



14th Annual Mild Cognitive Impairment Symposium
*The Wien Center for Alzheimer's Disease
and Memory Disorders, Mount Sinai Medical Center
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**Markers of inflammation and immune activation,
small vessel disease, amyloid deposition, and
progression to dementia in non-demented
individuals**

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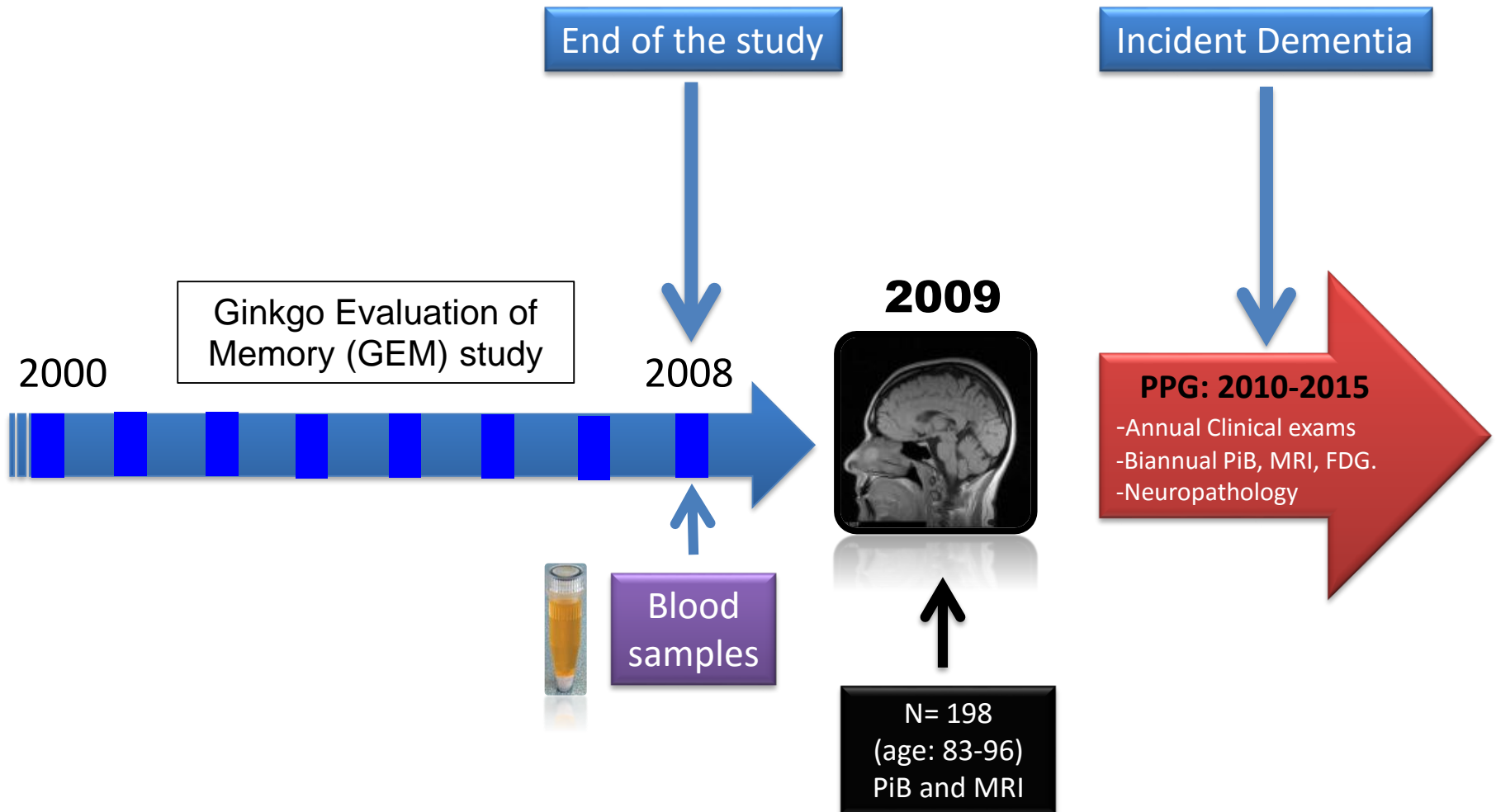
Introduction

The association between inflammatory markers and brain amyloid deposition measured *in vivo*.

The association between inflammatory markers and *MRI-identified* white matter lesions.

The association between inflammatory markers and incidence dementia.

Program Project Grant (PPG)



Study Measures

Plasma IL-6, sIL-2r, and sCD-14 were quantified by ELISA.

Plasma soluble sTNFr were quantified by Multiplex Millipore panel.

High-sensitivity CRP (hs-CRP) measured with laser nephelometry.

Brain amyloid by Positron Emission Tomography using Pittsburgh Compound B (PiB-PET), PIB+= SUVR ≥ 1.57

White matter lesions (WMLs) measured with MRI, WMLs >75 percentile.

