



Valutazione della fragilità: la sfida della gestione della complessità del paziente HIV-positivo che invecchia

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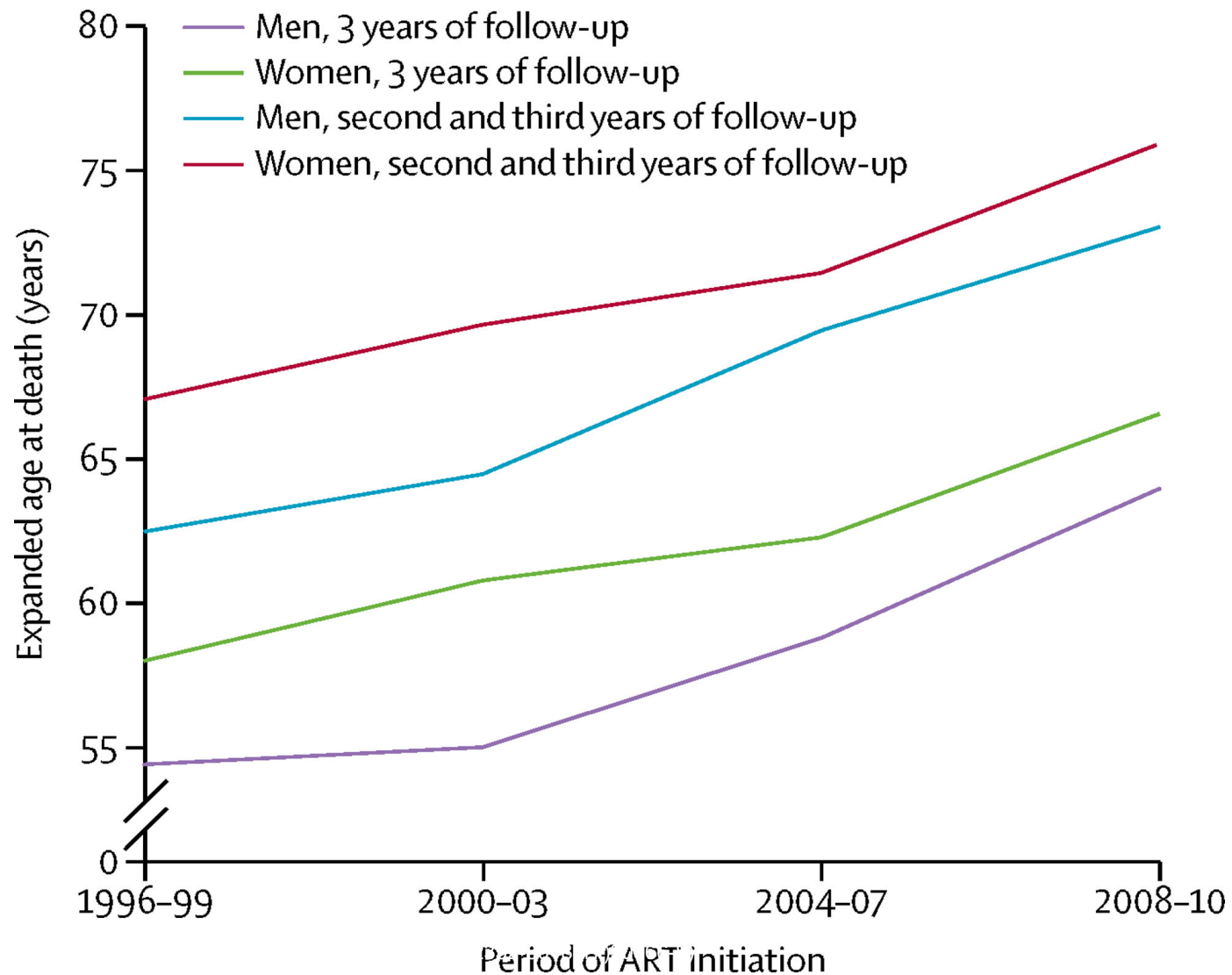
My talk today

- Presupposti teorici per la valutazione della frailty nelle persone che vivono con HIV
- Cosa è e come si misura la frailty
- Quali vantaggi con la misurazione della frailty
- Conclusioni

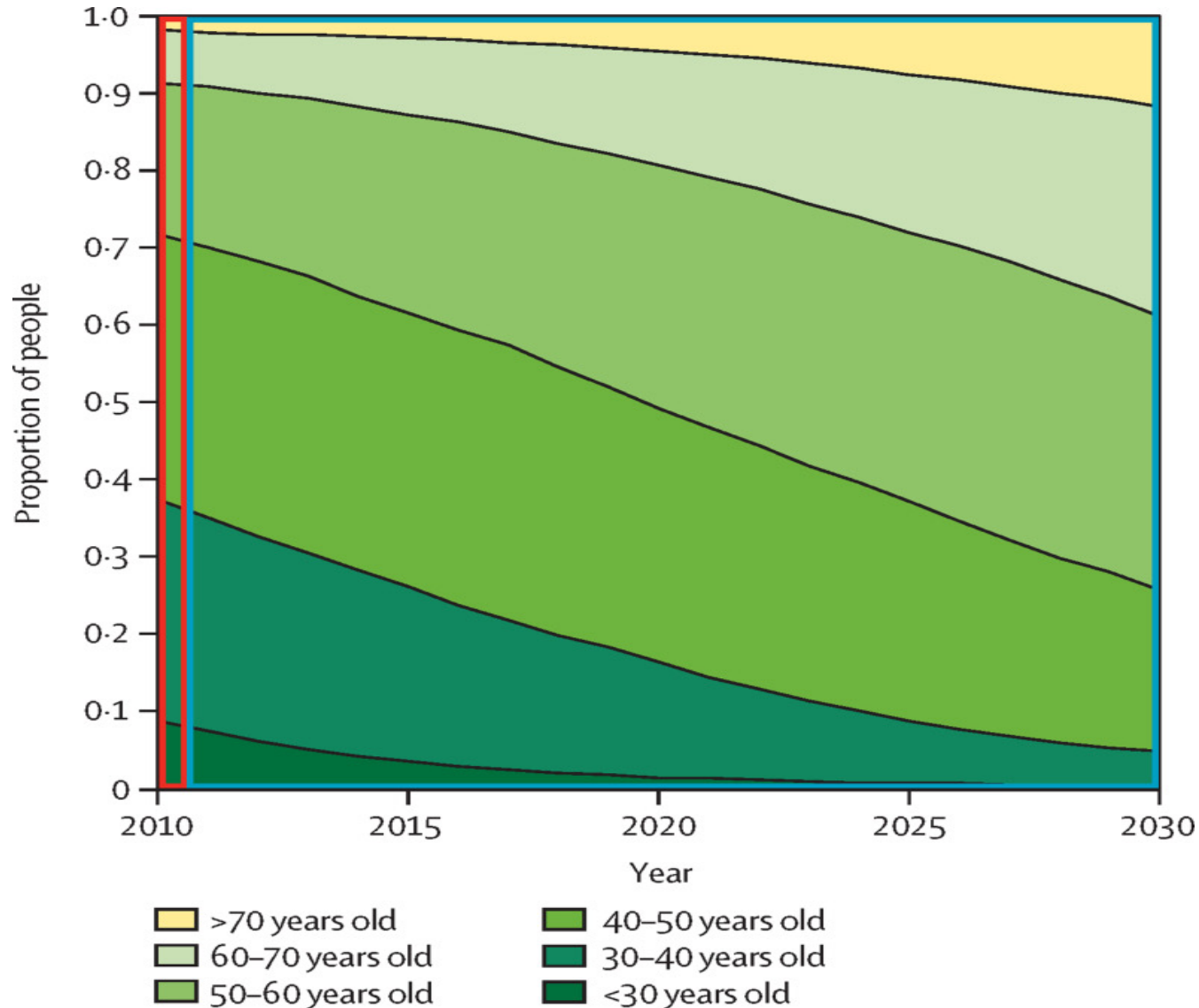
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Expected age at death of men and women living with HIV starting antiretroviral therapy (ART) aged 20 years, by period of initiation



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



Si prevede che:

- la % di pazienti con età ≥ 50 anni aumenterà dal 28% nel 2010 al 73% nel 2030,
- la % di pazienti con età ≥ 60 anni aumenterà dall'8% al 39%
- la % di pazienti con età ≥ 70 anni aumenterà dall'8% al 12%

Premature Age-Related Comorbidities Among HIV-Infected Persons Compared With the General Population

Guaraldi G, Clin Infect Disease 2011

Case-control study involving ART-experienced HIV- infected patients treated from 2002 through 2009 compared with age-, sex-, and race-matched adults from general population included in CINECA ARNO database

