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Albert Einstein College of Medicine
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The Contribution of Age-Related Changes in Adiposity to Inflammation and Disease

Derek M. Huffman, PhD

Albert Einstein College of Medicine

Department of Medicine, Division of Endocrinology

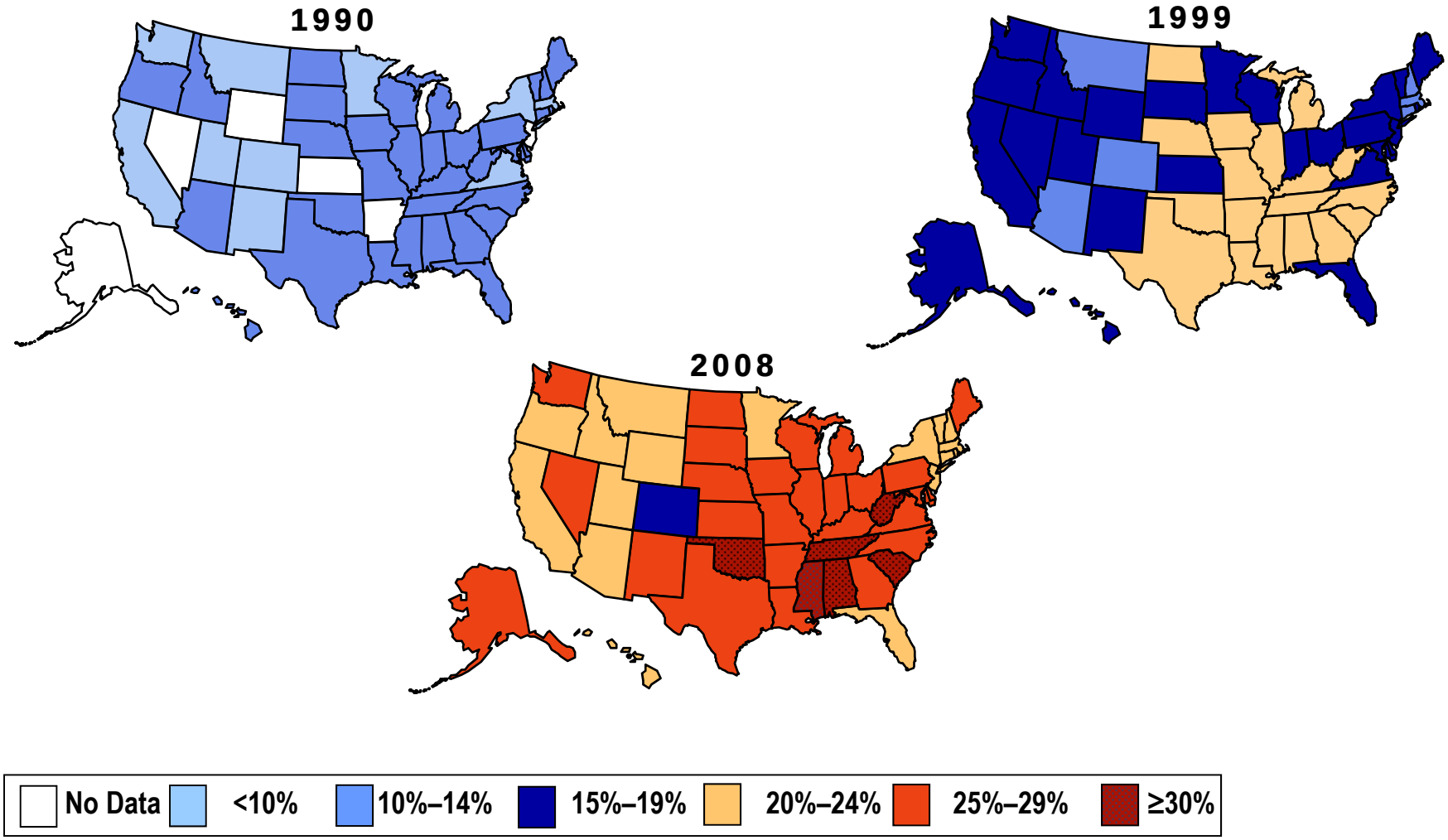
Institute for Aging Research

Bronx, NY

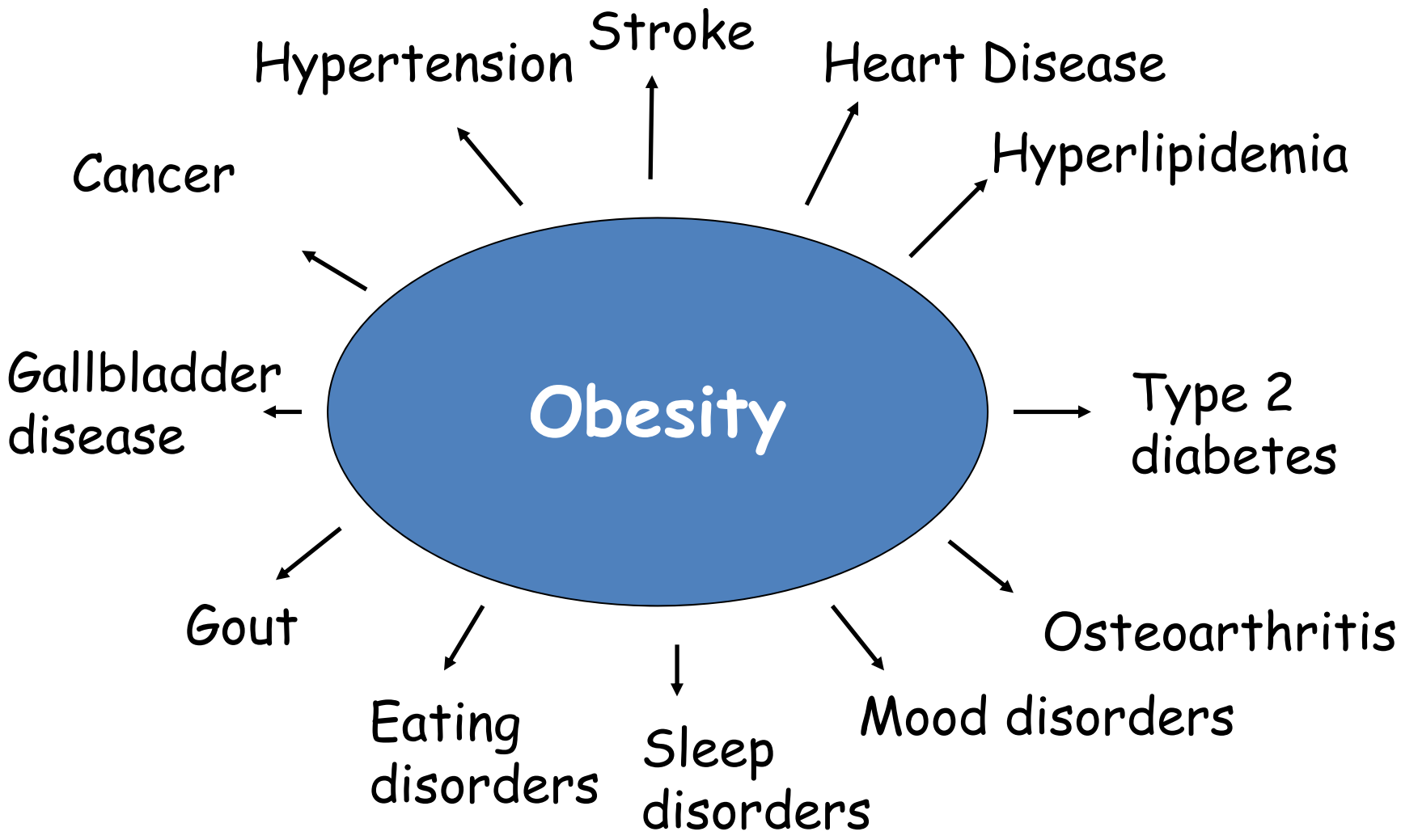
Obesity Trends* Among U.S. Adults

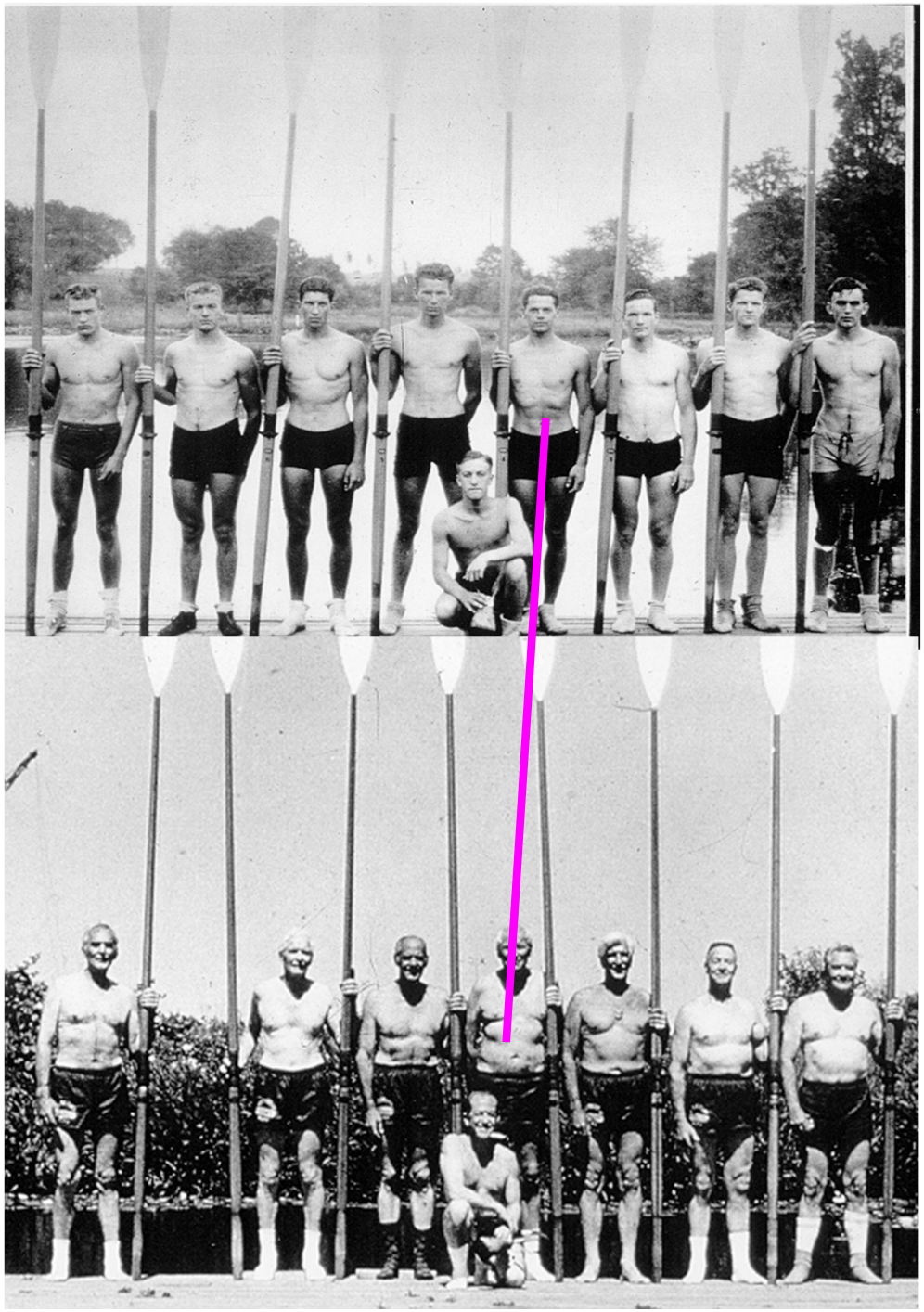
BRFSS, 1990, 1999, 2008

(*BMI ≥30, or about 30 lbs. overweight for 5'4" person)



