Obesity, Diabetes, and HIV: Intersecting Epidemic Contributing to NeuroAIDS?

Barcelona, May, 2013

Allen McCutchan, MD, MSc
Professor of Medicine
HIV Neurobehavioral Research Center
UC, San Diego

Background

- In HIV-uninfected populations, risk of neurocognitive impairment NCI), is increased by components of the metabolic syndrome:
  - » obesity (central > generalized),
  - » diabetes and and glucose intolerance
  - » atherogenic hyperlipidemias
  - » hypertension
- Mechanisms for these effects are unknown, but may include:
  - » Macro- or micro-vascular disease +/- stroke, or
  - » Neurotoxicity of insulin resistance or hyperglycemia, or
  - » Encephalopathy of systemic inflammation

Background

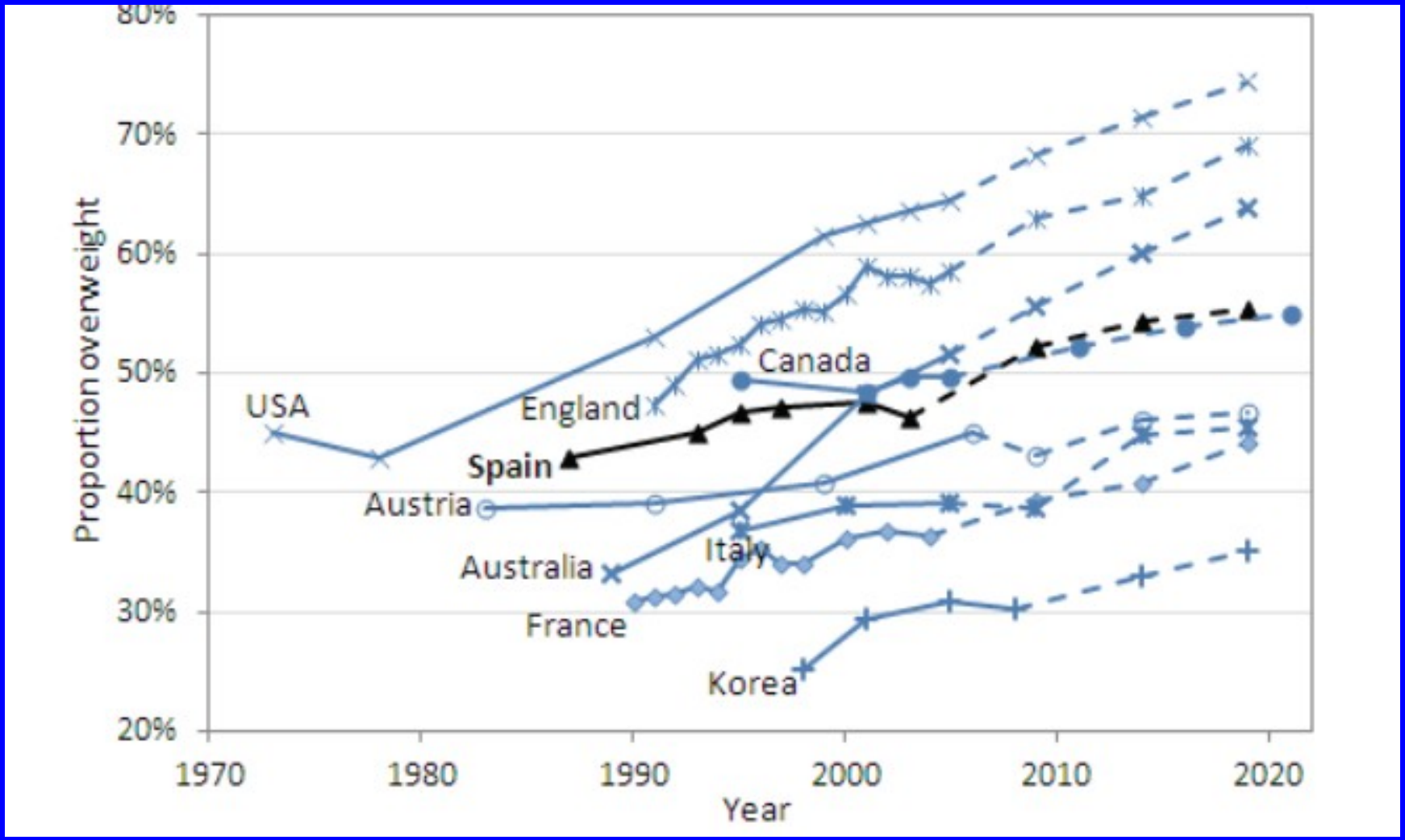
- In HIV-infected persons, additional mechanisms of neurocognitive impairment (NCI) may be also come directly from HIV and/or by exposure to ART through:
  - Failure: Continued HIV replication in the brain
  - Side effects: Subclinical IRIS to residual HIV in the brain
  - Possible neural toxicity: specific drugs such as efavirenz have clinical and in vitro neurotoxicity
- Diabetes and insulin resistance increased risk of NCI in older (>55) HIV-infected patients in the Hawaiian cohort. (Valcour, Sacktor, Paul, et al, J Acquir Immune Defic Syndr 2006 ;43:405-41

Background

Could obesity be contributing to NCI by direct mechanisms or through increasing prevalence of diabetes in HIV patients?

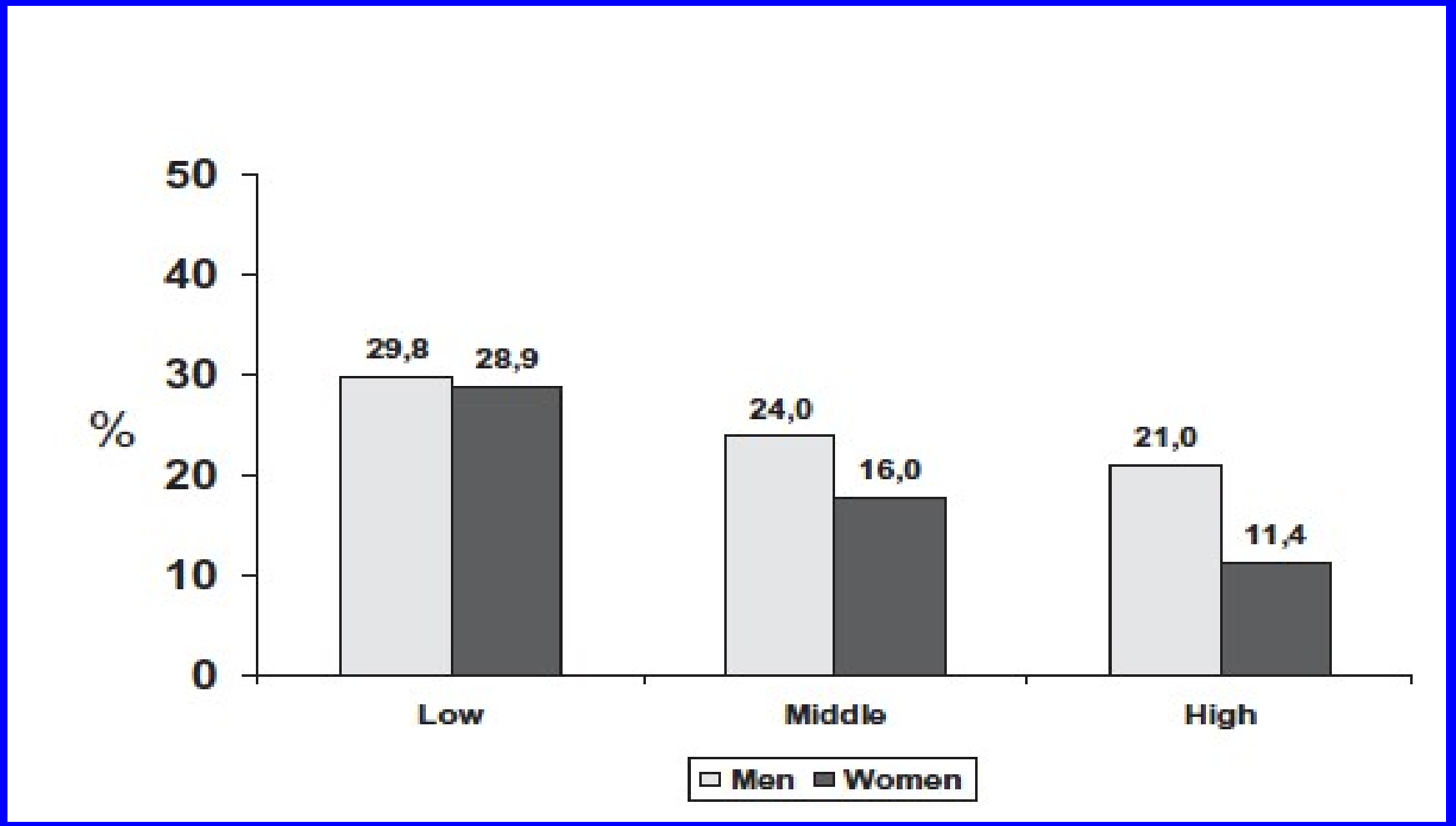
- Obesity, diabetes, and HIV have increased dramatically over the last 3 decades.
- Obesity affects the HIV-infected, antiretroviral-treated populations
  - » In the US Navy, the Body Mass Index is similar in HIV+ and HIV- personnel. (Crum-Cianflone N, Tejidor R, Medina S, et al. Obesity among patients with HIV: the latest epidemic. AIDS Patient Care STDS 2008;22:925-930.)