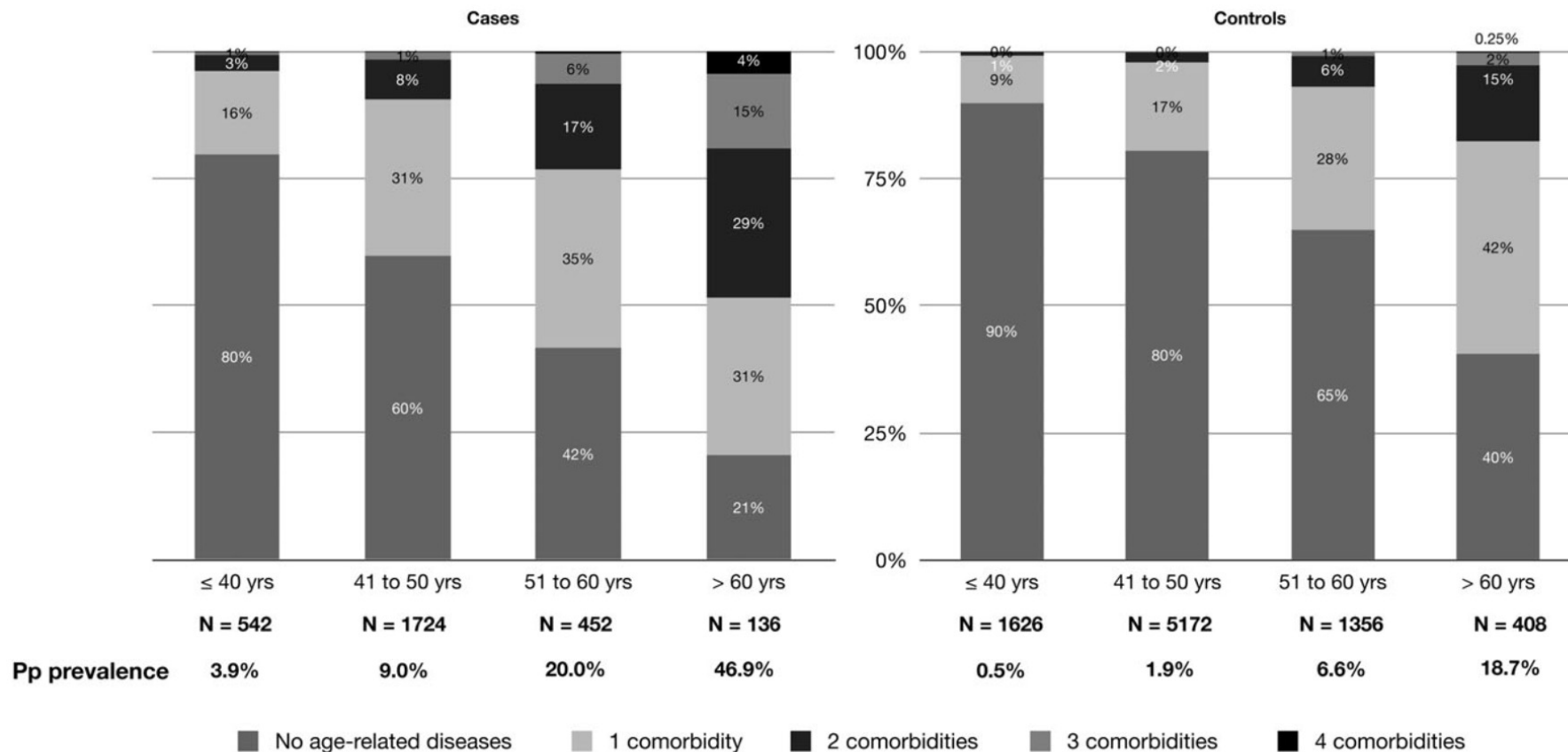
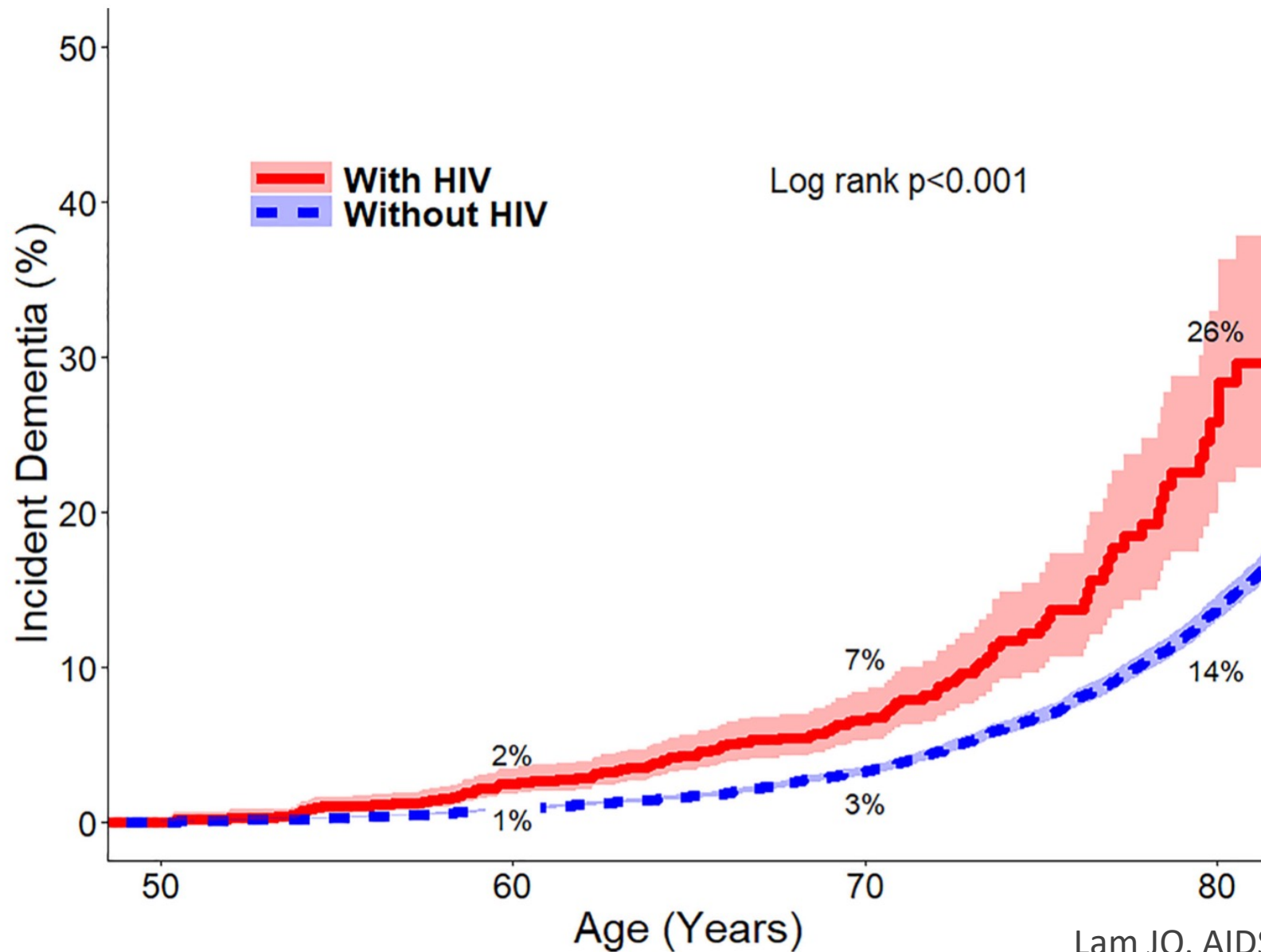


Figure 2. Polypathology (Pp) prevalence among patients and control subjects, by age categories. The following comorbidities were included: hypertension, diabetes mellitus, hypothyroidism, cardiovascular disease, and bone fractures.