Obesity: The Consequences

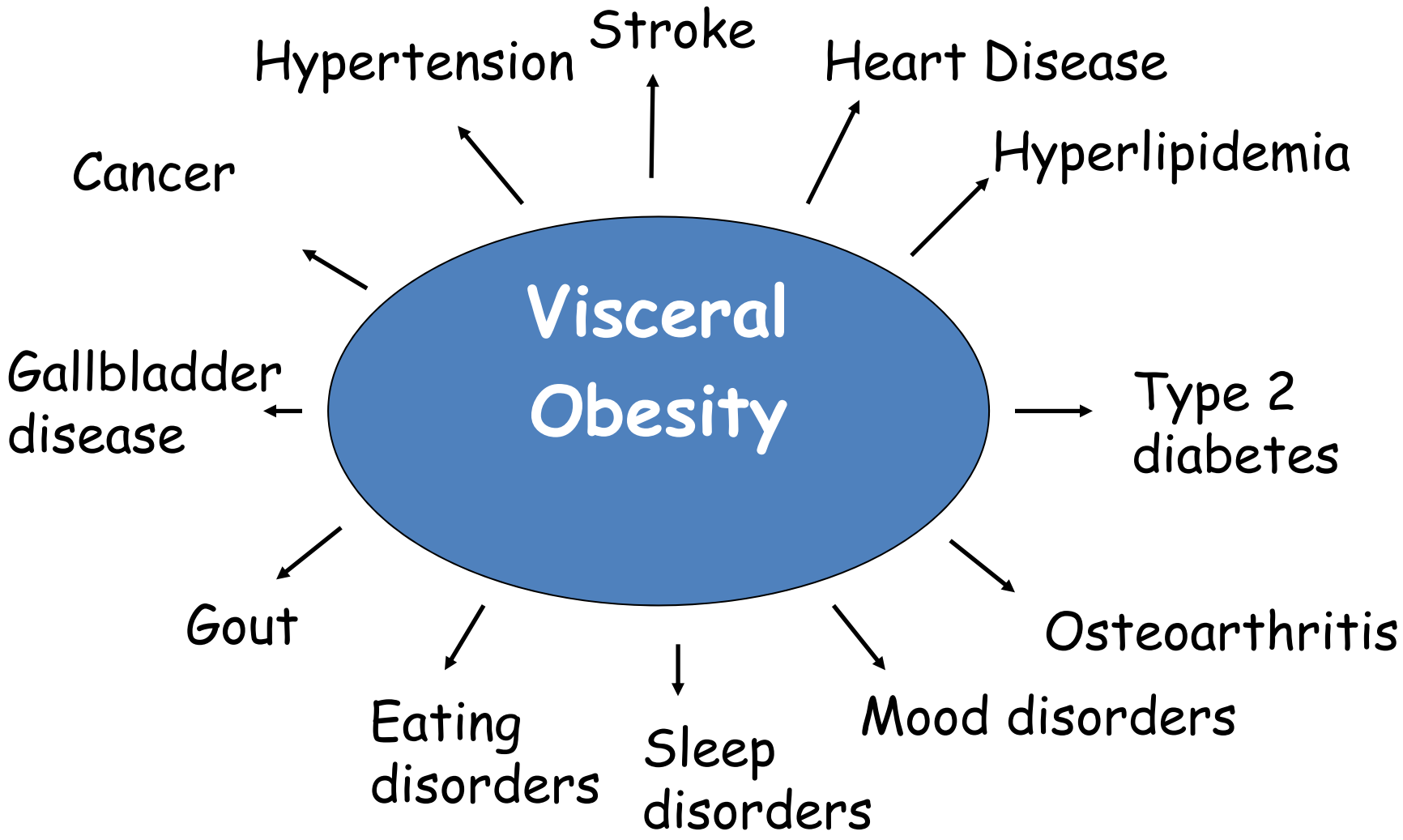




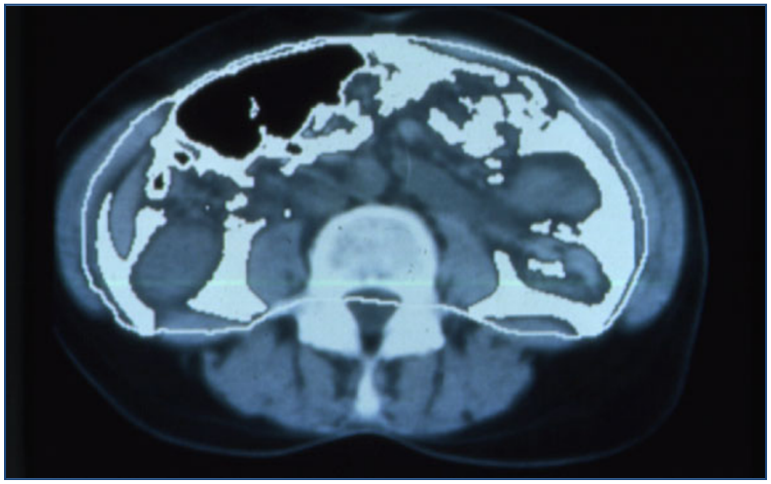
Factors that modulate visceral fat accumulation

- **Aging**
- Gender
- Race
- Diet
- Overall obesity
- Physical Activity
- **GH**
- **IGF-1**
- **Leptin**
- Sympathetic activity
- TZDs/ Metformin
- Glucocorticoids
- Estrogen
- Testosterone

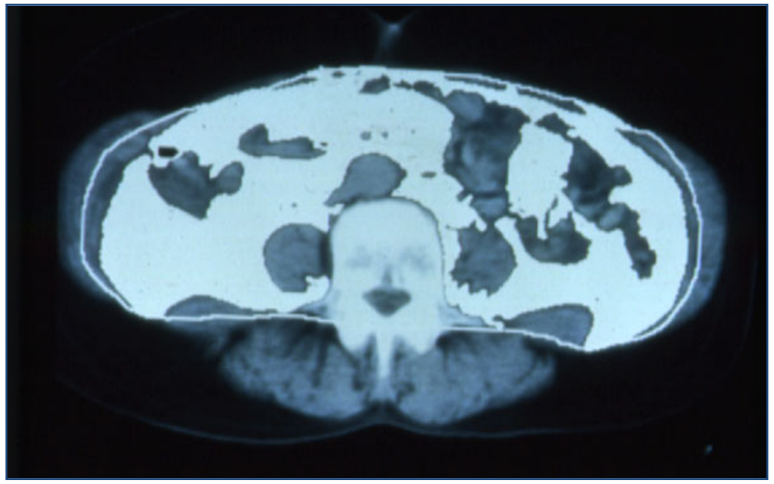
Obesity: The Consequences



Visceral Fat Distribution:
Normal vs Type 2 Diabetes

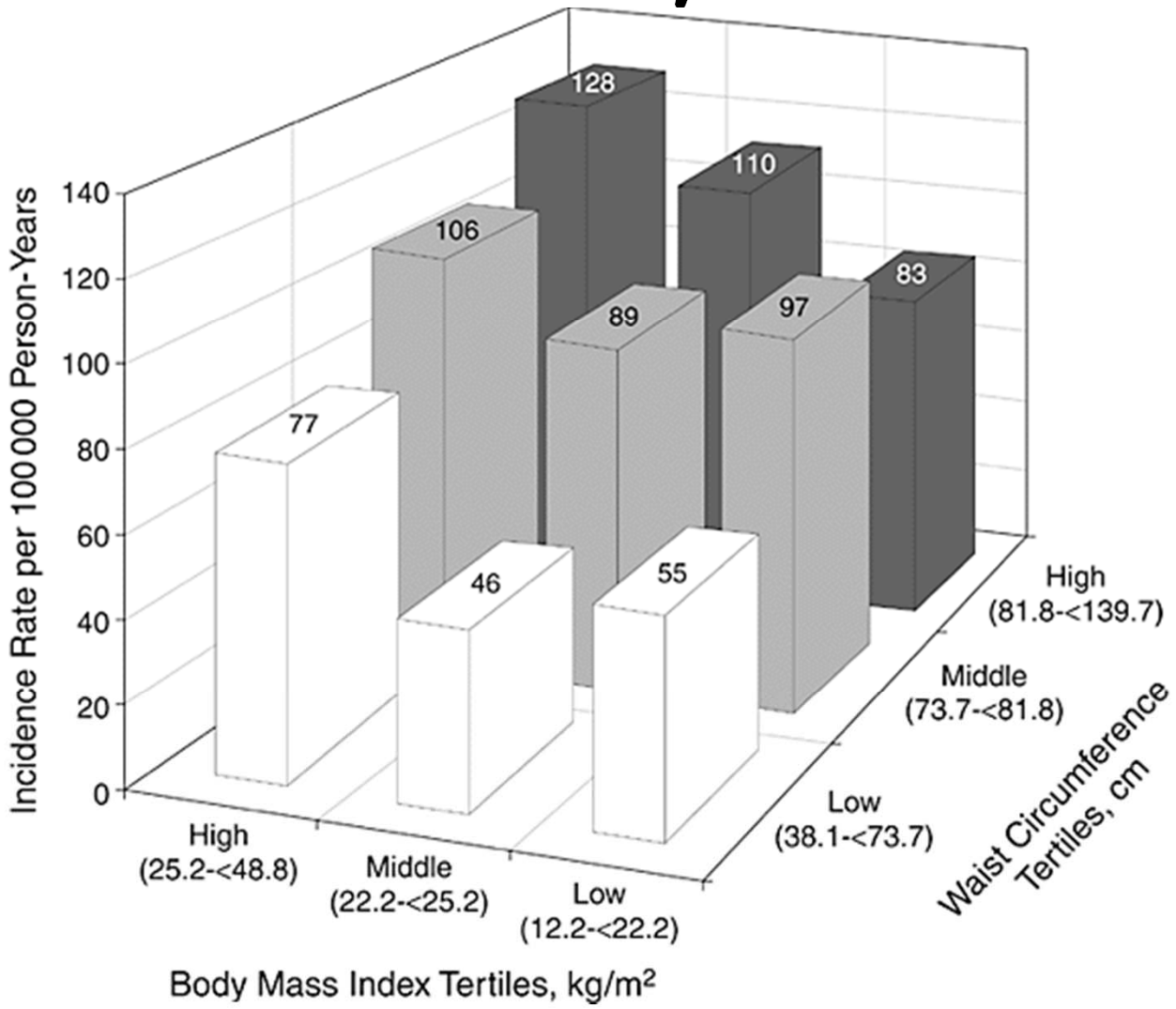


Normal



Type 2 Diabetes

Visceral obesity and BMI: Association with coronary disease

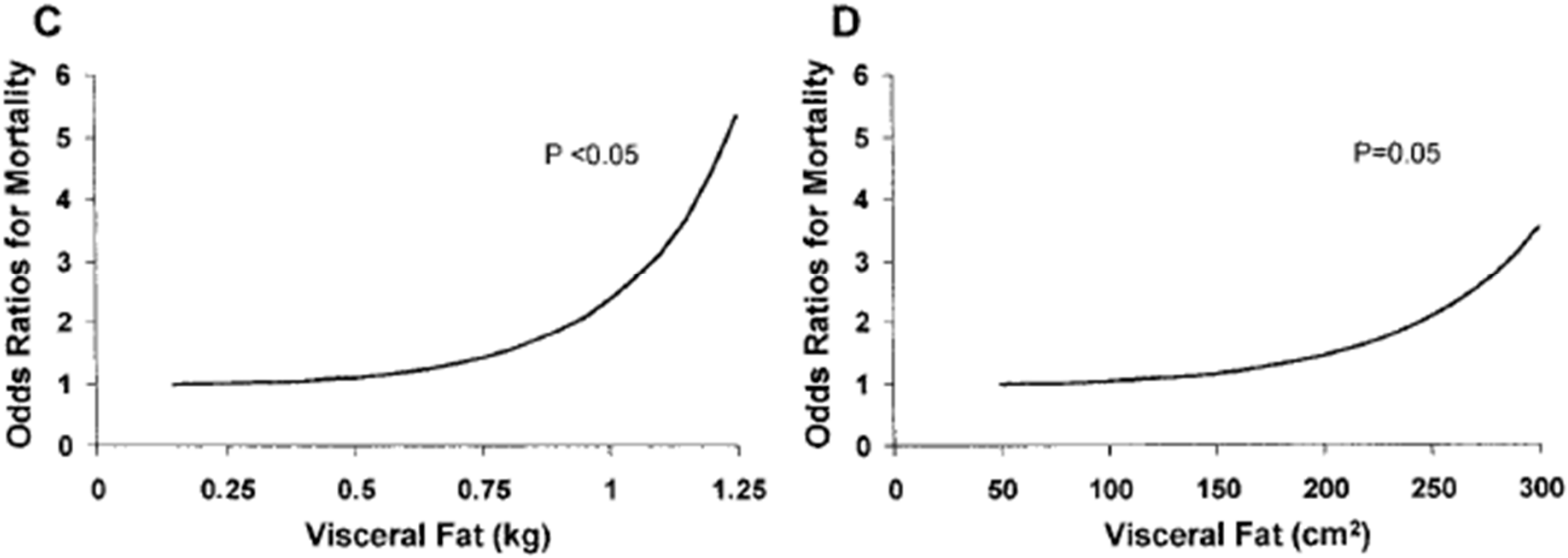


JAMA, December 2, 1998—Vol 280, No. 21

Visceral fat is an independent predictor of mortality risk

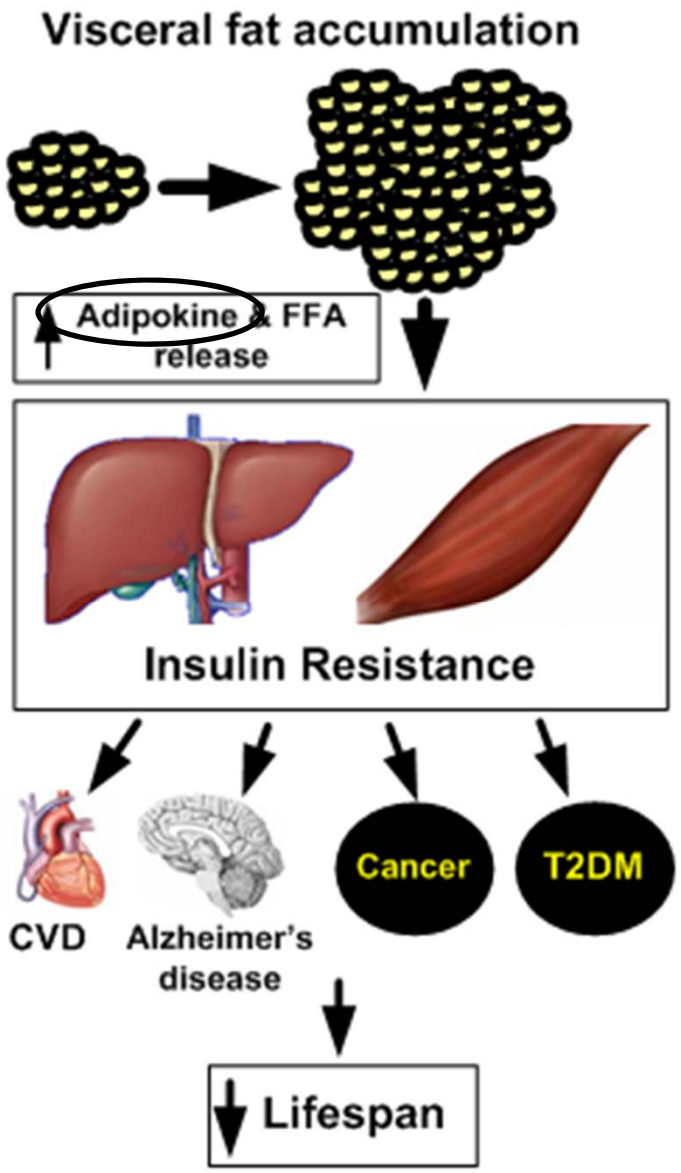
291 Men (56 12yrs)

