



Development and validation of a comorbidity index for people living with HIV and its ability to predict frailty and mortality

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on behalf of the POPPY study and the AGE_hIV cohort study

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Background



- In ageing populations of people with HIV (PWH), multi-morbidity is becoming increasingly prevalent
- A comorbidity index is a single-value summary of the aggregate effects of all comorbidities present in an individual on a given outcome (i.e. prognosis, QoL, etc.)
- Such an index can be used to stratify/adjust for comorbidity, identify high-risk individuals, and monitor interventions

Existing comorbidity indices

Charlson comorbidity index

Weight	Clinical condition
1	Myocardial infarct Congestive cardiac insufficiency Peripheral vascular disease Dementia Cerebrovascular disease Chronic pulmonary disease Diabetes without complications Peptic ulcers Connective tissue disease Chronic diseases of the liver or cirrhosis
2	Hemiplegia Moderate or severe kidney disease Diabetes with complications Tumours Leukaemia Lymphoma
3	Moderate or severe liver disease
6	Malignant metastatic tumour AIDS

Other indices developed for the general population

- Elixhauser index
- The Comorbidity Symptom Scale
- The multimorbidity interaction severity index
- Cumulative Illness Rating Scale (CIRS)
- Burden of Disease (BOD) index
- Index of coexisting diseases (ICED)
- Chronic disease score
- and many more

What is often used in studies of PWH

- Comorbidity count
- VACS index
- Frailty index

Aims

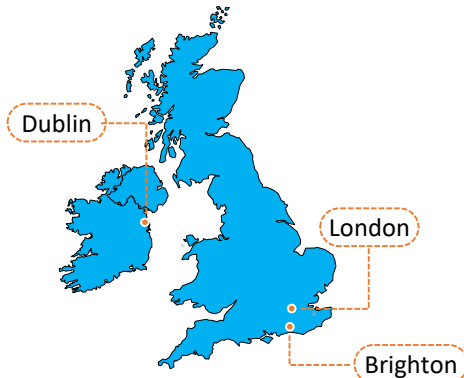


- To develop a comorbidity burden index (CBI), specific to PWH, to measure the overall comorbidity burden of an individual
- To externally validate concurrent and predictive validity of the CBI, also compared to the comorbidity count and VACS index

Methods: POPPY and AGE_hIV

Development cohort: POPPY (UK/Ireland)

- **1073 PWH** aged ≥ 18 from HIV-outpatient clinics in the UK/Ireland
- Baseline visit completed in 2016
- Used to derive the weighting system for the CBI



Validation cohort: AGE_hIV (The Netherlands)

- **598 PWH** aged ≥ 45 from HIV-outpatient clinics in Amsterdam
- Baseline visit completed in 2012
- Used to assess the validity of the index



Methods: POPPY and AGE_hIV



Development cohort: POPPY (UK/Ireland)

Baseline

- Assessment of **65 comorbidities** (structured interview detailing medical history, health care utilization and concomitant medications)

Validation cohort: AGE_hIV (The Netherlands)

Baseline

- Assessment of **42/65 comorbidities** (structured questionnaire detailing medical history, concomitant medications and participation in screening programs for comorbidities)
- CBI, comorbidity count and VACS index

Methods: POPPY and AGE_hIV



Development cohort: POPPY (UK/Ireland)

Baseline

- Assessment of **65 comorbidities** (structured interview detailing medical history, health care utilization and concomitant medications)
- SF-36 physical and mental health QoL

Validation cohort: AGE_hIV (The Netherlands)

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- Frailty (Fried phenotype)

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Year 4

- SF-36 physical and mental health QoL
- Frailty (Fried phenotype)

Year 6

- All-cause mortality (administrative data)

The comorbidity burden index (CBI)



1. Derive weights for each of the 65 comorbidities (and their pairwise interaction)

Development cohort: POPPY

The comorbidity burden index (CBI)



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➔ from age-adjusted regression coefficients of each comorbidity with the SF-36 physical health sub-scale

The comorbidity burden index (CBI)