PPG Inflammation markers

Biomarker	Definition
Interleukin 6 (IL-6)	T-cell derived cytokine
Soluble IL2 receptor (sIL2r)	Marker of T-cell activation.
Soluble TNFα receptor (sTNFαr) 1 and 2	Stimulates pro-inflammatory cytokines.
Soluble CD14 (sCD14)	Marker of monocyte activation
C-reactive protein (CRP)	Non-specific marker of inflammation

Correlations among markers of inflammation (all positive correlations)

	sIL2r	IL6	sTNF α 1	sTNF α 2	sCD-14	hsCRP
sIL2r		p= 0.30	p<0.001	p<0.001	p<0.001	p= 0.01
IL6	p=0.30		p=0.34	p= 0.26	p=0.003	p<0.001
sTNF α 1	p<0.001	p=0.34		p<0.001	p<0.001	p=0.47
sTNF α 2	p<0.001	p=0.26	p<0.001		p<0.001	p=0.53
sCD-14	p<0.001	p=0.003	p<0.001	p<0.001		p<0.001
hsCRP	p=0.01	p<0.001	p=0.47	p=0.53	p<0.001	

Characteristics of the participants

	Men (n=105)	Women (n=78)
Age, years	85.3 ± 2.87	85.8 ± 2.80
Education level, years	14.9 ± 2.6	14.6 ± 2.5
BMI, kg/m ²	26±3	26±5
Systolic BP, mmHg	125±17	130±19*
Hypertension	33 (31%)	30 (40.5%)
Diabetes mellitus	5 (5%)	5 (7%)
Heart disease**	20 (19%)	12 (16%)