Adjusted for age, liver fat, SC fat, follow-up time

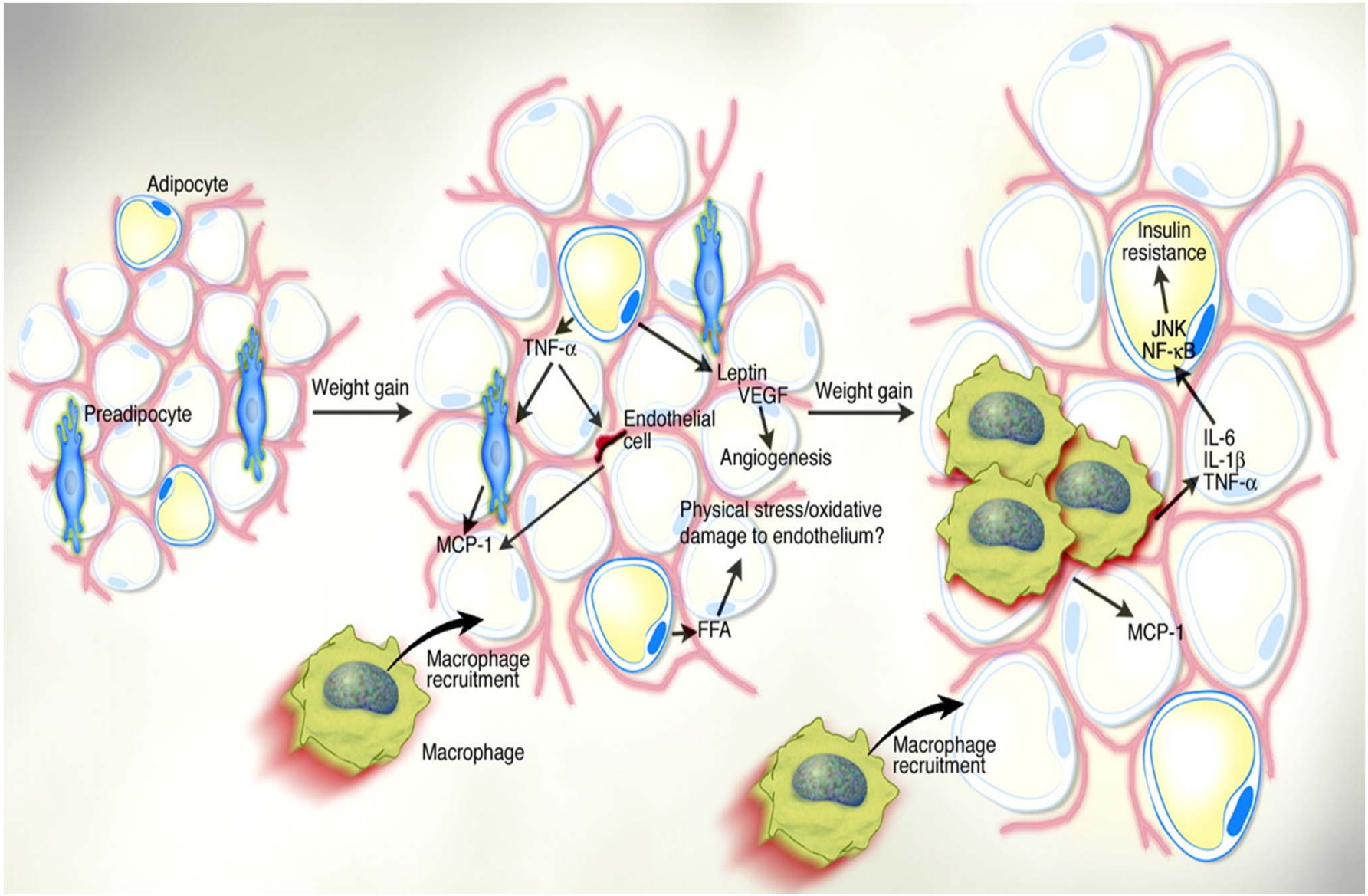


OBESITY Vol. 14 No. 2 February 2006

Visceral obesity and disease in humans: how are they linked?



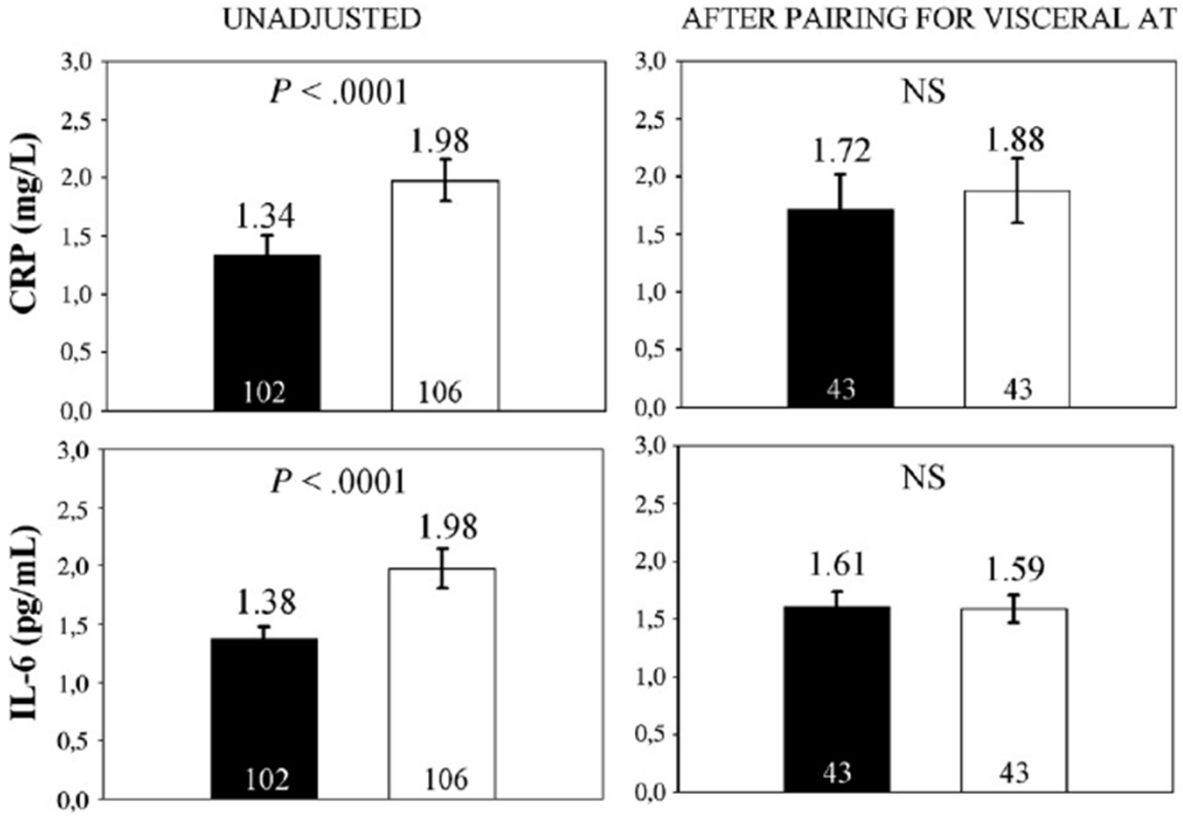
Adipose tissue macrophages and inflammation



Inflammatory markers associated with increasing visceral adiposity in humans

- **IL-6** (Diamant et al. *JCEM*. 2005)
- **Visfatin** (Fukahara et al *Science* 2005)
- **Leptin** (Ronnemaa et al *Ann Intern Med* 1997)
- **TNFa** (Hishinuma et al *J Stroke Cerebrovasc Dis* 2008)
- **PAI-1** (Giltay et al *Arterioscler Thromb Vasc Biol* 1998)
- **RBP-4** (Kloting et al *Cell Metab* 2007)
- **CRP** (Lemieux et al *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2001)
- **Adiponectin** (Asayama et al Obesity 2003)

Aging versus visceral adiposity on systemic inflammation



≤40yr old versus >40yr old

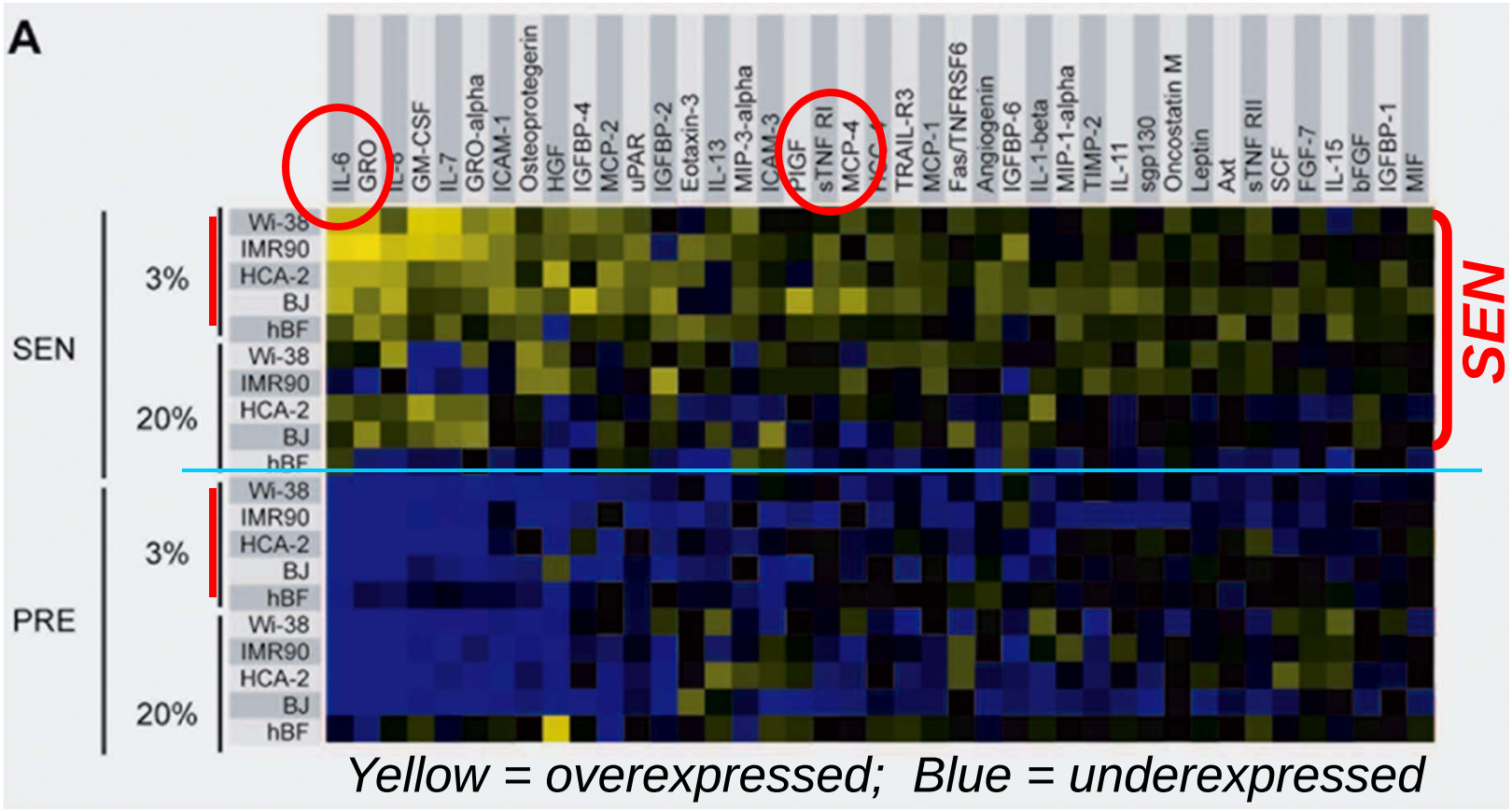
Mean: 28 versus 55 yrs old

Age-related differences in inflammatory markers in men: contribution of visceral adiposity

