63° CONGRESSO NAZIONALE SIGG

GLI ANZIANI: LE RADICI DA PRESERVARE

ROMA 28 novembre 01 dicembre 2018 Auditorium della Tecnica, Roma

INSULINO-RESISTENZA, INFIAMMAZIONE E GRASSO VISCERALE

Prof. Gianluigi Vendemiale

Cattedra di Medicina Interna e Geriatria

Università degli Studi di Foggia

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Il sottoscritto prof. Gianluigi Vendemiale

dichiara che negli ultimi due anni

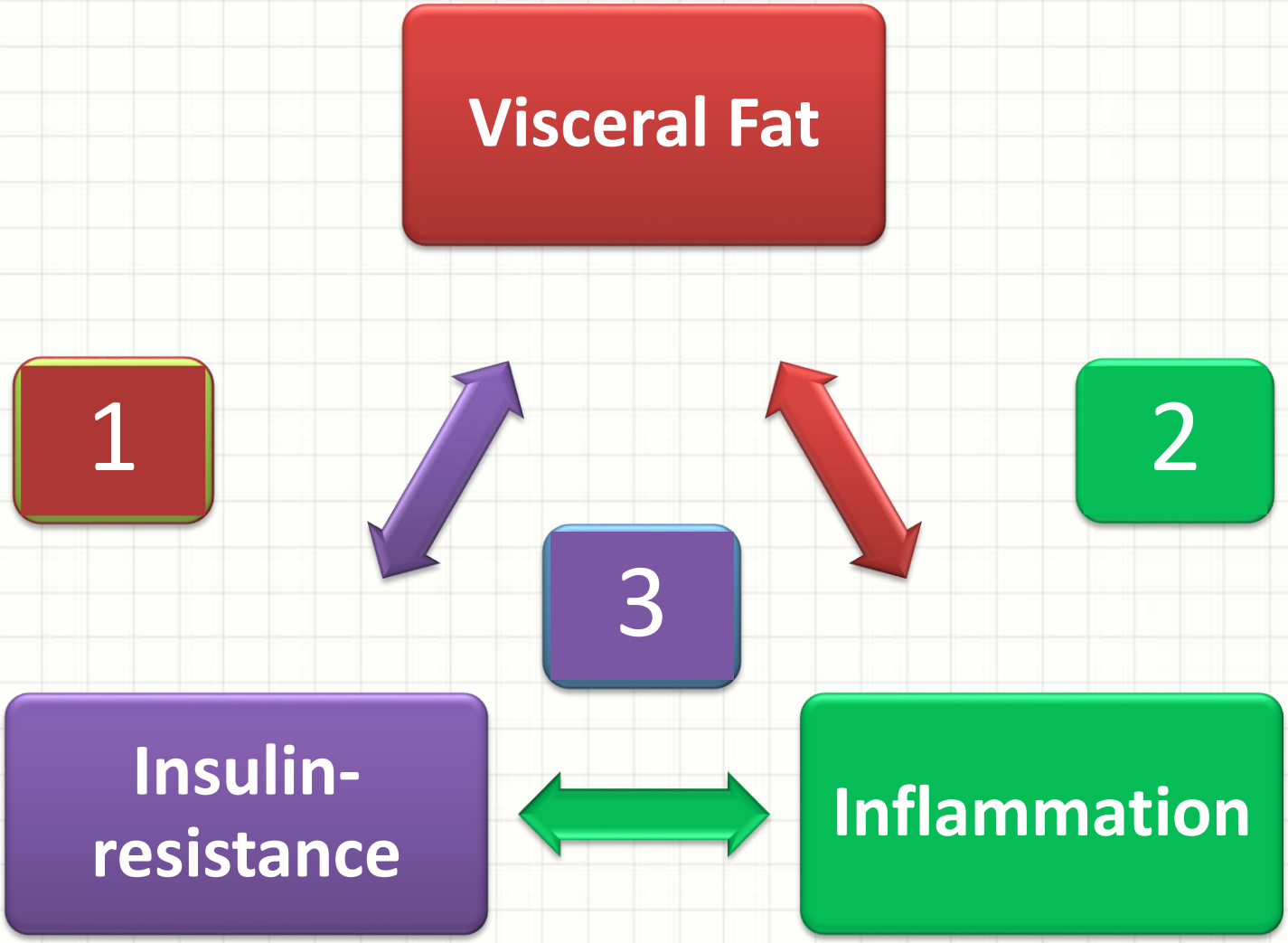
ha avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

Bristol-Myers Squibb S.r.l
Pfizer
Boehringer Ingelheim
Sanofi
ErreKappa

Il sottoscritto dichiara altresì che detti rapporti non sono tali da poter influenzare l'attività di docenza espletata nell'ambito di codesto evento pregiudicando la finalità esclusiva di educazione/formazione di professionisti.

Il prof. Gianluigi Vendemiale non si trova pertanto in una situazione di conflitto di interessi rispetto all'evento ai sensi e per gli effetti dell'Accordo Stato-Regioni del 2/02/2017

Which comes first?

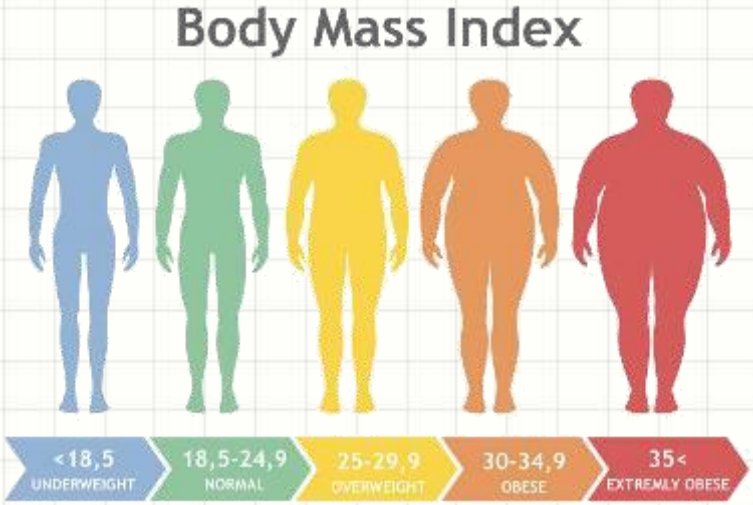


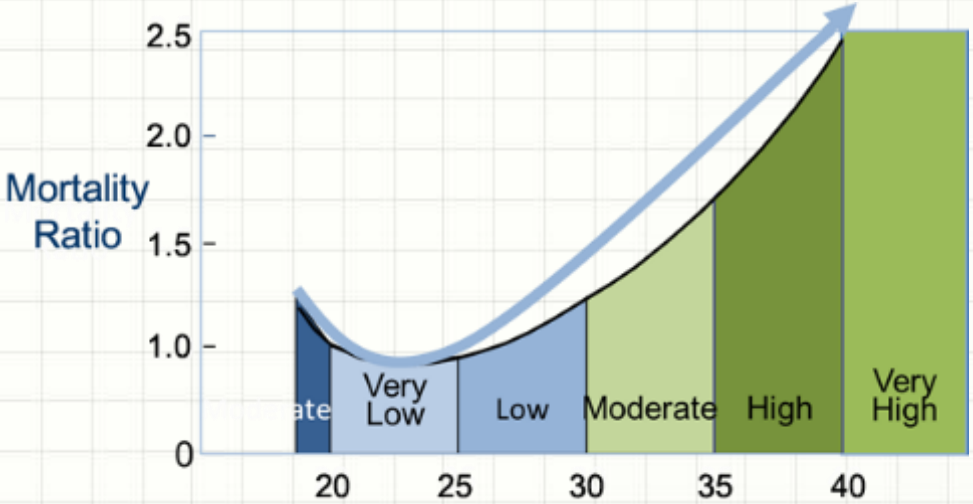
1

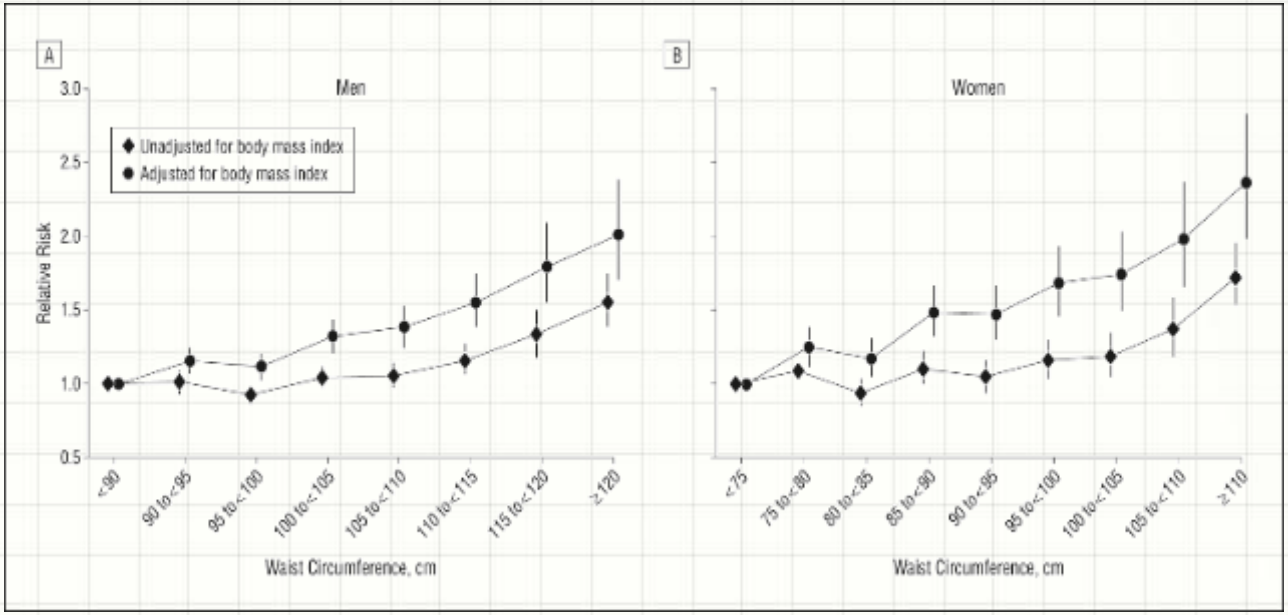
Visceral Fat

THIS WAY?