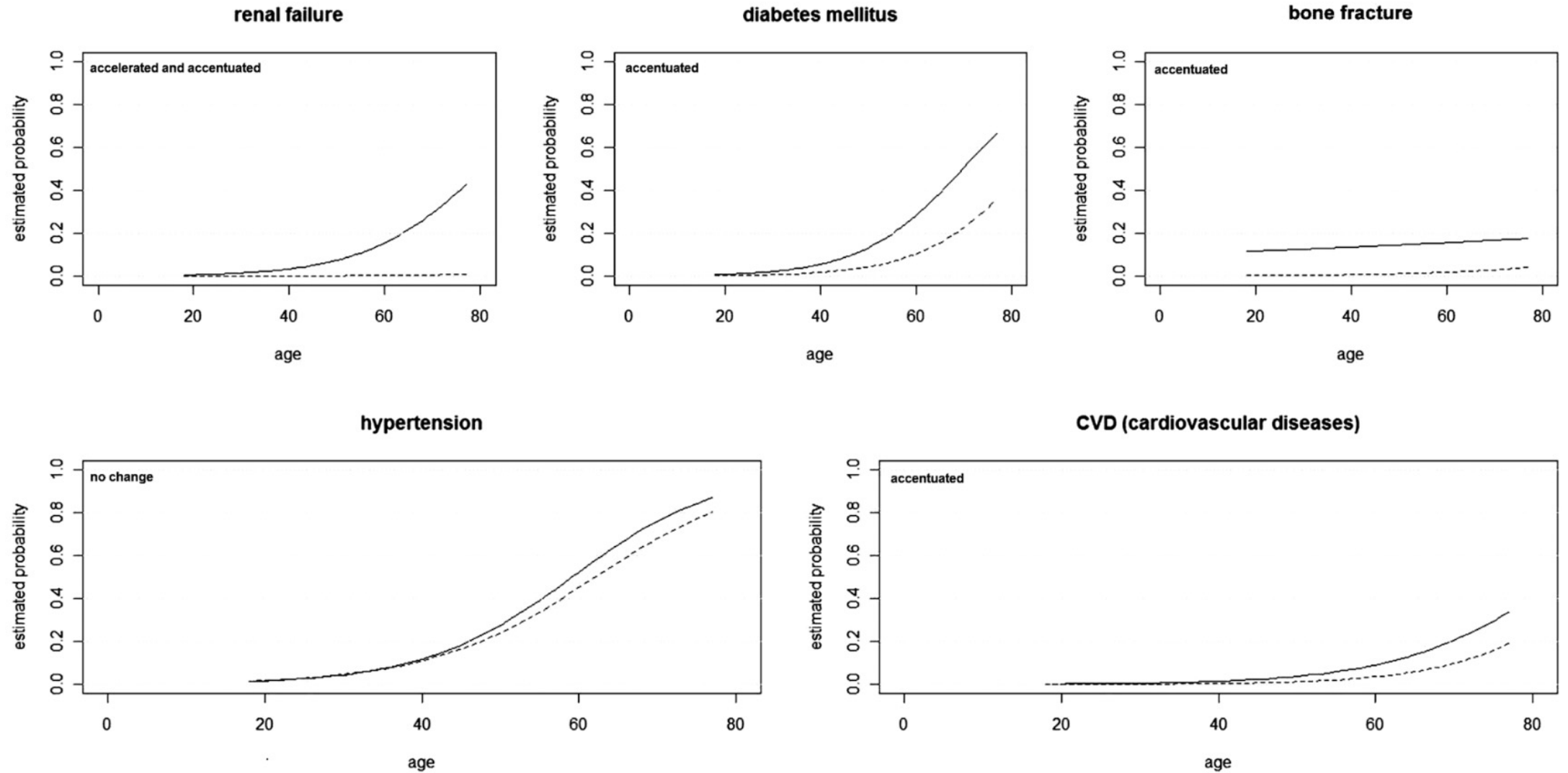
Comparison of dementia risk after age 50 between individuals with and without HIV infection

- Observational cohort study; participants were identified from 2013–2017 and followed through 2019.
- Methods: People with HIV (PWH) on antiretroviral therapy (ART) and demographically-similar people without HIV (PWOH), all ≥ 50 -years-old and with no prior diagnosis of dementia. The study setting was Kaiser Permanente Northern California, an integrated healthcare delivery system in the U.S.
- 5,381 PWH and 119,022 PWOH (average age at baseline: 57 and 58 years, respectively).
- Incident dementia was diagnosed in 117 PWH and 2,427 PWOH.

Cumulative proportion of incident dementia diagnoses by HIV status



Is HIV a Model of Accelerated or Accentuated Aging?



Geriatric-HIV Medicine Is Born

Giovanni Guaraldi¹ and Kenneth Rockwood²

¹University of Modena and Reggio Emilia, Italy and ²Dalhousie University, Halifax, Nova Scotia, Canada

- The prerequisite for geriatric medicine and HIV medicine to interact is that they share some basic geriatric nomenclature. This is not an option: by speaking the same language, we can share principles and tools
- There is more to understanding the complexity of health in aging than assessing noninfectious comorbidities and multimorbidity.

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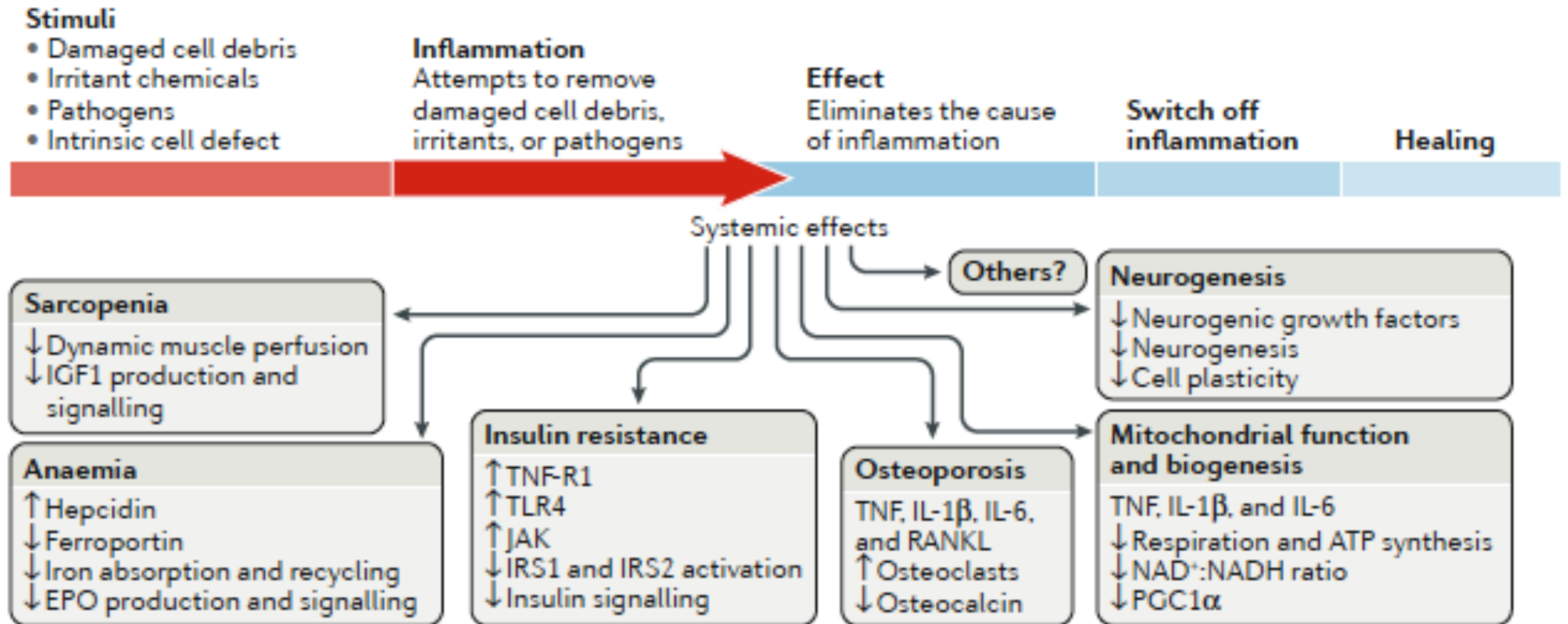
Special Article

Frailty Consensus: A Call to Action

John E. Morley MB, BCh^{a,*}, Bruno Vellas MD^{b,c}, G. Abellan van Kan MD^{b,c}, Stefan D. Anker MD, PhD^{d,e}, Juergen M. Bauer MD, PhD^f, Roberto Bernabei MD^g, Matteo Cesari MD, PhD^{b,c}, W.C. Chumlea PhD^h, Wolfram Doehner MD, PhD^{d,i}, Jonathan Evans MD^j, Linda P. Fried MD, MPH^k, Jack M. Guralnik MD, PhD^l, Paul R. Katz MD, CMD^m, Theodore K. Malmstrom PhD^{a,n}, Roger J. McCarter PhD^o, Luis M. Gutierrez Robledo MD, PhD^p, Ken Rockwood MD^q, Stephan von Haehling MD, PhD^r, Maurits F. Vandewoude MD, PhD^s, Jeremy Walston MD^t

“...Una sindrome medica con molteplici cause e determinanti, caratterizzata da una diminuzione della forza, della resistenza e della funzione, e che determina una maggior vulnerabilità dell’individuo a sviluppare eventi clinici avversi (tra cui dipendenza e morte) ...”

