Hostility, Adiposity and the Adrenal Medulla

Psychological Factors And The Physiology of Glucose Regulation

Richard S. Surwit

Disclosure: This work is supported by R01HL076020 and P01HL36587.

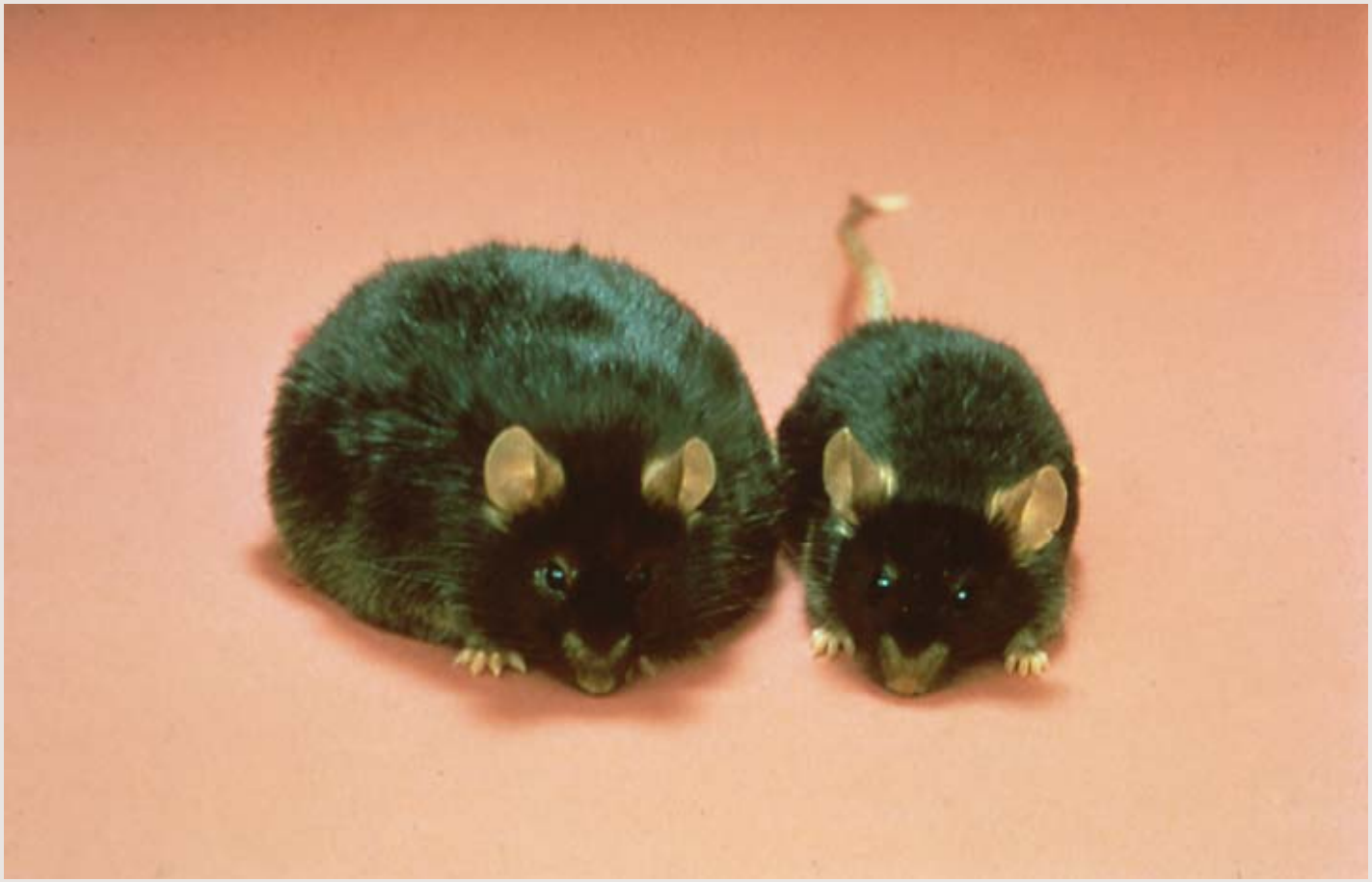
Duke
UNIVERSITY

Background

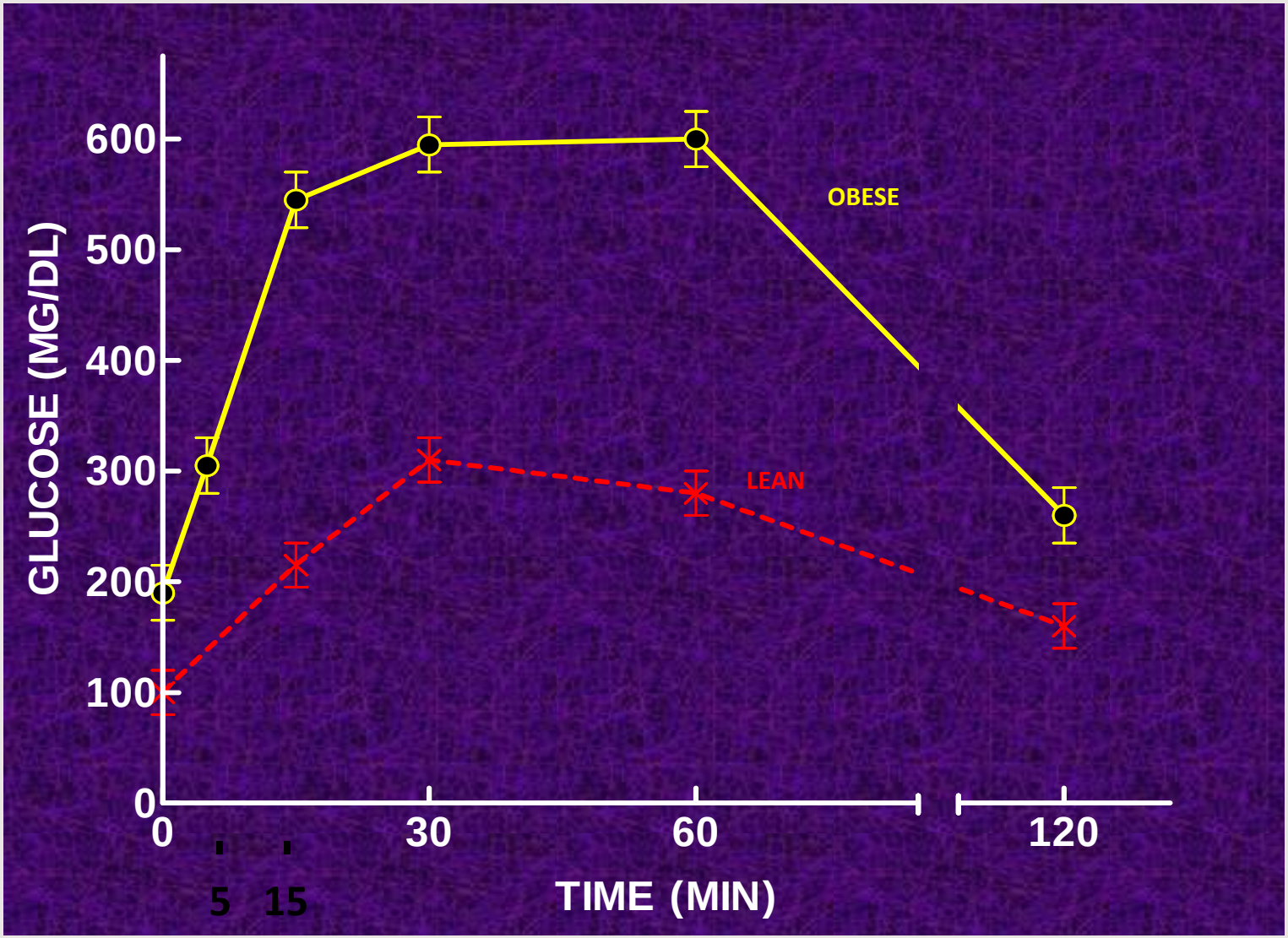
- Exaggerated glycemic response to stress and to epinephrine (EPI) have be found in animals and humans predisposed to obesity and diabetes

Duke
UNIVERSITY

C57BL6J *Ob/Ob* Mouse



Duke
UNIVERSITY

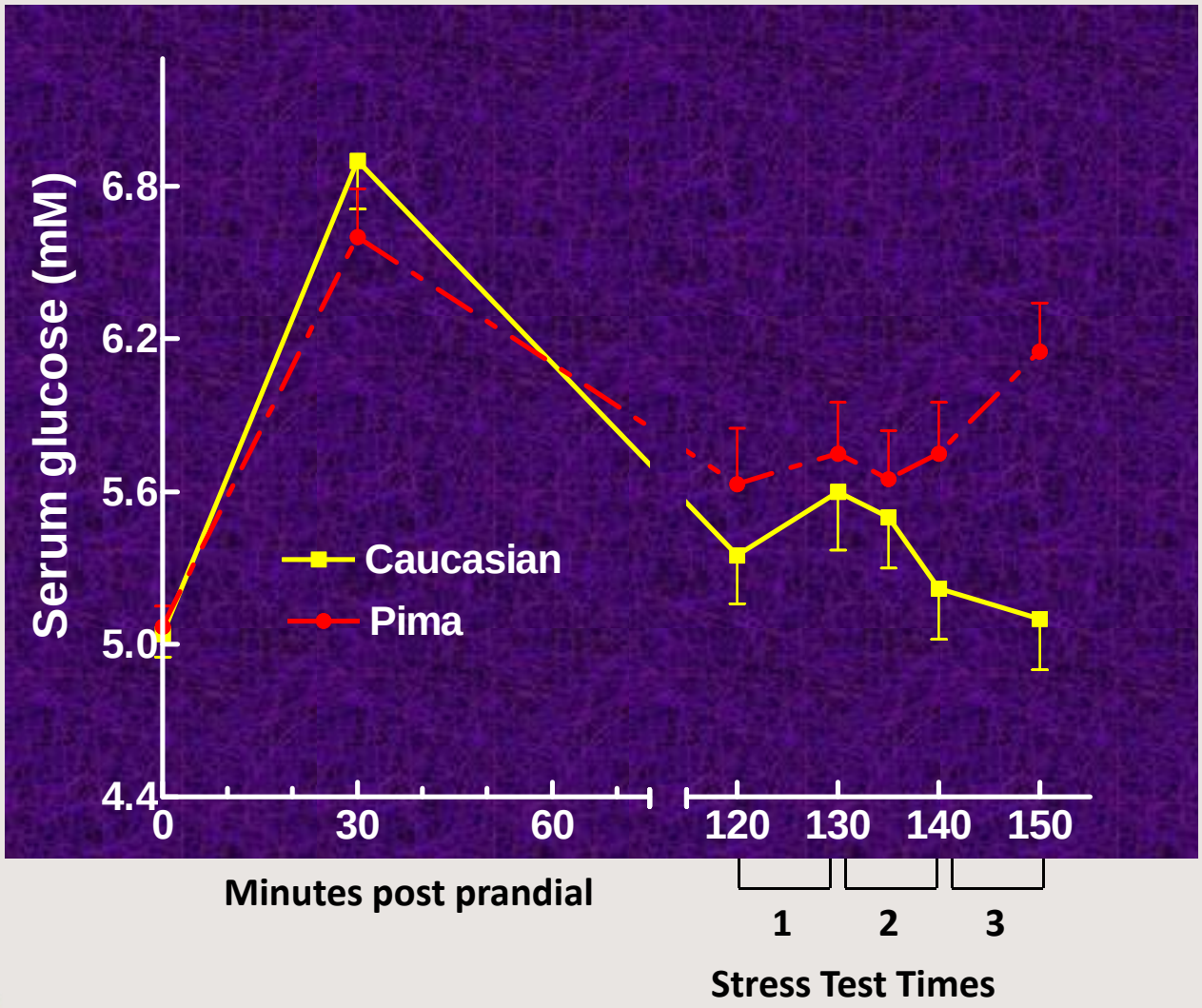


Duke UNIVERSITY

Kuhn et al: 1987, *PHARMACOLOGY, BIOCHEMISTRY & BEHAVIOR*

Pima Indians

Duke
UNIVERSITY



Esposito-del Puente, 1994, *International Journal of Obesity*

Personality Factors Have Also Been Related to Glucose Metabolism

- Depressed affect
- Hostility

Duke
UNIVERSITY

Hostility

- Hostility is a personality construct that has been associated with increased risk of cardiovascular disease and all cause mortality.

