Obesità e Infiammazione

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Obesità : Definizione OMS

Eccesso di Massa Grassa corporea con conseguenze negative sullo stato di salute e riduzione dell'aspettativa di vita media

OBESITY

Body Mass Index (BMI)

$$BMI = \frac{\text{weight (kg)}}{\text{height}^2\ \text{(m)}}$$

BMI	NIH Classification
<18.5	Underweight
18.5-24.9	Normal Weight
25-29.9	Overweight
30-34.9	Obesity I
35-39.9	Obesity II
>40	Extreme Obesity

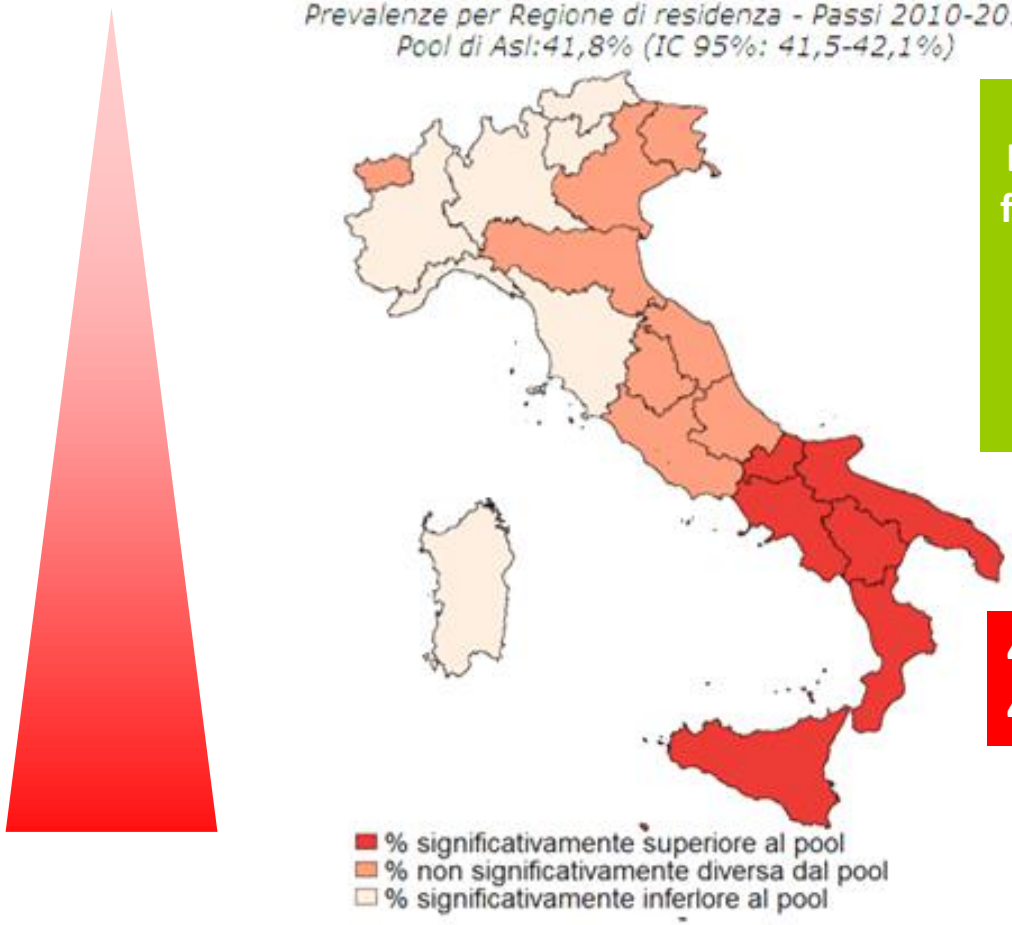
Ha un errore del 3% sulla popolazione e del 10% sul singolo individuo

Dai dati del sistema di sorveglianza Passi 2010-2013

32% degli adulti di 18-69 anni risulta sovrappeso e 11% obeso

Più di quattro persone su dieci risultano essere in eccesso ponderale (sovrappeso o obesi)

