Prognostic value of vitamin D level for all-cause mortality, and association with inflammatory markers in HIV-infected persons

Results from the EuroSIDA Cohort Study

JP VIARD[1], L SHEPHERD[2], JC SOUBERBIELLE[3], JP BASTARD[4], S FELLAHI[4], J CAPEAU[4], J REEKIE[2], P REISS[5], A BLAXHULT[6], M BICKEL[7], C LEEN[8], O KIRK[9], JD LUNDGREN[9], A MOCROFT[2], On behalf of EuroSIDA in EuroCOORD

[1]Hôtel-Dieu, Université Paris Descartes, Paris, France, [2]University College London, London, UK, [3]Hôpital Necker, Paris, France, [4]Hôpital Tenon, Paris, France, [5]Academic Medical Centre, University of Amsterdam, The Netherlands,[6]Dept. of Medicine, Div. of Infectious Diseases, Karolinska Institute, Stockholm, Sweden, [7]HIVCENTER Haus 68, Frankfurt, Germany, [8]Western General Hospital, Edinburgh, UK, [9]Copenhagen HIV Programme, University of Copenhagen, Dept. of Infectious Diseases, Rigshospitalet, Copenhagen, Denmark

Vitamin D Insufficiency / Deficiency

- **Assessed through measurement of 25OHD**
  - Insufficiency: < 30 ng/ml (75 nmol/l)
  - Deficiency: < 20 ng/ml (50 nmol/l)
  - Severe deficiency: <10 ng/ml (25 nmol/l)

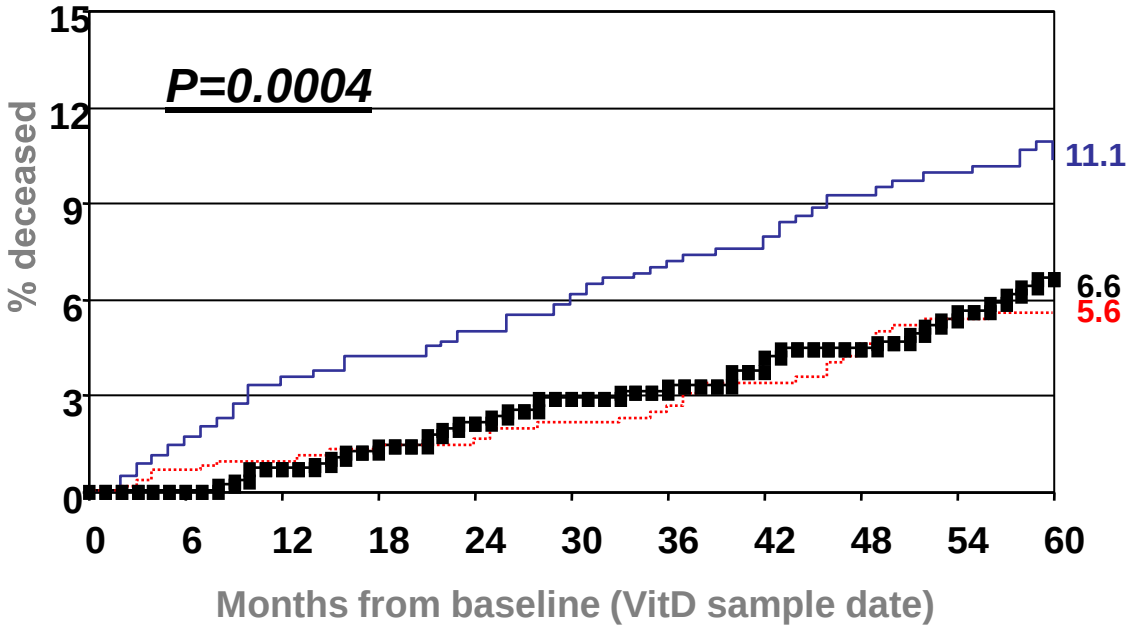
- **Associated with morbidity:**
  - Osteopenia, cancer, autoimmune diseases, infections (TB), CV disease, neurocognitive disorders, frailty …
  - Inflammation

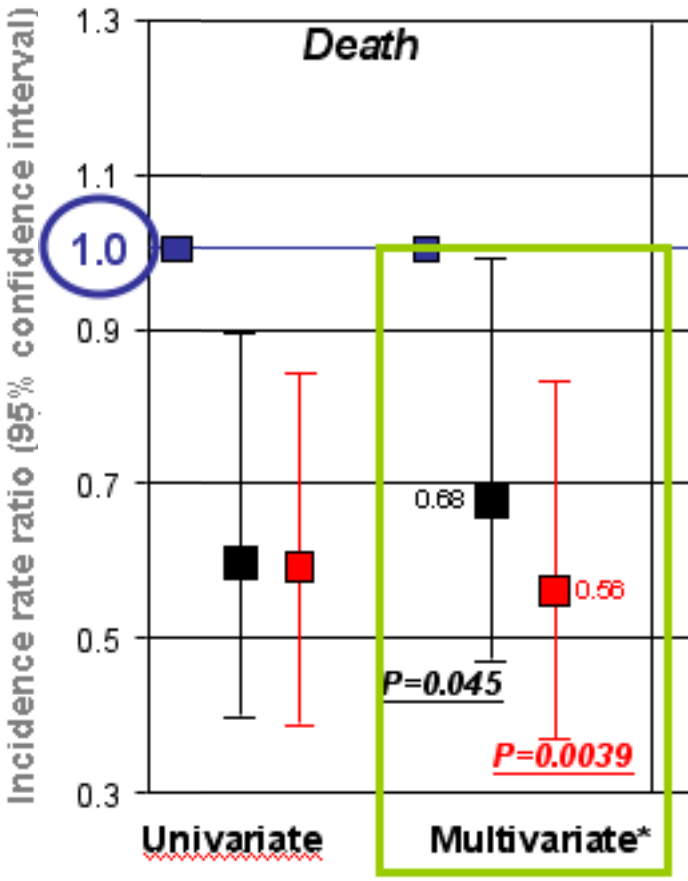
- **Associated with mortality in:**
  - Elderly, renal insufficiency, heart transplant, high CV risk, diabetes …
  - HIV infection (both ARV-treated and untreated)

Previous EuroSIDA study:
progression to and incidence rate ratios of death

25-hydroxyvitamin D tertiles (ng/ml)

Low (<12) **Medium (12-20)** **High (>20)**





*Adjusted for baseline values of gender, ethnic origin, HIV risk group, region of Europe, HBsAg and HCV antibody status, prior AIDS, exposure to antiretrovirals, age, CD4 count, CD4 nadir, HIV-RNA viral load, date of baseline sample, season of sample and date of recruitment to EuroSIDA

Viard et al. AIDS 2011

Objectives

- **To assess the prognostic value of 25OHD severe deficiency for events, in a longitudinal study**

- **To assess the association between 25OHD level and immunological/inflammatory markers, known to be prognostic of HIV disease evolution**

Methods

- Prospective 1-1 case control nested study
  - Cases and controls for
    - AIDS (n=50 pairs), non-AIDS (n=63), death (n=42) events
  - Selected from the 1985 participants in previous study
  - Matched on age, gender, region, study entry date, baseline CD4 & VL

- Measurements
  - 25OHD, hsIL-6, hsCRP, sCD14 in stored plasma
  - at study entry (baseline), time of event (or latest sample available for controls) and at midpoint of follow-up (if available)

- Time from 1st to last samples: 44.6 (IQR: 22.7-72.3) months
- Time from last sample to event: 3.1 (IQR: 1.4-6.4) months

Statistical analyses

- Associations between 25OHD levels and outcomes
  - Conditional logistic regression
- Associations between changes in markers and outcomes
  - Average absolute change per year (ACPY) and average % change per year (ACPY%) calculated between consecutive measurements of 25OHD, hsCRP, hsIL-6 and sCD14.
  - Conditional logistic regression investigated associations between changes in markers and outcomes.
- Associations between 25OHD level and hsCRP / hsIL-6 / sCD14 concentrations, and CD4 count
  - Mixed models with random intercepts

Baseline characteristics of cases and controls for AIDS, non-AIDS and death events.