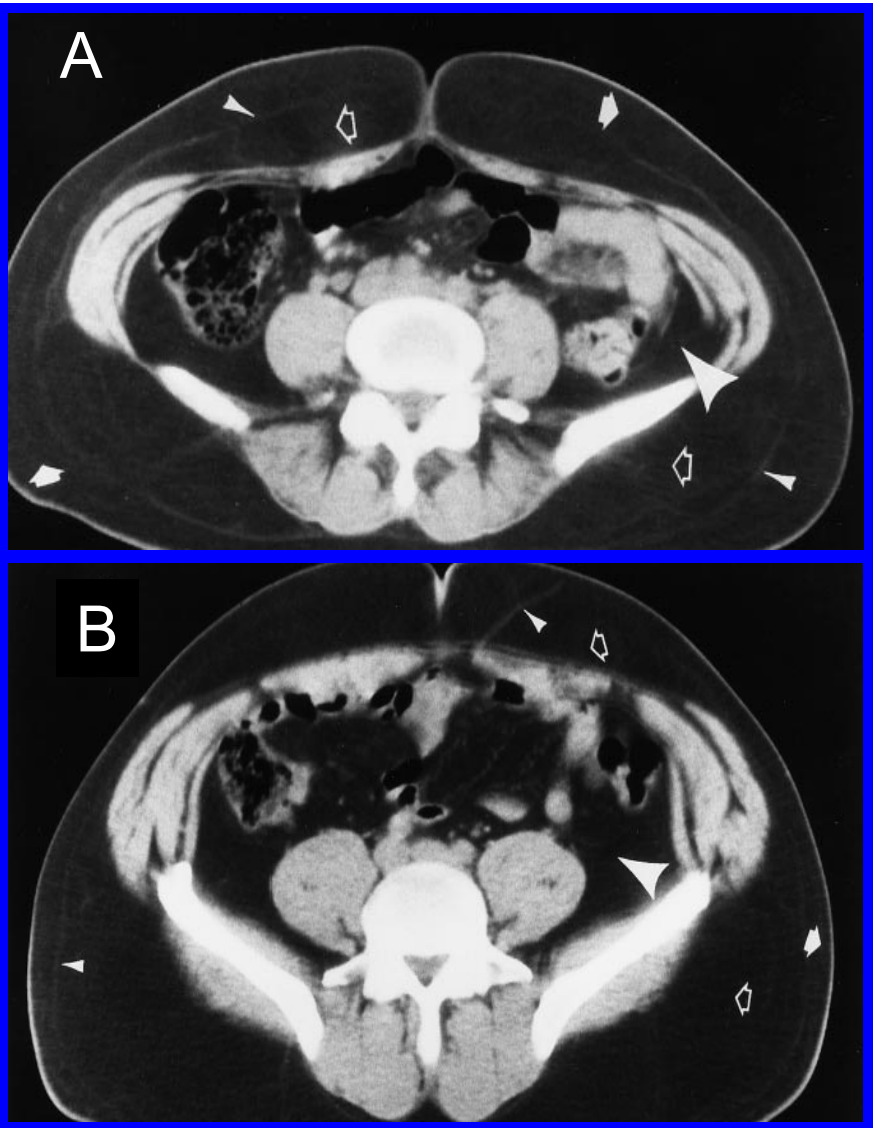
Proportion of Overweight Adults by Country



Prevalence of Obesity by Educational Levels in Spanish Adults 2008-2010

Obesity Reviews (2012) 13, 388–392





Anatomic Divisions of Abdominal Fat

- Subcutaneous fat (SAT) is divided into superficial and deep
- Visceral (VAT) is fat lying within the peritoneum.
- Histology of deep SAT resembles that of VAT.

Am J Physiol Endocrinol Metab 278:E941-948, 2000.

Patient	Superficial	Deep	Visceral
A = lean	144	126	84
B = obese	141	273	153

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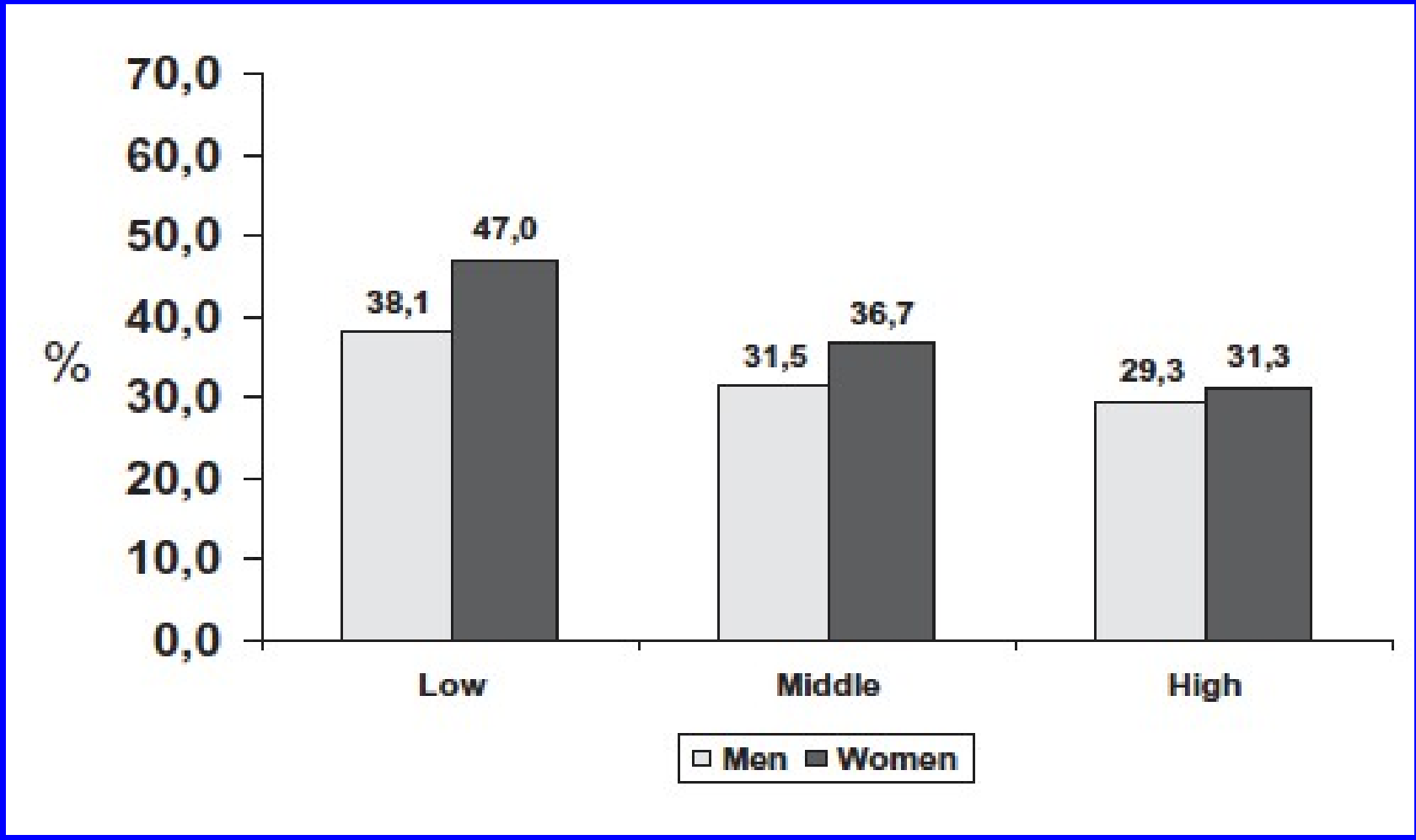
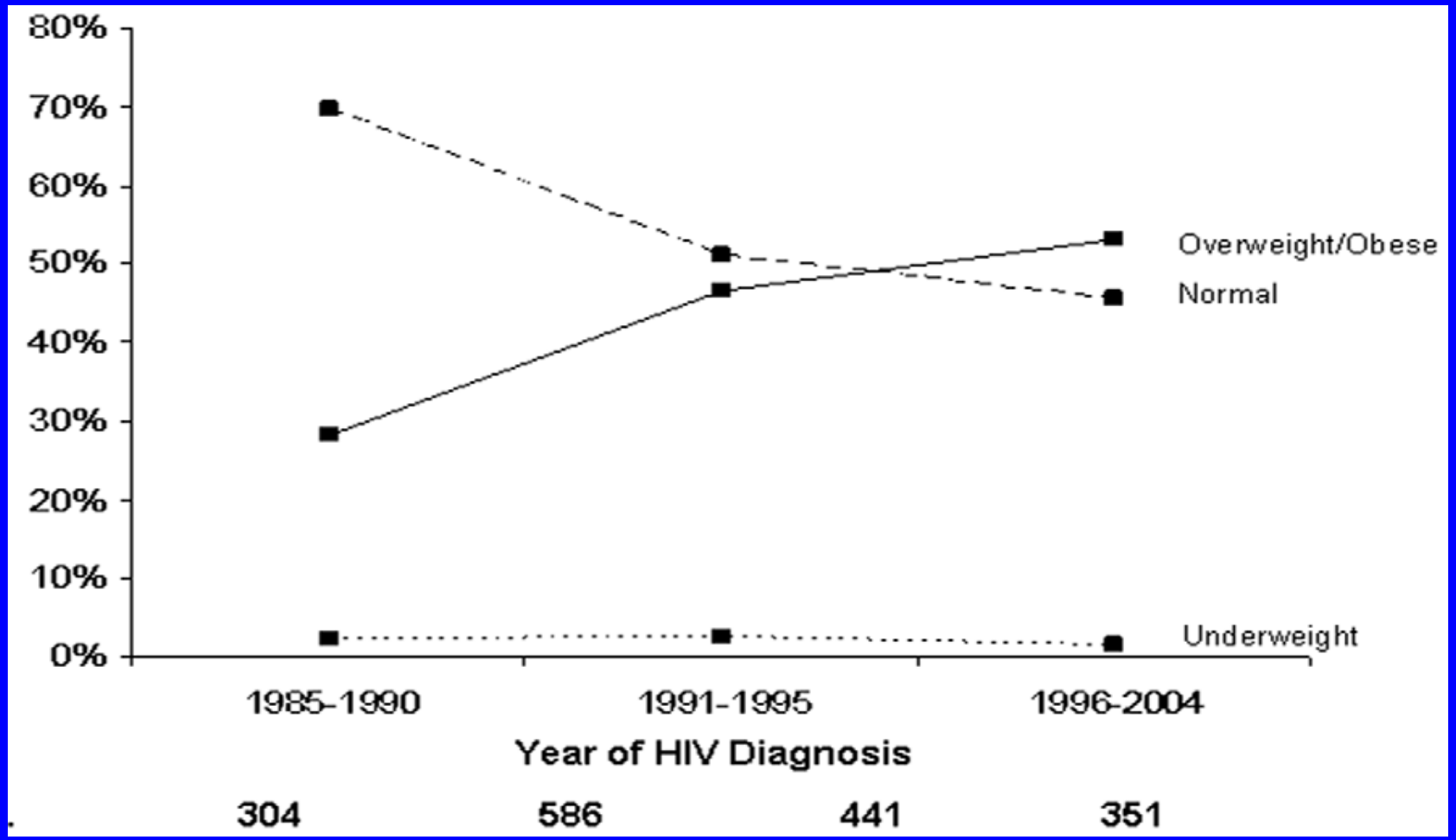