*p=0.03

**History of congestive heart failure, angina, myocardial infarction, valve replacement, Stent, or CABG

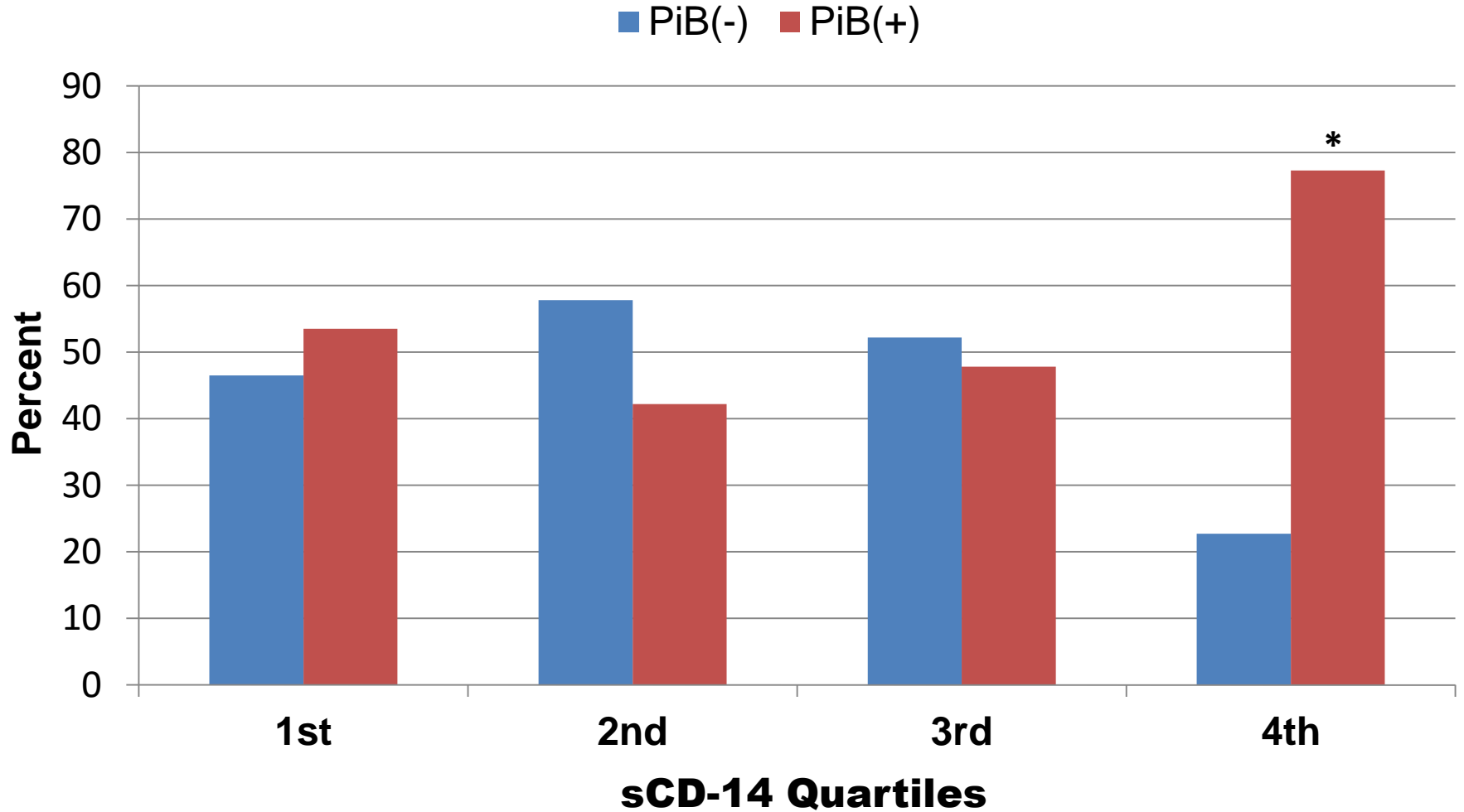
Inflammation markers

	Men (n=105)	Women (n=78)	p-value
hsCRP, mg/l	2.5±5.7	2.6±5.7	0.91
IL-6, µg/ml	2.6±1.7	3.2±3.5	0.13
sTNF-r1, pg/ml	1336.9±359	1230.4±432	0.07
sTNF-r2, pg/ml	6585.5±1734	6149.5±1951	0.33
sIL-2r, pg/ml	1160.2±435	1109.2±406	0.43
sCD-14, pg/ml	1341.7±293	1451.5±331	0.02

Inflammation markers and amyloid deposition

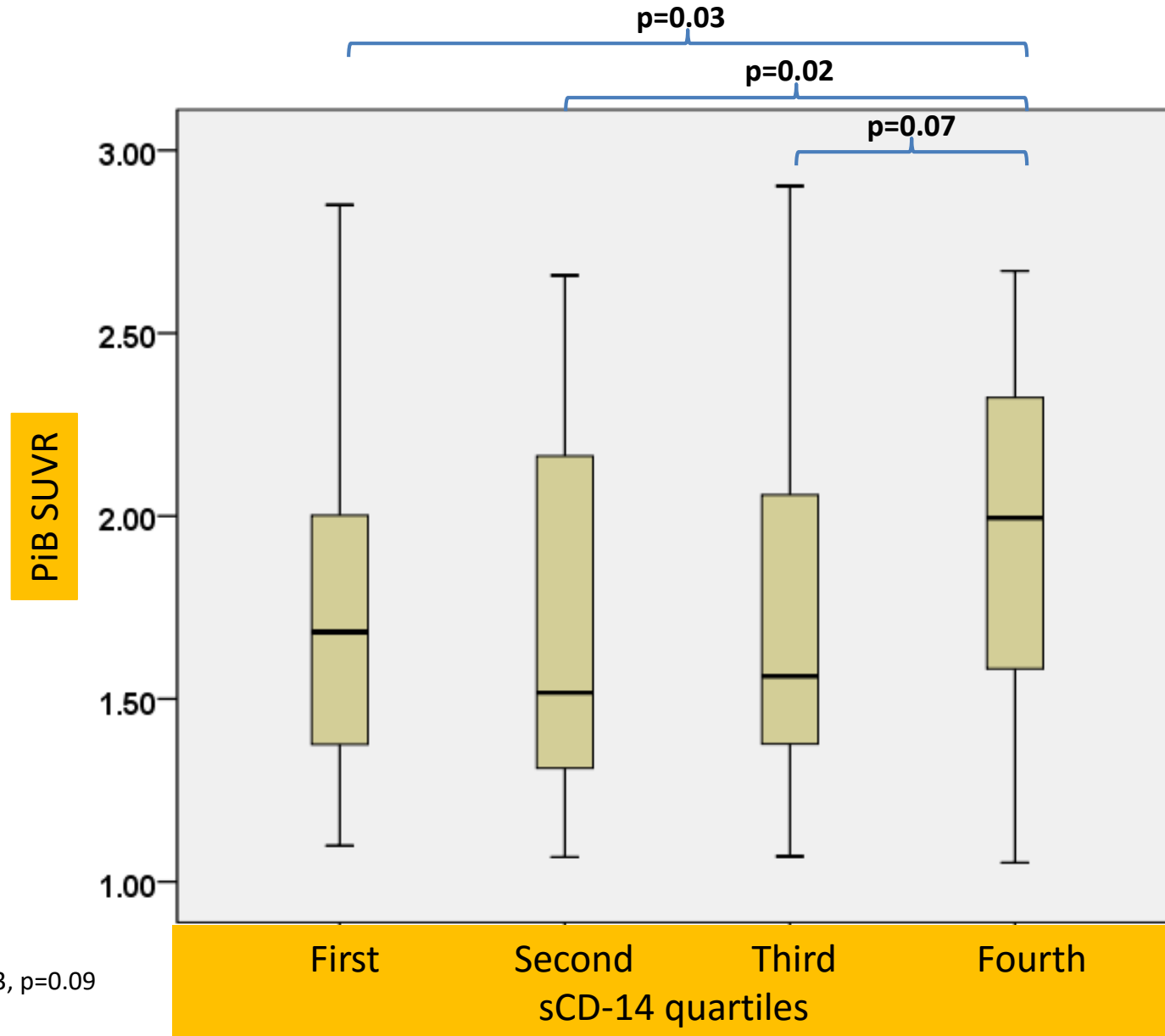
	PiB(-)	PiB(+)	p-value
hsCRP, mg/l	2.58±6.3	2.55±5.2	0.97
IL-6, µg/ml	2.8±3.1	2.9±2.0	0.95
sTNF-r1, pg/ml	1278.3±348	1305.5±427	0.21
sTNF-r2, pg/ml	6108.4±1672	6650.2±1930	0.06
sIL-2r, pg/ml	1160.2±435	1109.2±406	0.43
sCD-14, pg/ml	1342.8±311	1422.6±311	0.08