Duke
UNIVERSITY

Hostility is Commonly Measured By The 27 item Cook Medley Hostility Questionnaire (CMHOST)

Covers primary cognitive dimensions reflecting cynicism and mistrust

"I think most people would lie to get ahead."

"People often disappoint me."

"It's safer to trust nobody"

Duke
UNIVERSITY

The Mechanism of Hostility's Relationship to Disease is Unknown

- Hostility has been related to increased neuroendocrine response to stress.
- Hostility has also been associated with increased food intake, BMI, and decreased insulin sensitivity.

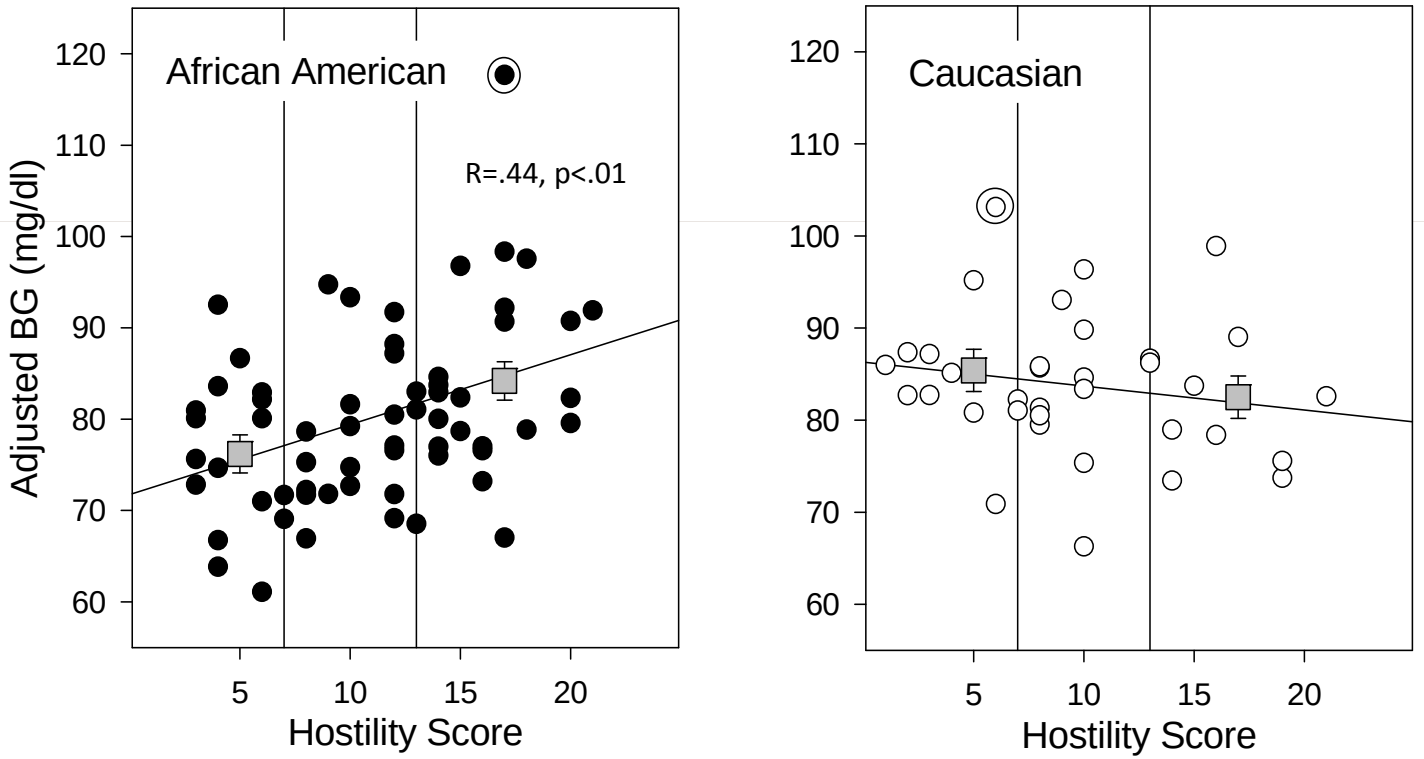
Duke
UNIVERSITY

Does Hostility Impact Glucose Metabolism?

- Fasting glucose and HbA1c are linearly related to risk for cardiovascular disease, even throughout the “normal” range.

Duke
UNIVERSITY

Hostility Is Correlated with Fasting Glucose in African Americans



Surwit et al 2002, *Diabetes Care*

Relationship of Hostility to Fasting Glucose Was Repeatedly Found in African American Women

	Study A N=101	Replication Study B N=44	Replication Study C N=38
Fasting glucose	.22*	.34*	.34*

*p<.04

Georgiades, et al, 2009 *Psychosomatic Medicine*

Duke UNIVERSITY

How Does Hostility Impact Glucose Metabolism?

- Determine the variables which may mediate Hostility's impact glucose metabolism in these populations
  - Sympathoadrenal activity
  - BMI
  - Physical Activity
- Determine the relationship between Hostility and glucose kinetics in healthy White and African American men and women

Surwit et al, 2009, *Psychosomatic Med*

Duke
UNIVERSITY

The Labeled IVGTT

- Enables modeling of glucose kinetics in vivo
- Enables separation of endogenous glucose (from liver and kidneys) from exogenous glucose

Duke
UNIVERSITY

Method

- 115 African American and White male and female volunteers
- Glucose bolus (300mg/kg) containing 2mg/kg (0.7%) $^{13}C_6$-glucose administered by IV push (1 min)
- Specimens collected at t= -1, 2, 3, 4, 5, 6, 10, 12, 15, 20, 30, 40, 60, 80, 100, 120, 140, 150, 180, 210, 240 min.
- Total Glucose & Insulin assayed
- Glucose Isotope ratio by mass spec

Duke
UNIVERSITY

Minimal Model of Glucose Kinetics

- **DI=** Glucose Disposition Index, reflects the ability of the beta cells in the pancreas to compensate for increased insulin resistance.
- **Sg=** Glucose effectiveness, is a measure of the ability of glucose to stimulate its own uptake independent of insulin.
- **AIRg=** Glucose-stimulated insulin release.
- **Si=** Insulin Sensitivity.
- **NEFA=** Non-esterified fatty acids.
- **EGP=** Endogenous glucose production, refers to glucose produced in the liver and kidneys through the process of gluconeogenesis.

Duke
UNIVERSITY

- Hostility was related to metabolic parameters *only* in African American Women

- Hostility was unrelated to self-report of physical activity as measured by the IPAQ.

Duke
UNIVERSITY

Hostility and BMI

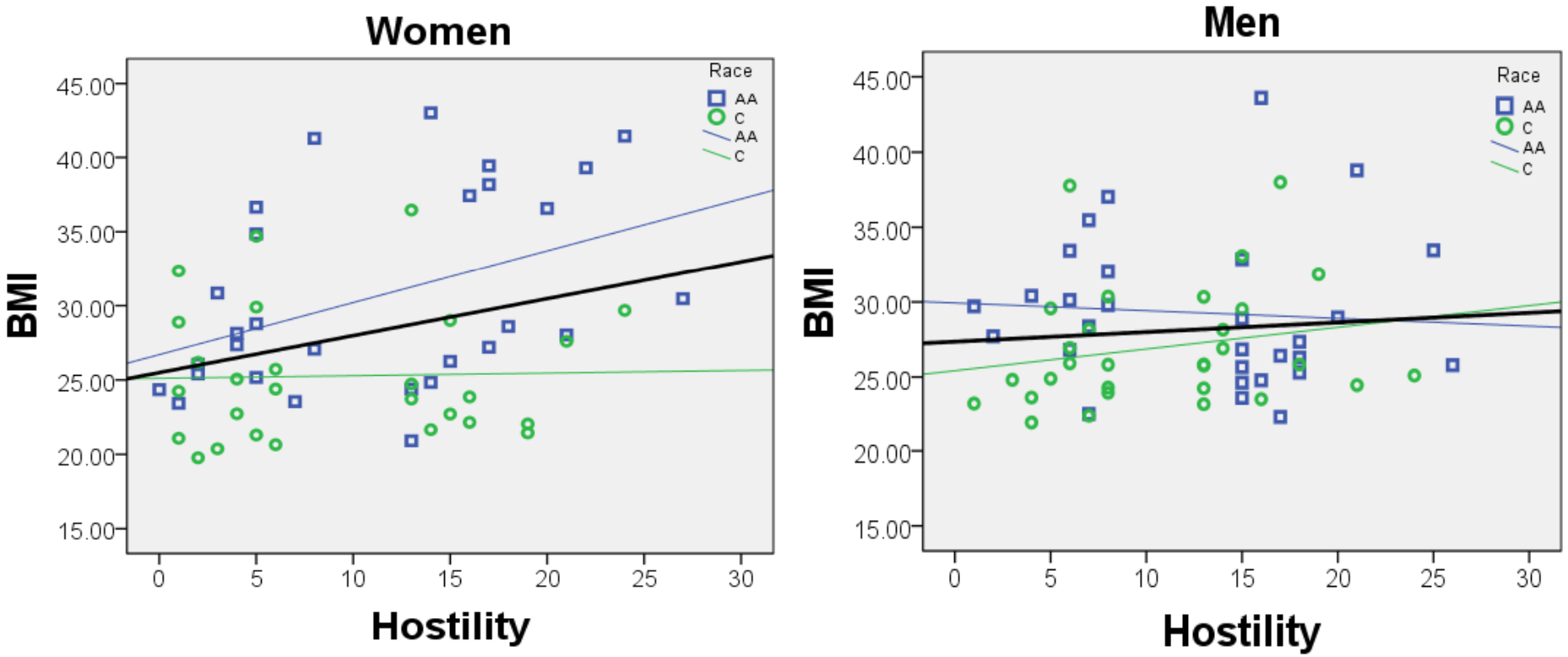
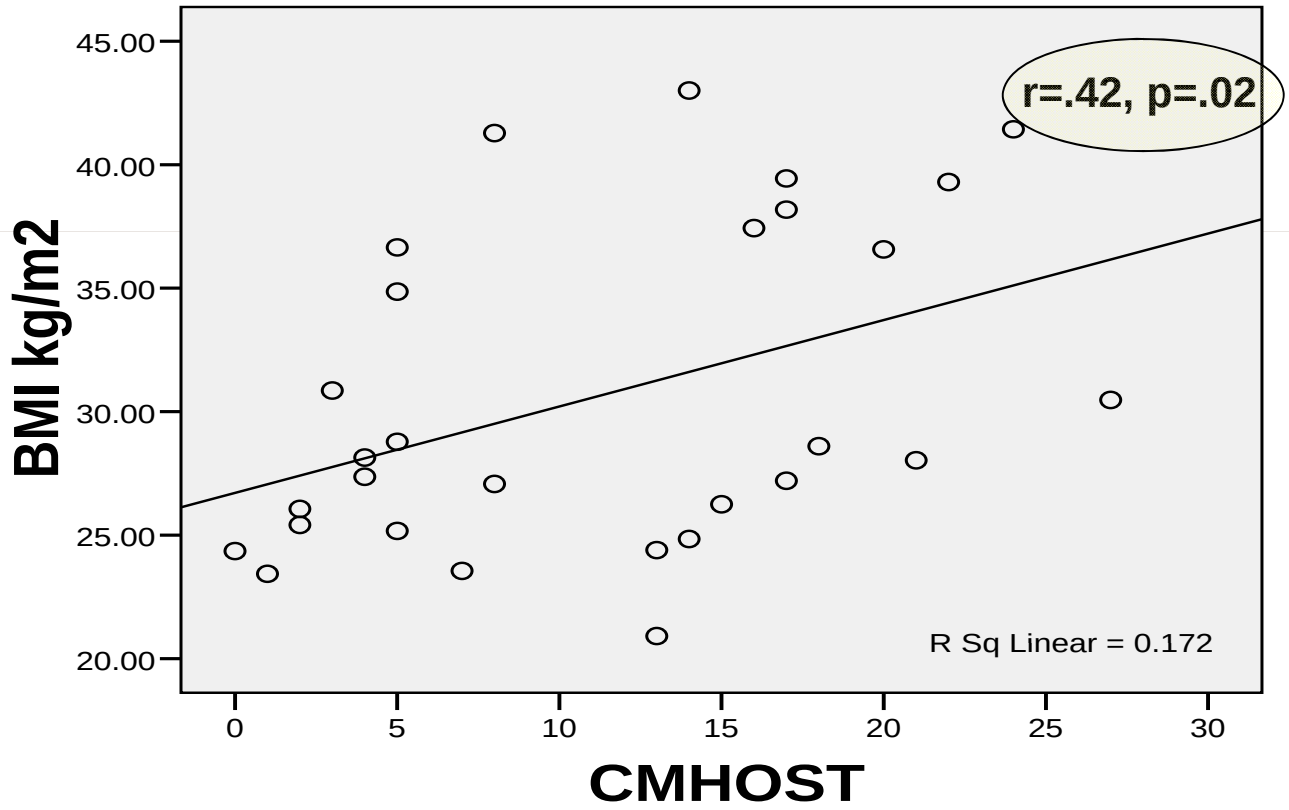


Figure 1. Association of Hostility to BMI in women and men. Blue squares and lines represent African Americans and green circles and lines represent Whites.