Systemic effects of inflammaging linked with frailty development



Faces of Frailty in Aging with HIV Infection

Rockwood frailty index and biomarkers (continuous variables) – Spearman’s rank correlation.

| Biomarker | Spearman’s rho | p Value |
|---------------------------------------|----------------|---------|
| Inflammation | | |
| IL-6, basal (pg/ml) | 0.086 | 0.023 |
| TNF-alpha, basal (pg/ml) | 0.101 | 0.007 |
| IL-6, post stimulation (pg/ml) | 0.046 | 0.229 |
| TNF-alpha, post stimulation(pg/ml) | 0.051 | 0.181 |
| CRP (mg/l) | 0.217 | <0.001 |
| Albumin (g/l) | -0.270 | <0.001 |
| White blood cells ($\times 10^9/l$) | 0.103 | 0.005 |
| Neutrophils ($\times 10^9/l$) | 0.185 | <0.001 |
| Monocytes ($\times 10^9/l$) | 0.020 | 0.579 |
| Eosinophils ($\times 10^9/l$) | -0.018 | 0.633 |
| Basophils ($\times 10^9/l$) | -0.064 | 0.080 |
| Immunosenescence | | |
| Lymphocytes ($\times 10^9/l$) | -0.076 | 0.039 |
| CD4/CD8 T cell ratio | 0.034 | 0.374 |
| Memory/naïve CD4 T cell ratio | -0.017 | 0.644 |
| Memory/naïve CD8 T cell ratio | -0.073 | 0.054 |
| Memory/naïve B cell ratio | -0.089 | 0.020 |
| Cellular ageing | | |
| Telomere length (bp) | -0.008 | 0.824 |
| DNA damage (%) | -0.028 | 0.452 |
| DNA repair (%) | -0.056 | 0.126 |
| Isoprostanes (ng/ml) | | |
| iPF2alpha-III | -0.041 | 0.278 |
| iPF2alpha-VI | 0.020 | 0.588 |

Table 1. Operationalizing a Phenotype of Frailty

| <i>A. Characteristics of Frailty</i> | <i>B. Cardiovascular Health Study Measure*</i> |
|--|--|
| <p>Shrinking: Weight loss (unintentional) Sarcopenia (loss of muscle mass) Weakness</p> <p>Poor endurance; Exhaustion Slowness</p> <p>Low activity</p> | <p>Baseline: >10 lbs lost unintentionally in prior year</p> <p>Grip strength: lowest 20% (by gender, body mass index) “Exhaustion” (self-report) Walking time/15 feet: slowest 20% (by gender, height) Kcals/week: lowest 20% males: <383 Kcals/week females: <270 Kcals/week</p> |
| | <p><i>C. Presence of Frailty</i></p> <p>Positive for frailty phenotype: ≥ 3 criteria present Intermediate or prefrail: 1 or 2 criteria present</p> |

*See Appendix.

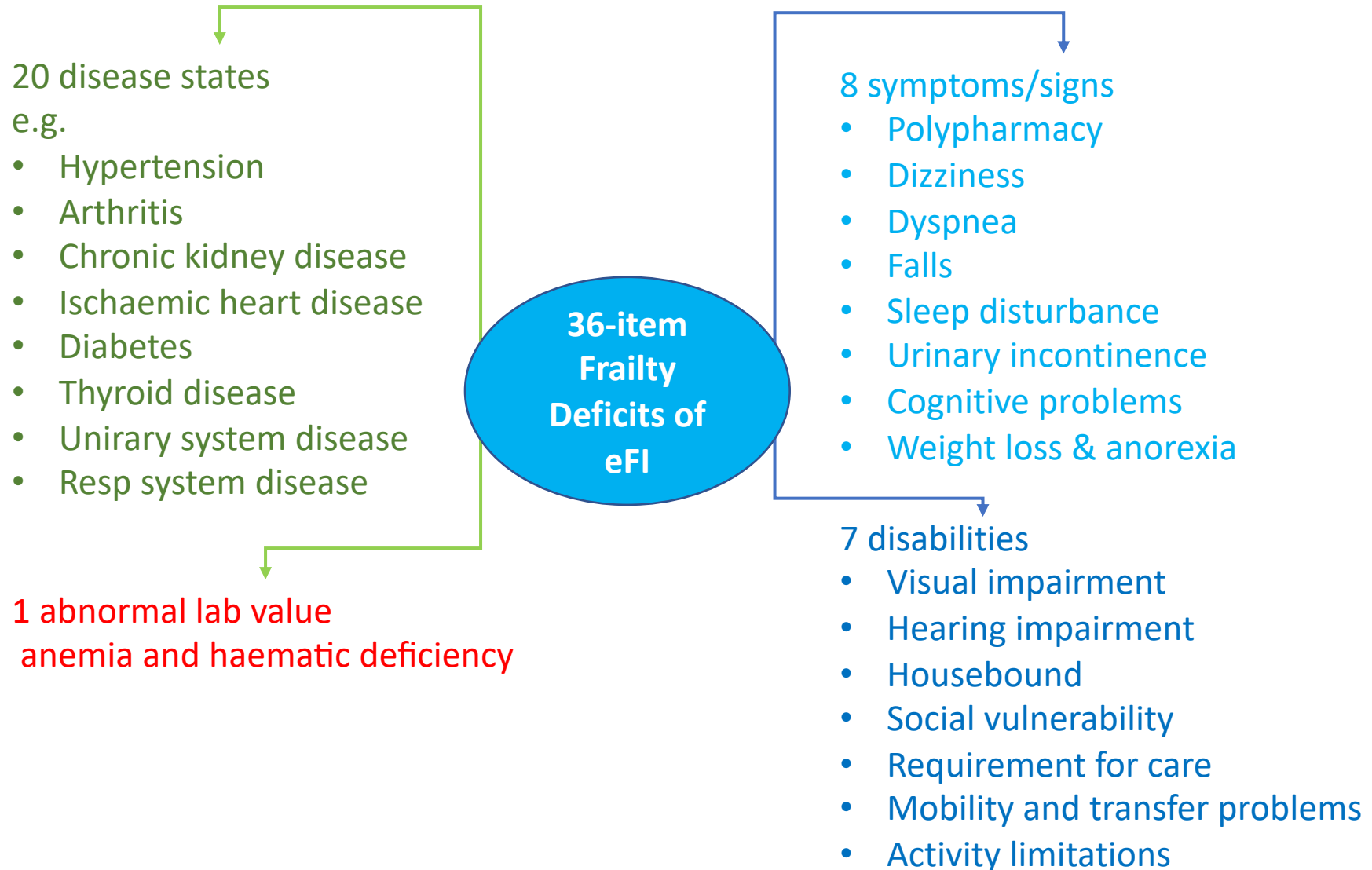
Accumulation of Deficits as a Proxy Measure of Aging

Arnold B. Mitnitski^{1,2}, Alexander J. Mogilner, and Kenneth Rockwood^{2,*}

“...a method for appraising health status in elderly people.

A frailty index was defined as the proportion of accumulated deficits (symptoms, signs, functional impairments, and laboratory abnormalities). It serves as an individual state variable, reflecting severity of illness and proximity to death...”

Electronic Frailty Index



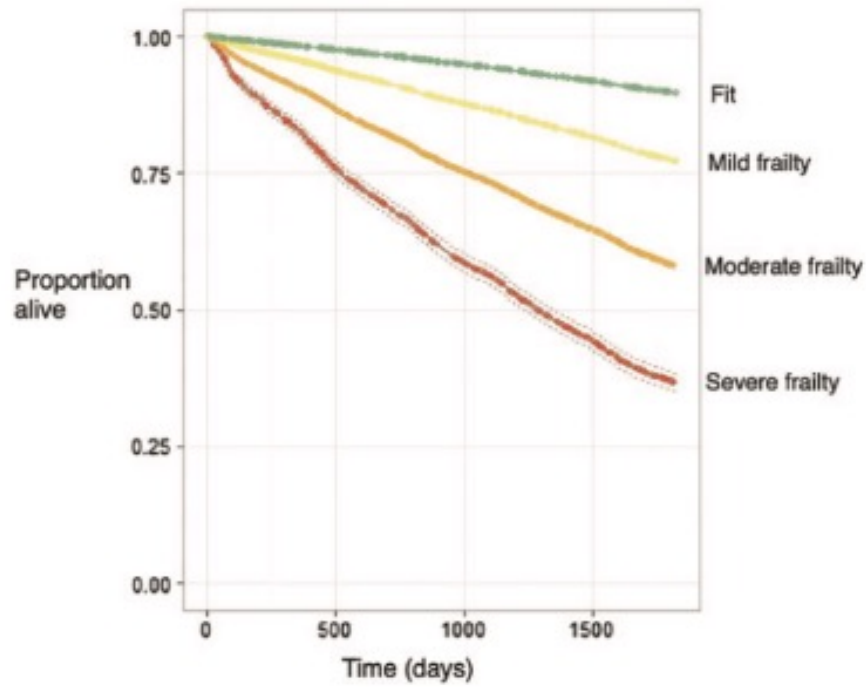


Figure 1. Five-year Kaplan–Meier survival curve for the outcome of mortality for categories of fit, mild frailty, moderate frailty and severe frailty (internal validation cohort).