PiB positivity by sCD-14 quartiles



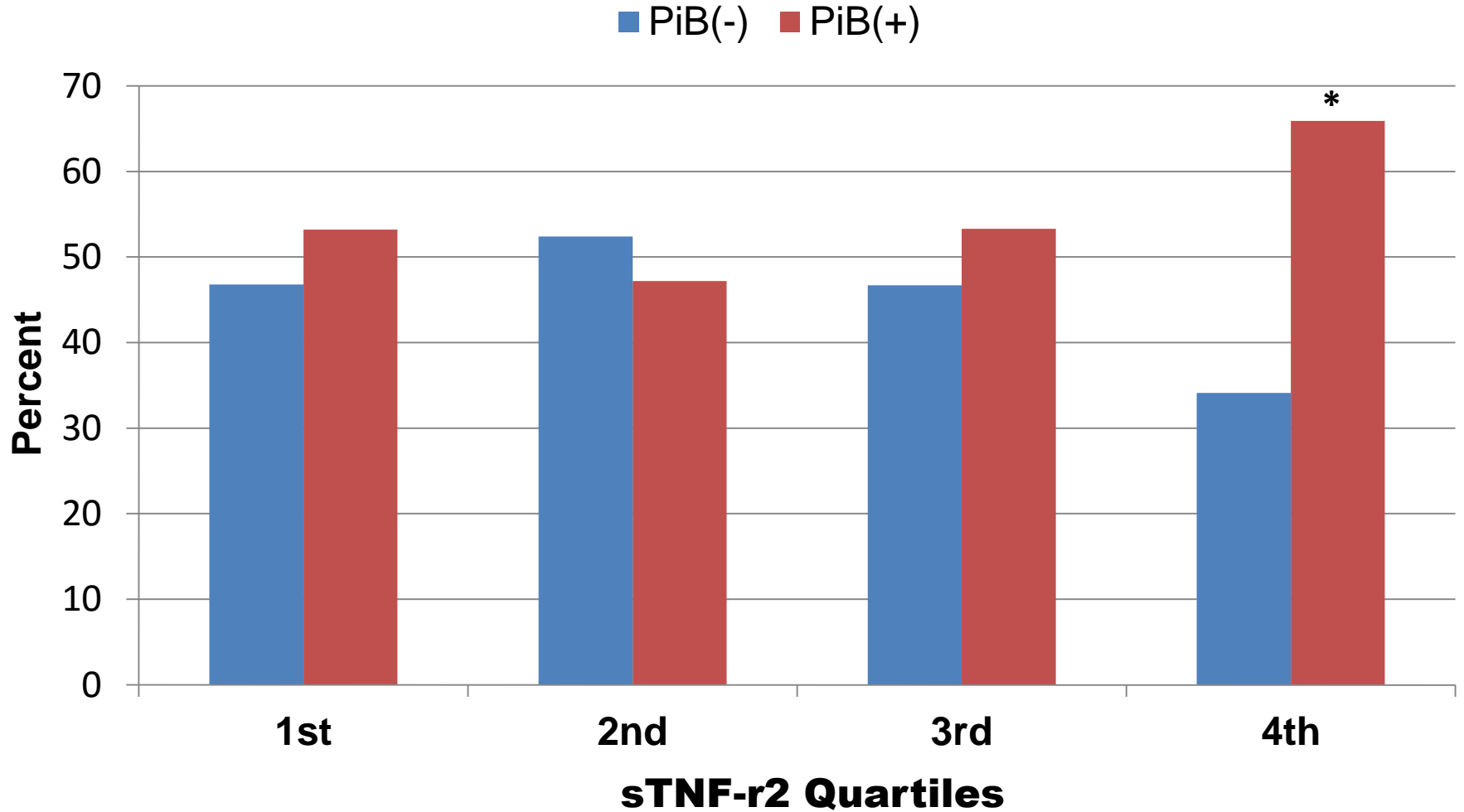
*p= 0.005

Amyloid deposition by sCD-14 quartiles



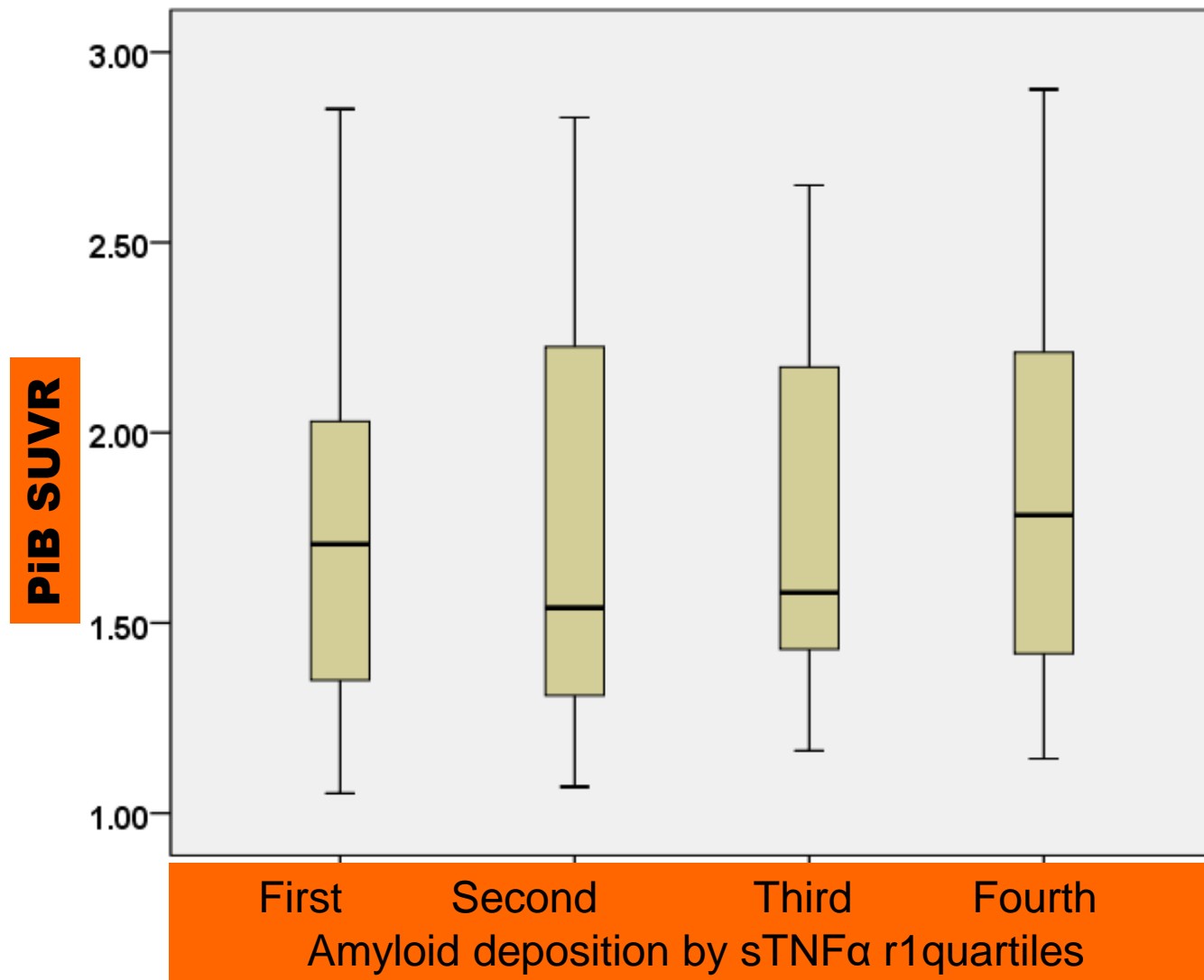