Dai dati del sistema di sorveglianza Passi 2010-2013

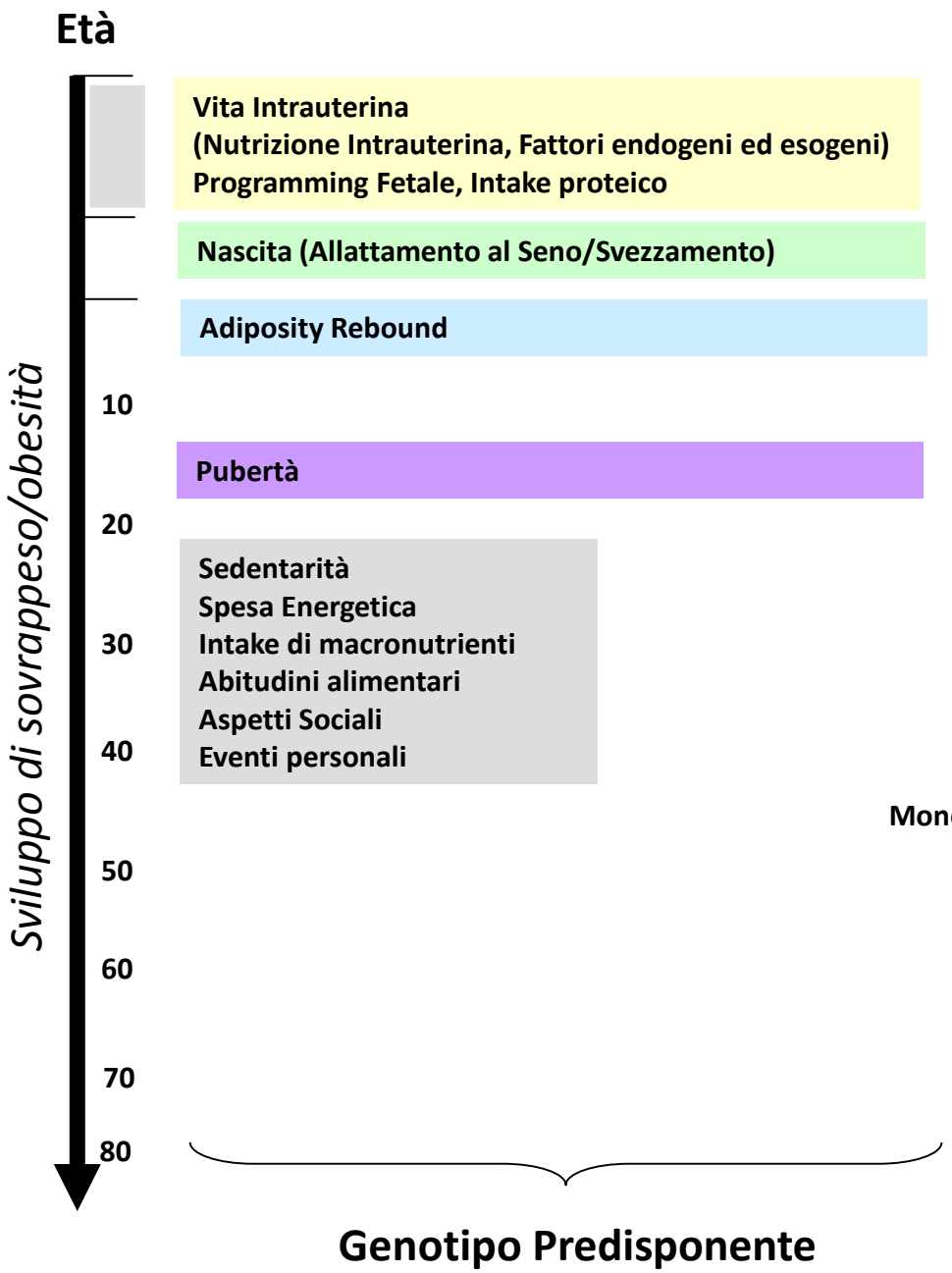


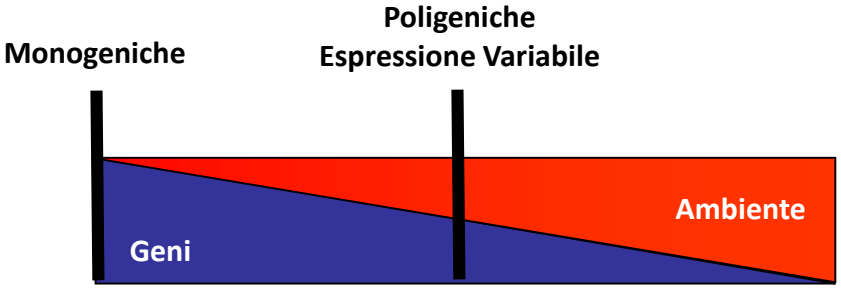
* In Lombardia non tutte le Asl hanno partecipato alla rilevazione.

L'eccesso ponderale è una condizione più frequente nel Sud Italia e in Regioni come la Campania, la Calabria e la Sicilia dove oltre il 48% degli adulti risultano in sovrappeso o obesi