Amélie Cartier[a,b], Mélanie Côté[a,b], Isabelle Lemieux[a], Louis Pérusse[a,c], Angelo Tremblay[a,c], Claude Bouchard[d], Jean-Pierre Després[a,c,*]

Metabolism Clinical and Experimental xx (2009) xxx – xxx

Senescence-associated secretory phenotype (SASP)

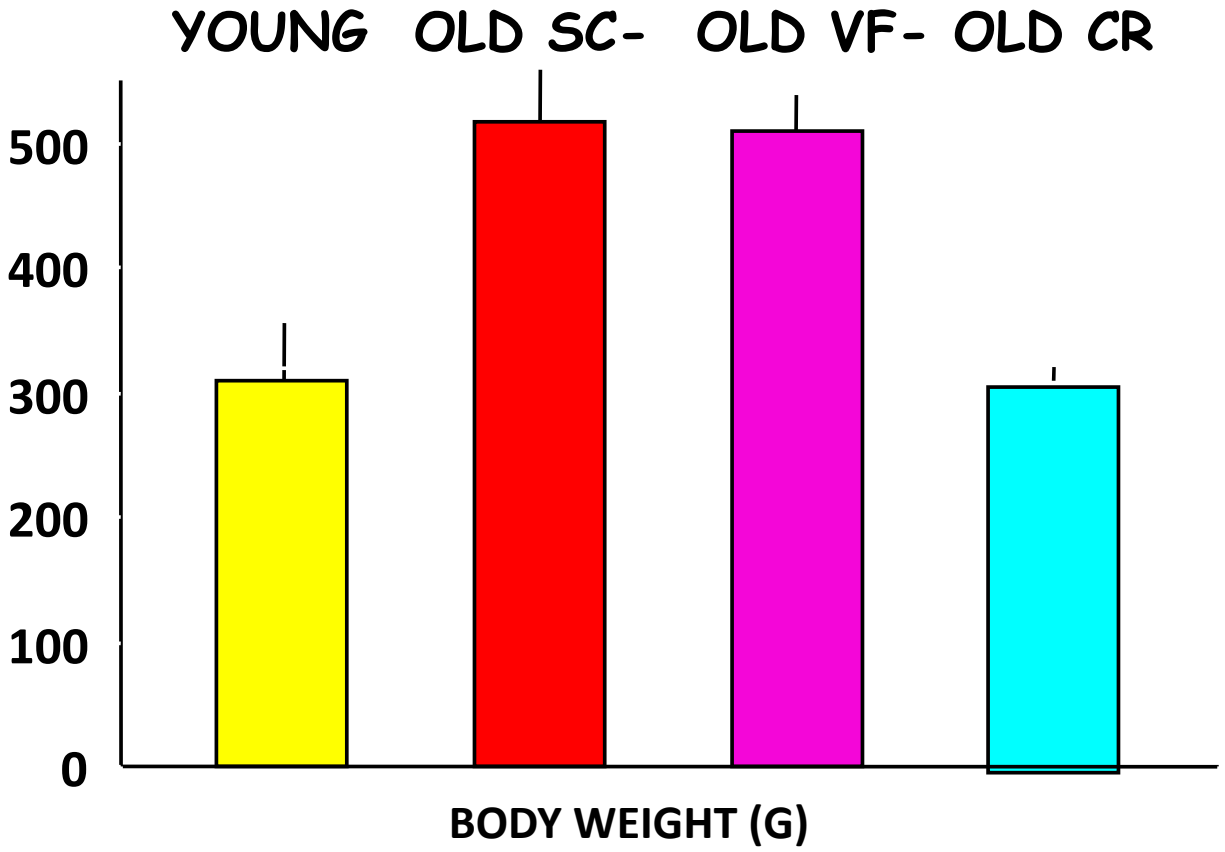


SASP is conserved among species (humans/mice), tissues, donors/ages SASP is a core, not rigid, phenotype

Judy Campisi, Jean-Philippe Coppe, Chris Patil, Francis Rodier

Visceral fat and insulin resistance: correlation or *causation*?

Does VF account for the effects of caloric restriction on insulin action in aging rats?



Diabetes; 51:2951,**2002**

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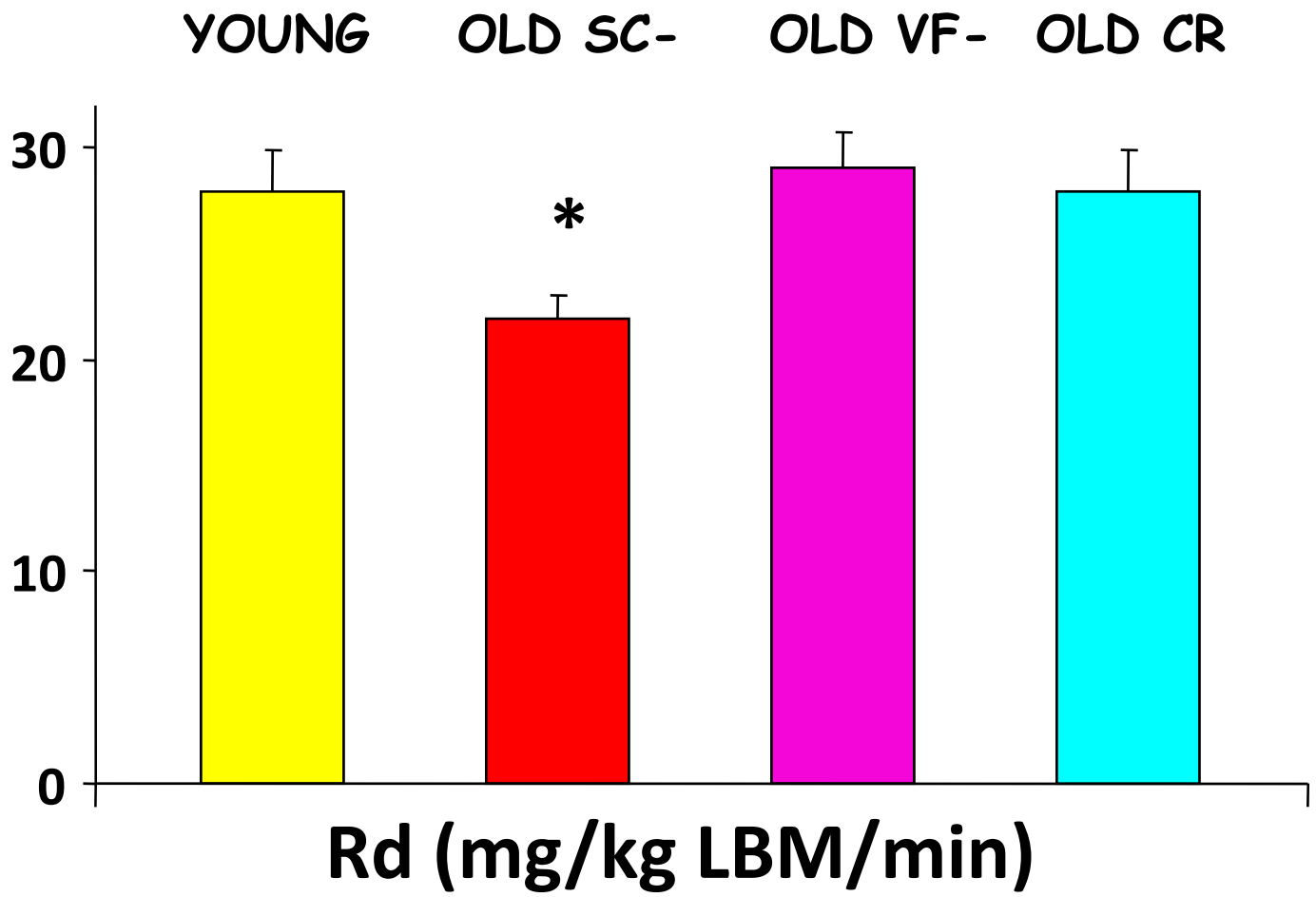
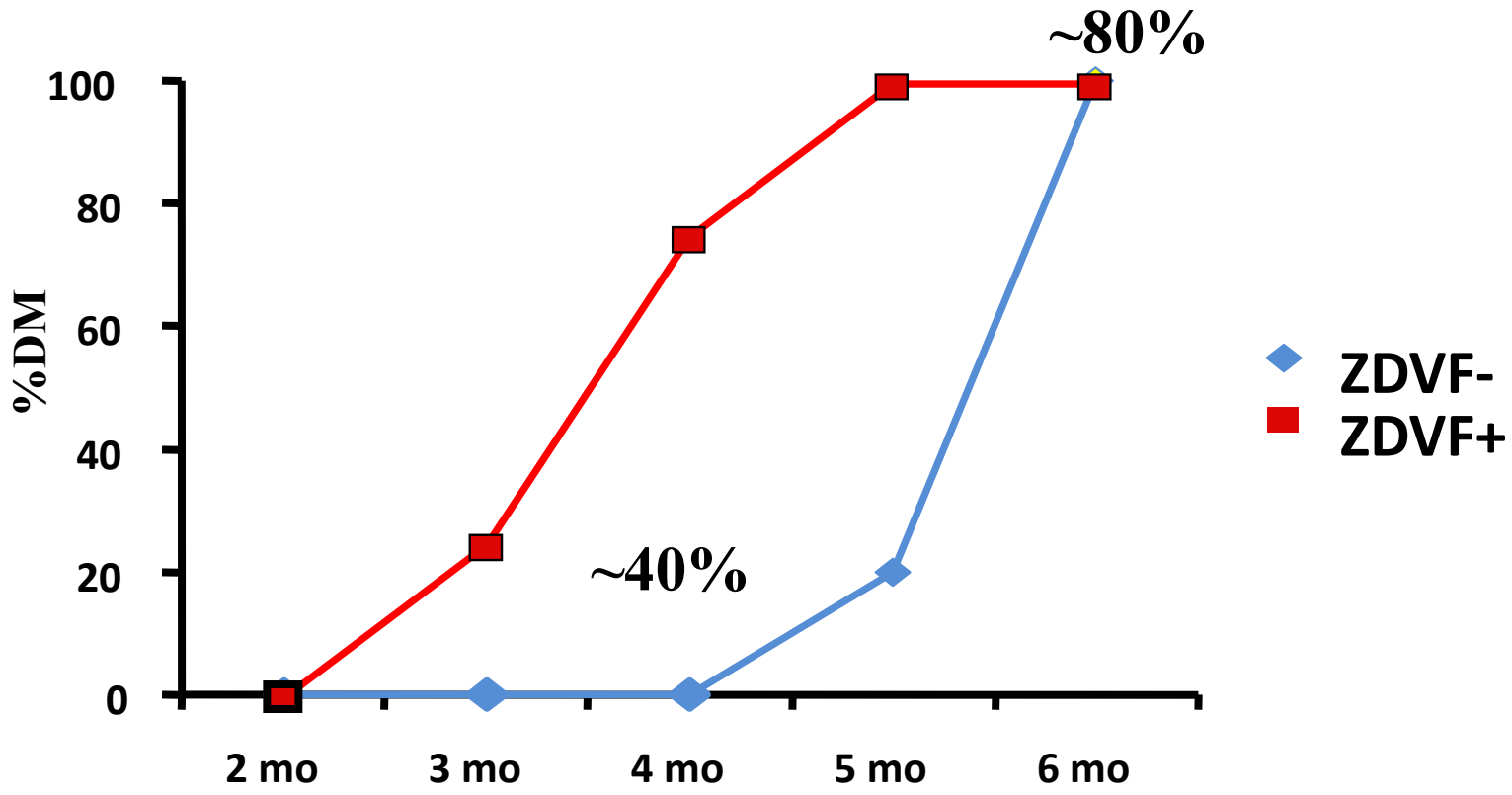


