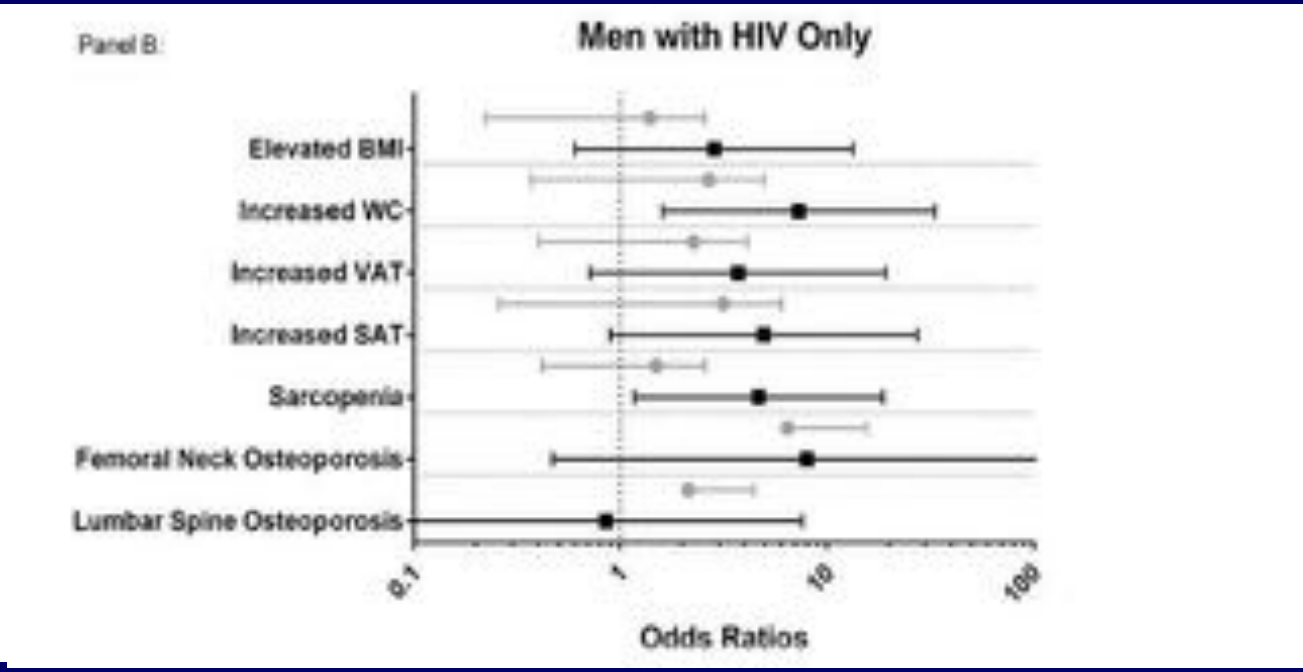
Palella Jr FJ, et al. Open Forum Infect Dis 2016;3:ofw098

Increase in Central Fat: Associations in PLWH

- Dyslipidemia (Wohl, JAIDS, 2008)
- NAFLD (Hadigan, JAIDS, 2007)
- Cognitive Impairment (Sattler, JAIDS, 2015)
- Non-calcified Coronary Plaque (Palella, OFID, 2016)
- ↓ Health-related QOL (Erlandson, PlosOne, 2015)
- Frailty (Hawkins, AIDS, 2018)
- Mortality (Scherzer, AIDS, 2011)

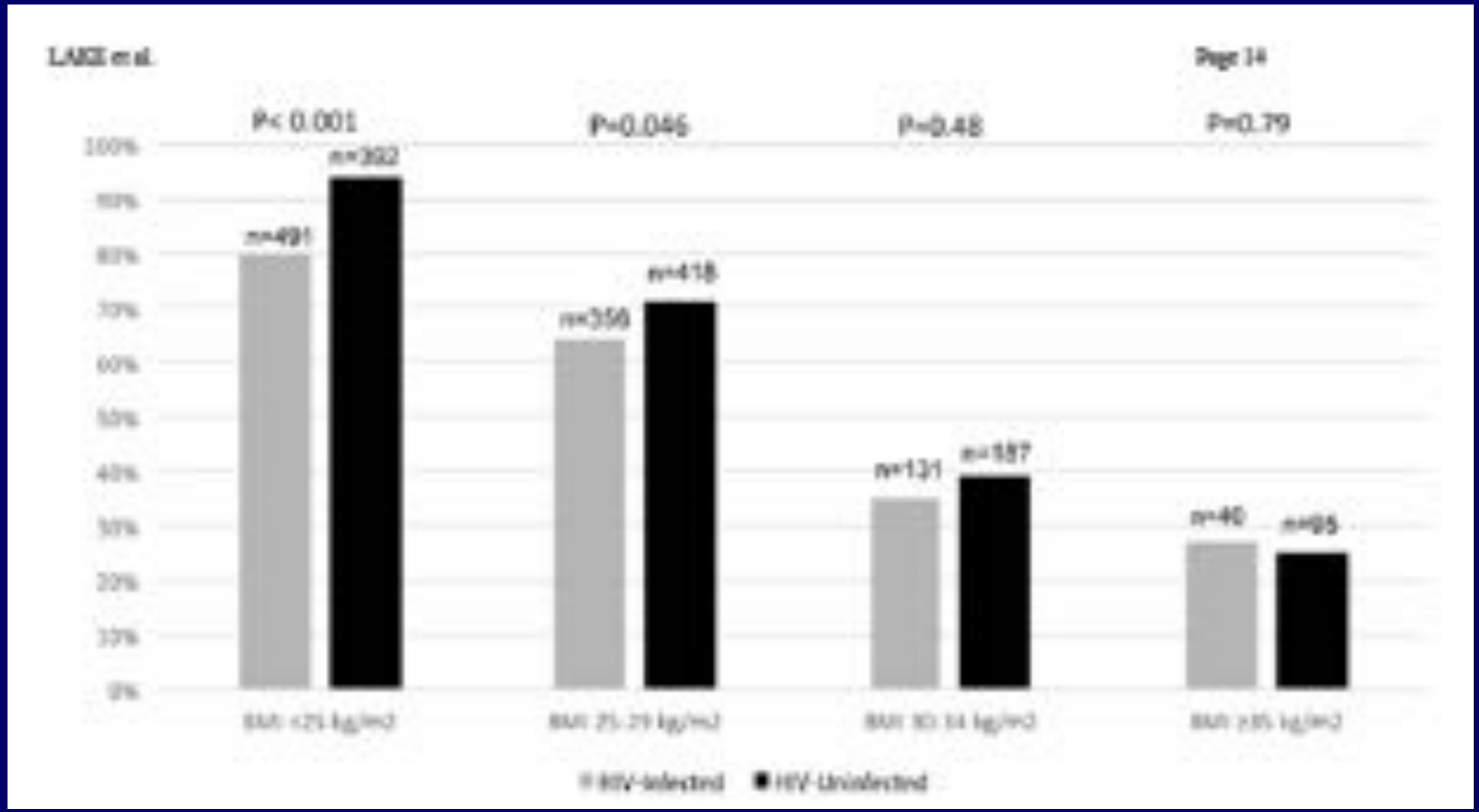
Central Adiposity and Sarcopenia, not BMI, Associated with Frailty in MACS





Hawkins, AIDS, 2019

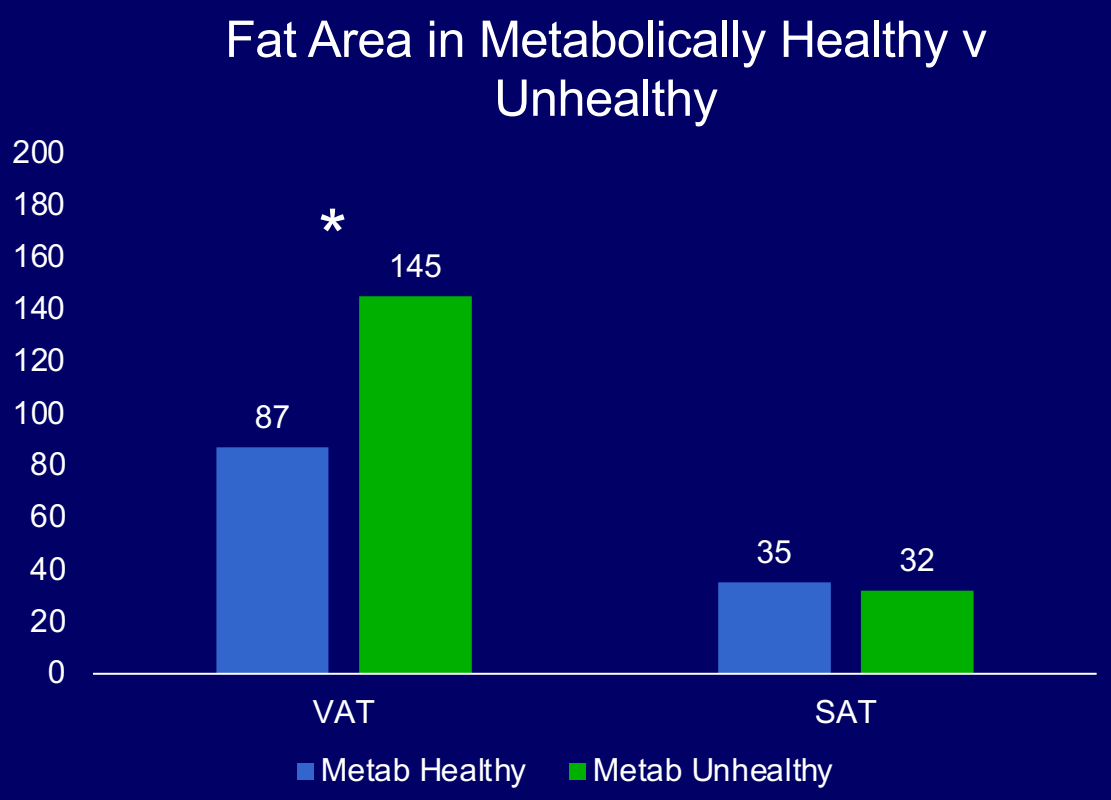
MLWH with a BMI < 25 kg/m^2 may not be normal metabolically: Prevalence of Metabolic Health in MACS CVD2



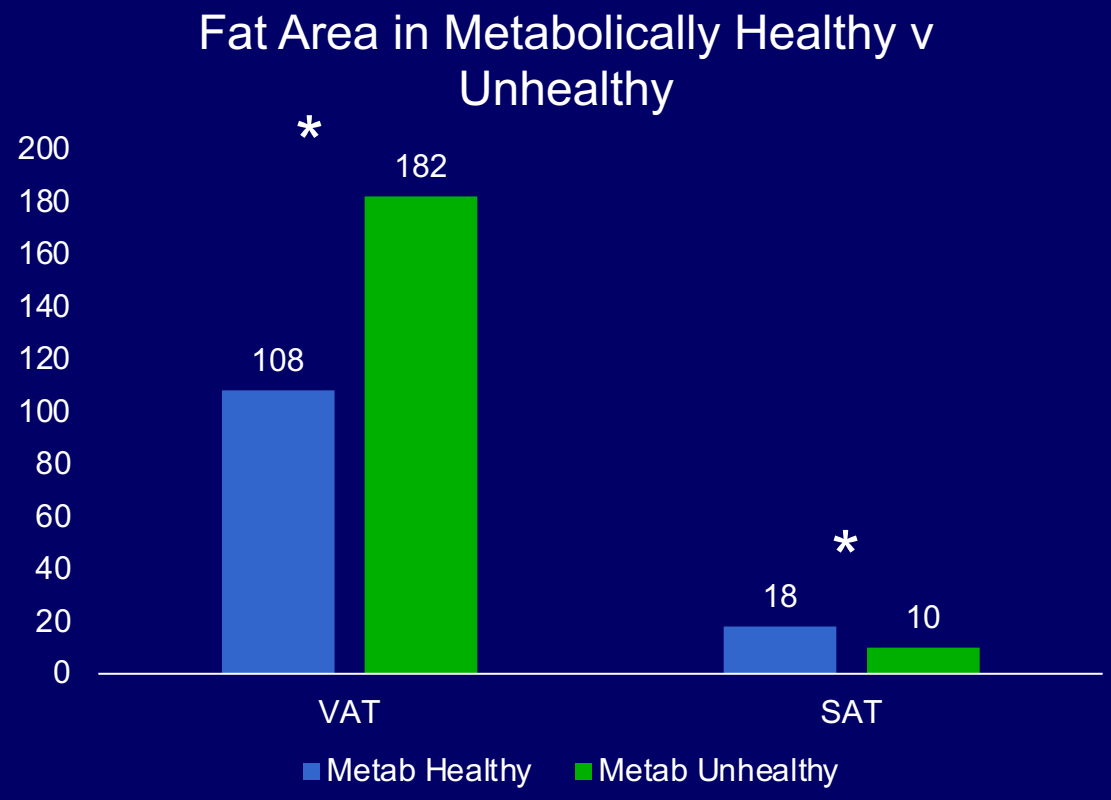
Lake , AIDS, 2018

Among men with BMI< 25, fat distribution differs by HIV serostatus in metabolically healthy vs unhealthy