	AIDS events		non-AIDS events		Deaths	
	Controls	Cases	Controls	Cases	Controls	Cases
Number of patients	*50*	*50*	*63*	*63*	*42*	*42*
			N (%)			
25OHD <10 ng/mL	9 (18)	16 (32)	14 (22)	16 (25)	9 (21)	10 (24)
Male	43 (86)	43 (86)	60 (95)	60(95)	40 (98)	40 (98)
White	44 (88)	42 (84)	44 (70)	56 (89)	36 (88)	37 (90)
Risk group						
Homosexual	23 (46)	23 (46)	39 (62)	39 (62)	22 (54)	23 (56)
Heterosexual	11 (22)	11 (22)	12 (19)	13 (21)	8 (20)	7 (17)
IDU	11 (22)	11 (22)	8 (13)	7 (11)	7 (17)	6 (15)
HBV +	6 (12)	3 (6)	2 (3)	4 (6)	4 (10)	3 (7)
HCV +	14 (28)	11 (22)	8 (13)	11 (17)	6 (15)	8 (20)
			Median (IQR)			
Age (years)	38 (33,44)	39 (34,46)	40 (37,46)	44 (39,48)	41 (36,49)	42 (38,51)
CD4 (cells/mm³)	270 (129,400)	251 (101,390)	279 (185,486)	321 (173,500)	293 (180,402)	234 (141,404)
Log_{10} HIV RNA /ml	2.70 (2.49,4.10)	3.04 (1.96,4.46)	2.48 (1.69,4.21)	2.63 (1.69,4.25)	2.70 (1.69,3.70)	2.74 (1.69,4.06)

Baseline characteristics of cases and controls for AIDS, non-AIDS and death events.

	AIDS events		non-AIDS events		Deaths	
	Controls	Cases	Controls	Cases	Controls	Cases
Number of patients	*50*	*50*	*63*	*63*	*42*	*42*
			N (%)			
25OHD <10 ng/mL	9 (18)	16 (32)	14 (22)	16 (25)	9 (21)	10 (24)
Male	43 (86)	43 (86)	60 (95)	60(95)	40 (98)	40 (98)
White	44 (88)	42 (84)	44 (70)	56 (89)	36 (88)	37 (90)
Risk group						
Homosexual	23 (46)	23 (46)	39 (62)	39 (62)	22 (54)	23 (56)
Heterosexual	11 (22)	11 (22)	12 (19)	13 (21)	8 (20)	7 (17)
IDU	11 (22)	11 (22)	8 (13)	7 (11)	7 (17)	6 (15)
HBV +	6 (12)	3 (6)	2 (3)	4 (6)	4 (10)	3 (7)
HCV +	14 (28)	11 (22)	8 (13)	11 (17)	6 (15)	8 (20)
			Median (IQR)			
Age (years)	38 (33,44)	39 (34,46)	40 (37,46)	44 (39,48)	41 (36,49)	42 (38,51)
CD4 (cells/mm^3)	270 (129,400)	251 (101,390)	279 (185,486)	321 (173,500)	293 (180,402)	234 (141,404)
Log_{10} HIV RNA /ml	2.70 (2.49,4.10)	3.04 (1.96,4.46)	2.48 (1.69,4.21)	2.63 (1.69,4.25)	2.70 (1.69,3.70)	2.74 (1.69,4.06)

Baseline characteristics of cases and controls for AIDS, non-AIDS and death events.

	AIDS events		non-AIDS events		Deaths	
	Controls	Cases	Controls	Cases	Controls	Cases
Number of patients	*50*	*50*	*63*	*63*	*42*	*42*
			N (%)			
25OHD <10 ng/mL	9 (18)	16 (32)	14 (22)	16 (25)	9 (21)	10 (24)
Male	43 (86)	43 (86)	60 (95)	60(95)	40 (98)	40 (98)
White	44 (88)	42 (84)	44 (70)	56 (89)	36 (88)	37 (90)
Risk group						
Homosexual	23 (46)	23 (46)	39 (62)	39 (62)	22 (54)	23 (56)
Heterosexual	11 (22)	11 (22)	12 (19)	13 (21)	8 (20)	7 (17)
IDU	11 (22)	11 (22)	8 (13)	7 (11)	7 (17)	6 (15)
HBV +	6 (12)	3 (6)	2 (3)	4 (6)	4 (10)	3 (7)
HCV +	14 (28)	11 (22)	8 (13)	11 (17)	6 (15)	8 (20)
			Median (IQR)			
Age (years)	38 (33,44)	39 (34,46)	40 (37,46)	44 (39,48)	41 (36,49)	42 (38,51)
CD4 (cells/mm³)	270 (129,400)	251 (101,390)	279 (185,486)	321 (173,500)	293 (180,402)	234 (141,404)
Log_{10} HIV RNA /ml	2.70 (2.49,4.10)	3.04 (1.96,4.46)	2.48 (1.69,4.21)	2.63 (1.69,4.25)	2.70 (1.69,3.70)	2.74 (1.69,4.06)

Baseline characteristics of cases and controls for AIDS, non-AIDS and death events.

	AIDS events		non-AIDS events		Deaths	
	Controls	Cases	Controls	Cases	Controls	Cases
Number of patients	*50*	*50*	*63*	*63*	*42*	*42*
			N (%)			
25OHD <10 ng/mL	9 (18)	16 (32)	14 (22)	16 (25)	9 (21)	10 (24)
Male	43 (86)	43 (86)	60 (95)	60(95)	40 (98)	40 (98)
White	44 (88)	42 (84)	44 (70)	56 (89)	36 (88)	37 (90)
Risk group						
Homosexual	23 (46)	23 (46)	39 (62)	39 (62)	22 (54)	23 (56)
Heterosexual	11 (22)	11 (22)	12 (19)	13 (21)	8 (20)	7 (17)
IDU	11 (22)	11 (22)	8 (13)	7 (11)	7 (17)	6 (15)
HBV +	6 (12)	3 (6)	2 (3)	4 (6)	4 (10)	3 (7)
HCV +	14 (28)	11 (22)	8 (13)	11 (17)	6 (15)	8 (20)
			Median (IQR)			
Age (years)	38 (33,44)	39 (34,46)	40 (37,46)	44 (39,48)	41 (36,49)	42 (38,51)
CD4 (cells/mm³)	270 (129,400)	251 (101,390)	279 (185,486)	321 (173,500)	293 (180,402)	234 (141,404)
Log_{10} HIV RNA /ml	2.70 (2.49,4.10)	3.04 (1.96,4.46)	2.48 (1.69,4.21)	2.63 (1.69,4.25)	2.70 (1.69,3.70)	2.74 (1.69,4.06)

Baseline characteristics of cases and controls for AIDS, non-AIDS and death events.

