POPPY

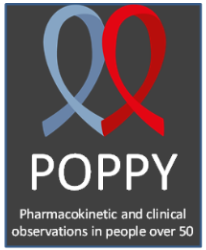
Pharmacokinetic and clinical observations in people over 50

Associations between cognitive function and cardiovascular risk factors: differences between people with HIV and HIV-negative controls

D. De Francesco[1], J. Underwood[2], J.H. Vera[3], E. Bagkeris[1], D. Asboe[4], P.W.G. Mallon[5], F.A. Post[6], M. Johnson[7], I. Williams[1], M. Boffito[4], P. Greliak[2], J. Anderson[8], C.A. Sabin[1] and A. Winston[2] on behalf of the POPPY study group

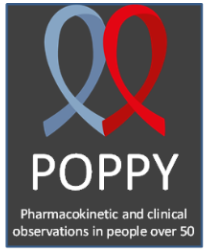
[1]UCL, London, UK [2]Imperial College London, UK [3]Brighton and Sussex Medical School, Brighton, UK
[4]Chelsea and Westminster Hospital, London, UK [5]UCD School Of Medicine, Dublin, Ireland
[6]Kings College Hospital, London, UK [7]Royal Free Hospital, London, UK [8]Homerton University Hospital, London, UK

Background



- People living with HIV (PLWH) may report reduced cognitive function, even with effective and virologically suppressive therapy
- The pathogenesis of this is not fully understood and likely involves, amongst other things, the impact of some age-associated comorbid conditions such as cardiovascular (CV) disease
- A link between CV disease/CV risk factors and poorer cognitive performance has been reported in the general population - there is, however, little evidence on such a link in PLWH

Aims

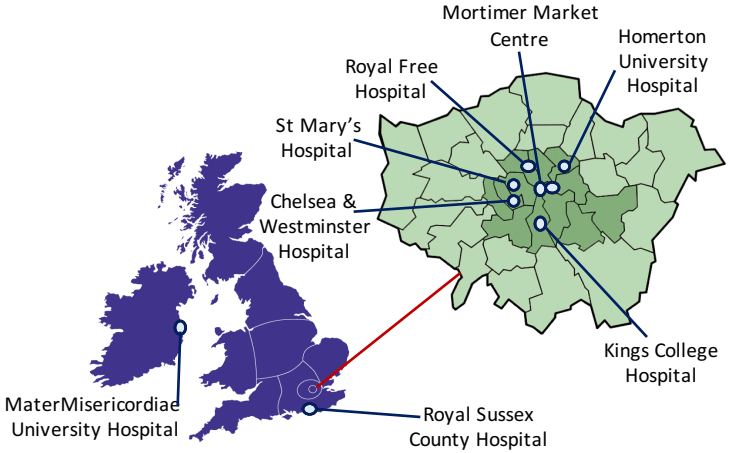


- To describe the associations of CV diseases and risk factors with cognitive performance among PLWH
- To compare associations to those found among HIV-negative individuals

The POPPY study

POPPY
Pharmacokinetic and clinical observations in people over 50

- Multicentre, prospective, observational study to examine the effects of ageing on the clinical outcomes of PLWH in UK and Ireland
- Cohorts of PLWH aged ≥50 and <50 years, and lifestyle-matched ≥50 HIV-negative individuals

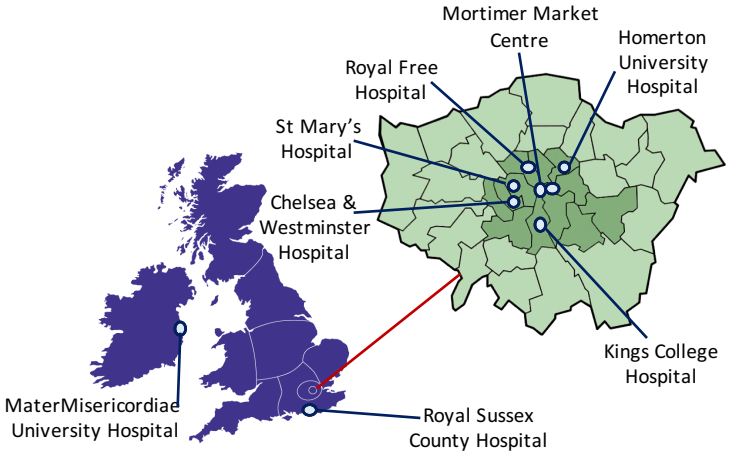


PLWH (recruited/analysed = 1073/977)
- white/black African ethnicity
- acquired HIV via sexual routes

The POPPY study

POPPY
Pharmacokinetic and clinical observations in people over 50

- Multicentre, prospective, observational study to examine the effects of ageing on the clinical outcomes of PLWH in UK and Ireland
- Cohorts of PLWH aged ≥50 and <50 years, and lifestyle-matched ≥50 HIV-negative individuals



PLWH (recruited/analysed = 1073/977)
- white/black African ethnicity
- acquired HIV via sexual routes

HIV- ≥50 yrs (recruited/analysed = 304/276)
frequency matched on gender, ethnicity, sexual orientation and location (in/out London)

Cognitive function

POPPY
Pharmacokinetic and clinical observations in people over 50

- Assessment of cognitive function using CogState battery
- 11 tests grouped into six cognitive domains
  - Visual learning
  - Psychomotor function
  - Visual attention
  - Executive function
  - Verbal learning
  - Working memory and attention
- Test scores standardized into Z-scores (mean 0, SD 1)
- **Global Z-score**: average across the 11 individual tests

Cardiovascular risk factors

POPPY
Pharmacokinetic and clinical observations in people over 50

Modifiable risk factors:

- Past/Current smoking
- Weight
- BMI
- Waist circumference
- Overweight (BMI ≥25 kg/m^2)

Cardiovascular risk factors

POPPY
Pharmacokinetic and clinical observations in people over 50

Modifiable risk factors:
- Past/Current smoking
- Weight
- BMI
- Waist circumference
- Overweight (BMI ≥25 kg/m^2)