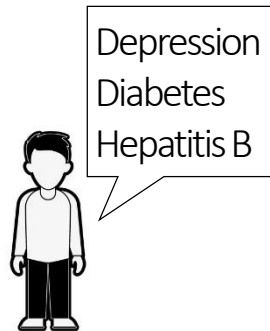


1. Derive weights for each of the 65 comorbidities (and their pairwise interaction)
2. Calculate the index for an individual as the sum of weights of all comorbidities (and their interactions), present in that individual

Development cohort: POPPY

The comorbidity burden index (CBI)

	Depression	Diabetes	Angina	Arthritis	Hepatitis B	...
Depression	6.8	0.6	0.9	-0.4	0.6	...
Diabetes		1.6	-0.3	-0.6	1.0	...
Angina			1.0	0.1	-0.1	...
Arthritis				9.8	0.4	...
Hepatitis B					2.1	...
...						...

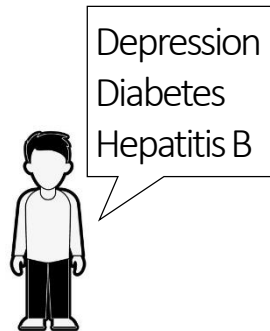


$$\text{CBI} = \underset{\substack{\uparrow \\ \text{Depression}}}{6.8} + \underset{\substack{\downarrow \\ \text{Diabetes}}}{1.6} + \underset{\substack{\uparrow \\ \text{Hepatitis B}}}{2.1} + \underset{\substack{\uparrow \\ \text{weights for the interactions}}}{(0.6+0.6+1.0)/3} = \mathbf{11.2}$$

\leftarrow number of comorbidities reported

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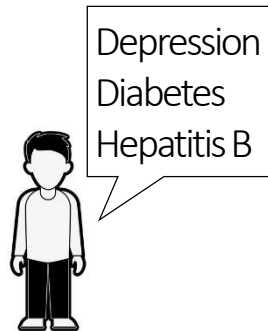


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Methods: statistical analysis

- Spearman's correlation (ρ) with Steiger's Z-test to compare correlations with continuous outcomes across indices
 - Physical health QoL
 - Mental health QoL
 - Change in physical health QoL
 - Change in mental health QoL
- C-statistic with DeLong's test to compare associations with binary outcomes
 - Frailty
 - Frailty development
 - Mortality

Participant characteristics

Median (IQR) or n (%)	POPpy (n=1073)	AGE _h IV(n=598)
Age [years]	52 (47, 59)	53 (48, 59)
Male sex	914 (85.2%)	524 (87.6%)
Black-African	171 (15.9%)	74 (12.4%)
MSM	816 (76.0%)	369 (70.4%)
BMI [kg/m ²]	25.5 (23.2, 28.2)	24.3 (22.4, 26.7)
Years since HIV diagnosis	13.2 (7.8, 20.5)	12.0 (6.6, 17.0)
Nadir CD4 [cells/ μ L]	202 (101, 304)	170 (70, 260)
CD4 at baseline [cells/ μ L]	624 (476, 811)	565 (433, 740)
HIV RNA <50 copies/mL	965 (89.9%)	545 (91.6%)

CBI and the other indices



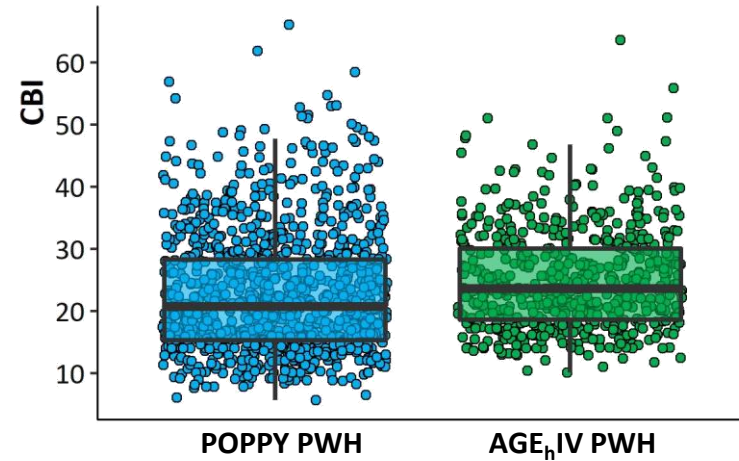
Top 10 comorbidities with highest weight