	AIDS events		non-AIDS events		Deaths	
	Controls	Cases	Controls	Cases	Controls	Cases
Number of patients	*50*	*50*	*63*	*63*	*42*	*42*
			N (%)			
25OHD <10 ng/mL	9 (18)	16 (32)	14 (22)	16 (25)	9 (21)	10 (24)
Male	43 (86)	43 (86)	60 (95)	60(95)	40 (98)	40 (98)
White	44 (88)	42 (84)	44 (70)	56 (89)	36 (88)	37 (90)
Risk group						
Homosexual	23 (46)	23 (46)	39 (62)	39 (62)	22 (54)	23 (56)
Heterosexual	11 (22)	11 (22)	12 (19)	13 (21)	8 (20)	7 (17)
IDU	11 (22)	11 (22)	8 (13)	7 (11)	7 (17)	6 (15)
HBV +	6 (12)	3 (6)	2 (3)	4 (6)	4 (10)	3 (7)
HCV +	14 (28)	11 (22)	8 (13)	11 (17)	6 (15)	8 (20)
			Median (IQR)			
Age (years)	38 (33,44)	39 (34,46)	40 (37,46)	44 (39,48)	41 (36,49)	42 (38,51)
CD4 (cells/mm³)	270 (129,400)	251 (101,390)	279 (185,486)	321 (173,500)	293 (180,402)	234 (141,404)
Log_{10} HIV RNA /ml	2.70 (2.49,4.10)	3.04 (1.96,4.46)	2.48 (1.69,4.21)	2.63 (1.69,4.25)	2.70 (1.69,3.70)	2.74 (1.69,4.06)

Baseline and latest levels of biomarkers in cases and controls

	AIDS events			non-AIDS events			Deaths		
	Controls	Cases	*P*	Controls	Cases	*P*	Controls	Cases	*P*
N. of patients	*50*	*50*		*63*	*63*		*42*	*42*	
				Median (IQR)					
25OHD (ng/ml)									
baseline	17 (12,26)	13 (9,24)	0.07	15 (10,21)	16 (9,26)	0.22	19 (12,27)	17 (10,24)	0.28
latest	17 (11,22)	13 (10,23)	0.65	18 (11,24)	21 (11,28)	0.29	19 (12,28)	12 (8,17)	0.03
hsIL-6 (pg/ml)									
baseline	1.7 (1.0, 2.8)	2.0 (1.4,4.2)	0.10	1.9 (1.03.6)	2.2 (1.4,3.4)	0.62	2.0 (1.1,2.8)	3.2 (2.6,4.7)	0.01
latest	1.6 (0.9,3,5)	3.0 (1.5,6.4)	0.01	1.6 (1.0,3.2)	2.4 (1.5,4.2)	0.02	2.1 (1.5,3.9)	6.7 (3.0,14.7)	<0.01
hsCRP (mg/ml)									
baseline	1.1 (0.6,3.5)	2.5 (1.1,4.7)	0.09	2.8 (1.0,4.9)	2.0 (1.1,4.6)	0.56	1.6 (0.8,4.8)	3.1 (2.0,8.7)	0.01
latest	1.7 (0.4,4.6)	2.9 (0.7,12.9)	<0.01	2.0 (0.7,3.9)	2.5 (1.2,5.7)	0.47	2.1 (0.9,4.3)	8.7 (3.3,30.0)	<0.01
sCD14 (ng/ml)									
baseline	1226 (922,1586)	1241 (1077,1526)	0.59	1329 (1056,1531)	1296 (971,1507)	0.96	1158 (882,1674)	1301 (1080,1517)	0.80
latest	1695 (1433,2324)	2170 (1860, 2617)	<0.01	2128 (1647,2505)	2132 (1634,2471)	0.38	1980 (1477,2373)	2507 (1954,2876)	<0.01

Baseline and latest levels of biomarkers in cases and controls

	AIDS events			non-AIDS events			Deaths		
	Controls	Cases	*P*	Controls	Cases	*P*	Controls	Cases	*P*
N. of patients	*50*	*50*		*63*	*63*		*42*	*42*	
	Median (IQR)								
25OHD (ng/ml)									
baseline	17 (12,26)	13 (9,24)	0.07	15 (10,21)	16 (9,26)	0.22	19 (12,27)	17 (10,24)	0.28
latest	17 (11,22)	13 (10,23)	0.65	18 (11,24)	21 (11,28)	0.29	19 (12,28)	12 (8,17)	**0.03**
hsIL-6 (pg/ml)									
baseline	1.7 (1.0, 2.8)	2.0 (1.4,4.2)	0.10	1.9 (1.03.6)	2.2 (1.4,3.4)	0.62	2.0 (1.1,2.8)	3.2 (2.6,4.7)	0.01
latest	1.6 (0.9,3,5)	3.0 (1.5,6.4)	0.01	1.6 (1.0,3.2)	2.4 (1.5,4.2)	0.02	2.1 (1.5,3.9)	6.7 (3.0,14.7)	<0.01
hsCRP (mg/ml)									
baseline	1.1 (0.6,3.5)	2.5 (1.1,4.7)	0.09	2.8 (1.0,4.9)	2.0 (1.1,4.6)	0.56	1.6 (0.8,4.8)	3.1 (2.0,8.7)	0.01
latest	1.7 (0.4,4.6)	2.9 (0.7,12.9)	<0.01	2.0 (0.7,3.9)	2.5 (1.2,5.7)	0.47	2.1 (0.9,4.3)	8.7 (3.3,30.0)	<0.01
sCD14 (ng/ml)									
baseline	1226 (922,1586)	1241 (1077,1526)	0.59	1329 (1056,1531)	1296 (971,1507)	0.96	1158 (882,1674)	1301 (1080,1517)	0.80
latest	1695 (1433,2324)	2170 (1860, 2617)	**<0.01**	2128 (1647,2505)	2132 (1634,2471)	0.38	1980 (1477,2373)	2507 (1954,2876)	**<0.01**

Baseline and latest levels of biomarkers in cases and controls

	AIDS events			non-AIDS events			Deaths		
	Controls	Cases	*P*	Controls	Cases	*P*	Controls	Cases	*P*
N. of patients	*50*	*50*		*63*	*63*		*42*	*42*	
	Median (IQR)								
25OHD (ng/ml)									
baseline	17 (12,26)	13 (9,24)	0.07	15 (10,21)	16 (9,26)	0.22	19 (12,27)	17 (10,24)	0.28
latest	17 (11,22)	13 (10,23)	0.65	18 (11,24)	21 (11,28)	0.29	19 (12,28)	12 (8,17)	**0.03**
hsIL-6 (pg/ml)									
baseline	1.7 (1.0, 2.8)	2.0 (1.4,4.2)	0.10	1.9 (1.03.6)	2.2 (1.4,3.4)	0.62	2.0 (1.1,2.8)	3.2 (2.6,4.7)	**0.01**
latest	**1.6** (0.9,3,5)	**3.0** (1.5,6.4)	**0.01**	**1.6** (1.0,3.2)	**2.4** (1.5,4.2)	**0.02**	**2.1** (1.5,3.9)	**6.7** (3.0,14.7)	**<0.01**
hsCRP (mg/ml)									
baseline	1.1 (0.6,3.5)	2.5 (1.1,4.7)	0.09	2.8 (1.0,4.9)	2.0 (1.1,4.6)	0.56	1.6 (0.8,4.8)	3.1 (2.0,8.7)	**0.01**
latest	1.7 (0.4,4.6)	2.9 (0.7,12.9)	**<0.01**	2.0 (0.7,3.9)	2.5 (1.2,5.7)	0.47	2.1 (0.9,4.3)	8.7 (3.3,30.**0**)	**<0.01**
sCD14 (ng/ml)									
baseline	1226 (922,1586)	1241 (1077,1526)	0.59	1329 (1056,1531)	1296 (971,1507)	0.96	1158 (882,1674)	1301 (1080,1517)	0.80
latest	1695 (1433,2324)	2170 (1860, 2617)	**<0.01**	2128 (1647,2505)	2132 (1634,2471)	0.38	1980 (1477,2373)	2507 (1954,2876)	**<0.01**