Weight categories in HIV+ US Navy personnel

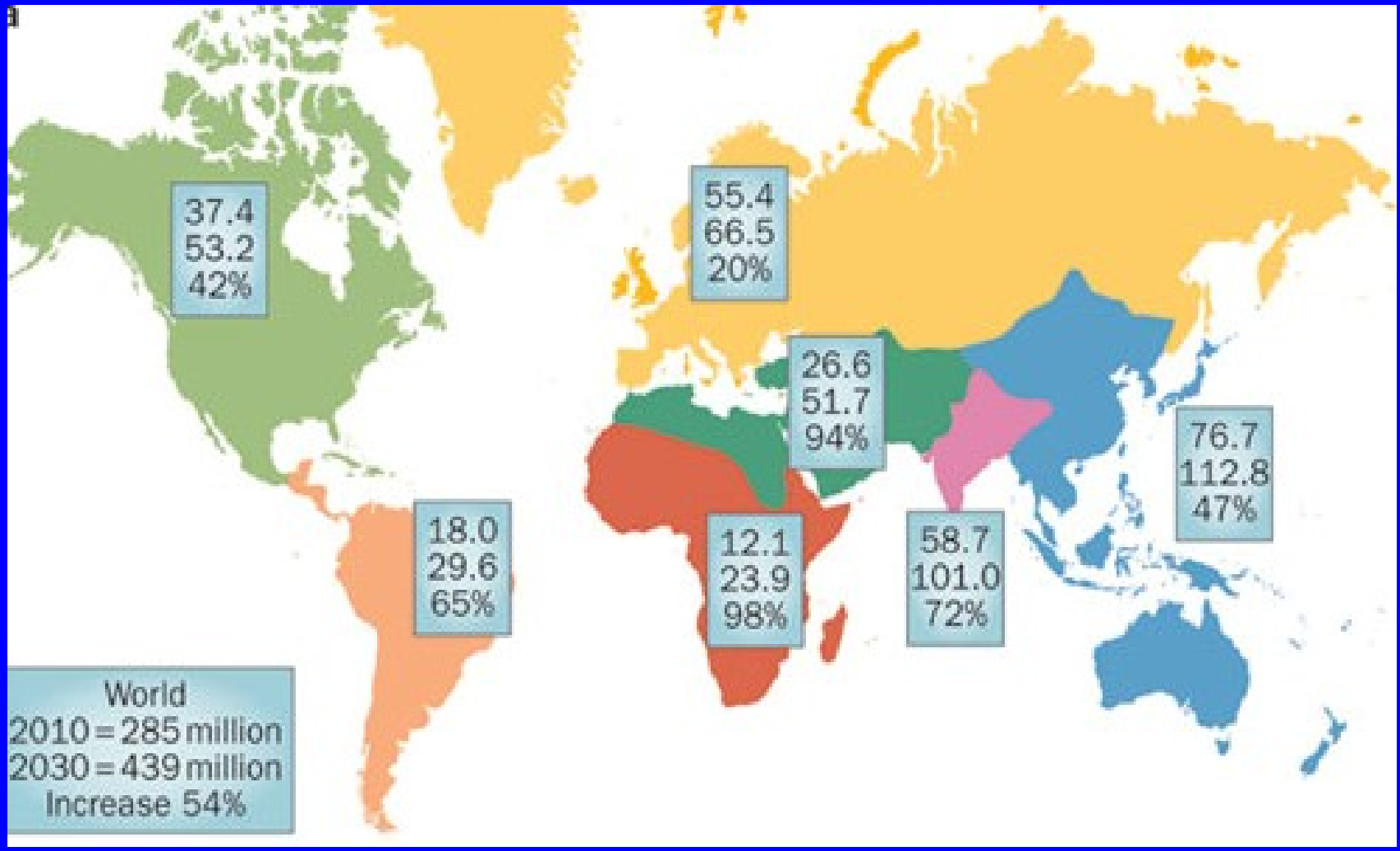


Crum-Cianflone N, et al (2010) PLoS ONE 5: e10106

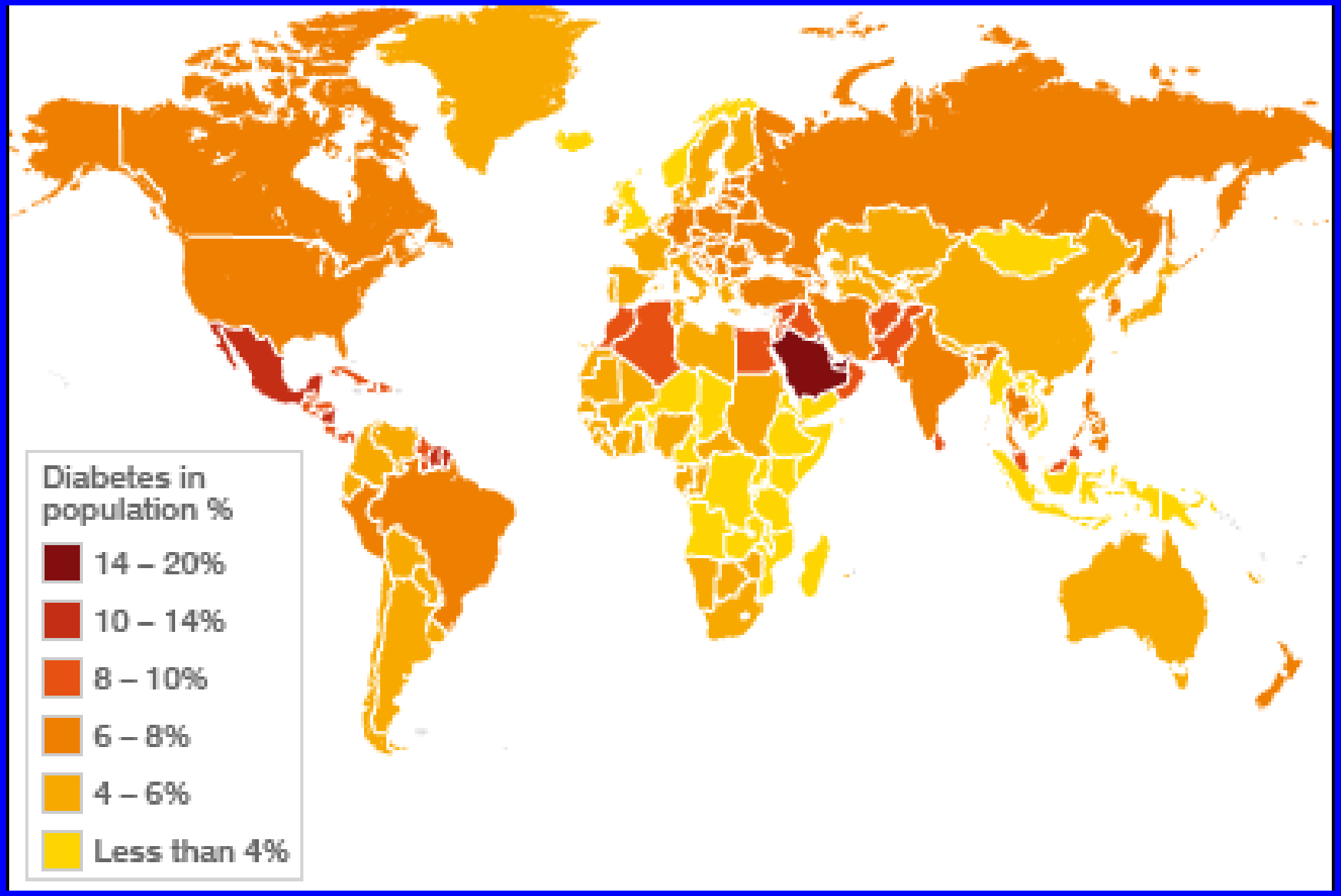
Body Mass Index (BMI) in HIV+ and HIV- American Women