ANOVA: $F=2.13$, $p=0.09$

PiB positivity by sTNF-r2 quartiles



*p= 0.09

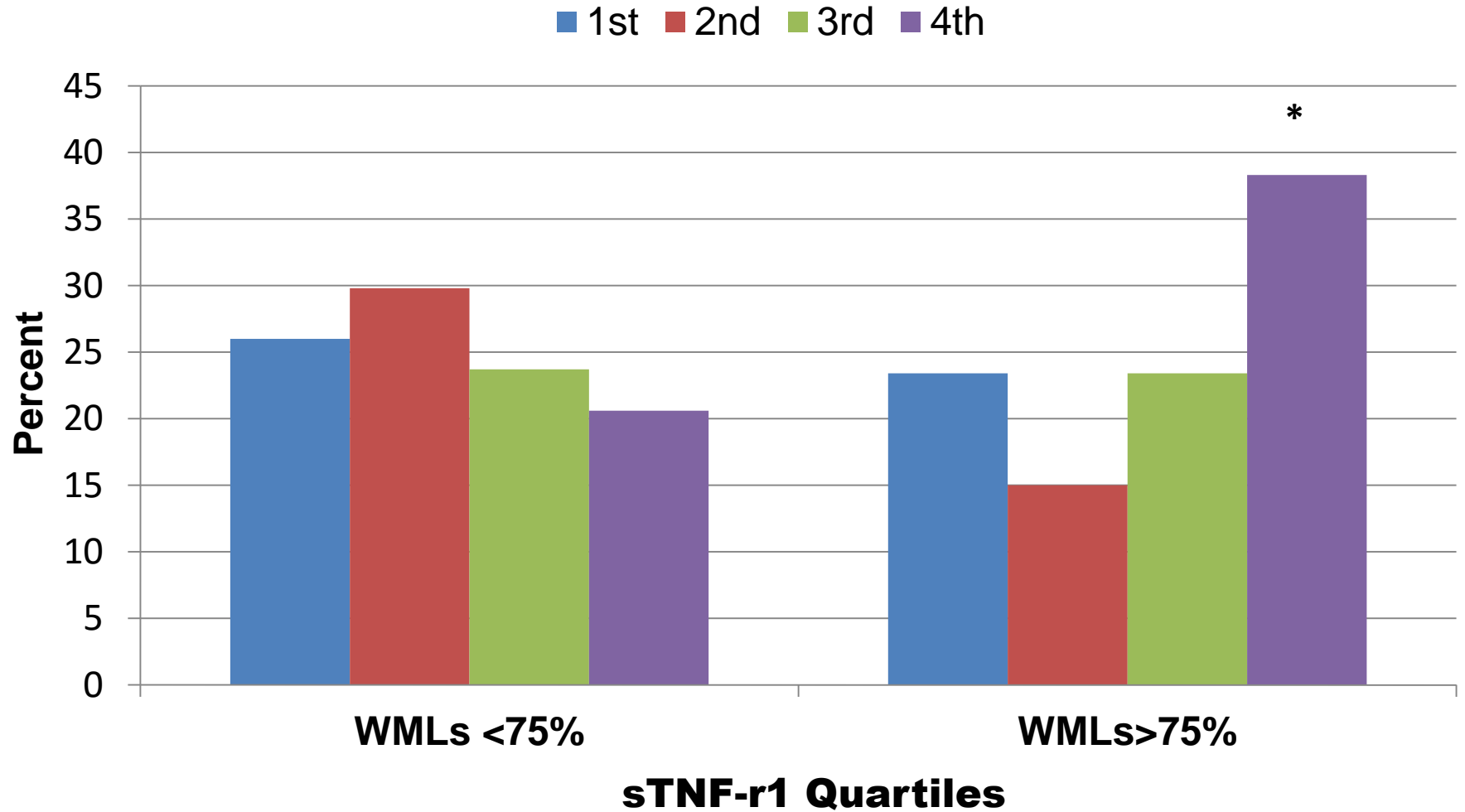
Amyloid deposition by sTNF α r1 quartiles