Baseline and latest levels of biomarkers in cases and controls

	AIDS events			non-AIDS events			Deaths		
	Controls	Cases	*P*	Controls	Cases	*P*	Controls	Cases	*P*
N. of patients	*50*	*50*		*63*	*63*		*42*	*42*	
				Median (IQR)					
25OHD (ng/ml)									
baseline	17 (12,26)	13 (9,24)	0.07	15 (10,21)	16 (9,26)	0.22	19 (12,27)	17 (10,24)	0.28
latest	17 (11,22)	13 (10,23)	0.65	18 (11,24)	21 (11,28)	0.29	19 (12,28)	12 (8,17)	**0.03**
hsIL-6 (pg/ml)									
baseline	1.7 (1.0, 2.8)	2.0 (1.4,4.2)	0.10	1.9 (1.03.6)	2.2 (1.4,3.4)	0.62	**2.0** (1.1,2.8)	**3.2** (2.6,4.7)	**0.01**
latest	**1.6** (0.9,3,5)	**3.0** (1.5,6.4)	**0.01**	**1.6** (1.0,3.2)	**2.4** (1.5,4.2)	**0.02**	**2.1** (1.5,3.9)	**6.7** (3.0,14.7)	**<0.01**
hsCRP (mg/ml)									
baseline	1.1 (0.6,3.5)	2.5 (1.1,4.7)	0.09	2.8 (1.0,4.9)	2.0 (1.1,4.6)	0.56	1.6 (0.8,4.8)	3.1 (2.0,8.7)	**0.01**
latest	1.7 (0.4,4.6)	2.9 (0.7,12.9)	**<0.01**	2.0 (0.7,3.9)	2.5 (1.2,5.7)	0.47	2.1 (0.9,4.3)	8.7 (3.3,30.**0**)	**<0.01**
sCD14 (ng/ml)									
baseline	1226 (922,1586)	1241 (1077,1526)	0.59	1329 (1056,1531)	1296 (971,1507)	0.96	1158 (882,1674)	1301 (1080,1517)	0.80
latest	1695 (1433,2324)	2170 (1860, 2617)	**<0.01**	2128 (1647,2505)	2132 (1634,2471)	0.38	1980 (1477,2373)	2507 (1954,2876)	**<0.01**

Baseline and latest levels of biomarkers in cases and controls

	AIDS events			non-AIDS events			Deaths		
	Controls	Cases	*P*	Controls	Cases	*P*	Controls	Cases	*P*
N. of patients	*50*	*50*		*63*	*63*		*42*	*42*	
	Median (IQR)								
25OHD (ng/ml)									
baseline	17 (12,26)	13 (9,24)	0.07	15 (10,21)	16 (9,26)	0.22	19 (12,27)	17 (10,24)	0.28
latest	17 (11,22)	13 (10,23)	0.65	18 (11,24)	21 (11,28)	0.29	19 (12,28)	12 (8,17)	**0.03**
hsIL-6 (pg/ml)									
baseline	1.7 (1.0, 2.8)	2.0 (1.4,4.2)	0.10	1.9 (1.03.6)	2.2 (1.4,3.4)	0.62	2.0 (1.1,2.8)	3.2 (2.6,4.7)	**0.01**
latest	**1.6** (0.9,3,5)	**3.0** (1.5,6.4)	**0.01**	**1.6** (1.0,3.2)	**2.4** (1.5,4.2)	**0.02**	**2.1** (1.5,3.9)	**6.7** (3.0,14.7)	**<0.01**
hsCRP (mg/ml)									
baseline	1.1 (0.6,3.5)	2.5 (1.1,4.7)	0.09	2.8 (1.0,4.9)	2.0 (1.1,4.6)	0.56	1.6 (0.8,4.8)	3.1 (2.0,8.7)	**0.01**
latest	**1.7** (0.4,4.6)	**2.9** (0.7,12.9)	**<0.01**	2.0 (0.7,3.9)	2.5 (1.2,5.7)	0.47	**2.1** (0.9,4.3)	**8.7** (3.3,30.**0**)	**<0.01**
sCD14 (ng/ml)									
baseline	1226 (922,1586)	1241 (1077,1526)	0.59	1329 (1056,1531)	1296 (971,1507)	0.96	1158 (882,1674)	1301 (1080,1517)	0.80
latest	1695 (1433,2324)	2170 (1860, 2617)	**<0.01**	2128 (1647,2505)	2132 (1634,2471)	0.38	1980 (1477,2373)	2507 (1954,2876)	**<0.01**

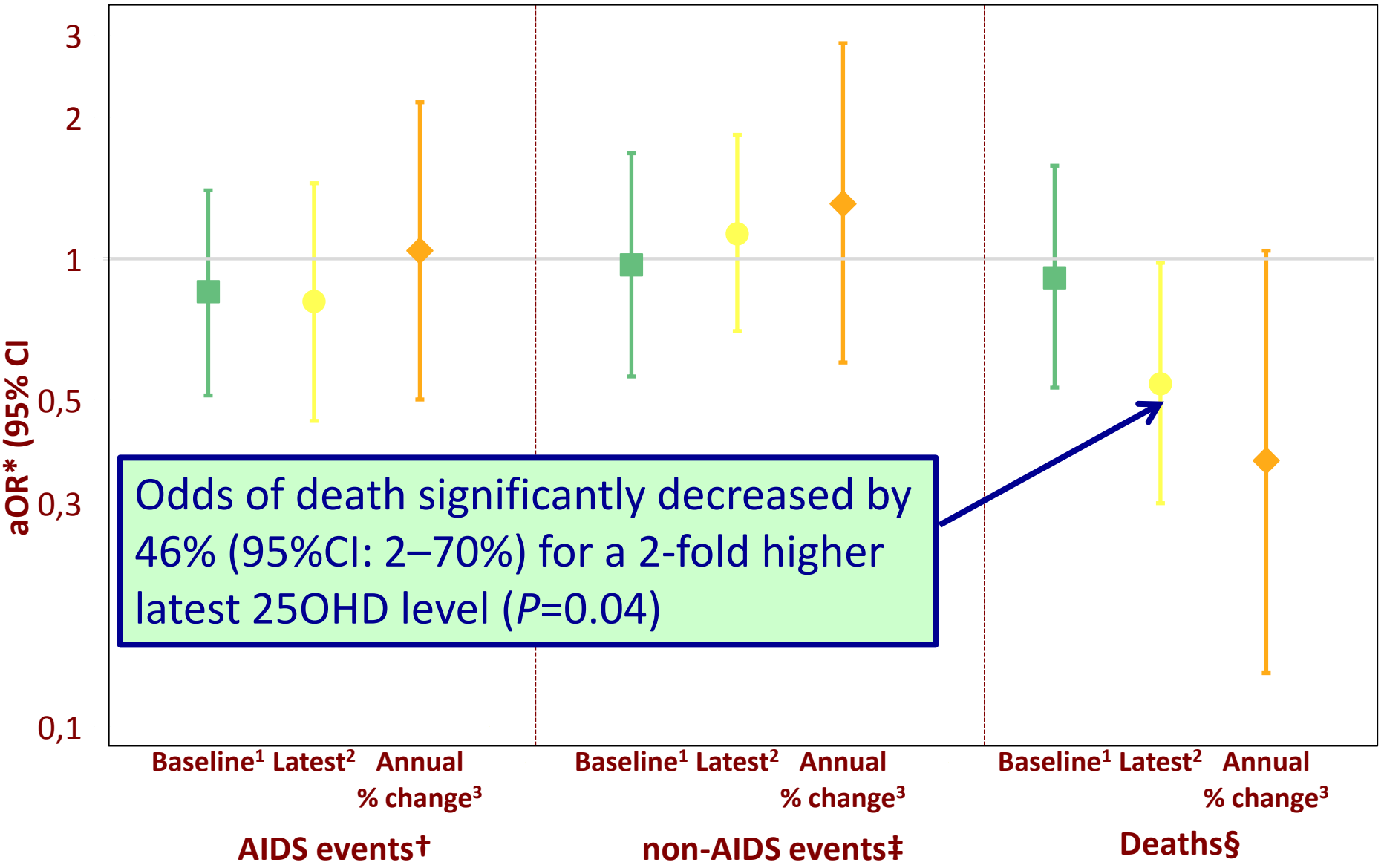
Baseline and latest levels of biomarkers in cases and controls