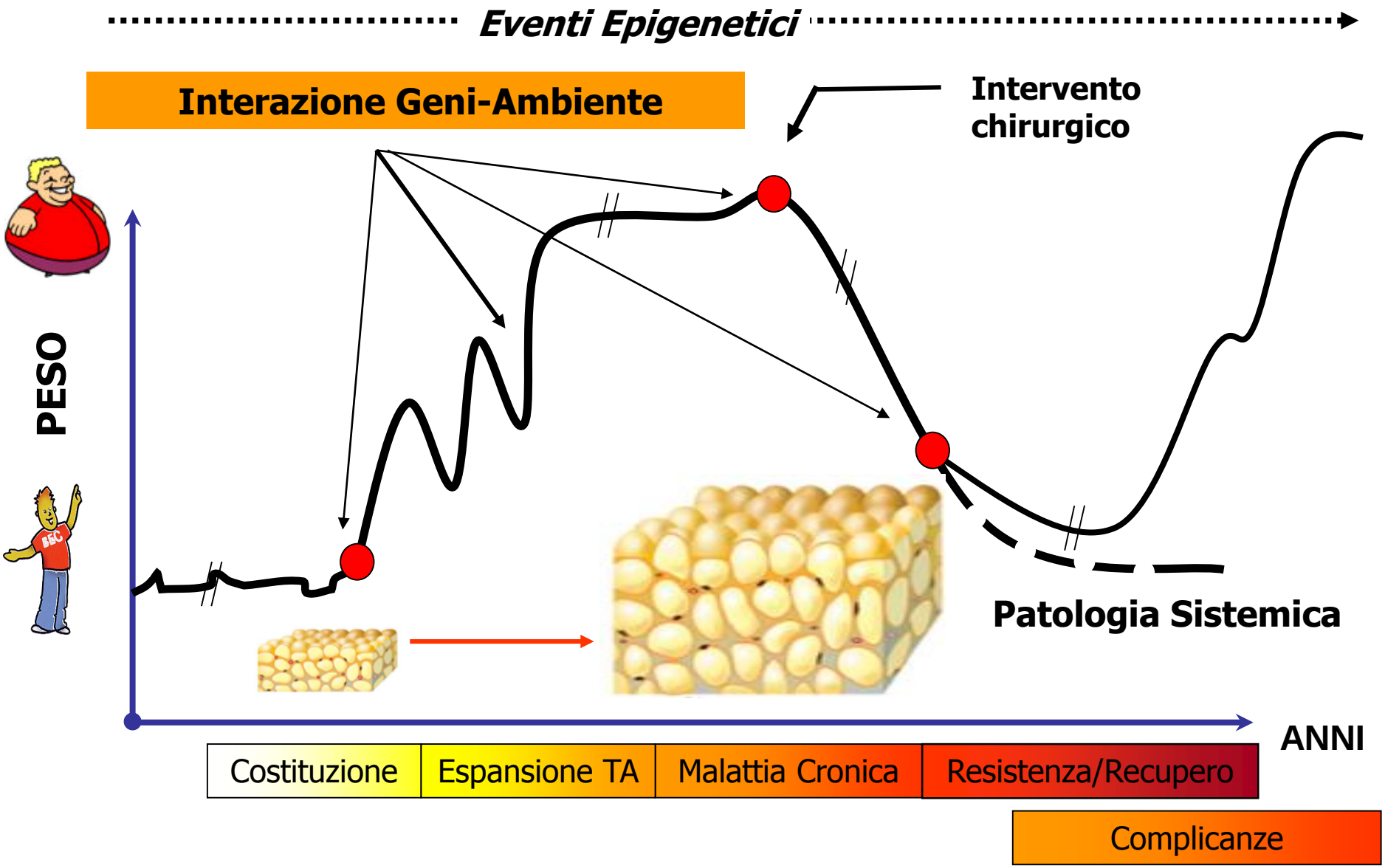
48% Campania
49% Basilicata

Il Peso Corporeo è un elemento dinamico influenzato da molteplici fattori





Obesità: malattia cronica con differenti fasi di sviluppo

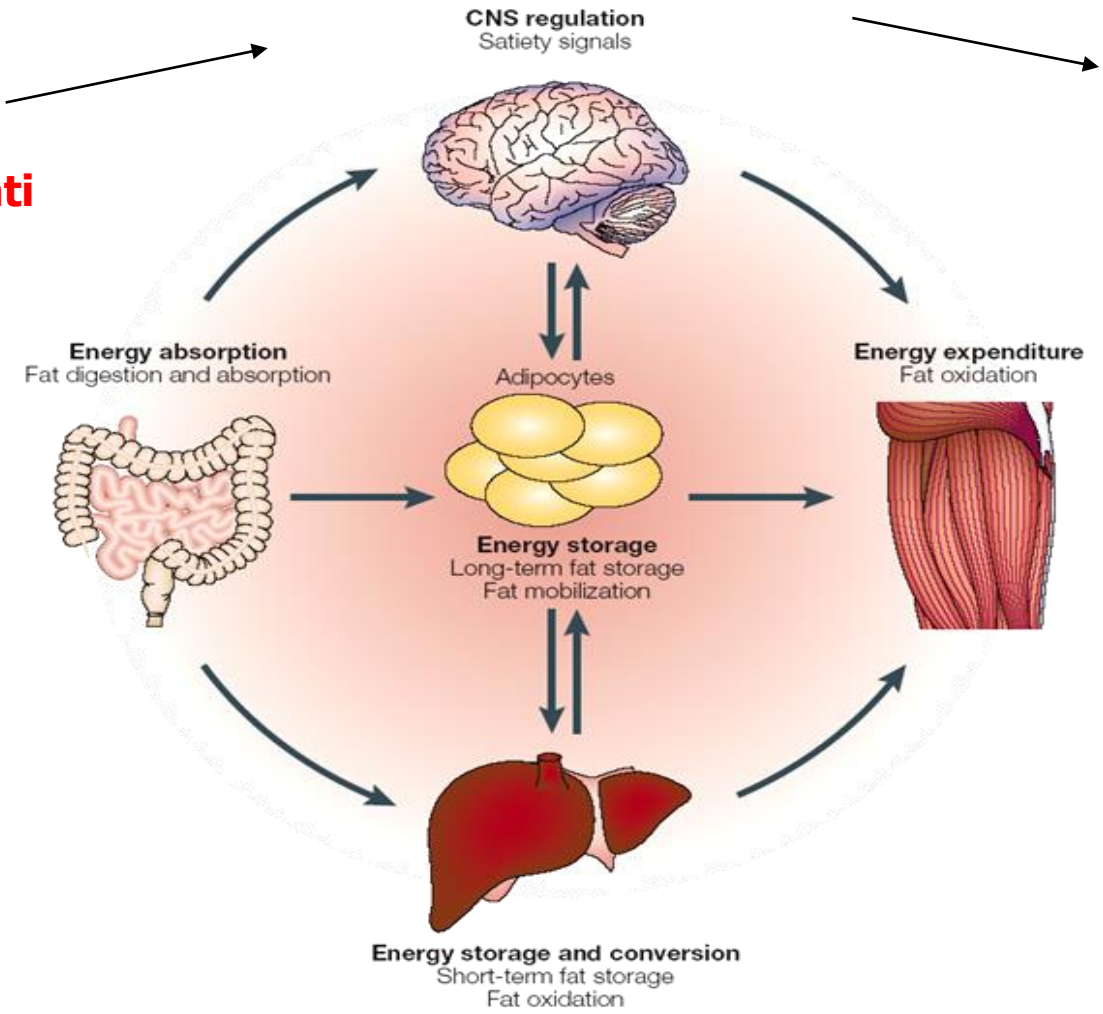


Obesità: Fisiopatologia Complessa