Men without HIV



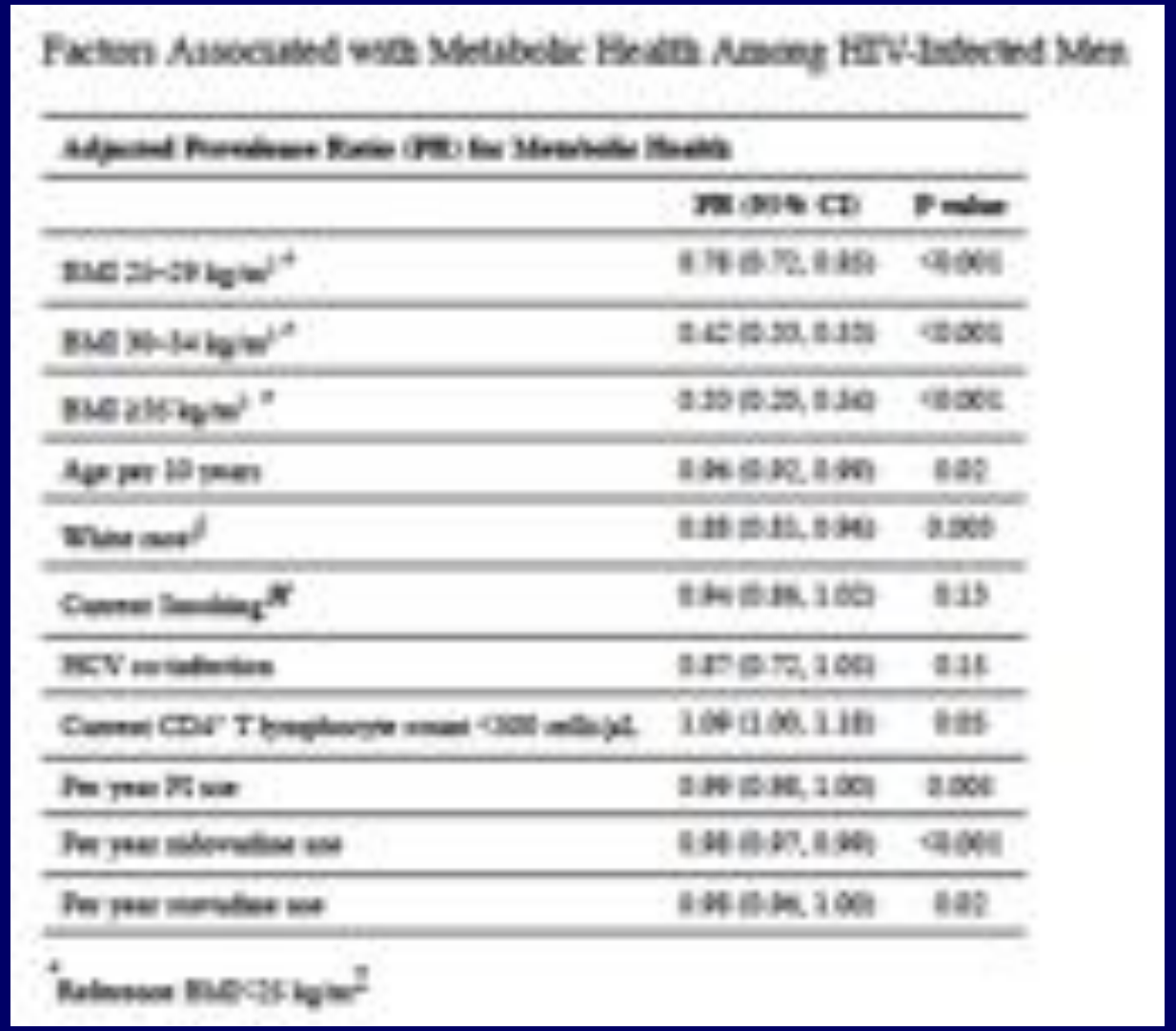
Men with HIV



*p<0.01

Lake , AIDS, 2018

Factors Associated with Metabolic Health among MLWH

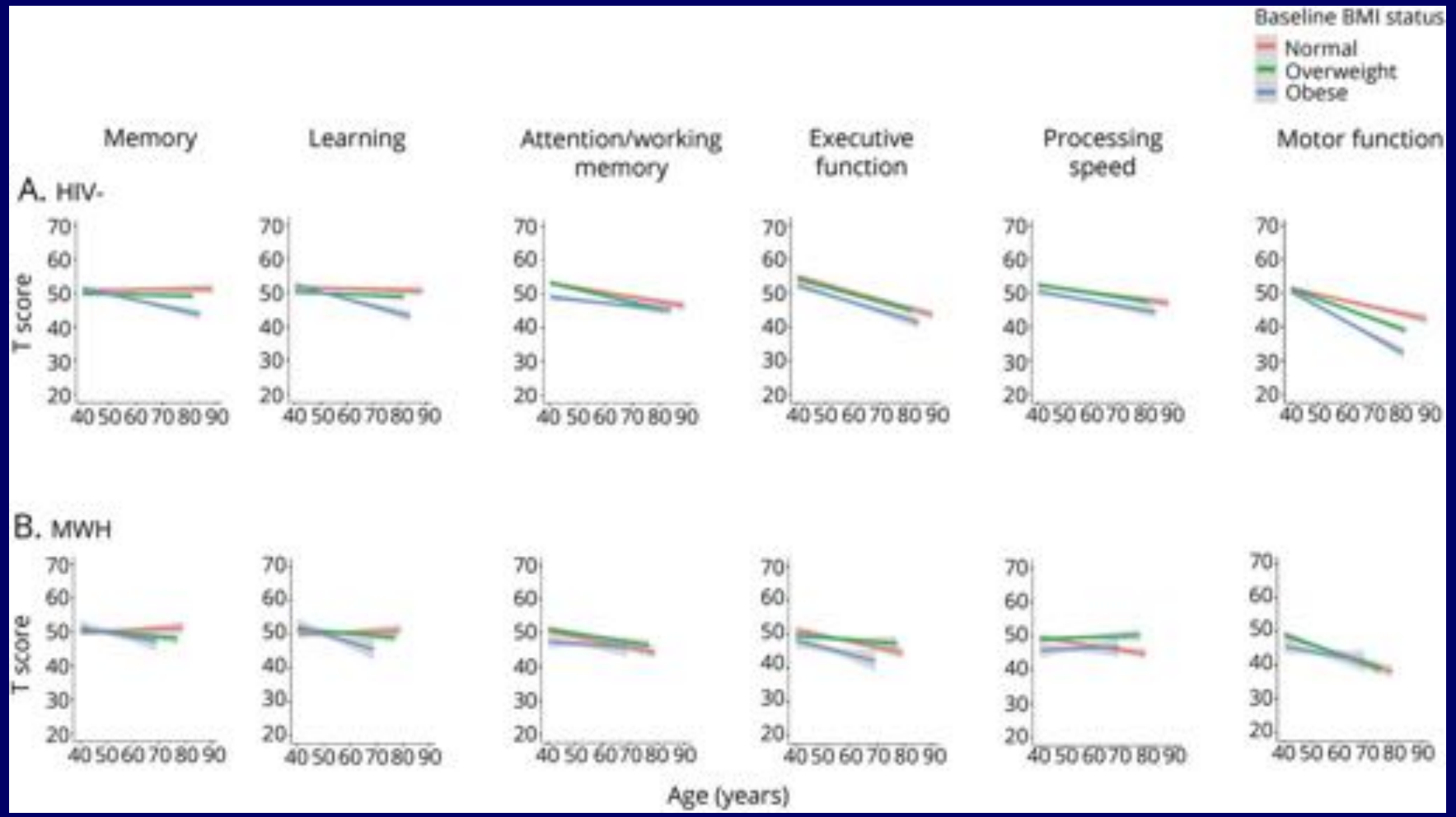


Factors Associated with Metabolic Health Among HIV-Infected Men

Adjusted Prevalence Ratio (PR) for Metabolic Health		
	PR (95% CI)	P value
BMI 25–29 kg/m²[a]	0.78 (0.72, 0.85)	<0.001
BMI 30–34 kg/m²[a]	0.47 (0.39, 0.55)	<0.001
BMI ≥35 kg/m²[a]	0.30 (0.25, 0.36)	<0.001
Age per 10 years	0.96 (0.92, 0.99)	0.02
White race[b]	0.88 (0.83, 0.94)	0.001
Current Smoking[c]	0.94 (0.88, 1.02)	0.15
HCV co-infection	0.87 (0.77, 1.00)	0.04
Current CD4+ T lymphocyte count <500 cells/μL	1.09 (1.00, 1.18)	0.05
Per year PI use	0.99 (0.98, 1.00)	0.004
Per year zidovudine use	0.98 (0.97, 0.99)	<0.001
Per year stavudine use	0.98 (0.96, 1.00)	0.02

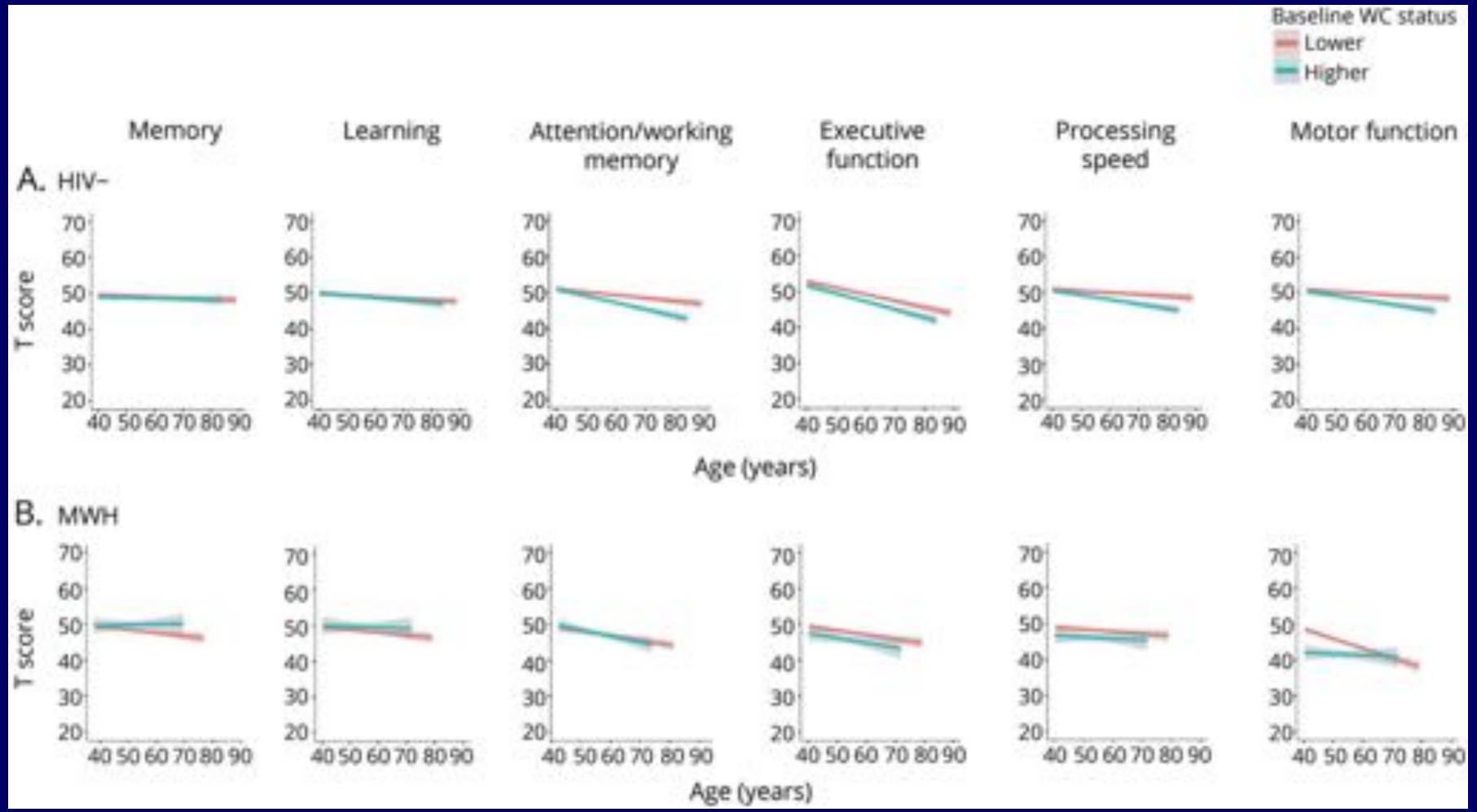
[a] Reference BMI <25 kg/m²

Obesity is a better predictor of cognitive decline in HIV-uninfected men vs MLWH



Rubin, Neurology, 2019

Waist circumference is a better predictor of cognitive decline in HIV-uninfected men vs MLWH



Rubin, Neurology, 2019

Age and Ageing 2016; 45: 14–21
doi: 10.1093/ageing/afv151

SYSTEMATIC REVIEWS

The risk of overweight/obesity in mid-life and late life for the development of dementia: a systematic review and meta-analysis of longitudinal studies

Results: of the 1,612 abstracts identified and reviewed, 21 completely met the inclusion criteria. Being obese below the age of 65 years had a positive association on incident dementia with a risk ratio (RR) 1.41 (95% confidence interval, CI: 1.20–1.66), but the opposite was seen in those aged 65 and over, RR 0.83 (95% CI: 0.74–0.94).