BMI	HIV - N=573	%	HIV+ N=1208	%
Low <18.5	11	1.9	3	0.25
Nomal 18.5-4	135	23	411	34
Overweight 25-30	**152**	**27**	**347**	**29**
Obese >30	**251**	**44**	**371**	**31**

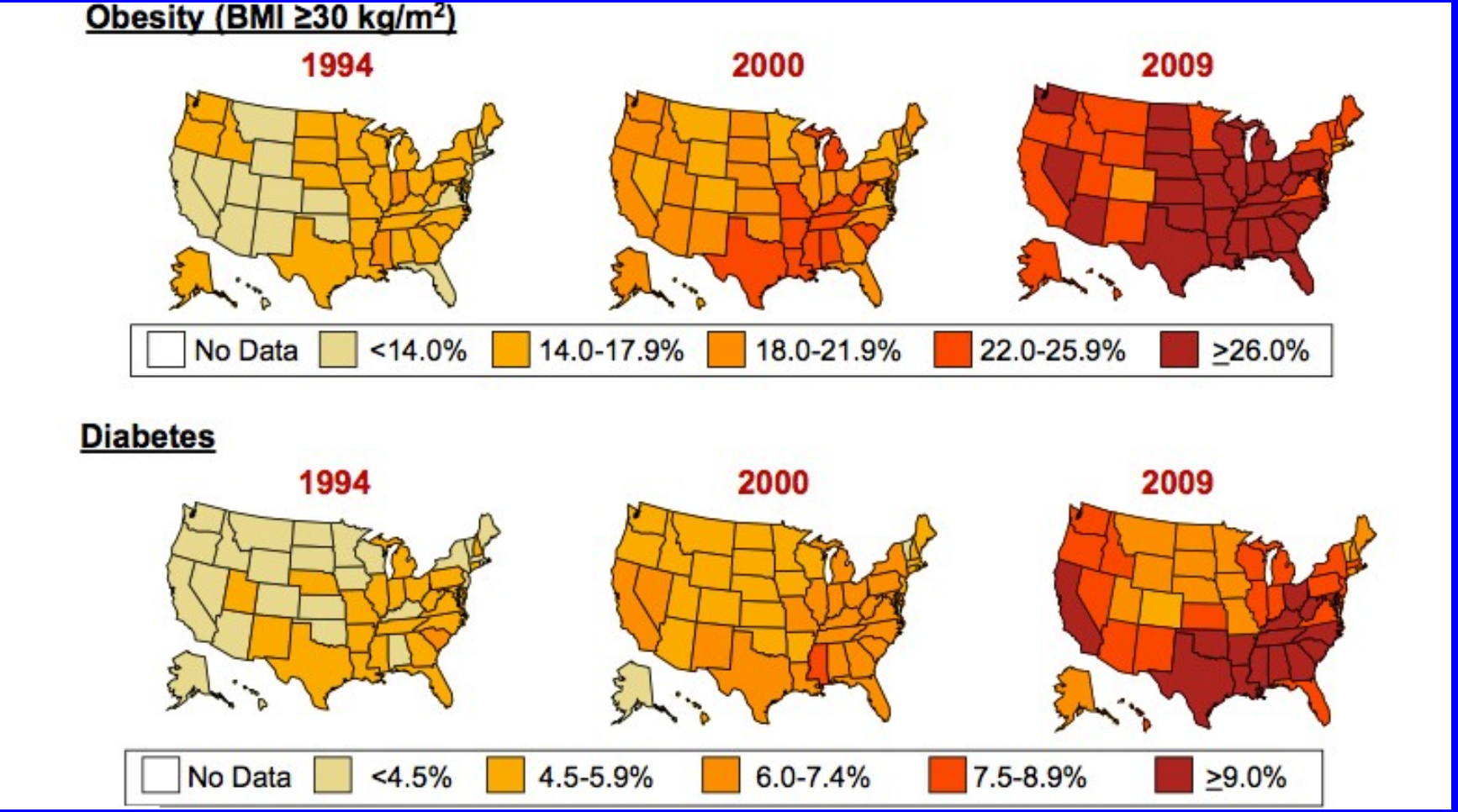
Increased Global Absolute Prevalence of Diabetes from 2010 to 2030



Global Projected Diabetes Prevalence (ages 20-79) in 2030



Prevalence of Obesity and Diabetes in the US Adults 1994 to 2009



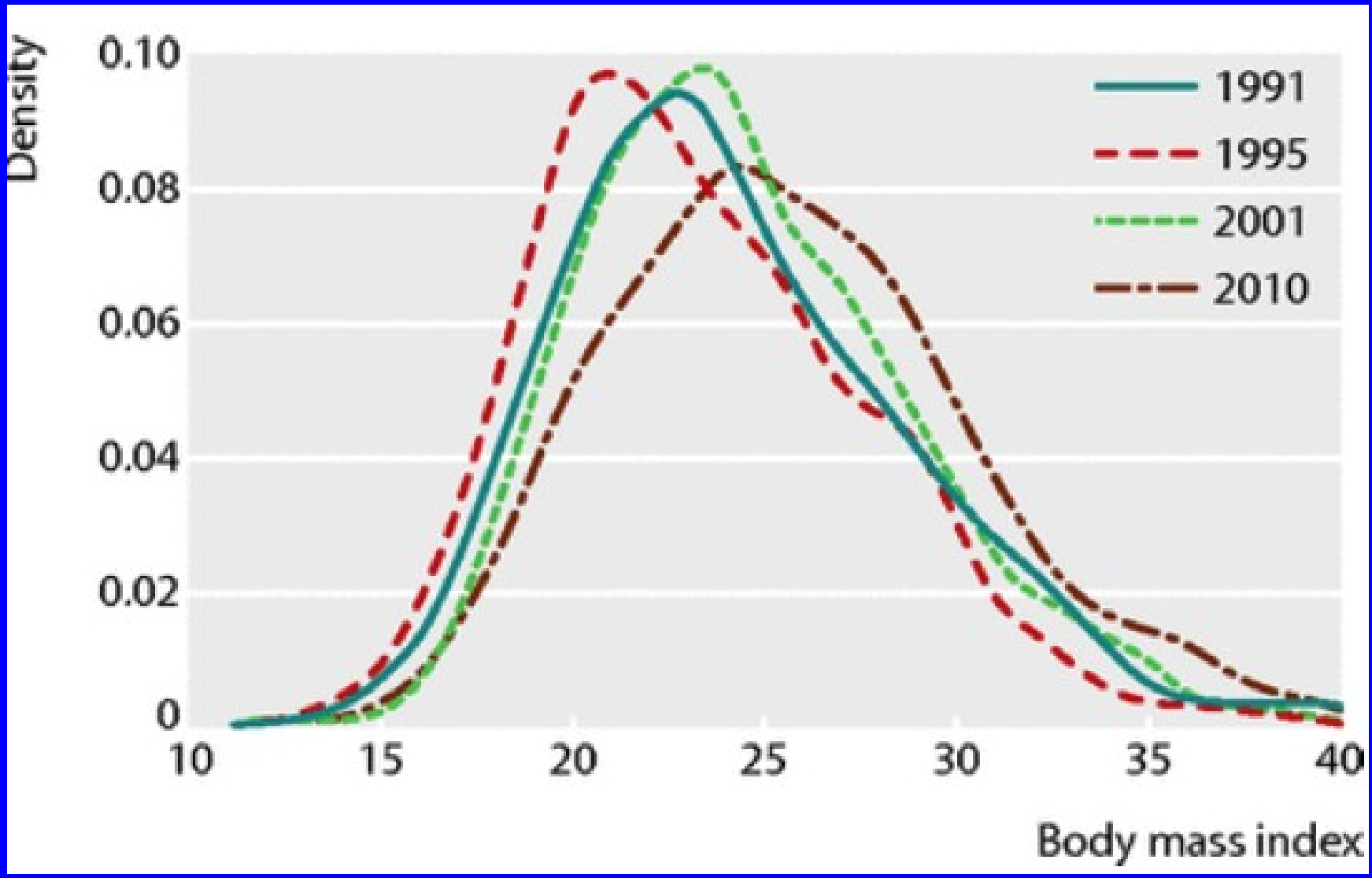
Has the obesity epidemic caused the diabetes epidemic?

Population-wide weight loss and regain in relation to diabetes burden in Cuba 1980-2010: repeated cross sectional surveys and ecological comparison of secular trends