Diabetes; 51:2951,**2002**

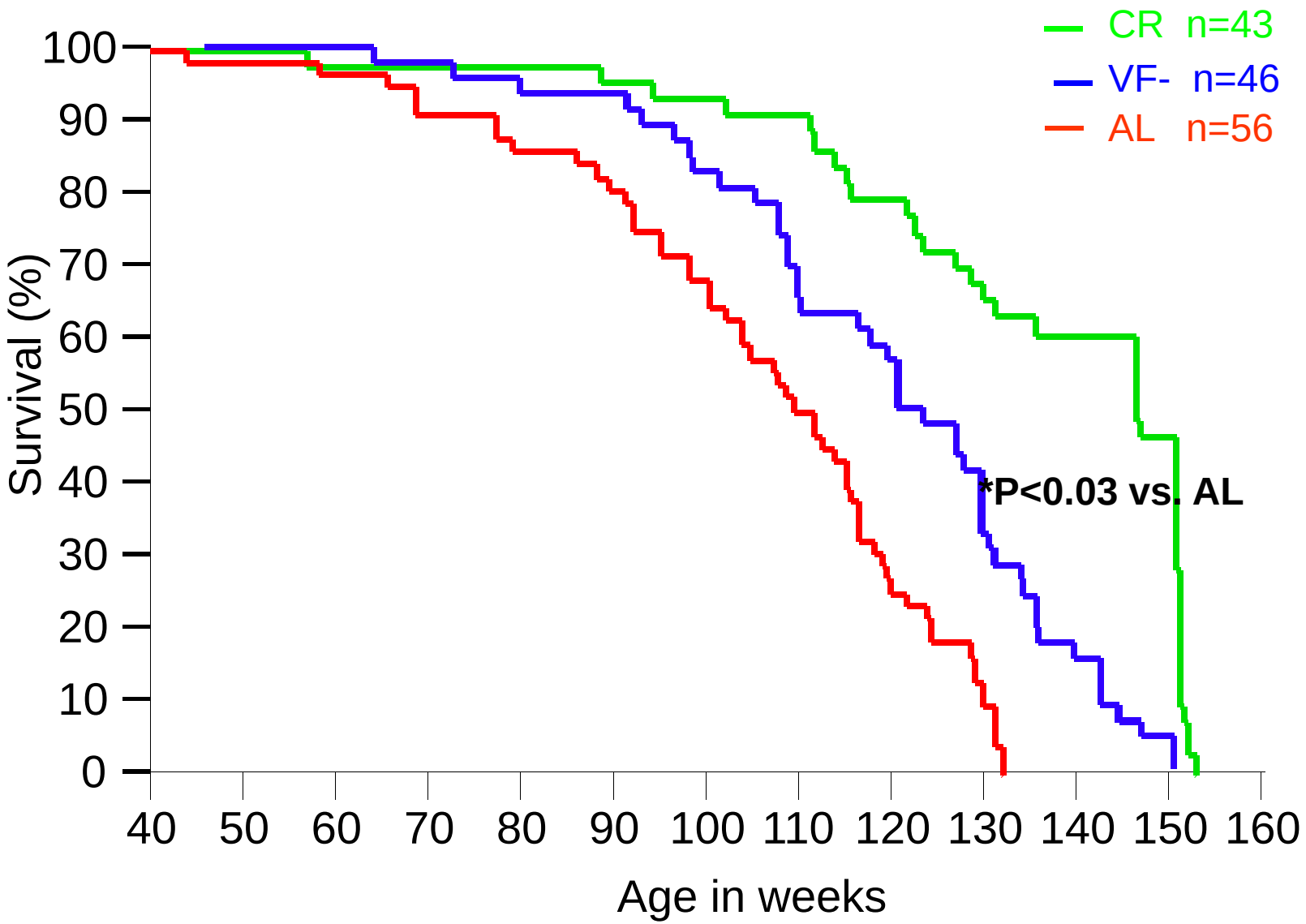
'Knock out' of VF prevents diabetes in Zucker diabetic fatty rats



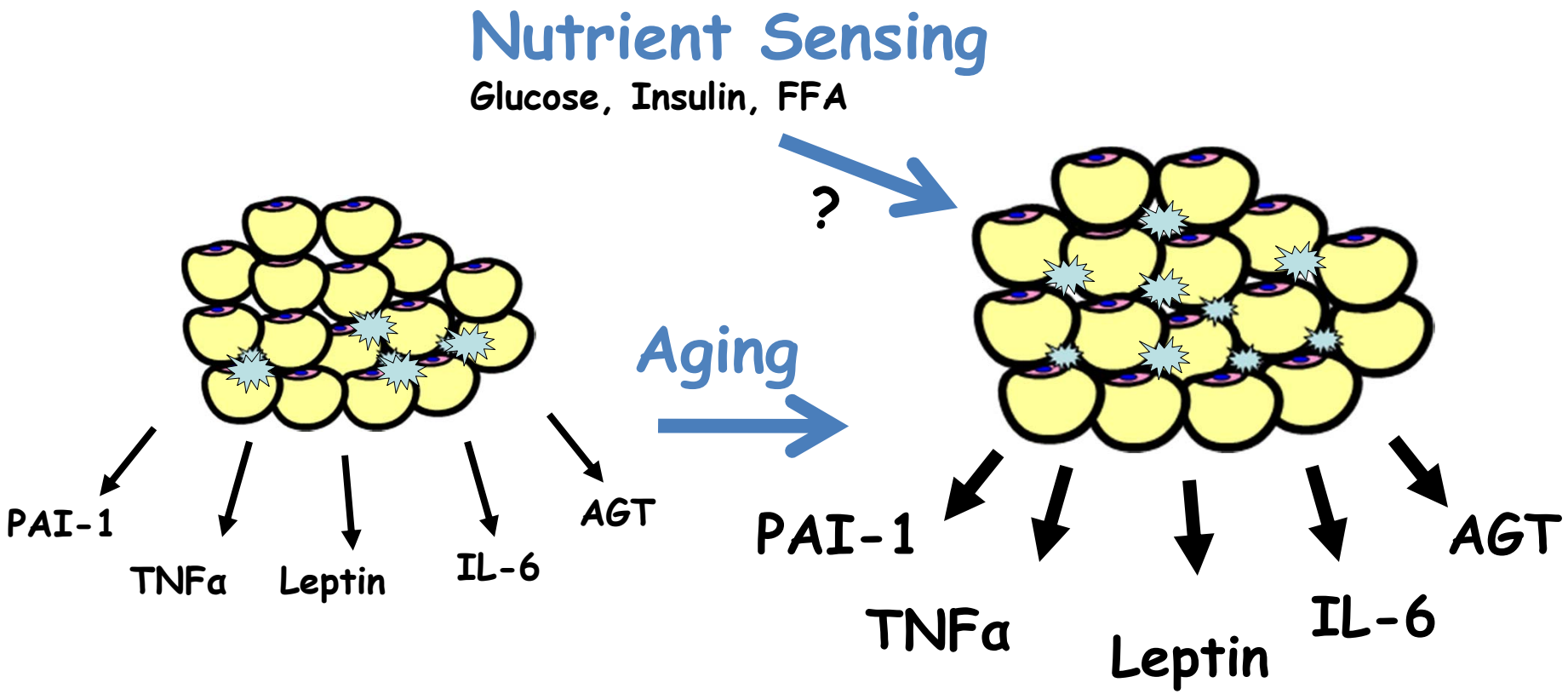
Diabetes; 51:2951,2002

Does visceral fat modulate lifespan?

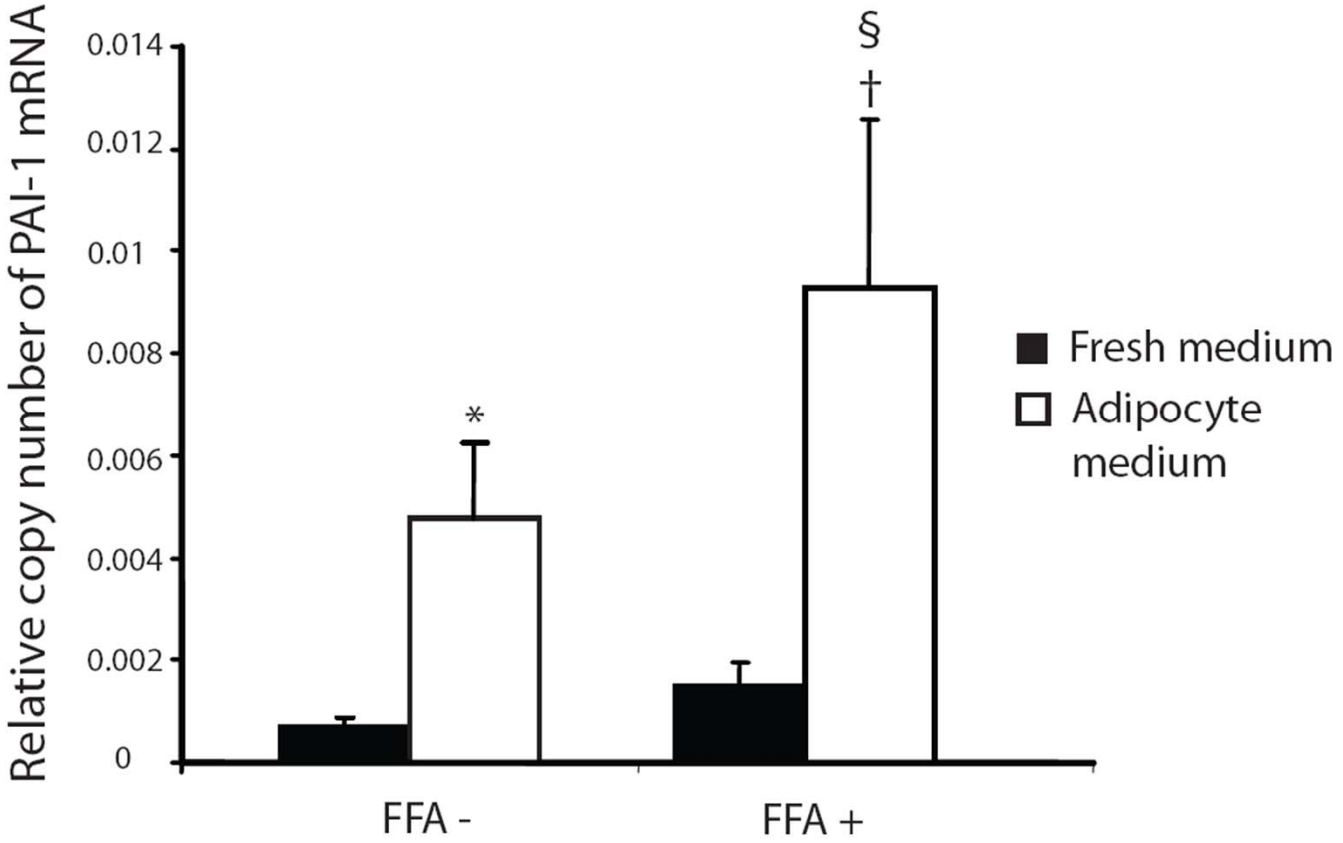
Muzumdar, Huffman, Atzmon, Barzilai et al *Aging Cell*. 2008 Mar 18.



Aging *per se* leads to increased visceral fat accrual, macrophage accumulation and sensitivity to nutrients



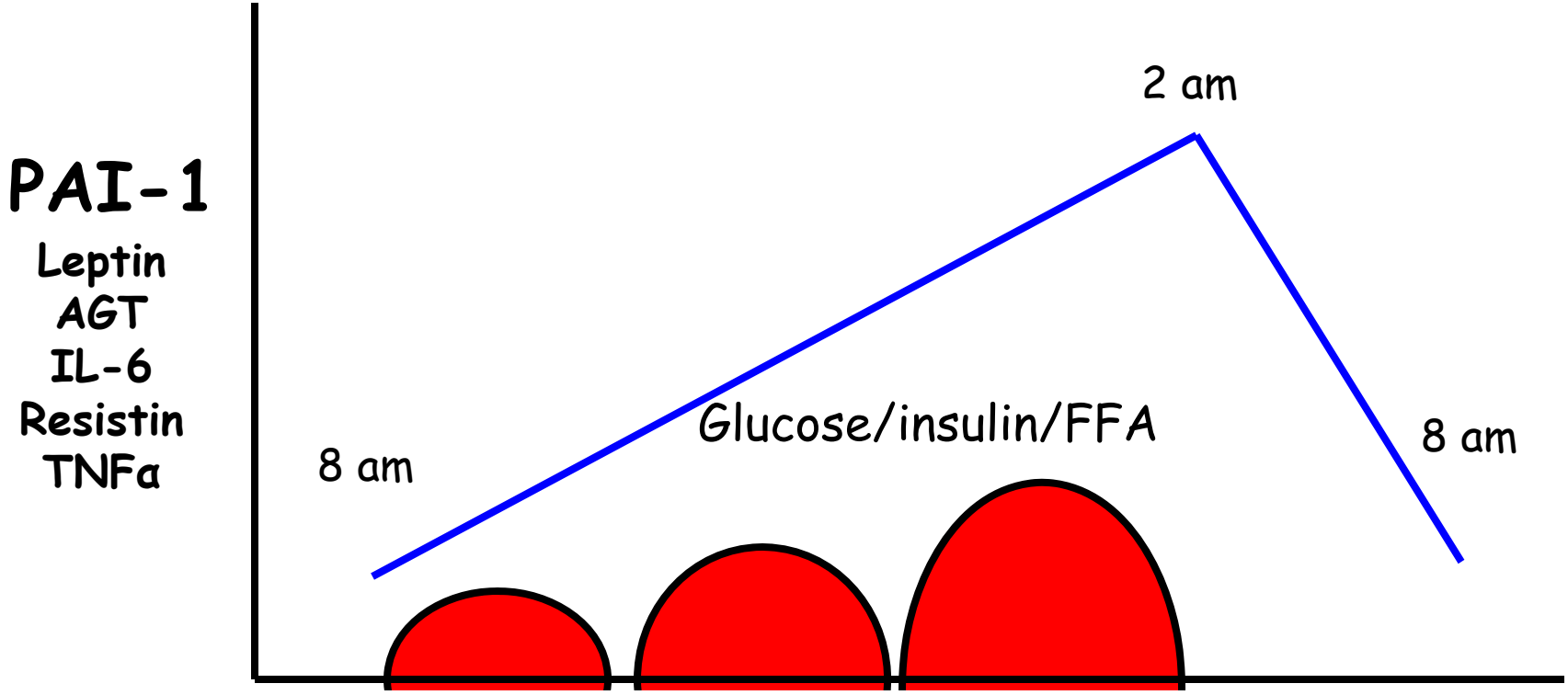
Fatty acids provoke PAI-1 transcription levels in cultured macrophages