Self-reported history of:
- Hypertension
- Type 2 diabetes
- Dyslipidaemia
- Myocardial infarction (MI)
- Angina pectoris
- Peripheral vascular disease
- Heart failure,
- Ischemic heart disease (IHD)
- Transient ischemic attack (TIA)/stroke
  Coronary artery bypass grafting
- Any cardiovascular disease (CVD)
- Any problem of the nervous system

Use of:
- Anti-hypertensive drugs
- Lipid-lowering drugs

Family history of:
- Hypertension
- MI
- High cholesterol
- Dementia
- TIA/Stroke
- Heart bypass
- Diabetes
- Angina pectoris
- Heart failure
- Other CVD

Cardiovascular risk factors

POPPY
Pharmacokinetic and clinical observations in people over 50

Modifiable risk factors:
- Past/Current smoking
- Weight
- BMI
- Waist circumference
- Overweight (BMI ≥25 kg/m^2)

Lipids:
- Total cholesterol
- High-density lipoproteins (HDL)
- Low-density lipoproteins (LDL)
- Triglycerides

Renal function:
- eGFR (CKD-EPI formula)
- Chronic kidney disease (CKD: eGFR ≤ 60)
- Creatinine clearance

Self-reported history of:
- Hypertension
- Type 2 diabetes
- Dyslipidaemia
- Myocardial infarction (MI)
- Angina pectoris
- Peripheral vascular disease
- Heart failure,
- Ischemic heart disease (IHD)
- Transient ischemic attack (TIA)/stroke Coronary artery bypass grafting
- Any cardiovascular disease (CVD)
- Any problem of the nervous system

Use of:
- Anti-hypertensive drugs
- Lipid-lowering drugs

Family history of:
- Hypertension
- MI
- High cholesterol
- Dementia
- TIA/Stroke
- Heart bypass
- Diabetes
- Angina pectoris
- Heart failure
- Other CVD

Cardiovascular risk factors

POPPY
Pharmacokinetic and clinical observations in people over 50

Modifiable risk factors:
- Past/Current smoking
- Weight
- BMI
- Waist circumference
- Overweight (BMI ≥25 kg/m^2)

Lipids:
- Total cholesterol
- High-density lipoproteins (HDL)
- Low-density lipoproteins (LDL)
- Triglycerides

Renal function:
- eGFR (CKD-EPI formula)
- Chronic kidney disease (CKD: eGFR ≤ 60)
- Creatinine clearance

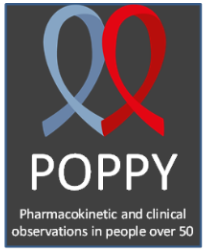
Self-reported history of:
- Hypertension
- Type 2 diabetes
- Dyslipidaemia
- Myocardial infarction (MI)
- Angina pectoris
- Peripheral vascular disease
- Heart failure,
- Ischemic heart disease (IHD)
- Transient ischemic attack (TIA)/stroke Coronary artery bypass grafting
- Any cardiovascular disease (CVD)
- Any problem of the nervous system

Use of:
- Anti-hypertensive drugs
- Lipid-lowering drugs

Family history of:
- Hypertension
- MI
- High cholesterol
- Dementia
- TIA/Stroke
- Heart bypass
- Diabetes
- Angina pectoris
- Heart failure
- Other CVD

Other:
- Systolic blood pressure
- Diastolic blood pressure
- Haemoglobin
- Framingham risk score
- Serum albumin

Statistical methods



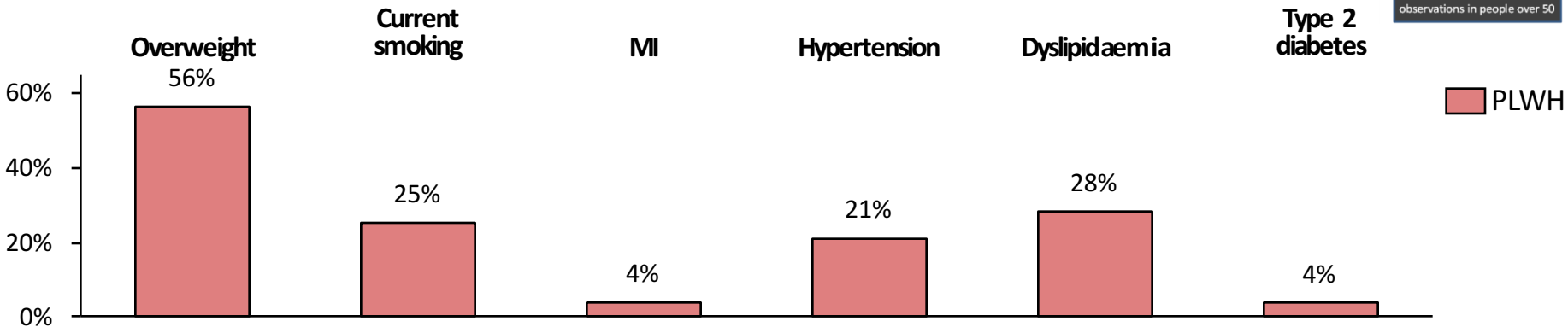
- Chi-square to compare CV risk factors between PLWH and HIV-negative individuals
- Multiple imputation with fully conditioned models
- Median regression models (accounting for socio-demographics) to investigate associations between CV risk factors and cognitive performance and the interaction with HIV-status
- Stepwise model selection to identify significant independent associations (sensitivity analyses with backward and forward model selection)