Comorbidity	weight	prev.
Joint inflammation/Arthritis	9.81	21%
Peripheral neuropathy	6.98	4%
Depression	6.77	34%
Dizziness/Vertigo	6.49	11%
Joint replacement	5.55	2%
Other AIDS events	4.07	12%
Osteopenia/Osteoporosis	4.03	6%
Chest infection	3.87	11%
Joint/Back pain	3.51	11%
Asthma/Bronchitis/COPD	3.44	25%

CBI and the other indices

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Asthma/Bronchitis/COPD	3.44	25%



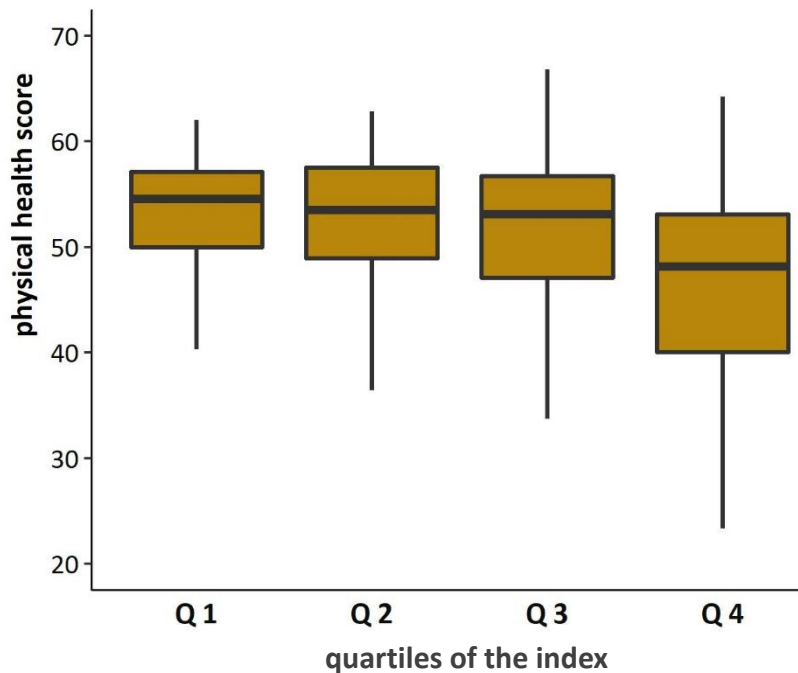
	POPPY	AGE _h IV
	median (IQR)	median (IQR)
CBI	20.7 (15.3, 28.4)	23.6 (18.6, 30.1)
Count	5 (3, 7)	5 (3, 7)
VACS index	N/A	50 (40, 56)