Insulin-resistance







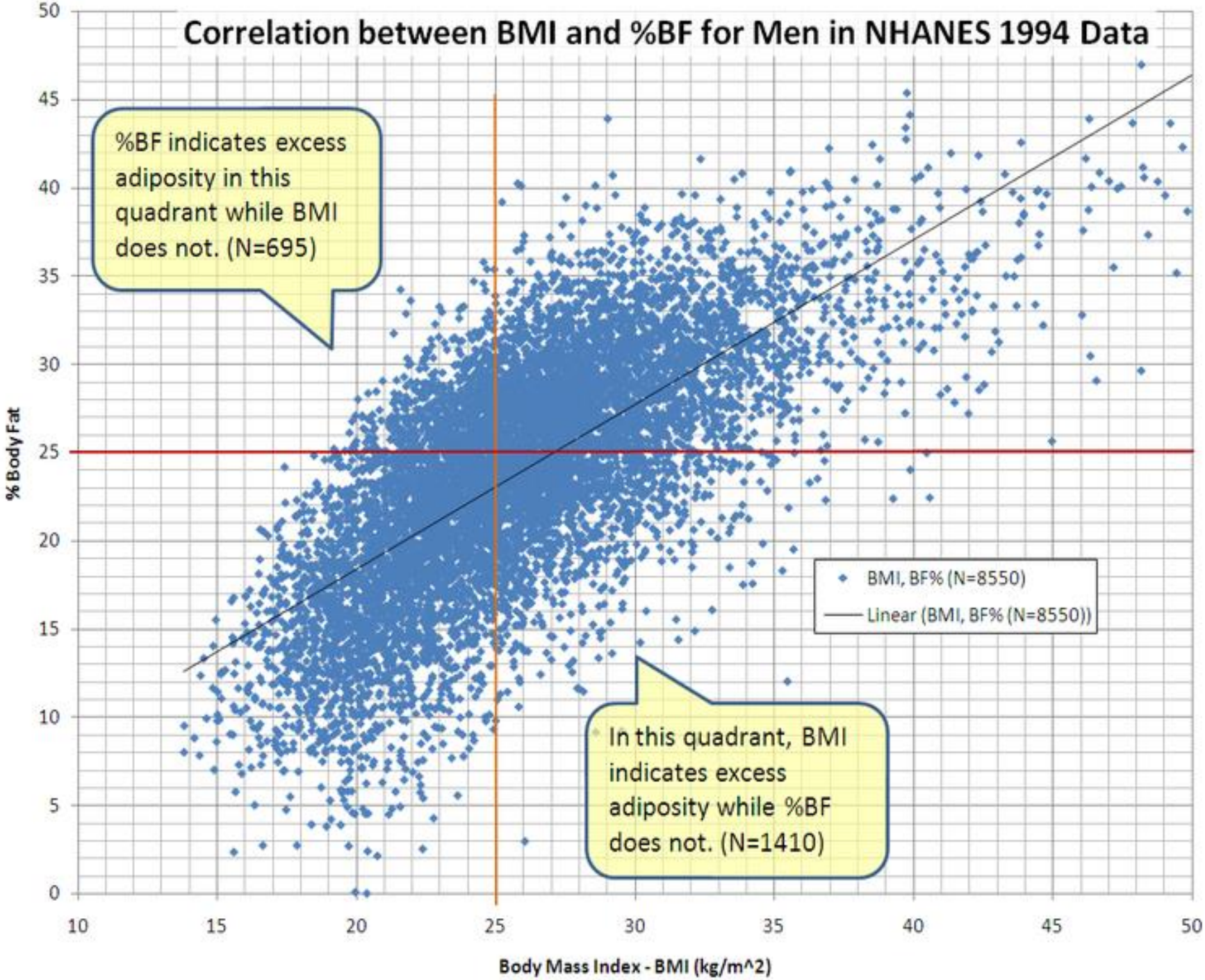
Jacobs EJ et al., Arch Intern Med, 2010

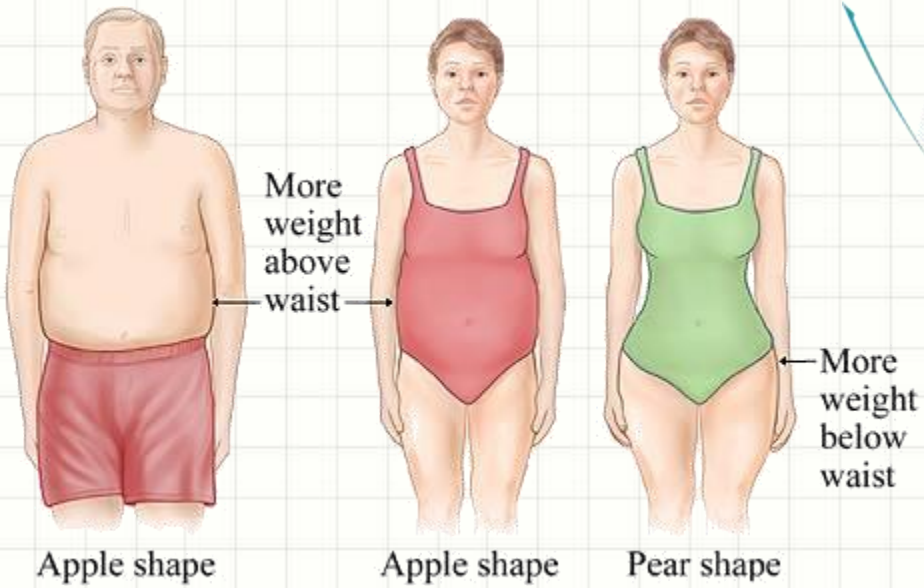
Circonferenza addominale, BMI ed insulino-resistenza

Stefan N et al., Arch Intern Med, 2008

		BMI		
		Normal weight	Overweight	Obese
Metabolically abnormal	Metabolically healthy	Metabolically healthy normal weight	Metabolically healthy overweight	Metabolically healthy obese (MHO)
	Metabolically unhealthy	Metabolically unhealthy normal weight	Metabolically unhealthy overweight	Metabolically unhealthy obese (MUHO)

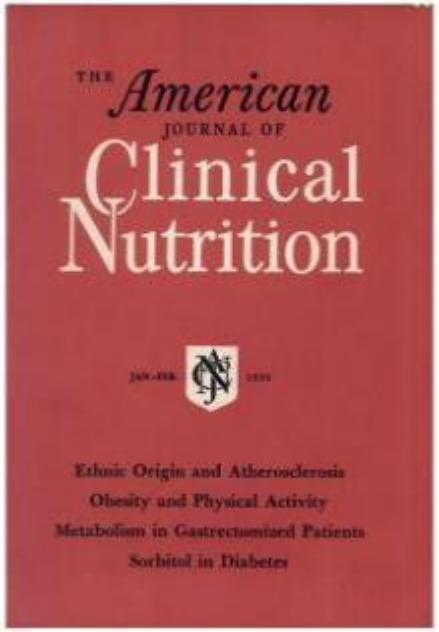
Stefan N et al, The Lancet Diabetes Endocrinol, 2013


Correlation between BMI and %BF for Men in NHANES 1994 Data
%BF indicates excess adiposity in this quadrant while BMI does not. (N=695)
In this quadrant, BMI indicates excess adiposity while %BF does not. (N=1410)
BMI, BF% (N=8550)
Linear (BMI, BF% (N=8550))
% Body Fat
Body Mass Index - BMI (kg/m^2)
0
5
10
15
20
25
30
35
40
45
50
10
15
20
25
30
35
40
45
50

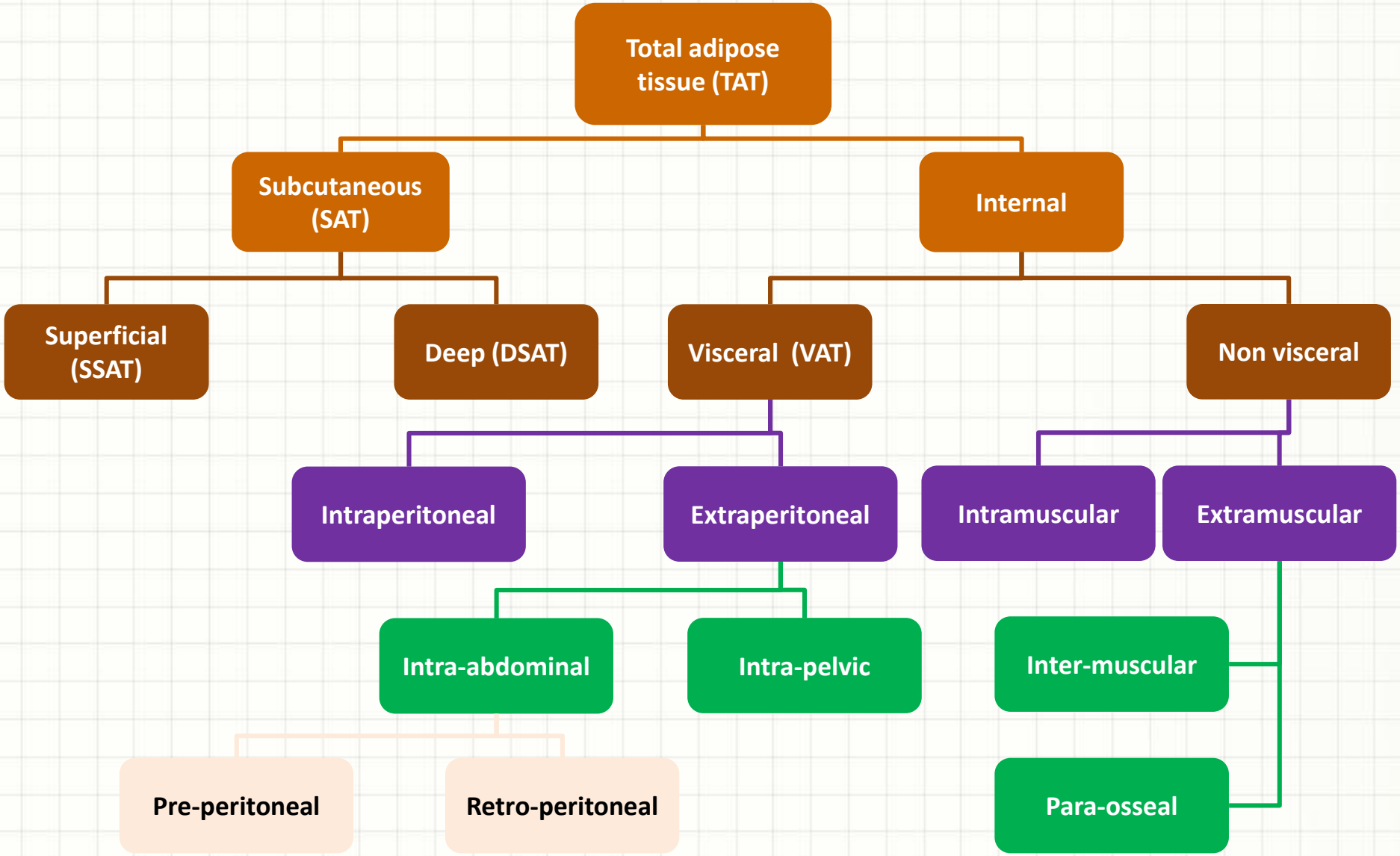


The degree of masculine differentiation of obesities: a factor determining predisposition to diabetes, atherosclerosis, gout, and uric calculous disease.