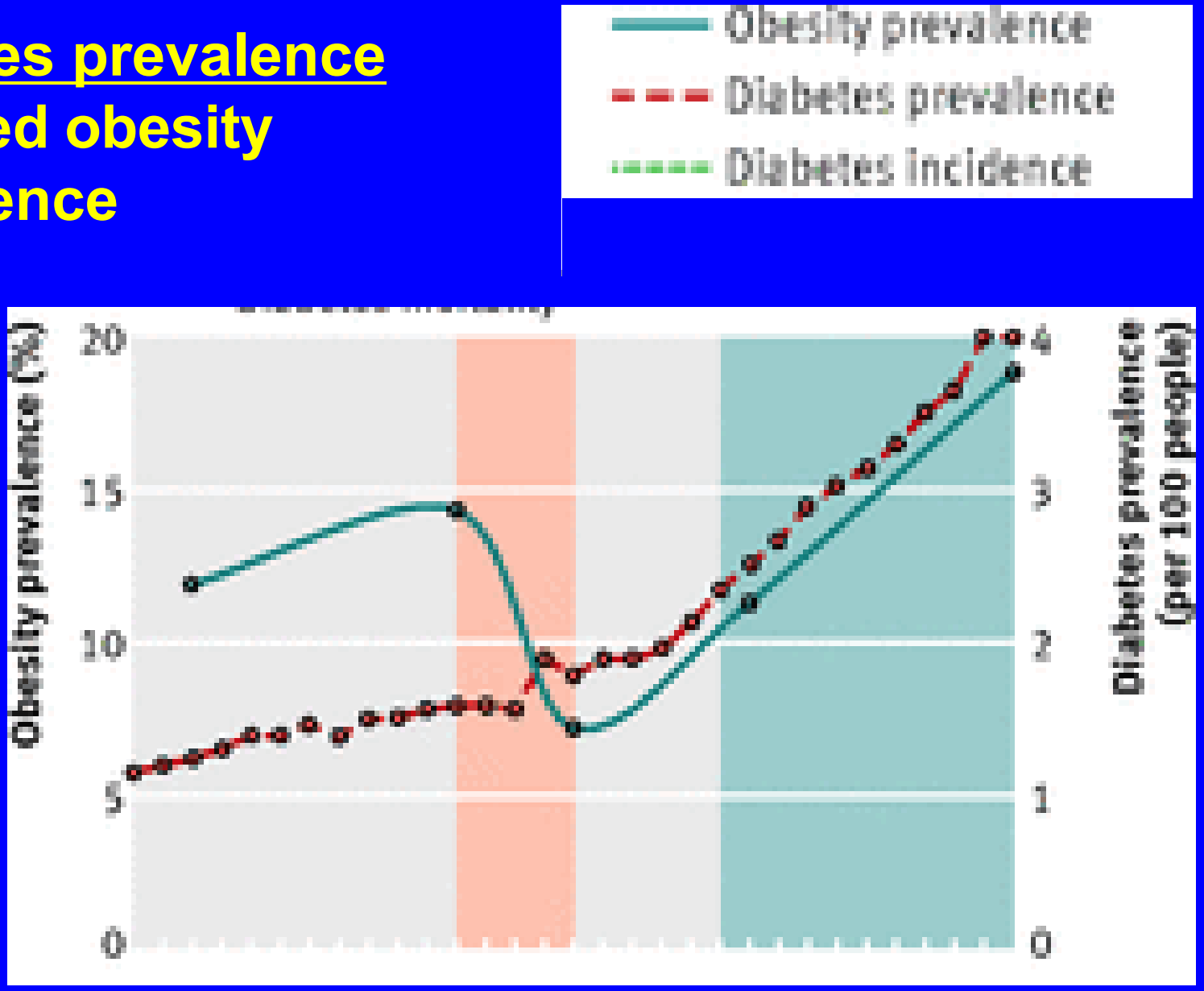
Franco, M et al BMJ 2013

- Design: Repeated cross sectional surveys and ecological comparison of secular trends.
- Setting: Cuban province of Cienfuegos from 1991, 1995, 2001 in representative samples of 1657, 1351, 1667, and 1492 adults.
- Economic recession following loss of Soviet support (1990-1995) with decreased availability of food and documented population-wide weight loss.

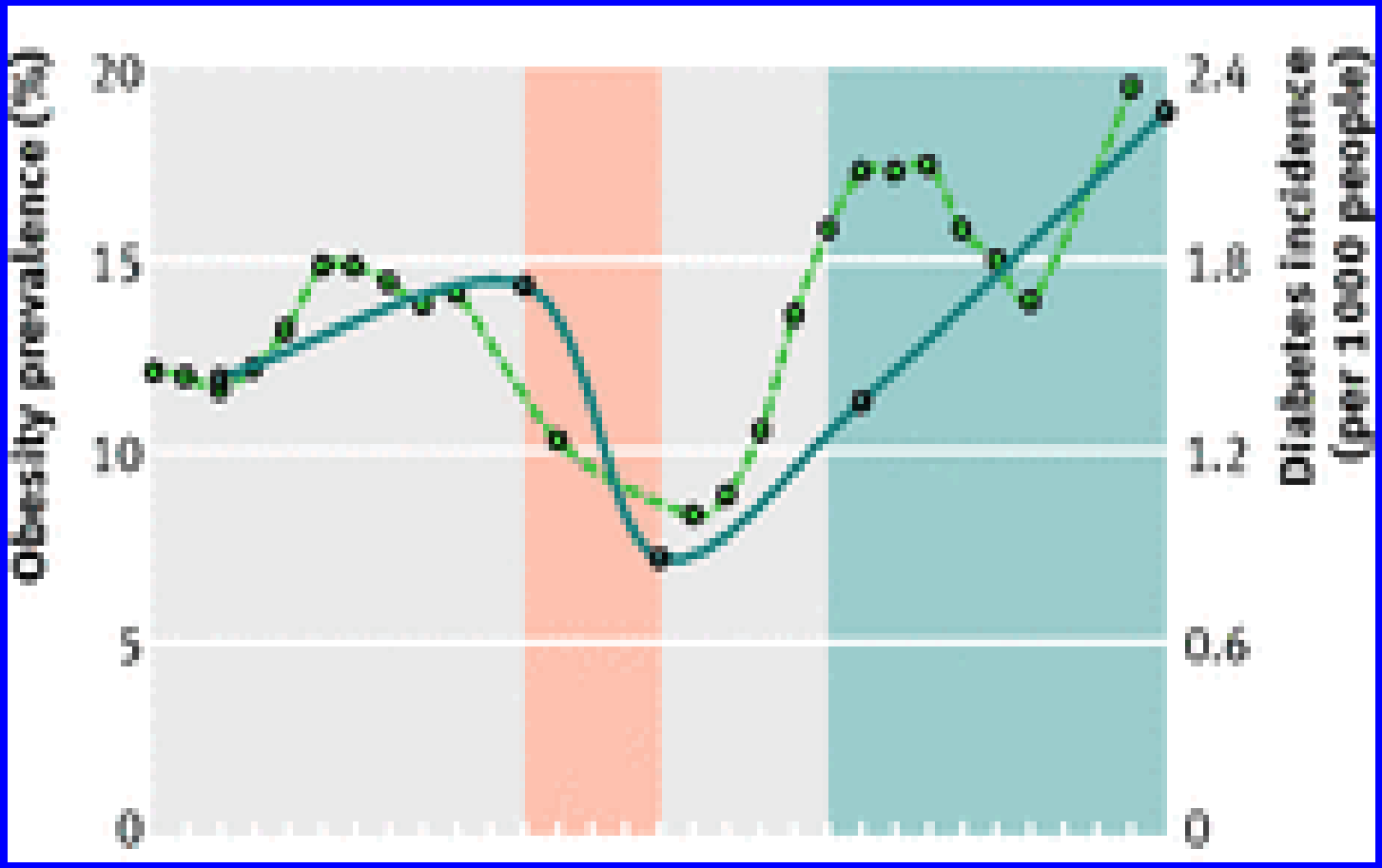
Weight distributions in Cuba caused by economic reversals in 1991-95



Diabetes prevalence followed obesity prevalence



Diabetes incidence followed obesity prevalence



Conclusions

- During periods of population-wide loss followed by gain in weight in Cuba, the incidence and prevalence of diabetes closely followed the prevalence of obesity.

- This ecological study supports that hypothesis that the obesity epidemic is a major factor causing the diabetes epidemic.

How are diabetes and obesity related to neurocognitive impairment (NCI)?

In HIV-uninfected persons,

- Diabetes, BMI and central obesity (WC or WHR) all correlate with:
  - » Prevalence of NCI in cross sectional studies
  - » Incidence of NCI in longitudinal studies
- Diabetes is consistently associated with NCI and cortical atrophy in MRI.
- In statistical models, central obesity is better than BMI in predicting NCI.

Since obesity and diabetes contribute to NCI in HIV-uninfected persons, do they contribute to NCI in HIV-infected patients?

Role of Obesity, Metabolic Variables, and Diabetes in HIV-Associated Neurocognitive Disorder (HAND)

J. Allen McCutchan, M.D., M.Sc.[1], Jennifer A. Marquie-Beck, M.P.H.[1], Chelsea A. FitzSimons, M.P.H[1], Scott L. Letendre, M.D.[1], Ronald J. Ellis, M.D., Ph.D.[1], Robert K. Heaton, Ph.D.[1],…Igor Grant, MD and the CHARTER Group *Neurology* 2012

Objective

To examine the relationship between HAND and metabolic variables in HIV+ participants in CHARTER, an observational, multicenter cohort study of patients on HAART.

Methods

- In a cross-sectional study 130 HIV+ CHARTER participants
- Neurocognitive impairment (NCI) was defined by performance on neuropsychological tests adjusting for age, education, gender and race/ethnicity.
- Global ratings and global deficit scores (GDS) were determined by standardized demographically corrected tests.