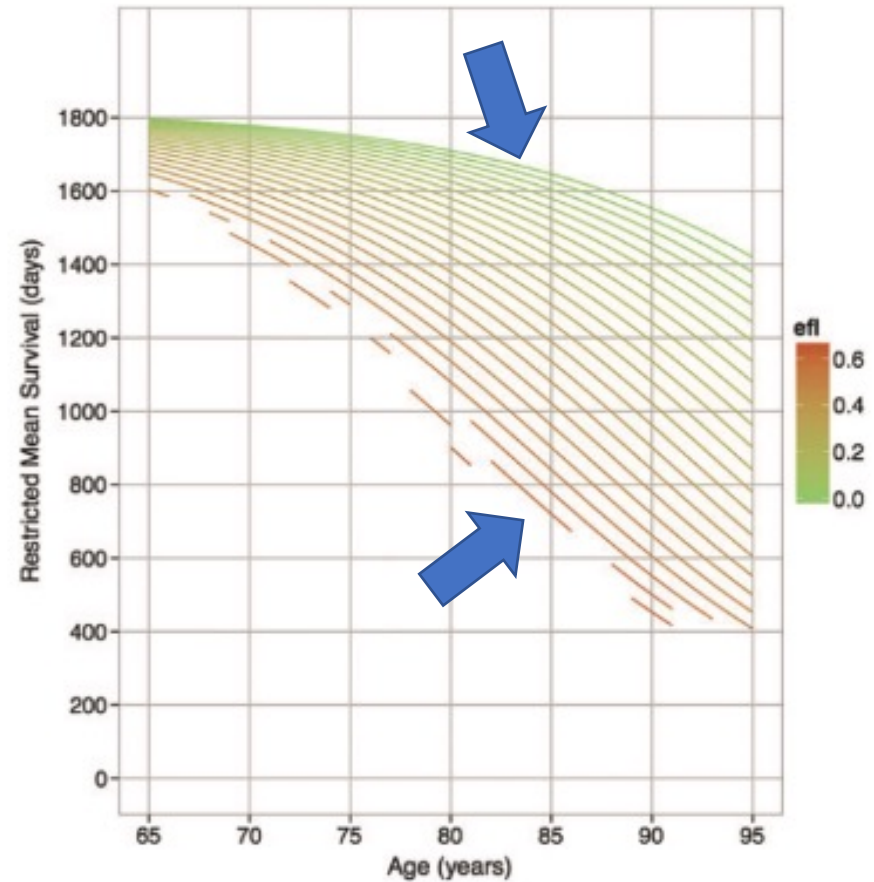
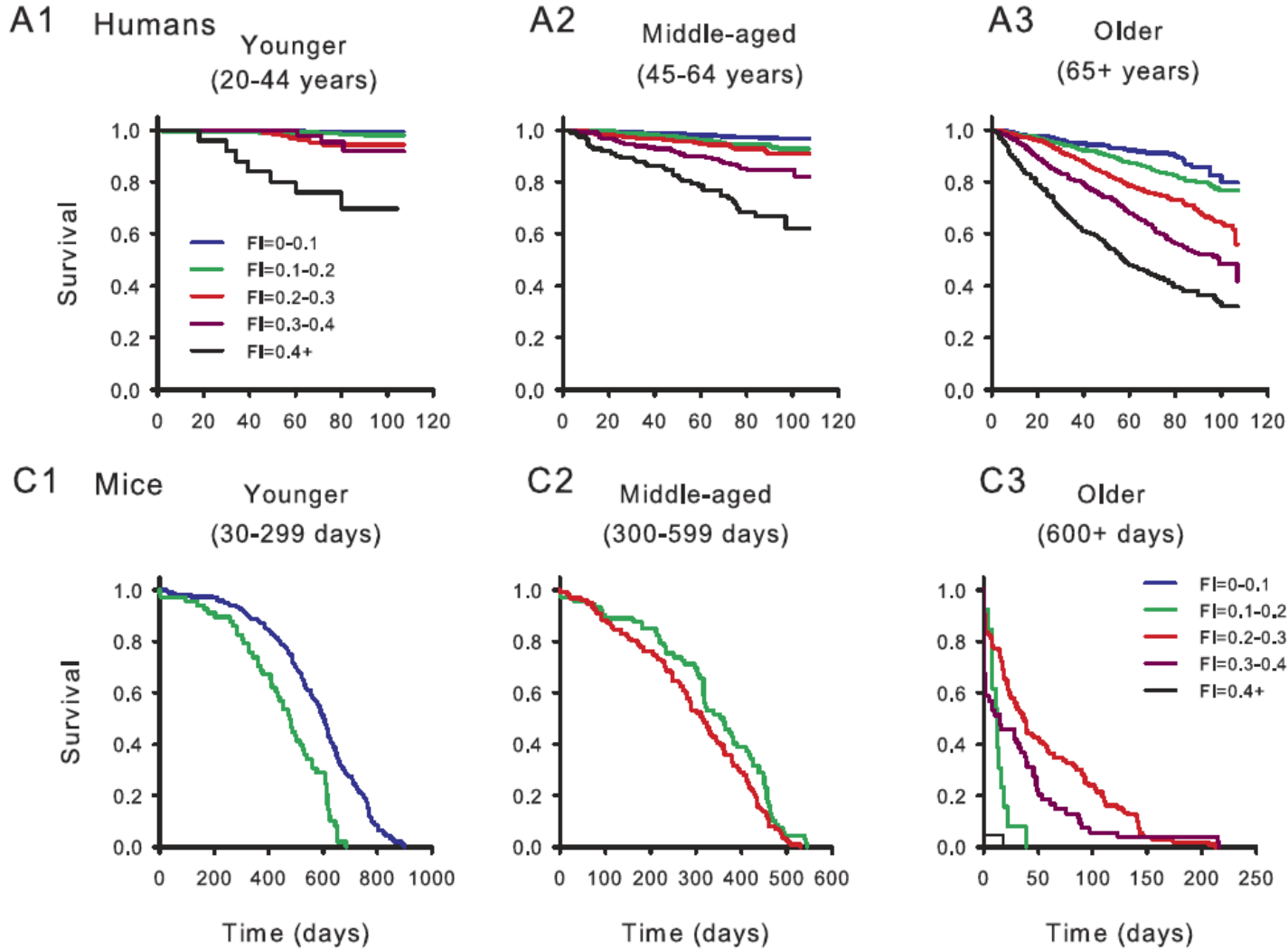


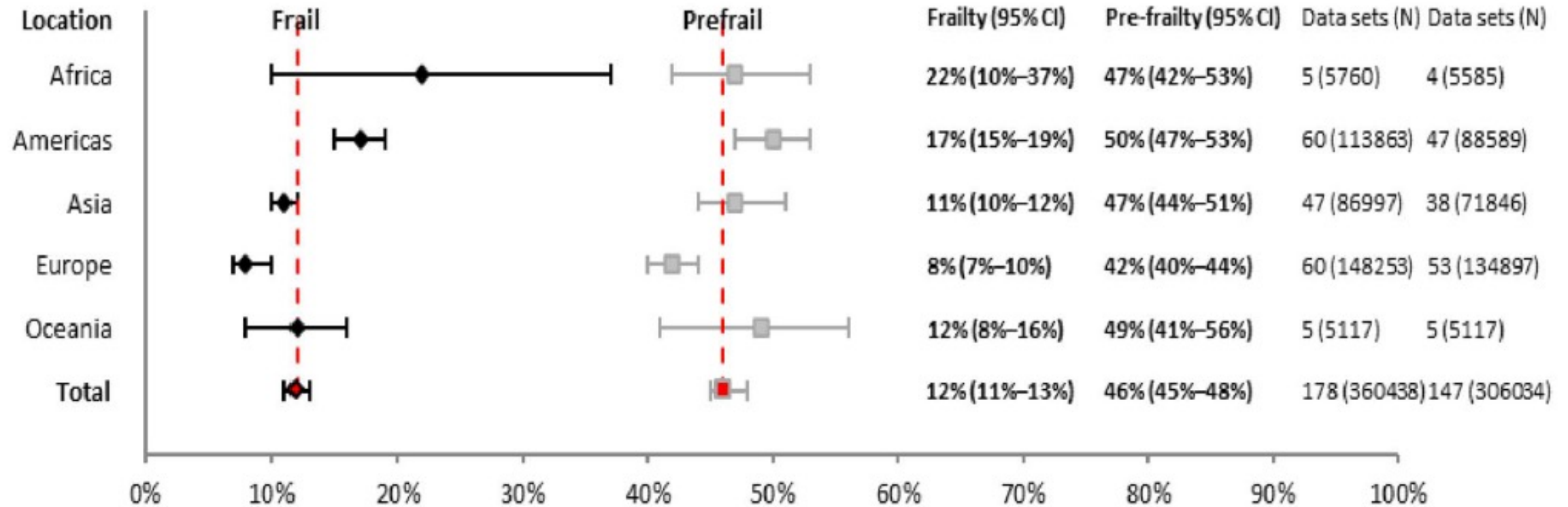
Figure 2. Relationship between age, electronic frailty index score and mortality (internal validation cohort).