Vague J, 1956

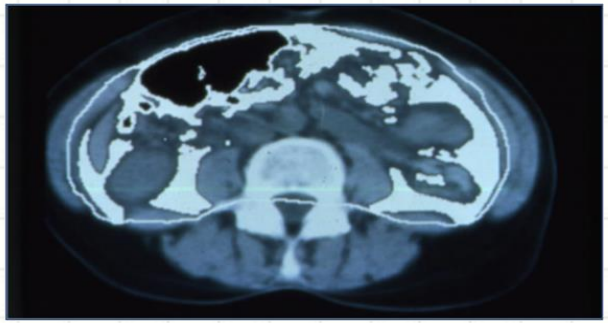


Abdominal adipose tissue classification

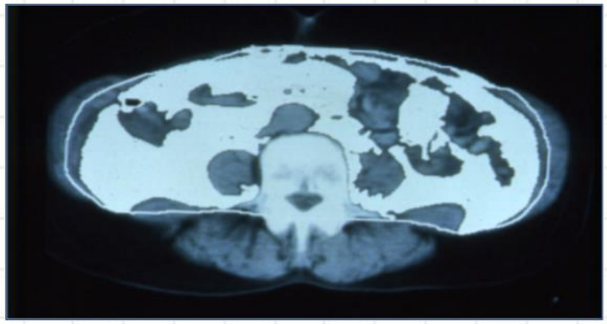


Shen W et al., Obes Res, 2003

Visceral fat distribution: normal vs T2DM

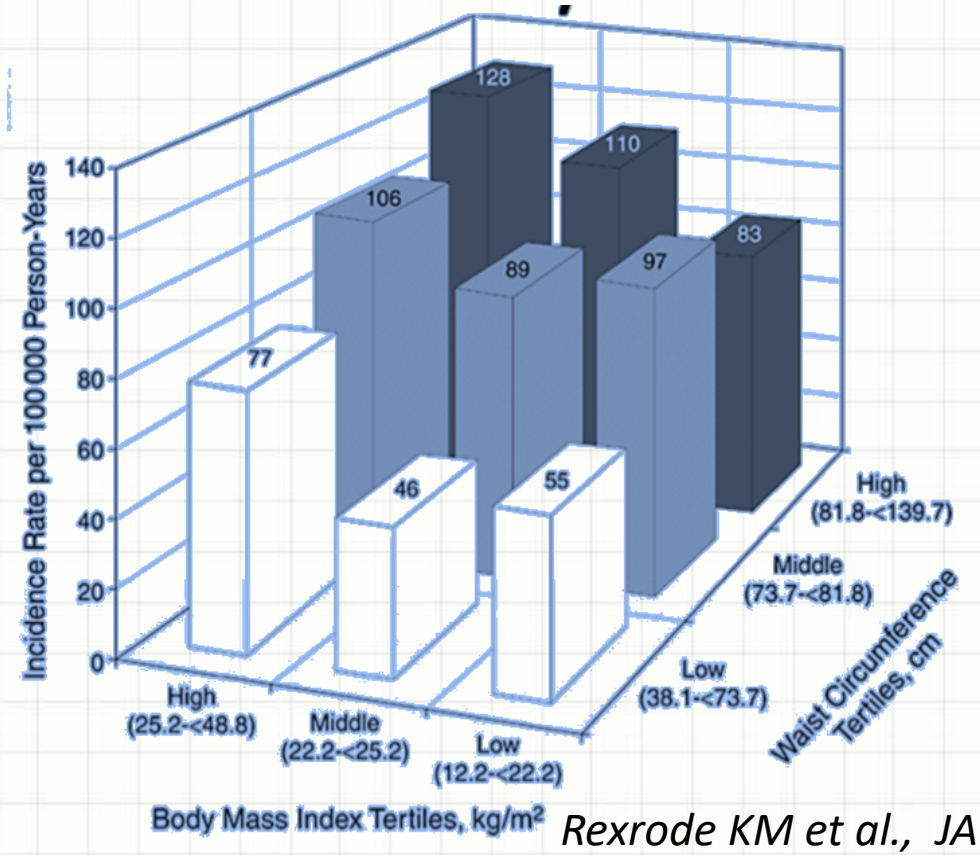


Normal

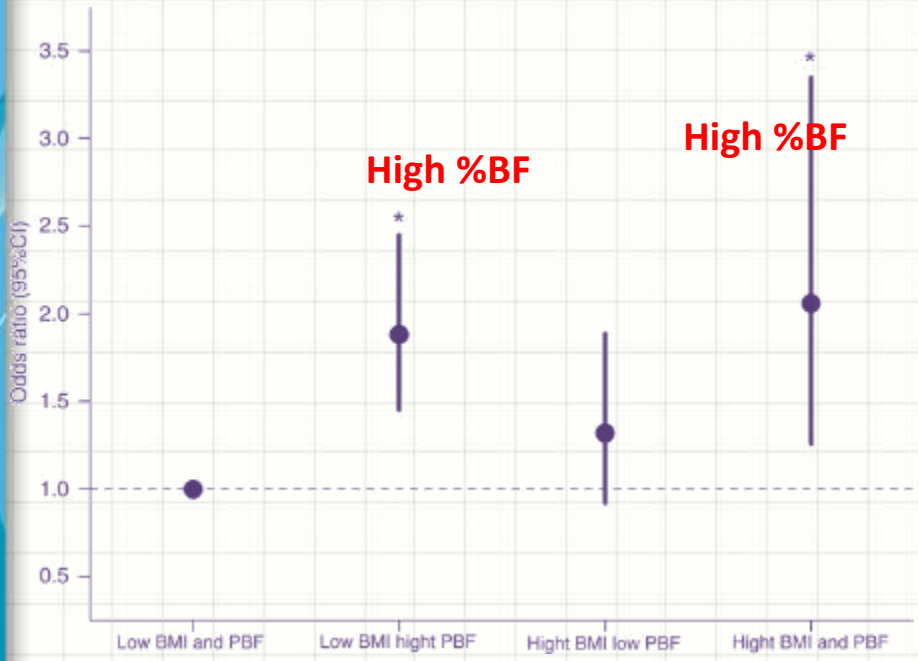


Type 2 Diabetes

Abdominal obesity and BMI: association with coronary disease



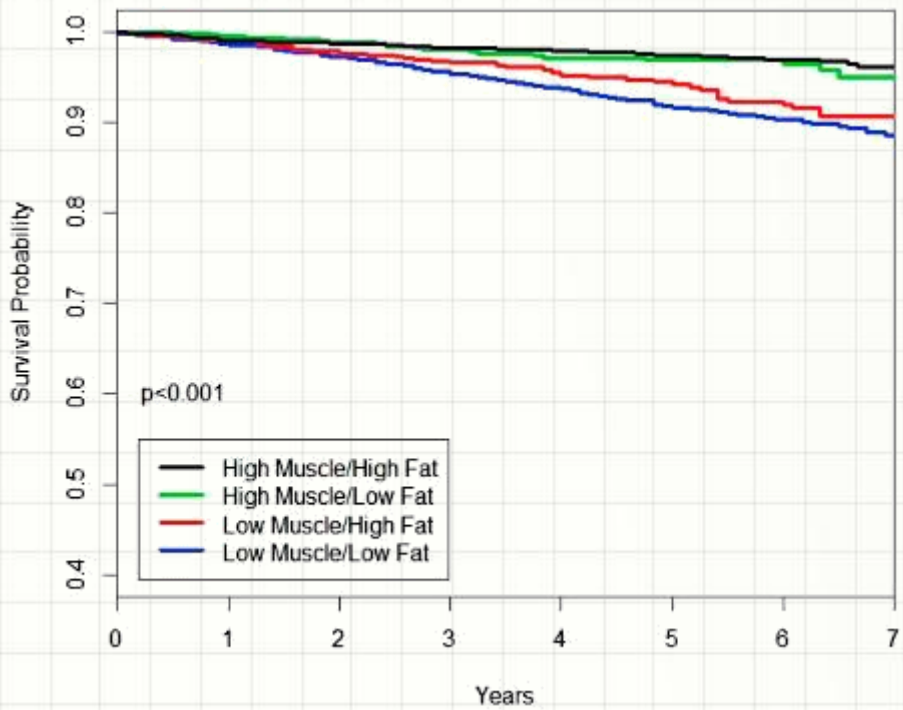
Rexrode KM et al., JAMA, 2008



Risk of CV disease taking into account BMI and % Fat Mass

Zeng Q et al., Braz J Med Biol Res, 2012

CV mortality taking into account both muscle and fat mass

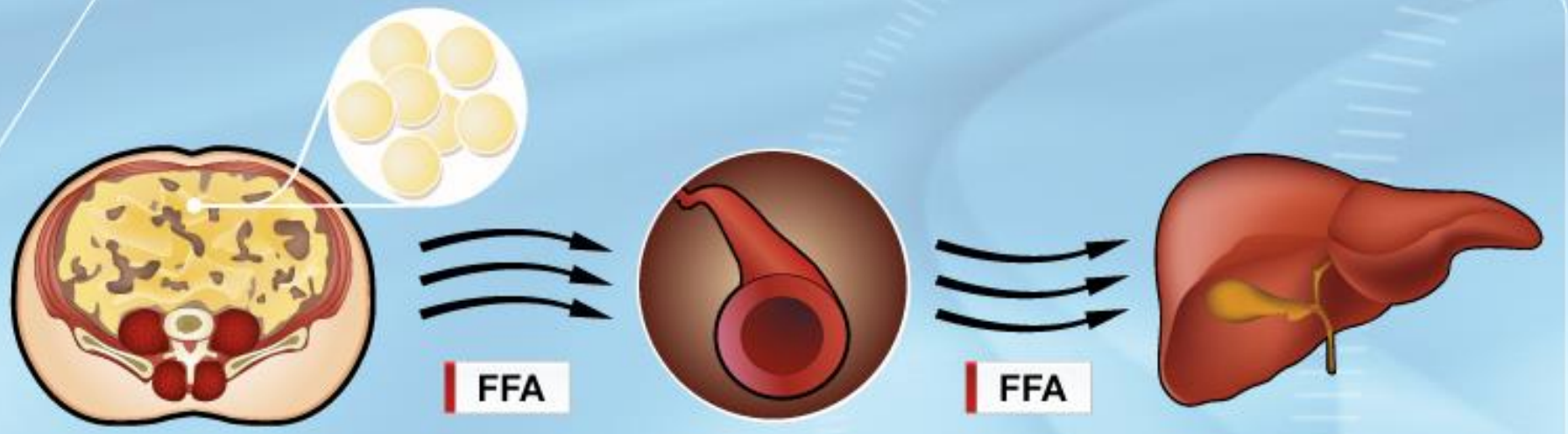


Srikanthan P et al., Am J Cardiol, 2016

Causes of obesity-associated IR

1. The portal theory
2. Reduced WAT glucose uptake
3. The hormonal theory
4. The pro-inflammatory theory

SIMPLIFIED MODEL OF THE "PORTAL" THEORY



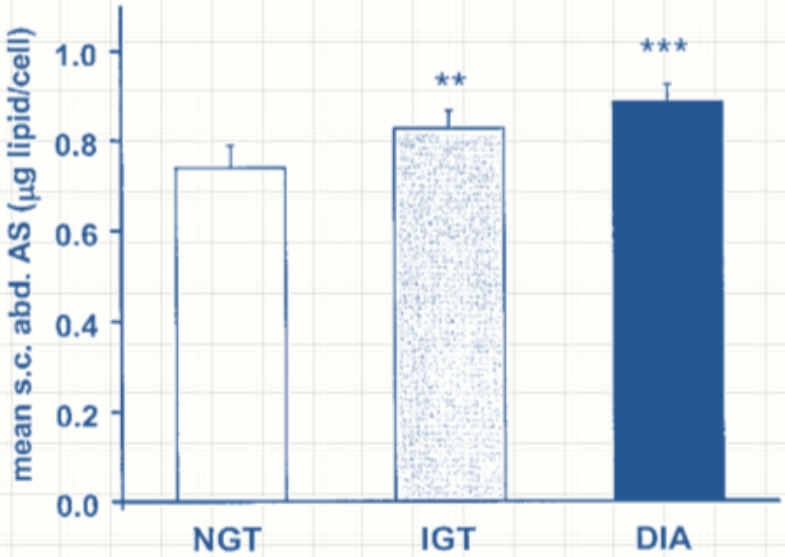
Release of free fatty acids (FFA) from an expanded, and highly active intra-abdominal adipose tissue depot

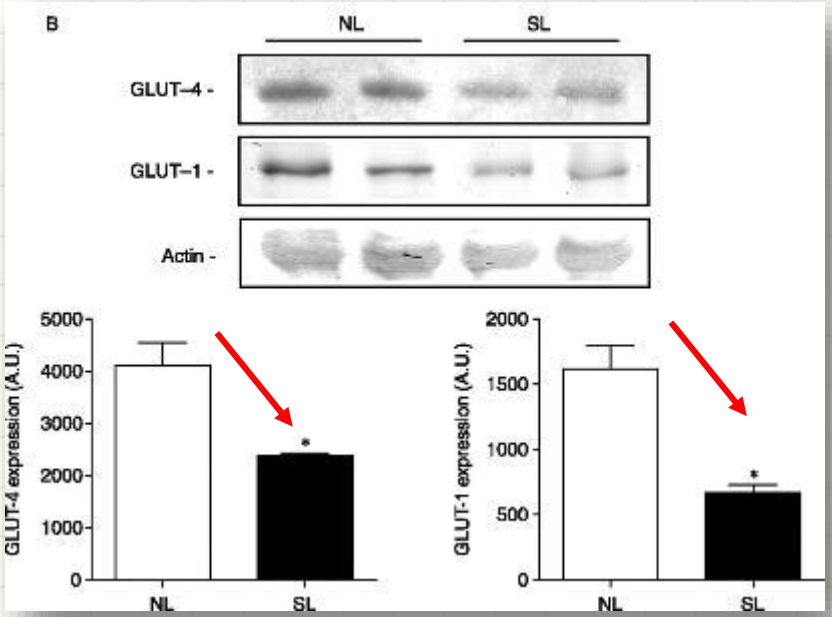
Products released from the intra-abdominal depot are drained via the portal vein, leading directly to the liver

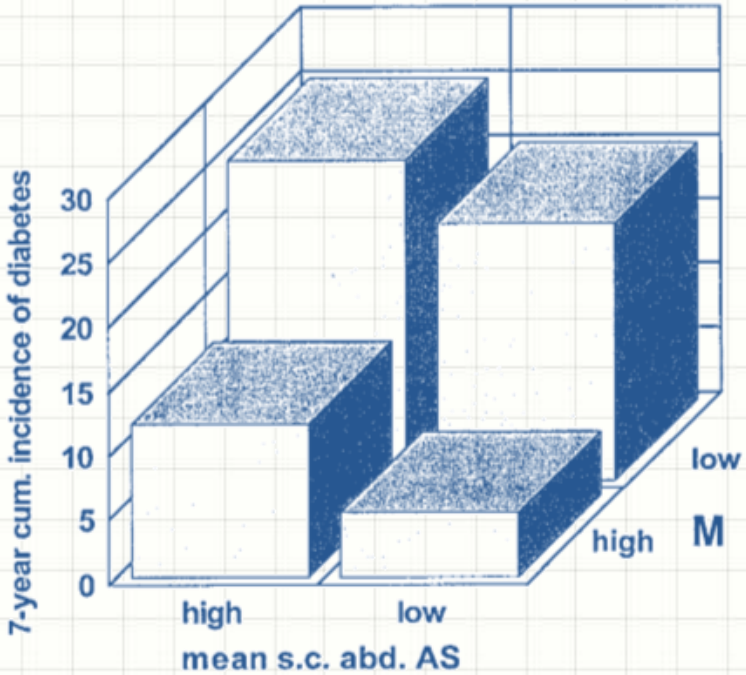
Increased exposure to FFA leads to hepatic insulin resistance, fat deposition, lipotoxicity and metabolic derangements

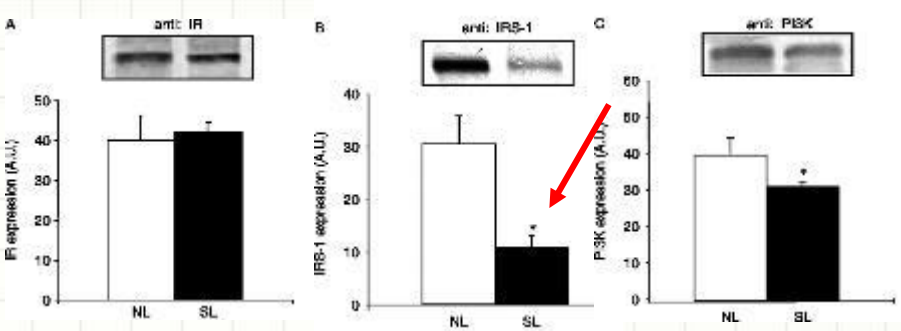
Source: International Chair on Cardiometabolic Risk
www.cardiometabolic-risk.org

Adipocyte size and diabetes



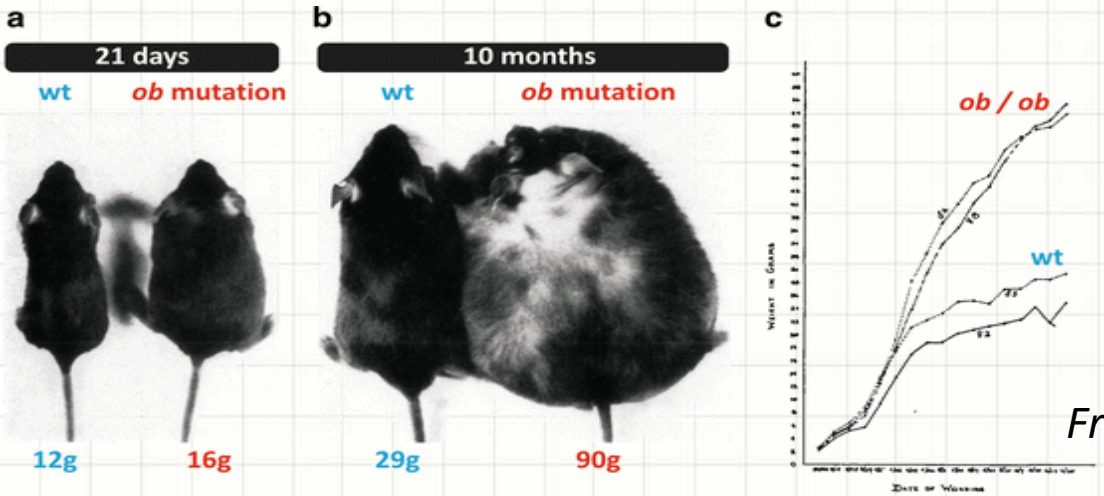






Weyer C et al., Diabetologia, 2000

Rodrigues AL et al., J of Endocrinol, 2007



Friedman JM et al., Nature, 1994

Secretory cells of adipose tissue

- Adipocytes
- Precursor cells
- Endothelial cells
- Macrophages
- Foam cells
- Neutrophils
- Lymphocytes
- Fibroblasts
- Others