Duke
UNIVERSITY

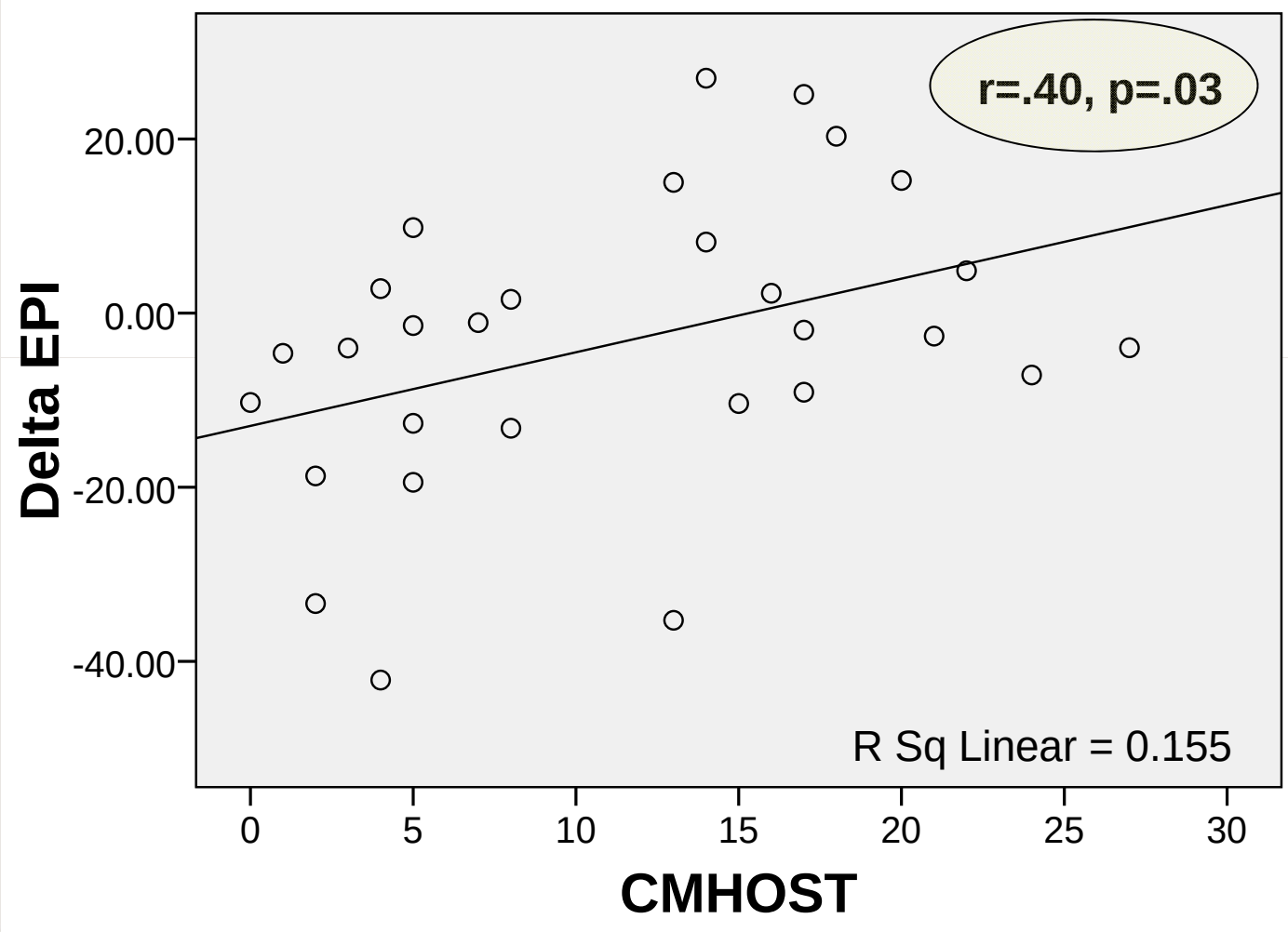
Relationship of Hostility to BMI in African American Women



Duke UNIVERSITY

Surwit, R. S. et al. *Psychosomatic Medicine*, 2009

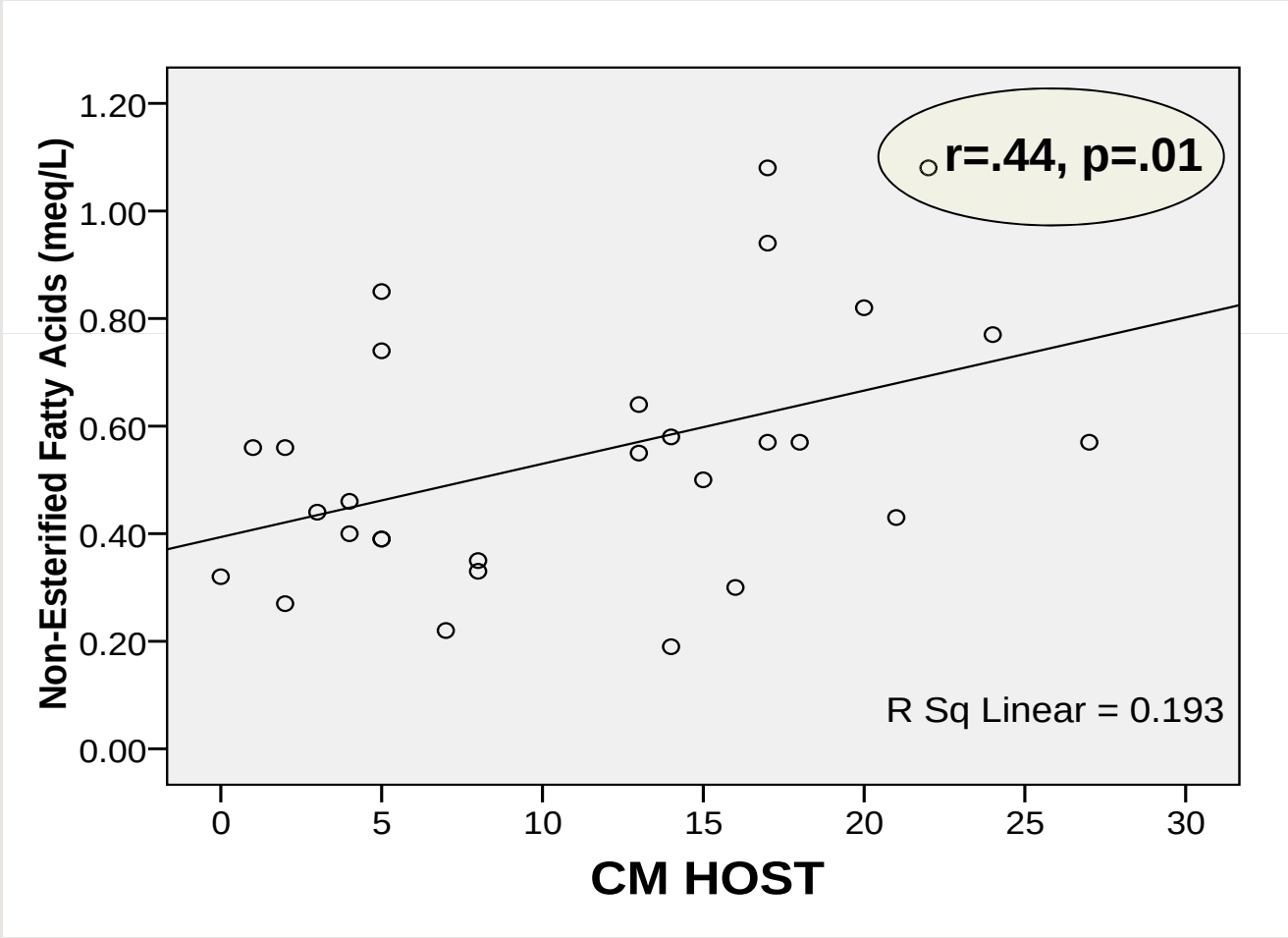
Relationship of Hostility to Epinephrine Change in African American Women



Duke UNIVERSITY

Surwit, R. S. et al. *Psychosomatic Medicine*, 2009

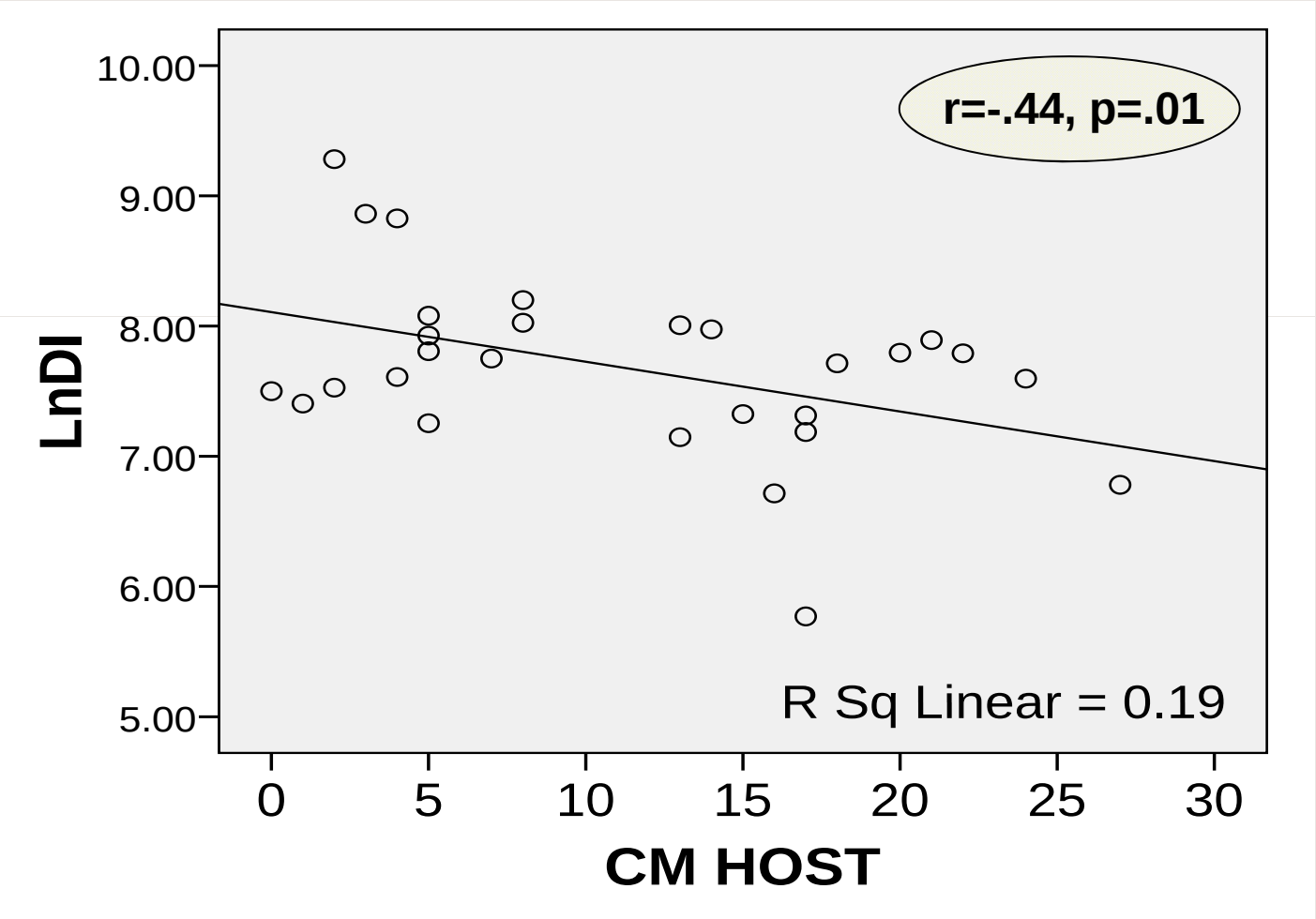
Relationship of Hostility to Fasting NEFA in African American Women