Address correspondence to: N. Beckett. Tel: (+44) 0207 188 7188. Email: nigel.beckett@gstt.nhs.uk

Abstract

Scope: it has been suggested that overweight/obesity as a risk factor for incident dementia differs between mid-life and later life. We performed a systematic review and meta-analysis of the up-to-date current literature to assess this.
Search Methods: inclusion criteria included epidemiological longitudinal studies published up to September 2014, in participants without cognitive impairment based on evidence of cognitive assessment and aged 30 or over at baseline assessment with at least 2 years of follow-up. Pubmed, Medline, EMBASE, PsychInfo and the Cochrane Library were searched using combinations of the search terms: Dementia, Alzheimer disease, Vascular Dementia, Multi-Infarct Dementia, Cognitive decline, Cognitive impairment, Mild Cognitive Impairment, Obesity, Overweight, Adiposity, Waist circumference (limits: humans, English language). Handsearching of all papers meeting the inclusion criteria was performed. A random effects model was used for the meta-analysis.
Results: of the 1,612 abstracts identified and reviewed, 21 completely met the inclusion criteria. Being obese below the age of 65 years had a positive association on incident dementia with a risk ratio (RR) 1.41 (95% confidence interval, CI: 1.20–1.66), but the opposite was seen in those aged 65 and over, RR 0.83 (95% CI: 0.74–0.94).
Conclusions: this systematic review and meta-analysis suggests a positive association between obesity in mid-life and later dementia and the opposite in late life. Whether weight reduction in mid-life reduces risk is worthy of further study.

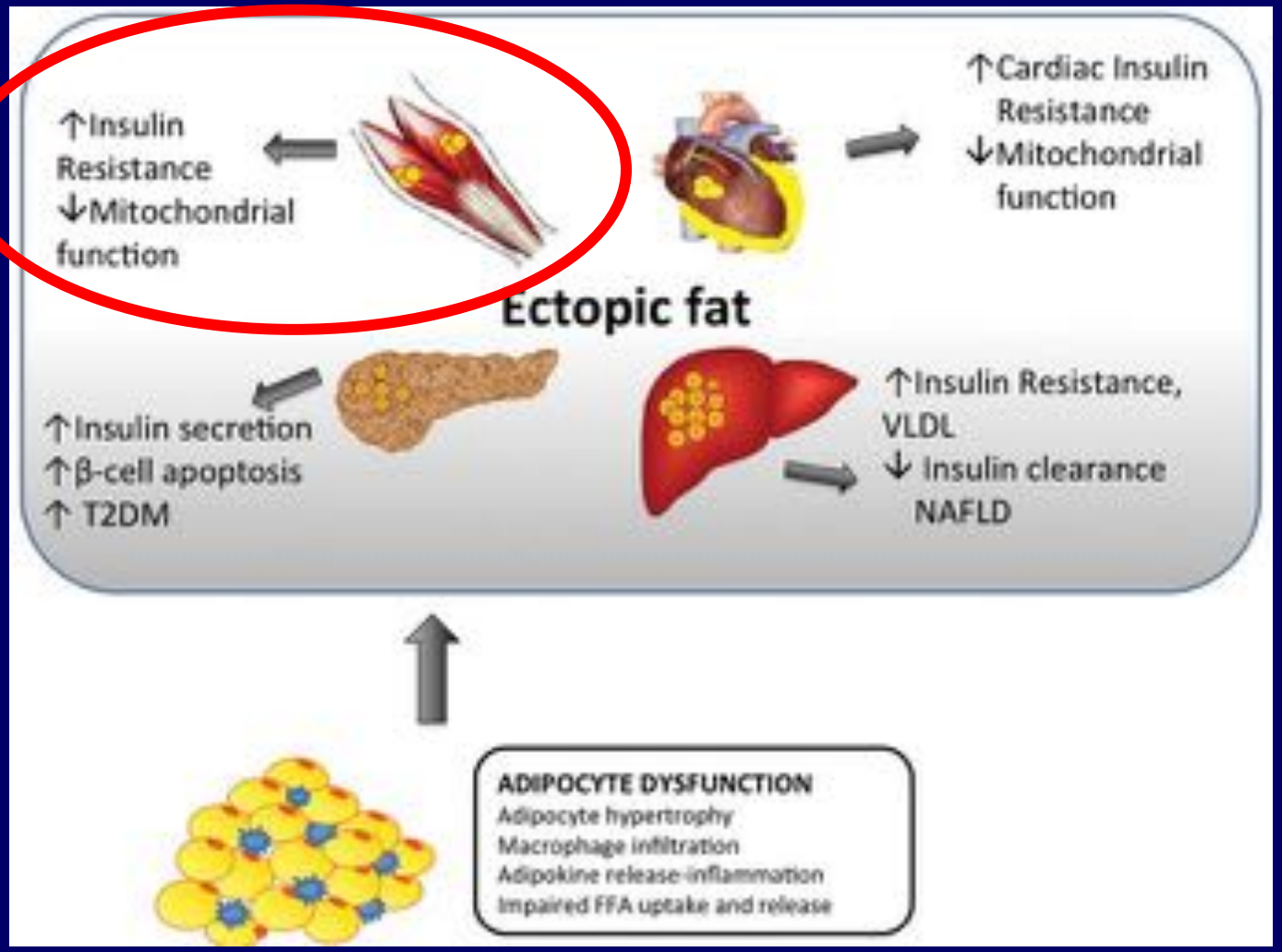
Keywords: obesity, overweight, dementia, aged, systematic review, older people

Body fat changes and ectopic fat deposition in the elderly

If loss of muscle mass or strength

Sarcopenic obesity

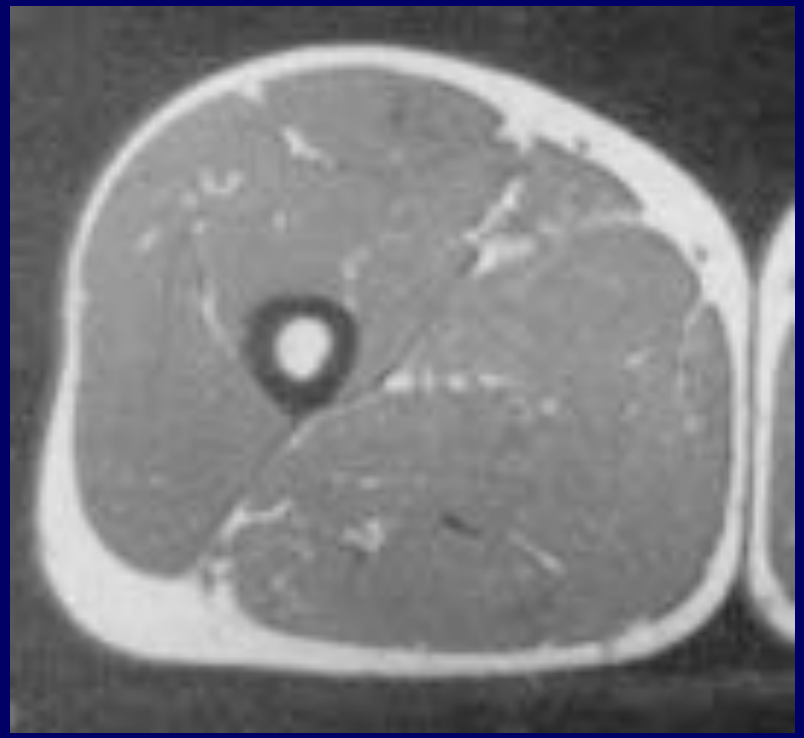
Adiposity and Ectopic Fat



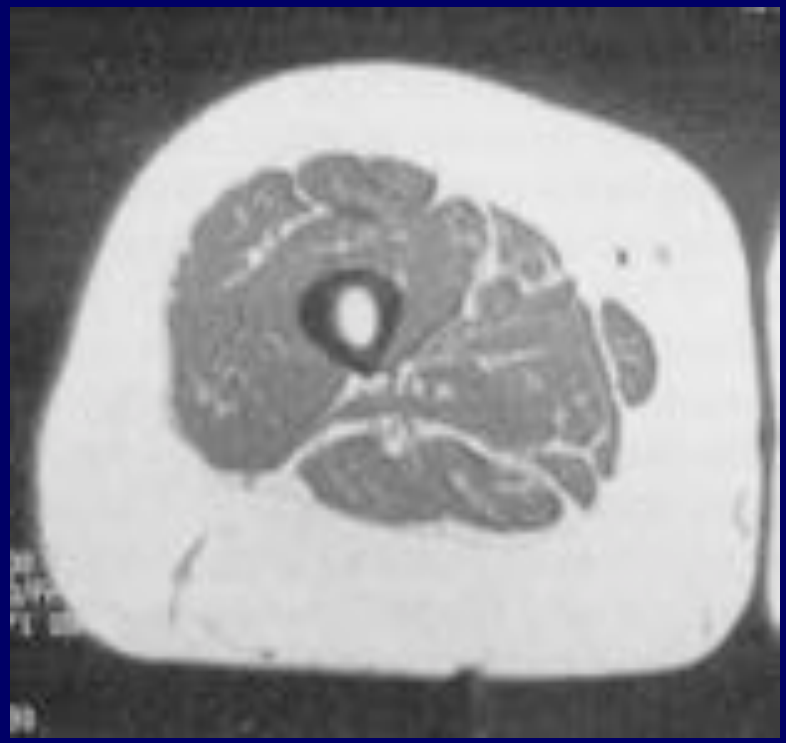
Gaggini M, et al. Horm Mol Biol Clin Investig 2015;22:7–18