High frailty index (FI) scores predict mortality at all ages both in humans and in mice



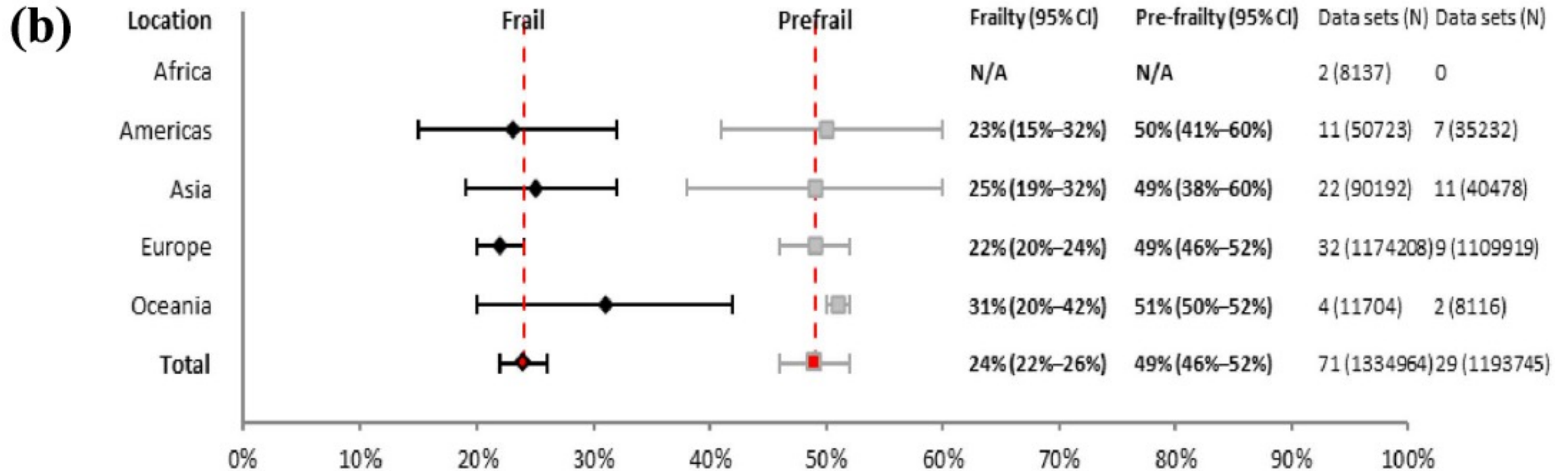
Prevalence of frailty in 62 countries worldwide

(a)

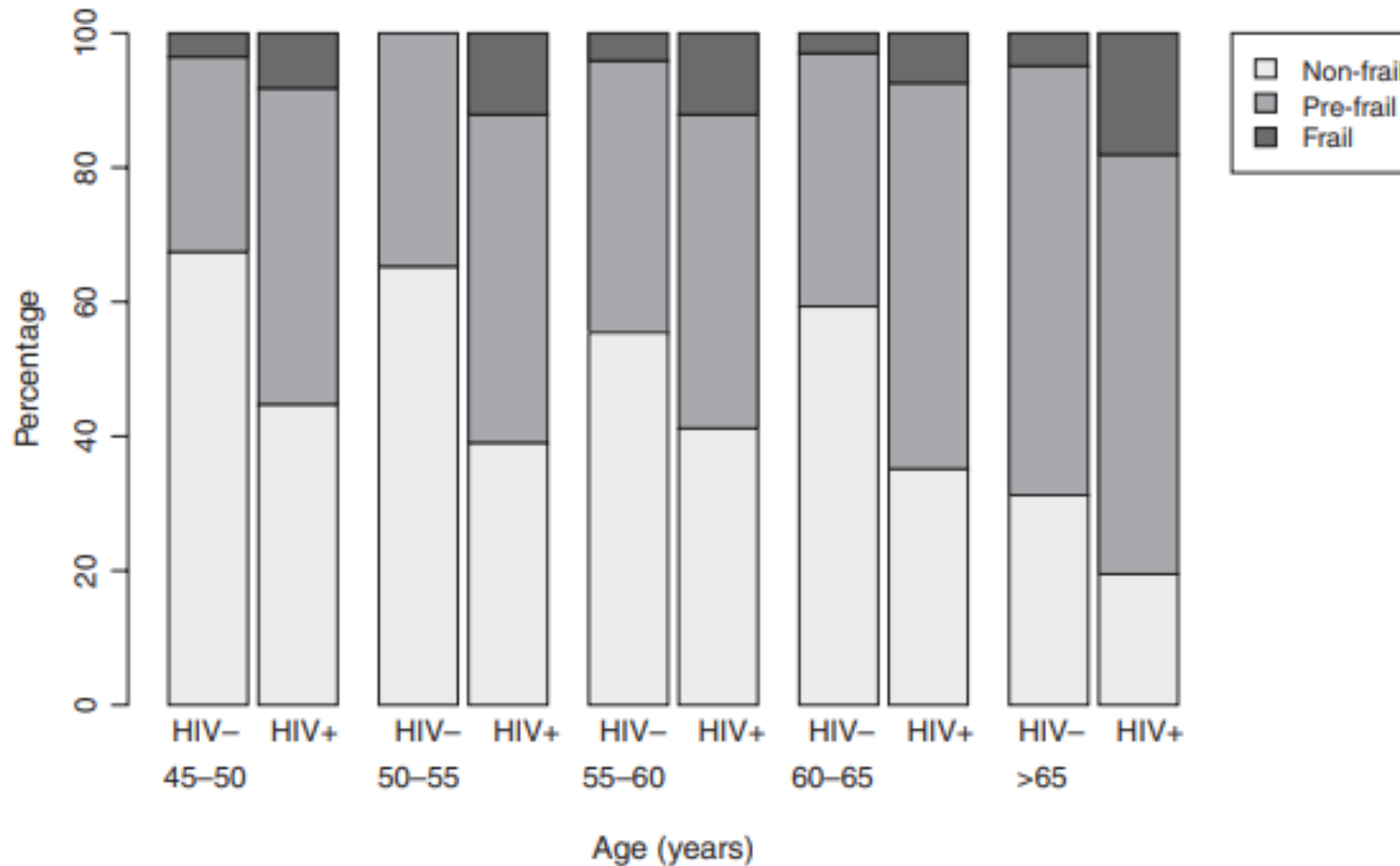


Prevalence of frailty in 62 countries worldwide

12% usando il modello fenotipo e 24% usando il modello accumulo deficit



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



Prevalenza della fragilità (Fried's phenotype) per età in persone HIV-uninfected e HIV-infected

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A frailty index predicts survival and incident multimorbidity independent of markers of HIV disease severity

Table 2. Descriptive characteristics of the sample at first study visit.

| | |
|---|---------------|
| Sample size, <i>n</i> | 2722 |
| Age, mean \pm SD | 46 \pm 8 |
| Women, <i>n</i> (%) | 867 (32) |
| Current CD4 ⁺ cell count, mean \pm SD | 588 \pm 267 |
| Nadir CD4 ⁺ cell count, mean \pm SD | 209 \pm 163 |
| Undetectable HIV viral load, <i>n</i> (%) | 2577 (93) |
| VACS index, mean \pm SD | 16 \pm 15 |
| Pack-years smoking, mean \pm SD | 16 \pm 16 |
| Injection drug use, <i>n</i> (%) | 730 (27) |
| Multimorbidity ^a , <i>n</i> (%) | 390 (14) |
| Cardiovascular disease, <i>n</i> (%) | 95 (4) |
| Hypertension, <i>n</i> (%) | 752 (28) |
| Type 2 diabetes mellitus, <i>n</i> (%) | 254 (9) |
| Chronic kidney disease, <i>n</i> (%) | 14 (1) |
| Hepatic cirrhosis, <i>n</i> (%) | 150 (6) |
| Chronic obstructive pulmonary disease, <i>n</i> (%) | 60 (2) |
| Osteoporosis, <i>n</i> (%) | 368 (14) |
| Cancer, <i>n</i> (%) | 26 (1) |