Methods

- Demographics, biomarkers of HIV disease, metabolic variables, anthropomorphic measures, CART history, other drug exposures, and self reported diabetes were collected.
- Multivariate models predicted NCI using variables that are selected for best overall goodness of fit criteria in two subgroups limited by availability of measures of obesity:
  - » Model 1- Body Mass Index (BMI) alone, n=90
  - » Model 2- BMI and waist circumference (WC), n=55

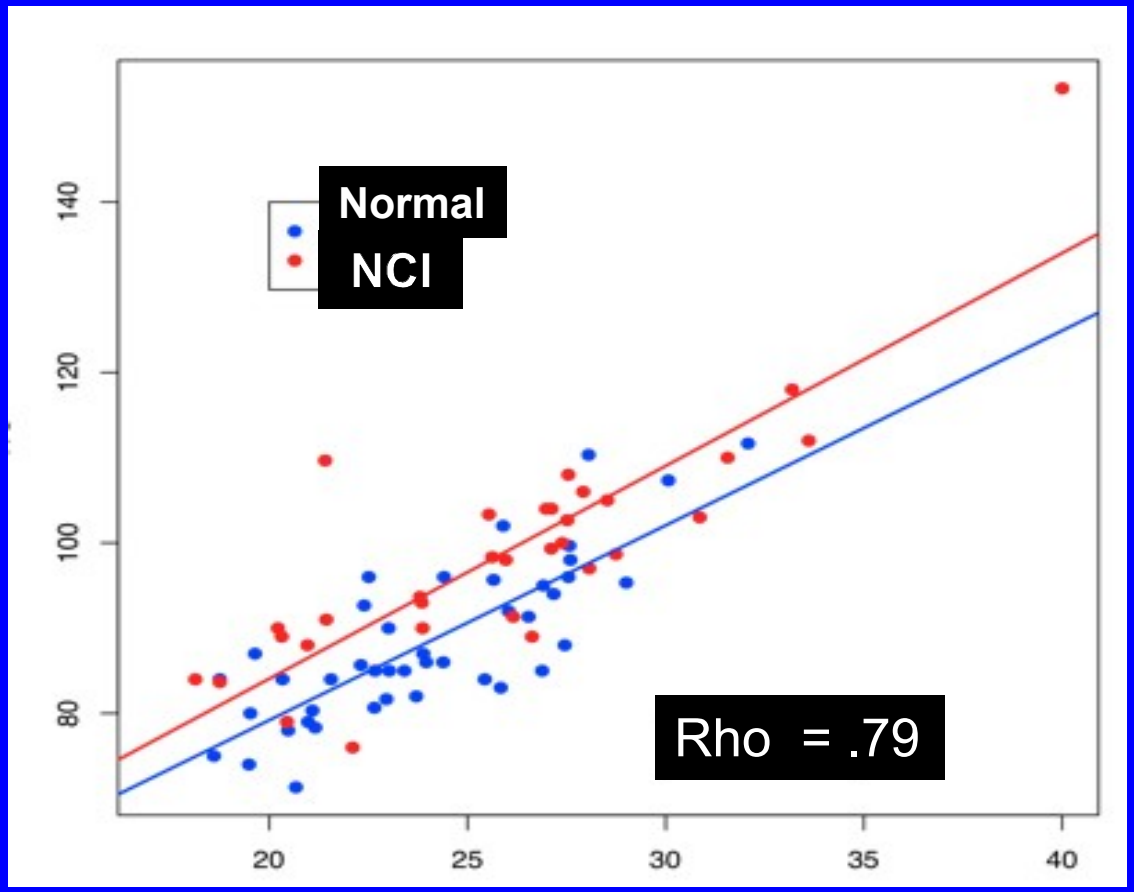
Results: Impaired versus unimpaired

	Metabolic Group (n=130)	Impaired (n=52)	Unimpaired (n=78)	p-value #
Demographic Characteristics				
*Age, years[1]	46.2 (8.8)	48.3 (7.5)	44.9 (9.4)	0.02
*Gender, Male[2]	113 (87%)	45 (87%)	68 (87%)	0.92
*Ethnicity, White[2]	74 (57%)	35 (67%)	39 (50%)	0.07
Education, years[1]	13.1 (2.6)	13 (2.4)	13 (2.8)	0.68
HV Disease Status				
*AIDS diagnosis[2]	91 (70%)	41 (79%)	50 (64%)	0.08
*Duration of HIV Infection: years[1]	13 (6.5)	14.5 (6.0)	12.0 (6.7)	0.03
*Current CD4[3]: cells/mm^3	501 (305-708)	556 (326-757)	458 (305-669)	0.09
*Nadir CD4[3]: cells/mm^3	120 (50-250)	101 (50-217)	175 (58-254)	0.20
Plasma viral load				
c/mL (log_{10})[3]	1.7 (1.7-2.4)	1.7 (1.7-2.1)	1.7 (1.7-2.4)	0.51
*Detectable[2]	40 (35%)	16 (33%)	24 (36%)	0.84
CSF viral load (n=99)				
c/mL (log_{10})[3]	1.7 (1.7-1.7)	1.7 (1.7-1.7)	1.7 (1.7-1.7)	0.65
Detectable[2]	15 (17%)	6 (15%)	9 (18%)	0.78
Antiretroviral Characteristics				
*ARV status[2]				0.90
Currently on	107 (82%)	43 (83%)	64 (82%)	
Past use only	14 (11%)	6 (12%)	8 (10%)	
ARV naïve	9 (7%)	3 (6%)	6 (8%)	
Duration of current regimen, mths[3]	21 (13-40)	23 (14-46)	21 (11-38)	0.57

Results:

BMI and WC are highly correlated (rho = .79) and WC increases NCI at all levels of BMIs

Waist Circumference (cm)



Body Mass Index

Results: Multiple Regression Analysis

Model 1: Multivariate regression based on AIC to model NCI as a function of demographic, medical and metabolic predictors of interest including BMI (n=90)

Variable	Odds Ratio	95% CI	p-value
Age	1.06	1.01, 1.12	0.027
Diabetes	6.08	0.61, 60.7	0.12
BMI	1.12	1.01, 1.24	0.039

Model 2:. Multivariate Regressions based on AIC to model NCI as a function of demographic, medical and metabolic predictors of interest including BMI and average mid waist circumference (n=55)

Variable	Odds Ratio	95% CI	p-value
AIDS	49.57	2.26, 1089	0.013
Diabetes	17.6	0.76, 409	0.07
BMI	**0.69**	0.49, 0.98	0.038
WC	**1.34**	1.13, 1.60	0.001
Triglycerides	**0.32**	0.09, 1.21	0.09

AIC= Akaike Information Criterion

NCI= Neurocognitive impairment

Summary of Results

- NCI (global impairment rating ≥ 5) was diagnosed in 40%.
- In univariate analyses, NCI was associated with:
  - » age,
  - » longer duration of HIV infection,
  - » central obesity (waist circumference (WC), but not general obesity (BMI),
  - » Diabetes: self-reported diabetes was also associated with NCI in those aged >55 years in the CHARTER cohort with n=1325.
- Multivariate logistic regression analyses using BMI alone and BMI plus WC demonstrated that only central obesity independently increased risk of NCI.

Conclusions

- As in HIV-uninfected persons, either BMI or WC increases the risk of NCI in HIV+ persons.
- When both BMI and WC are in the model, the effect of BMI is reversed, ie it protects from NCI.
- Diabetes increased risk of NCI most clearly in older (> 55 years) HIV-infected persons.
- Reduction of central adiposity might protect from or help to reverse neurocognitive impairment in HIV-infected persons.

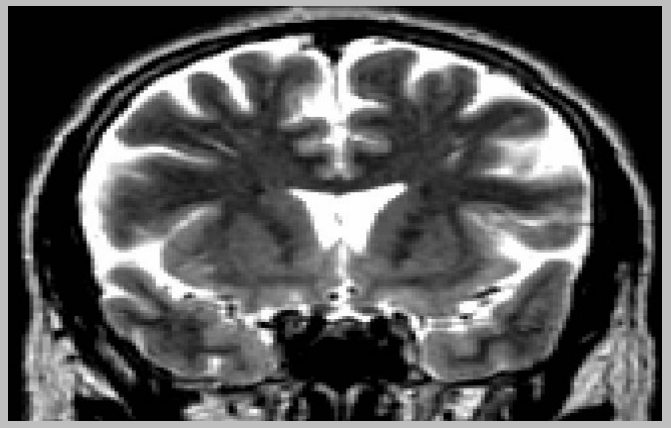
NeuroImaging Morphometric Correlates of Metabolic Variables in HIV: The CHARTER Study

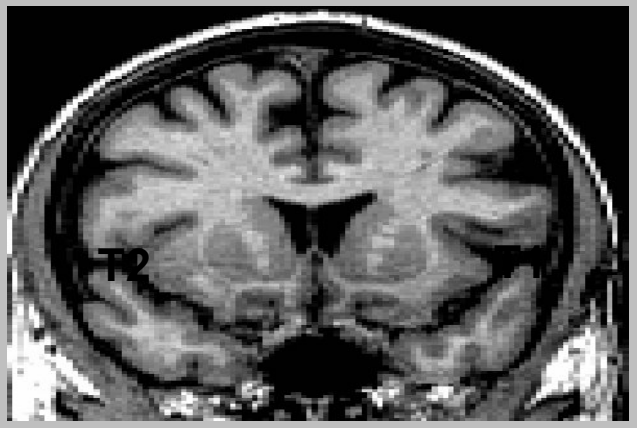
Sarah L. Archibald,
Christine Fennema-Notestine,
J. Allen McCutchan, et al
In preparation

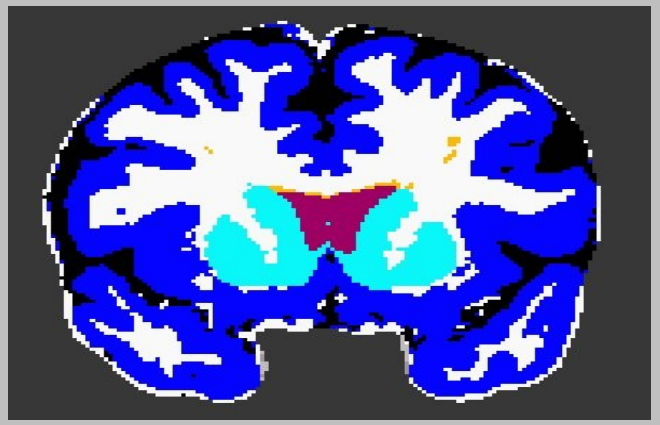
Metabolic Characteristics of 223 participants