Duke UNIVERSITY

Surwit, R. S. et al. *Psychosomatic Medicine*

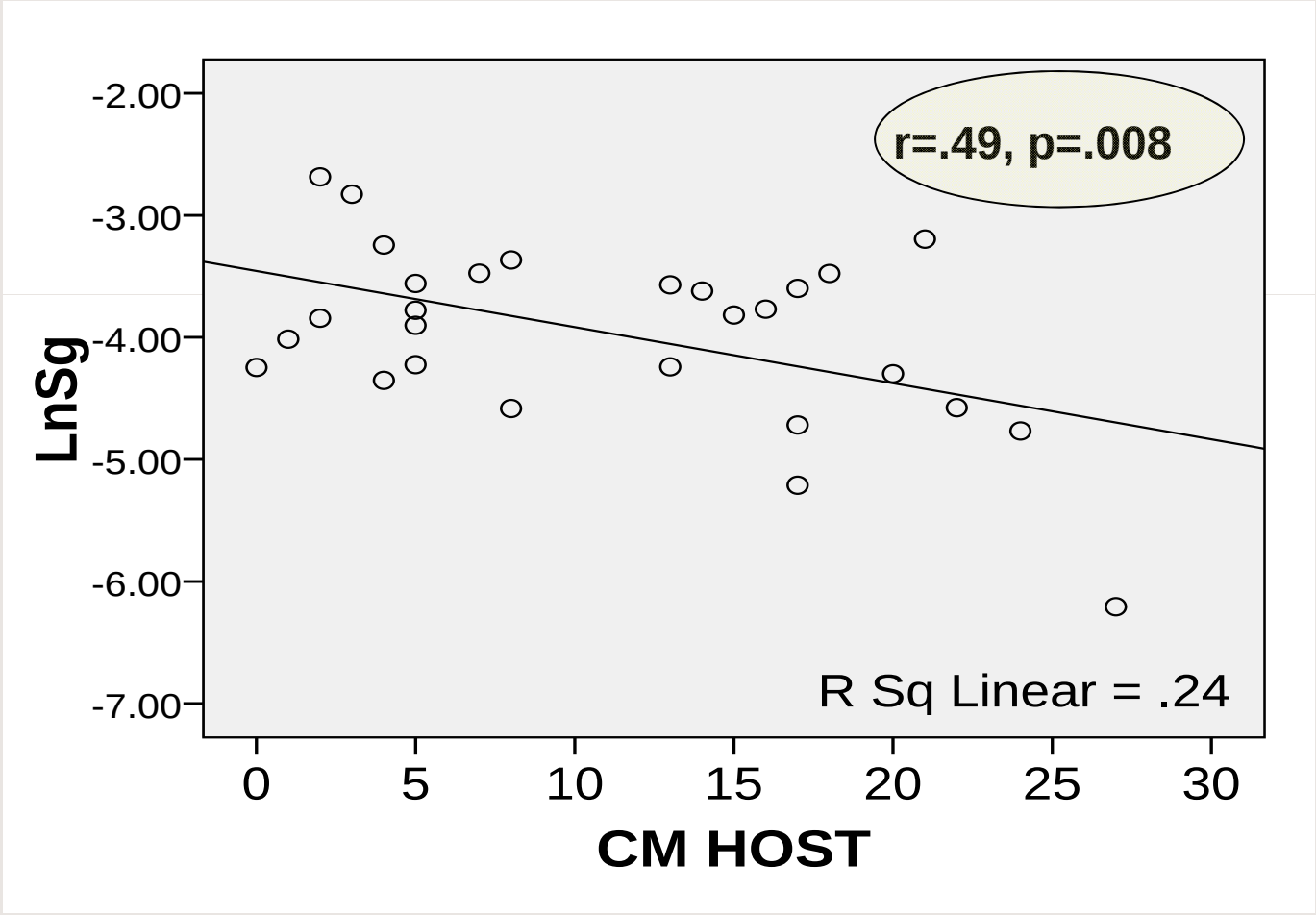
Relationship of Hostility to DI in African American Women



Duke UNIVERSITY

Surwit, R. S. et al. *Psychosomatic Medicine*, 2009

Relationship of Hostility to Sg in African American Women



Duke UNIVERSITY

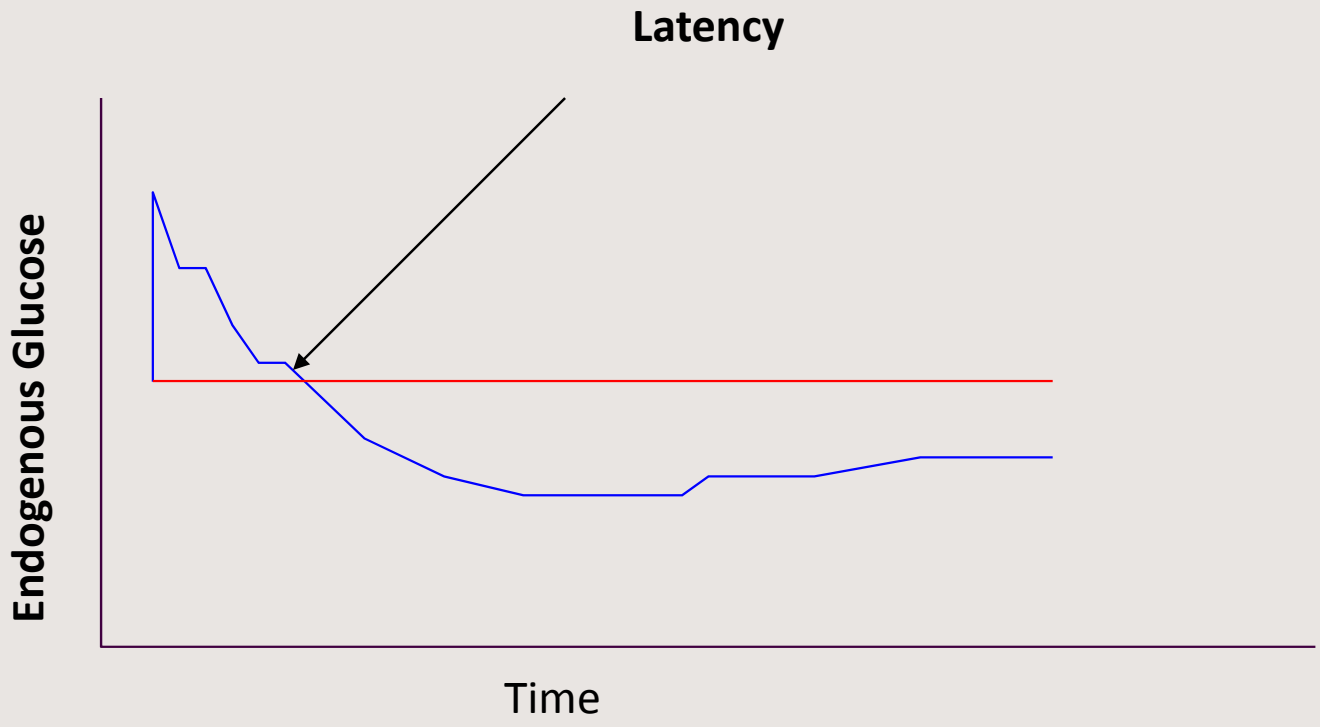
Surwit, R. S. et al. *Psychosomatic Medicine*, 2009

Hostility is Related to Hepatic Glucose Production

- Hepatic glucose production was estimated by assessing the ratio of labeled to unlabeled glucose and then measuring the latency of suppression of hepatic glucose following the IV bolus

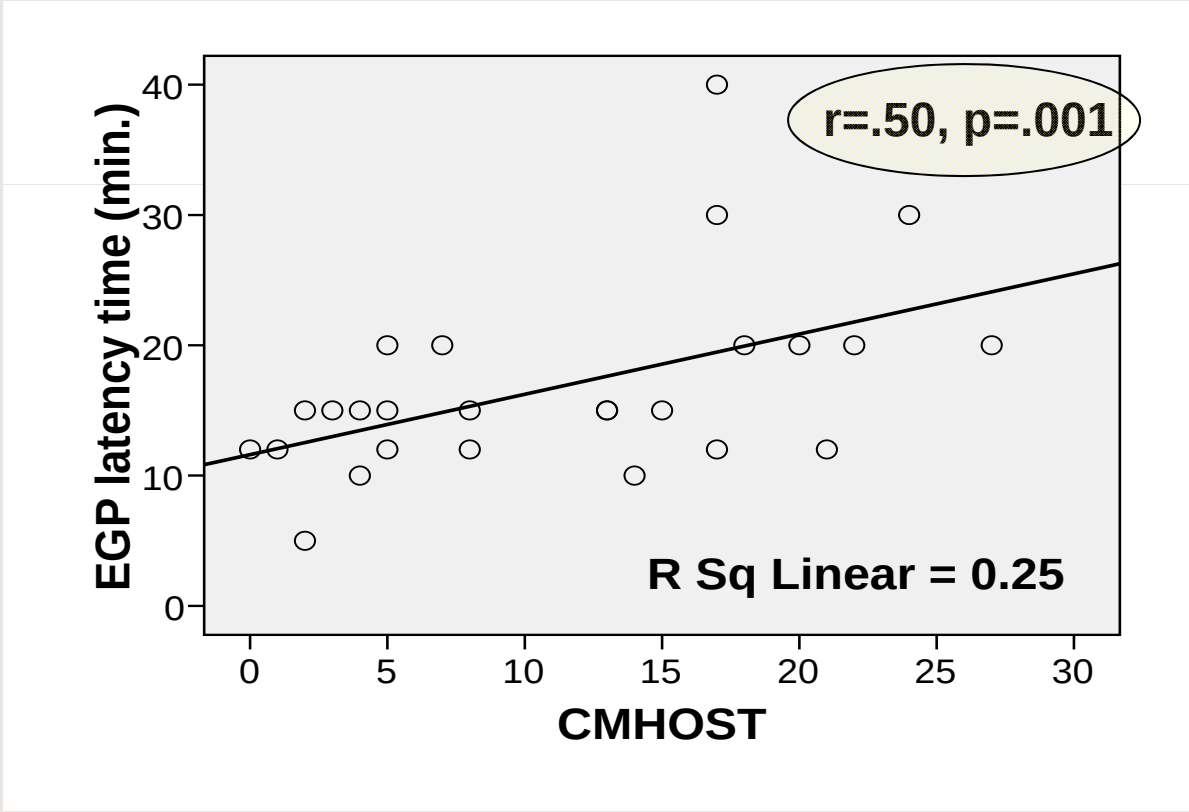
Duke
UNIVERSITY

Latency Time of Endogenous Glucose Suppression During the IVGTT



Duke
UNIVERSITY

Hostility Was Associated with Increased Time to Suppression of Endogenous Glucose in African American Women