Kishore and Hawkins et al unpublished data

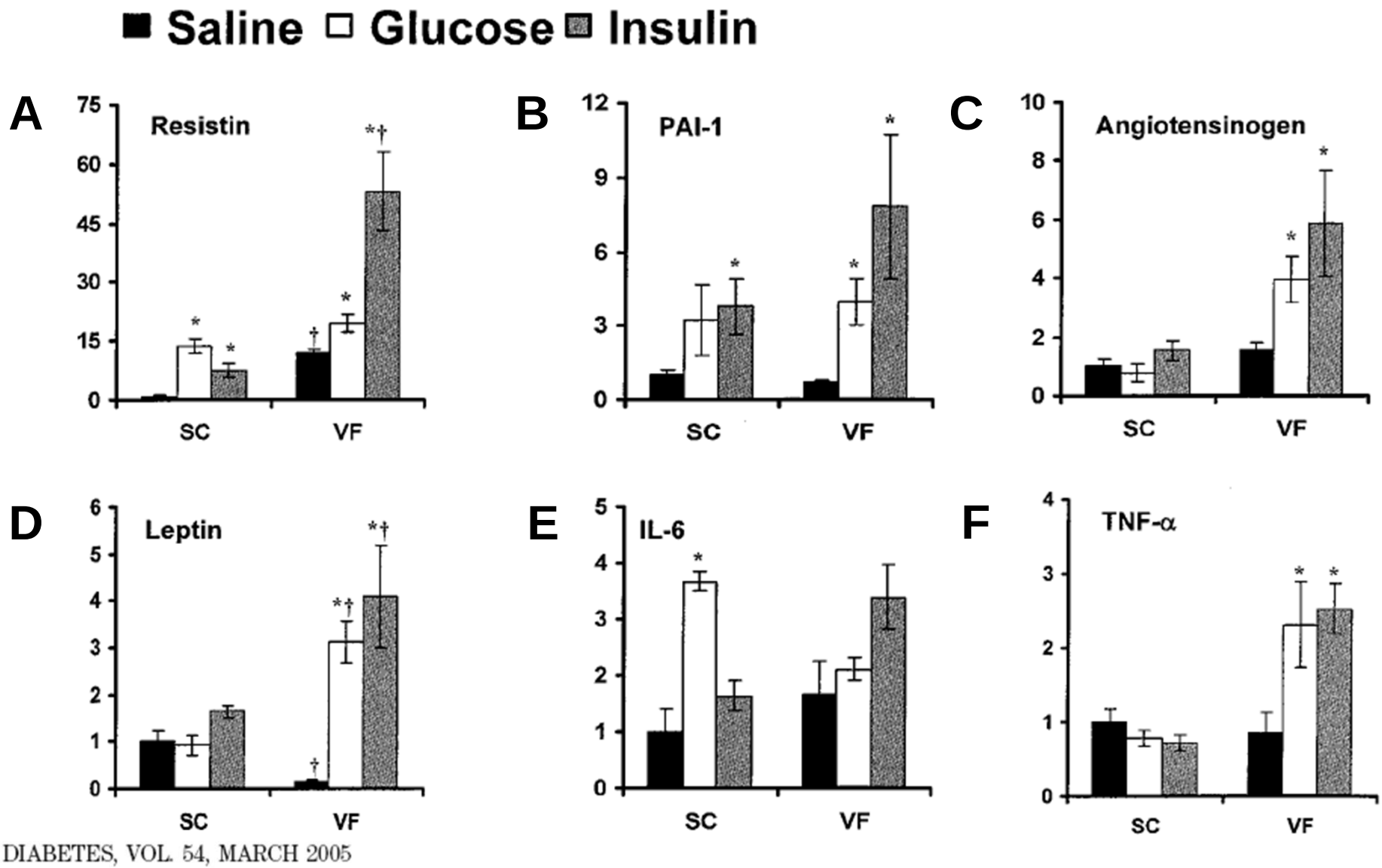
Importance of nutrients to inflammation

Interaction of Adipose tissue and Nutrients on transcription of inflammatory peptides



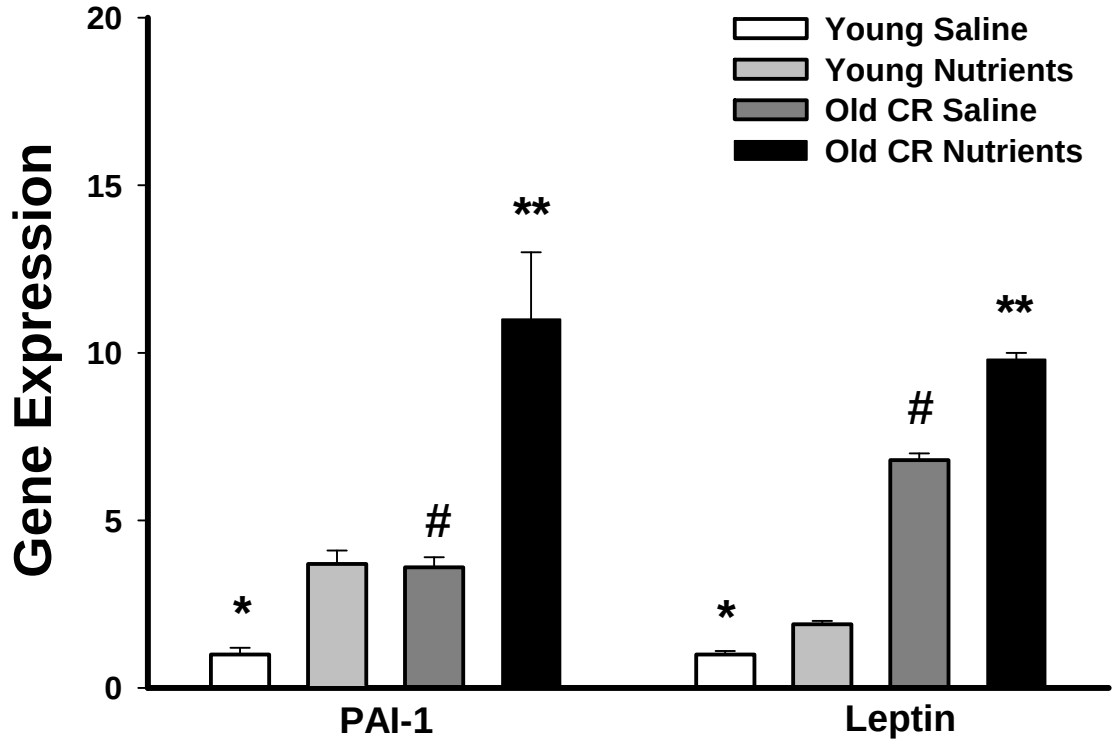
Clinical trials are standardized by fasting levels, and are Underestimating daily transcription of peptides!

Differential response of fat depots to nutrients



DIABETES, VOL. 54, MARCH 2005

Aging *per se* increases the susceptibility of visceral fat to nutrients



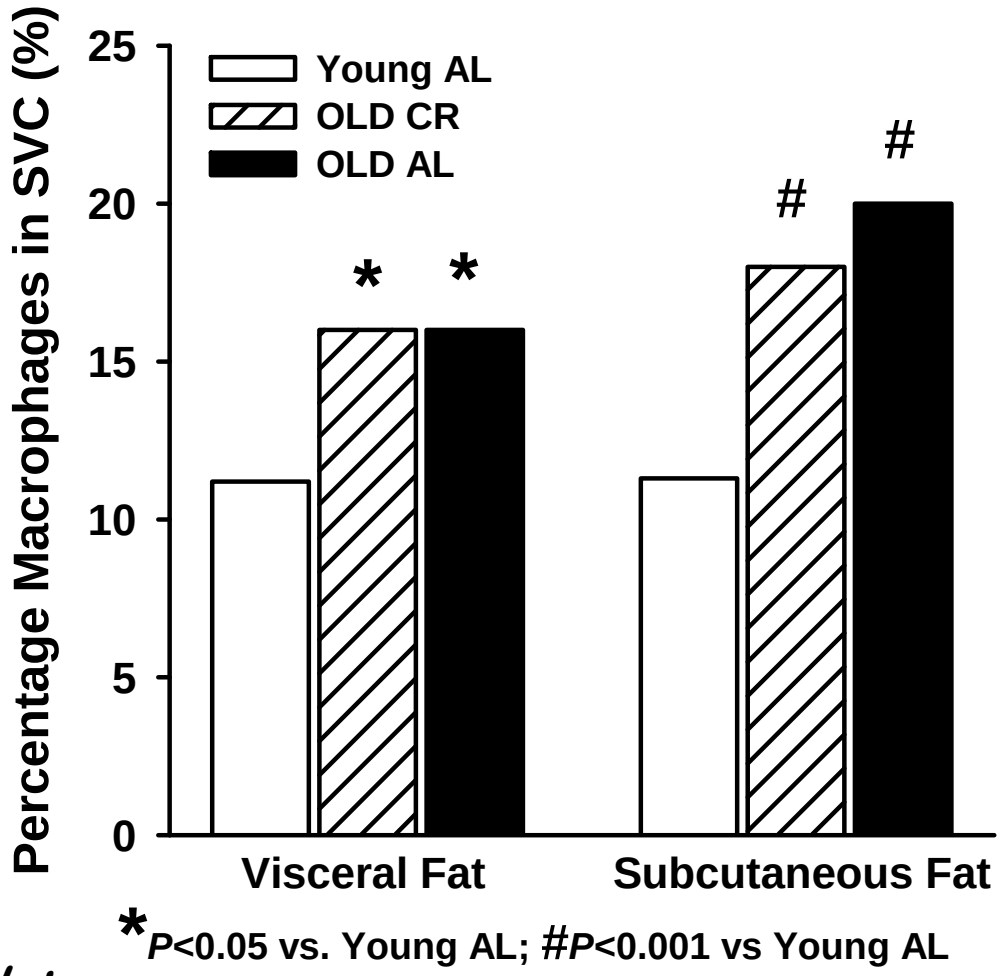
***p<0.01 vs. all others. #p<0.01 vs. age-matched nutrients.**
****p<0.01 vs. Young Nutrients**

Enhanced activation of a "nutrient-sensing" pathway with age contributes to insulin resistance

Francine H. Einstein,*,† Sigal Fishman,* Jeffery Bauman,* Reid F. Thompson,* Derek M. Huffman,* Gil Atzmon,* Nir Barzilai,*,‡,1 and Radhika H. Muzumdar*,§

FASEB J. 22, 3450–3457 (2008)

Aging per se in rats is associated with increased macrophage infiltration into fat

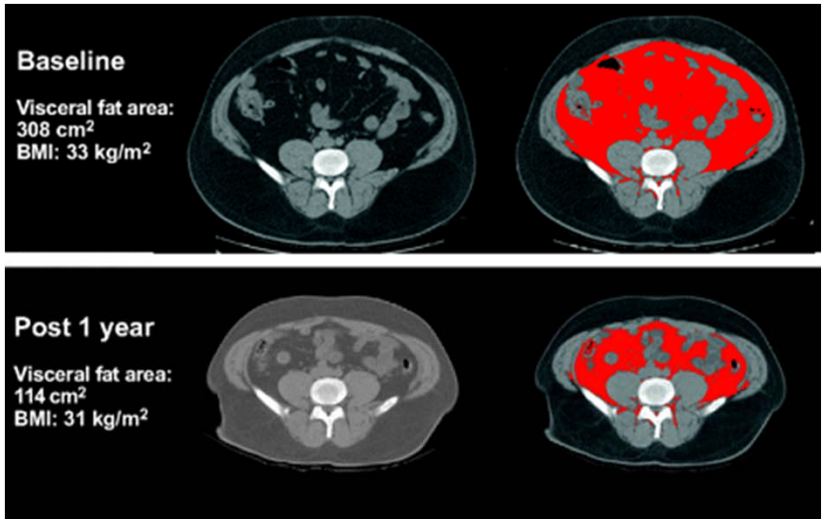


*$P<0.05$ vs. Young AL; #$P<0.001$ vs Young AL

unpublished data

Treatments: Behavorial strategies

- **Exercise and diet** to promote loss of visceral adiposity



(*Hypertension*. 2009;53:577-584.)