Baseline characteristics

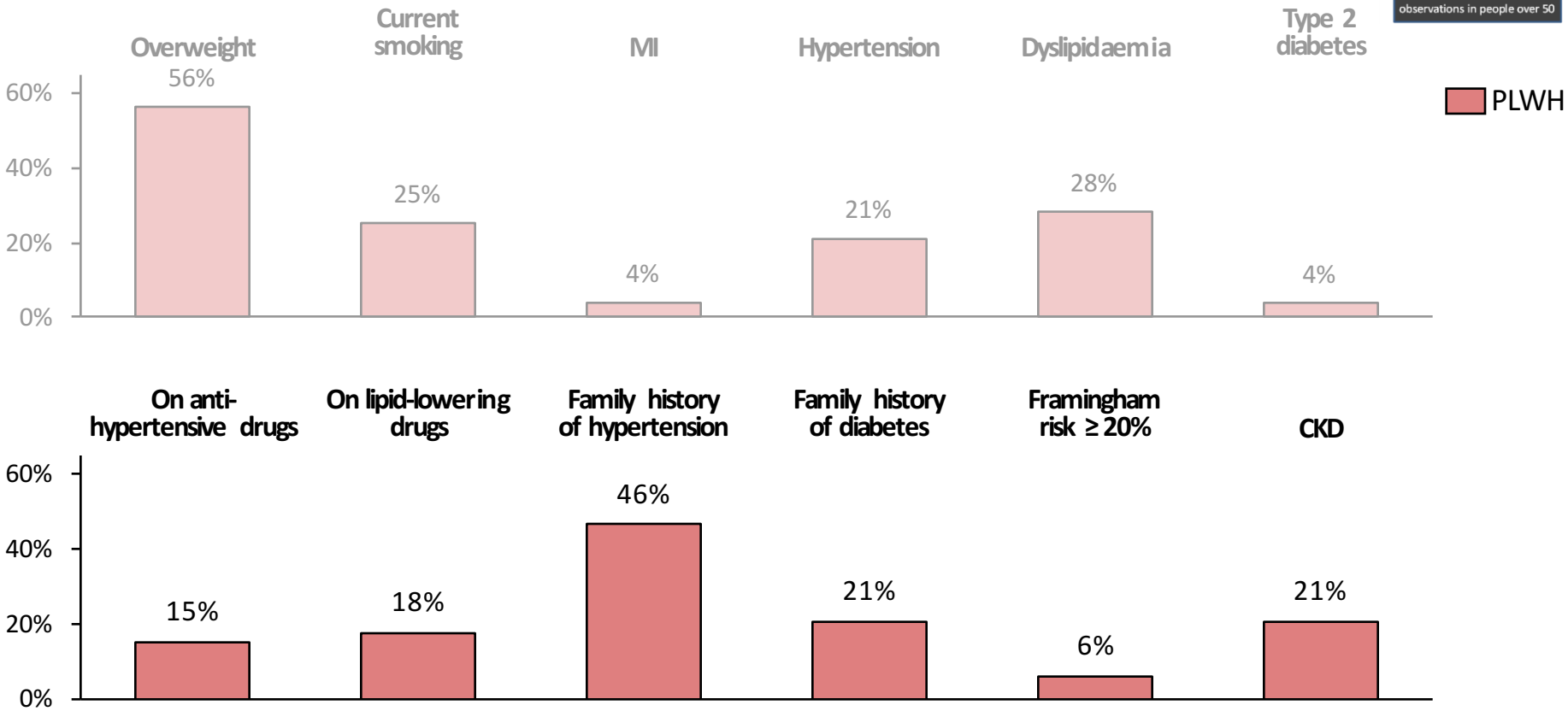
POPPY
Pharmacokinetic and clinical observations in people over 50

n (%) or median (IQR)	HIV- (N=276)	PLWH <50 (N=340)	PLWH ≥50 (N=637)
Male gender	180 (65.2%)	275 (80.9%)	564 (88.5%)
White ethnicity	252 (94.3%)	274 (80.6%)	560 (87.9%)
Age [years]	58 (53, 63)	43 (37, 47)	56 (53, 62)
Man having sex with men (MSM)	138 (50.0%)	246 (72.4%)	509 (79.9%)
PHQ-9 score	1 (0, 3)	4 (1, 8)	4 (1, 10)
Current/past ID use	6 (2.2%)	46 (13.6%)	59 (9.3%)
Recreational drugs use 6 months before visit	42 (15.2%)	116 (34.1%)	164 (25.8%)
Viral load <50 copies/mL	N/A	290 (85.8%)	586 (92.3%)
CD4 count [cells/µL]	N/A	654 (490, 833)	620 (470, 799)

