UNIMORE
UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

Elixir of youth: can we counteract the mechanisms of aging?

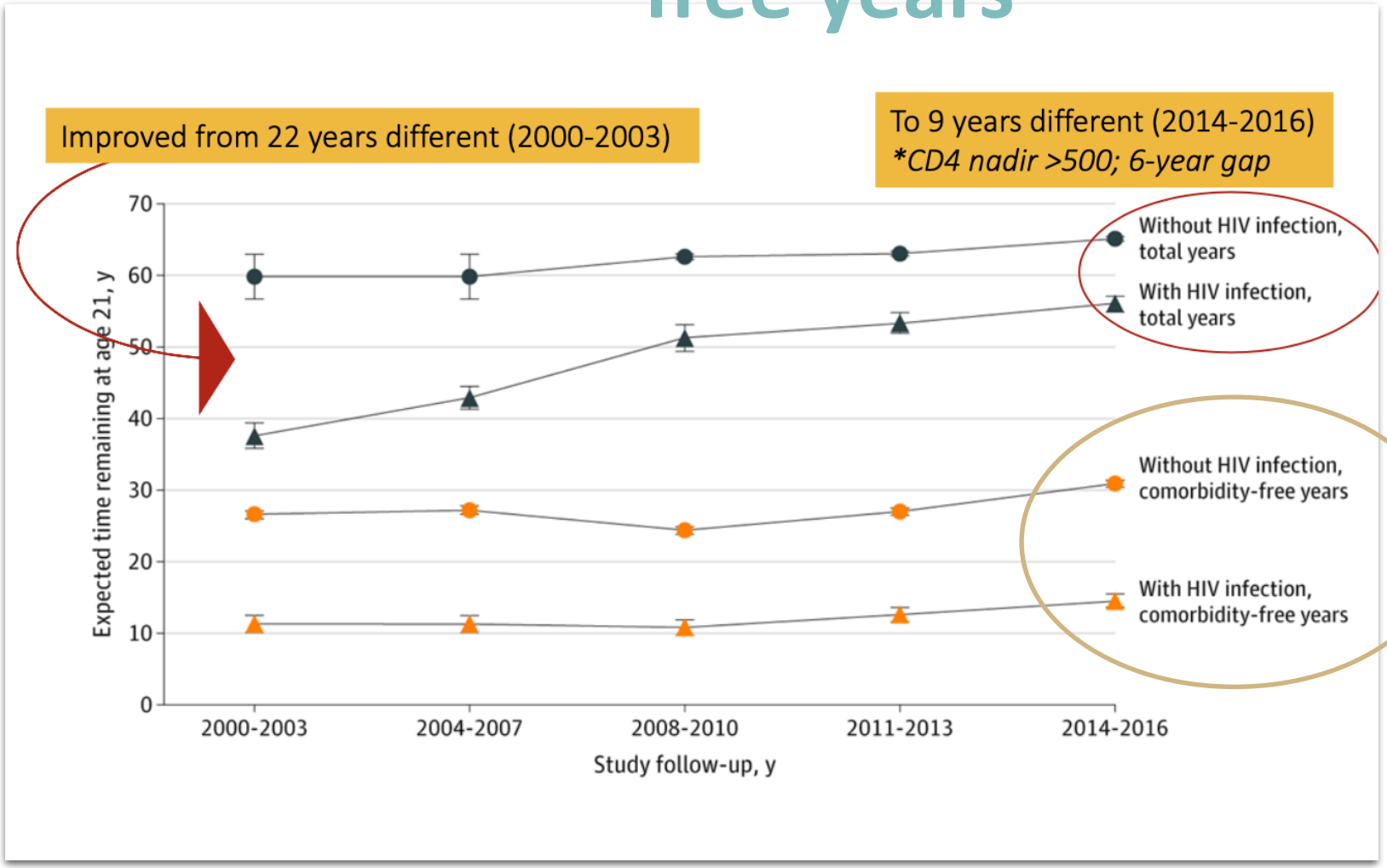
Modena HIV Metabolic Clinic
Università di Modena e Reggio Emilia

Giovanni Guaraldi

Disclosures

- GG received research grant speaker honorarium and attended advisory boards from Gilead, ViiV, MSD and Pfizer.

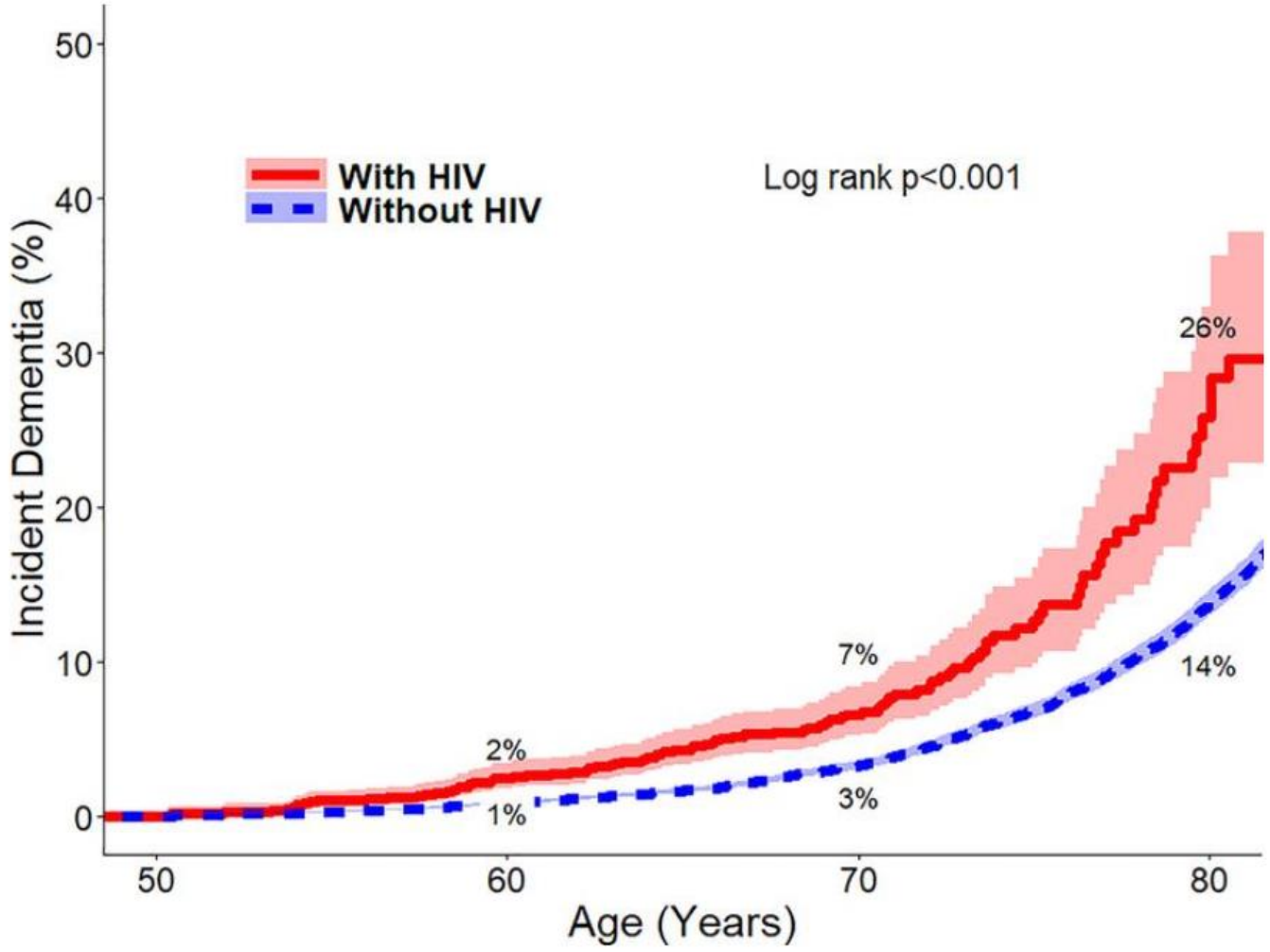
People with HIV have a MUCH LOWER comorbidity free years



PWH spent 15 years less without comorbidities, with no improvement across time

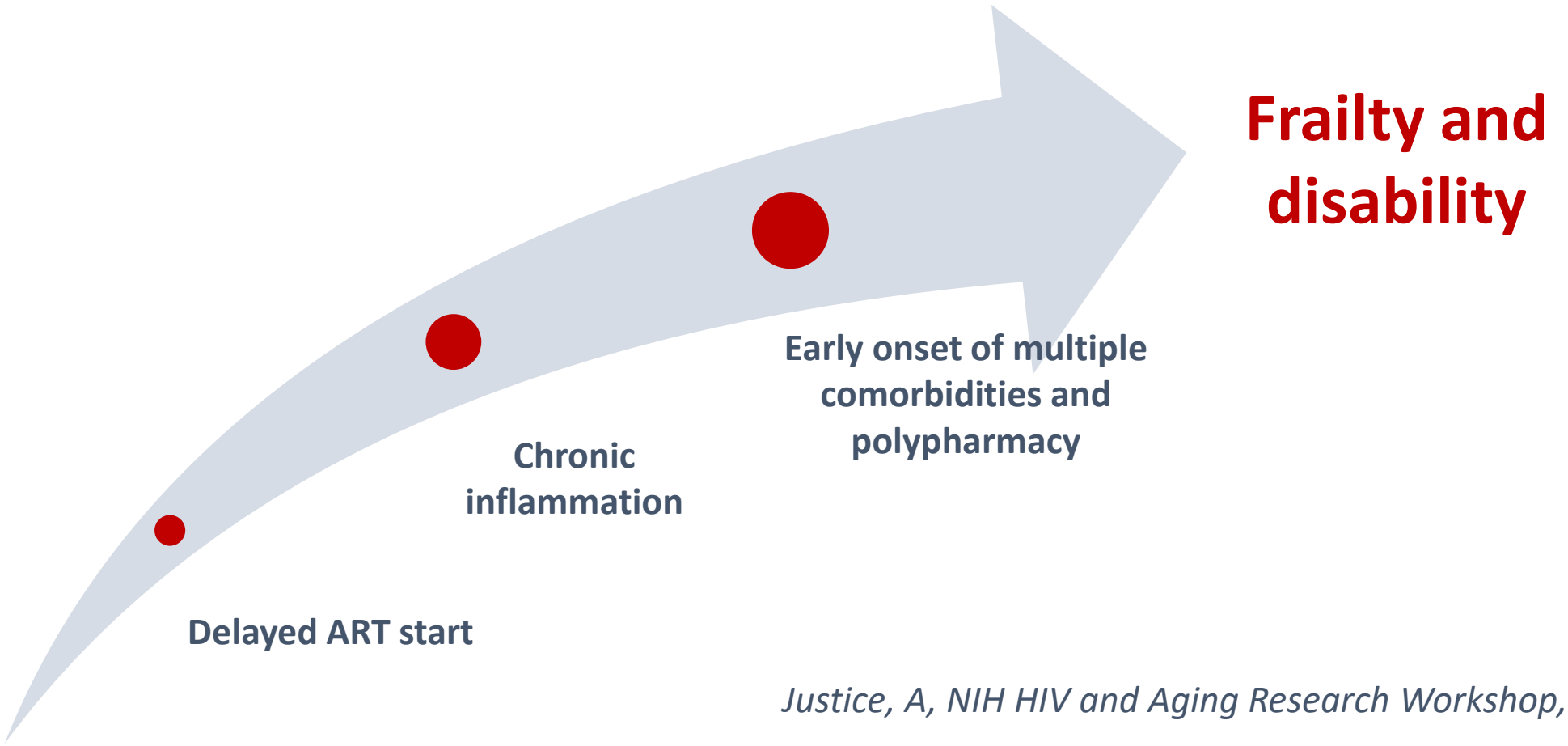
JAMA Network Open. 2020;3(6):e207954. doi:10.1001/jamanetworkopen.2020.7954