- **Exercise *per se*** is anti-inflammatory and may diminish WAT inflammation (*Viera et al Cytokine 2009*)

Pharmacologic strategies

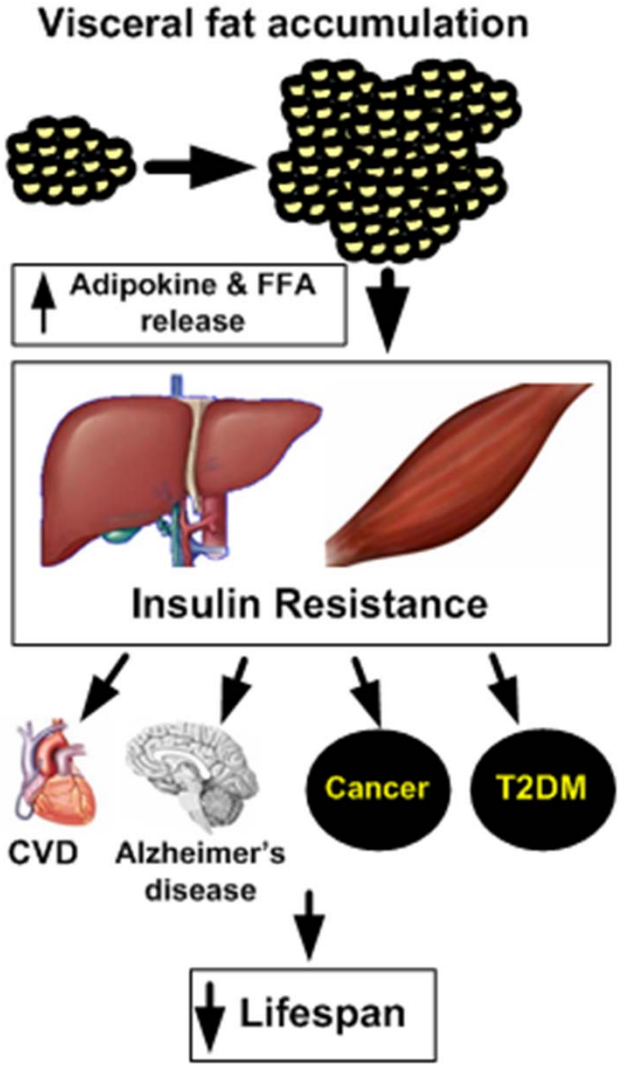
- **CCR2 antagonists:** limits macrophage infiltration and improves inflammation and insulin resistance in mice (*Weisberg et al J Clin Invest 2006*)

- **Leptin:** selectively depletes VF stores (*Barzilai et al J Clin Invest 1998*)

- **TZD's:** PPARγ agonists with anti-inflammatory properties, redistribute VF and ectopic fat to subcutaneous fat depot and increase adiponectin

Summary

- A hallmark of aging is an increase in visceral fat
- Visceral fat is more strongly associated with disease than total adiposity or BMI (and potentially mortality)
- The link between visceral fat and disease is ***causal***
- Consideration of the fat x nutrient interaction for provoking inflammatory peptides is often overlooked



Acknowledgments

Einstein

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Barzilai Lab

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AFAR
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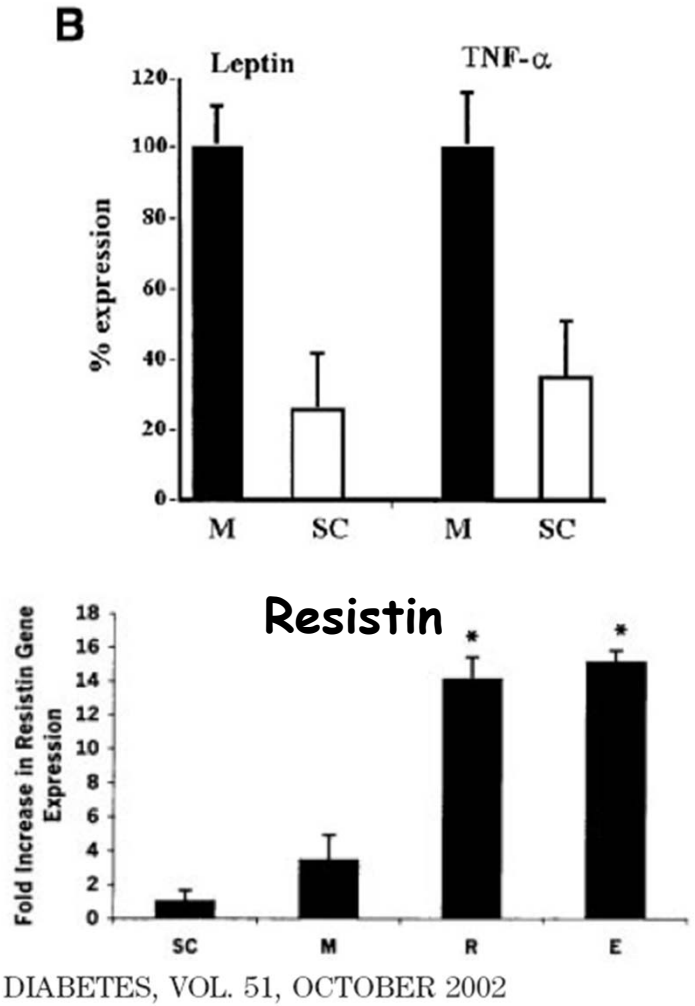
Extra Slides---Not part of presentation (#31-39)

Remaining gaps

- Is there a causal role of VF in humans with age-related diseases? Is it even more severe in humans than rodents?
- What is the contribution of a changing secretory phenotype in aging to inflammation?
- Interaction of nutrients and inflammation with aging in humans?
- What leads to the accrual of macrophages with aging (without obesity)?
- What are the implications of behavioral and pharmacologic strategies to limit visceral fat accrual and adipose-associated inflammation with aging?

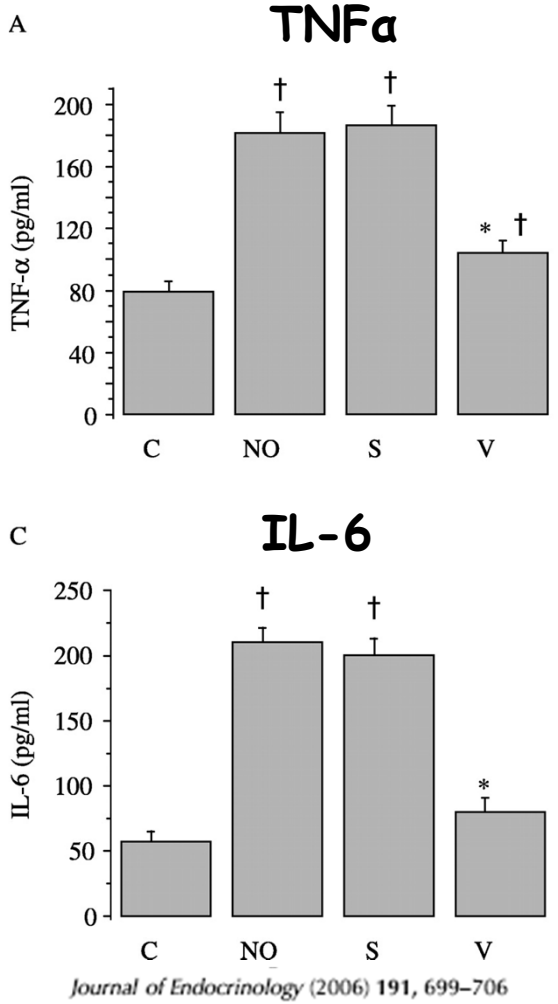
Influence of fat depots on adipokine expression and serum levels

Gene Expression by fat depot



DIABETES, VOL. 51, OCTOBER 2002

Visceral fat removal and serum adipokines



Journal of Endocrinology (2006) **191**, 699–706

Future directions and recommendations

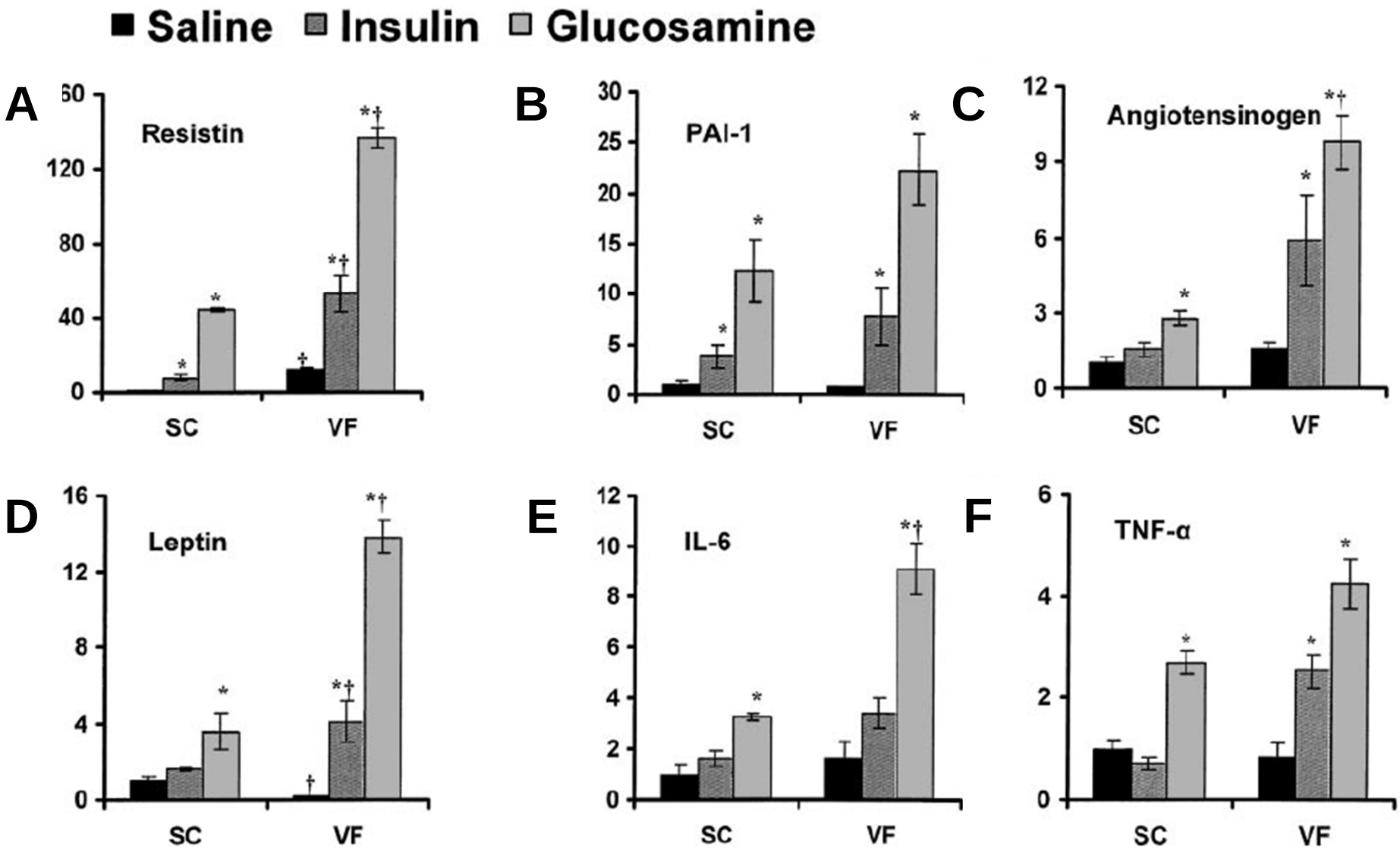
-Human studies should consider analyzing both basal and stimulated (nutrients) circulating inflammatory markers

-Contribution of senescent cells with aging to the inflammatory profile from fat

-Human studies should also consider alternatives to BMI alone when analyzing disease risk (waist circumference, waist-to-hip ratio, waist-to-height, ect)

-Clinical evaluation/progress should emphasize a reduction in waist circumference for patients at risk

-Many questions remain regarding the long-term effects of diet (quality & quantity) and physical activity with aging on macrophage content and activation