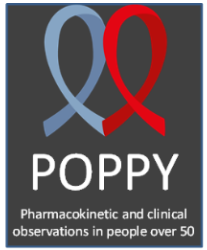
CV risk factors



CV risk factors



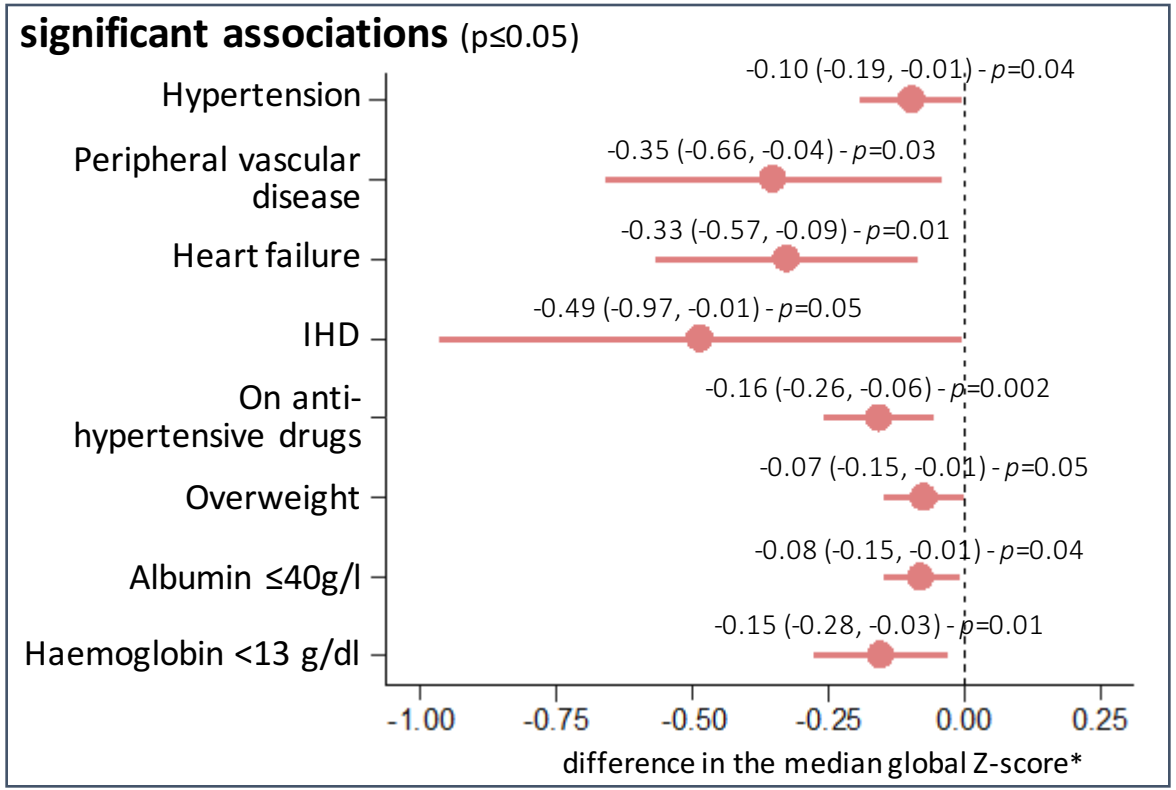
Aims



- To describe the associations of CV disease and risk factors with cognitive performance among PLWH
- To compare associations to those found among HIV-negative individuals

Associations with cognitive scores

Model: one factor at the time

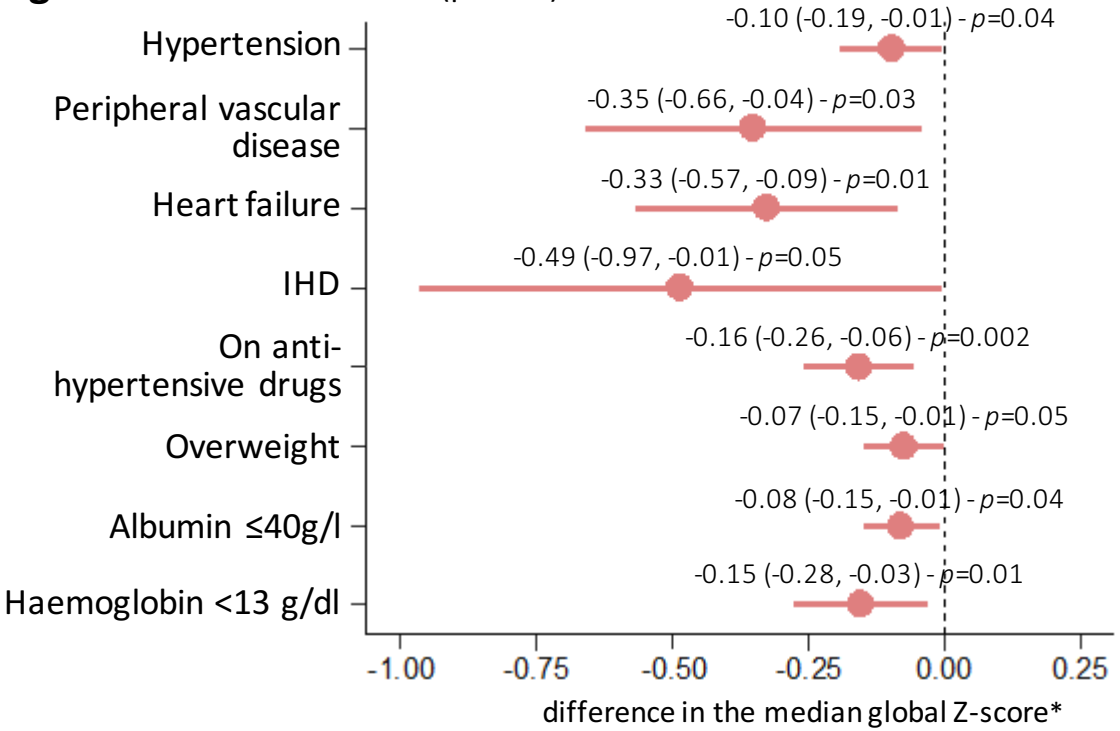


* Adjusted for age, gender, ethnicity, education and depressive symptoms

Associations with cognitive scores

Model: one factor at the time

significant associations (p≤0.05)



non-significant associations (p>0.05)