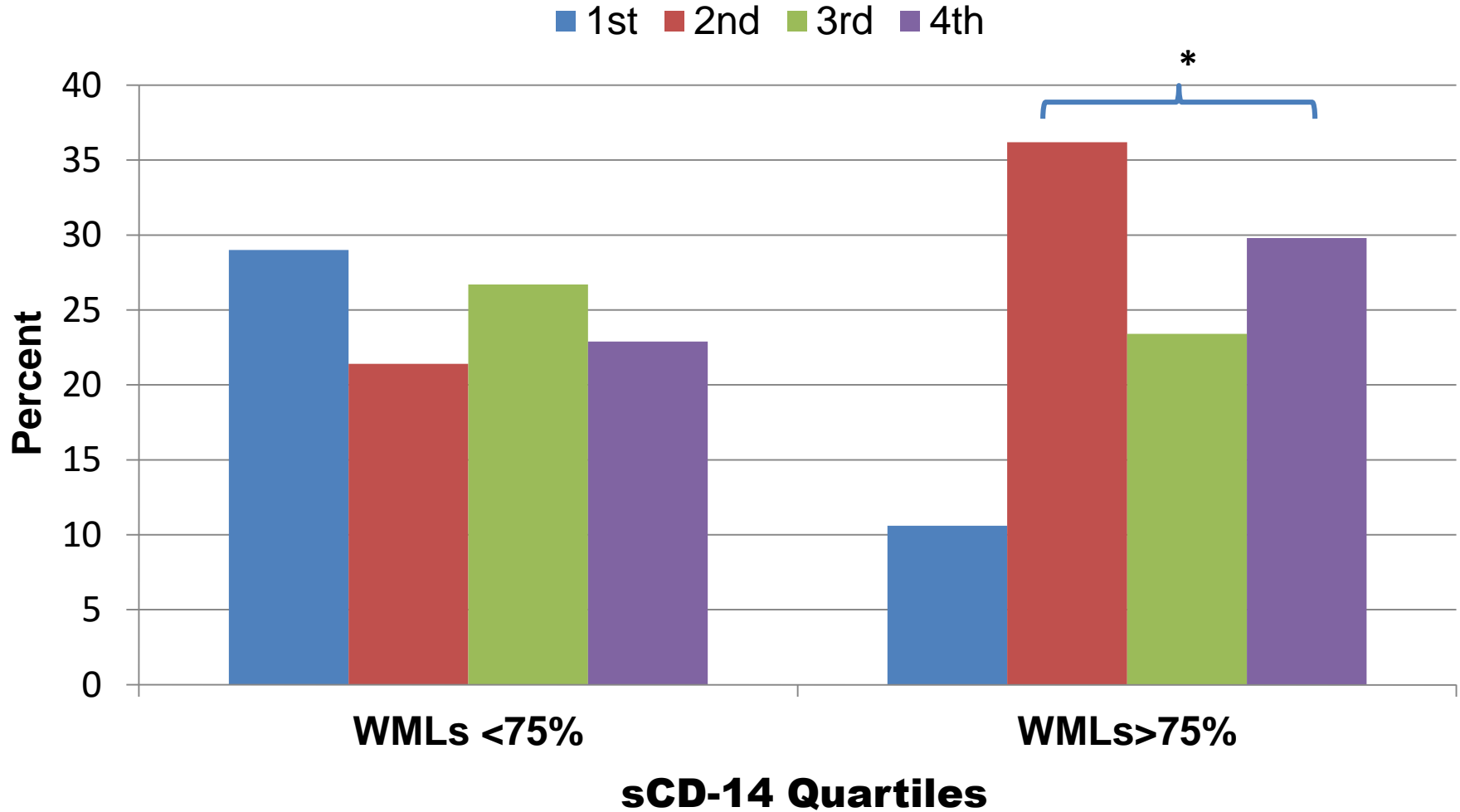
Inflammation markers and white matter lesions (WMLs) volume