Saline
Insulin
Glucosamine
A
Resistin
60
120
80
40
0
SC
VF
B
PAI-1
30
25
20
15
10
5
0
SC
VF
C
Angiotensinogen
12
9
6
3
0
SC
VF
D
Leptin
16
12
8
4
0
SC
VF
E
IL-6
12
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8
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VF
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TNF-α
6
4
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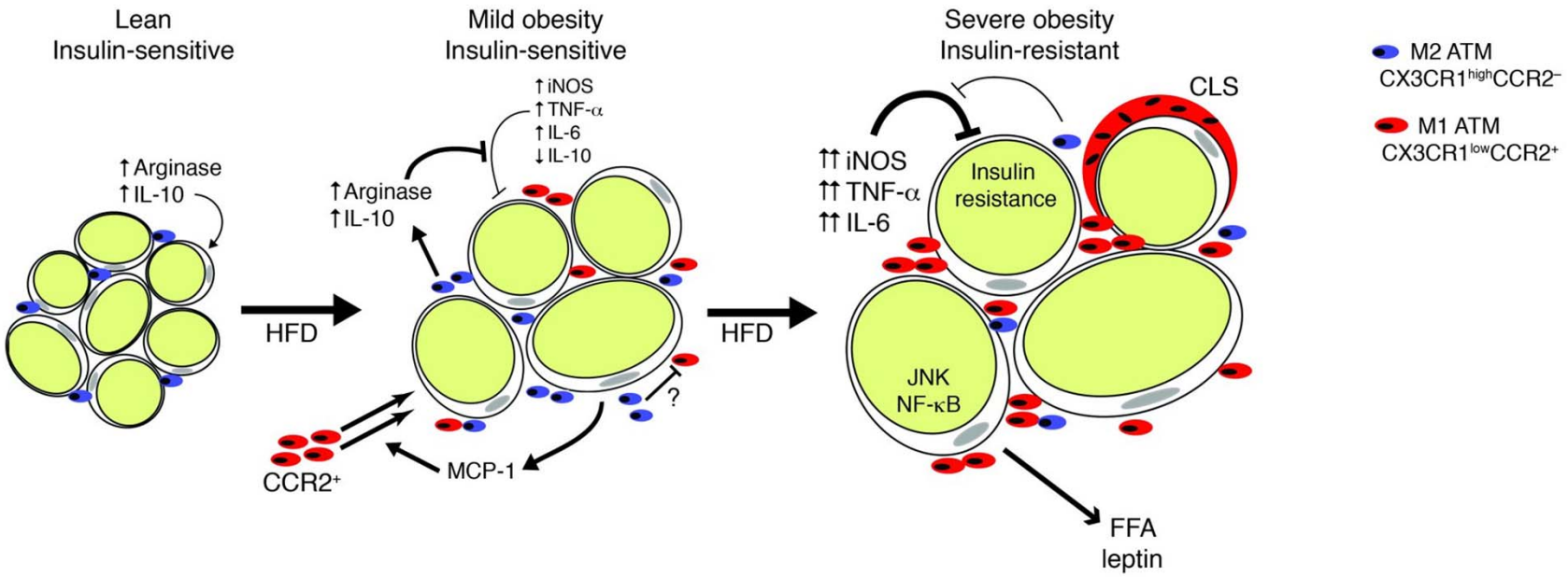
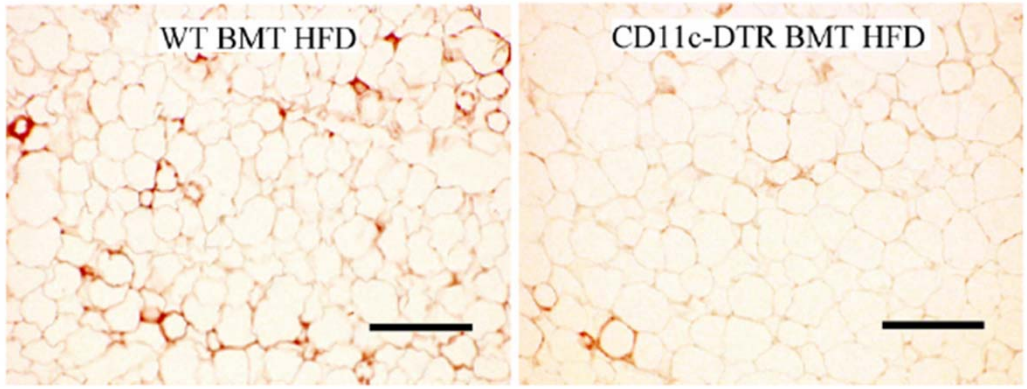
SC
VF

Classic versus alternative activation of macrophages



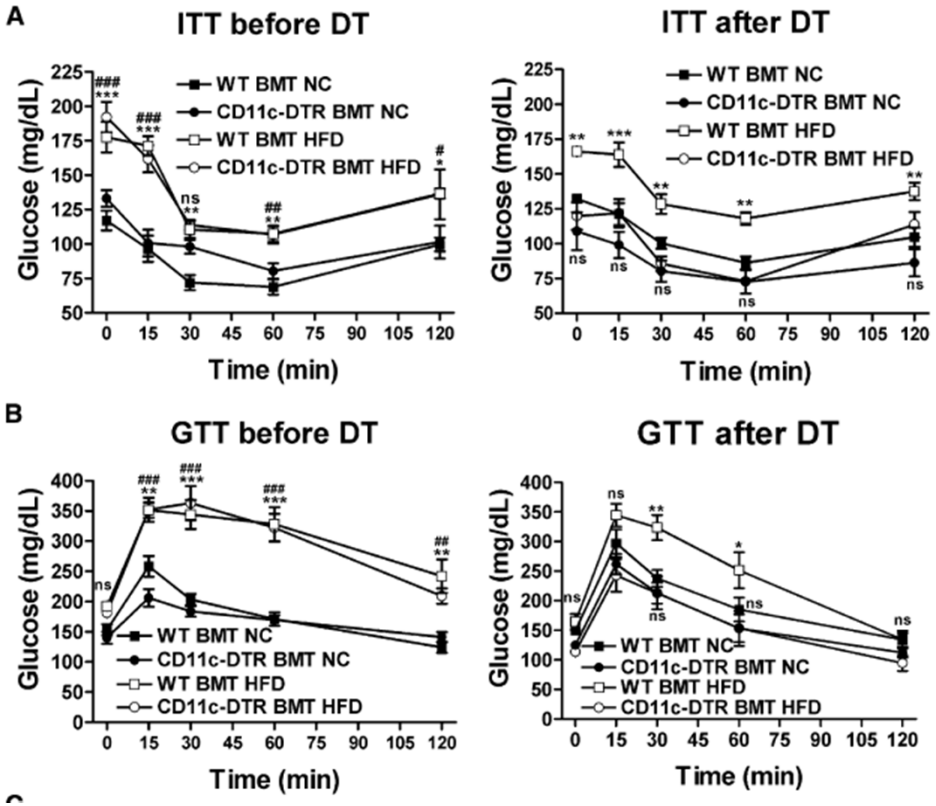
J. Clin. Invest. **117**:175–184 (2007)

Importance of Macrophages



Ablation of CD11c-Positive Cells Normalizes Insulin Sensitivity in Obese Insulin Resistant Animals

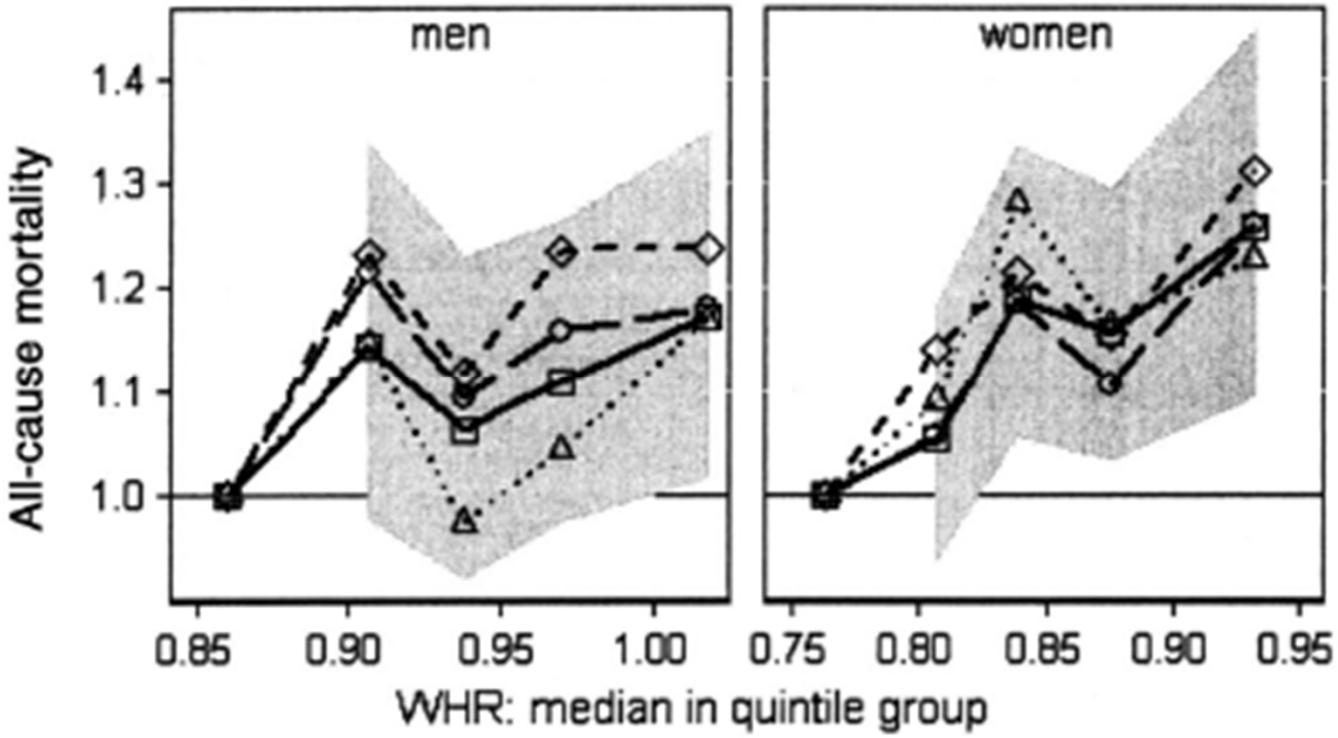
Cell Metabolism *8*, 301–309, October 8, 2008



Waist-to-hip ratio trumps BMI for mortality risk in the elderly

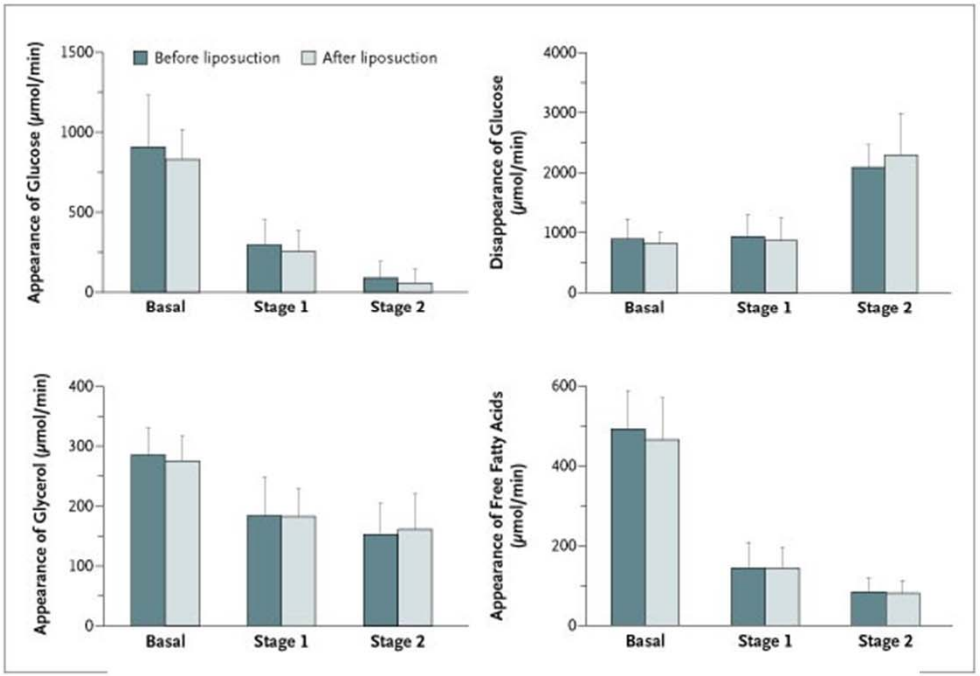
Men and Women >75 yrs (mean age ~81yrs)

Greater risk with higher WHR

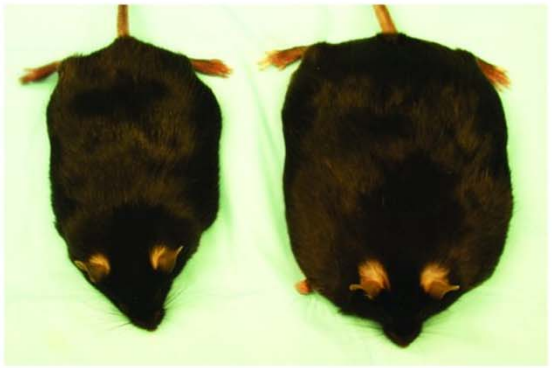


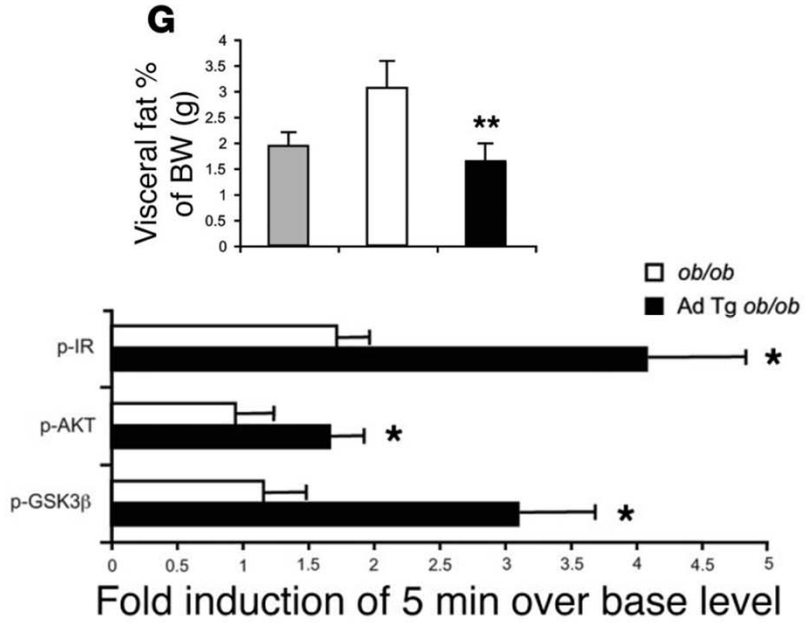
Am J Clin Nutr 2006;84:449–60.

Subcutaneous fat and metabolic disease



N ENGL J MED 350;25 WWW.NEJM.ORG JUNE 17, 2004





J. Clin. Invest. 117:2621–2637 (2007).

Body fat distribution:101