	AIDS events			non-AIDS events			Deaths		
	Controls	Cases	*P*	Controls	Cases	*P*	Controls	Cases	*P*
N. of patients	*50*	*50*		*63*	*63*		*42*	*42*	
	Median (IQR)								
25OHD (ng/ml)									
baseline	17 (12,26)	13 (9,24)	0.07	15 (10,21)	16 (9,26)	0.22	19 (12,27)	17 (10,24)	0.28
latest	17 (11,22)	13 (10,23)	0.65	18 (11,24)	21 (11,28)	0.29	19 (12,28)	12 (8,17)	**0.03**
hsIL-6 (pg/ml)									
baseline	1.7 (1.0, 2.8)	2.0 (1.4,4.2)	0.10	1.9 (1.03.6)	2.2 (1.4,3.4)	0.62	2.0 (1.1,2.8)	3.2 (2.6,4.7)	**0.01**
latest	**1.6** (0.9,3,5)	**3.0** (1.5,6.4)	**0.01**	**1.6** (1.0,3.2)	**2.4** (1.5,4.2)	**0.02**	**2.1** (1.5,3.9)	**6.7** (3.0,14.7)	**<0.01**
hsCRP (mg/ml)									
baseline	1.1 (0.6,3.5)	2.5 (1.1,4.7)	0.09	2.8 (1.0,4.9)	2.0 (1.1,4.6)	0.56	**1.6** (0.8,4.8)	**3.1** (2.0,8.7)	**0.01**
latest	1.7 (0.4,4.6)	2.9 (0.7,12.9)	**<0.01**	2.0 (0.7,3.9)	2.5 (1.2,5.7)	0.47	2.1 (0.9,4.3)	8.7 (3.3,30.**0**)	**<0.01**
sCD14 (ng/ml)									
baseline	1226 (922,1586)	1241 (1077,1526)	0.59	1329 (1056,1531)	1296 (971,1507)	0.96	1158 (882,1674)	1301 (1080,1517)	0.80
latest	1695 (1433,2324)	2170 (1860, 2617)	**<0.01**	2128 (1647,2505)	2132 (1634,2471)	0.38	1980 (1477,2373)	2507 (1954,2876)	**<0.01**

Baseline and latest levels of biomarkers in cases and controls

	AIDS events			non-AIDS events			Deaths		
	Controls	Cases	*P*	Controls	Cases	*P*	Controls	Cases	*P*
N. of patients	*50*	*50*		*63*	*63*		*42*	*42*	
	Median (IQR)								
25OHD (ng/ml)									
baseline	17 (12,26)	13 (9,24)	0.07	15 (10,21)	16 (9,26)	0.22	19 (12,27)	17 (10,24)	0.28
latest	17 (11,22)	13 (10,23)	0.65	18 (11,24)	21 (11,28)	0.29	19 (12,28)	12 (8,17)	**0.03**
hsIL-6 (pg/ml)									
baseline	1.7 (1.0, 2.8)	2.0 (1.4,4.2)	0.10	1.9 (1.03.6)	2.2 (1.4,3.4)	0.62	2.0 (1.1,2.8)	3.2 (2.6,4.7)	**0.01**
latest	**1.6** (0.9,3,5)	**3.0** (1.5,6.4)	**0.01**	**1.6** (1.0,3.2)	**2.4** (1.5,4.2)	**0.02**	**2.1** (1.5,3.9)	**6.7** (3.0,14.7)	**<0.01**
hsCRP (mg/ml)									
baseline	1.1 (0.6,3.5)	2.5 (1.1,4.7)	0.09	2.8 (1.0,4.9)	2.0 (1.1,4.6)	0.56	1.6 (0.8,4.8)	3.1 (2.0,8.7)	**0.01**
latest	1.7 (0.4,4.6)	2.9 (0.7,12.9)	**<0.01**	2.0 (0.7,3.9)	2.5 (1.2,5.7)	0.47	2.1 (0.9,4.3)	8.7 (3.3,30.**0**)	**<0.01**
sCD14 (ng/ml)									
baseline	1226 (922,1586)	1241 (1077,1526)	0.59	1329 (1056,1531)	1296 (971,1507)	0.96	1158 (882,1674)	1301 (1080,1517)	0.80
latest	**1695** (1433,2324)	**2170** (1860, 2617)	**<0.01**	2128 (1647,2505)	2132 (1634,2471)	0.38	**1980** (1477,2373)	**2507** (1954,2876)	**<0.01**

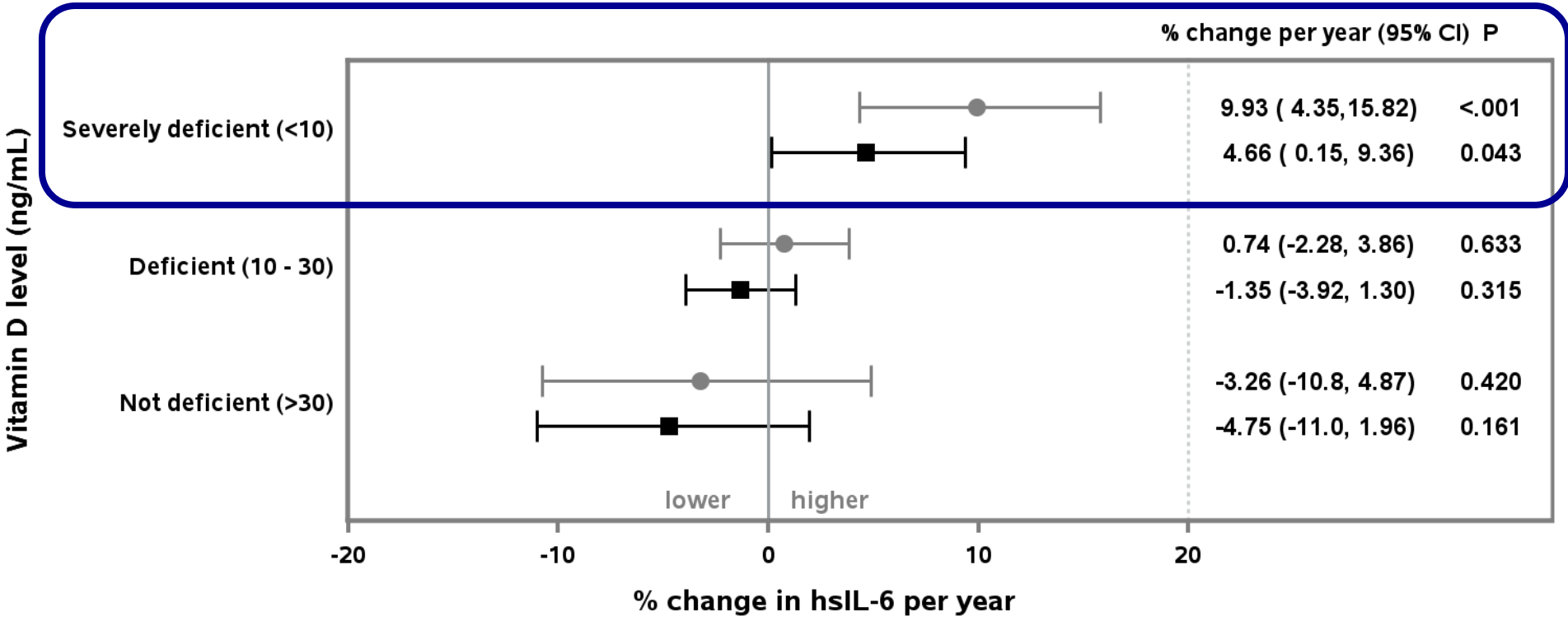
Adjusted odds ratios (95% CI) of AIDS, non- AIDS and death events for a two-fold higher baseline, latest and annual % change from baseline 25OHD level