Duke UNIVERSITY

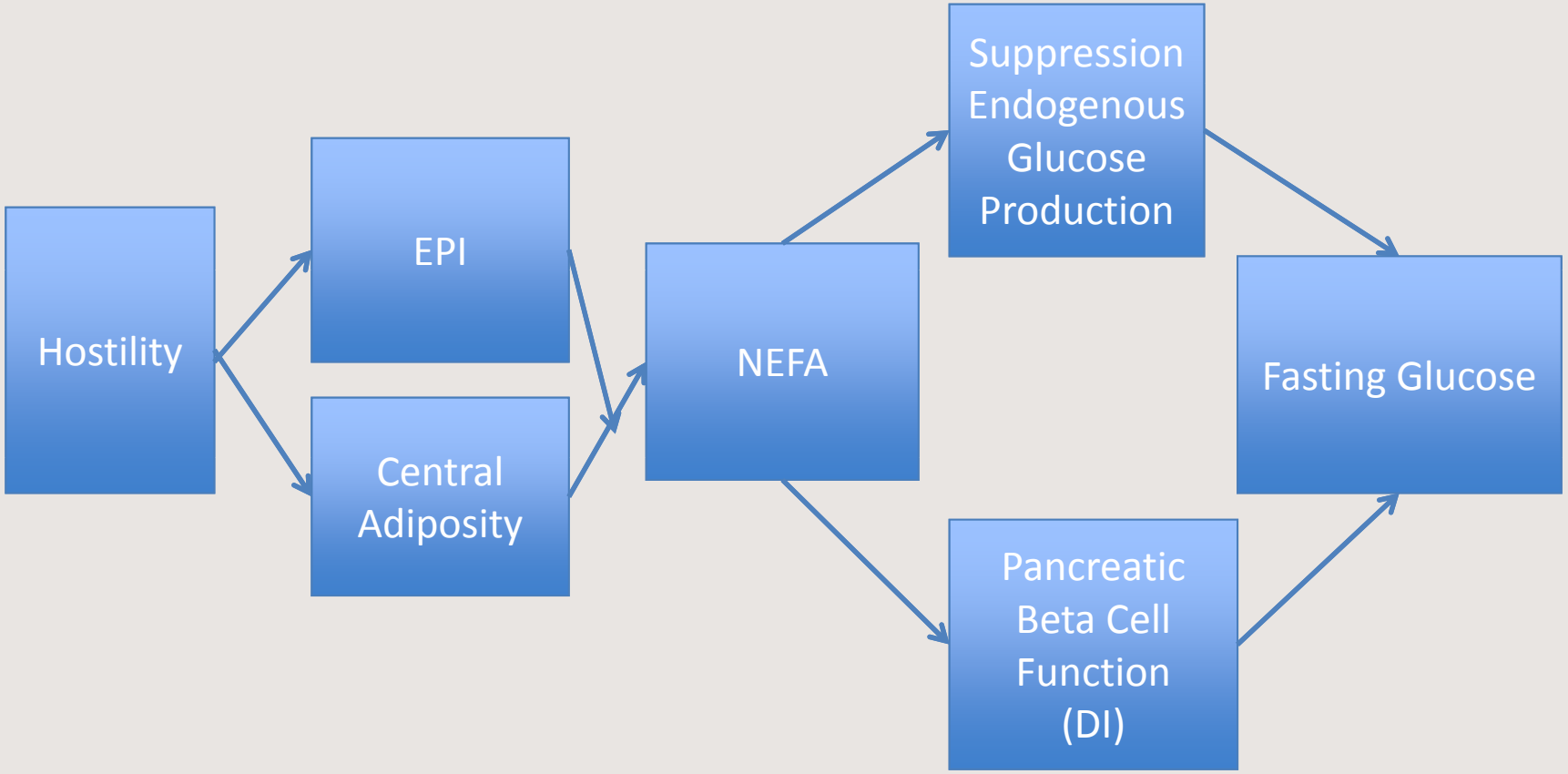
Endogenous Glucose Latency Time in Relation to NEFA and Sg

	Spearman's rho
NEFA	.50*
Sg	.50*

* *P*<.01

Duke UNIVERSITY

How Hostility Appears to Impact Fasting Glucose



Duke
UNIVERSITY

Hostility, Metabolism and Serotonin

- Recent studies showed that AN SSRI (citalopram) successfully reduced hostility and improved metabolic parameters in high hostile individuals. Kamarck et al, Psychosomatic Medicine, 2009, Psychoneuroendocrinology, 2011).

Duke
UNIVERSITY

Does Serotonin Metabolism Play a Role in the Relationship of Hostility to Metabolic Function?

Duke
UNIVERSITY

Methods

Sample

37 healthy African American women. Mean age 32(9) years.

Measures

Hostility was assessed by a 27-item version of the Cook-Medley Hostility Scale. Tryptophan (TRYP), 5-OH-tryptophan (5HTP) and 5HIAA was assayed from cerebrospinal fluid drawn after lumbar puncture. Glucose and insulin were assayed from blood samples drawn after an overnight fast.

Duke
UNIVERSITY

Associations Among Study Variables

	TRYP	5HTP	5HIAA	Hostility	Glucose	Insulin
TRYP	1.00	.37*	.01	-.03	-.06	.16
5HTP		1.00	.52**	.43**	.42**	.56**
5HIAA			1.00	.46**	.38*	.29
Hostility				1.00	.52**	.41**
Glucose					1.00	.68**
Insulin						1.00

* $P<.05$, ** $P<.01$

Duke UNIVERSITY

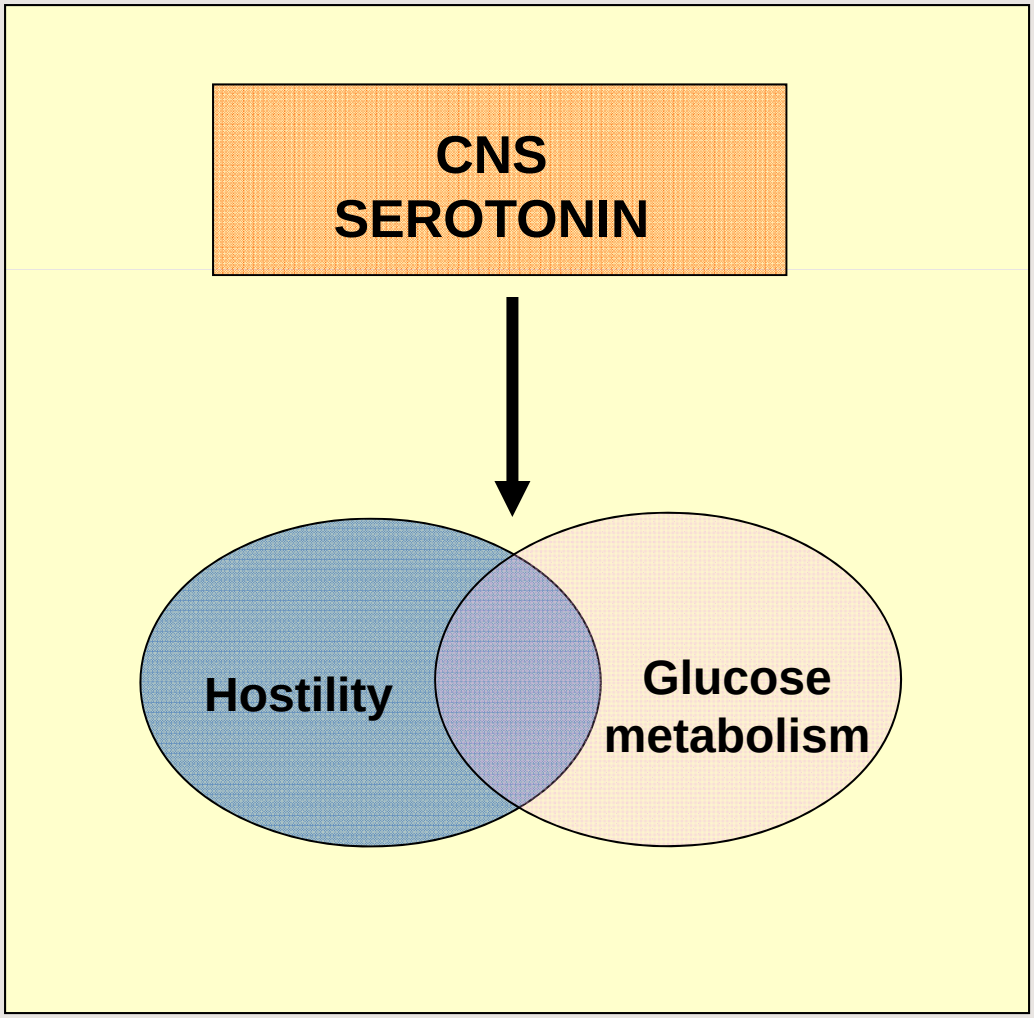
Boyle et al, 2010, *Psychosomatic Medicine*

Common Factor Analysis

A common factor analysis performed on age-adjusted hostility scores, fasting glucose and insulin, 5HTP and 5HIAA yielded a single factor (Eigenvalue = 2.31) in which all variables loaded above .55.

Duke
UNIVERSITY

Hypothesized Interrelations Between Central Serotonin, Hostility and Glucose Metabolism



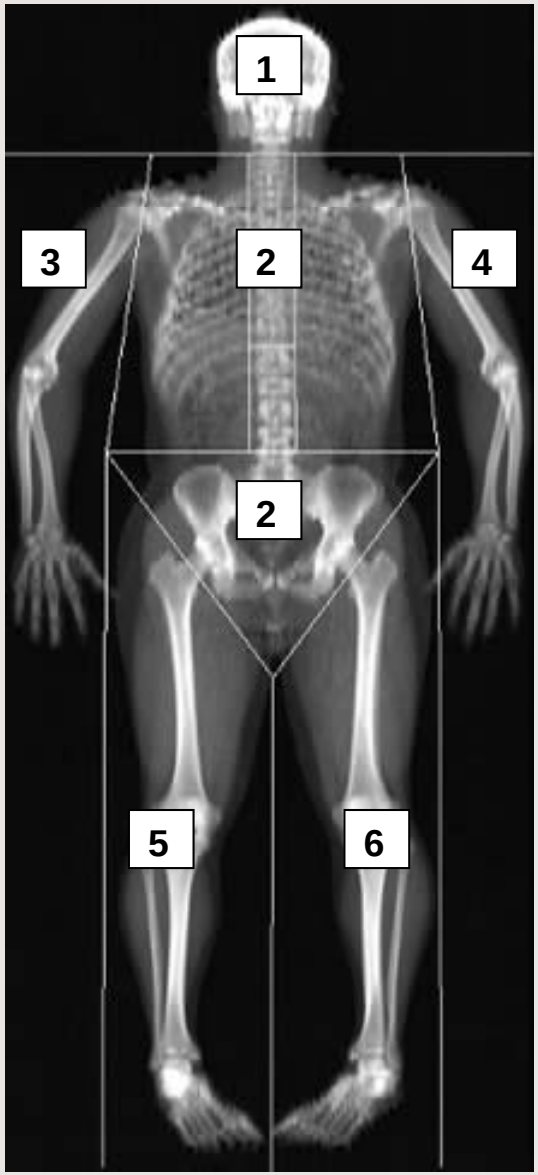
Duke
UNIVERSITY

Do Central Adiposity and Epinephrine Interact to Determine Glucose Levels in African American Women?