Concurrent validity: physical health

Validation cohort: AGE_hIV

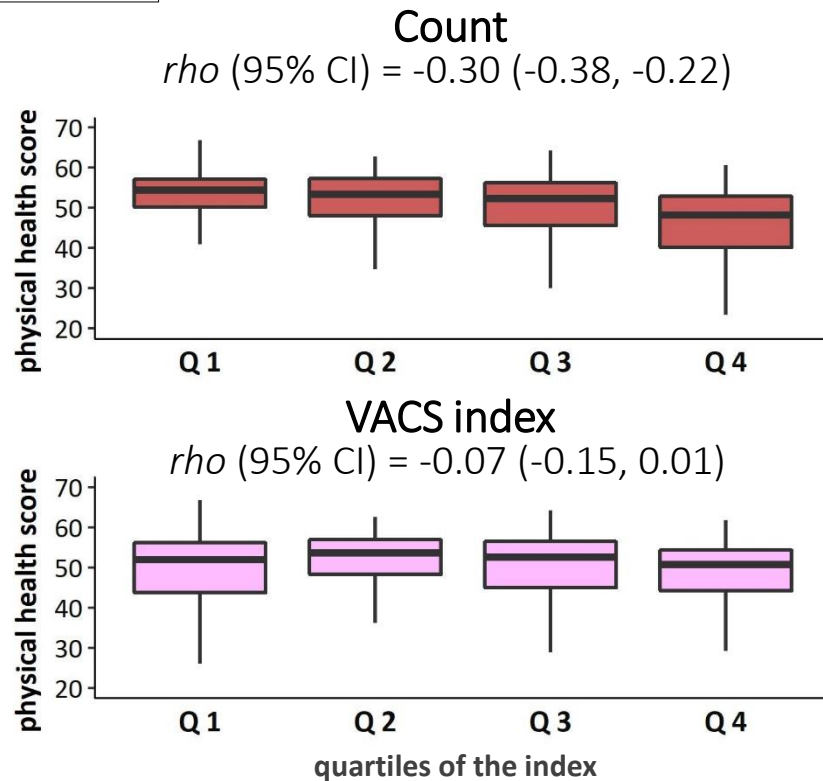
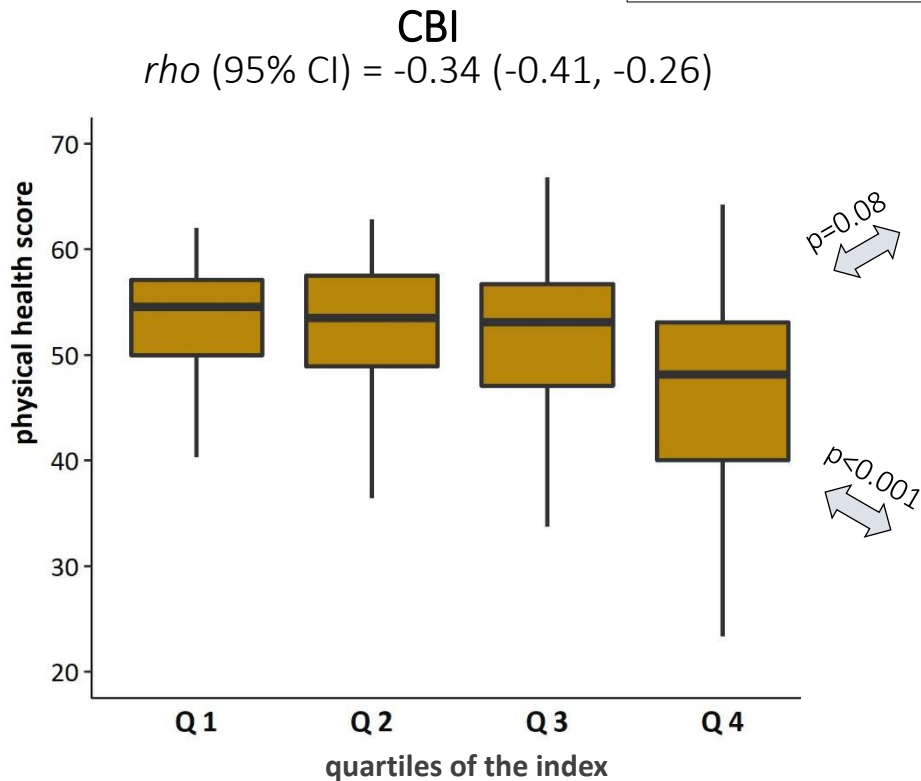
CBI

ρ (95% CI) = -0.34 (-0.41, -0.26)