	WMLs <75 percentile	WMLs >75 percentile	p-value
hsCRP, mg/l	2.79±6.5	1.93±1.89	0.38
IL-6, µg/ml	2.8±2.9	3.2±2.1	0.35
sTNF-r1, pg/ml	1251.9±362	1408.5±452	0.01
sTNF-r2, pg/ml	6279.4±1804	6761.3±1887	0.12
sIL-2r, pg/ml	1120.7±423	1191.1±422	0.43
sCD-14, pg/ml	1342.8±311	1422.6±311	0.27

WMLs volume by sTNF-r1 quartiles



WMLs volume by sCD-14 quartiles



*p= 0.03

Diagnoses at the last clinic visit in 2010-2015

	Normal cognition	MCI	Dementia
N of participants	56	67	60
Age at baseline	84.9 \pm 2.5	85.6 \pm 3.0	86.0 \pm 2.9
Men/Women	32/24	40/27	35/25
Education level	15.2 \pm 2.8	14.2 \pm 2.4	14.6 \pm 2.6
BMI	26.3 \pm 4.0	26.5 \pm 5.5	25.6 \pm 4.8
Hypertension	12 (22%)	28 (43%)*	23 (39%)*
Diabetes mellitus	2 (4%)	4 (6%)	4 (7%)
Heart disease**	10 (18%)	9 (28%)	13 (22%)

*p= 0.03

**History of congestive heart failure, angina, myocardial infarction, valve replacement, Stent, or CABG

Inflammation markers by diagnoses at 2010-2015

	Normal cognition	MCI	Dementia	
hsCRP, mg/l				
IL-6, µg/ml				
sTNF-r1, pg/ml				
sTNF-r2, pg/ml				
sIL-2r, pg/ml				
sCD-14, pg/ml				

Inflammation markers by diagnoses at 2010-2015

	Normal cognition	MCI incident or prevalent	Dementia < 2.5 years	Dementia >2.5 years
N of participants	56	69	34	27
hsCRP, mg/l	2.09 ± 1.9	2.69 ± 6.9	2.99 ± 8.0	2.33 ± 3.8
IL-6, µg/ml	2.92 ± 3.3	2.60 ± 1.6	3.90 ± 3.3*	2.19 ± 0.80
sTNF-r1, pg/ml	1250.1 ± 380	1293.5 ± 404	1378.1 ± 404	1277.2 ± 320
sTNF-r2, pg/ml	6171.8 ± 2022	6486.9 ± 1657	6598.5 ± 1915	6398.5 ± 1628
sIL-2r, pg/ml	1142.6 ± 423	1103.6 ± 395	1192.4 ± 477	1151.7 ± 420
sCD-14, pg/ml	1356.9 ± 269	1390.7 ± 336	1420.8 ± 317	1359.0 ± 305

ANOVA: F= 281, p=0.04

Comments

They are higher among women than men.

They are weakly associated with amyloid deposition in the brain (PiB+)

They are weakly associated with white matter lesions volume.

There is a trend for the prediction of imminent incident dementia (within 2.5 years).

They are not long term predictors of dementia

Characteristics of 1,319 participants of the GEM Study included in the study

	Female (n= 597)		Male (n=722)		
	Mean / N	(SD / %)	Mean / N	(SD / %)	p-value
Age	79.12	3.66	78.87	3.23	0.18
Race					
White	562	94.14%	692	95.84%	0.15
Non-White	35	5.86%	30	4.16%	
Education (years)	13.93	2.94	14.75	3.42	<0.001
Hypertension	343	57.45%	378	52.35%	0.06
Diabetes	47	7.87%	73	10.11%	0.16
History of CHD¹	172	28.81%	289	40.03%	<0.001
BMI [†]	26.89	4.93	27.31	3.64	0.08
Alcohol (drinks/wk)	2.08	4.69	4.86	7.61	<0.001
Smoking status					
Never smoked	338	57.39%	200	28.25%	<0.001
Former smoker	237	40.24%	472	66.67%	
Current smoker	14	2.38%	36	5.08%	
APOE4 carrier	138	28.99%	125	22.16%	0.012

Risk of incident dementia and subtype of dementia for a standard deviation increase in PTX3 and SAP