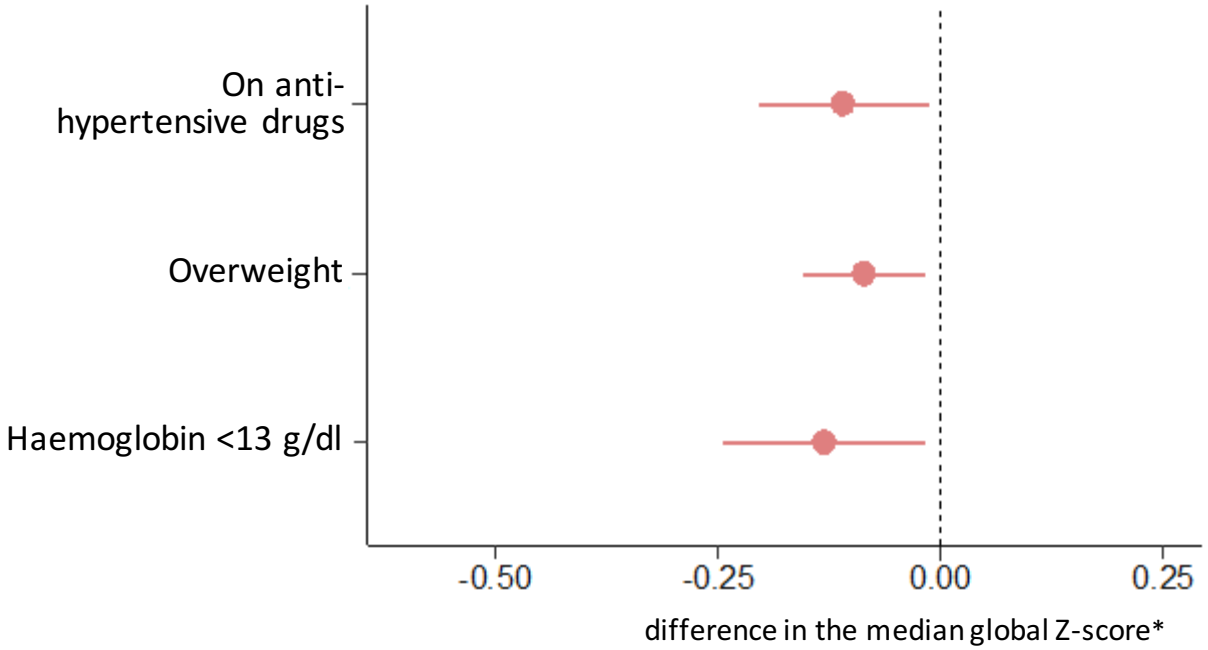
- Past/Current smoking
- Weight, BMI, waist circumference
- History of dyslipidaemia, MI, angina pectoris, TIA/stroke, CABG, any CVD, type 2 diabetes
- Family history of CVD
- Lipid-lowering medication
- Lipids
- BP and Framingham risk score
- CKD, eGFR and creatinine clearance

* Adjusted for age, gender, ethnicity, education and depressive symptoms

Associations with cognitive scores

POPPY
Pharmacokinetic and clinical observations in people over 50

Multivariable model (stepwise selection)



-0.11 (-0.21, -0.01) - *p*=0.03

-0.09 (-0.15, -0.02) - *p*=0.02

-0.13 (-0.24, -0.02) - *p*=0.02

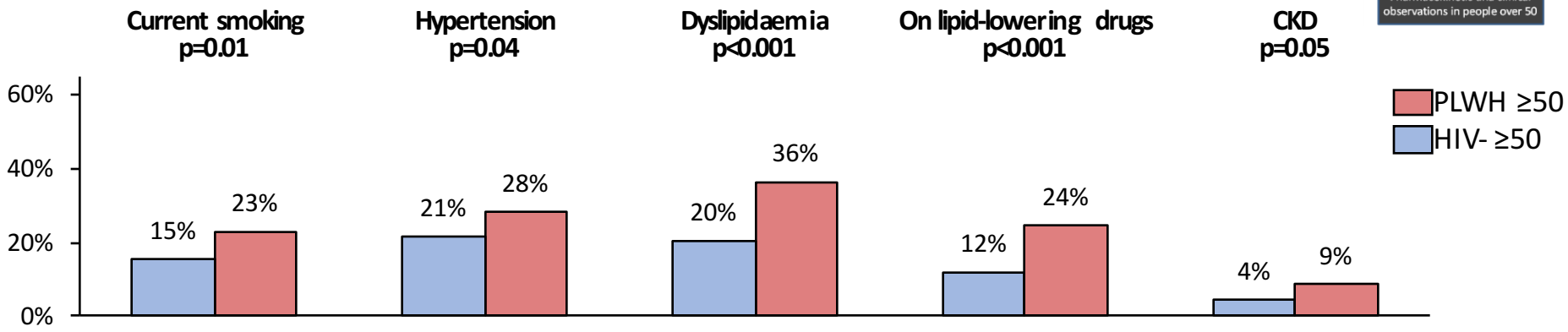
* Adjusted for age, gender, ethnicity, education and depressive symptoms