Concurrent validity: physical health

Validation cohort: AGE_hIV

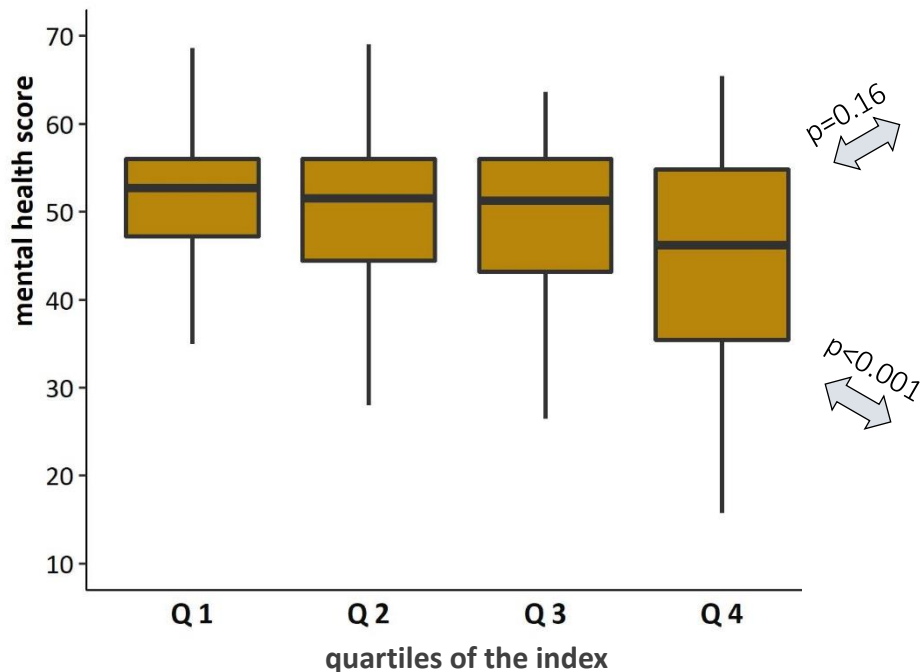


Concurrent validity: mental health

Validation cohort: AGE_hIV

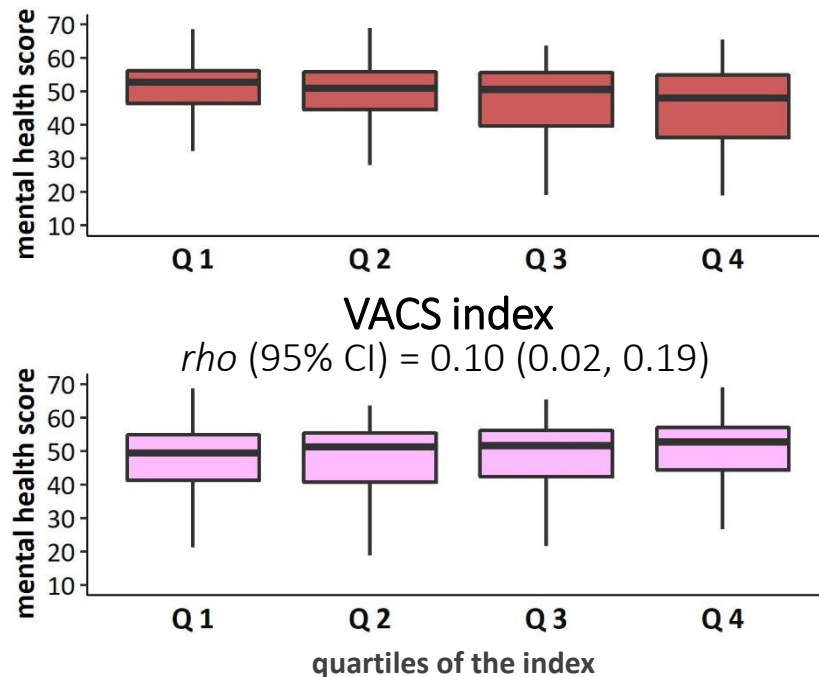
CBI

ρ (95% CI) = -0.18 (-0.26, -0.10)



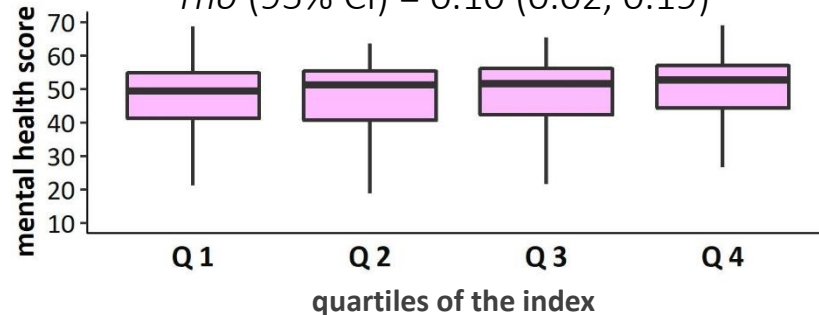
Count

ρ (95% CI) = -0.15 (-0.23, -0.07)