Metabolic Factor	Mean (stdev.)
BMI (kg/m^2)	25.9 (4.5)
C-LDL (mM)	99.9 (35.4)
C-HDL (mM)	48.7 (20.6)
Systolic BP (mm Hg)	125.3 (15.2)
Diastolic BP (mm Hg)	76.4 (10.8)
Blood glucose (mM)	95.8 (24.1)
Diabetes (prevalence in %)	7.2

Imaging Protocol and Analysis







- Ventricular CSF
- Subarachnoid CSF
- Abnormal White
- Total White Matter
- CortexCortex
- Subcortical Gray

Statistical Analyses

- Multiivariate regression models to predict each brain volume from each metabolic factor:
  - » Control: age, gender, ethnicity, education, scanner/site, cranial vault, Current CD4, CD4 nadir
  - » Metabolic variables: BMI, TC, LDL-C, HDL-C, blood pressure (diastolic and systolic), blood glucose level and diabetes
- Regression model to predict each metabolic variable from CD4 change
  - » Control: age, gender, ethnicity, education, site, CD4nadir, vault
  - » Immune response: CD4 change (current - six months prior)

Results: Regression Analyses

n=223	Abnormal White Matter		Total White Matter		Cortical Gray Matter		Subcortical Gray Matter		Ventricular Fluid		Sulcal Fluid	
	t ratio	p	t ratio	p	t ratio	p	t ratio	p	t ratio	p	t ratio	p
BMI	-0.90	.367	**4.25**	**.0001**	**-4.10**	**<.0001**	-0.52	.604	-1.43	.155	-0.65	.518
BMI (m)	-0.90	.368	**3.76**	**.0002**	**-4.16**	**<.0001**	-0.43	.670	-1.55	.123	-0.08	.933
HDL-C	0.20	.838	-1.61	.109	-1.31	.193	-1.97	.050	1.57	.118	**2.45**	**.015**
HDL-C (m)	-0.21	.830	-1.50	.136	-1.68	.095	-1.95	.052	**2.01**	**.046**	**2.41**	**.017**
LDL-C	-0.15	.878	**2.54**	**.012**	-1.33	.184	-1.05	.295	-0.17	.866	-1.68	.094
LDL-C (m)	-0.09	.930	1.67	.096	-0.44	.660	-0.96	.340	0.17	.865	-1.59	.113
Cholesterol	0.11	.914	1.26	.210	**-2.26**	**.025**	-1.83	.068	1.20	.233	0.34	.734
Glucose	**2.71**	**.007**	-0.27	.789	-0.02	.981	-0.57	.572	1.33	.186	0.71	.479
Glucose (m)	1.91	.058	0.06	.951	-0.01	.994	-0.12	.907	0.25	.800	0.51	.609
Diabetes	**2.33**	**.021**	1.13	.258	-0.68	.500	0.65	.515	**-2.42**	**.016**	-0.58	.562
Diabetes (m)	1.39	.168	1.72	.086	-0.87	.384	0.71	.480	**-2.51**	**.013**	-0.54	.593

Control variables include scanner, age, ethnicity, CD4 nadir, and cranial vault
Multi-metabolic model (m) includes BMI, HDL-C, LDL-C, Glucose, Diabetes

Results: Univariate analysis

Examining each metabolic variable separately to predict brain volumes

1. Greater BMI was associated with smaller cortex and larger white matter
2. Hyperglycemia or diabetes was associated with abnormal white matter
3. Blood pressure was not related to any of the brain volume or density measures.

Results: Multivariate Analysis

Examining combined effects of metabolic variables found:

1. similar correlations to the univariate analysis suggesting these effects have distinct mechanisms
2. CD4 change over 6 months (? reflecting IRIS) was not associated with metabolic variables

Summary

1) Elevated BMI, total cholesterol, glucose, and diabetes correlated with altered gray and white matter volumes in HIV-infected patients on HAART.
2) Glucose dysregulation (hyperglycemia and diabetes) was associated with white matter enlargement and more abnormal signal suggesting edema in white matter.
3) Presumed WM edema could be caused by several mechanisms:
    1) Cerebral macro- or micro-vascular disease
    2) Hyperglycemia or insulin resistance
    3) Neural toxicity of ART

Conclusions and Implications

Clarification of the causal mechanisms of the combined effects of HIV and metabolic variables on brain structure could lead to targeted interventions.

We hypothesized that pro-inflammatory cytokines generated in inflamed central fat could mediate the brain damage that causes NCI.

Mechanisms: Obesity and Inflammation

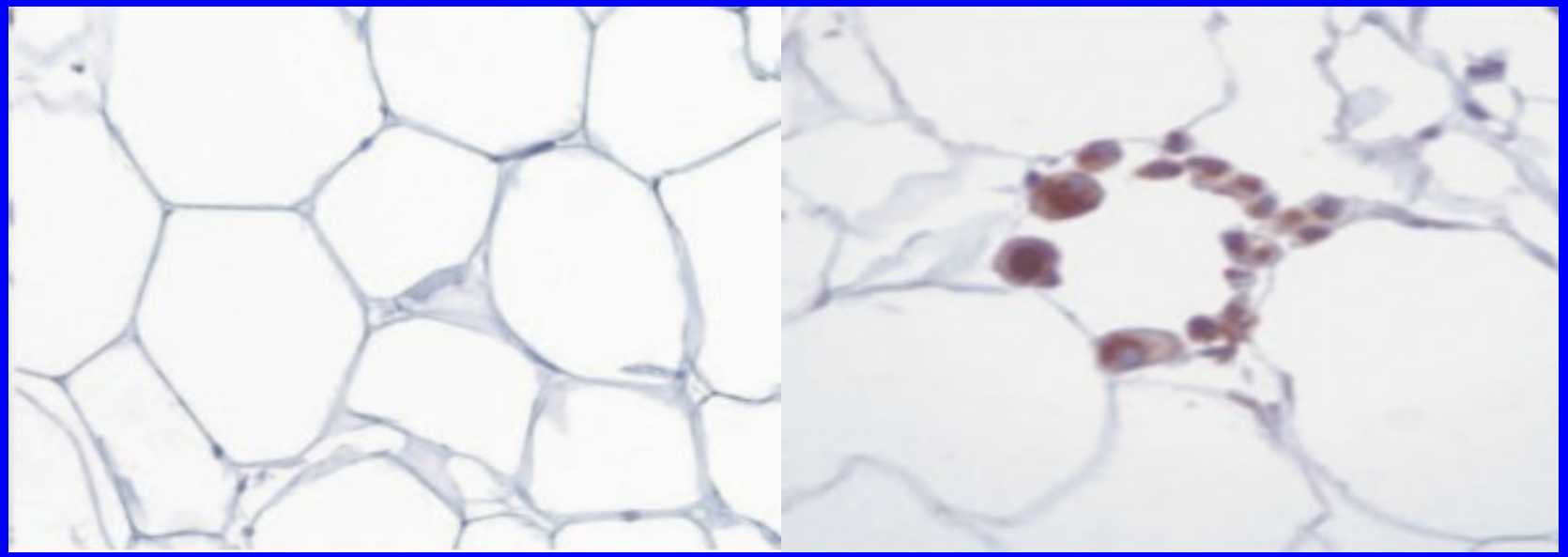
- Central obesity leads to invasion of the deep subcutaneous and visceral adipose tissues by activated macrophages that form “crown-like structures” (CLS) around adipocytes.

- Fred Sattler (USC), Scott Letendre (UCSD), and I have measured selected cytokines in 130 CHARTER patients and found that interleukin 6 (IL-6), a pro-inflammatory cytokine appeared to mediate the relationship of central obesity to NCI.

Obesity and adipose tissue inflammationinflammation

Normal Fat

Inflammed fat with crown-like structures CLS = M1)