Aims

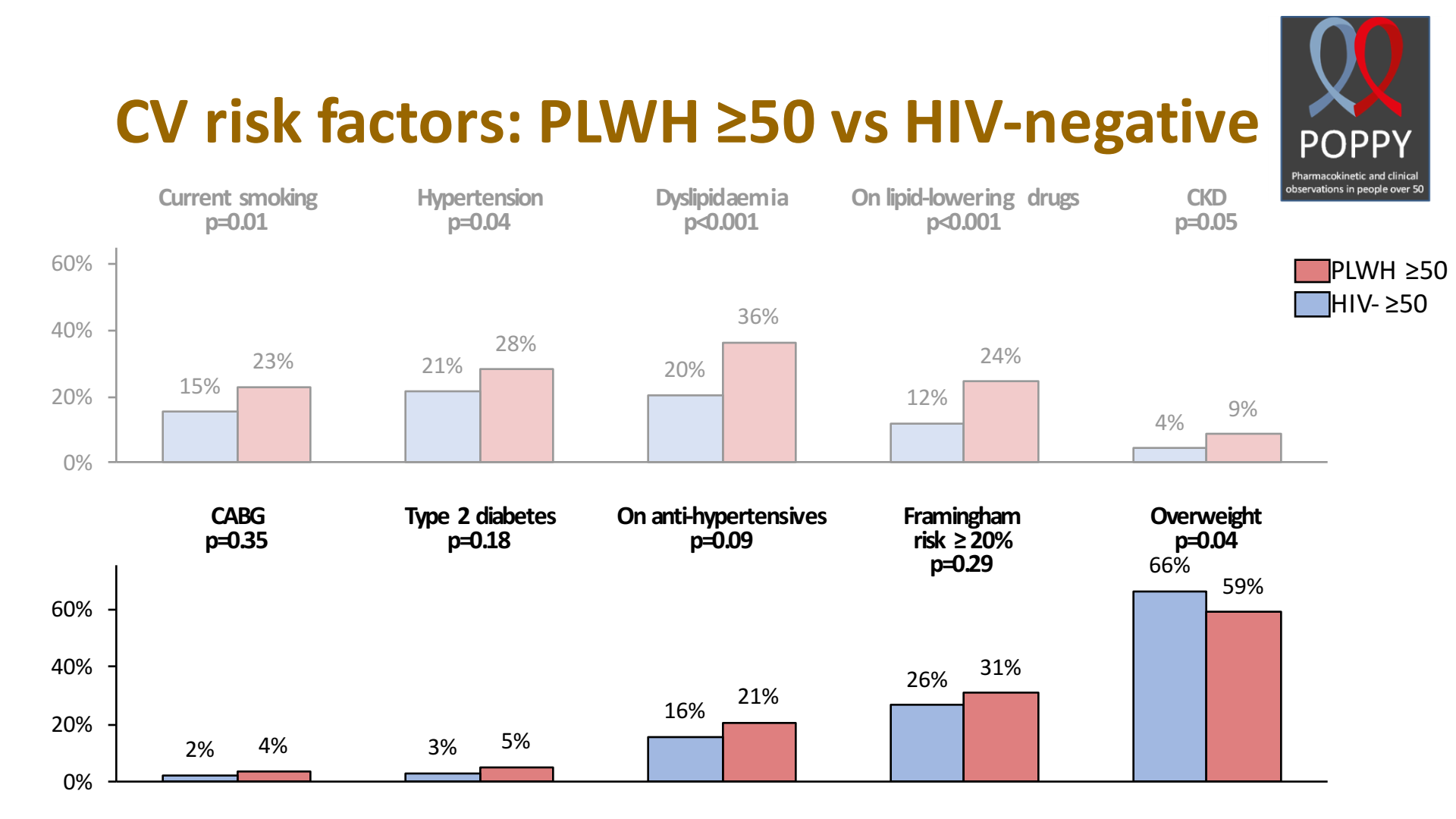
POPPY
Pharmacokinetic and clinical observations in people over 50

- To describe the associations of CV diseases and CV risk factors with cognitive performance among PLWH
- To compare associations with those found among HIV-negative individuals