The incidence of dementia in older people with HIV



Bobrow K et al AIDS 2020

Modifiable root causes of unhealthy aging in PLWH



Justice, A, NIH HIV and Aging Research Workshop, 2023, modified

EACS GUIDELINES: COMMON AGE-ASSOCIATED COMORBIDITIES OBSERVED IN PEOPLE WITH HIV[a]

Pulmonary disease

- Respiratory symptoms, risk factors and spirometry

Glucose

- Serum glucose

Liver disease

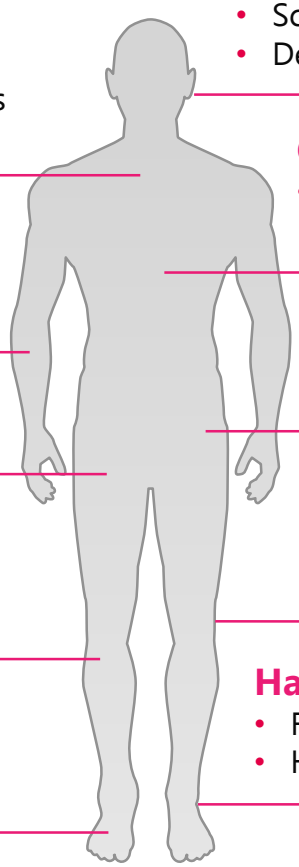
- Risk assessment and ALT/AST, ALP and bilirubin
- Staging of liver fibrosis and hepatic ultrasound

Cancer

- Mammography, cervical PAP/lipid-based cytology, rectal exam/anoscopy, ultrasound/alpha-fetoprotein and others

Bone disease

- Bone profile, calcium, PO_4, ALP
- Risk assessment (FRAX®) and 25(OH) vitamin D



Neurocognitive impairment

- Screening questionnaire
- Depression questionnaire

Cardiovascular disease

- Risk assessment (Framingham score), ECG prior to ARVs, hypertension (blood pressure) and lipids

Kidney disease

- Risk assessment, eGFR and urine dipstick analysis

Body composition

- BMI

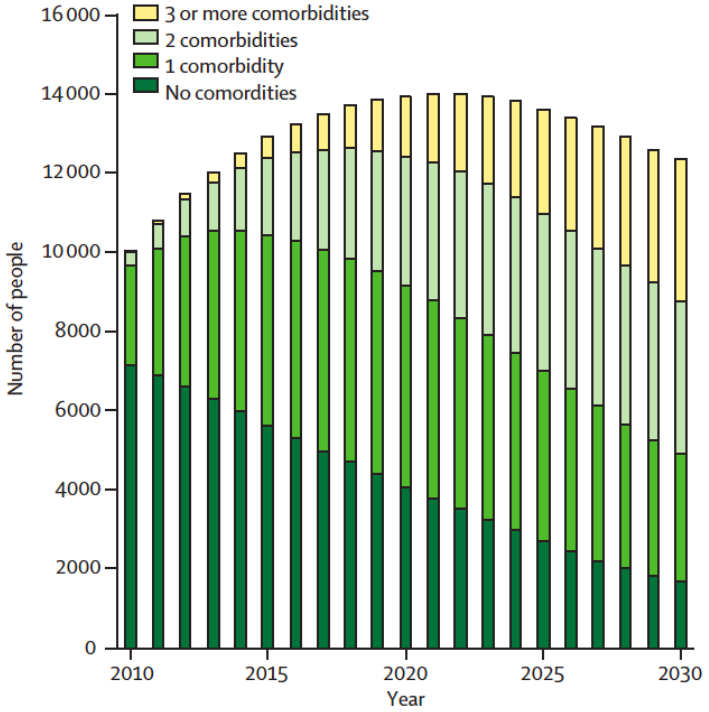
Haematology

- FBC and G6PD
- Haemoglobinopathies

[a]See guidelines for detail on follow-up frequence, subgroups to be screened, and further information.

Is aging with HIV different?

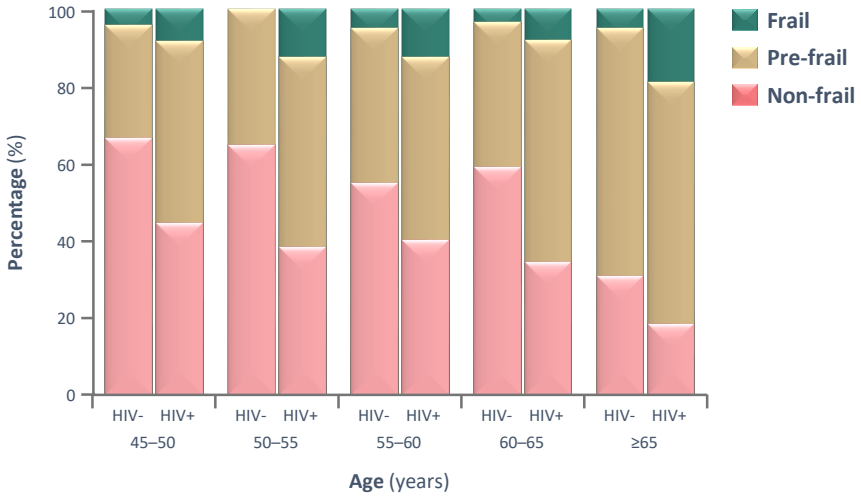
Future challenges for clinical care of an ageing population infected with HIV: a modelling study



PWH have **higher burden of NCDs**

Smit M et al. The Lancet Infectious Diseases. 2015;15(7):810-818

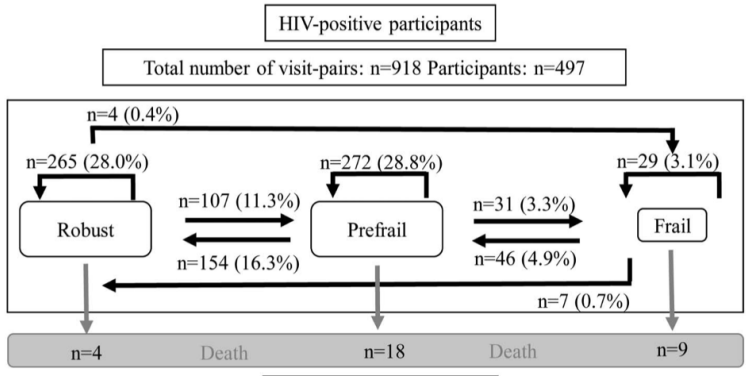
HIV infection is independently associated with frailty in middle-aged HIV type 1-infected individuals compared with similar but uninfected controls



PWH have **higher burden frailty** and frailty occurs at an early age.

AIDS 2016 Jan;30(2):241-50

Frequency, Risk Factors, and Mediators of Frailty Transitions During Long-Term Follow-Up Among People With HIV and HIV-Negative AGE$_h$IV Cohort Participants



PWH are at **increased risk of transitioning to frailty,** and increased risk of adverse health outcomes.

J Acquir Immune Defic Syndr 2021;86:110–118

What is the optimal ART for frail PWH?

Efficacy	(?)
Impact on frailty/geriatric syndromes	(?)
Toxicity	(kidney)
Impact on Comorbidities	(CVD, CKD, OO, NCI)
DDI	(polypharmacy)
Pill burden	(polypharmacy)
PRO	(sleep)
Metabolic health	(Weight, Metabolic syndrome, Cardiac health, Diabetes, Insulin resistance, Lipids, NAFLD, kidney, bone)

Can we revert frailty in HIV?

Conditions	Mitigation interventions
Geriatric syndromes	
• Polypharmacy	Medication reconciliation at each visit Deprescribing
• Cognitive impairment	Early initiation of ART Physical activity Vaccines
• Falls and fractures	Falls questionnaire Frailty screening Physical activity
• Sarcopenia	Screening and diagnosis of frailty with Frailty score and Frailty phenotype criteria Anaerobic physical activity three times a week Protein supplementation
• Malnutrition or overweight/obesity	Adequate daily caloric intake Nutritional counselling Physical activity

nature aging

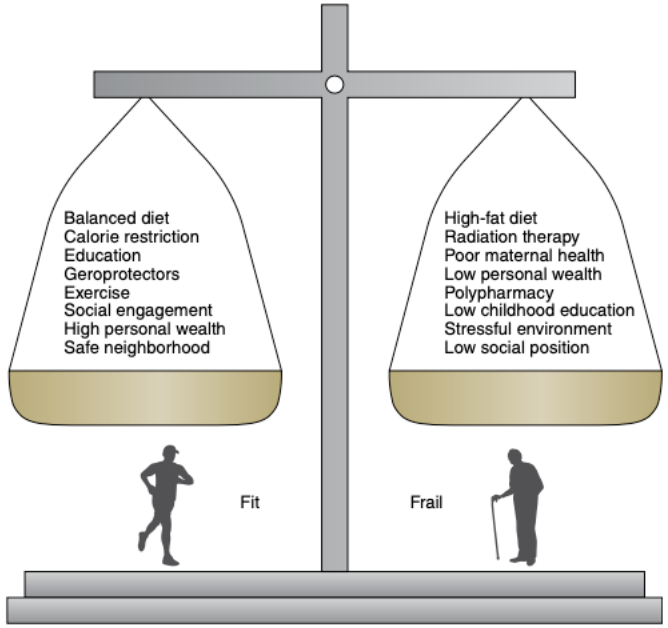
REVIEW ARTICLE

https://doi.org/10.1038/s43587-021-00099-3

Check for updates

The degree of frailty as a translational measure of health in aging

Susan E. Howlett[1,2], Andrew D. Rutenberg[3] and Kenneth Rockwood[1]✉



Medical interventions, lifestyle factors and social factors have a strong impact on the prevalence of frailty.