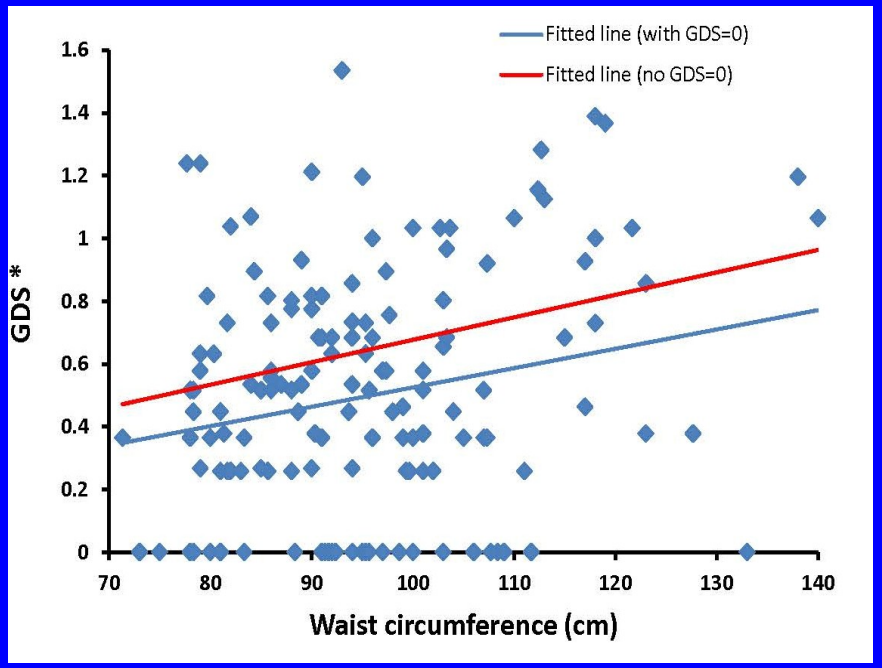


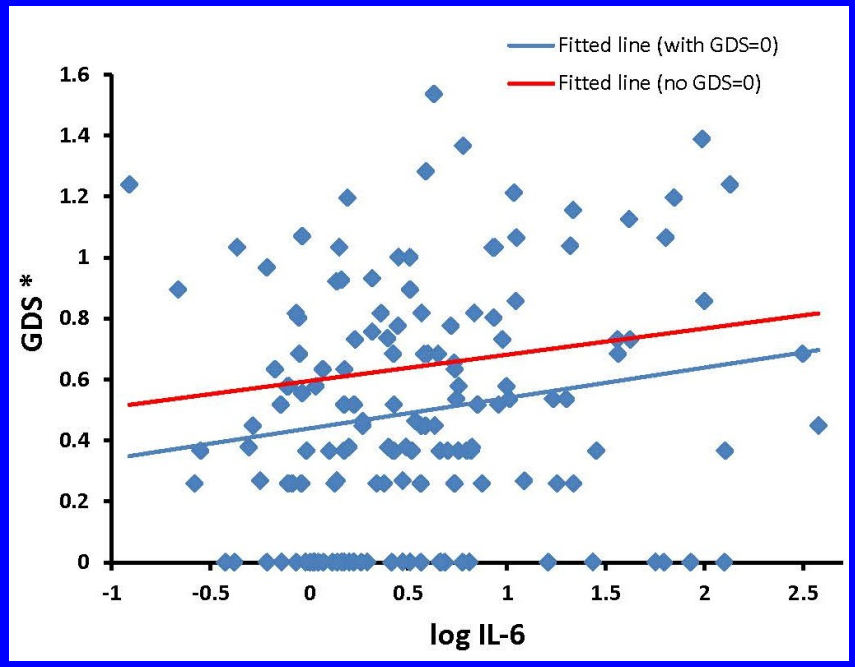
M2: "Alternatively Activated" Anti-inflammatory
(IL-4, IL-13, PPARγ and PPARα)

M1: "Classically Activated" Pro-inflammatory
(LPS, IFNγ, FFA stimulation TLR4)

Apovian 2008; Lumeng, 2008

Both waist circumference and IL-6 increase with higher GDS (NCI)



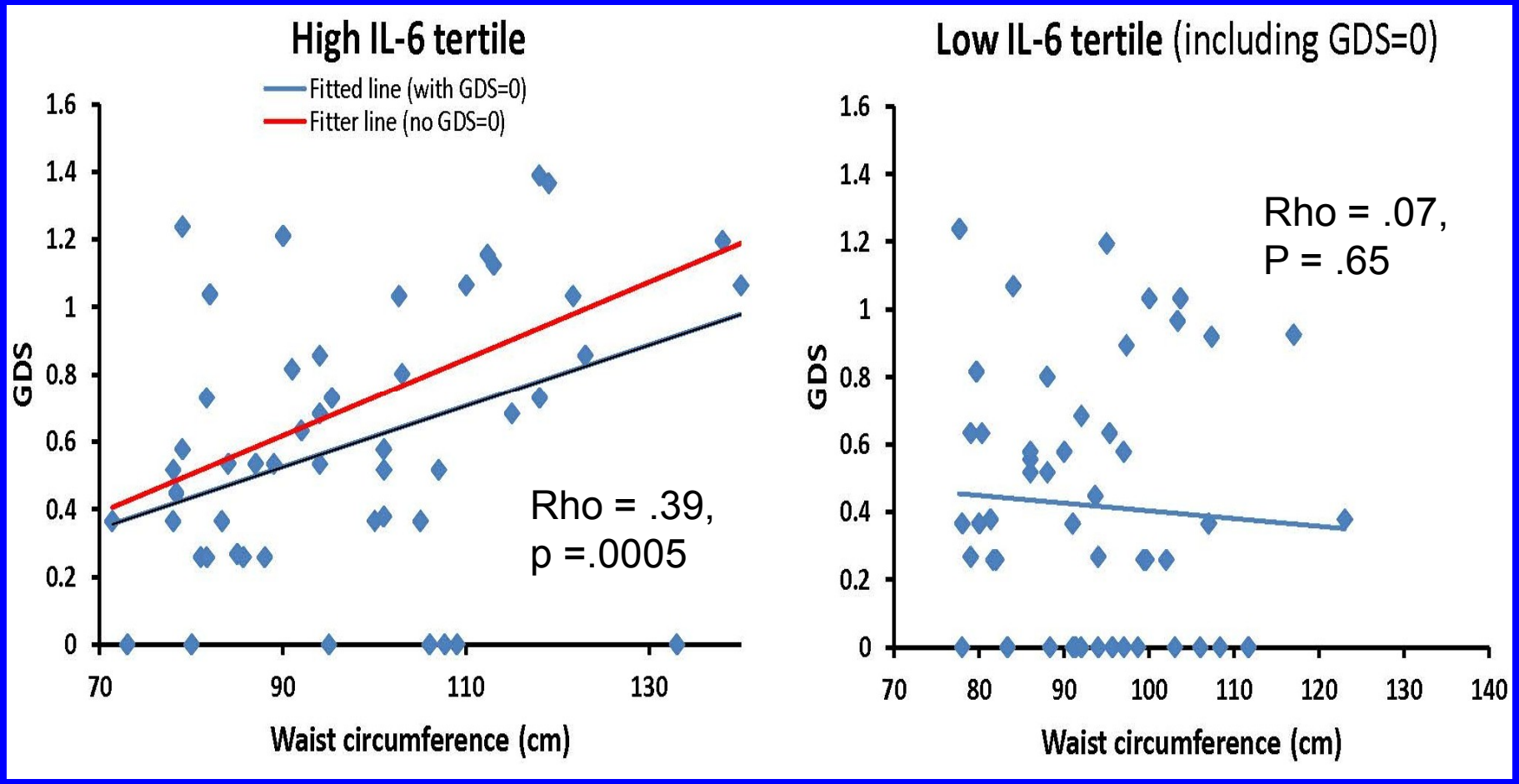


	rho	P value
WC with n=152	0.21	0.009
WC w/o GDS=0	0.31	0.0006

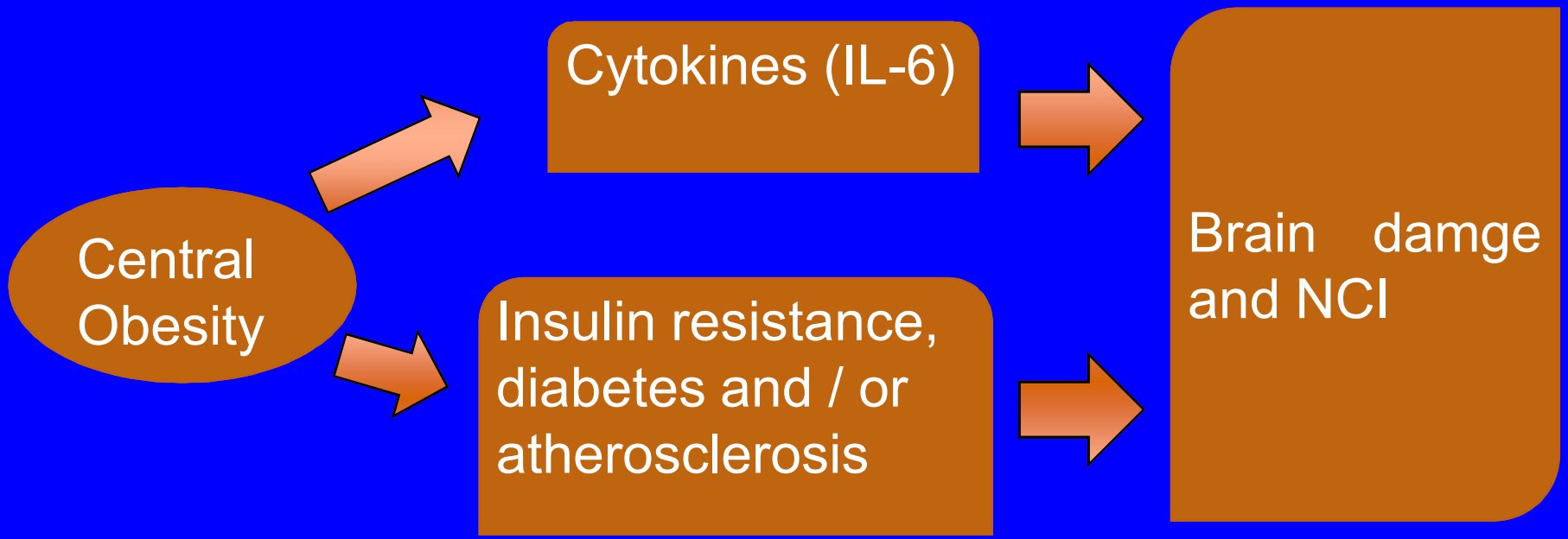
	rho	P value
IL-6 with n=152	0.17	0.04
IL-6 w/o GDS=0	0.18	0.055

* Square root of Global Deficit Score

WC correlates with GDS only in those with the highest tertile (1/3) of blood IL-6 levels



Proposed mechanism for effects of central obesity on NCI



Overall Conclusions

- HIV+ populations have elevated levels of NCI and aging will expose them to added risk from diabetes and obesity.
- Thus, combined effects of these 3 common, global, epidemic diseases (HIV, obesity, and diabetes) will contribute to an increasing prevalence of HAND and its consequences.
- Therapy for this mechanism of HAND might target:
  - » Reducing generalized and central obesity (eg, exercise, tesamorlin (growth hormone releasing factor agonist), or bariatric surgery), or
  - » Anti-inflammatory drugs (eg, NSAIDs)

Support

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