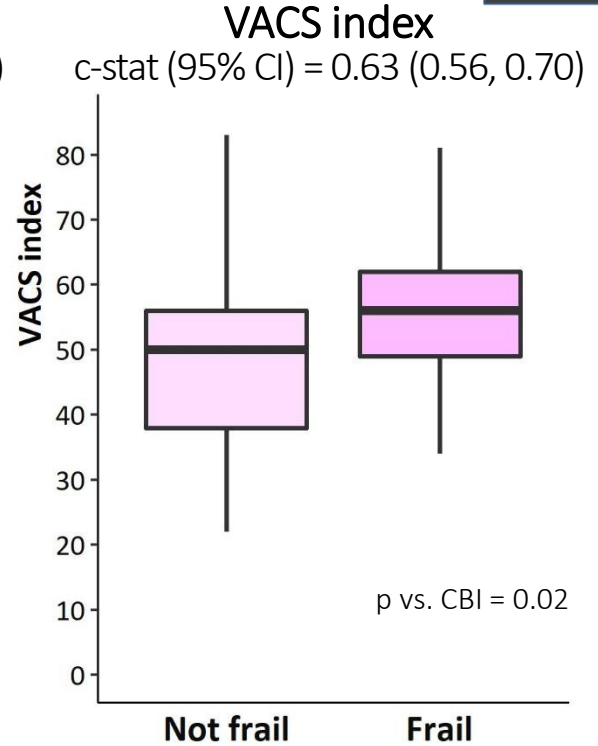
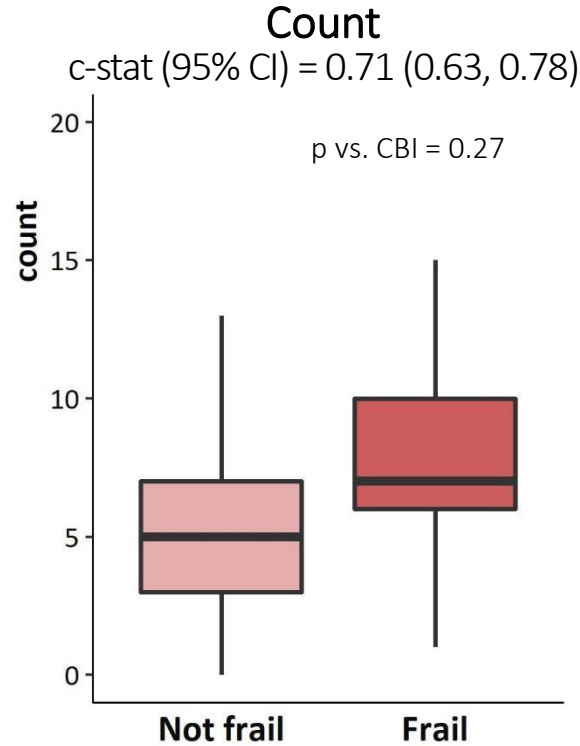
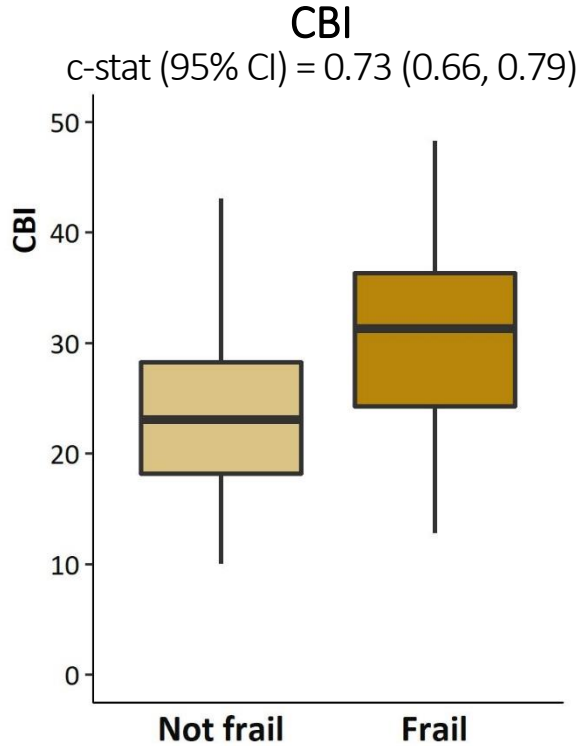