Cytokine and cytokine-like proteins
TNFα
IL-6
MCP-1
Resistin
Progranulin

Proteins of the fibrinolytic system
PAI-1
Tissue factor

Complement and complement-related proteins
Adipsin
Complement factor B
ASP
CTRPs

Enzymes
DPP-4

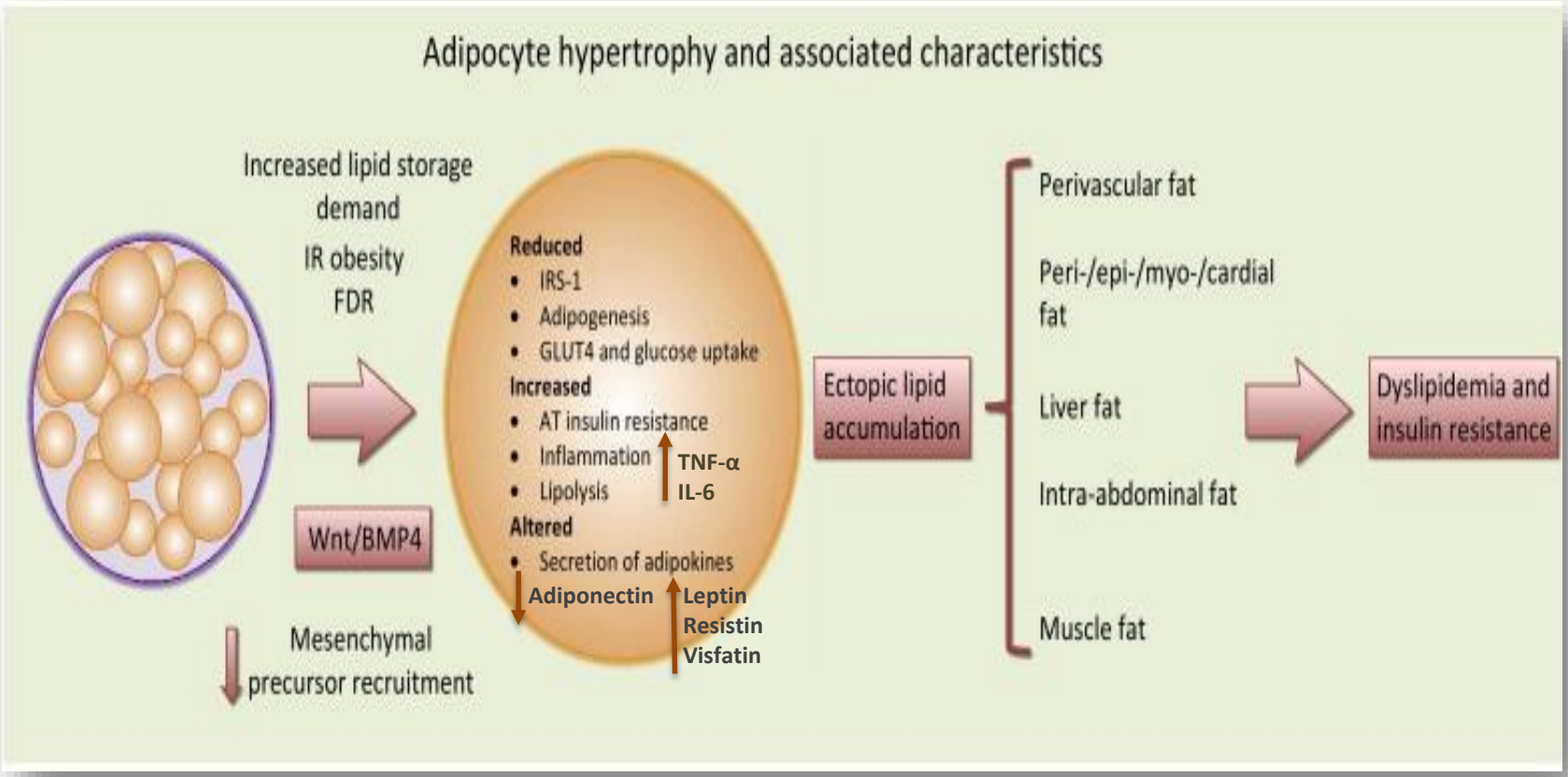
Lipid transport
Apolipoprotein E
Cholesterol ester transfer protein
Lipoprotein lipase

Adipokines
Leptin
Adiponectin
Visfatin/Nampt/PBEF
Vaspin
RBP4
FGF21
BMPs
Nesfatin-1
Cathepsins
Apelin
Omentin
Lipocalin
and hundreds more

Proteins of RAS
Angiotensinogen

Endocannabinoids and other lipids
Anandamide
2-AG
Free fatty acids

TRENDS in Pharmacological Sciences



Gustafson B et al., Trends Endocrinol Metab, 2015

1

THIS WAY?

Visceral Fat

Insulin-resistance

Cell Metabolism
Previews

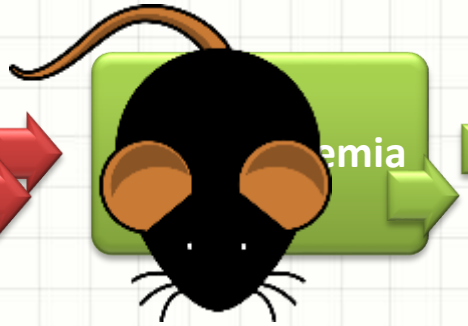
Is Hyperinsulinemia Required to Develop Overeating-Induced Obesity?

Christoph Buettner[1,*]
[1]Department of Medicine, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029-6574, USA
*Correspondence: christoph.buettner@mssm.edu
http://dx.doi.org/10.1016/j.cmet.2012.11.009

Modello «tradizionale»

High-Fat Diet → Obesità → Insulino-resistenza

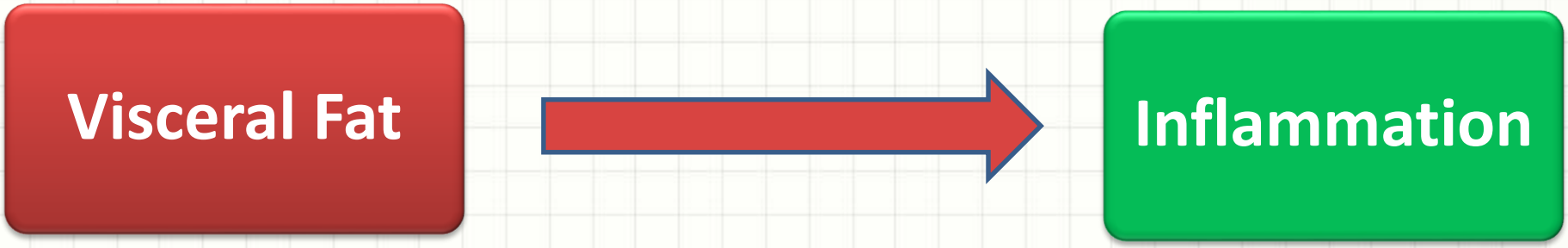
Nuovo Modello

High-Fat Diet →  → No obesità

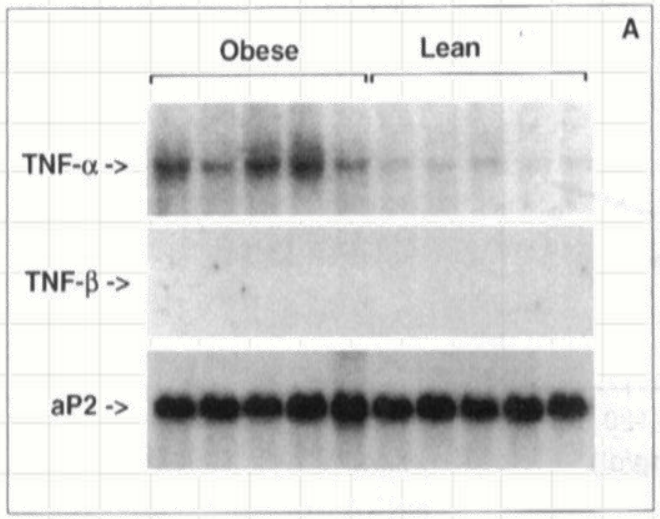
Topi KO per il gene dell'insulina

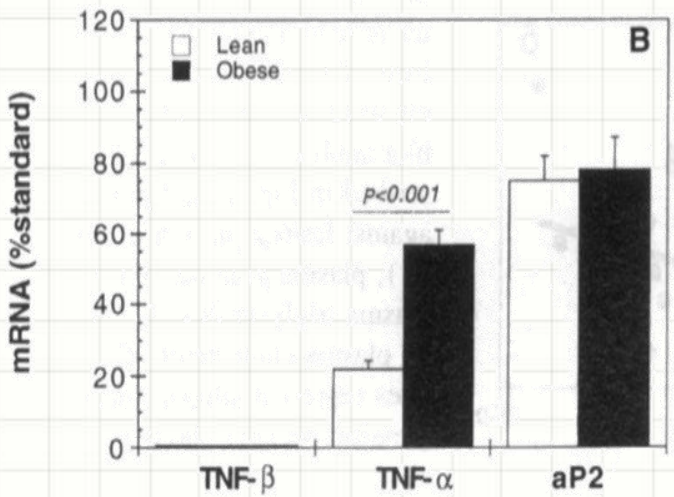
Mehran AE et al, Cell Metab, 2012

2



Increased adipose tissue expression of tumor necrosis factor-α in human obesity





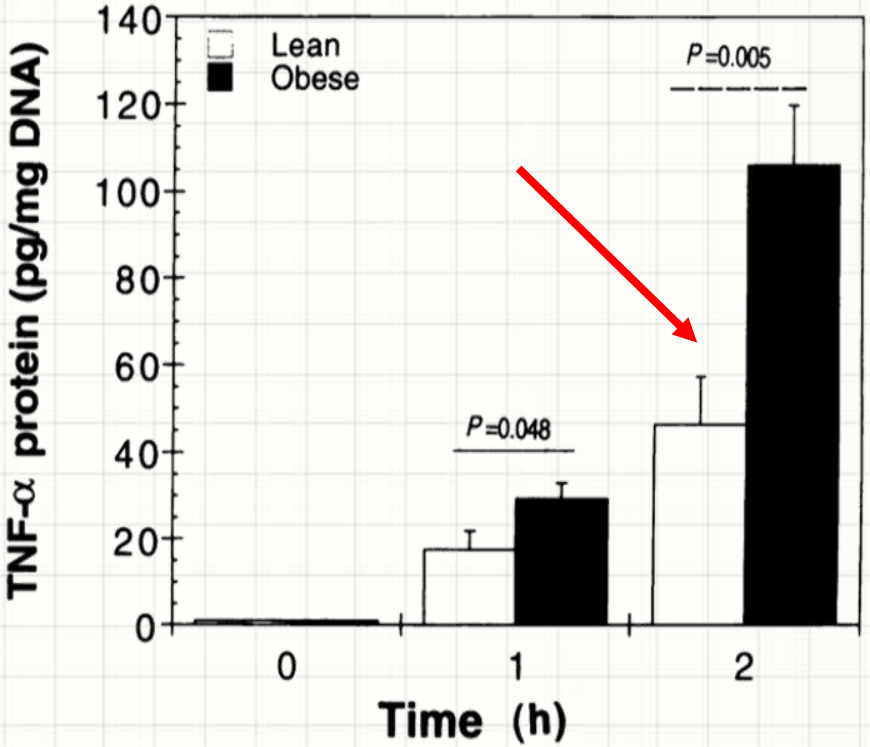
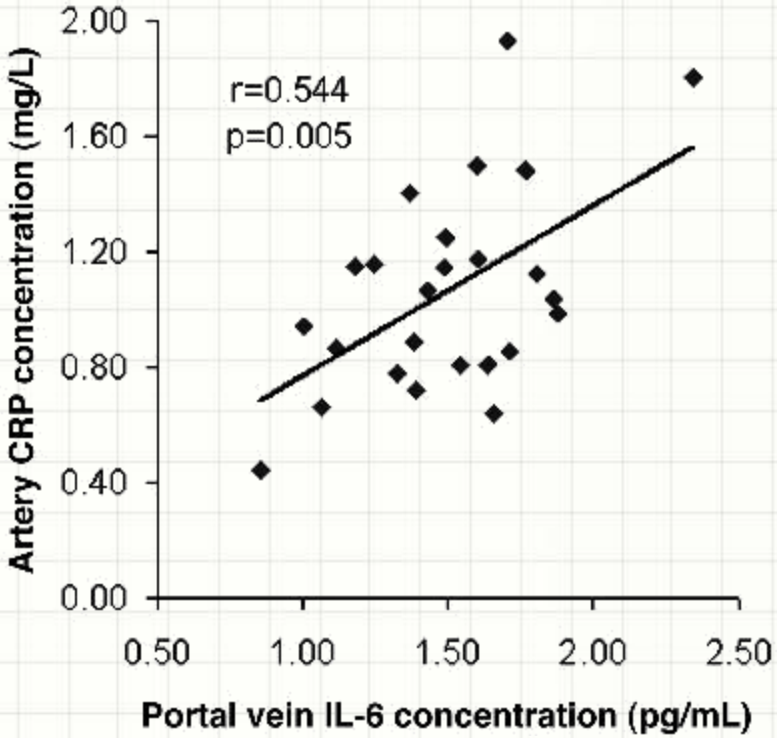


Figure 2. Secretion of TNF-α protein from the explanted adipose tissue of lean and obese female subjects. After 1 and 2 h incubation of fresh adipose tissue, TNF-α protein was measured in conditioned media by ELISA. Protein quantities were expressed as picograms protein per milligram total tissue DNA that is extracted from the adipose tissue at the end of the incubation period.