Duke UNIVERSITY

Surwit et al, 2010, *Obesity*

DEXA scan

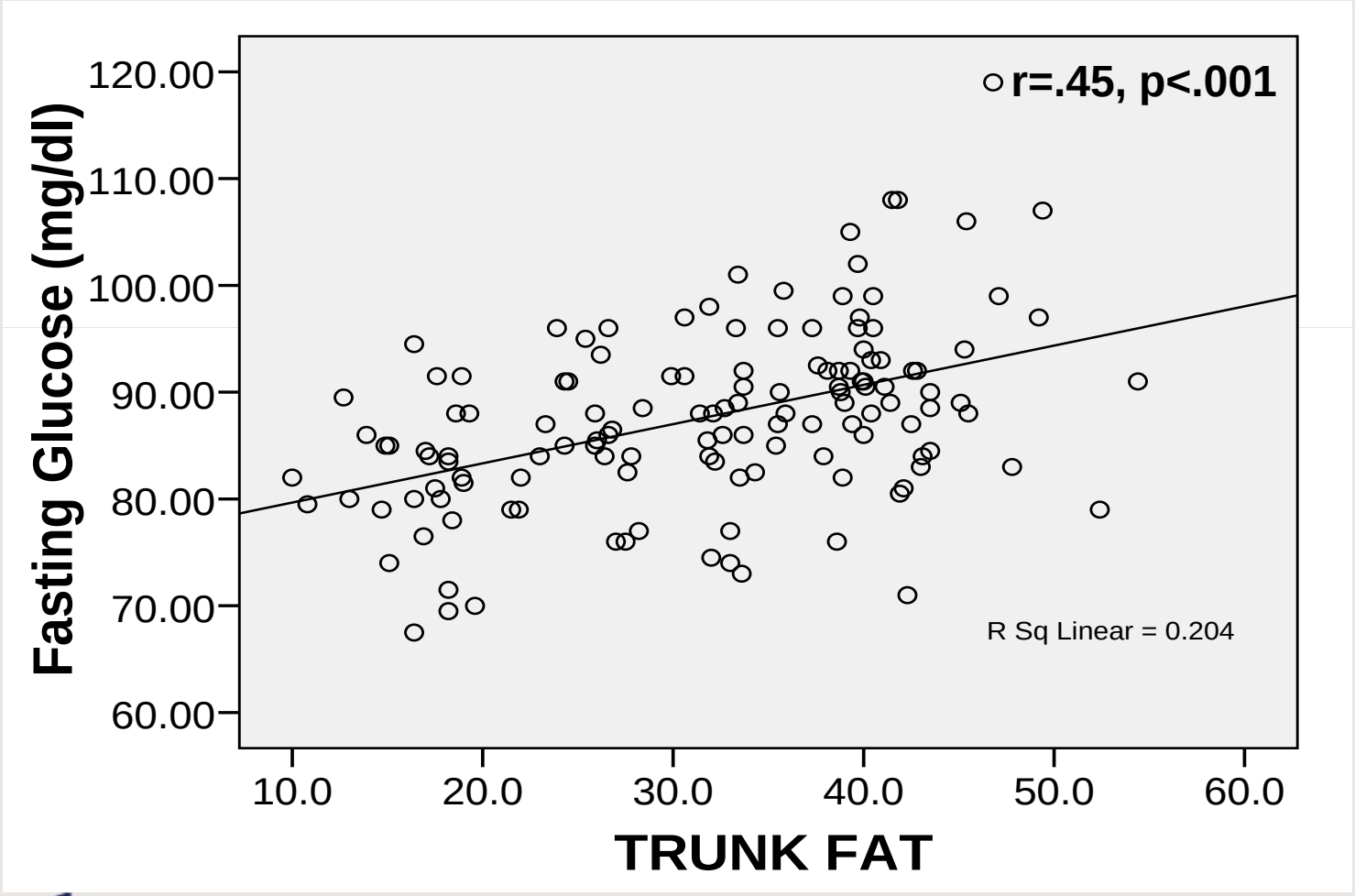


Standard regions of a DEXA scan:

1. head
2. trunk
3. right arm
4. left arm
5. right leg
6. left leg

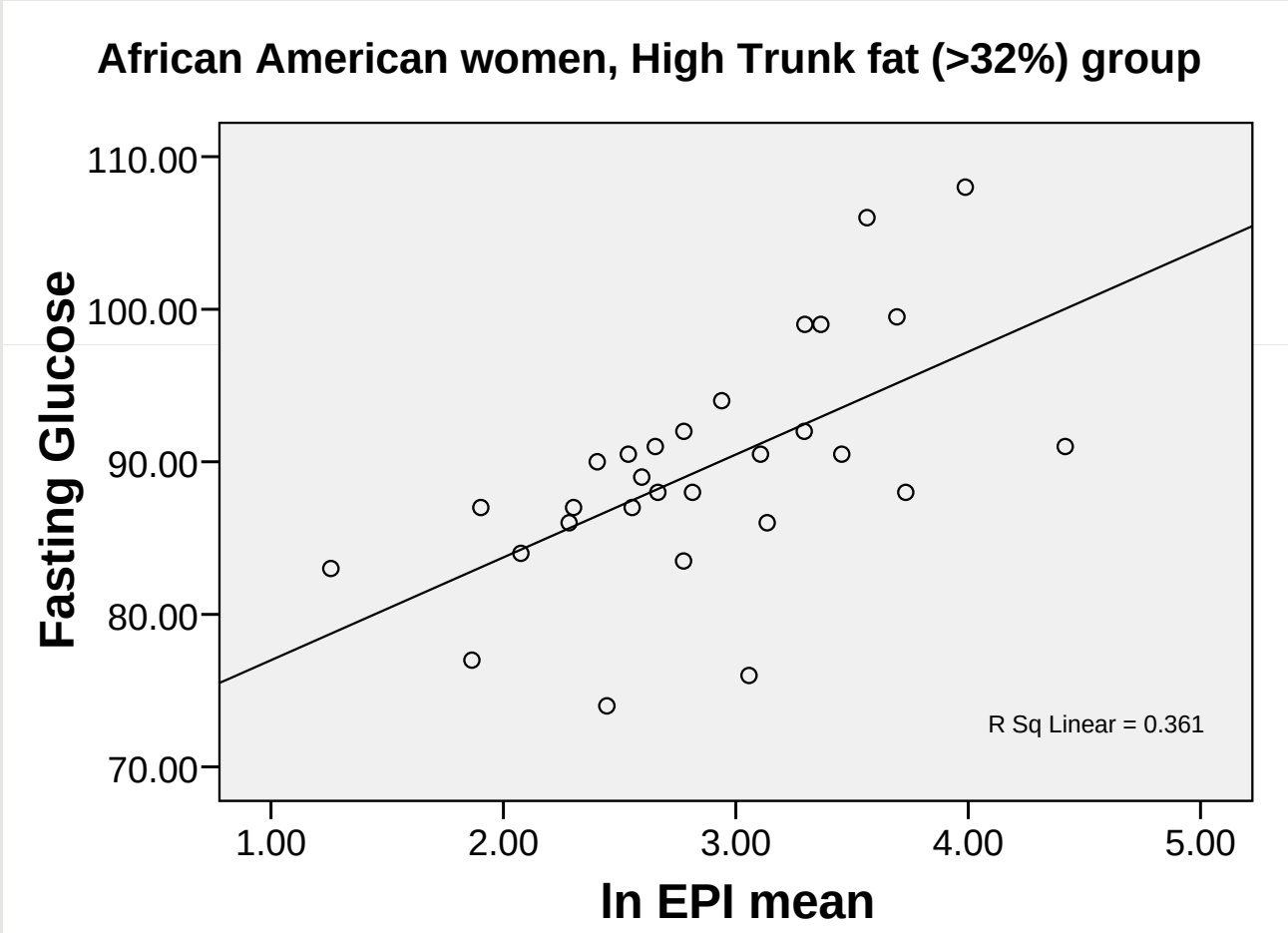
Duke UNIVERSITY

Association between % Trunk Fat and Fasting Glucose in African American Women



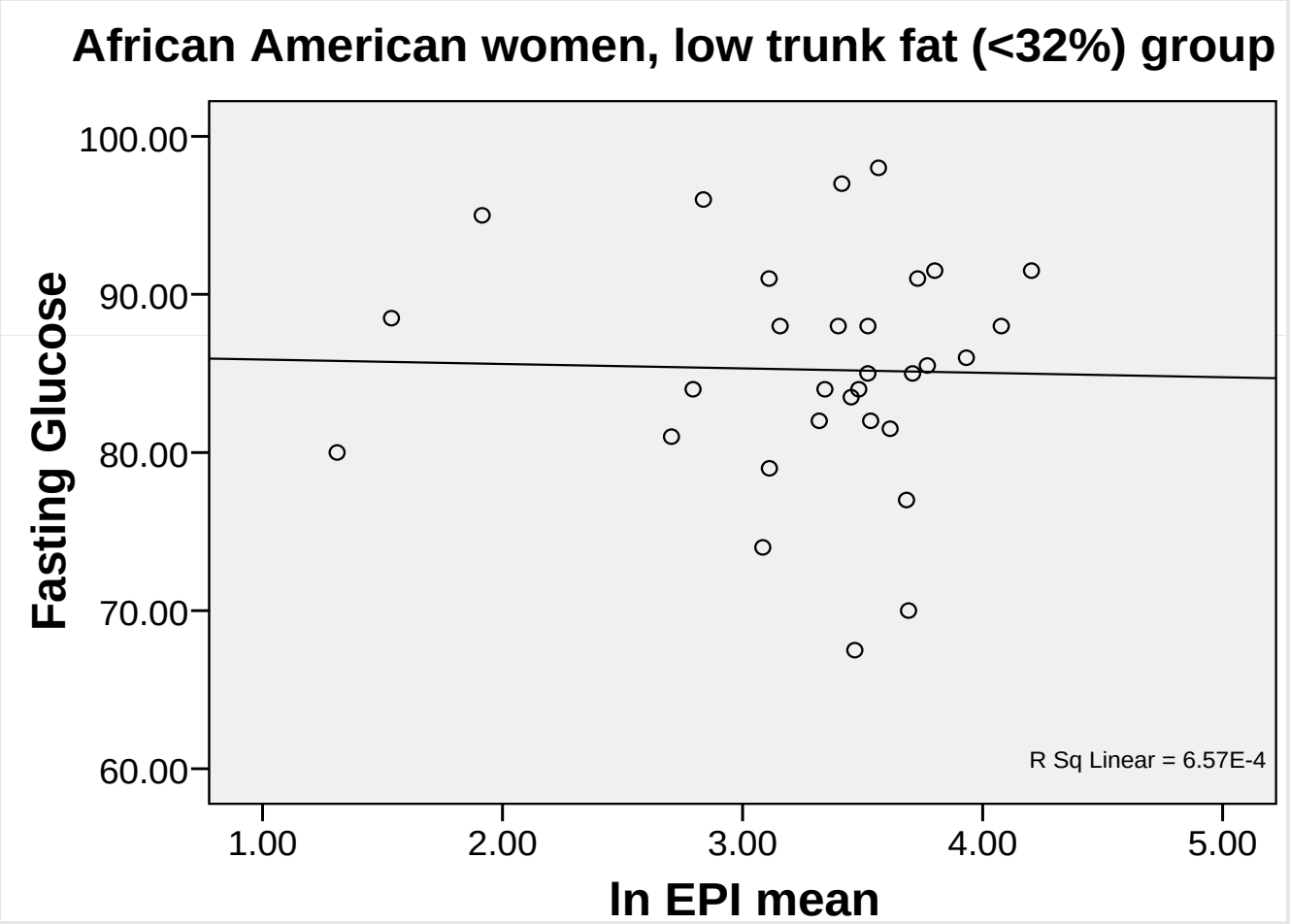
Duke UNIVERSITY

Association Between Plasma EPI Levels and Fasting Glucose in African American Women with High Central Adiposity