IPOTALAMO

Segnali Afferenti

Ghrelin
PYY
Insulin
Amylin
Leptin
Adiponectin
others

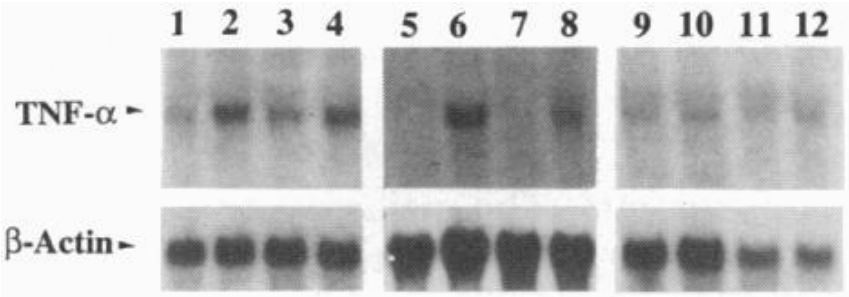


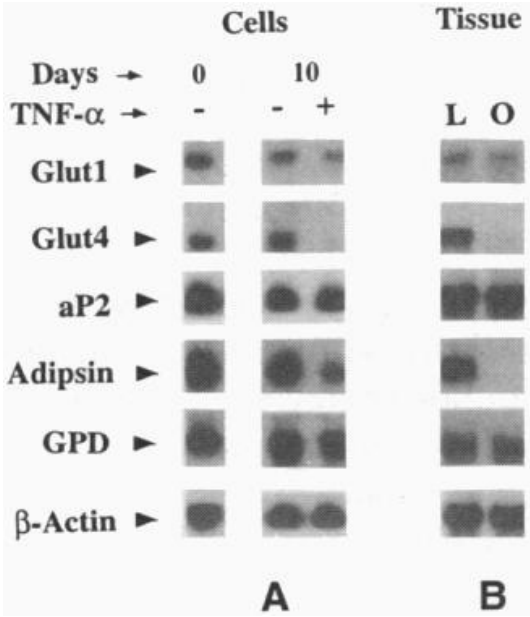
Segnali Efferenti

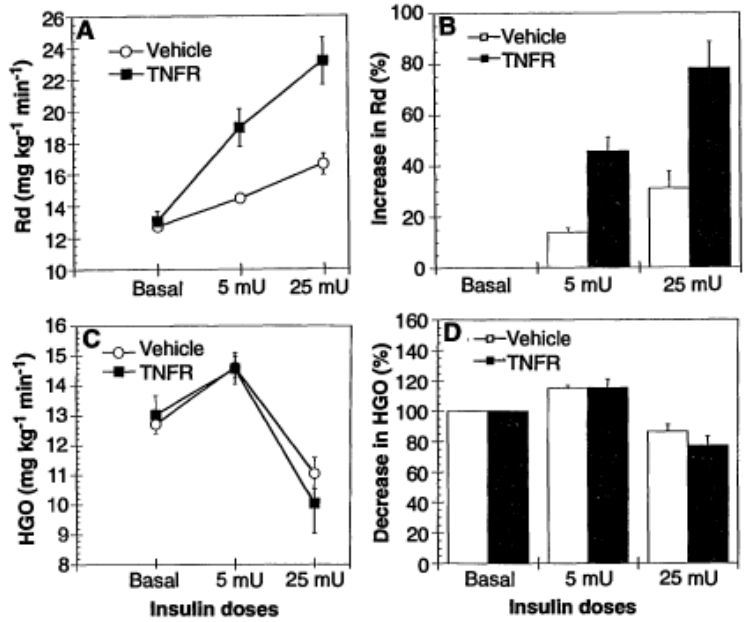
Sympathic
Parasympathic
Thyroid
Hormones