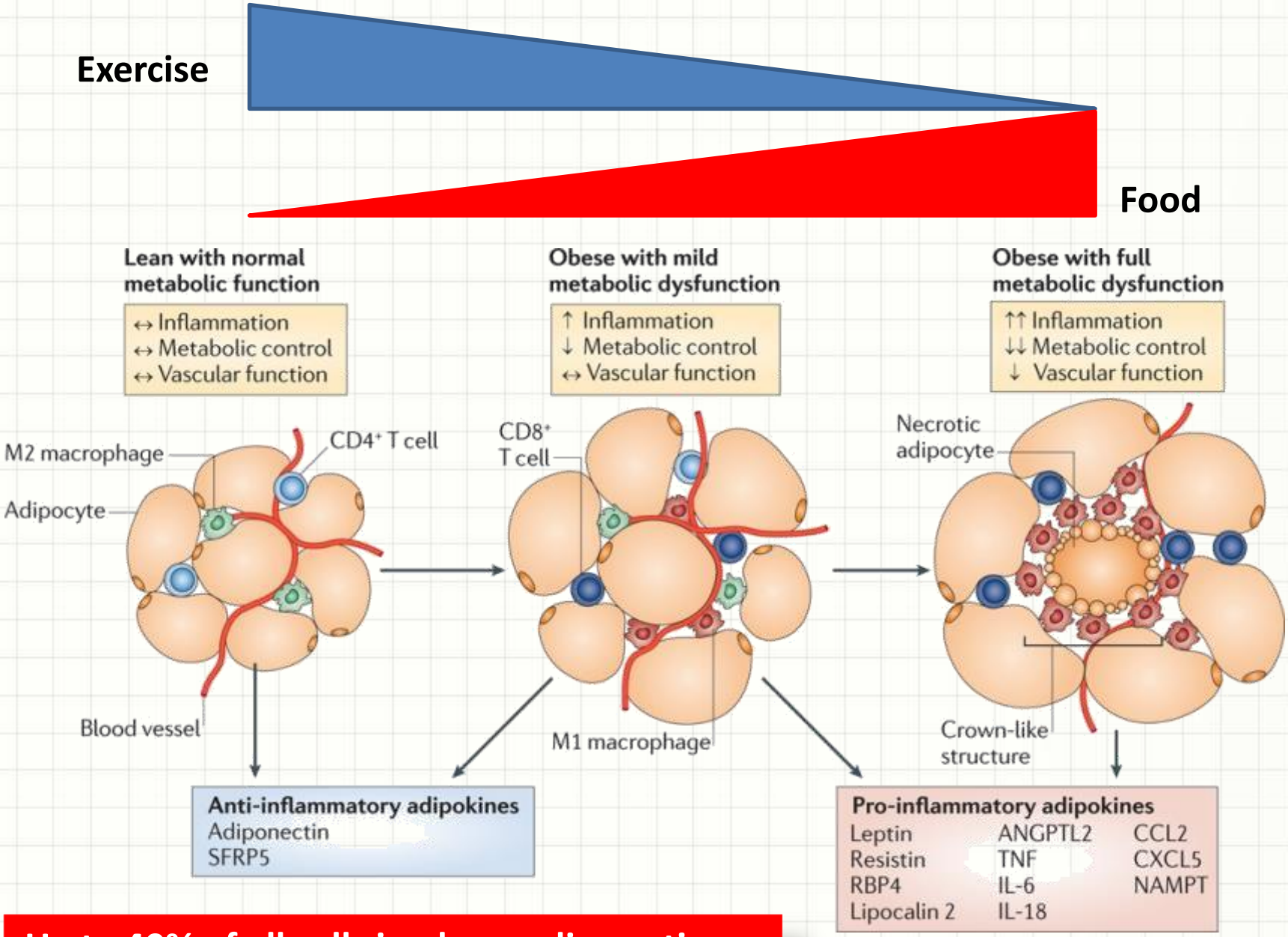
Hotamislgil GS et al., J Clin Invest, 1995

Visceral fat adipokine secretion is associated with systemic inflammation in obese humans



25 extremely obese subjects undergoing gastric bypass surgery

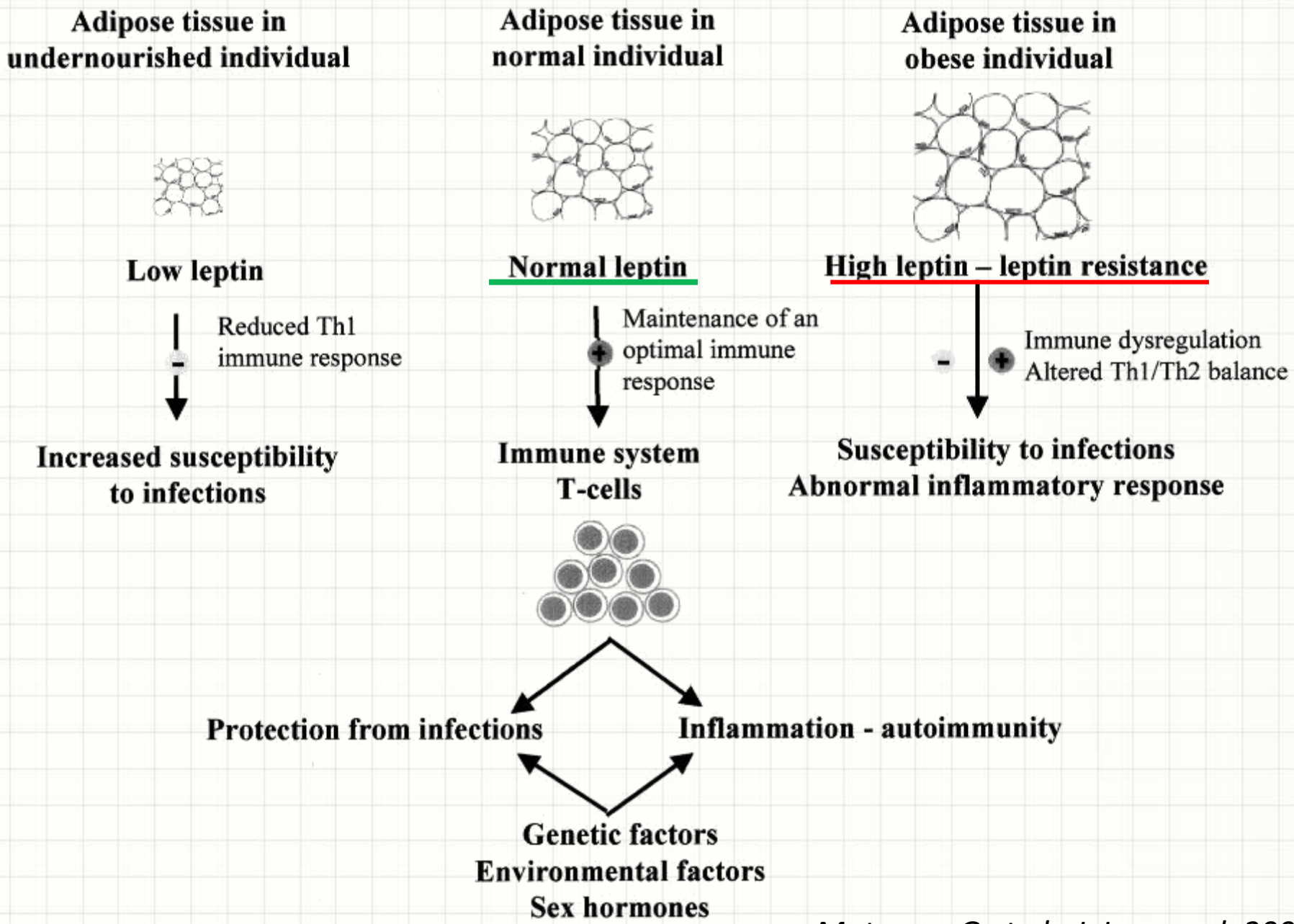
Fontana L et al., Diabetes, 2007



Up to 40% of all cells in obese adipose tissue are infiltrating macrofages (M1)

Ouchi N et al., Nat Rev Immunol, 2011

Leptin, inflammation and immune response



Matarese G et al., J Immunol, 2005

Leading Edge
Perspective

Cell

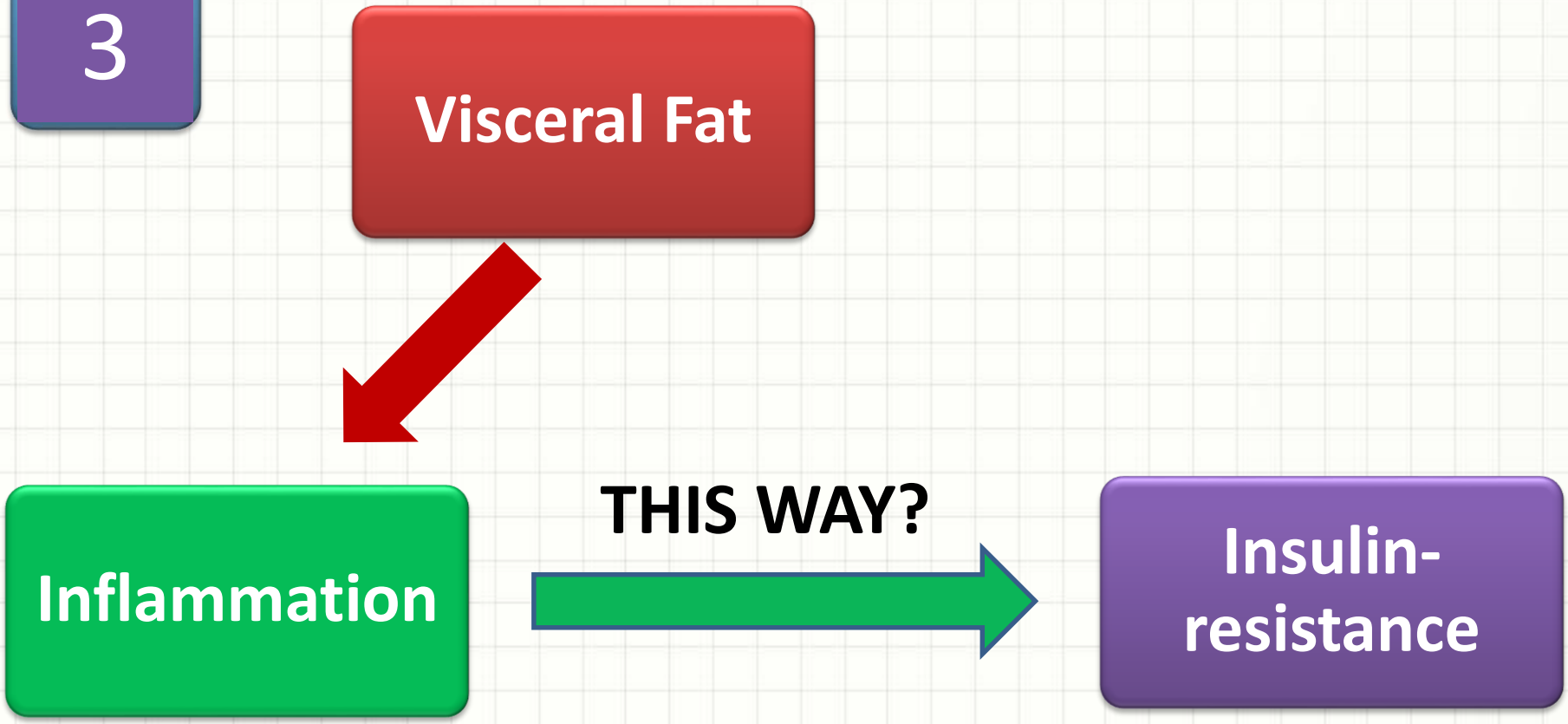
The Origins and Drivers of Insulin Resistance

Andrew M.F. Johnson[1] and Jerrold M. Olefsky[1,*]
[1]Department of Medicine, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0673, USA
*Correspondence: jolefsky@ucsd.edu
http://dx.doi.org/10.1016/j.cell.2013.01.041

Hypothalamic inflammation in obesity

The High local hypotalamic production of proinflammatory cytokines causes central leptin resistance, a key feature of obesity