Age is Associated With Lower Muscle Mass and Quality

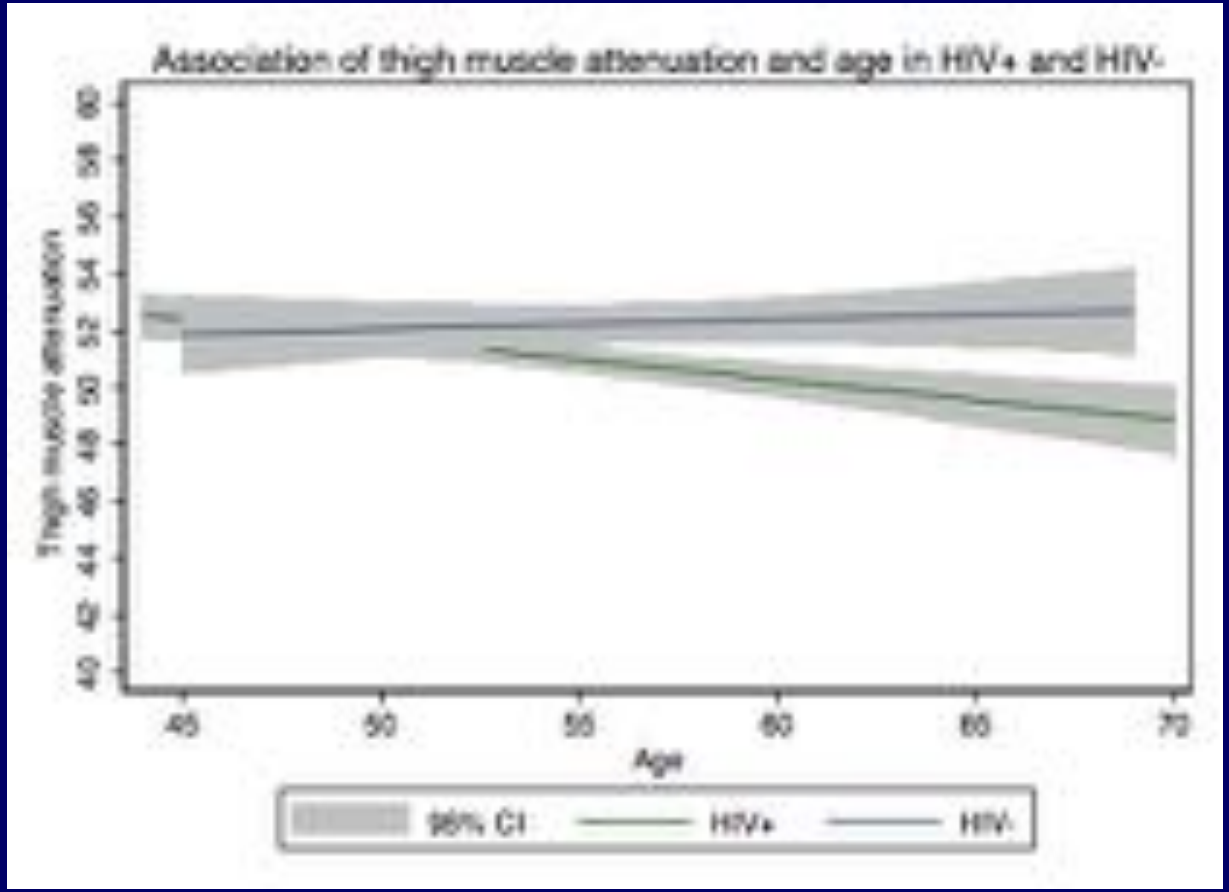
40-year-old



70-year-old sarcopenic

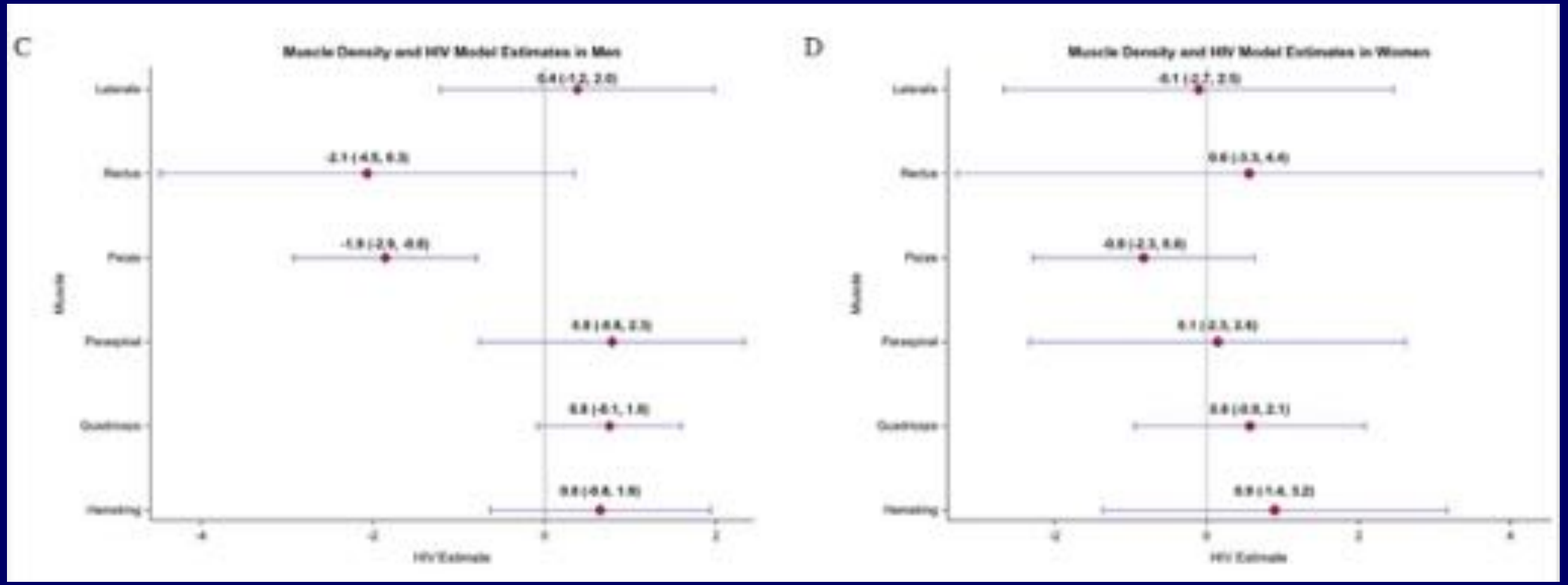


Muscle Quality: Effect of HIV-status and Age



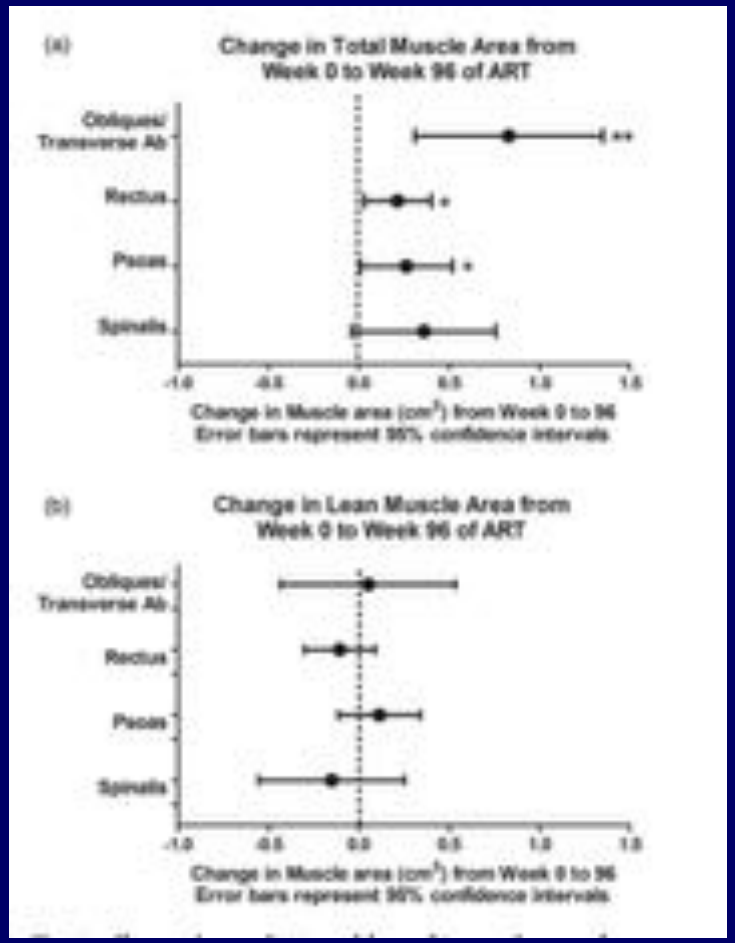
Natsag J, et al. PLoS One 2017;12:e1069194

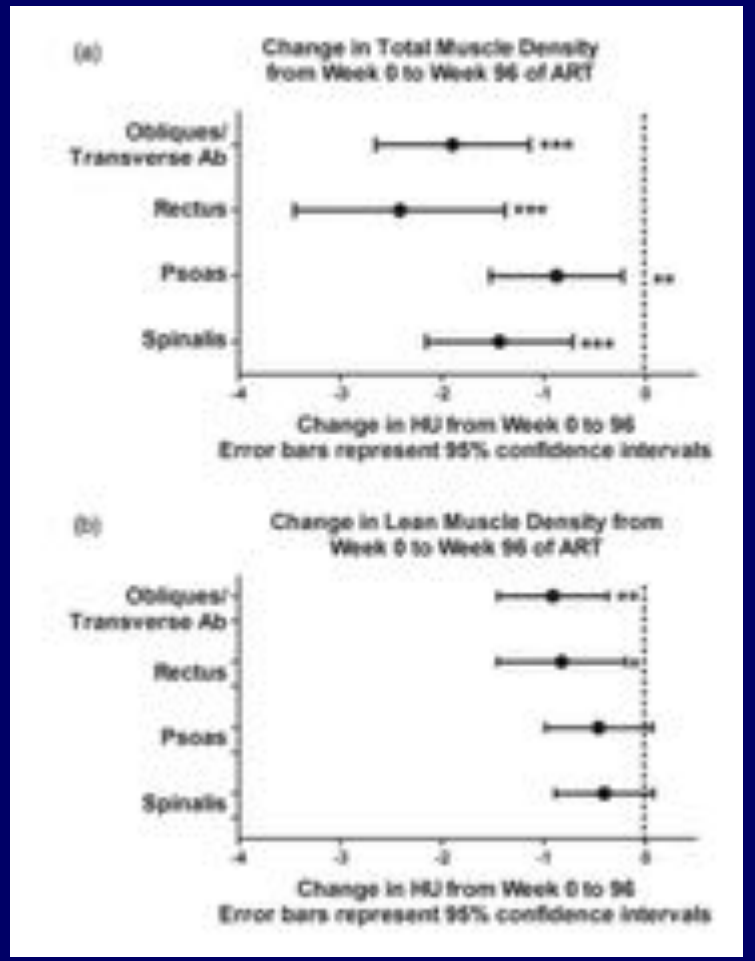
Associations Between Muscle Density and HIV Vary by Sex and Muscle Group



Erlandson KM, et al. J Frailty Aging 2022;11:309–17

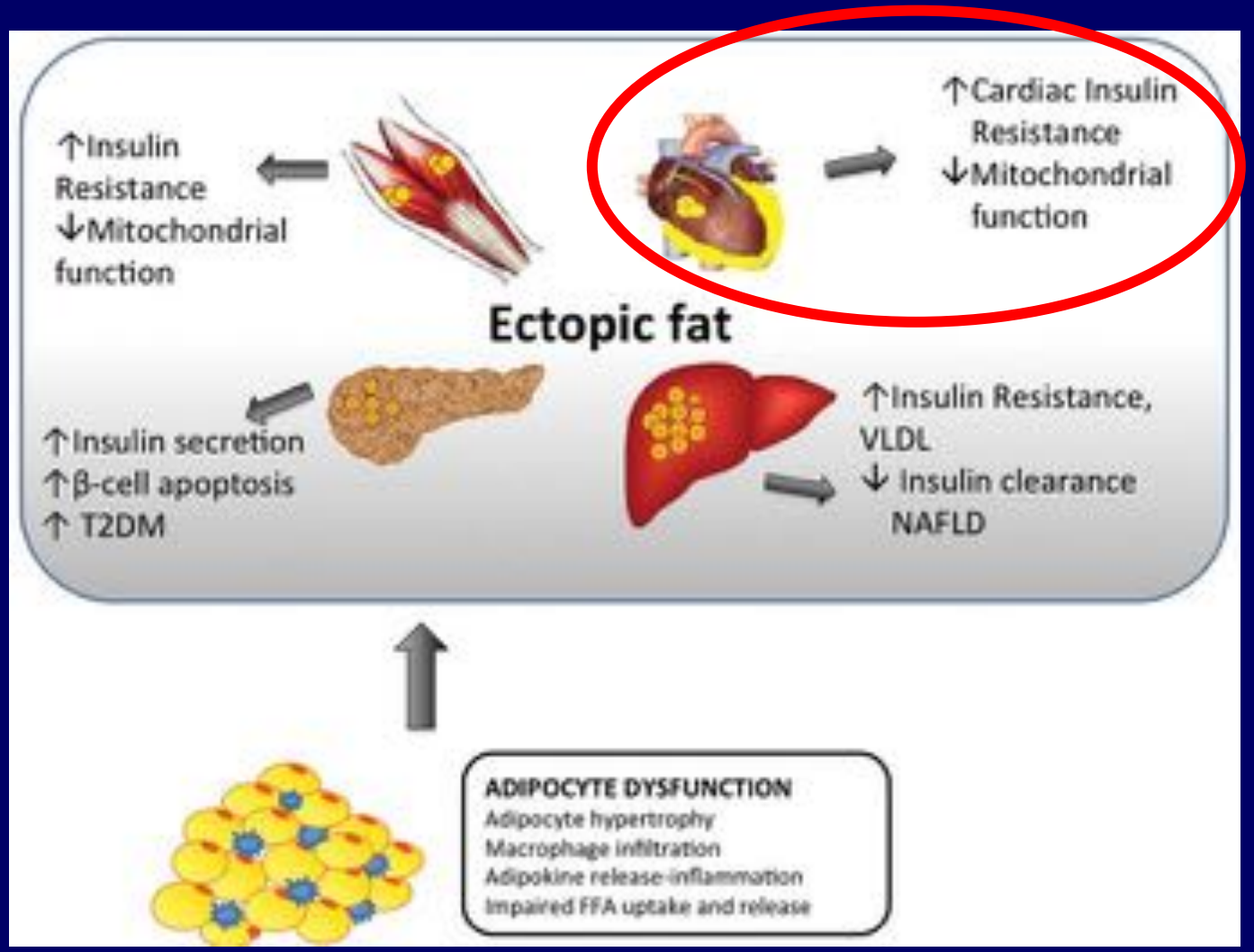
Muscle mass increases with ART initiation, but becomes more fatty