Il tessuto Adiposo è oggi considerato un Organo Endocrino

Obesità e Infiammazione…la storia (1993)
Tumor Necrosis Factor-alpha



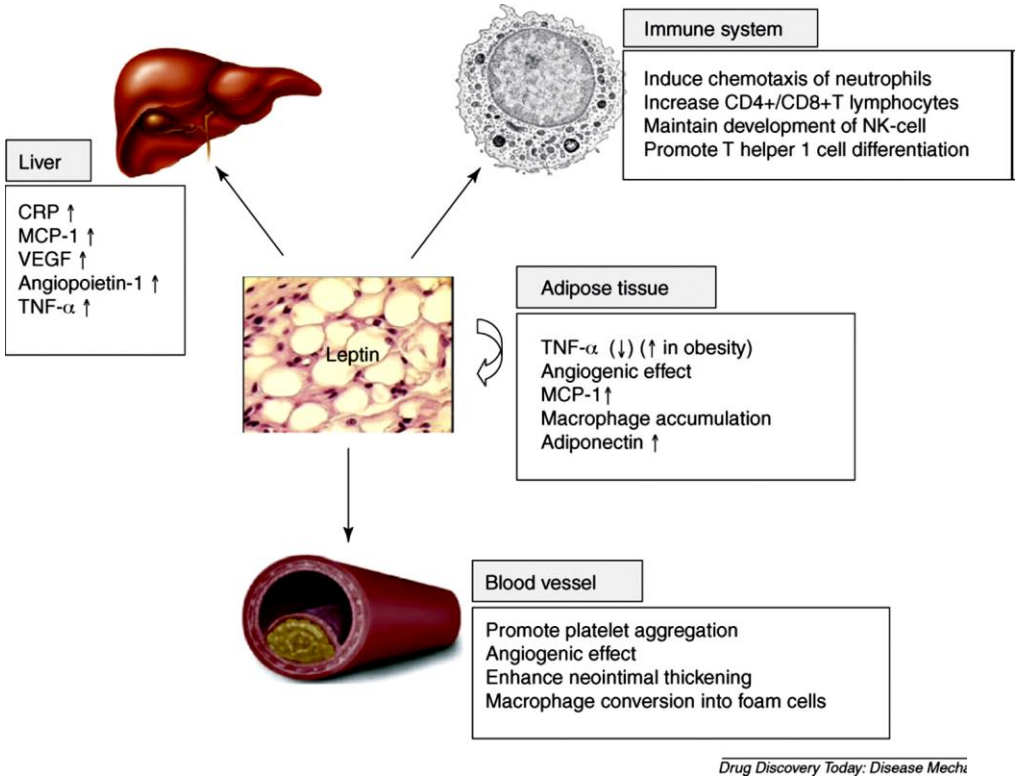


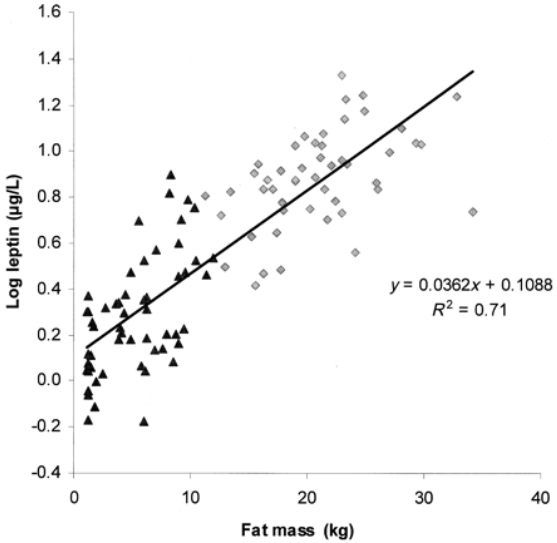


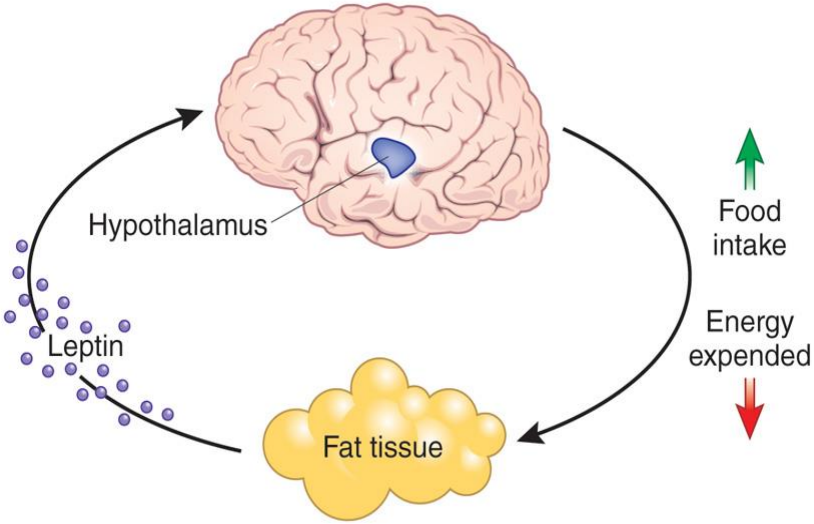
NFkB

Hotamisligil, G.S., Shargill, N.S. and Spiegelman, B.M. (1993) Adipose Expression of Tumor Necrosis Factor-Alpha: Direct Role in Obesity-Linked Insulin Resistance. Science, 259, 87-91.