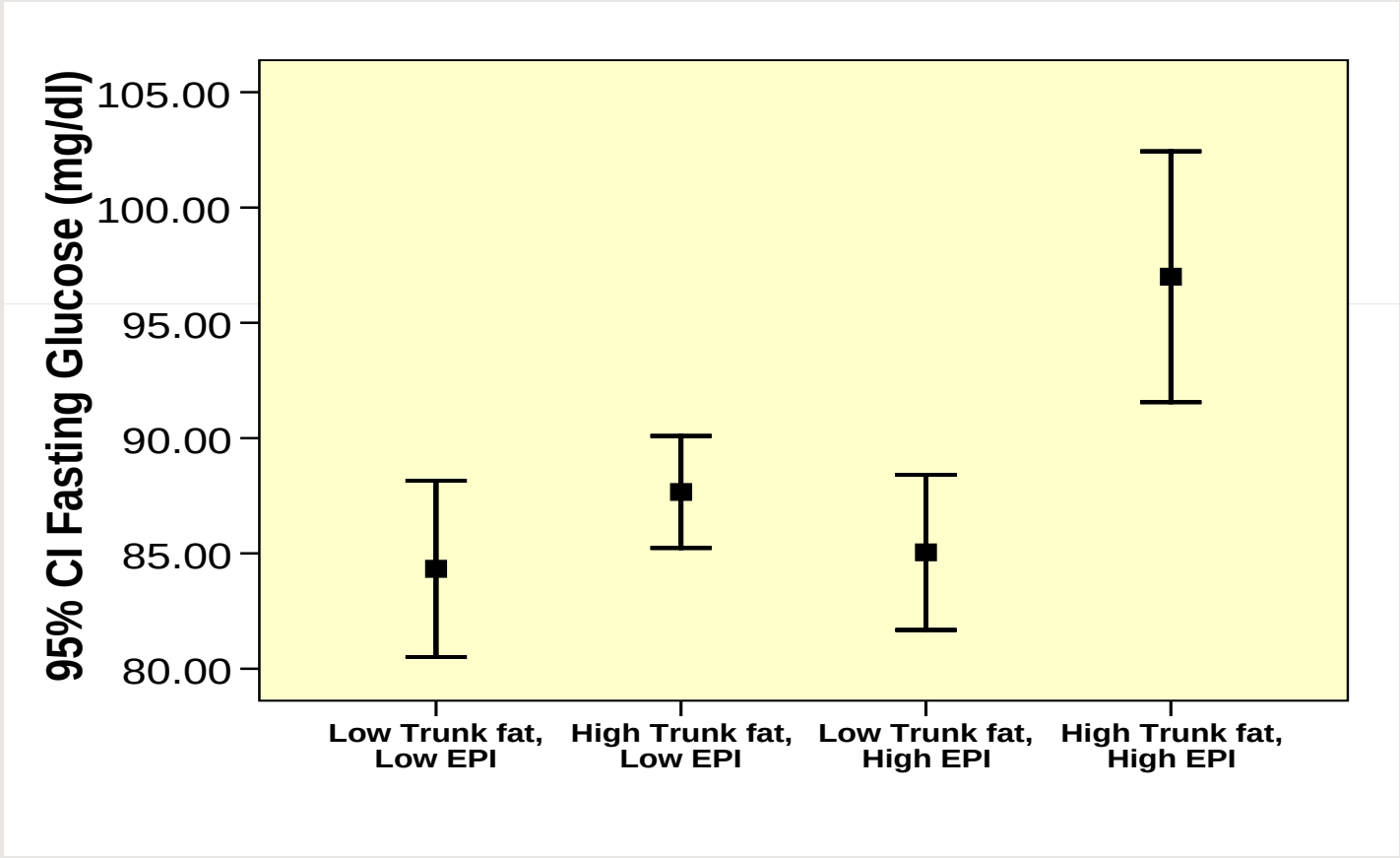
Duke
UNIVERSITY

Association Between Plasma EPI Levels and Fasting Glucose in African American Women with Low Central Adiposity



Duke
UNIVERSITY

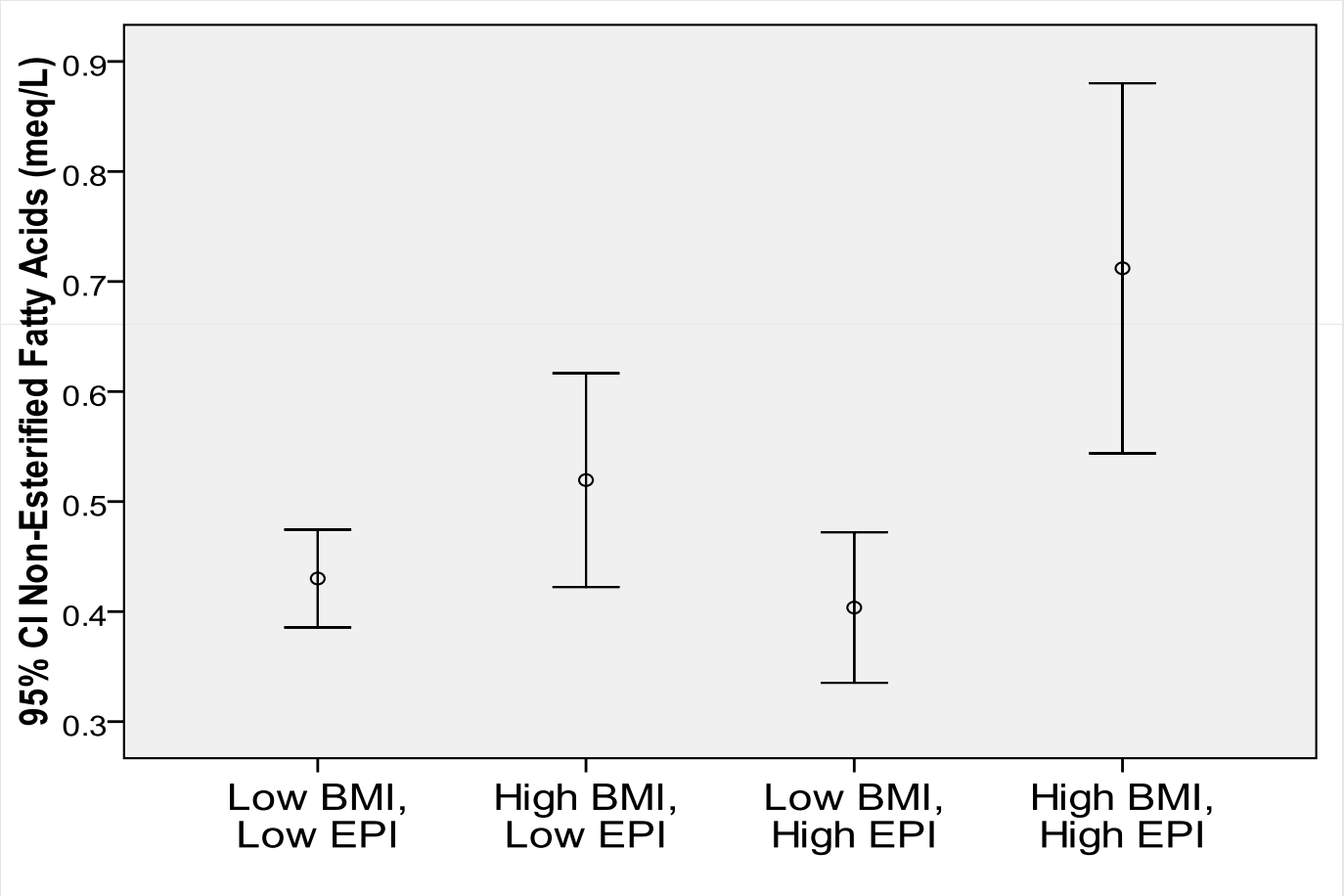
Fasting Glucose Levels by Trunk Fat Group (Low/High) and Epinephrine Group (Low/High)



Surwit et al. 2010, *Obesity*

Duke UNIVERSITY

NEFA levels by EPI and Obesity Group in African American Women



Duke UNIVERSITY

Conclusion

- Epinephrine interacts with central adiposity in determining fasting NEFA and fasting glucose in African American women

Duke
UNIVERSITY

Does Adrenal Medullary Function Play a Role in Maintaining Euglycemia?

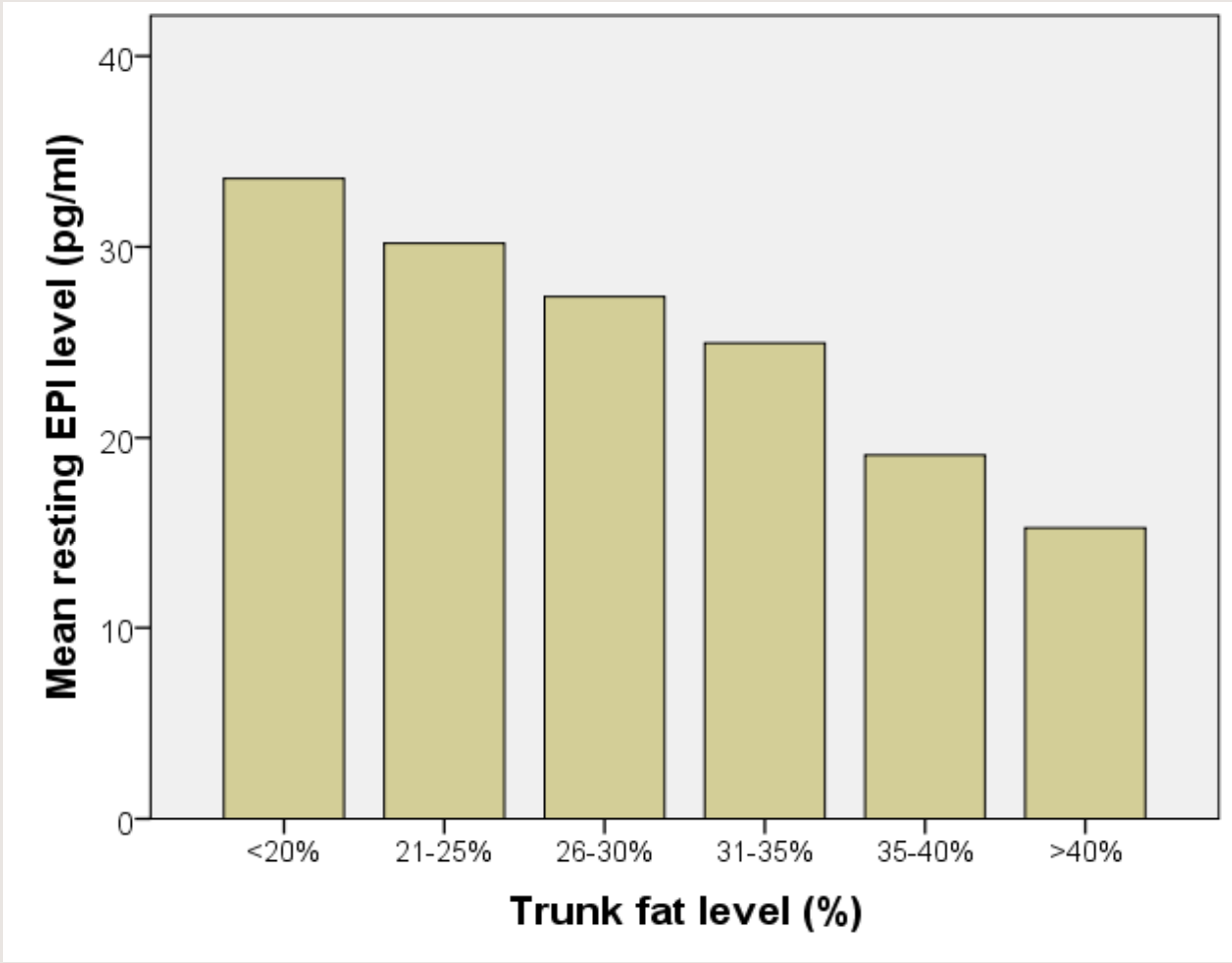
Duke
UNIVERSITY

Method

We examined 445 healthy euglycemic individuals (159 white women, 156 white men, 75 AA women and 55 AA men) who had completed a DEXA scan as well as collection of both plasma and urine epinephrine measurements.