Table 2 | Frailty interventions in preclinical studies

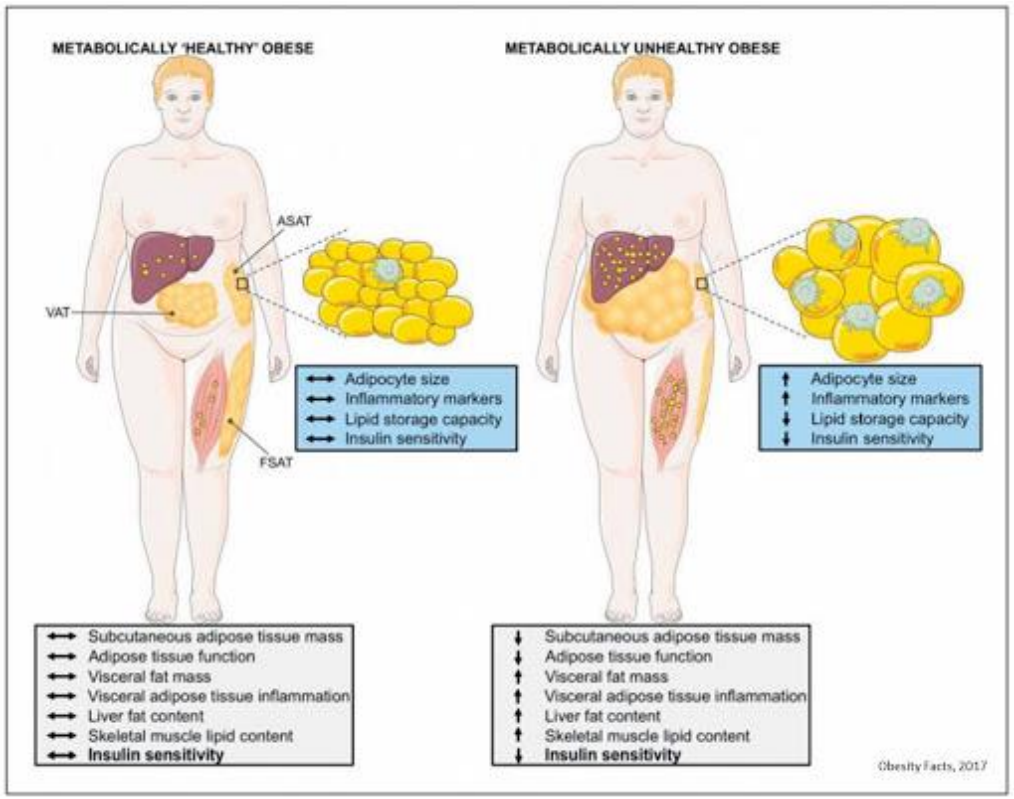
Model	Age	Sex	Key findings	Effect on frailty	Refs
C57BL/6 mice	6 and 28+ mos.	M	An aerobic exercise program (voluntary wheel running) improves physical performance and reverses frailty, assessed with the frailty phenotype tool, in aging mice.	↓	186
C57Bl/6J mice	3 to 28+ mos.	M	Lifelong aerobic exercise (voluntary wheel running) reduces frailty assessed with the frailty phenotype. Sedentary animals become frail as they age.	↓	187
C57BL/6 and short-lived DBA/2J mice	18 to 24 mos.	M/F	Known longevity interventions (for example, CR and resveratrol treatment) reduce FI scores in C57BL/6J mice. Short-lived male mice (for example, DBA/2J) are frailer than controls (effect not seen in females).	↓	190
NIH Swiss mice	2 to 24 mos.	M/F	Rapamycin (an mTOR inhibitor) increases longevity in female mice but not in male mice. Rapamycin has no effect on frailty in either sex, except that it reduces frailty in male mice fed a high-fat diet.	↔↓	181
NIH Swiss mice	2 to 24 mos.	M/F	A high-fat diet reduces life span and increases frailty in male mice but has no effect in female mice.	↑	181
C57BL/6 mice	2–4 mos. to 30 mos.	M	A ketogenic diet, which mimics aspects of CR, reduces midlife mortality but not life span, improves memory, with only a modest effect of FI scores in aging mice.	↔	193
Nonhuman primates (rhesus monkeys)	10–28 years	M/F	CR reduces frailty (assessed via frailty phenotype) and increases healthy life span in nonhuman primates. CR reduced frailty and mortality in both sexes. No obvious sex differences.	↓	71
C57BL/6J	24 to 28 mos.	M	High-intensity interval training reduces frailty, assessed with the phenotype approach in aging mice, in aged male mice.	↓	188
C57BL/6J	24 to 26 mos.	F	High-intensity interval training reduces FI scores in aging female mice, even when started late in life.	↓	189
C57BL/6 mice; NF-κB KO mice	4 to 24+ mos.	M	Rapamycin (an mTOR inhibitor) treatment extends health span and reduces FI scores in mice with enhanced NF-κB signaling and accelerated aging (the *Nfκb1*$^{-/-}$ mouse model).	↓	191
Hypothalamic mTORC2 KO	4–6 mos. to 22+ mos.	M/F	mTORC2 signaling in brain regulates metabolism in aging. Genetic ablation of mTORC2 in hypothalamic neurons impairs glucose homeostasis, reduces life span and increases frailty in both sexes.	↑	200
AQ-RKO mice	2–3 mos. to 40+ mos.	M/F	Adipose-specific deletion of mTORC *Rictor* (AQ-RKO) disrupts adipose mTORC2 and blunts metabolic adaptations to CR. Despite this, CR reduces FI scores and increases life span in AQ-RKO mice in both sexes, as it does in wild-type mice.	↓	192,145
C57BL/6 mice	9–13 mos. and 16–25 mos.	M/F	Enalapril (an angiotensin-converting enzyme inhibitor) treatment reduces FI scores in both sexes, via reducing pro-inflammatory cytokines in females and increasing anti-inflammatory cytokines in males. FI scores are higher in females than males.	↓	182
C57BL/6 mice	5–12 mos. and 22 mos.	M	Treatment of 5- to 6-month-old male mice with three sessions of sublethal irradiation increases FI scores at 12 mos. to levels like those seen in much older (22 mos.) nonirradiated mice.	↑	202
C57BL/6 mice	18 to 33+ mos.	M/F	Dietary supplementation with alpha-ketoglutarate (major metabolite in tricarboxylic acid cycle) extends life span in middle-aged female mice and reduces FI scores across the life course in both sexes. No apparent sex differences in frailty.	↓	199
C57BL/6J mice	19 to 27+ mos.	F	Replacement of aged hematopoietic stem cells with donor cells from young mice increases life span and reduces frailty in aging mice.	↓	196
Fischer 344 rats	6 to 21 mos.	M	Allicin, a component of garlic that attenuates inflammation, attenuates osteoporosis by reducing bone turnover and reduces FI scores in aging rats.	↓	198
C57BL/6J mice	12 to 24+ mos.	M	Mice treated with a chronic polypharmacy regimen with a high drug burden index have high FI scores and poor physical function. These adverse effects are attenuated by de-prescribing.	↑	201
C57BL/6 mice	21 to 39+ mos.	M	With machine-learning approaches, longitudinal FI scores can be used to develop the FRIGHT clock (predictor of biological age) and the AFRAID clock (predictor of life expectancy). Both clocks respond to interventions that attenuate frailty (for example, enalapril and a methionine-restricted diet).	↓	197
C57BL/6 mice	16 to 36+ mos.	M/F	A protein-restricted diet low in BCAAs reduces FI scores and increases life span in male but not female wild-type mice. A low-BCAA diet also increases survival in two short-lived progeroid mouse models.	↓	194
C57BL/6 mice	20 to 39+ mos.	M/F	Intermittent fasting in late life reduces frailty components in males not females. Effects of dietary restriction depend on increased renal H_2S production; H_2S levels were increased by intermittent fasting and correlated with lower frailty in males only.	↓	195

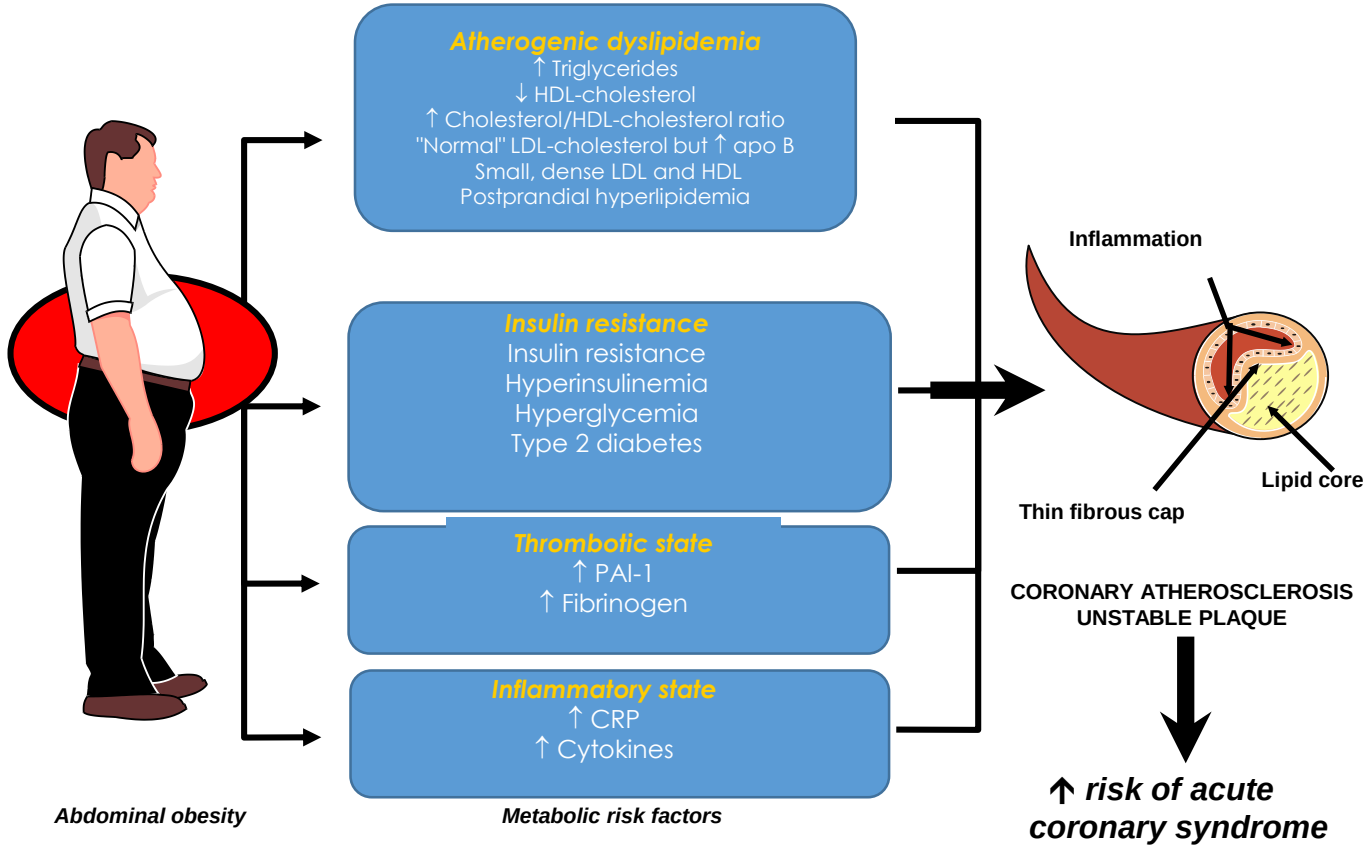
AQ-RKO, adipose-specific *Rictor* KO mice; BCAAs, branched-chain amino acids; CR, calorie restriction; F, female; FI, frailty index; H_2S, hydrogen sulfide; KO, knockout; M, male; mTORC2, mTOR complex 2; NIH, National Institutes of Health; NF-κB, nuclear factor kappa 8.

Knowledge and research gaps

Kehler DS. BMC Geriatr. 2022;22(1):919.

Fat quantity, quality and function





***Lancet Diabetes Endocrinol* 2019**
July 10, 2019 http://dx.doi.org/10.1016/ S2213-8587(19)30084-1

WHAT IS METABOLIC HEALTH?

- ✓ Metabolic health refers to a clinical construct that considers the net **patients' advantage regarding multiple metabolic parameters** captured by: body composition data (including beyond BMI, visceral and liver fat accumulation), lipid fractions, glucose and insulin resistance, kidney function and bone turnover.

- ✓ Metabolic health is not just the absence of metabolic diseases but rather **a road map for heathy living.**

- ✓ The pathway to improve metabolic health include firstly **lifestyle interventions** and secondly a **proactive antiretroviral approach to be considered in a patient-centred intervention**.