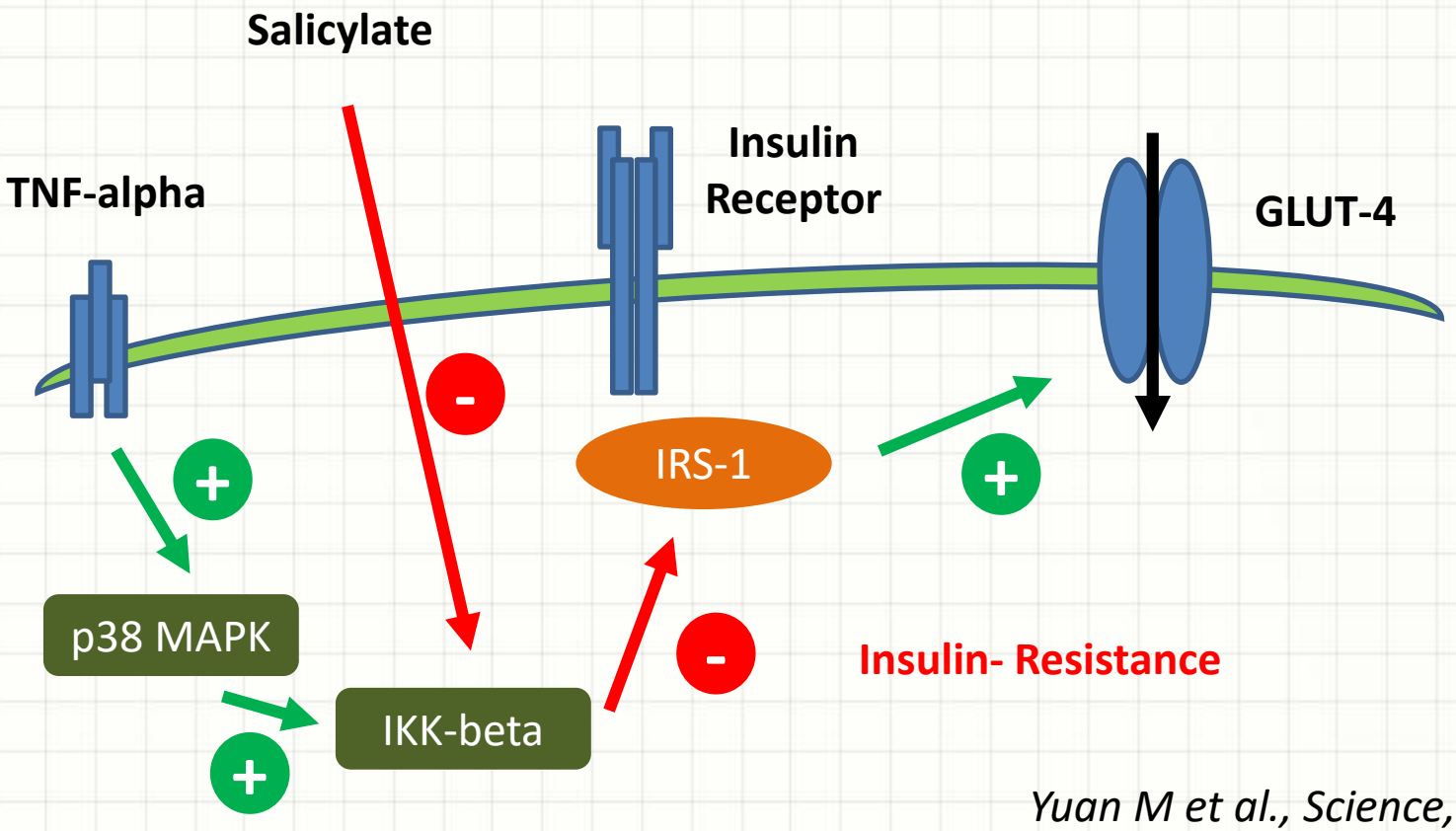
3



DIABETES MELLITUS WITH SODIUM SALICYLATE.

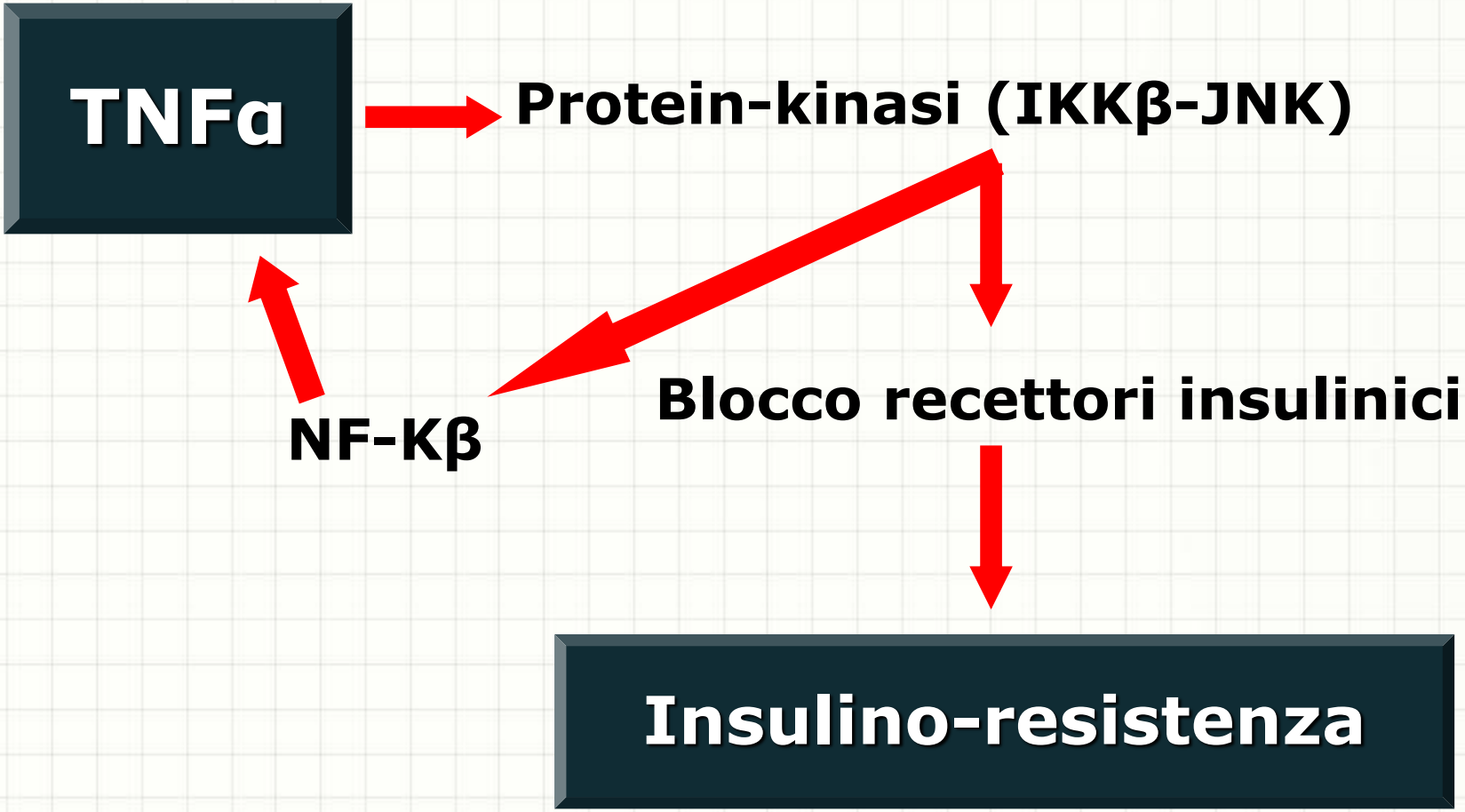
By R. T. WILLIAMSON, M.D.Lond., F.R.C.P.,
Physician to the Ancoats Hospital, Manchester, and Assistant Lecturer on Medicine, Owens College.

Br Med J, 1901



Yuan M et al., Science, 2001

Mediatori molecolari di insulino-resistenza



3

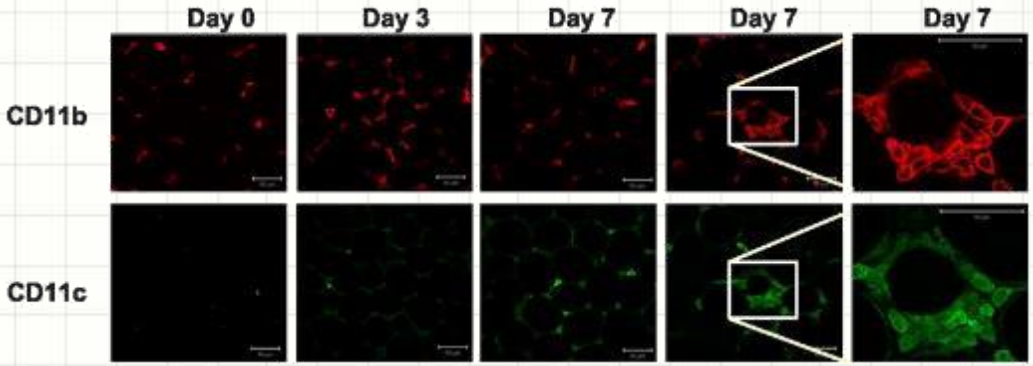
THIS WAY?

Inflammation

Insulin-resistance

Inflammation is not necessary for HFD-induced insulin-resistance

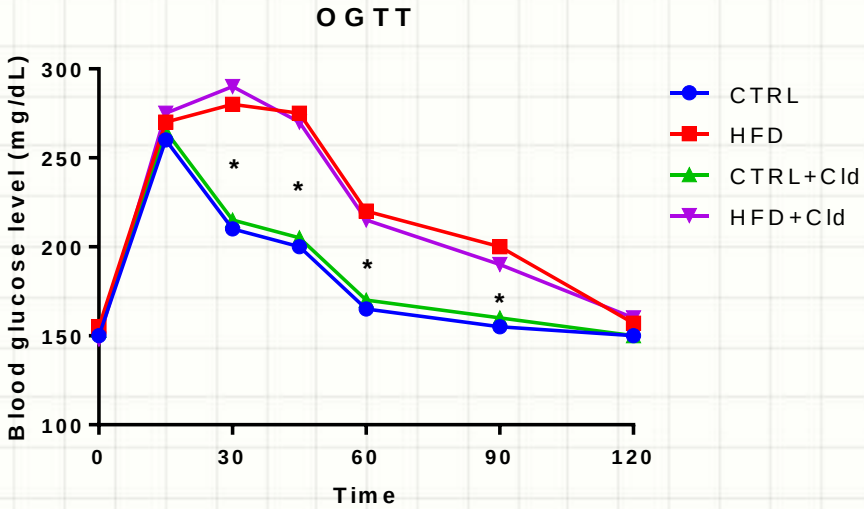
High-Fat diet (Dietary IR)

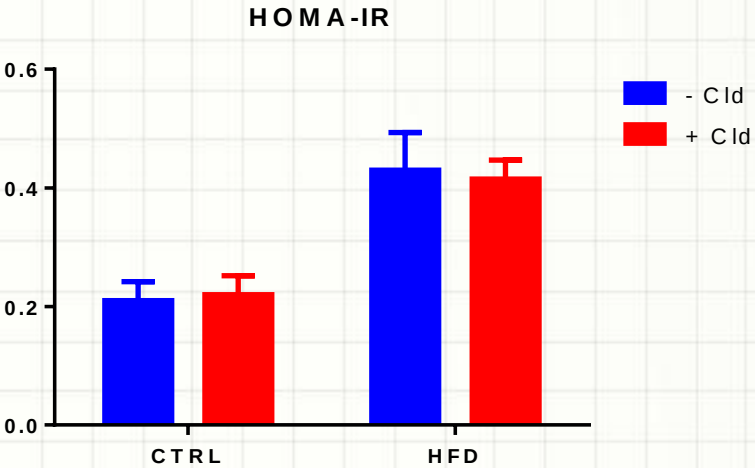


Increased M1 macrophages (CD11+) in adipose tissue

Clodronate (Cld) injection (pharmacological depletion of macrophages)

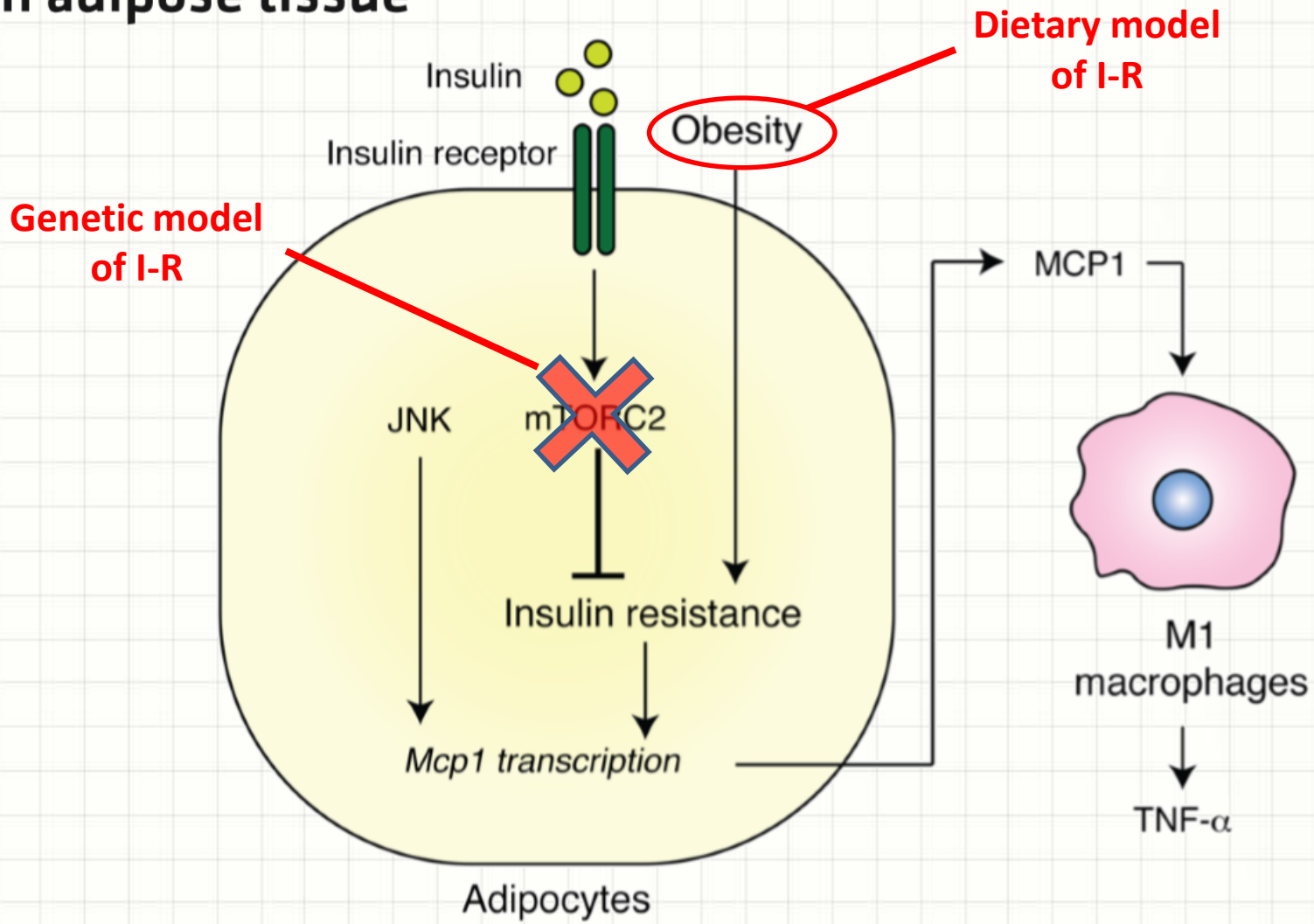
High-Fat diet (Dietary IR)