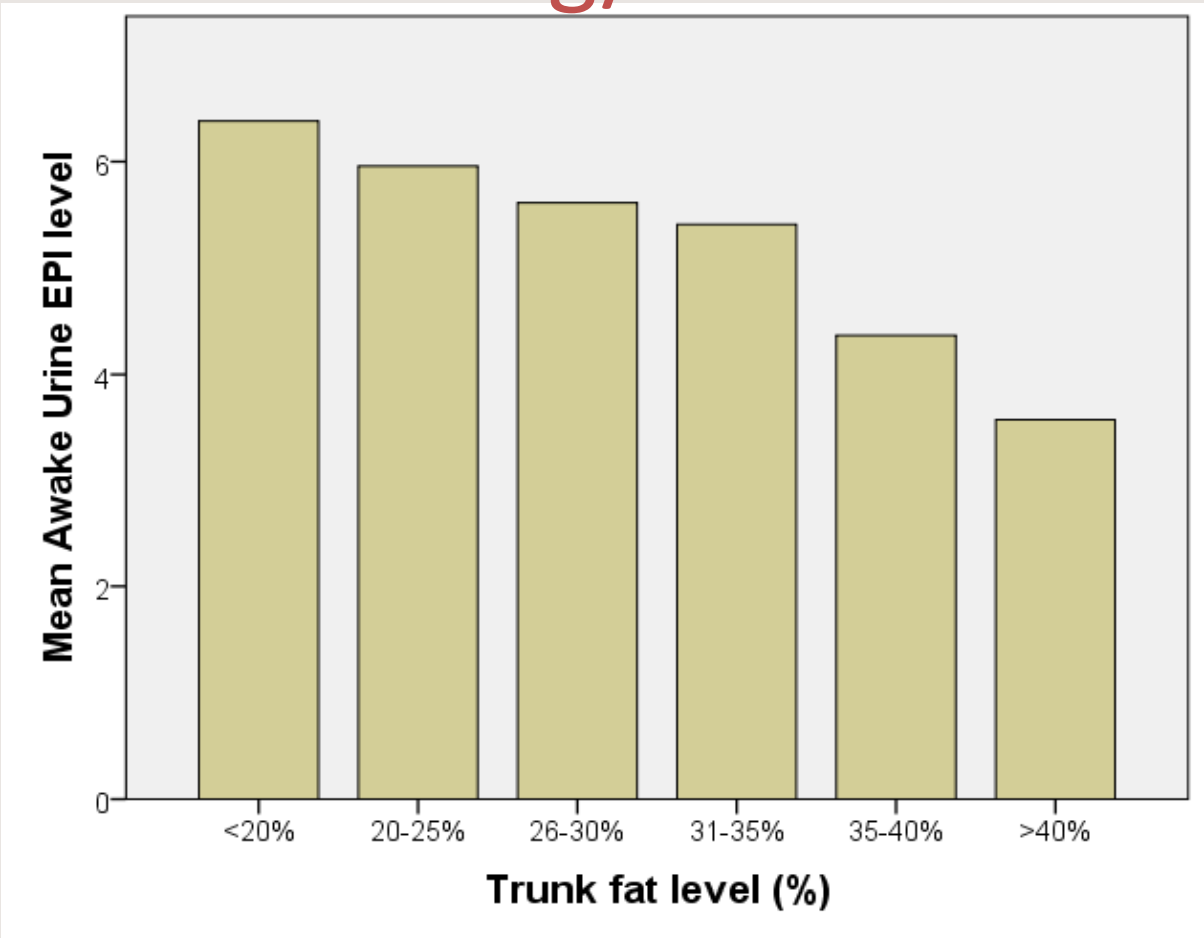
Duke
UNIVERSITY

Plasma Epinephrine Levels In Men and Women With Fasting Glucose <95 mg/dl



Duke
UNIVERSITY

Urinary Epinephrine Levels in Men and Women With Fasting Glucose < 95 mg/dl



Duke
UNIVERSITY

Relationship of Urinary Epinephrine to BMI in Chinese Euglycemic Subjecs

BMI	16-20	21-23	24-25	26-28	28-38	N=577
Urinary EPI (nm/dl)	72	67	53	62	41	P<.001

Lee et al, 2001, *Metabolism*

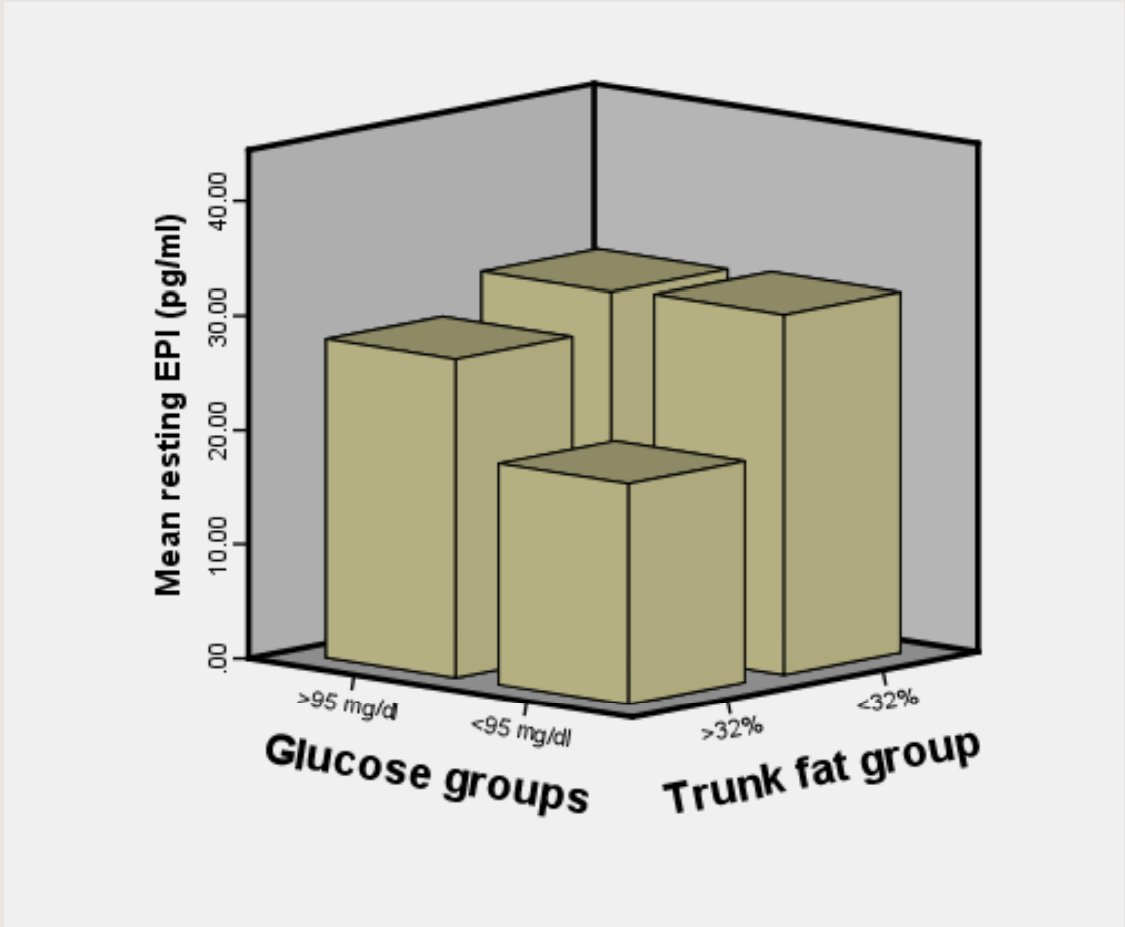
Duke UNIVERSITY

Several Smaller Studies Show the Same Phenomenon in Other Populations

- Caucasian men. Loebig et al, 2010, *PloS One*.
- Adolescent Boys. Jabbour et al, 2011, *Medicine and Science in Sports & Exercise*.

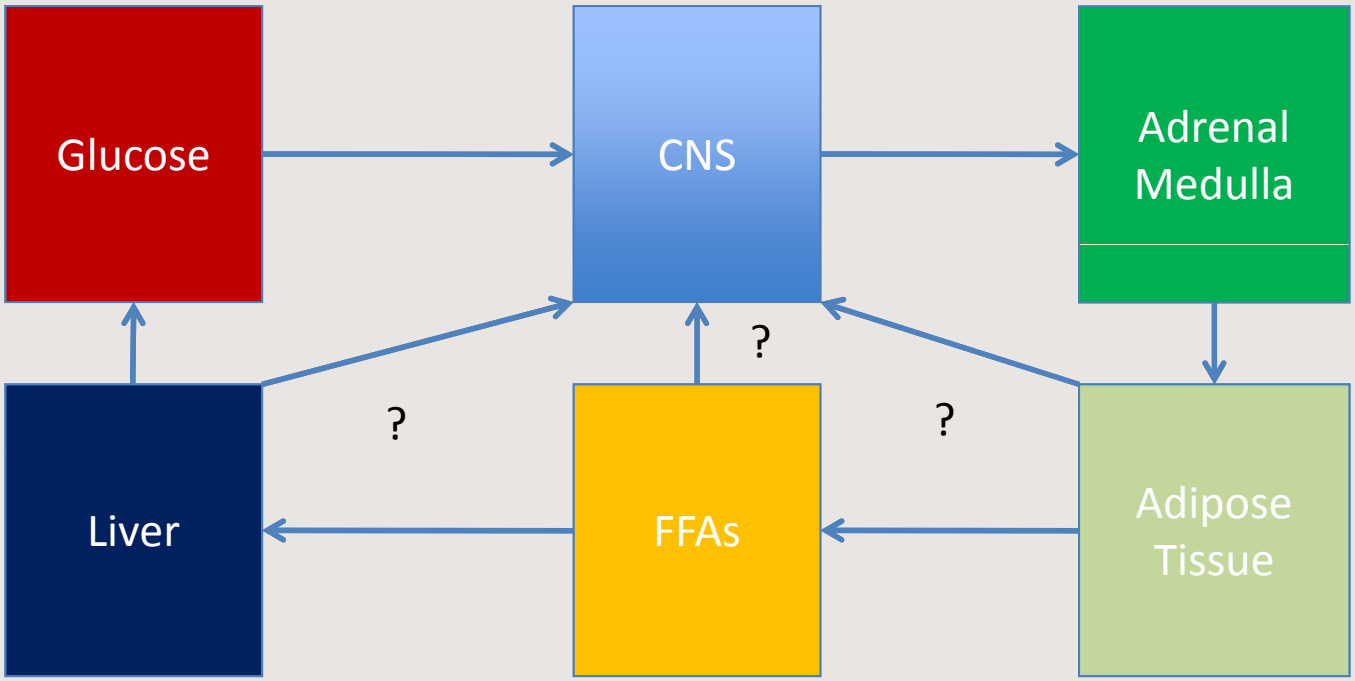
Duke
UNIVERSITY

EPI Does Not Decrease With Increasing BMI When Fasting Glucose > 95 mg/dl



Duke
UNIVERSITY

Does Adipose Tissue Mass Feed Back To Limit Adrenal Medullary Function to Maintain Euglyemia



Duke UNIVERSITY

Summary

- Hostility is related to body weight, adrenal medullary function, and CNS serotonin metabolism, and fasting glucose.
- Adrenal medullary function interacts with central adiposity to determine fasting NEFA and fasting glucose.
- Adrenal medullary function decreases with increasing adiposity in euglycemic individuals, but not in individuals with impaired fasting glucose.
- Abnormal glucose metabolism could be due, in part, to a failure of the adrenal medulla to adapt to increasing adiposity.

Duke
UNIVERSITY

Collaborators

- Anastasia Georgiades
- David Millington
- James Lane
- Mark Feinglos
- Sharon Minda
- Haoyue Zyang
- Raymond Boston
- Rhonda Merwin
- Redford Williams
- Ilene Siegler
- John Barefoot
- Cynthia Kuhn
- Stephen Boyle
- Rima Kaddurah-Daouk

Duke
UNIVERSITY