Mussini C, Guaraldi G, Milic J The lancet Infect Dis, 2023

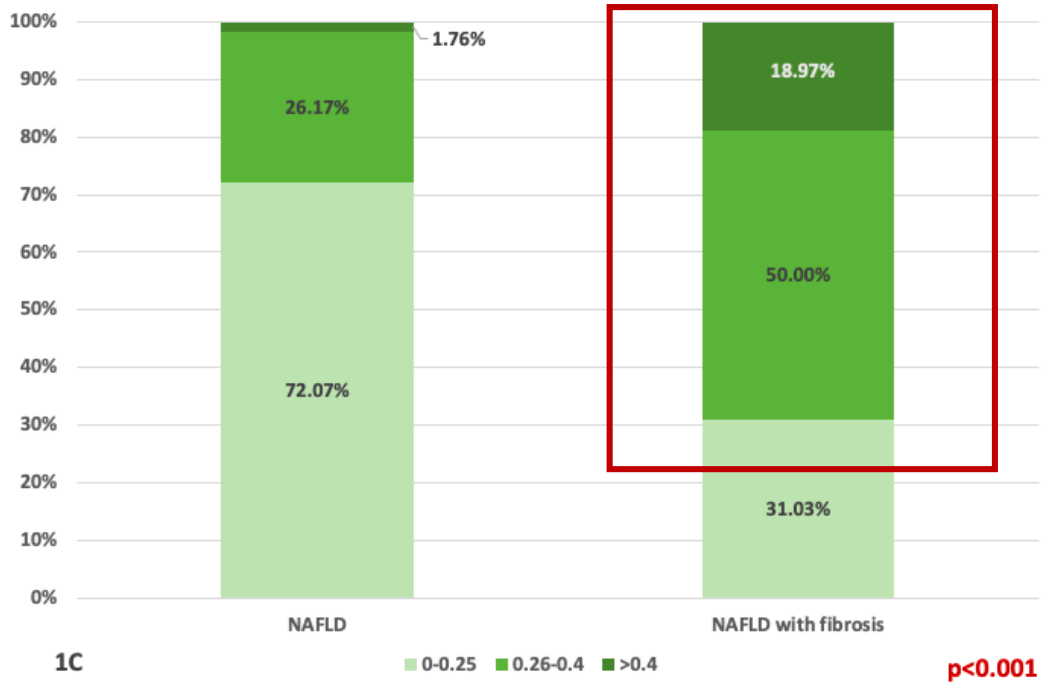
CLINICAL SCIENCE

Liver steatosis and nonalcoholic fatty liver disease with fibrosis are predictors of frailty in people living with HIV

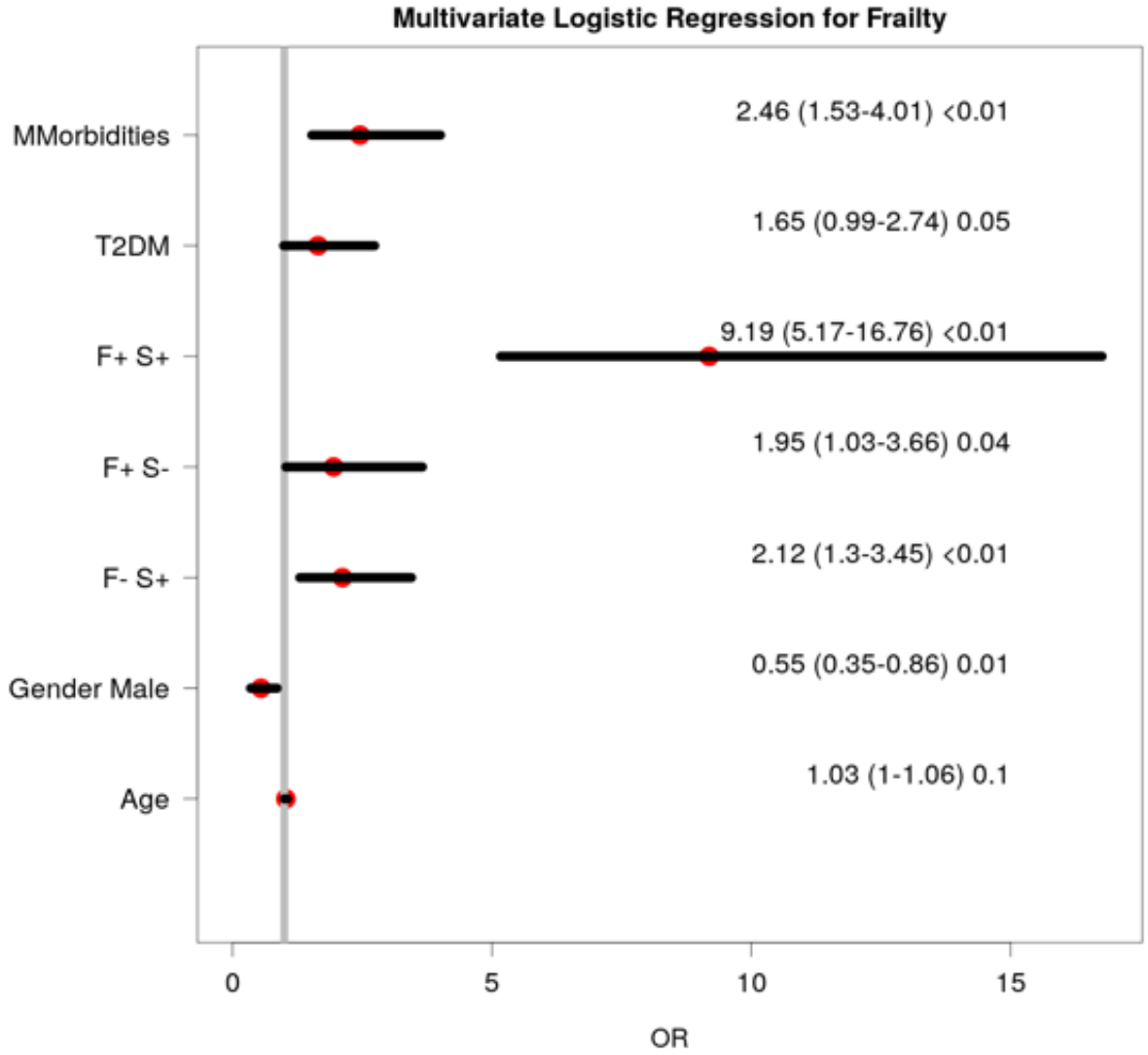
Milic, Jovana[a,b]; Menozzi, Valentina[c]; Schepis, Filippo[d]; Malagoli, Andrea[a]; Besutti, Giulia[b]; Franconi, Iacopo[a]; Raimondi, Alessandro[a]; Carli, Federica[a]; Mussini, Cristina[a]; Sebastiani, Giada[e]; Guaraldi, Giovanni[a] Author Information

AIDS: November 01, 2020 - Volume 34 - Issue 13 - p 1915-1921
doi: 10.1097/QAD.0000000000002650

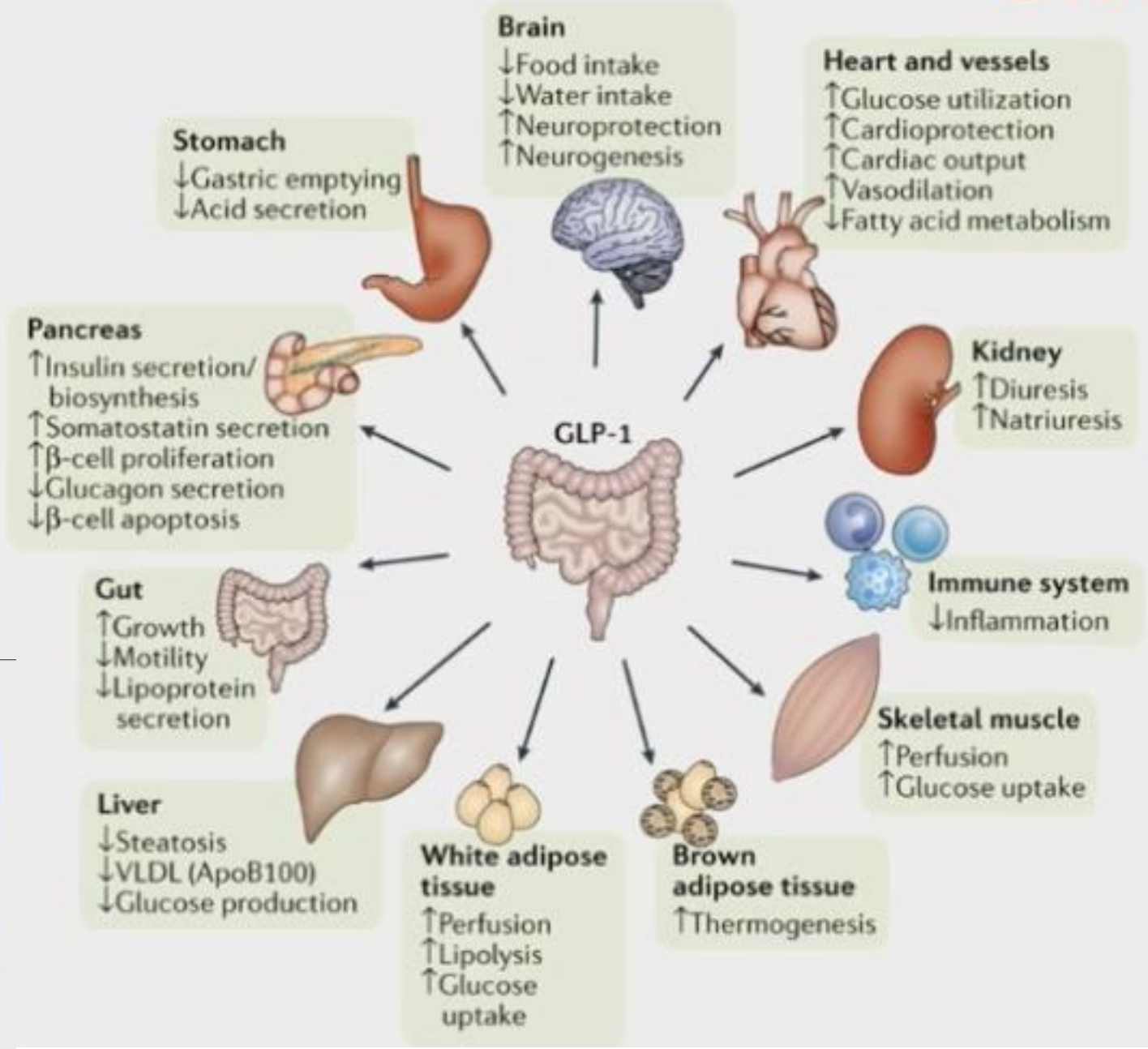
Almost 70% of PLWH with NAFLD with fibrosis are frail.



NAFLD with fibrosis predicts frailty three times better than multimorbidity.



Multiple Sites of Action of GLP-1 RA



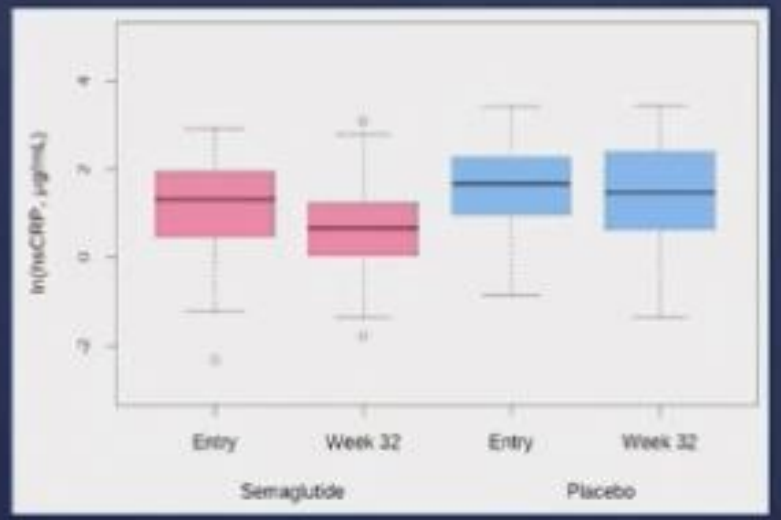
GLP1 RAs in Diabetes: Effects on Cardiovascular Events

Drug	Duration	Glucose Effect	Weight Effect	Reduction in MACE
Exenatide	24 weeks	-0.9%	-2.9 kg	NO
Liraglutide	52 weeks	-1.1 %	-2.5 Kg	↓ 14%
Lixisenatide	24 weeks	-0.72%	-2.7 kg	NO
Dulaglutide	36 weeks	-1.8%	-4.6 kg	↓ 12%
Semaglutide	40 weeks	-2.1%	-6.4 kg	↓ 26%