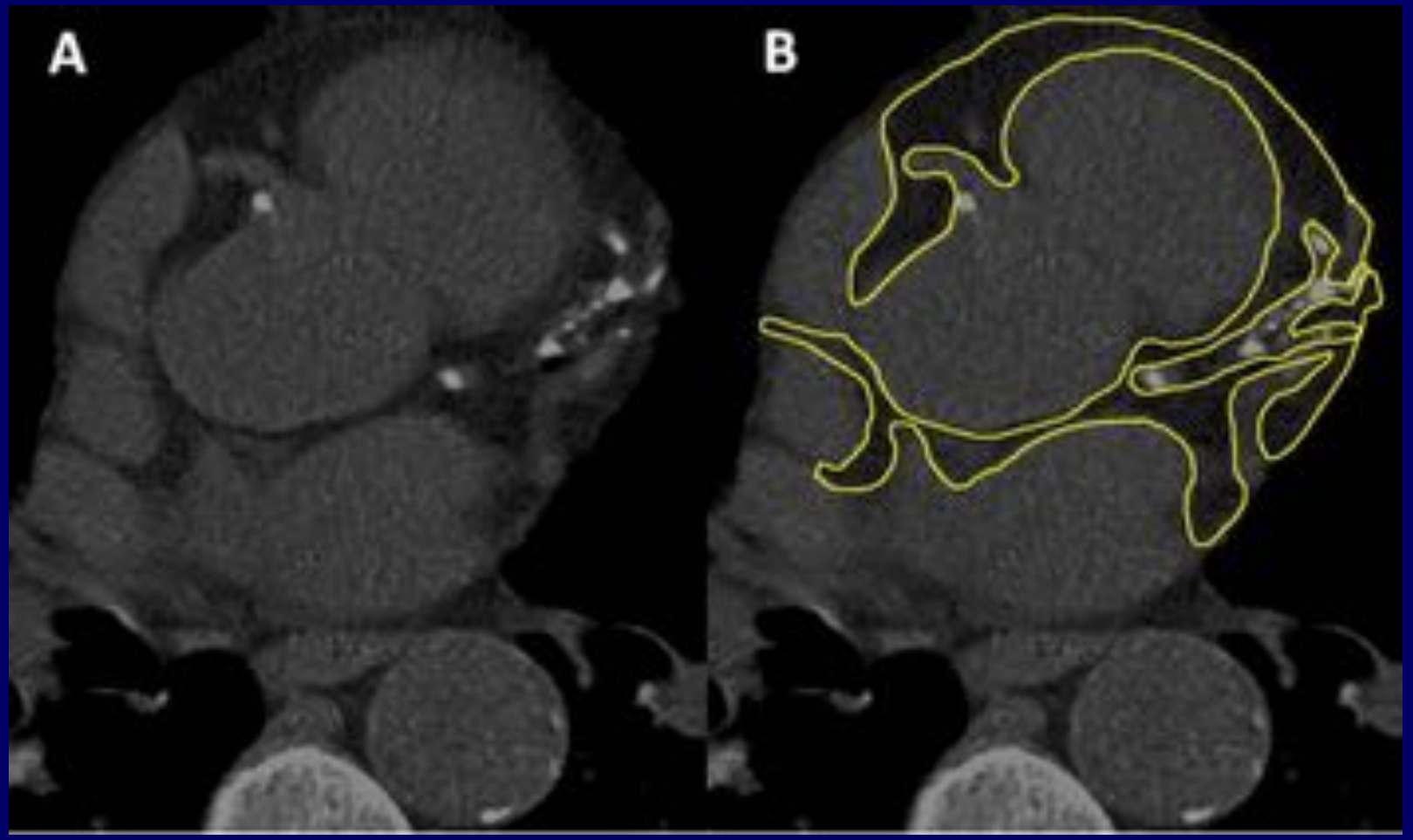
Erlandson, AIDS, 2017

Adiposity and Ectopic Fat



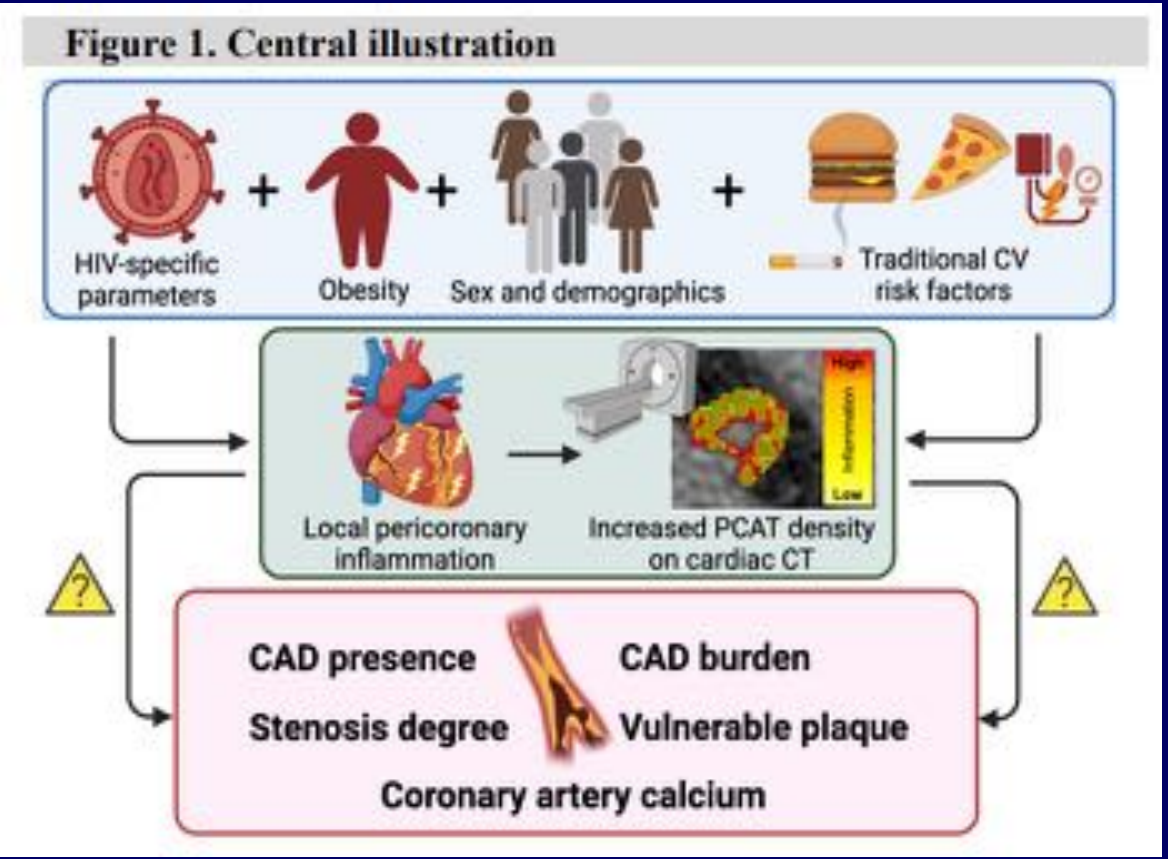
Gaggini M, et al. Horm Mol Biol Clin Investig 2015;22:7–18

Epicardial Adipose Tissue on CT Scan



- EAT is greater in HIV+ vs HIV- in MACS (Brener, AIDS, 2015)
- EAT predicts CVD event in HIV (Raggi, J of Cardiovascular CT, 2015)

Inflammation in fat surrounding coronary arteries associated with coronary plaque



Multivariable regression relating PCAT to plaque phenotypes

- PCAT density was associated with CT-derived CAD measures **independent** of ASCVD risk score, smoking & substance use, BMI, ART parameters and systemic inflammatory biomarkers (**Table 2**).

Table 2: Association of PCAT density with CAD in REPRIEVE

	Univariable			Model 1			Model 2		
Presence of	OR	95%CI	p	OR	95%CI	p	OR	95%CI	p
Coronary Plaque	1.3	1.13–1.50	<0.001	1.3	1.10–1.50	0.002	1.4	1.21–1.70	<0.001
Coronary Calcium	1.5	1.28–1.74	<0.001	1.5	1.26–1.75	<0.001	1.6	1.35–1.94	<0.001
Vulnerable plaque	1.3	1.10–1.54	0.002	1.3	1.06–1.51	0.01	1.3	1.07–1.57	0.008
Leaman >5	1.5	1.27–1.87	<0.001	1.6	1.27–1.93	<0.001	1.9	1.47–2.37	<0.001

Model 1: ASCVD risk, substance use, BMI, HIV parameters; **Model 2:** Model 1 + systemic biomarkers (MCP-1, IL-6, LpPLA2, oxLDL, hsCRP). ORs are per 10 HU of PCAT density.

Foldyna, 649

Older PLWH gain more weight with ART initiation

Table 3. Risk Factors for Any Weight Gain in Individuals Initiating Antiretroviral Therapy

Variable	Difference, kg	95% CI	*P* Value
CD4 count (<200 vs ≥200 cells/μL)	2.97	(2.81–3.13)	<.001
IV drug use (no vs yes)	1.41	(.97–1.85)	<.001
Race (black vs non-black)	0.99	(.87–1.11)	<.001
HIV RNA (>100K vs ≤100K copies/mL)	0.96	(.84–1.08)	<.001
Symptomatic HIV (yes vs no)	0.51	(.36–.65)	<.001
Sex (female vs male)	0.23	(.07–.4)	.006
Age (<50 vs ≥50 y)	0.22	(.07–.37)	.004
BMI			
Obese vs normal	0.21	(.06–.36)	.005
Overweight vs normal	0.24	(−.36 to −.13)	<.001

Stepwise model selection was used to identify baseline risk factors associated with weight gain in individuals initiating antiretroviral therapy, resulting in the inclusion of the above 8 baseline risk factors in the mixed-effect model. Difference, 95% CI, and *P* values were determined from the mixed-effect model including these 8 baseline risk factors and visit as fixed effects and participants as a random effect.

Abbreviations: BMI, body mass index; CI, confidence interval; HIV, human immunodeficiency virus; IV, intravenous.

Sax, CID, 2020

Older PLWH gain more weight switching to InSTI

Table 2. Annual Rate of Weight Change Pre-/Post-switch to Integrase Strand Transfer Inhibitors

	All	Women	Men	White Race[a]	Black Race	Age <40 Years[b]	Age ≥60 Years	BMI <18.5 kg/m^2[b]	BMI >30 kg/m^2
Pre-INSTI	0.4 (<.001)	0.3 (.05)	0.5 (<.001)	0.4 (<.001)	0.3 (.04)	1.1 (<.001)	−0.03 (.8)	0.8 (.7)	0.02 (.9)
Post-INSTI	0.6 (<.001)	1.6 (<.0001)	0.4 (.0009)	0.4 (.002)	1.2 (<.001)	−0.3 (.42)	1.2 (<.001)	1.4 (.03)	0.5 (.05)
Pre-post difference	0.2 (.22)	1.3 (<.001)	−0.1 (.6)	0.01 (.97)	0.9 (.002)	−1.4 (.01)	1.2 (.001)	0.5 (.6)	0.5 (.2)

Weight change shown in kilograms/year (*P* value) for 2 years before and after switch to INSTIs in virologically suppressed adults (n = 691).

Abbreviations: BMI, body mass index; INSTI, integrase strand transfer inhibitor.

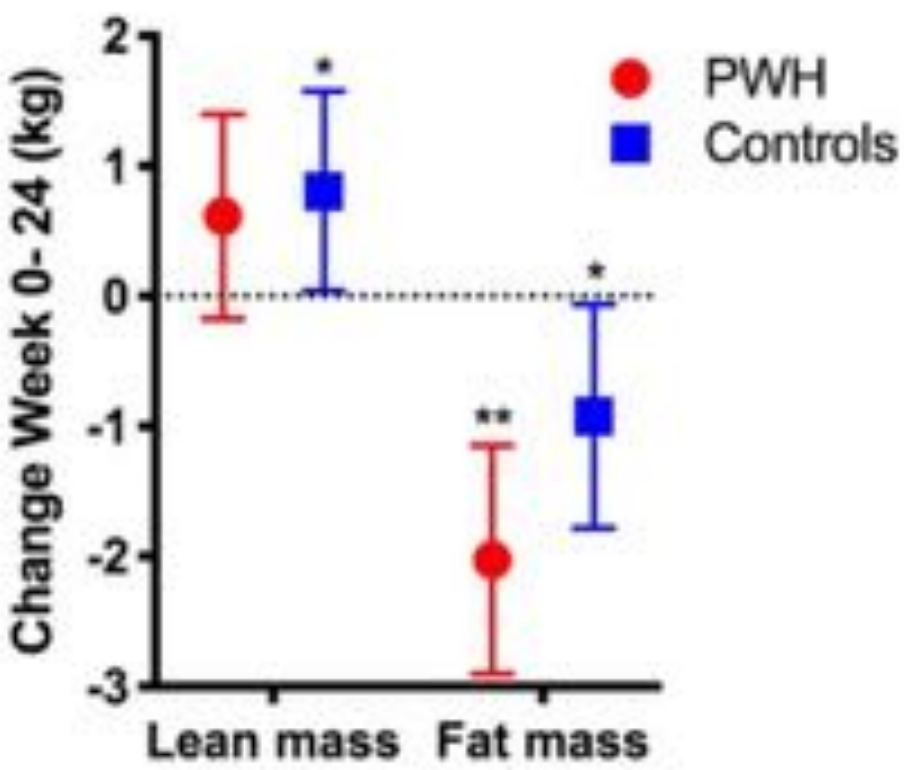
[a]Results for Hispanic ethnicity were similar to those for white race.

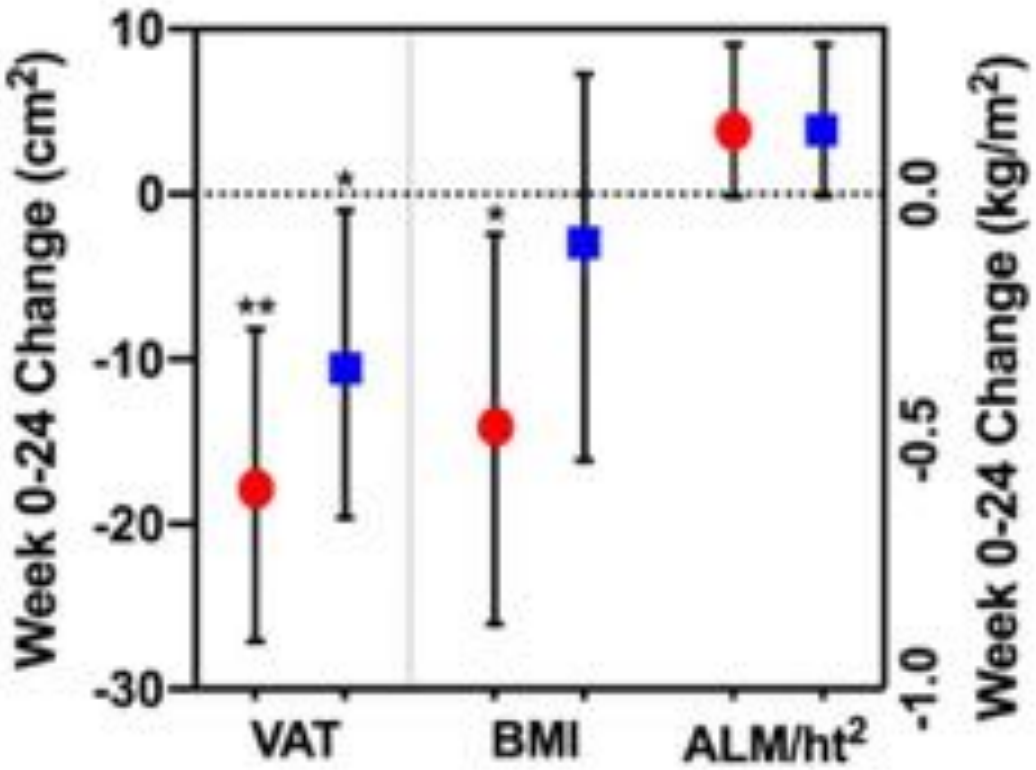
[b]No significant change in slope of weight gain among persons 40–60 years of age or for BMI 18.5–30 kg/m^2.