*Models adjusted for baseline season, prior AIDS and ethnicity

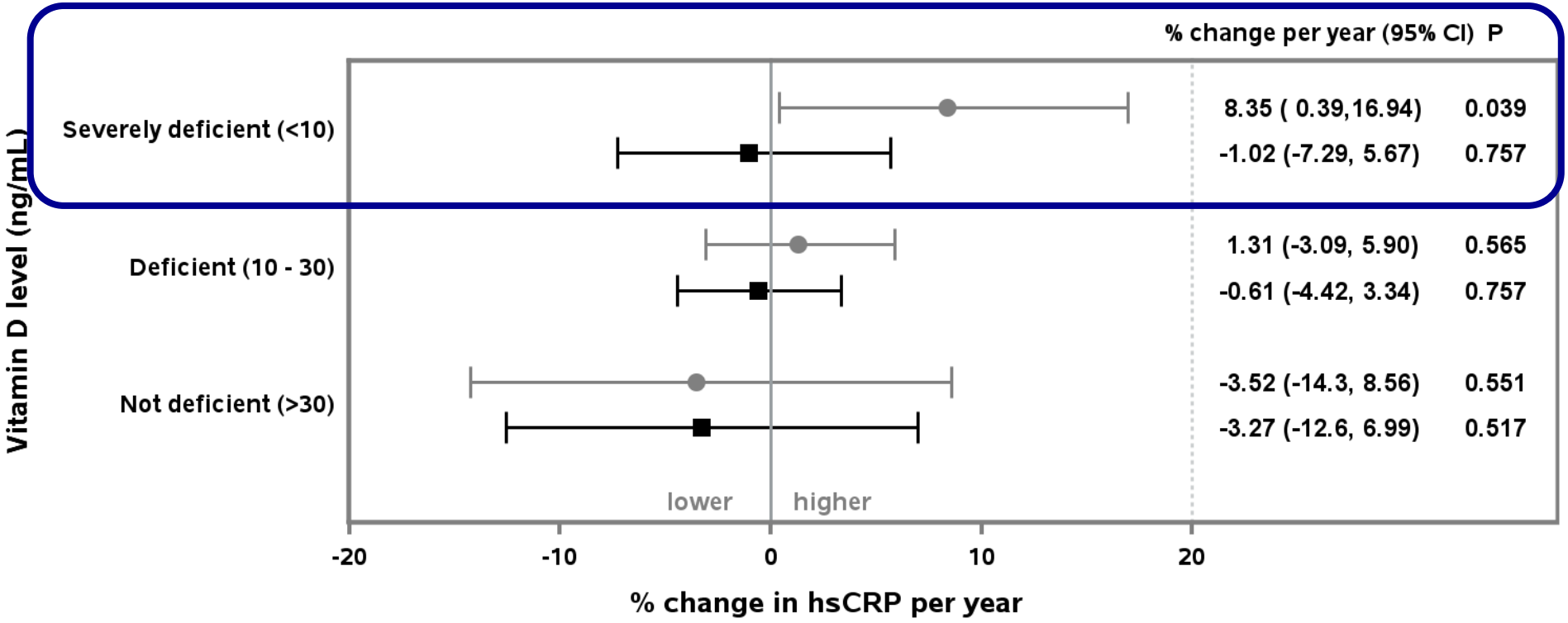
Matched pairs: †N1 =50, N2 = 44, N3=48; ‡N1 =63, N2 = 61, N3=62; §N1 =41, N2 = 38, N3=41

Percentage Change in hsIL-6, hsCRP, sCD14 and CD4 per year according to current 25OHD deficiency category



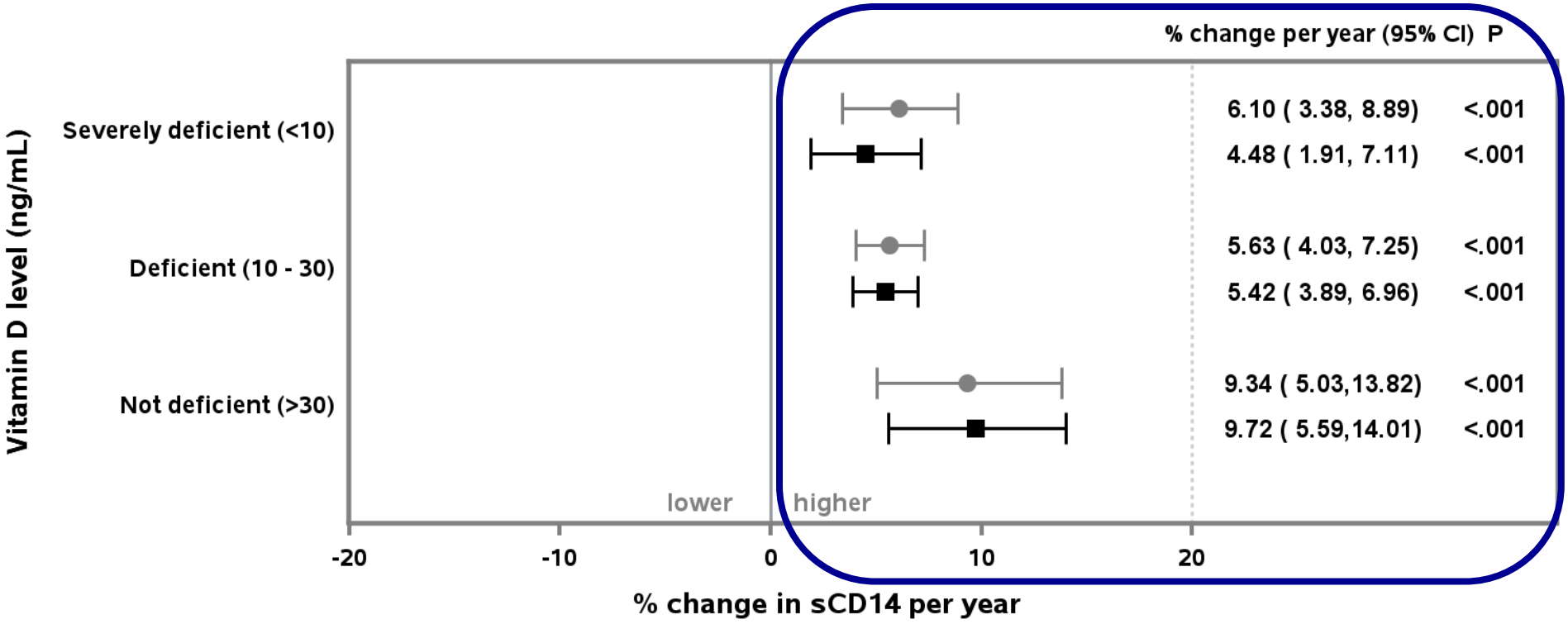
- Mixed model adjusted for season, gender, age, region, ethnicity, baseline CD4,HIV RNA & treatment, HCV & HBV, prior AIDS
- Mixed model further adjusted for current $\log_2$ hsCRP, sCD14 and CD4