VACS index

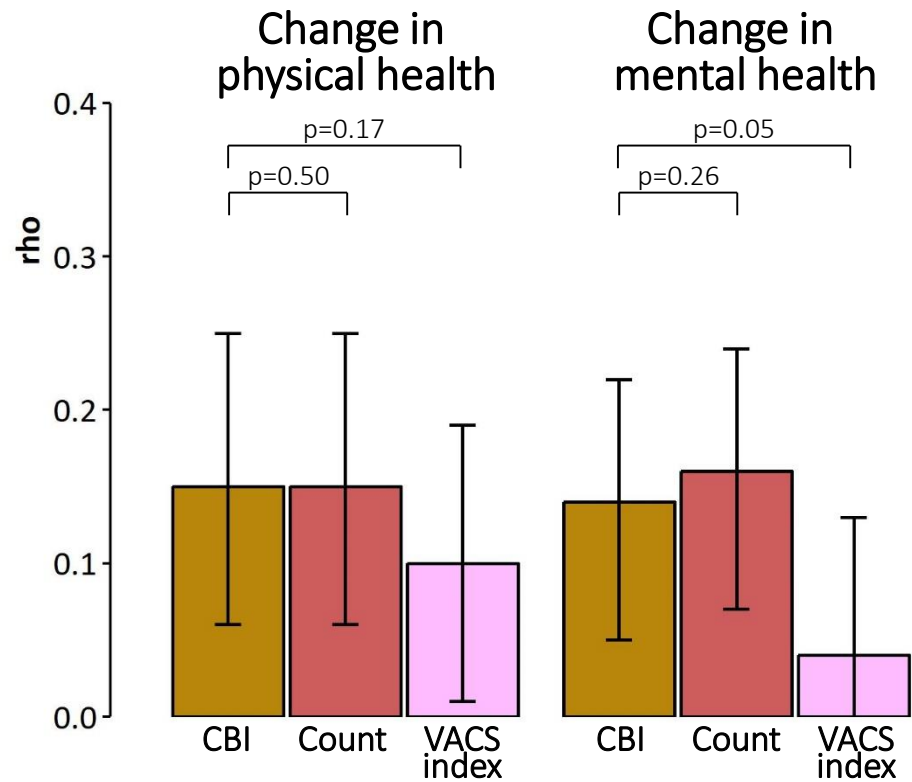
ρ (95% CI) = 0.10 (0.02, 0.19)