Lake, CID, 2020

Lifestyle Changes as the Cornerstone of Treatment

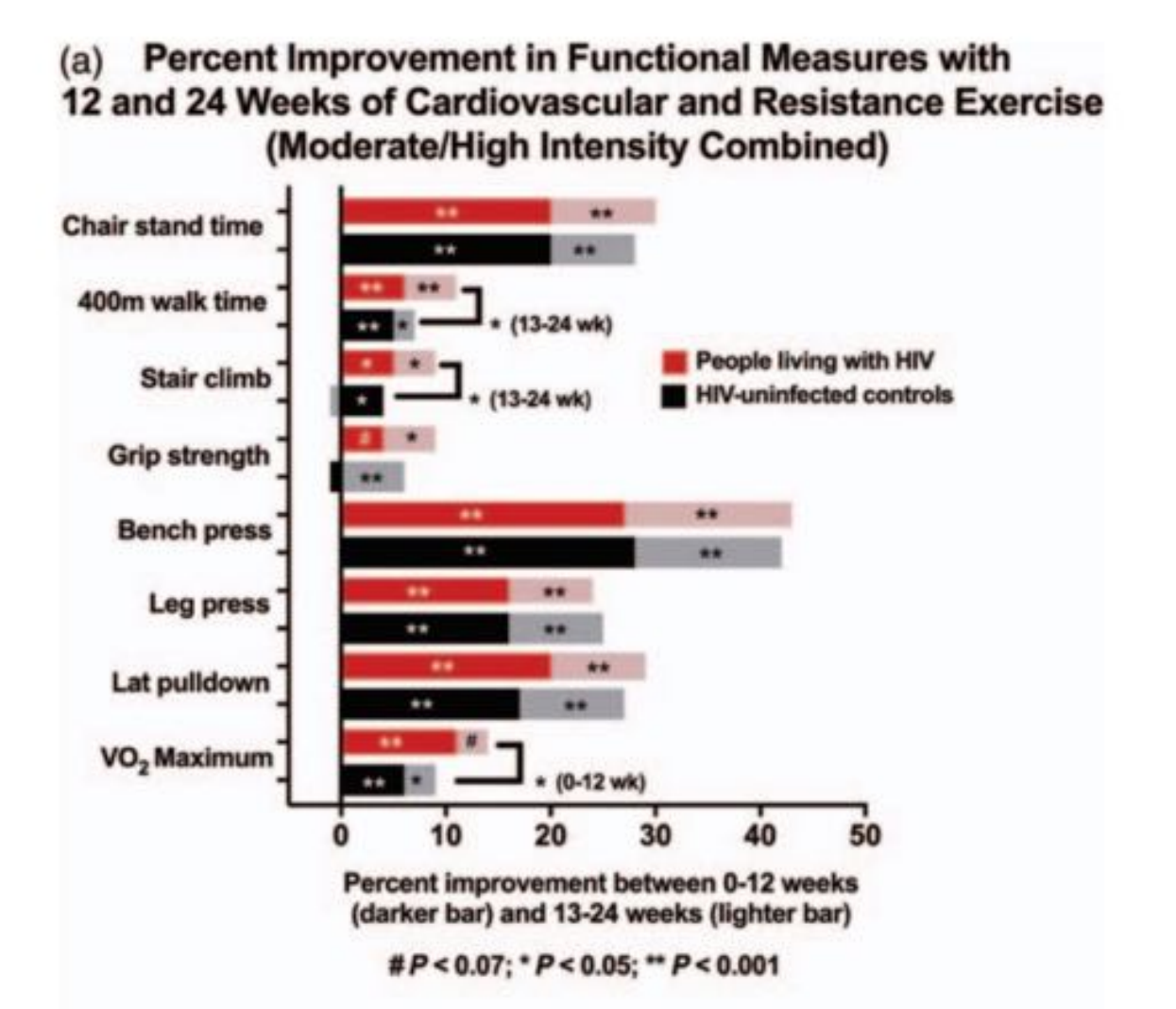
Exercise decreases VAT in PWH





Jankowski, JAIDS, 2021

Exercise improves physical function in PWH



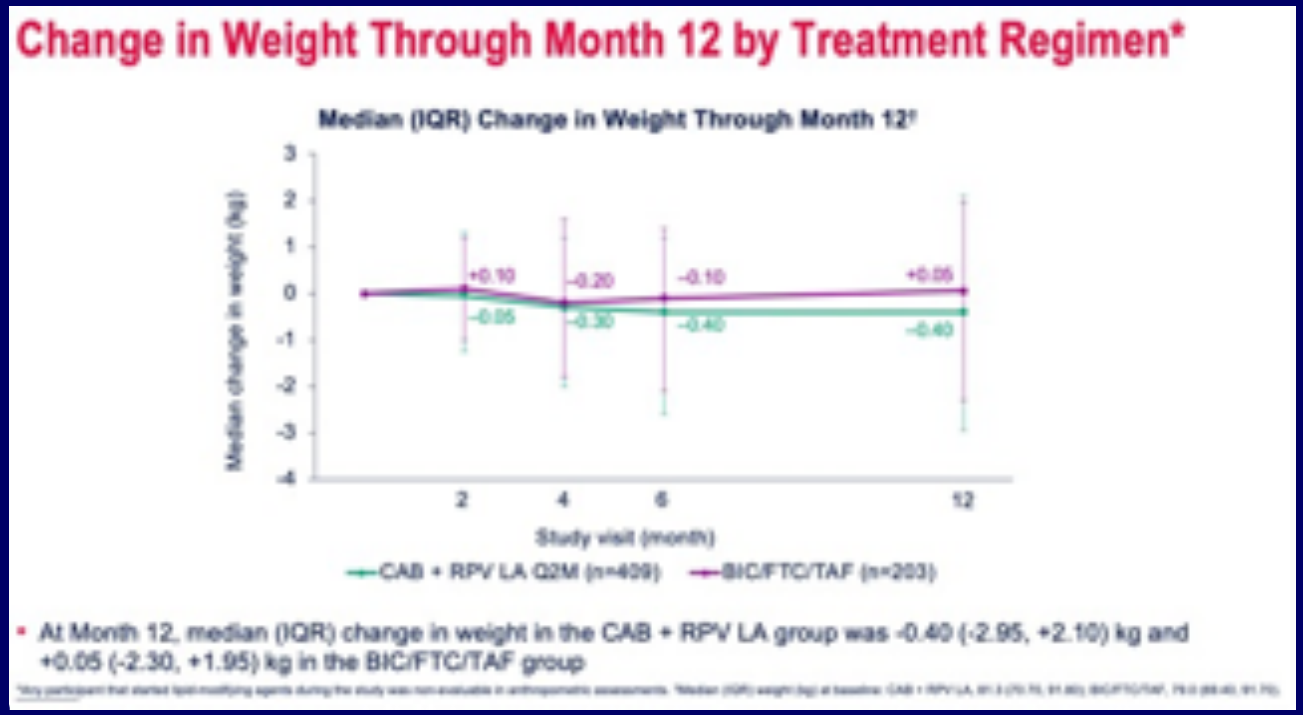
Erlandson, AIDS, 2018

Does switching off TAF and/or InSTI decrease weight?

Does switching off of TAF and BIC to CAB/RPV decrease weight?

SOLAR:

- PWH on F/TAF/BIC randomized 2:1 to CAB LA or stay on F/TAF/BIC over 12M.
- Median age 37, 88% men, 60% overweight or obese.