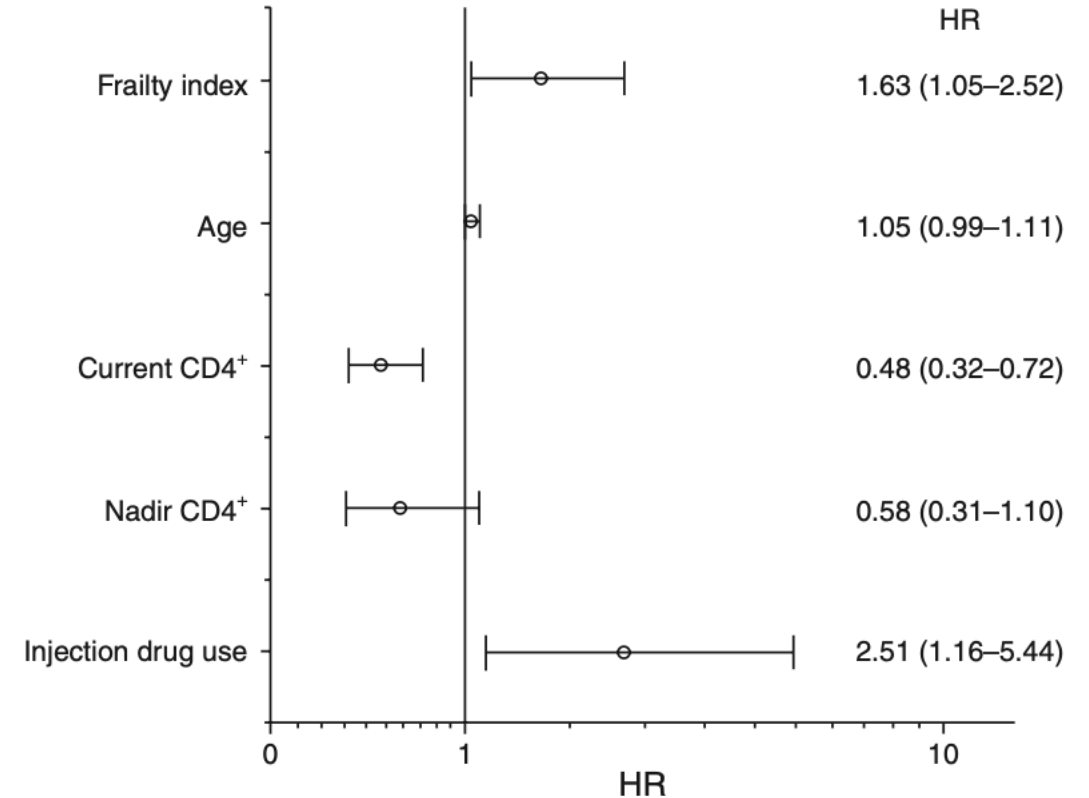


Fig. 1. Predictors of survival in multivariate analysis. Points represent adjusted HRs and whiskers 95% confidence intervals. HR, hazard ratio.

Polypharmacy

Retrospective chart review of 89 HIV-positive individuals aged 60 and older, University of California

Table 2. Summary of Medications per Participant

| Medication | Median (Interquartile Range) | Common Examples, n (%) |
|------------------------------------|---------------------------------|--|
| Total | 13 (9–17) ^a | |
| Antiretrovirals | 4 (3–5) | Tenofovir, 55 (62) Ritonavir, 43 (48) Emtricitabine, 41 (46) |
| Nonantiretrovirals | 6 (3–9) | Aspirin, 45 (51) Acyclovir, 22 (25) Atorvastatin, 21 (24) |
| Vitamins, minerals, supplements | 2 (0–5) | Multivitamin, 48 (54) Omega-3, 30 (34) Calcium, 24 (27) |

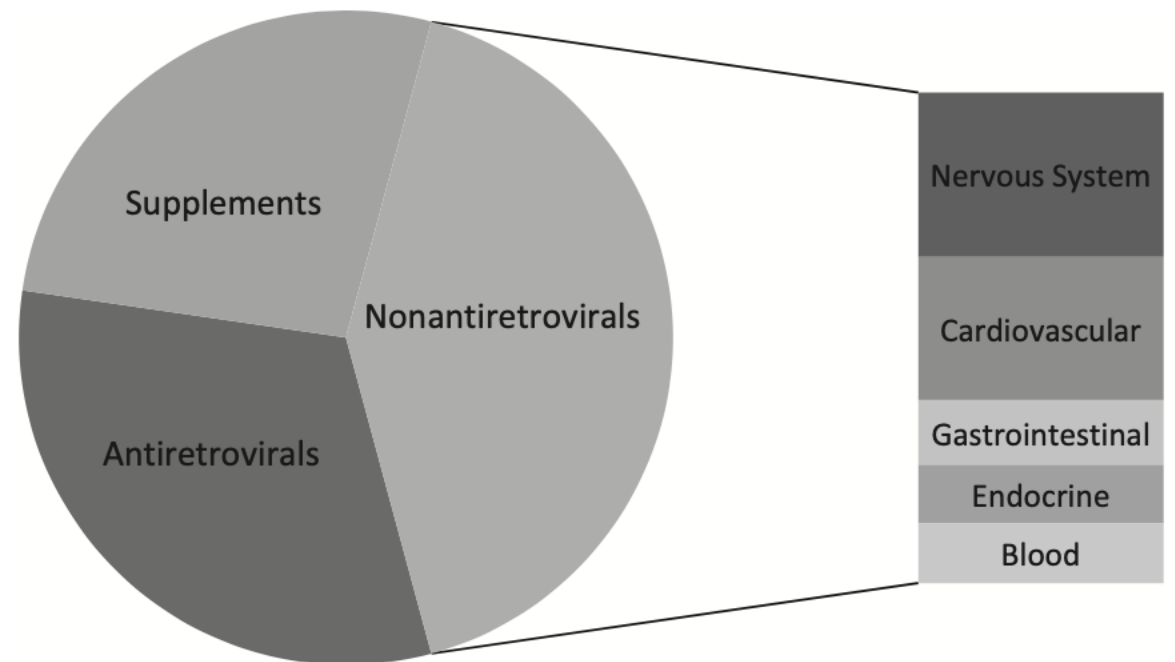


Table 3. Drug–Drug

Type of Drug–Drug Interaction

Total drug–drug interactions, Antiretroviral/nonantiretroviral

Nonantiretroviral/nonantiretroviral

Antiretroviral/antiretroviral, n

^aConsider therapy modification

^bAvoid combination.

^cAll examples of drug–drug interaction in HIV = Human Immunodeficiency Virus

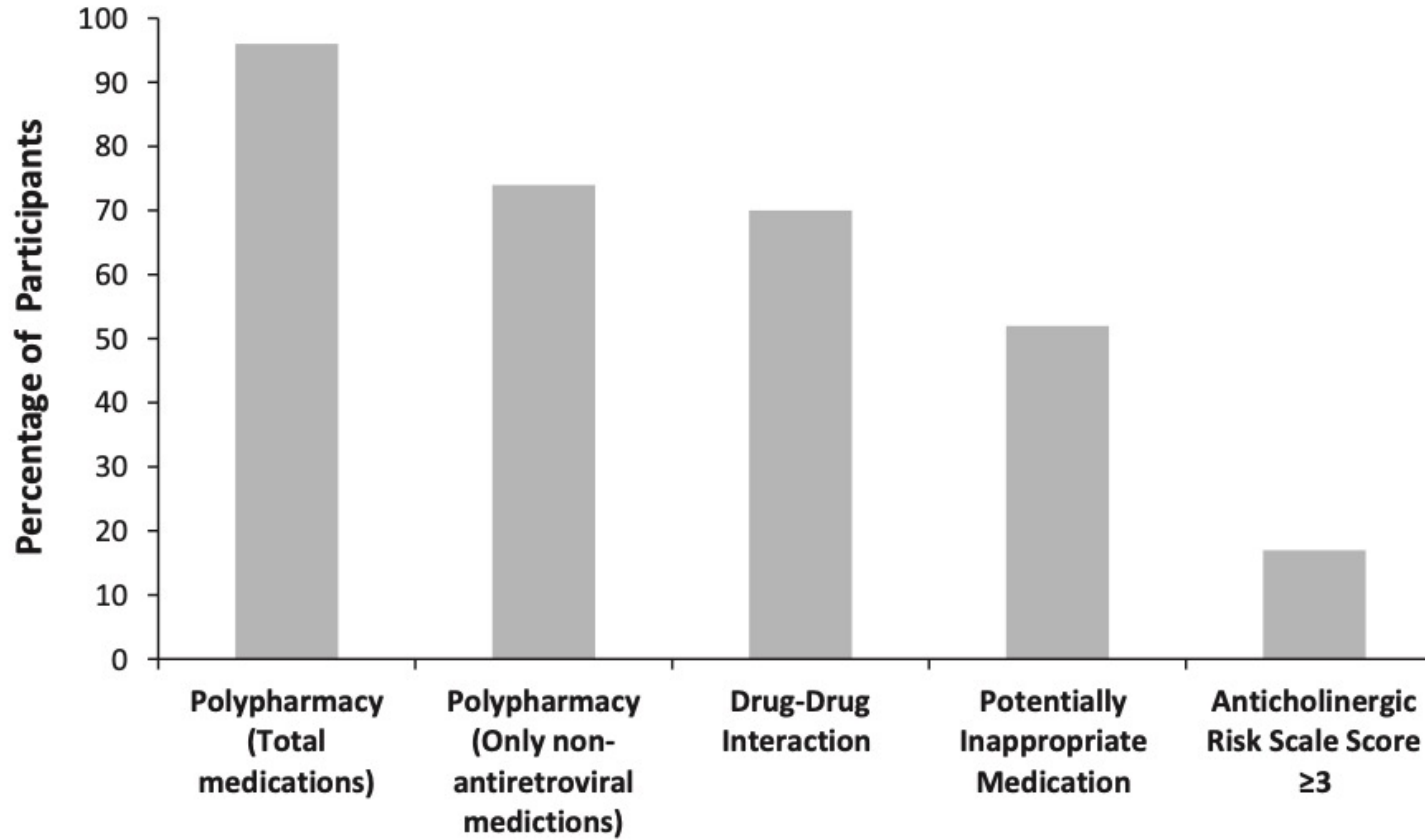


Figure 2. Percentage of HIV-positive participants with medication-related problems. Each bar represents the percentage of participants with each listed medication-related problem. In this figure, polypharmacy is defined as ≥ 5 medications. HIV = human immunodeficiency virus.