Percentage Change in hsIL-6, hsCRP, sCD14 and CD4 per year according to current 25OHD deficiency category



- Mixed model adjusted for season, gender, age, region, ethnicity, baseline CD4,HIV RNA & treatment, HCV & HBV, prior AIDS
- Mixed model further adjusted for current $\log_2$ hsIL-6, sCD14 and CD4

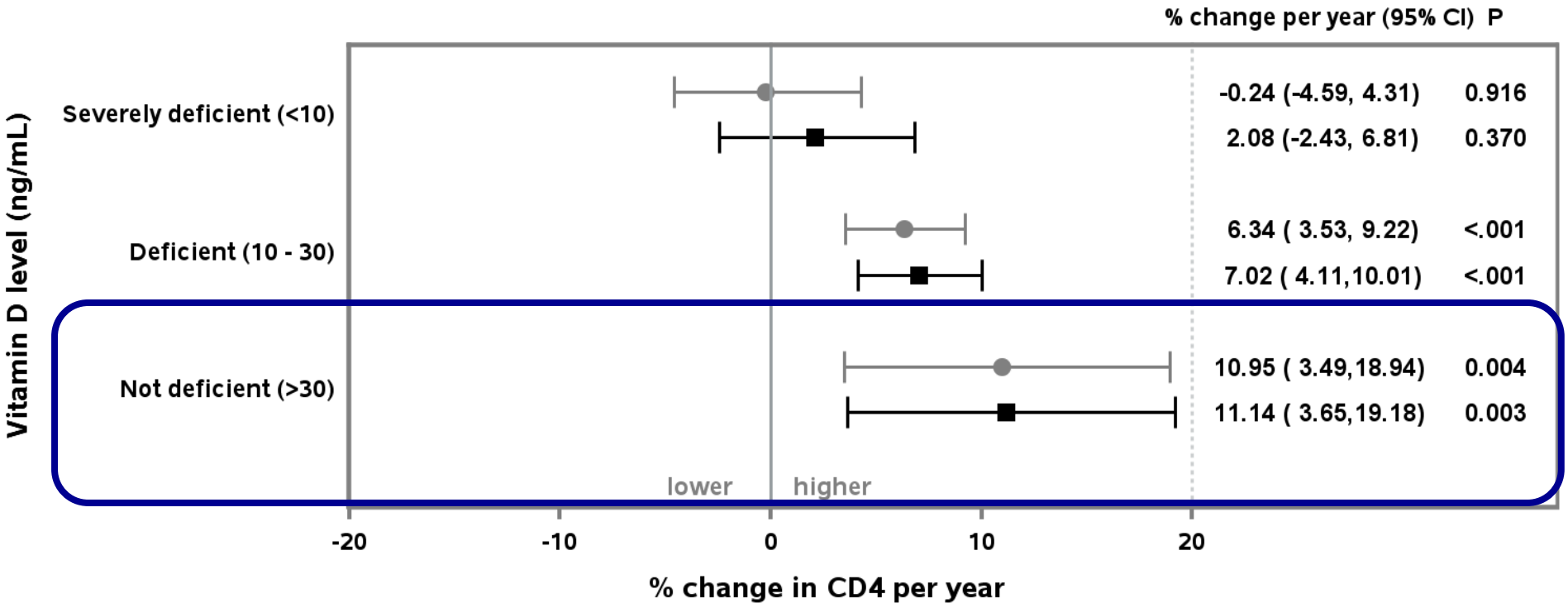
Percentage Change in hsIL-6, hsCRP, sCD14 and CD4 per year according to current 25OHD deficiency category



Mixed model adjusted for season, gender, age, region, ethnicity, baseline CD4,HIV RNA & treatment, HCV & HBV, prior AIDS

Mixed model further adjusted for current $\log_2$ hsIL-6, hsCRP, and CD4

Percentage Change in hsIL-6, hsCRP, sCD14 and CD4 per year according to current 25OHD deficiency category



- Mixed model adjusted for season, gender, age, region, ethnicity, baseline CD4,HIV RNA & treatment, HCV & HBV, prior AIDS
- Mixed model further adjusted for current $\log_2$ hsIL-6, hsCRP, and sCD14

Conclusion and Discussion (1)

- Current 25OHD level (3 months to event) was associated with death, but not with AIDS or non-AIDS events.
- Earlier 25OHD levels failed to predict death, suggesting the association diminishes with time.
- Current 25OHD<10 ng/ml was significantly associated with increasing hsIL-6 over time.
- CD4 count increased only when current 25OHD was >30 ng/ml

Conclusion and Discussion (2)

- Severe vitamin D deficiency may represent a modifiable risk factor for increased inflammation and immune activation.
- Reverse causality cannot be excluded.
- Studies examining the effects of vitamin D supplementation on inflammation and immune activation markers are warranted.