Switching off TAF to TDF decreases weight in women: CHARACTERISE

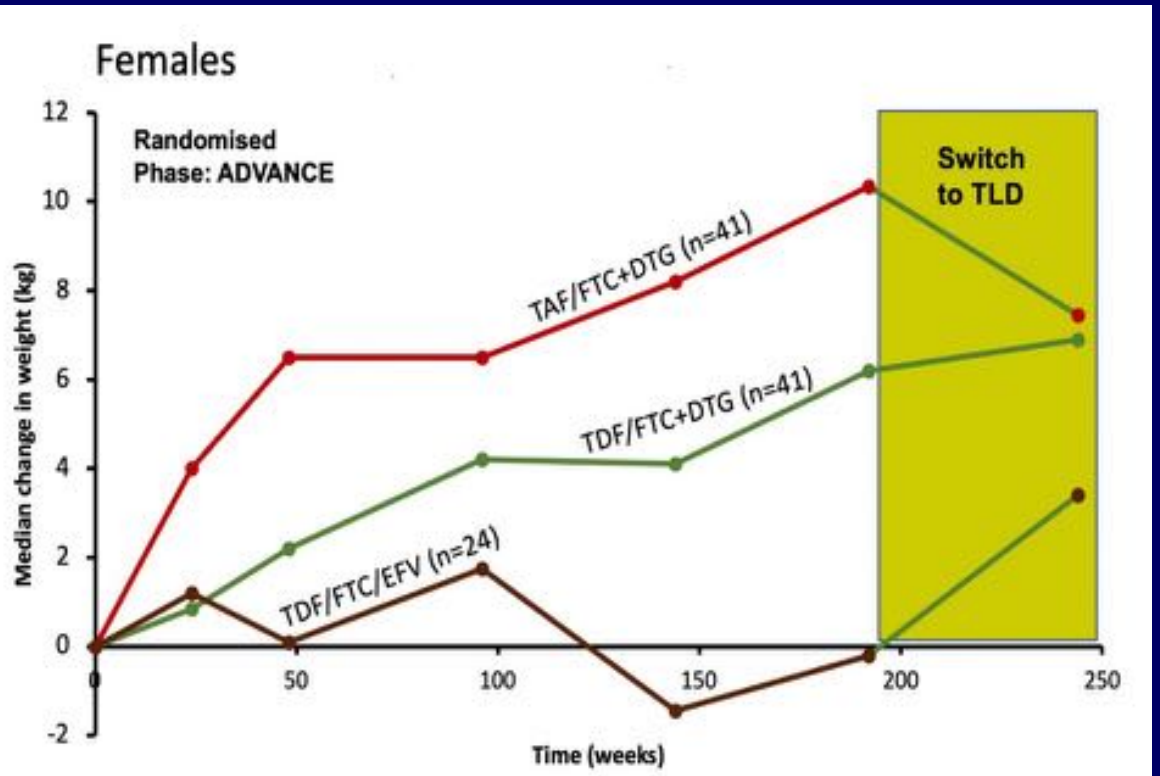


Figure 1: Median weight change for females

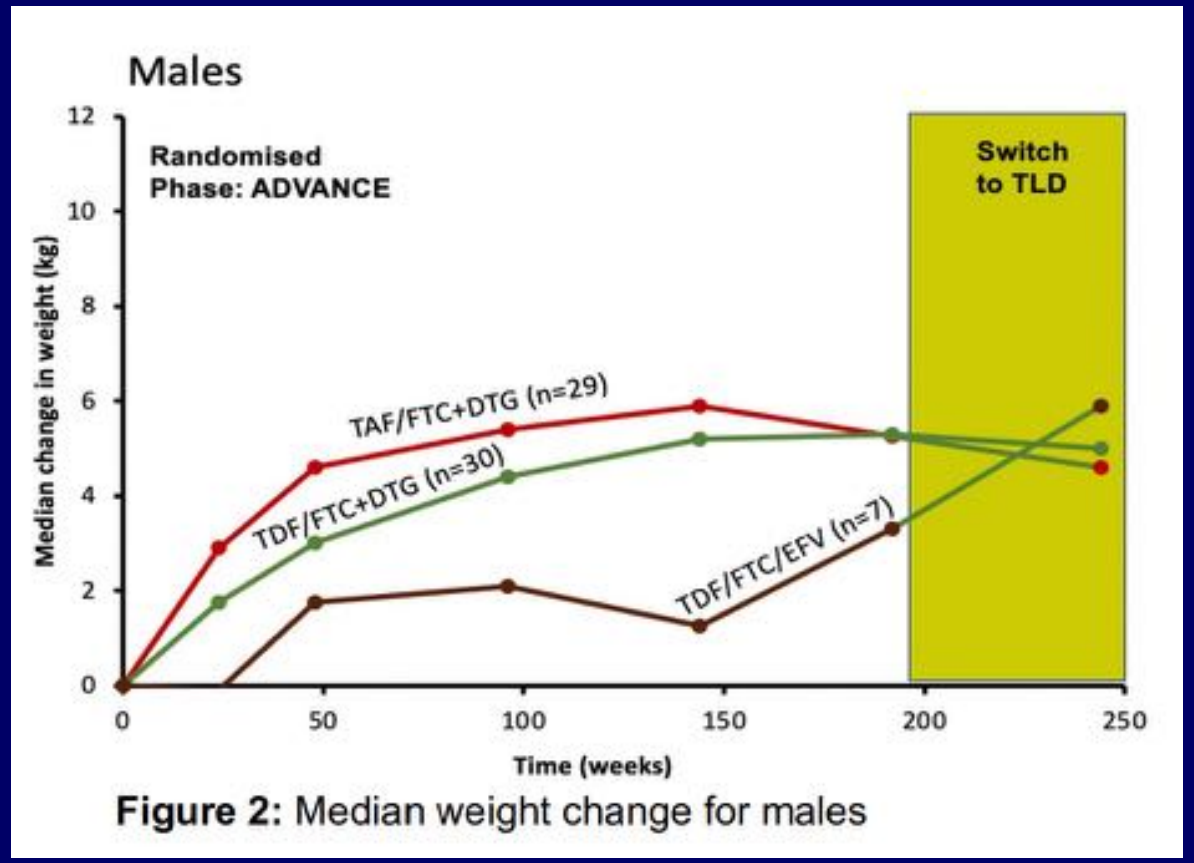


Figure 2: Median weight change for males

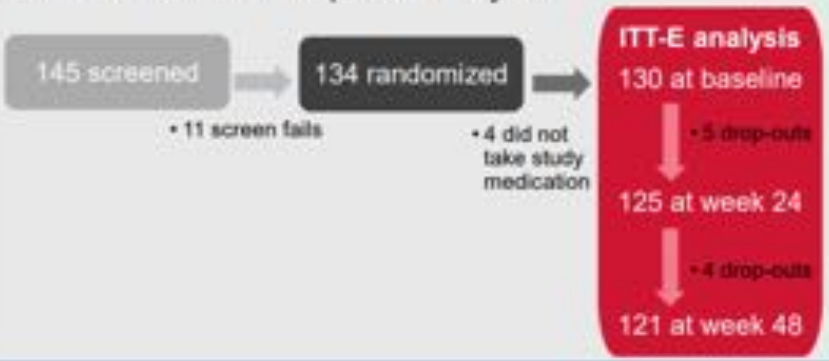
Bosch, 671

Switching from F/TAF/BIC to DTG/3TC

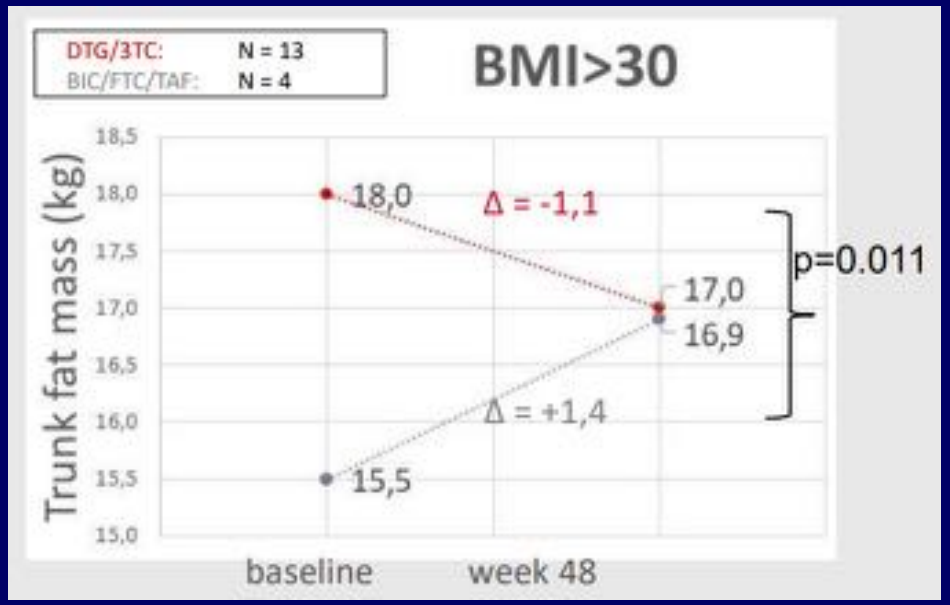
METHODS

- Randomized, open-label controlled trial (2:1)

- Longitudinal follow-up: baseline, week 24, week 48
- Outcomes (2ary): weight, BMI, waist, lipids, insulin resistance, DXA scan, fibroscan
- Linear mixed models with covariance patterns
- Intention to treat – exposed analysis

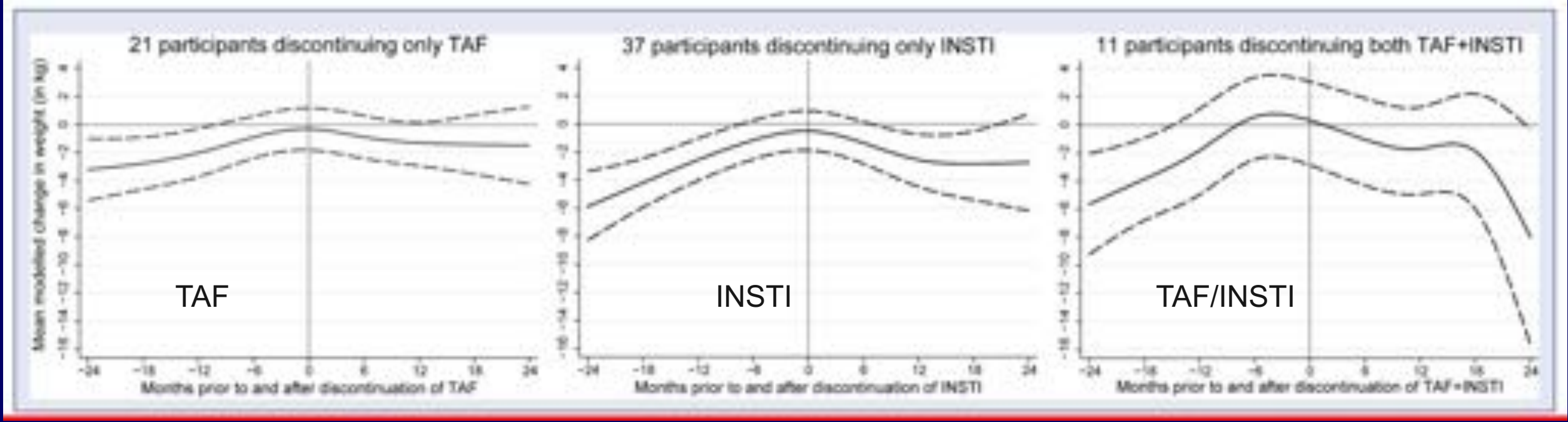


	DTG/3TC	BIC/FTC/TAF	p-value
ALT (U/L)	- 0.73	+ 4.55	0.040
HDL (mg/L)	- 0.043	- 2.84	0.043
Lean trunk mass (gram)	+ 112	- 474	0.032
Trunk fat mass (gram)	+ 41	+ 719	0.043
Fat percentage	- 0.04	+ 1.32	0.003