CV risk factors: PLWH ≥50 vs HIV-negative

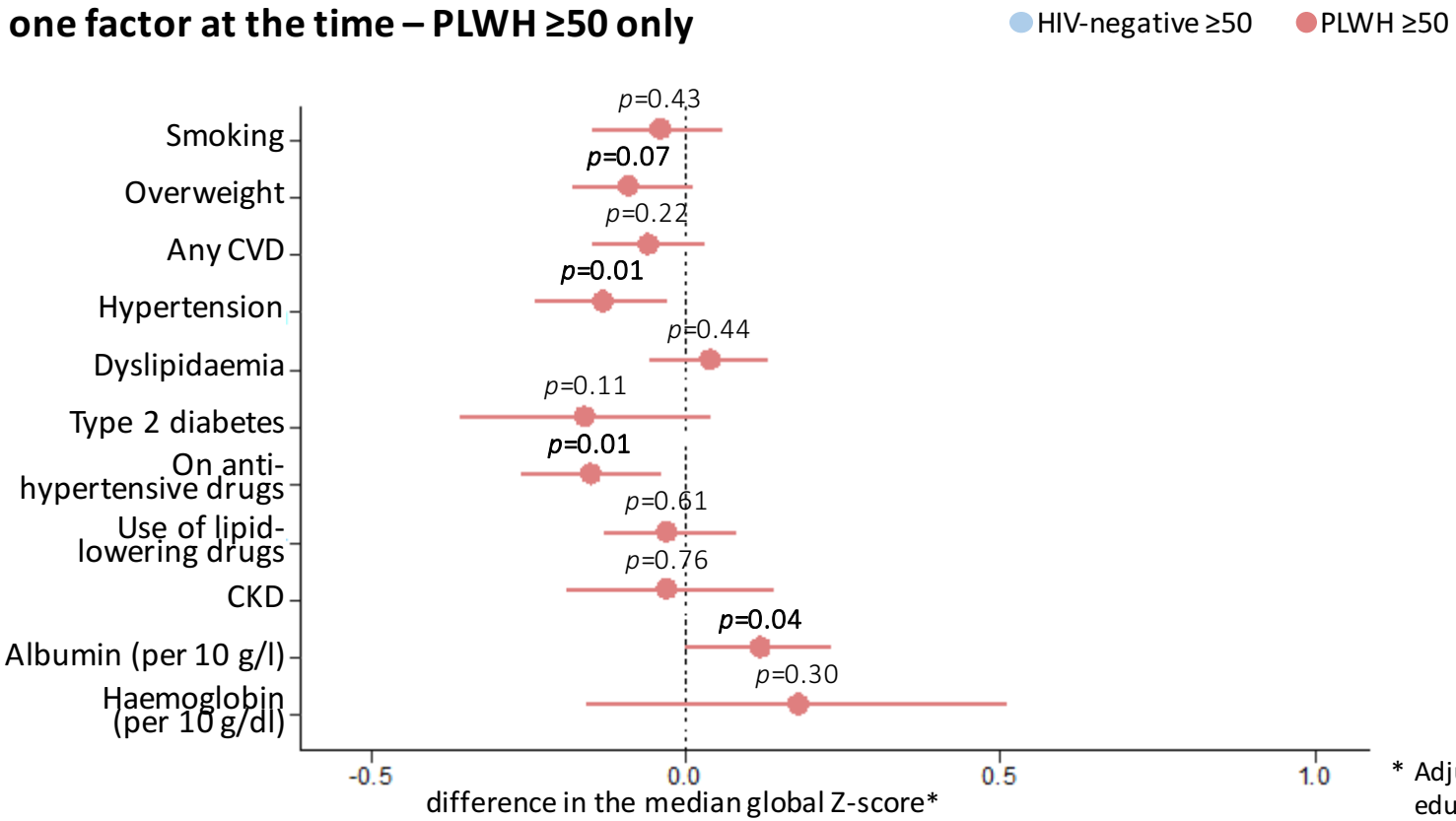


CV risk factors: PLWH ≥50 vs HIV-negative



Associations with cognitive scores /2

one factor at the time – PLWH ≥50 only

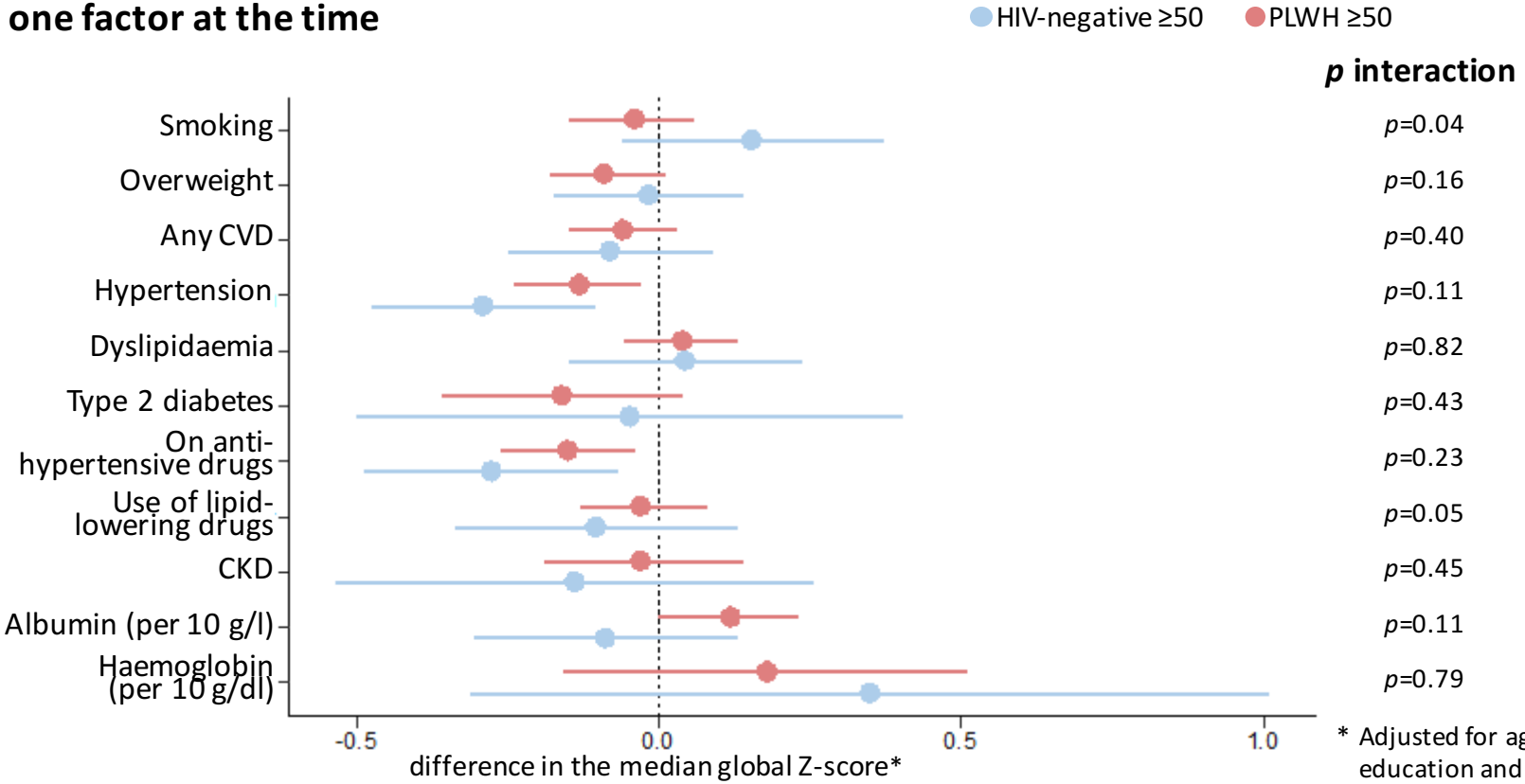


* Adjusted for age, gender, ethnicity, education and depressive symptoms

Associations with cognitive scores /2

POPPY
Pharmacokinetic and clinical observations in people over 50

one factor at the time

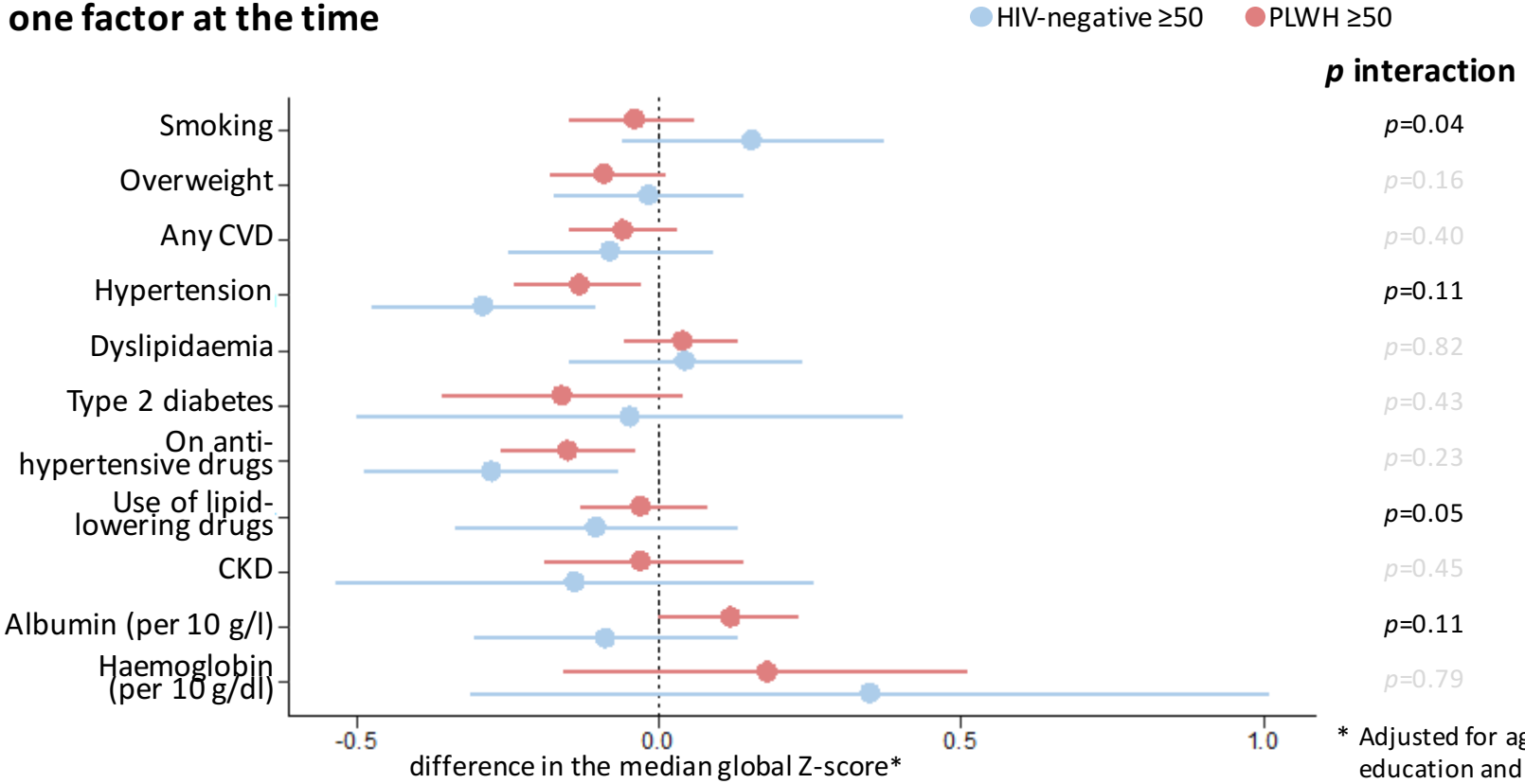


* Adjusted for age, gender, ethnicity, education and depressive symptoms

Associations with cognitive scores /2

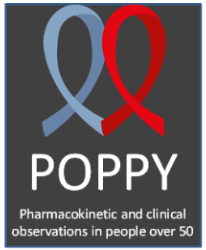
POPPY
Pharmacokinetic and clinical observations in people over 50

one factor at the time



* Adjusted for age, gender, ethnicity, education and depressive symptoms

Conclusions



- Some CV risk factors appear to correlate with cognitive health in virally suppressed PLWH
- On the whole, associations are similar to those seen in comparable HIV-negative individuals
- Given the higher burden of CV disease in PLWH, prevention and active management of CV disease and its risk factors may reduce the risk of cognitive disorders

Acknowledgments

POPPY Management Team: Daphne Babalis, Marta Boffito, Laura Burgess, Paddy Mallon, Frank Post, Caroline Sabin, Memory Sachikonye, Alan Winston

POPPY Scientific Steering Committee: Jane Anderson, David Asboe, Marta Boffito, Lucy Garvey, Paddy Mallon, Frank Post, Anton Pozniak, Caroline Sabin, Memory Sachikonye, Jaime Vera, Ian Williams, Alan Winston

POPPY Sites and Trials Unit:

- Elton John Centre, Brighton and Sussex University Hospital (Martin Fisher, Amanda Clarke, Jaime Vera, Andrew Bexley, Celia Richardson, Sarah Kirk, Rebecca Gleig)