Glucose and weight data from FDA Package Inserts at highest approved dose

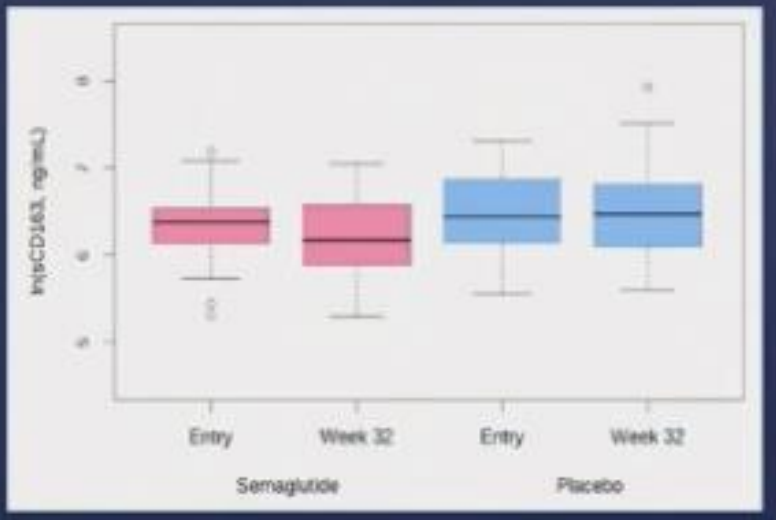
Effects of Semaglutide on Inflammation and Immune Activation

Summary of key linear regression models adjusted for baseline marker values, smoking, male sex ± age*



hsCRP
-39.9%

IL-6
-18.8%

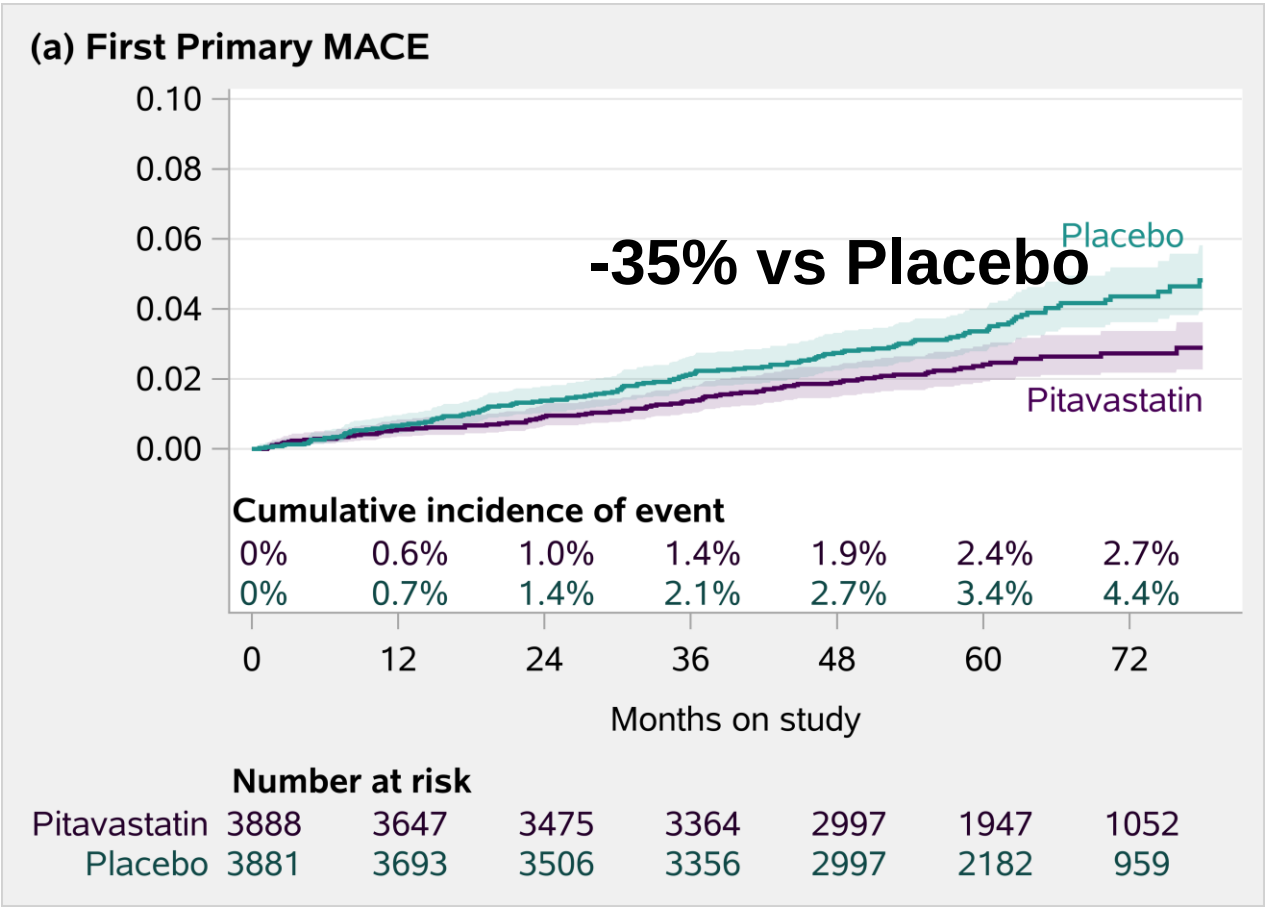


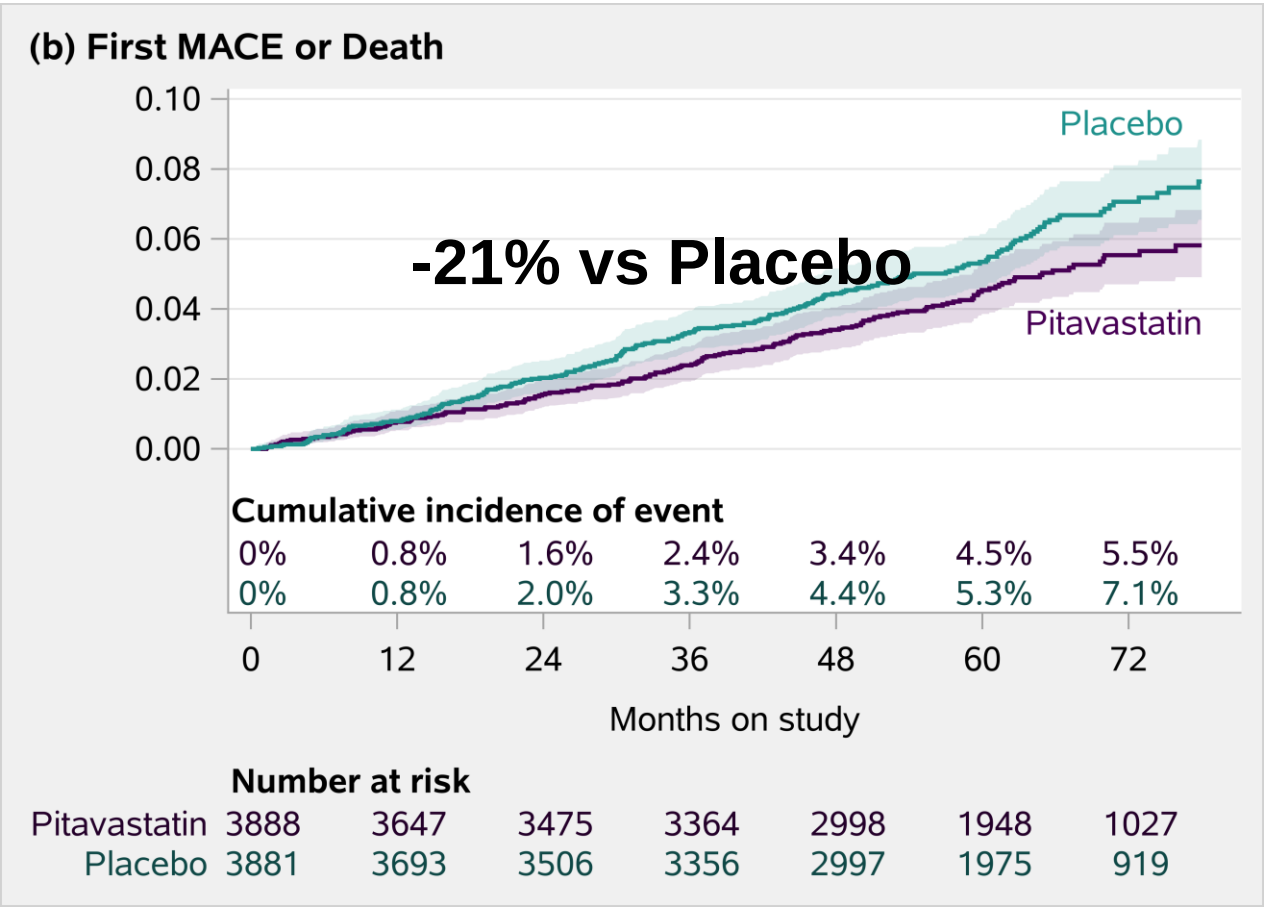
sCD163
-12.3%

*β coefficients estimate adjusted effects of semaglutide treatment vs. placebo at 32 weeks; % change estimates calculated using the formula: $100(e^{\beta}-1)$

ln(hsCRP): β -0.51, 95% CI [-0.87, -0.15]; p=0.006
ln(sCD163): β -0.13, 95% CI [-0.26, -0.002]; p=0.046
ln(IL-6): β -0.21, 95% CI [-0.44, 0.02]; p=0.074