Common Examples^c

- zidovudine and atorvastatin (9)
- zidovudine and calcium carbonate (7)
- ibuprofen and aspirin (11)
- atorvastatin and niacin (5)
- zidovudine and tenofovir (12)
- zidovudine and efavirenz (3)

n in parentheses.

Risk Factors for Falls in HIV-Infected Persons

TABLE 1. Odds of Recurrent Falling by Demographic Characteristics

| Demographic | Nonfallers, n = 250 (%) | Single Fallers, n = 43 (%) | Recurrent Fallers, n = 66 (%) | Odds Ratio (95% CI)* |
|---------------------------------------|----------------------------|-------------------------------|----------------------------------|-------------------------|
| Age in yrs (mean ± SE) | 52.0 ± 0.3 | 51.8 ± 0.7 | 52.1 ± 0.5 | 1.0 (0.96 to 1.1) |
| Female gender | 31 (12) | 6 (14) | 17 (26) | 2.5 (1.3 to 4.8) |
| White | 177 (71) | 35 (81) | 53 (80) | 1.7 (0.9 to 3.3) |
| Hispanic ethnicity | 45 (18) | 5 (12) | 15 (23) | 1.3 (0.7 to 2.6) |
| Current tobacco use | 74 (30) | 18 (42) | 31 (47) | 2.1 (1.2 to 3.7) |
| Alcohol use >7 drinks/wk | 11 (4) | 3 (7) | 1 (2) | 0.3 (0.04 to 2.7) |
| Current illicit drugs | 80 (32) | 11 (26) | 12 (18) | 0.5 (0.2 to 0.9) |
| Years since HIV diagnosis (mean ± SE) | 14.0 ± 0.5 | 16.8 ± 1.1 | 15.8 ± 0.9 | 1.0 (1.0 to 1.1)† |
| Current CD4 count (mean ± SE) | 595 ± 20 | 586 ± 28 | 599 ± 38 | 1.0 (1.0 to 1.1)‡ |
| Nadir CD4 count (mean ± SE) | 168 ± 10 | 169 ± 27 | 164 ± 17 | 1.0 (0.9 to 1.1)‡ |
| HIV-1 RNA below detection | 238 (95) | 40 (93) | 64 (97) | 1.6 (0.4 to 7.4) |
| VACS index score (mean ± SE) | 17.6 ± 0.9 | 17.9 ± 2.4 | 20.7 ± 1.8 | 1.0 (1.0 to 1.03)† |

*Odds ratio comparing nonfallers and recurrent fallers.

†per 1 unit.

‡per 50 cells.

SE, standard error.

TABLE 4. Risk Factors for Recurrent Falls From Multivariate Logistic Regression Models

| Parameter | Odds Ratio (95% CI) |
|-------------------------------|----------------------------|
| Difficulty with tandem stand* | 13.5 (3.0 to 60.5) |
| Antidepressant use | 3.7 (1.8 to 7.7) |
| Exhaustion† | 3.7 (1.8 to 7.7) |
| Diabetes | 3.6 (1.4 to 9.4) |
| Female gender | 3.5 (1.4 to 8.8) |
| Shrinking‡ | 3.4 (1.2 to 10.1) |
| Opiate use | 3.1 (1.5 to 6.5) |
| Current/prior didanosine | 2.6 (1.2 to 5.4) |
| Sedative use | 2.5 (1.1 to 5.5) |

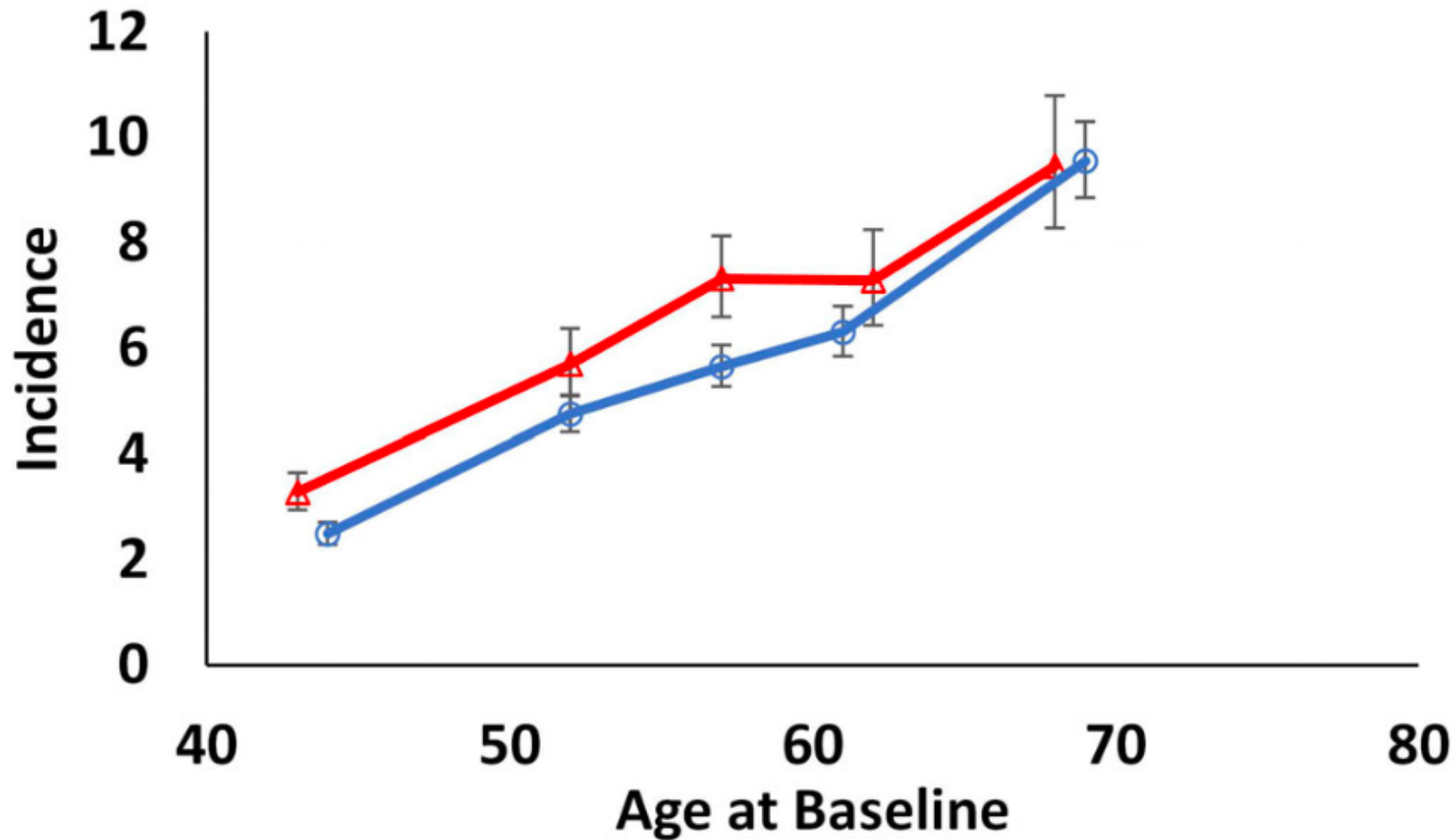


FIGURE 1 Delirium incidence per/1000 person years, by HIV status. PWH, people with HIV; PWoH, people without HIV. Red line = PWH and Blue line = PWoH.

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HIV & frailty: che fare

- Assessment of patients
- Assessment of care providers: a common lexicon
- Choosing patients for consultation and clarifying the role of the geriatrician
- Determination of workflow: how will the geriatrician interface with the other specialists?
- Salary support: How will the physician bill?
- Nonclinical programs for patients aging with HIV