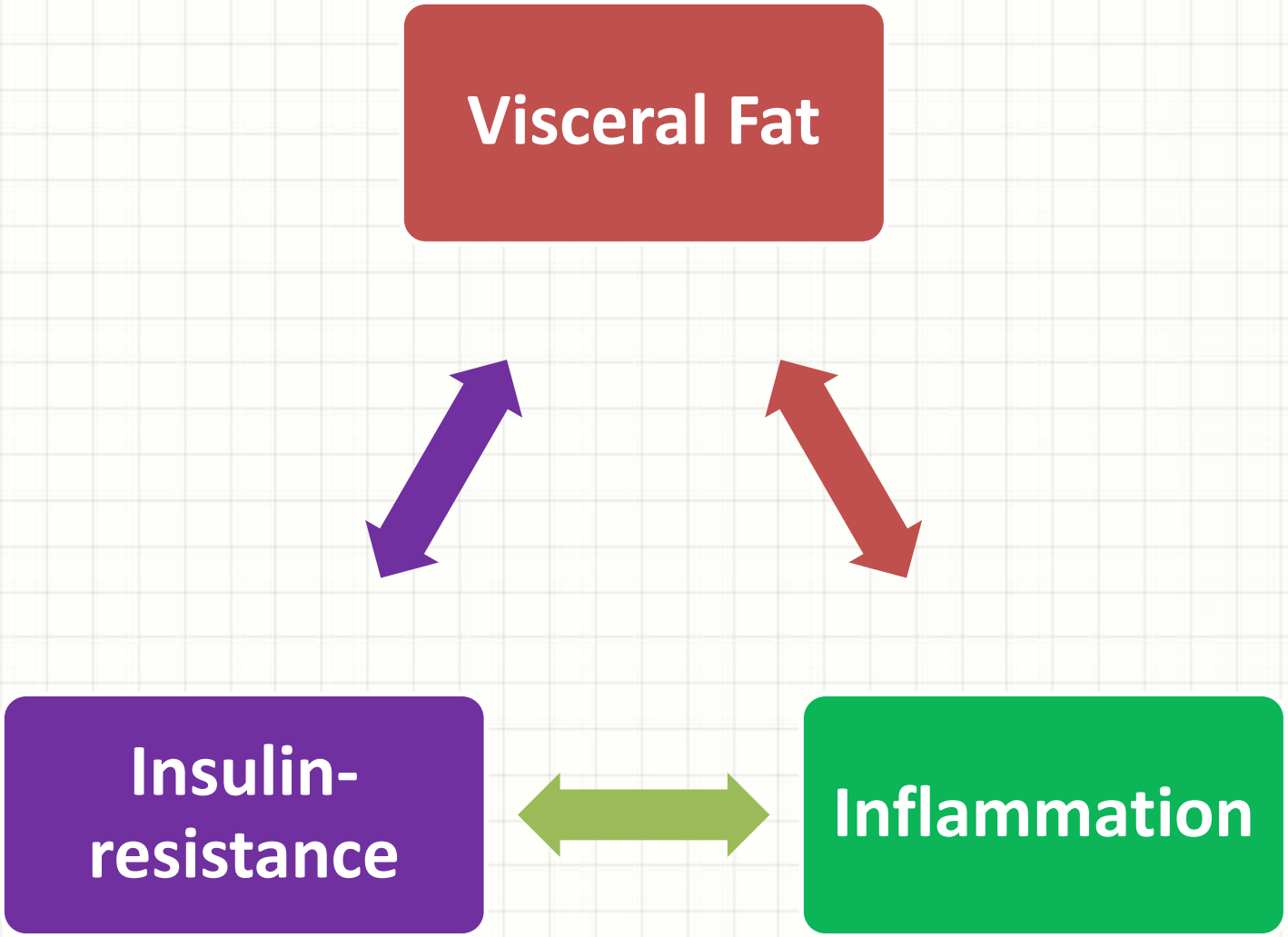
Lee YS et al., Diabetes, 2011

Insulin resistance causes inflammation in adipose tissue



Shimobayashi M et al., J Clin Invest, 2018

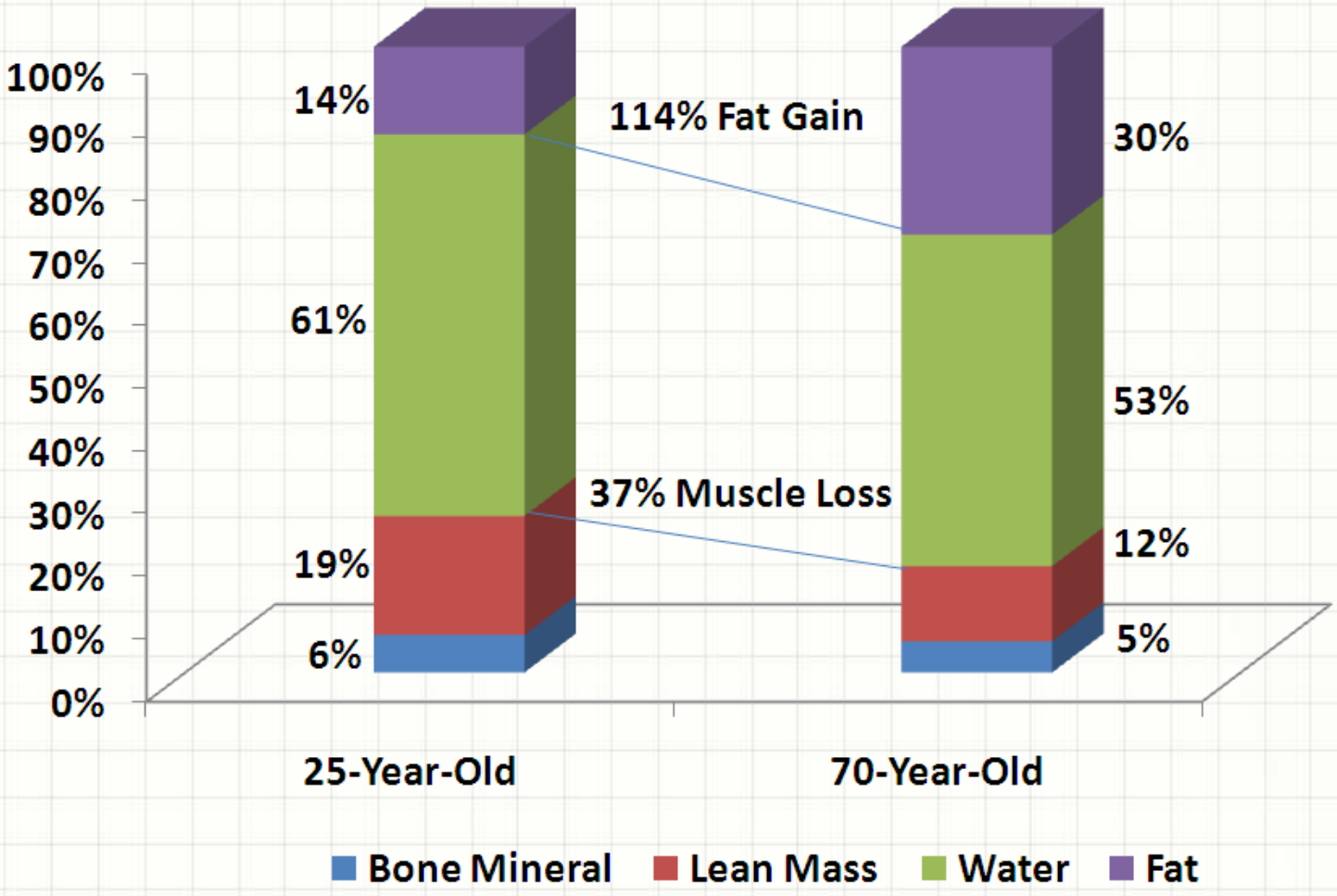
4 Changes in aging



1976

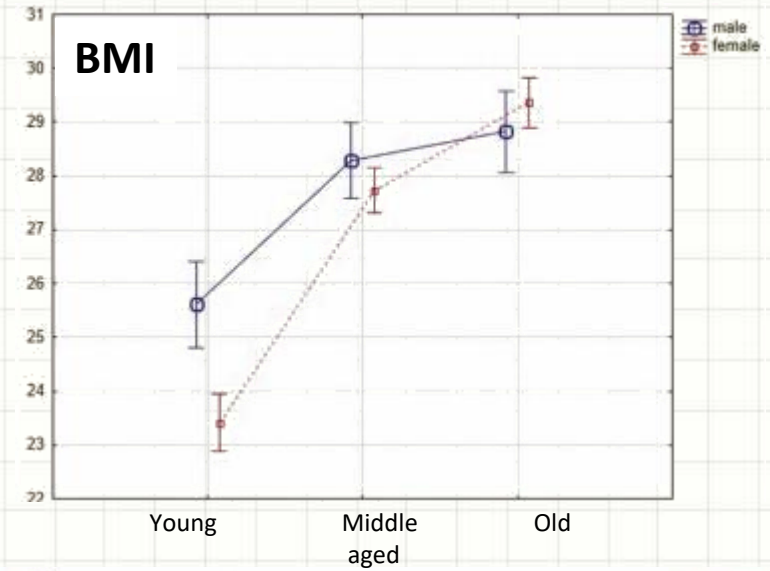
2016

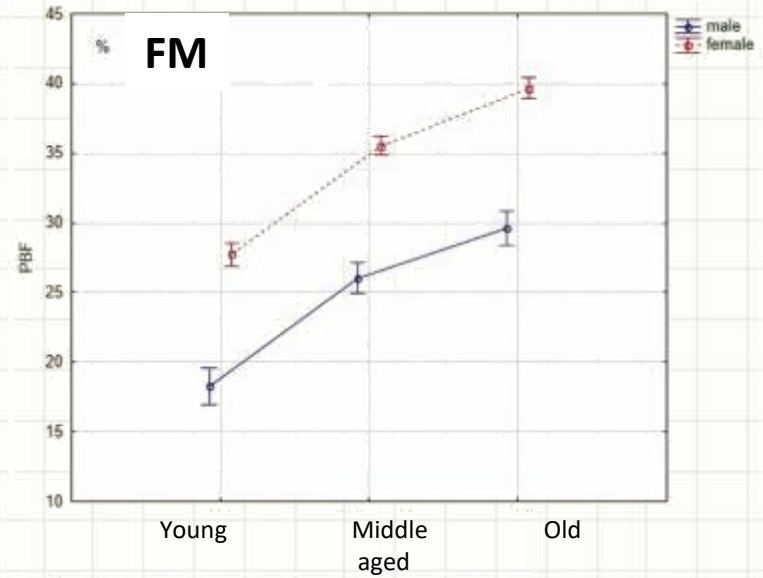
Invecchiamento e composizione corporea

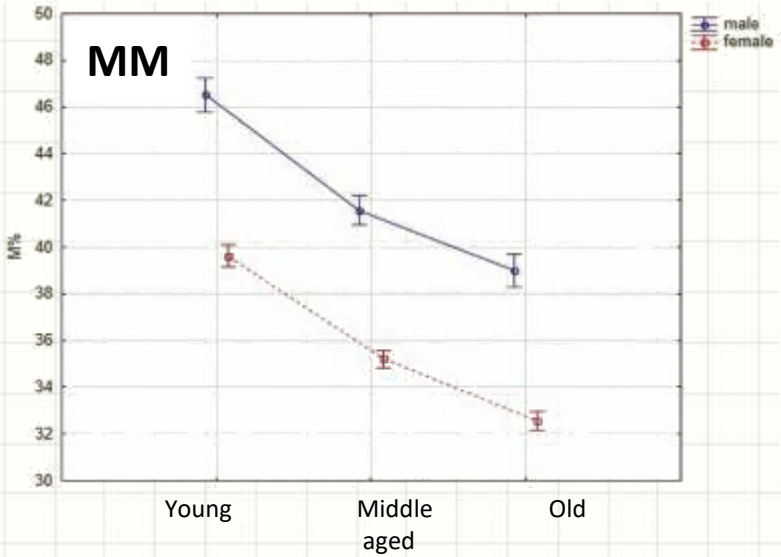


Shock NW et al., Nat Inst Health, 1984

Variazione della composizione corporea con l'età

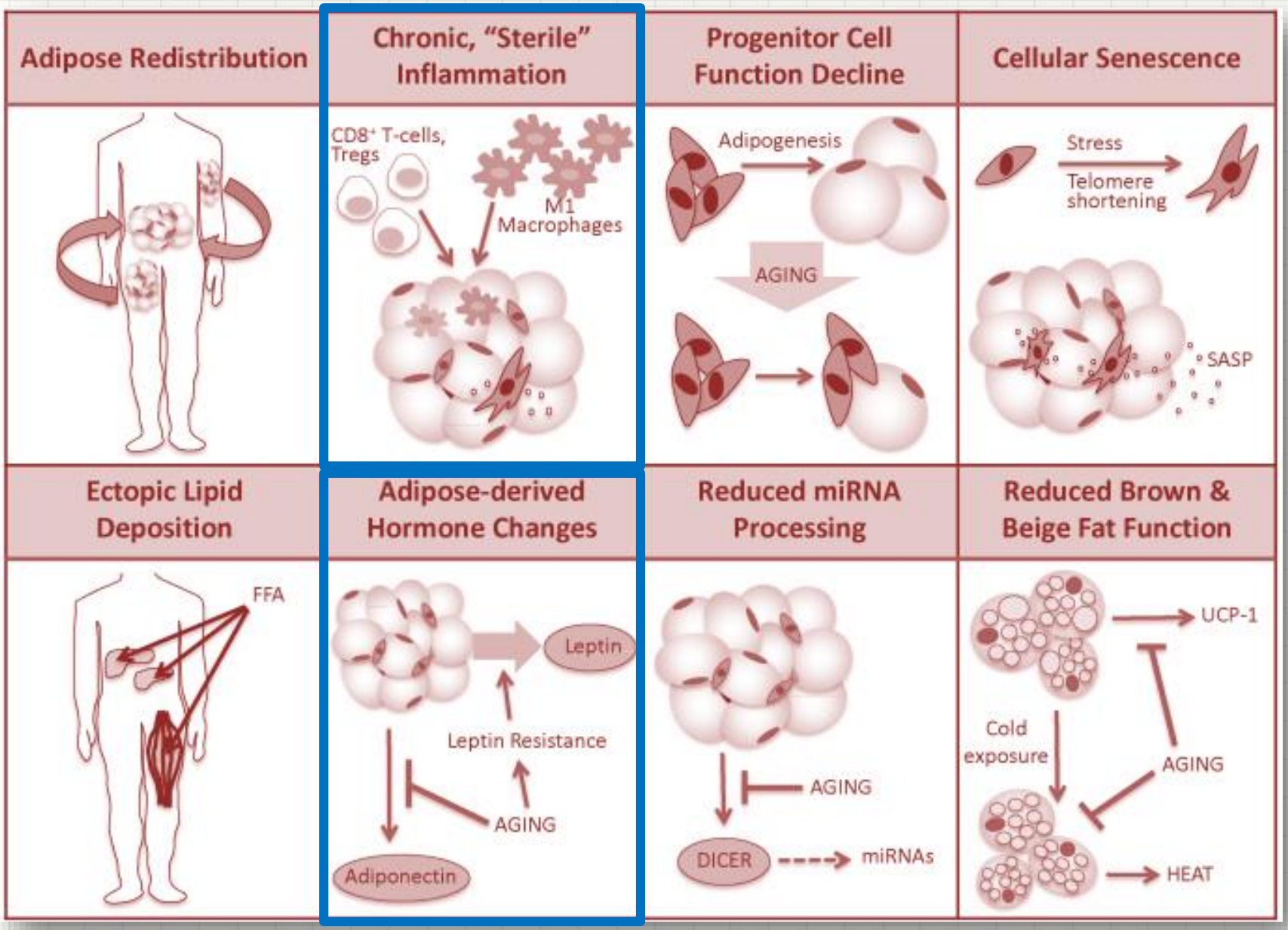






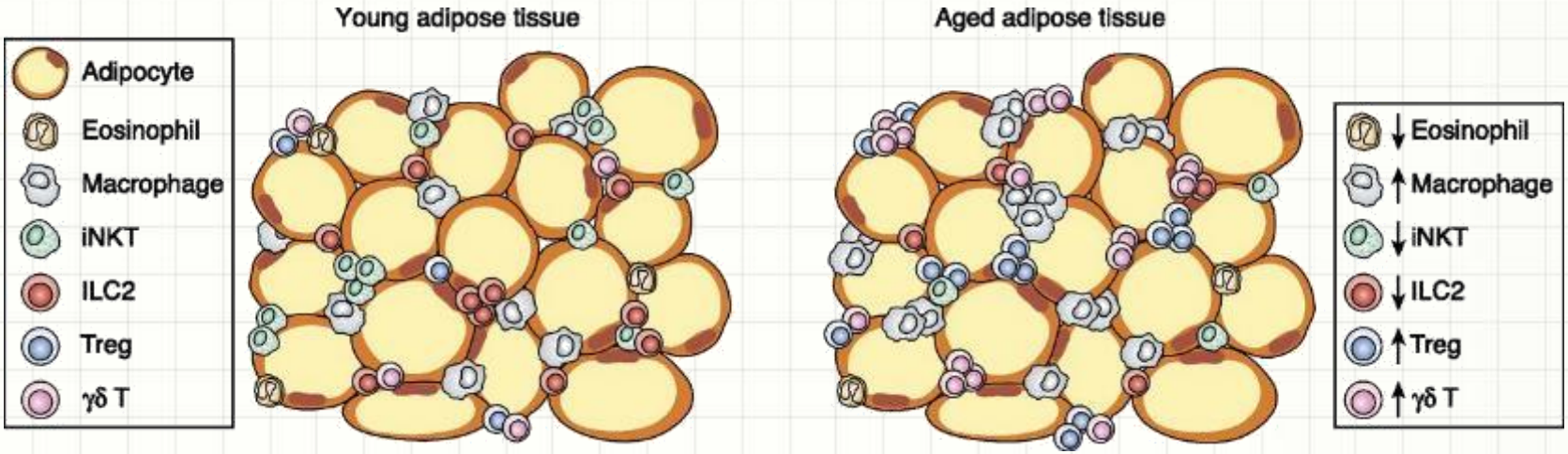
Ihasz F et al., Int J Morphol, 2015

I cambiamenti del tessuto adiposo nell'anziano



Palmer AK et al, Exp Gerontol, 2016

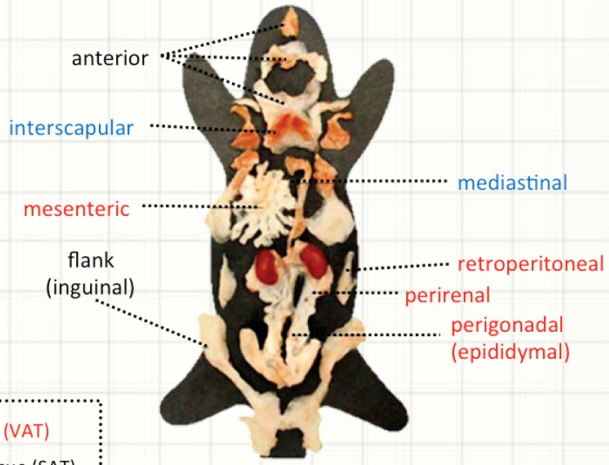