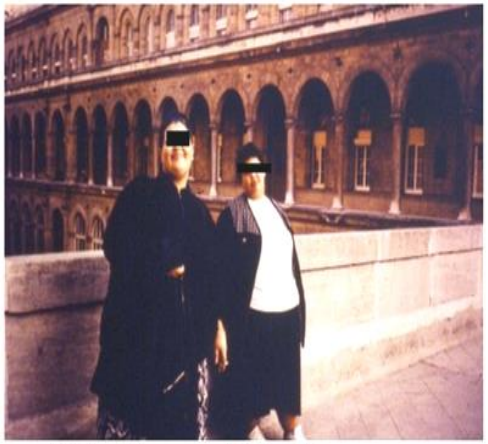
Adipocita: cellula endocrina Leptina (1994)







Obesità Genetiche
Lept/LeptRec mutations



160 kg 17ans, 140 kg 13 ans
200 kg 22 ans

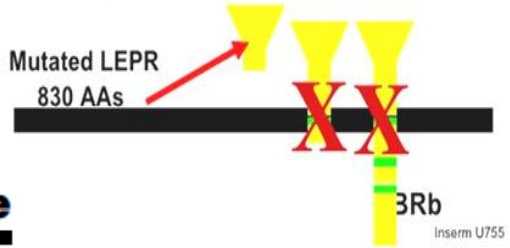
Impulsivité alimentaire

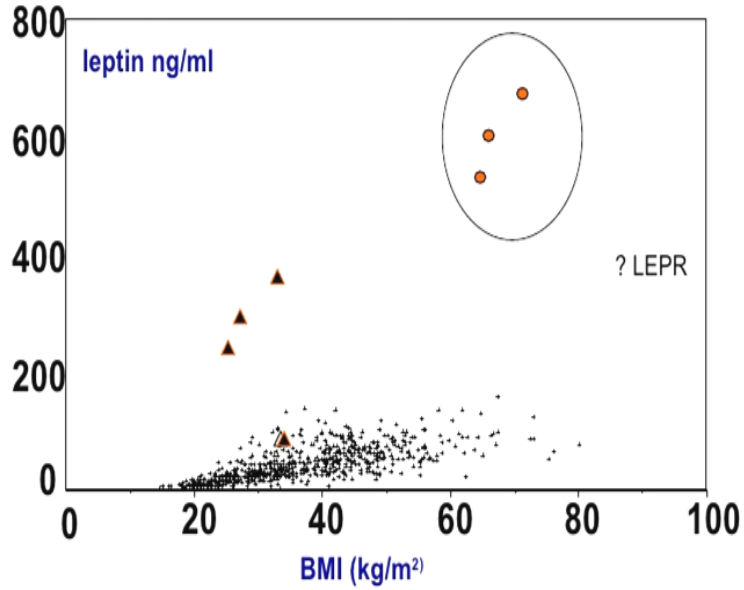
Ipogonadismo

Deficit GH

Ipotiroidismo

Disfunzioni Immunitarie





*Clément, Vaisse et al, Nature 1998

Inserm U755

letters to nature

A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction

Karine Clément*†‡, Christian Vaisse*†‡, Najiba Lahlou§, Sylvie Cabrol‖, Veronique Pelloux*, Dominique Cassuto*, Micheline Gourmelen‖, Christian Dina†, Jean Chambaz¶, Jean-Marc Lacorte¶, Arnaud Basdevant*†, Pierre Bougnères¶, Yves Leboucl, Philippe Froguel*† & Bernard Guy-Grand*†

Congenital leptin deficiency is associated with severe early-onset obesity in humans