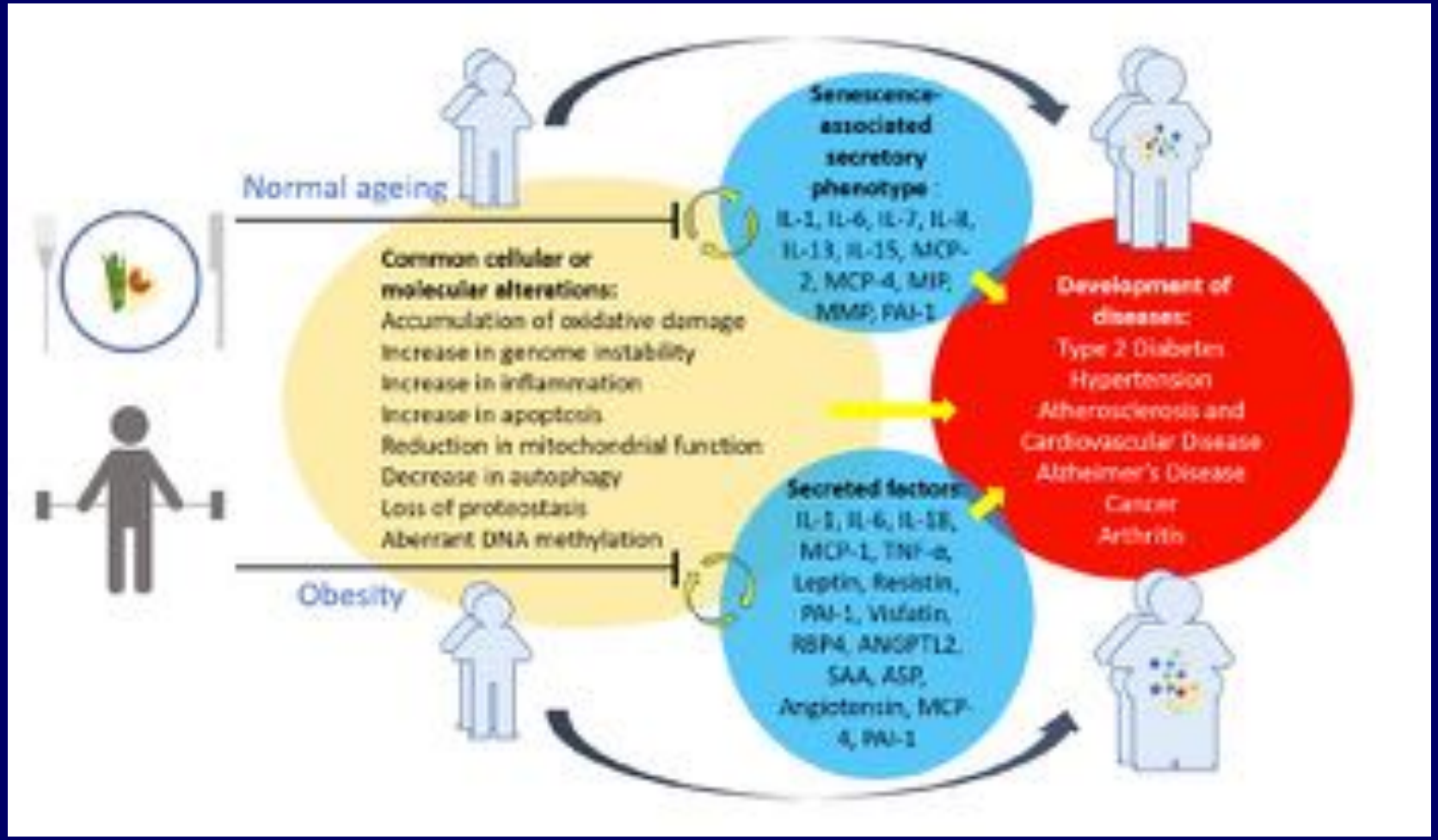
Degroote, CROI 2023, 672

Switching off of TAF, INSTIs, or Both in PWH with >7% weight gain: ATHENA Cohort



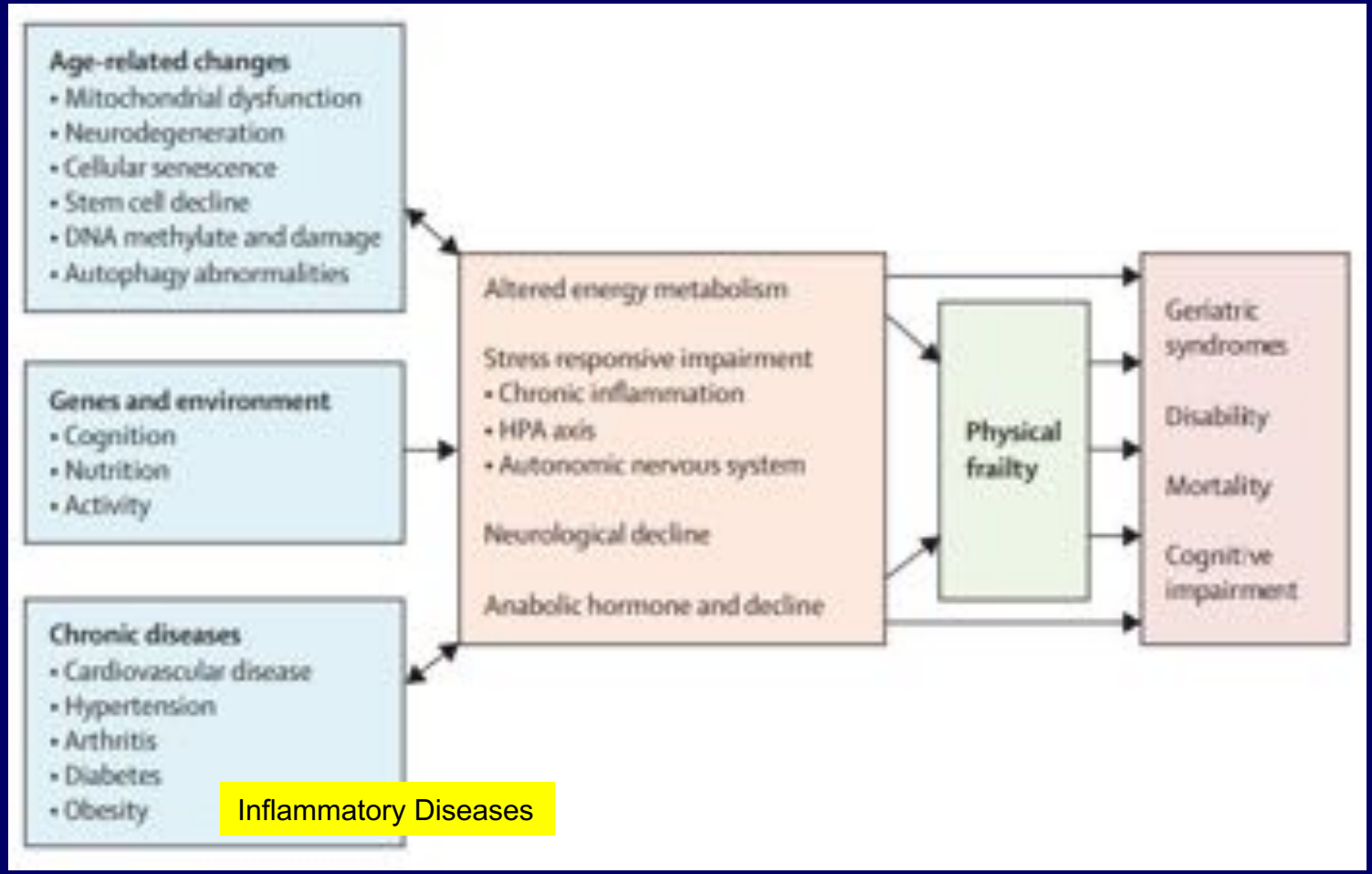
Verburgh, 673

Shared Mechanisms of Obesity and Aging in the Pathogenesis of Comorbid Disease

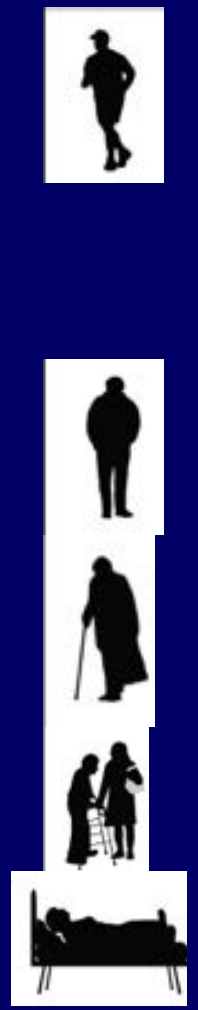


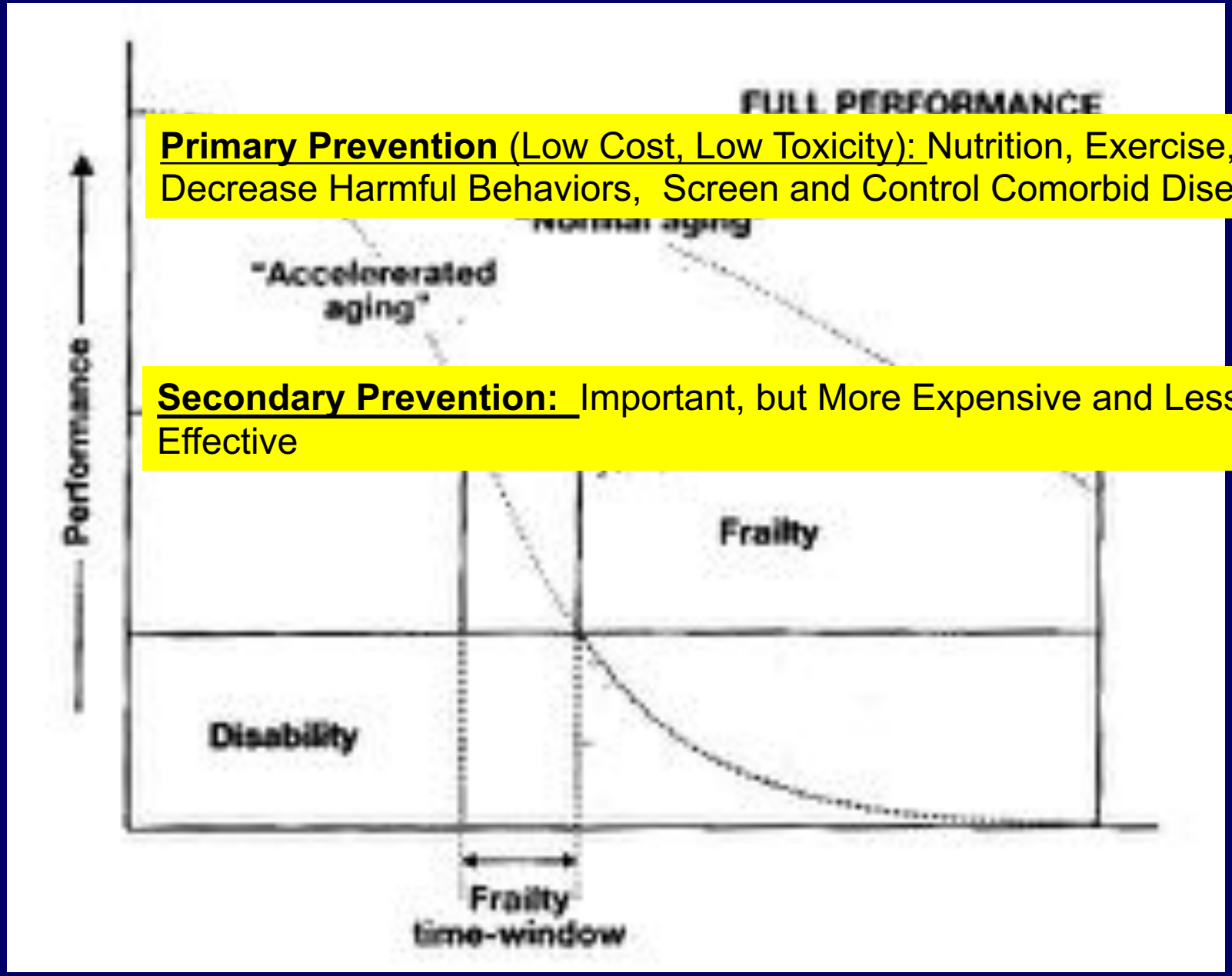
Tam, Obesity Reviews, 2019

Model Pathway for Frailty



Dent, Lancet, 2019

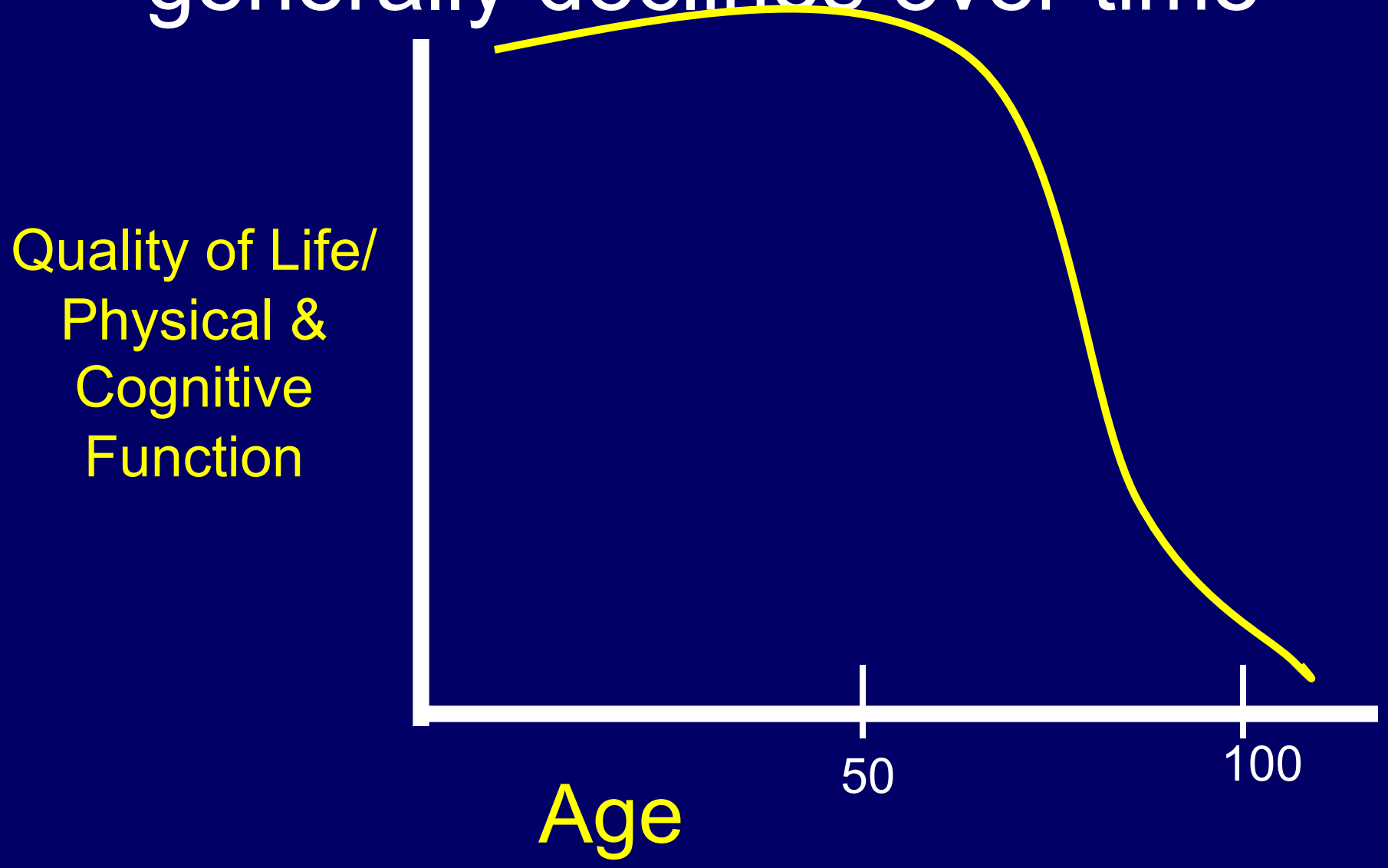




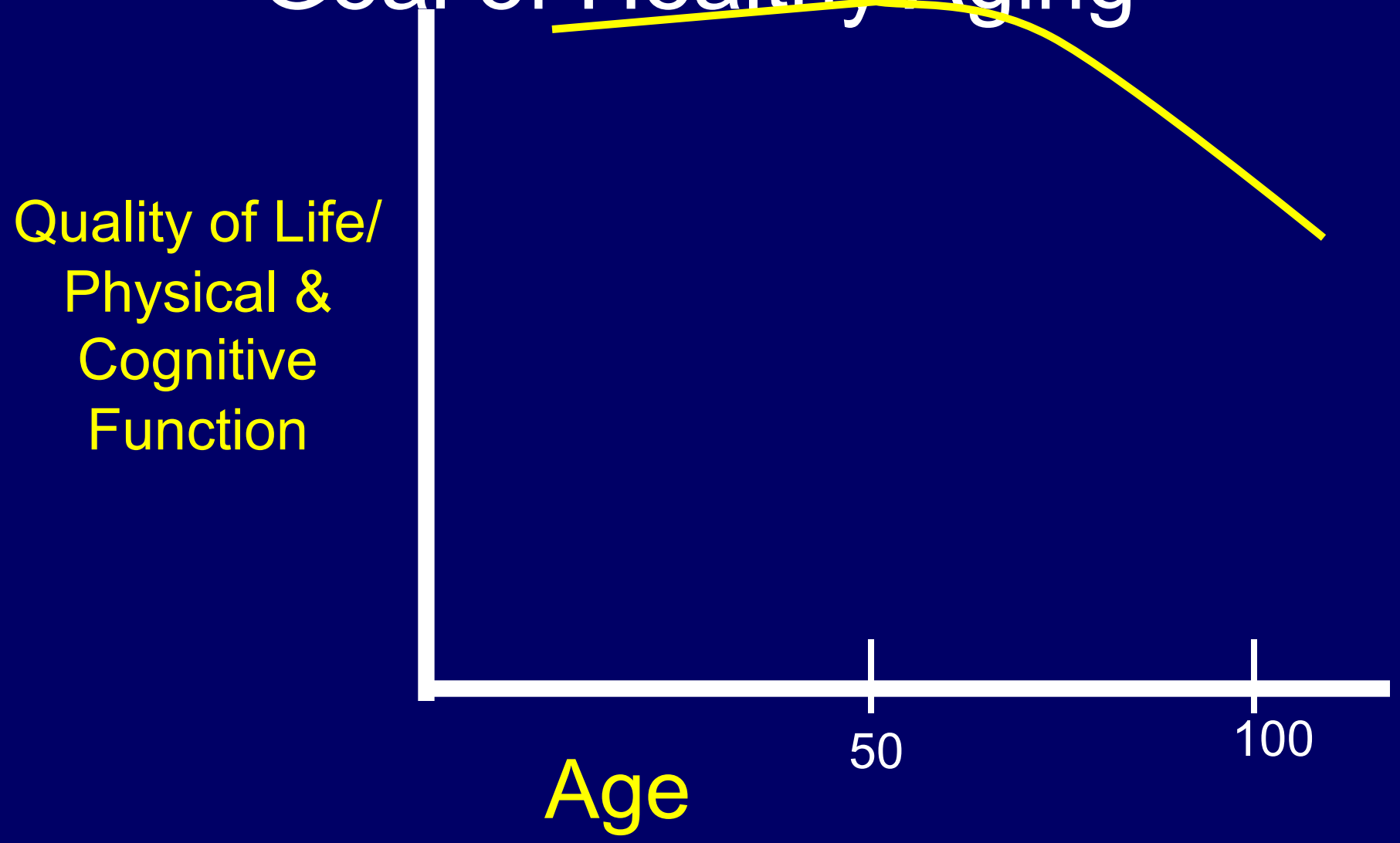
Primary Prevention (Low Cost, Low Toxicity): Nutrition, Exercise, Decrease Harmful Behaviors, Screen and Control Comorbid Diseases

Secondary Prevention: Important, but More Expensive and Less Effective

Physical & cognitive function generally declines over time



Bending the Curve Upwards is the Essential Goal of Healthy Aging



Conclusions

- Obesity is increasing in prevalence in older adults and is associated with multiple aging-related outcomes (DM, CVD, Cognitive Dysfunction, Frailty).
- Distribution of fat is important in understanding downstream outcomes
- Ectopic fat (e.g. muscle, heart) may be a major driver of obesity-related outcomes
- Associations may differ by HIV and sex
- PLWH may have additional risk factors that amplify clinical consequences of adiposity (eg specific ART)
- Switching off of TAF or INSTI may decrease weight, but more data are needed
- Attention to diet and physical activity are critical tools to decrease adiposity


Thank You for Your Attendance!
Please visit us at:
www.prn.org