Aging is associated with an increase in T cells and inflammatory macrophages in visceral adipose tissue



Lumeng CN et al., J Immunol, 2011

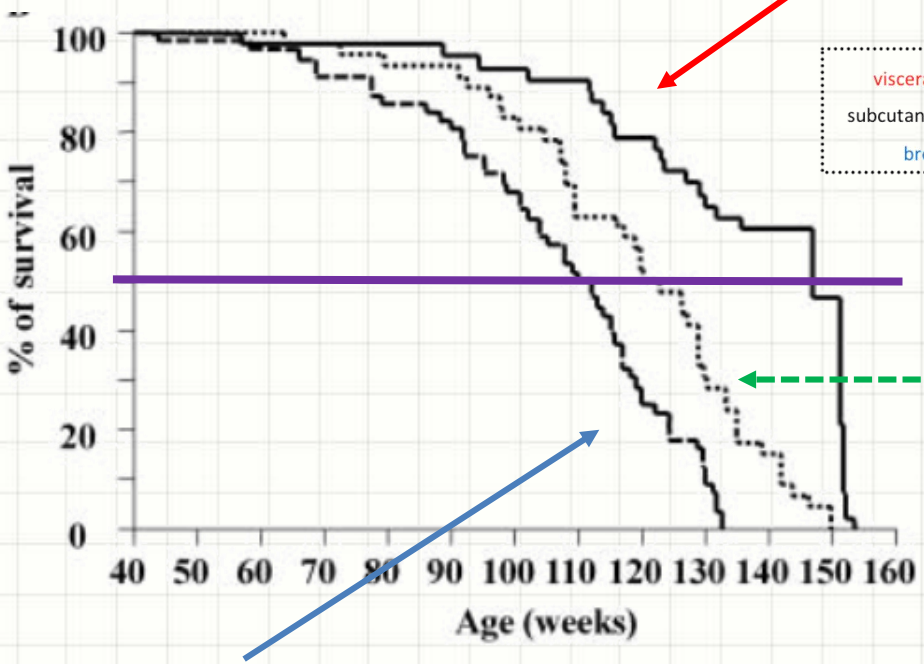
Visceral adipose tissue modulates mammalian longevity

Rodent fat deposits



visceral adipose tissue (VAT)
subcutaneous adipose tissue (SAT)
brown adipose tissue

Visceral fat
Surgical removal



Caloric Restriction

Controls

Muzumdar R et al, Aging Cell, 2008

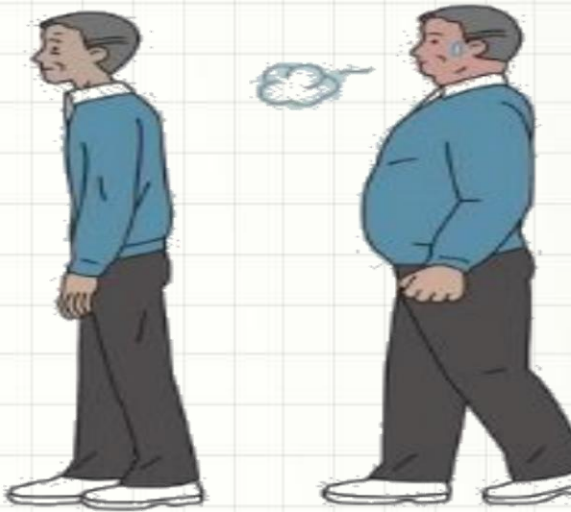
Conclusion

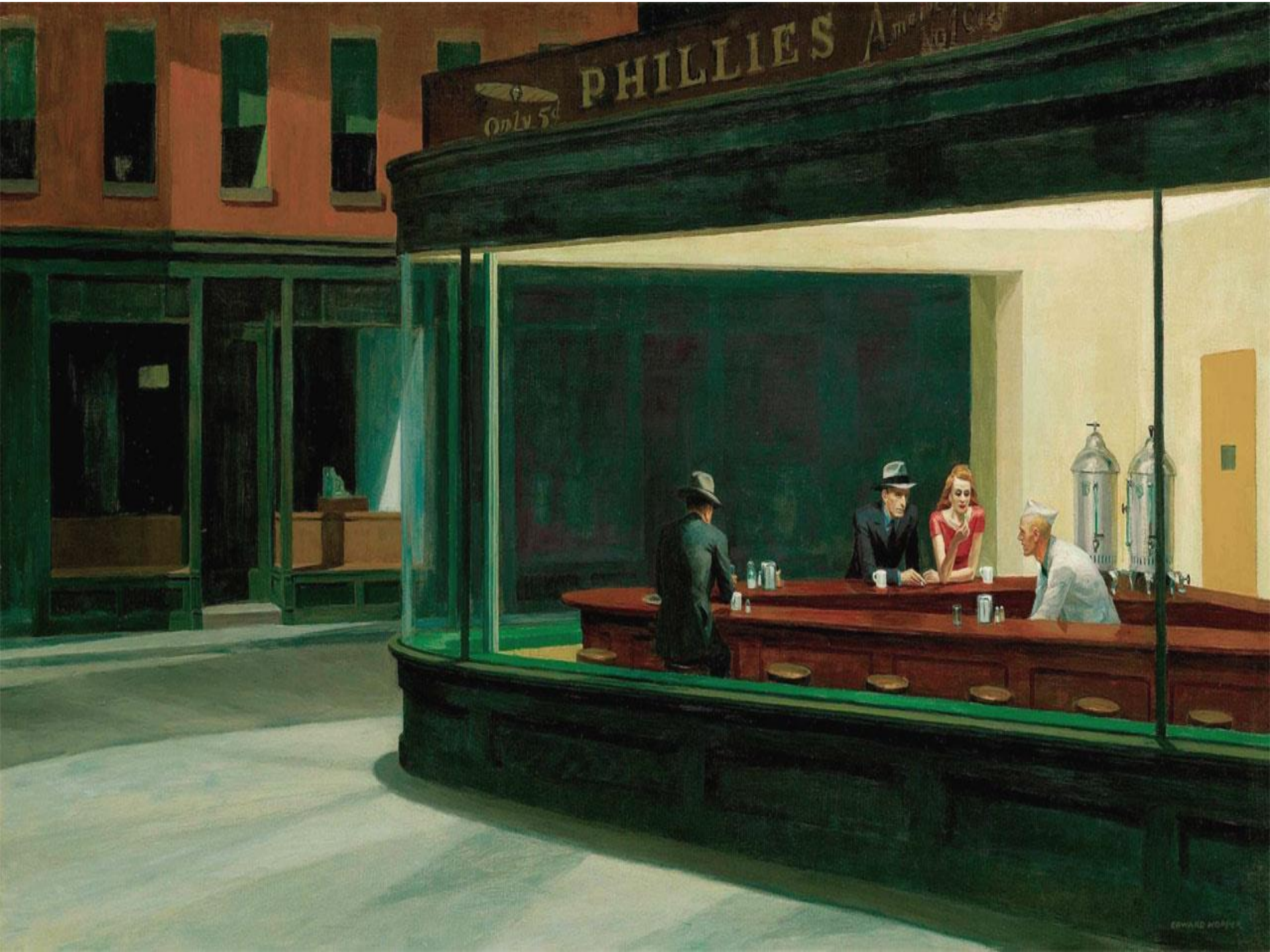
«Cause and effect are two sides of one fact»

Ralph Waldo Emerson

'Adipaging': ageing and obesity share biological hallmarks related to a dysfunctional adipose tissue

Pérez LM et al., J Physiol, 2016

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