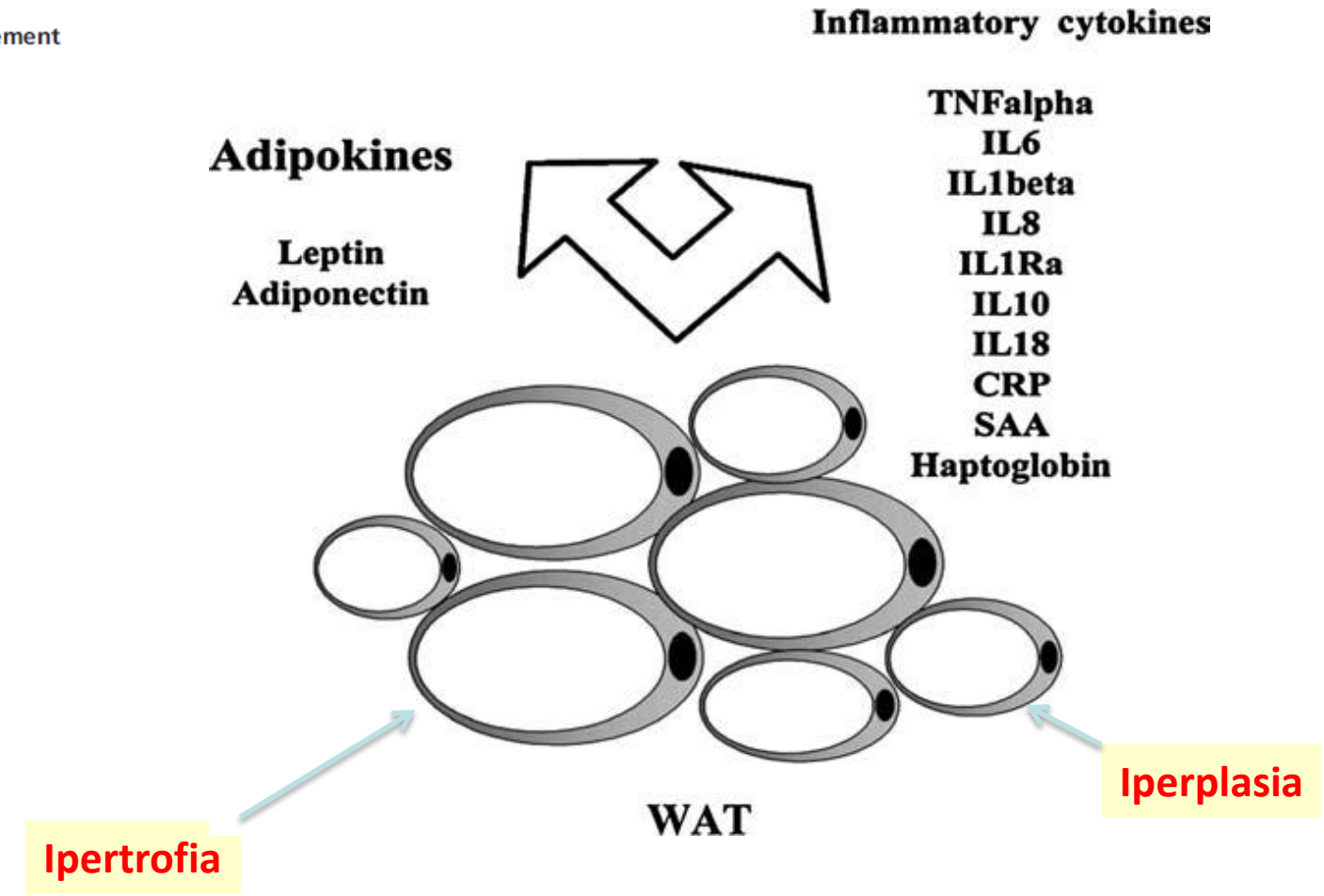
Carl T. Montague*†, I. Sadaf Farooqi*†‡, Jonathan P. Whitehead*‡, Maria A. Soos*‡, Harald Rau*‡, Nicholas J. Wareham§, Ciaran P. Sewter*‡, Janet E. Digby*‡, Shehla N. Mohammed‖, Jane A. Hurst¶, Christopher H. Cheetham#, Alison R. Earley#, Anthony H. Barnett☆, Johannes B. Prins*‡ & Stephen O'Rahilly*‡

DI: 10.1111/j.1471-0528.2006.01004.x
www.blackwellpublishing.com/bjog

Review article

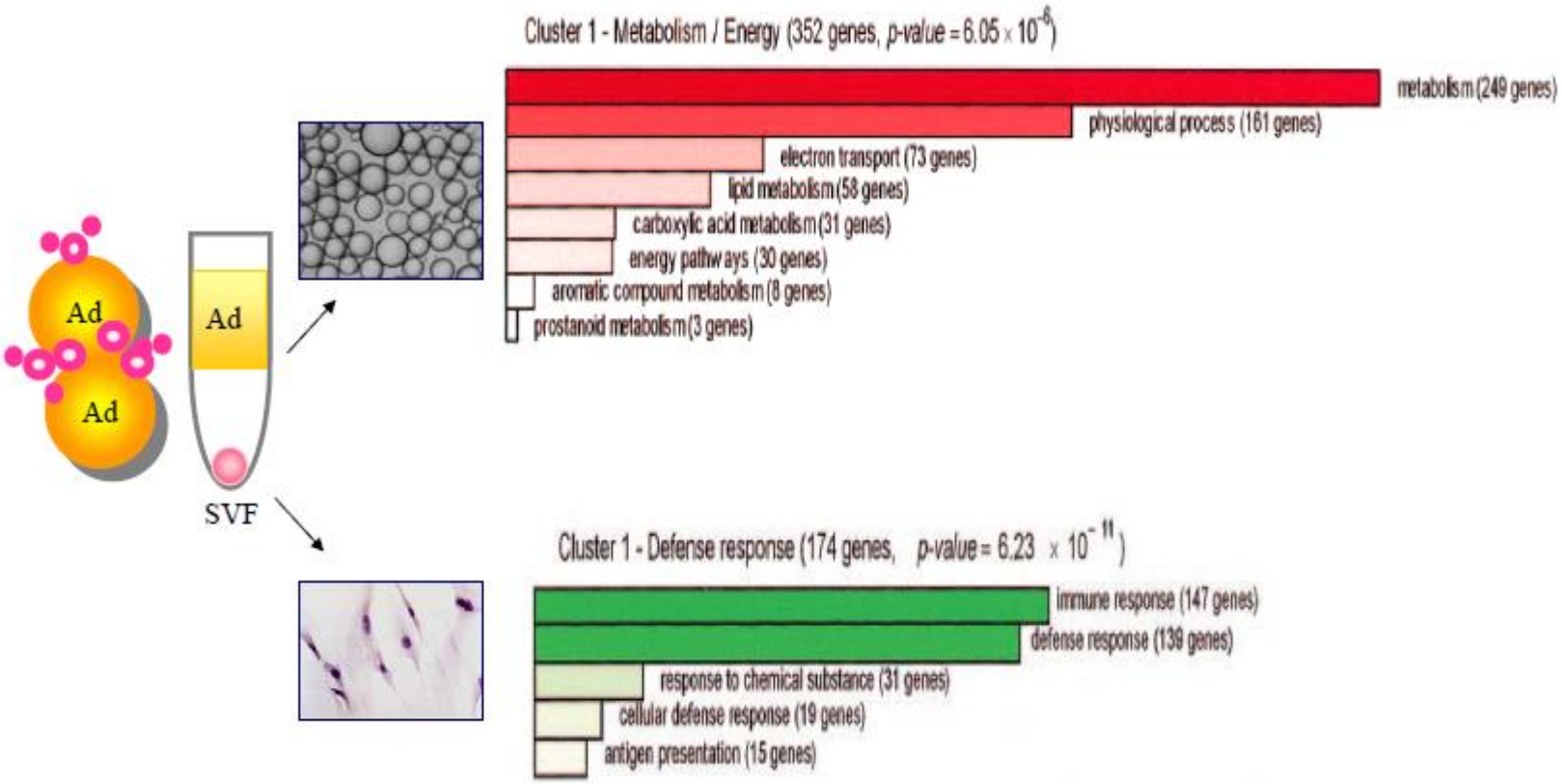
Is obesity an inflammatory illness? Role of low-grade inflammation and macrophage infiltration in human white adipose tissue