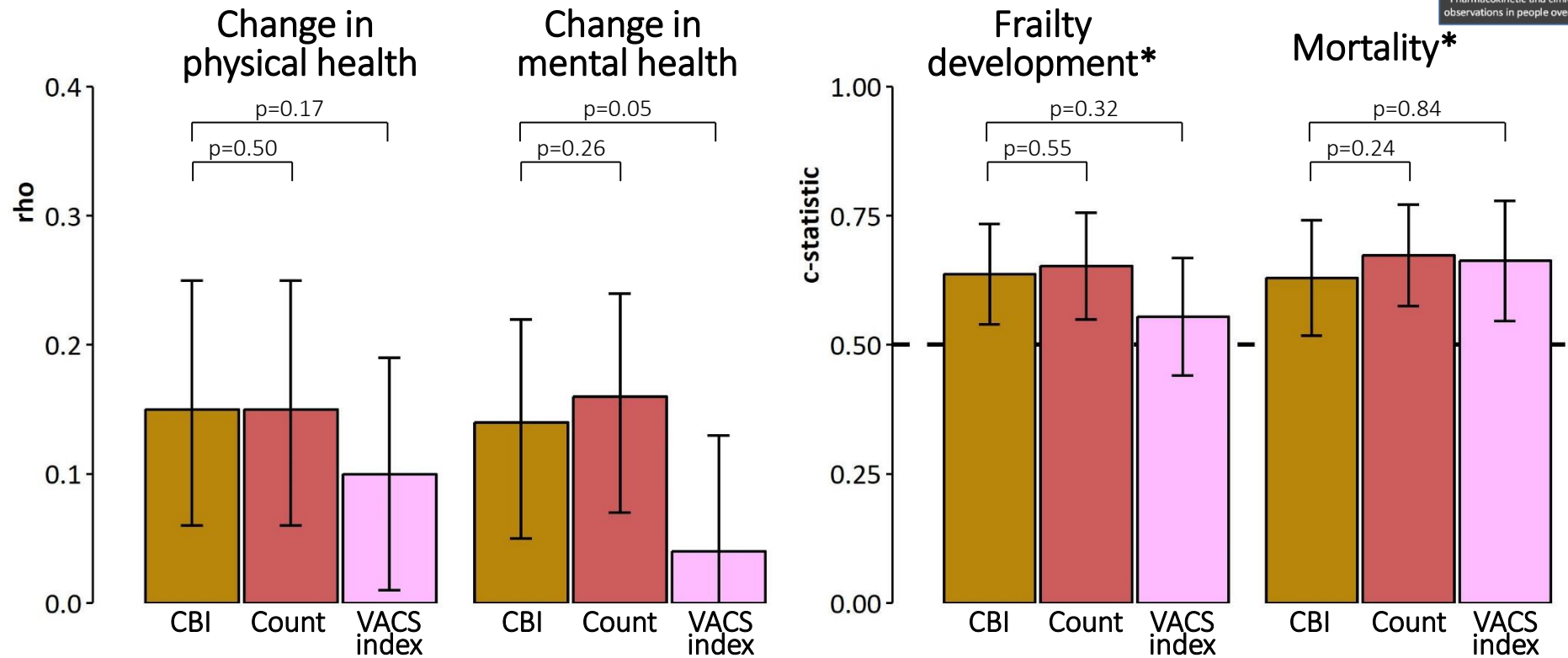
Concurrent validity: frailty*



Predictive validity



Predictive validity



Validation cohort: AGE_hIV

*33 AGE_hIV PWH developed frailty (incidence: 14.6/1000 PYFU) and 31 died (rate: 9.8/1000 PYFU)

Summary



- The CBI shows strong associations with QoL, frailty and mortality, supporting its validity
- Concurrent validity is generally better than that of existing indices, with mixed results for predictive validity
- Future works are warranted to further validate and improve the practicality of the CBI by, for example, relying on a reduced list of comorbidities

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AGE_hIV Scientific oversight and coordination: P. Reiss (PI), F.W.N.M. Wit, M. van der Valk, R.A. Van Zoest, E. Verheij, S.O. Verboeket, B.C. Elsenga (Amsterdam UMC (AUMC), University of Amsterdam (UvA), Department of Global Health/Amsterdam Institute for Global Health and Development (AIGHD)); M. Prins (co-PI), M.F. Schim van der Loeff, M. Dijkstra, L. Del Grande, I. Agard (Public Health Service Amsterdam, Department of Infectious Diseases). **Data management:** S. Zaheri, M.M.J. Hillebregt, Y.M.C. Ruijs, D.P. Benschop, A. el Berkaoui (HIV Monitoring Foundation). **Project management and administrative support:** W. Zikkenheiner (AIGHD). **Central laboratory support:** N.A. Kootstra, A.M. Harskamp-Holwerda, I. Maurer, M.M. Mangas Ruiz, A.F. Girigorie, B. Boeser-Nunnink (AUMC, UvA, Laboratory for Viral Immune Pathogenesis and Department of Experimental Immunology). **Participating HIV physicians and nurses:** G. de Bree, S.E. Geerlings, A. Goorhuis, J.W.R. Hovius, B.A. Lemkes, F.J.B. Nellen, T. van der Poll, J.M. Prins, P. Reiss, M. van der Valk, M. van Vugt, W.J. Wiersinga, F.W.N.M. Wit, M. van Duinen, J. van Eden, A. Hazenberg, A.M.H. van Hes, F.J.J. Pijnappel, S. Smalhout, A. Weijsenfeld (AUMC, UvA, Division of Infectious Diseases). **Financial support:** The Netherlands Organisation for Health Research and Development (ZonMW) grant nr. 300020007 & Stichting AIDS Fonds grant nr. 2009063. Additional unrestricted scientific grants from: Gilead Sciences, ViiV Healthcare Merck & Co, Janssen