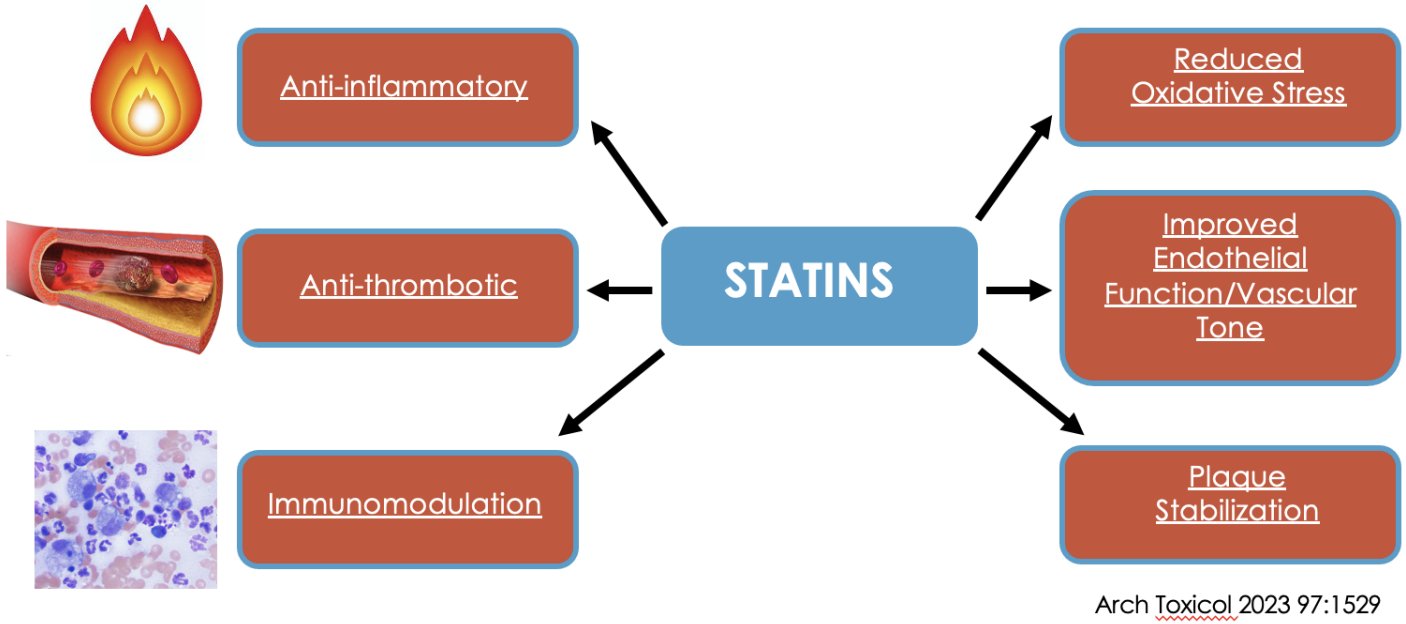
Primary and Key Secondary Endpoints





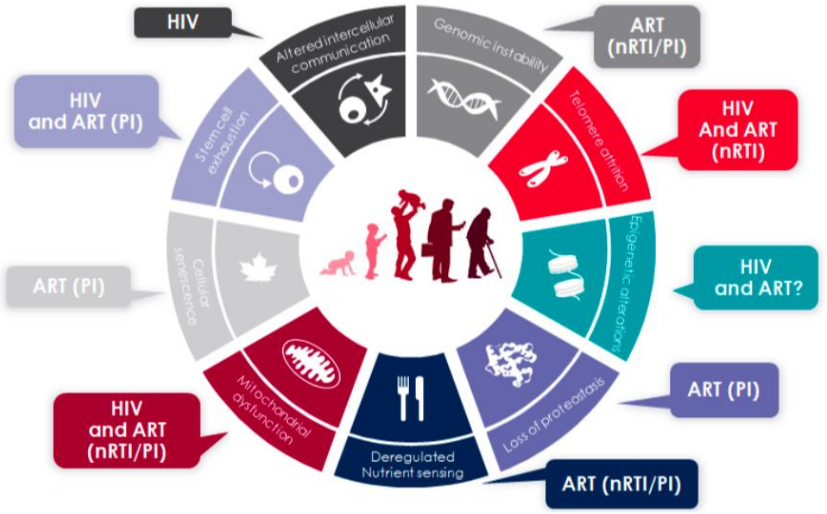
Grinspoon et al. NEJM 2023

Beyond LDL: Pleiotropic Effects of Statins



Arch Toxicol 2023 97:1529

The Hallmarks of Ageing can be Affected by Both HIV and ART



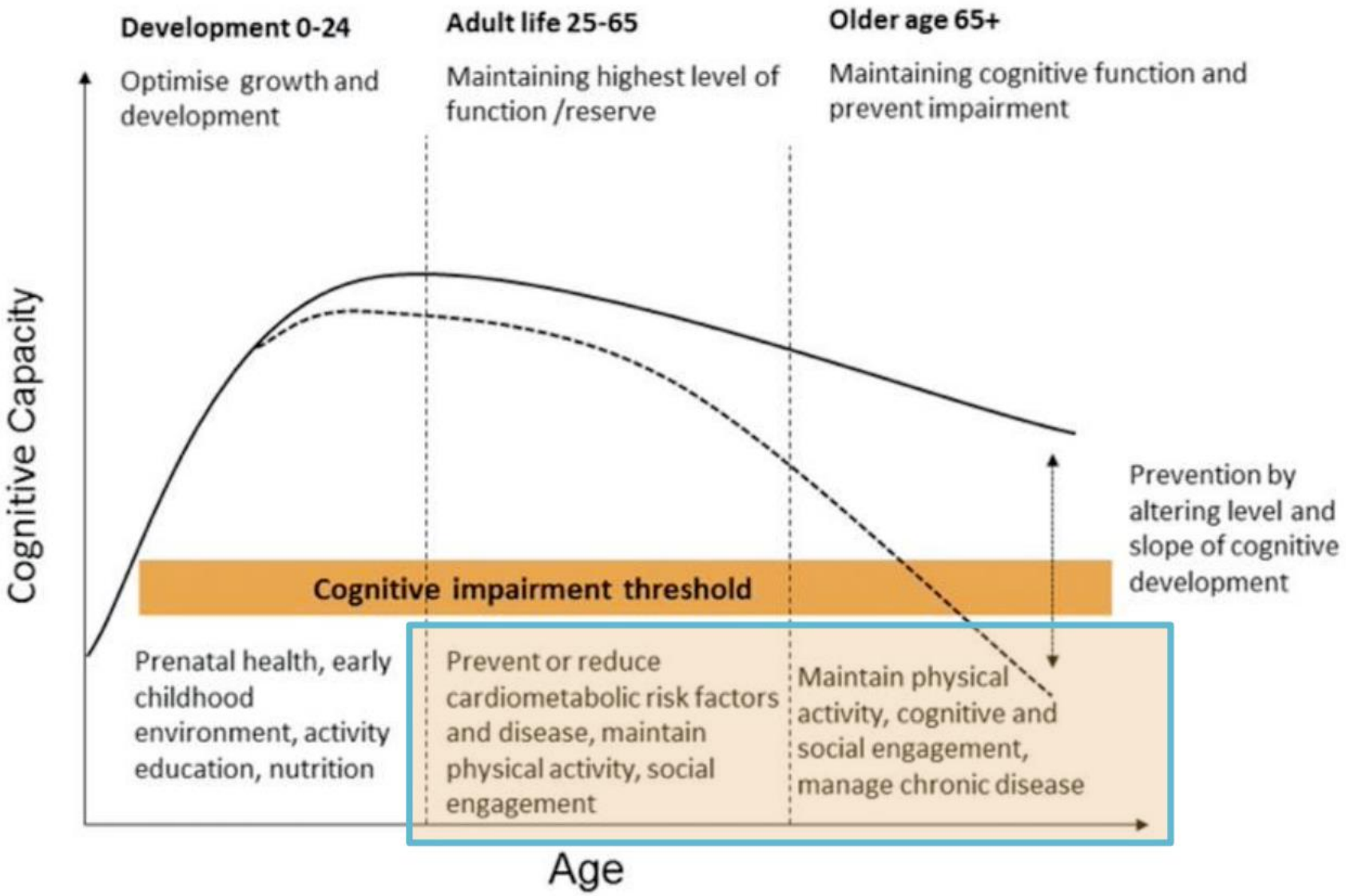
HIV alters **biological mechanisms of aging** and contribute to chronic diseases and disabilities

ARV acts as geroterapeutics agents and senomorfic drugs (statins) may be particular important in PWH in a GEROSCIENCE perspective

ICOPE

INTEGRATED CARE FOR OLDER PEOPLE

World Health Organization



Cognitive rehabilitation

Abstraction and executive function

Source	Participants, No. CCT	Control	SE	SMD (95% CI)	Weight, %
Fazeli et al,[49] 2019	17	16	0.35	0.24 (-0.45 to 0.92)	16.2
Livelli et al,[45] 2015	16	16	0.38	1.14 (0.39 to 1.88)	14.3
Ownby et al,[54] 2017	6	5	0.61	0.02 (-1.17 to 1.21)	6.6
Pope et al,[48] 2018	15	15	0.38	0.93 (0.18 to 1.68)	14.1
Vance et al,[44] 2012	22	24	0.30	0.18 (-0.40 to 0.76)	20.3
Vance et al,[56] 2021	48	40	0.22	0.74 (0.31 to 1.18)	28.4
Total	124	116	NA	0.58 (0.26 to 0.91)	100.0

Heterogeneity: $\tau^2 = 0.05$; $\chi^2 = 7.11$; $df = 5$; $P = .21$; $I^2 = 30\%$

Test for overall effect: $z = 3.50$; $P < .001$

Attention and working memory

Source	Participants, No. CCT	Control	SE	SMD (95% CI)	Weight, %
Chang et al,[40] 2017	34	20	0.30	1.01 (0.43 to 1.60)	12.9
Cody et al,[41] 2020	17	16	0.35	0.03 (-0.66 to 0.71)	10.9
Fazeli et al,[49] 2019	17	16	0.35	0.38 (-0.31 to 1.07)	10.8
Livelli et al,[45] 2015	16	16	0.40	1.54 (0.75 to 2.32)	9.1
Ownby et al,[54] 2017	6	5	0.63	0.82 (-0.41 to 2.06)	4.6
Towe et al,[46] 2017	29	29	0.48	1.22 (0.28 to 2.15)	7.1
Towe et al,[47] 2021	11	10	0.27	0.50 (-0.02 to 1.02)	14.4
Vance et al,[44] 2012	22	24	0.30	0.32 (-0.27 to 0.90)	13.0
Vance et al,[56] 2021	48	40	0.22	0.41 (-0.01 to 0.83)	17.2
Total	200	176	NA	0.62 (0.33 to 0.91)	100.0

Heterogeneity: $\tau^2 = 0.08$; $\chi^2 = 14.04$; $df = 8$; $P = .08$; $I^2 = 43\%$

Test for overall effect: $z = 4.21$; $P < .001$

Memory

Source	Participants, No. CCT	Control	SE	SMD (95% CI)	Weight, %
Ezeamama et al,[42] 2020	41	40	0.23	0.64 (0.20 to 1.08)	28.1
Fazeli et al,[49] 2019	17	16	0.35	0.11 (-0.57 to 0.79)	18.6
Livelli et al,[45] 2015	16	16	0.40	1.45 (0.67 to 2.22)	15.9
Ownby et al,[54] 2017	6	5	0.62	0.61 (-0.60 to 1.82)	8.3
Vance et al,[56] 2021	48	40	0.22	0.36 (-0.06 to 0.78)	29.1
Total	128	117	NA	0.59 (0.20 to 0.97)	100.0

Heterogeneity: $\tau^2 = 0.09$; $\chi^2 = 7.64$; $df = 4$; $P = .11$; $I^2 = 48\%$

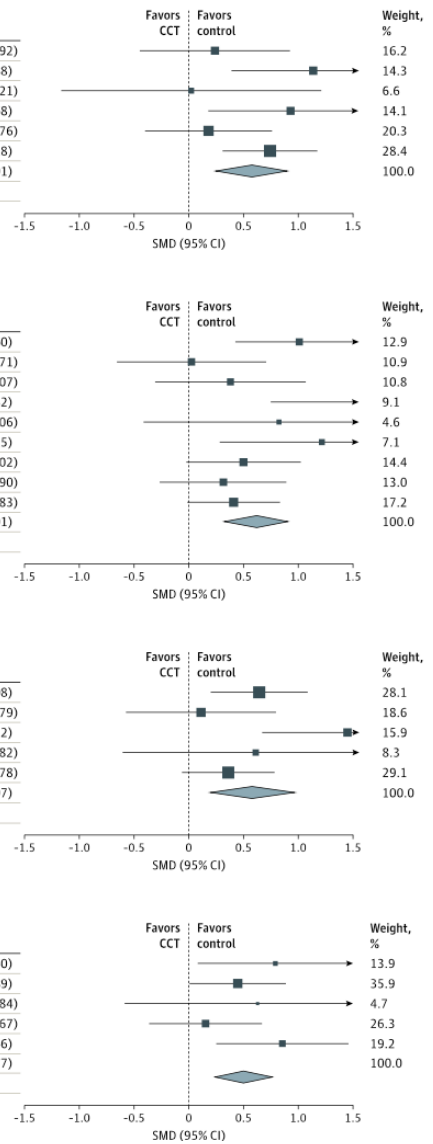
Test for overall effect: $z = 2.97$; $P = .003$

Motor skills

Source	Participants, No. CCT	Control	SE	SMD (95% CI)	Weight, %
Cody et al,[41] 2020	17	16	0.36	0.79 (0.08 to 1.50)	13.9
Ezeamama et al,[42] 2020	41	40	0.22	0.45 (0.01 to 0.89)	35.9
Ownby et al,[54] 2017	6	5	0.62	0.63 (-0.59 to 1.84)	4.7
Towe et al,[47] 2021	29	29	0.26	0.15 (-0.36 to 0.67)	26.3
Vance et al,[44] 2012	22	24	0.31	0.85 (0.25 to 1.46)	19.2
Total	115	114	NA	0.50 (0.24 to 0.77)	100.0

Heterogeneity: $\tau^2 = 0$; $\chi^2 = 3.82$; $df = 4$; $P = .43$; $I^2 = 0\%$

Test for overall effect: $z = 3.74$; $P < .001$



Vei J et al JAMA Open 2022

Vaccination

Open access Original research

BMJ Open

Shingles, Zostavax vaccination and risk of developing dementia: a nested case–control study—results from the UK Biobank cohort

Artitaya Lophatananon [1], Krisztina Mekli,[1] Rachel Cant,[2] Alistair Burns,[3] Curtis Dobson,[2] Ruth Itzhaki,[4] Kenneth Muir [1]

To cite: Lophatananon A, Mekli K, Cant R, *et al*. Shingles, Zostavax vaccination and risk of developing dementia: a nested case–control study—results from the UK Biobank cohort. *BMJ Open* 2021;**11**:e045871. doi:10.1136/bmjopen-2020-045871

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-045871).