- St Stephen's Centre, Chelsea and Westminster Hospital (Marta Boffito, David Asboe, Anton Pozniak, Margherita Bracchi, Nicole Pagani, Maddalena Cerrone, Daniel Bradshaw, Francesca Ferretti, Chris Higgs, Elisha Seah, Stephen Fletcher, Michelle Anthonipillai, Ashley Moyes, Katie Deats, Irtiza Syed, Clive Matthews, Peter Fernando, Chido Chiwome, Shane Hardwick)
- Homerton Sexual Health Services, Homerton University Hospital (Jane Anderson, Sifiso Mguni, Rebecca Clark, Rhiannon Nevin-Dolan, Sambasivarao Pelluri)
- Caldecot Centre, King's College Hospital (Frank Post, Lucy Campbell, Selin Yurdakul, Sara Okumu, Louise Pollard, Beatriz Santana Suárez)
- HIV Molecular Research Group, School of Medicine, University College Dublin (Paddy Mallon, Alan Macken, Bijan Ghavani-Kia, Joanne Maher, Maria Byrne, Ailbhe Flaherty, Sumesh Babu)
- Department of Infection and Population Health, University College London (Ian Williams, Damilola Otiko, Laura Phillips, Rosanna Laverick, Michelle Beynon, Anna-Lena Salz, Abigail Severn)
- St. Mary's Hospital London, Imperial College Healthcare NHS Trust (Alan Winston, Lucy Garvey, Jonathan Underwood, Lavender Tembo, Matthew Stott, Linda McDonald, Felix Dransfield)
- Imperial Clinical Trials Unit, Imperial College London (Andrew Whitehouse, Laura Burgess, Daphne Babalis)
- Ian Charleson Day Centre, Royal Free Hospital (Margaret Johnson, Nnenna Ngwu, Nargis Hemat, Anne Carroll, Sabine Kinloch, Mike Youle, Sara Madge)

POPPY methodology/statistics/analysis: Caroline Sabin, Davide De Francesco, Emmanouil Bagkeris

Funders: The POPPY study is funded from investigator initiated grants from BMS, Gilead Sciences, Janssen, MSD and ViiV Healthcare.