	Adjusted for Demographics ¹		Adjusted for CVD Risk Factors ²		Adjusted Physical Function and APOE-4 ³	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
All Dementia	(523/1319)*		(504/1271)*		(379/997)*	
PTX3 (ng/mL)	1.20 (1.12 -1.29)	<0.001	1.19 (1.10 to 1.28)	<0.001	1.16 (1.06 to 1.26)	0.001
SAP (ng/mL)	0.91 (0.83 to 1.00)	0.06	0.93 (0.84 to 1.03)	0.14	0.95 (0.84 to 1.07)	0.40
AD	(353/1319)*		(341/1271)*		(252/997)*	
PTX3 (ng/mL)	1.16 (1.05 to 1.28)	0.003	1.14 (1.02 to 1.26)	0.02	1.12 (1.00 to 1.26)	0.06
SAP (ng/mL)	0.84 (0.75 to 0.95)	0.004	0.88 (0.78 to 0.99)	0.04	0.92 (0.79 to 1.07)	0.28
Mixed/ VaD	(148/1319)*		(142/1271)*		(106/997)*	
PTX3 (ng/mL)	1.17 (1.08 to 1.27)	<0.001	1.15 (1.06 to 1.26)	0.001	1.12 (1.02 to 1.24)	0.02
SAP (ng/mL)	0.90 (0.82 to 1.00)	0.04	0.93 (0.83 to 1.03)	0.15	0.94 (0.83 to 1.07)	0.35

(1) Adjusted for age, gender, race, education, clinic, and GEMS treatment assignment..

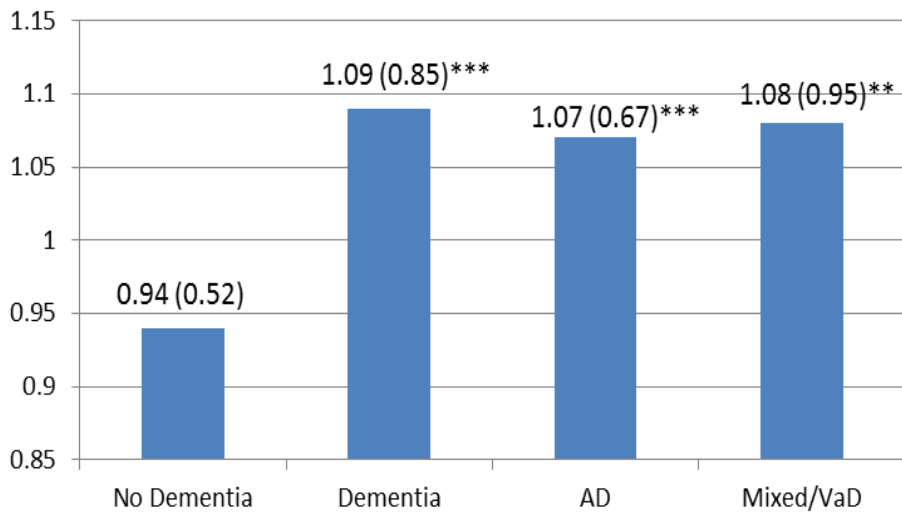
(2) Adjusted for demographics + hypertension, diabetes, history of MI, angina, heart failure, stroke, TIA, cardiac procedures, BMI, use of tobacco and alcohol.

(3) Adjusted for demographics, CVD RFs + gait speed, activities of daily life and ApoE genotype.

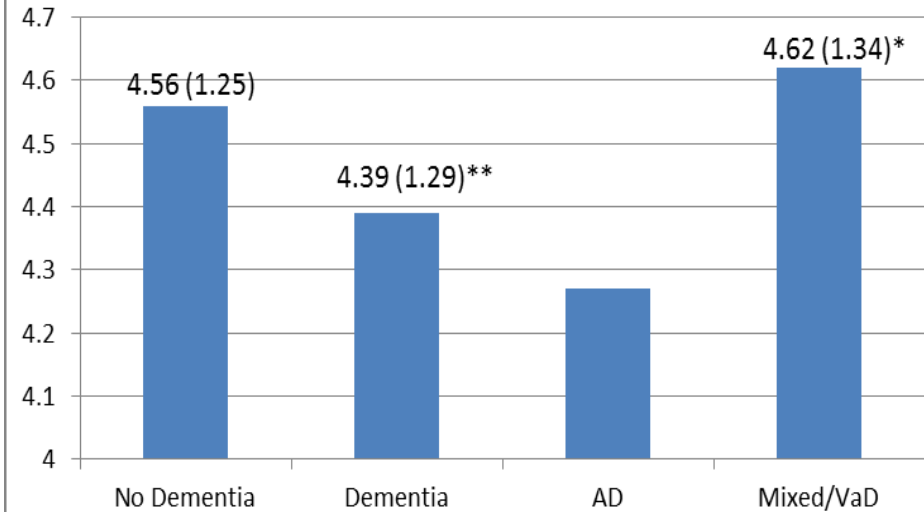
(4) * N = dementia cases / total sample.

Mean serum levels of PTX3 and SAP at baseline by dementia status of participants at end of follow-up

Mean PTX3 by Dementia Status



Mean SAP by Dementia Status



* $p > 0.50$; ** $p=0.01$; *** $p < 0.001$