CD, RI and KM are joint senior authors.

Received 15 October 2020
Accepted 12 September 2021

ABSTRACT

Objectives To investigate the association between shingles and dementia, and between Zostavax vaccination and dementia.

Design Nested case–control study.

Settings Data were drawn from the UK Biobank cohort study with a total of 228 223 participants with Hospital Episodes Statistics and primary care linkage health records.

Participants The analyses included 2378 incident dementia cases and 225 845 controls. Inclusion criteria for incident cases were a dementia diagnosis 3 years or more after the first assessment date derived from all sources including International Classification of Diseases (ICD)-10, ICD-9, self-report and primary care linkage records. Subjects with no dementia code from all sources were coded as controls. Both shingles and Zostavax vaccination were investigated for their association with dementia risk.

Results There was a small but non-significant increase in the risk of dementia in subjects with shingles diagnosed 3 years or more prior to dementia diagnosis (OR: 1.088 with 95% CI: 0.978 to 1.211). In those subjects who had had Zostavax vaccination, the risk of dementia significantly decreased (OR: 0.808 with 95% CI: 0.657 to 0.993).

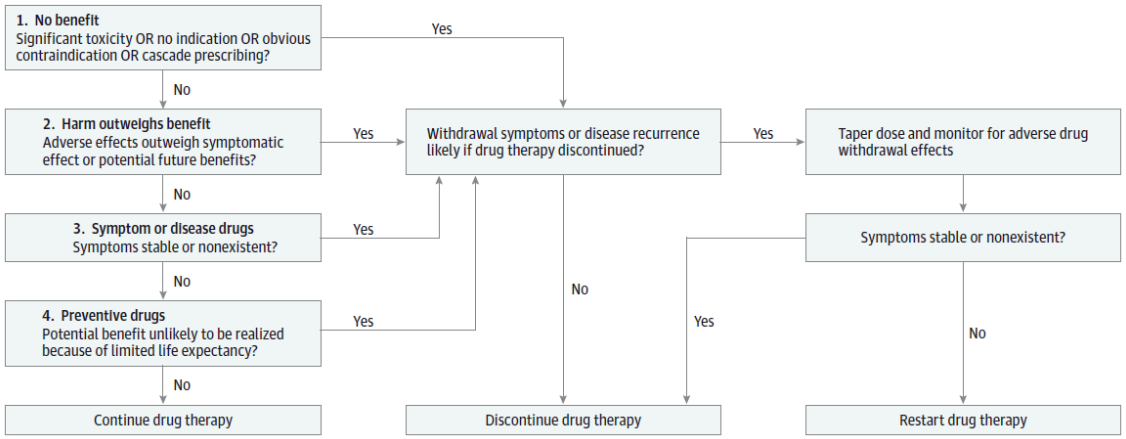
Conclusion A history of shingles was not associated with an increased risk of dementia. In subjects who were eligible for the immunisation and vaccinated with Zostavax, we saw reduced risk of developing dementia.

Strengths and limitations of this study

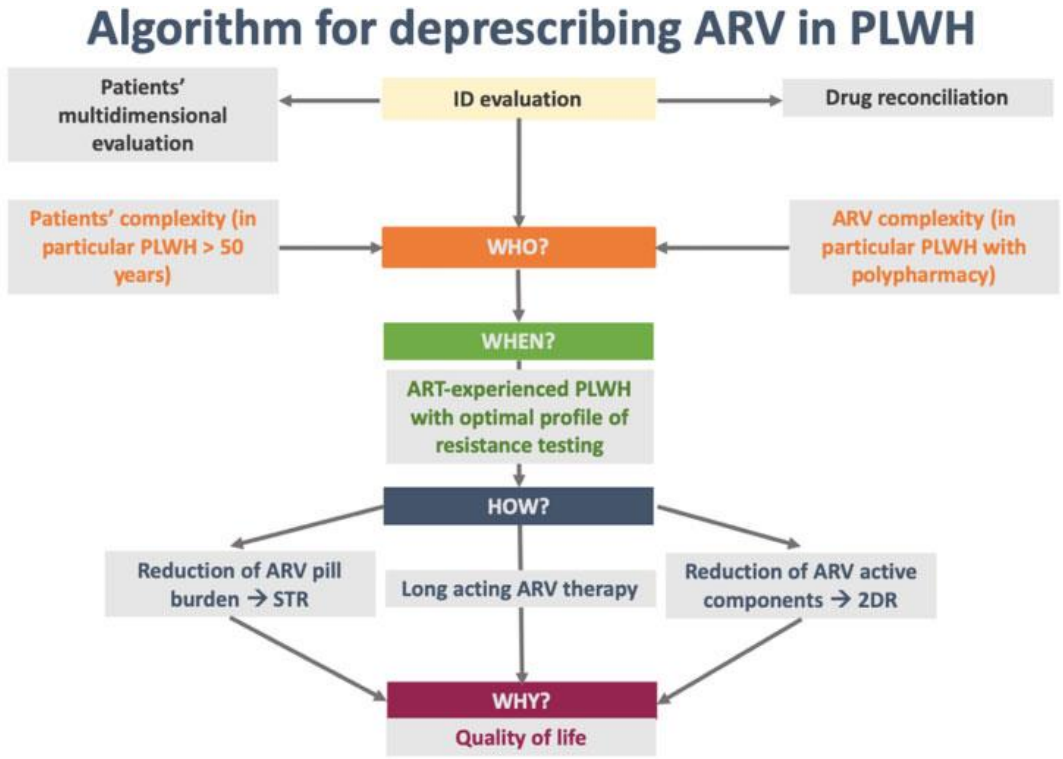
- This study used a subset of UK Biobank cohort, and disease outcomes and exposures were ascertained through sources including the Hospital Episodes Statistics primary care data linkage.
- As varicella-zoster virus is the only herpes virus for which an effective vaccine (Zostavax) is approved, we have also been able to establish whether vaccination against a herpes virus influences dementia.
- The analysis of vaccination was based only on eligible subjects.
- This study inherits some weakness in that the UK Biobank study participants are not fully representative of the UK population, as suggested by low prevalence of dementia compared with the general population.
- We did not investigate other types of herpes viruses that may also play a role in dementia aetiology.

attention is whether viruses may have a role in initiating or aiding the development of dementia. For example, we previously proposed that herpes simplex virus type 1 (HSV1), which is present in latent form in the postmortem brains of elderly people, causes both direct viral damage and inflammation

A patient-centred approach
ARVs and non ARVs?

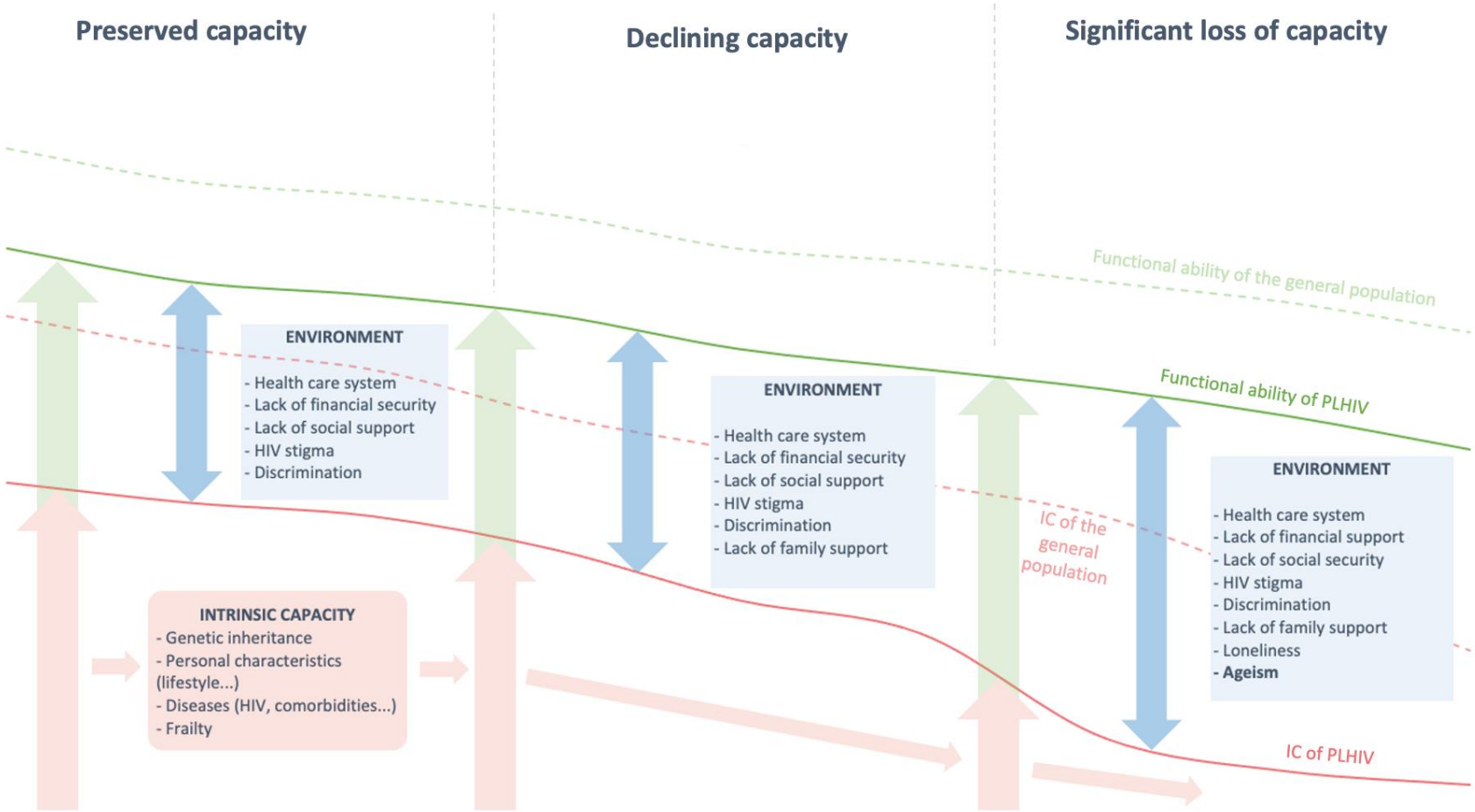


STOPP/START or BEERS criteria
http://medstopper.com
http://deprescribing.org



Guaraldi G, et al. JAC 2020

Relationship between intrinsic capacity and functional ability throughout aging trajectories



WHO definition

of Ageism refers to;

1, stereotypes (how we think),

1. prejudice (how we feel),
2. discrimination (how we act)

on the basis of age.