Acknowledgements

The EuroSIDA Study Group **Argentina:** (M Losso), M Kundro, Hospital JM Ramos Mejia, Buenos Aires. **Austria:** (N Vetter), Pulmologisches Zentrum der Stadt Wien, Vienna; R Zangerle, Medical University Innsbruck, Innsbruck. **Belarus:** (I Karpov), A Vassilenko, Belarus State Medical University, Minsk, VM Mitsura, Gomel State Medical University, Gomel; O Suetnov, Regional AIDS Centre, Svetlogorsk. **Belgium:** (N Clumeck), S De Wit, M Delforge, Saint-Pierre Hospital, Brussels; E Florence, Institute of Tropical Medicine, Antwerp; L Vandekerckhove, University Ziekenhuis Gent, Gent. **Bosnia-Herzegovina:** (V Hadziosmanovic), Klinicki Centar Univerziteta Sarajevo, Sarajevo. **Bulgaria:** (K Kostov), Infectious Diseases Hospital, Sofia.**Croatia:** (J Begovac), University Hospital of Infectious Diseases, Zagreb. **Czech Republic:** (L Machala), D Jilich, Faculty Hospital Bulovka, Prague; D Sedlacek, Charles University Hospital, Plzen. **Denmark:** (J Nielsen), G Kronborg,T Benfield, M Larsen, Hvidovre Hospital, Copenhagen; J Gerstoft, T Katzenstein, A-B E Hansen, P Skinhøj, Rigshospitalet, Copenhagen; C Pedersen, Odense University Hospital, Odense; L Ostergaard, Skejby Hospital, Aarhus, U B Dragsted, Roskilde Hospital, Roskilde; L N Nielsen, Hillerod Hospital, Hillerod. **Estonia:** (K Zilmer), West-Tallinn Central Hospital, Tallinn; Jelena Smidt, Nakkusosakond Siseklinik, Kohtla-Järve. **Finland:** (M Ristola), Helsinki University Central Hospital, Helsinki. **France:** (C Katlama), Hôpital de la Pitié-Salpétière, Paris; J-P Viard, Hôtel-Dieu, Paris; P-M Girard, Hospital Saint-Antoine, Paris; P Vanhems, University Claude Bernard, Lyon; C Pradier, Hôpital de l'Archet, Nice; F Dabis, D Neau, Unité INSERM, Bordeaux, C Duvivier, Hôpital Necker-Enfants Malades, Paris. **Germany:** (J Rockstroh), Universitäts Klinik Bonn; R Schmidt, Medizinische Hochschule Hannover; J van Lunzen, O Degen, University Medical Center Hamburg-Eppendorf, Infectious Diseases Unit, Hamburg; HJ tellbrink, IPM Study Center, Hamburg; M Bickel, JW Goethe University Hospital, Frankfurt; J Bogner, Medizinische Poliklinik, Munich; G. Fätkenheuer, Universität Köln, Cologne. **Greece:** (J Kosmidis), P Gargalianos, G Xylomenos, J Perdios, Athens General Hospital; H Sambatakou, Ippokration Genereal Hospital, Athens. **Hungary:** (D Banhegyi), Szent Lásló Hospital, Budapest. **Iceland:** (M Gottfredsson), Landspitali University Hospital, Reykjavik. **Ireland:** (F Mulcahy), St. James's Hospital, Dublin. **Israel:** (I Yust), D Turner, M Burke, Ichilov Hospital, Tel Aviv; S Pollack, G Hassoun, Rambam Medical Center, Haifa; S Maayan, Hadassah University Hospital, Jerusalem. **Italy:** (A D'Arminio Monforte), Istituto Di Clinica Malattie Infettive e Tropicale, Milan; R Esposito, I Mazeu, C Mussini, Università Modena, Modena; C Arici, Ospedale Riuniti, Bergamo; R Pristera, Ospedale Generale Regionale, Bolzano; F Mazzotta, A Gabbuti, Ospedale S Maria Annunziata, Firenze; V Vullo, M Lichtner, University di Roma la Sapienza, Rome; A Chirianni, E Montesarchio, M Gargiulo, Presidio Ospedaliero AD Cotugno, Monaldi Hospital, Napoli; G Antonucci, A Testa, G D`Offizi, C Vlassi, M Zaccarelli, A Antorini, Istituto Nazionale Malattie Infettive Lazzaro Spallanzani, Rome; A Lazzarin, A Castagna, N Gianotti, Ospedale San Raffaele, Milan; M Galli, A Ridolfo, Osp. L. Sacco, Milan.**Latvia:** (B Rozentale), I Zeltina, Infectology Centre of Latvia, Riga. **Lithuania:** (S Chaplinskas), Lithuanian AIDS Centre, Vilnius. **Luxembourg:** (T Staub), R Hemmer, Centre Hospitalier, Luxembourg. **Netherlands:** P Reiss), Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam. **Norway:** (V Ormaasen), A Maeland, J Bruun, Ullevål Hospital, Oslo. **Poland:** (B Knysz) J Gasiorowski, Medical University, Wroclaw; A Horban, E Bakowska, Centrum Diagnostyki i Terapii AIDS, Warsaw; A Grzeszczuk, R Flisiak, Medical University, Bialystok; A Boron-Kaczmarska, M Pynka, M Parczewski, Medical Univesity, Szczecin; M Beniowski, E Mularska, Osrodek Diagnostyki i Terapii AIDS, Chorzow; H Trocha, Medical University, Gdansk; E Jablonowska, E Malolepsza, K Wojcik, Wojewodzki Szpital Specjalistyczny, Lodz. **Portugal:** (F Antunes), M Doroana, L Caldeira, Hospital Santa Maria, Lisbon; K Mansinho, Hospital de Egas Moniz, Lisbon; F Maltez, Hospital Curry Cabral, Lisbon. **Romania:** (D Duiculescu), Spitalul de Boli Infectioase si Tropicale: Dr. Victor Babes, Bucarest. **Russia:** (A Rakhmanova), Medical Academy Botkin Hospital, St Petersburg; A Rakhmanova, St Petersburg AIDS Centre, St Peterburg; S Buzunova, Novgorod Centre for AIDS, Novgorod, I Khromova, Centre for HIV/AIDS & and Infectious Diseases, Kaliningrad; E Kuzovatova, Nizhny Novgorod Scientific and Research Institute, Nizhny Novogrod. **Serbia:** (D Jevtovic), The Institute for Infectious and Tropical Diseases, Belgrade. **Slovakia:** (M Mokráš), D Staneková, Dérer Hospital, Bratislava.**Slovenia:** (J Tomazic), University Clinical Centre Ljubljana, Ljubljana. **Spain:** (J González-Lahoz), V Soriano, P Labarga, Hospital Carlos III, Madrid; S Moreno, J. M. Rodriguez, Hospital Ramon y Cajal, Madrid; B Clotet, A Jou, R Paredes, C Tural, J Puig, I Bravo, Hospital Germans Trias i Pujol, Badalona; JM Gatell, JM Miró, Hospital Clinic i Provincial, Barcelona; P Domingo, M Gutierrez, G Mateo, MA Sambeat, Hospital Sant Pau, Barcelona; J Medrano, Hospital Universitario de Alava, Vitoria-Gasteiz. **Sweden:** (A Blaxhult), Venhaelsan-Sodersjukhuset, Stockholm; L Flamholc, Malmö University Hospital, Malmö, A Thalme, A Sonnerborg, Karolinska University Hospital, Stockholm. **Switzerland:** (B Ledergerber), R Weber, University Hospital, Zürich; P Francioli, M Cavassini, Centre Hospitalier Universitaire Vaudois, Lausanne; B Hirschel, E Boffi, Hospital Cantonal Universitaire de Geneve, Geneve; H Furrer, Inselspital Bern, Bern; M Battegay, L Elzi, University Hospital Basel; P Vernazza, Kantonsspital, St. Gallen. **Ukraine:** (E Kravchenko), N Chentsova, Kiev Centre for AIDS, Kiev; V Frolov, G Kutsyna, Luhansk State Medical University; Luhansk; S Servitskiy, Odessa Region AIDS Center, Odessa; A Kuznetsova, Kharkov State Medical University, Kharkov; G Kyselyova, Crimean Republican AIDS centre, Simferopol. **United Kingdom:** (B Gazzard), St. Stephen's Clinic, Chelsea and Westminster Hospital, London; AM Johnson, D Mercey, Royal Free and University College London Medical School, London (University College Campus); A Phillips, MA Johnson, A Mocroft, Royal Free and University College Medical School, London (Royal Free Campus); C Orkin, Royal London Hospital, London; J Weber, G Scullard, Imperial College School of Medicine at St. Mary's, London; M Fisher, Royal Sussex County Hospital, Brighton; C Leen, Western General Hospital, Edinburgh.

Steering Committee: : J Gatell, B Gazzard, A Horban, I Karpov, B Ledergerber, M Losso, A D'Arminio Monforte, C Pedersen, A Rakhmanova, M Ristola, J Rockstroh (Chair), S De Wit (Vice-Chair) **Additional voting members:** J Lundgren, A Phillips, P Reiss. **Coordinating Centre Staff:** O Kirk, A Mocroft, A Cozzi-Lepri, D Grint, A Schultze, L Shepherd, M Sabin, D Podlekareva, J Kjær, L Peters, J E Nielsen, J Tverland, A H Fischer

FUNDING : NEAT (25-OH vitamin D and biomarkers measurements).

Primary support for EuroSIDA is provided by the European Commission BIOMED 1(CT94-1637), BIOMED 2 (CT97-2713), the 5th Framework (QLK2-2000-00773), the 6th Framework (LSHP-CT-2006-018632), and the 7th Framework (FP7/2007-2013,EuroCoord n° 260694) programmes.

Current support also includes unrestricted grants by Bristol-Myers Squibb, Janssen R&D, Merck and Co. Inc., Pfizer Inc., GlaxoSmithKline LLC.

The participation of centres from Switzerland was supported by The Swiss National Science Foundation (Grant 108787).

Change in other markers and events

- Significant association between ACPY in hsCRP and death
  - aOR for a 1 unit increase : 1.33 (95%CI:1.03,1.72)
  - P=0.03 after adjustment (including on other markers)
- Doubling ACPY% of hsCRP associated with increased odds of death
  - 2.76 (95%CI:1.06,7.16) –fold increase
  - P=0.04 after adjustment
- No significant association in ACPY or ACPY% of any marker with AIDS- or non-AIDS-defining events