Intersectionality of HIV stigma and ageism drives the gap between IC and functional ability

Guaraldi G et al., the lancet HIV, 2023

Recommendations to fight ageism

INSTITUTIONAL AGEISM

- Clinical care systems need to be reshaped to meet the needs of older PLWH including geriatric syndromes screening, integrated care, support and a referral, and support system.
- HIV doctors and clinicians should receive training on how to comprehensively provide comprehensive care for older PLWH.

INTERPERSONAL AGEISM

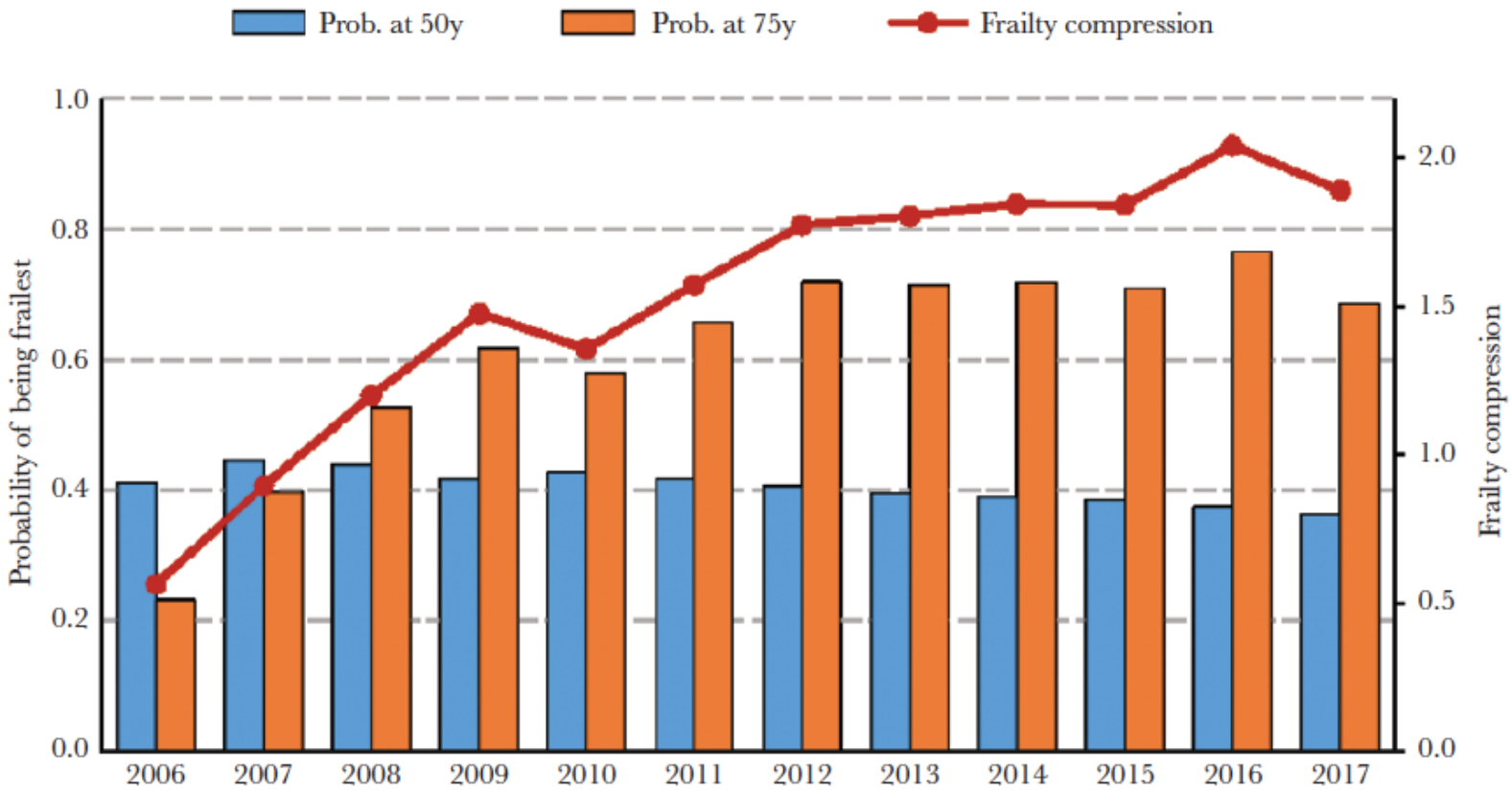
- Elaborate educational programs and inter-generational dialogue
- Community co-produced educational activities to engage younger community members with older members and the scientific community, more generally.

SELF-AGEISM

- More research into the effects of social isolation and, specifically, loneliness on HIV outcomes

Guaraldi G et al., the lancet HIV, 2023

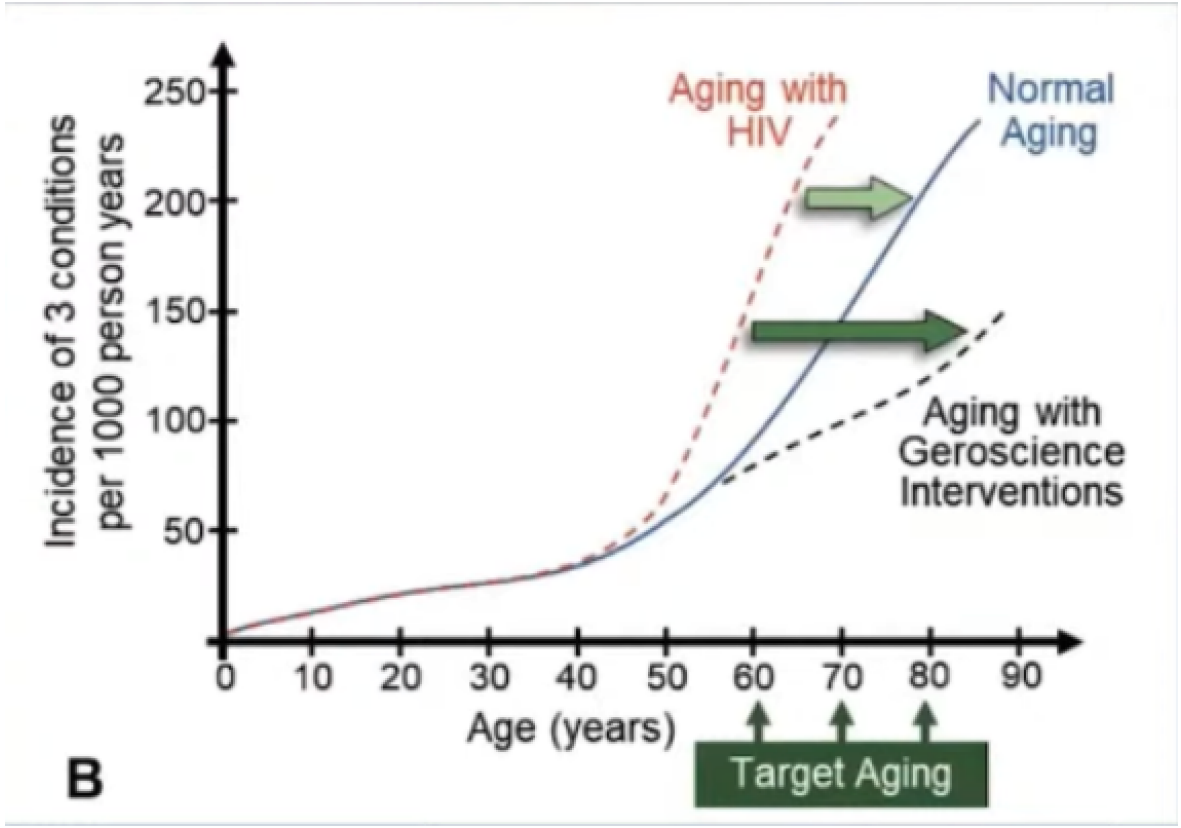
Frailty prevalence over the past decade has decreased in PLWH aged 50, whereas it increased in those aged 75



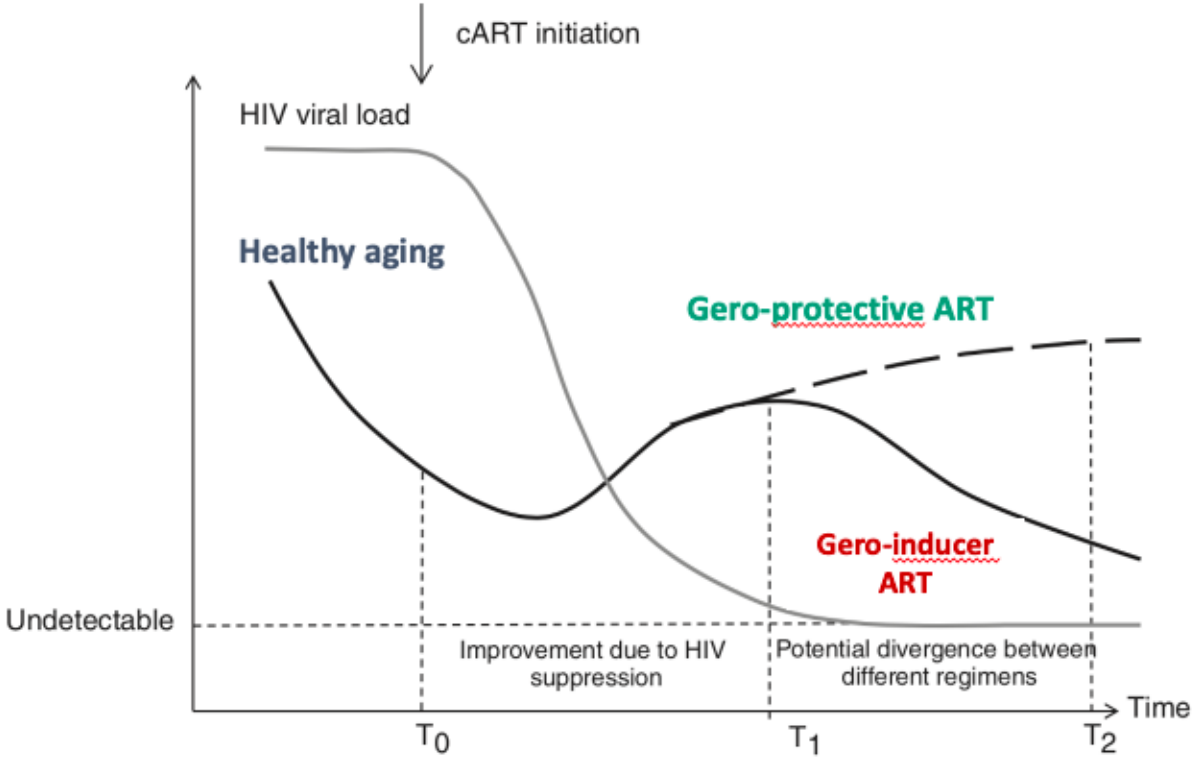
- The frailty compression ratio (FCR) was defined as the ratio between the probability of being frail at age of 75 years and the probability of frail category at the age of 50 years.
- Frailty compression was independently associated with male sex, nadir CD4+ T-cell count, and HIV duration >20 years.

Guaraldi G, OFID 2019;6(5):ofz199

HIV as additional consideration in geroscience-guided approaches for delaying onset and progression of multiple chronic diseases and frailty



Masters MC et al. JAIDS 2022; 89:S34



Guaraldi G, OFID 2019;6(5):ofz199

Take home messages

- Frailty is a biological, clinical, and public health priority in a world characterized by global aging.

- Frailty should replace the concept of chronological age to drive research and clinical activities towards biology and reduce stigma.

- HIV treatment is already not only based on ART only but also include metabolic and serotherapeutic innervations able to mitigate the impact of HIV on the accelerated aging process