R Cancello, K Clément



Cancello R BJOG 2006

Componente infiammatoria nella frazione stromavascolare del Tessuto Adiposo



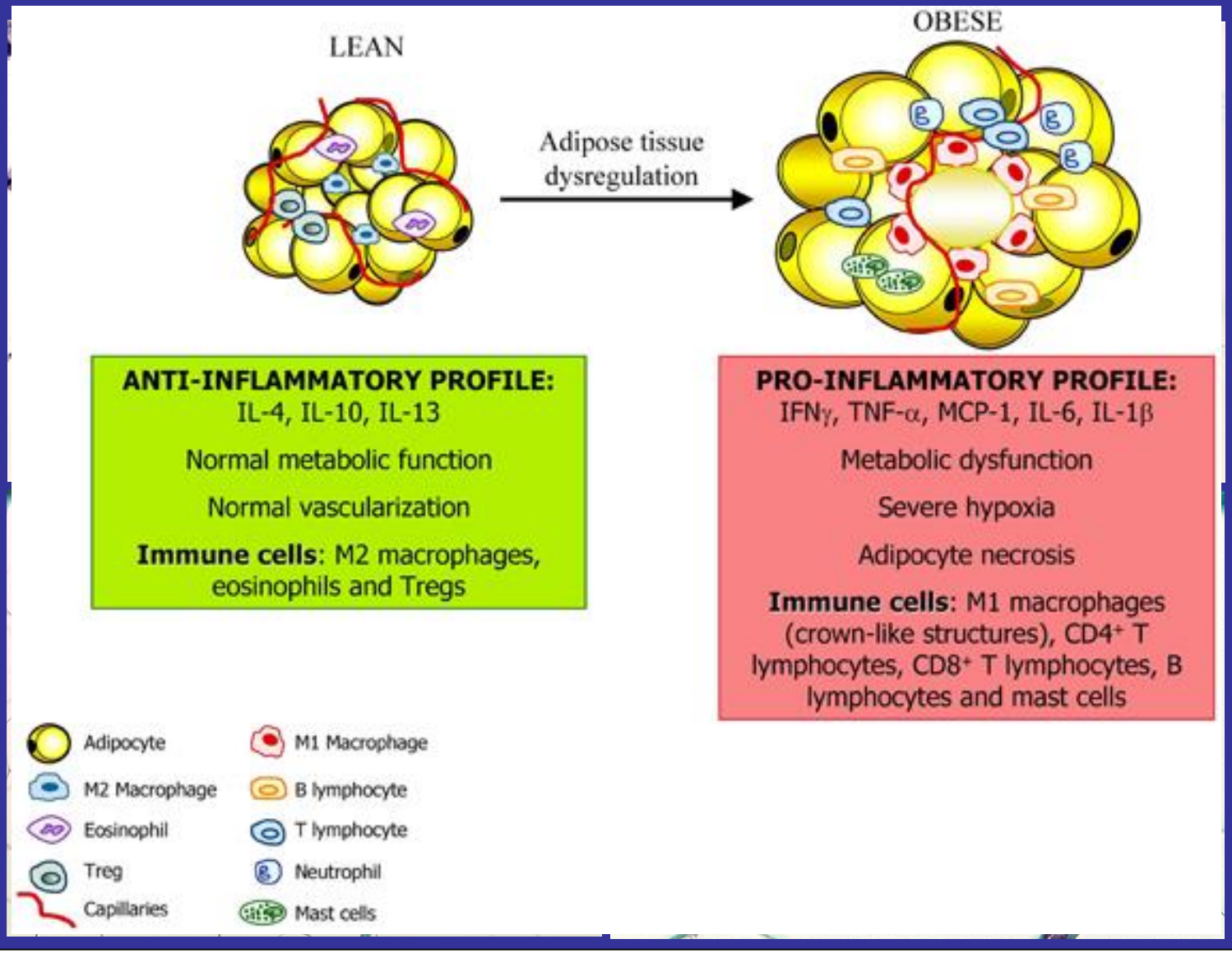
Nell'obesità adipociti e SVF attivano geni infiammatori (IL6, TNFalpha, CTSS, SAA, etc.)

Cancello et al. Diabetes, 2005

Obesità: patologia dell’organo adiposo

40X

100X

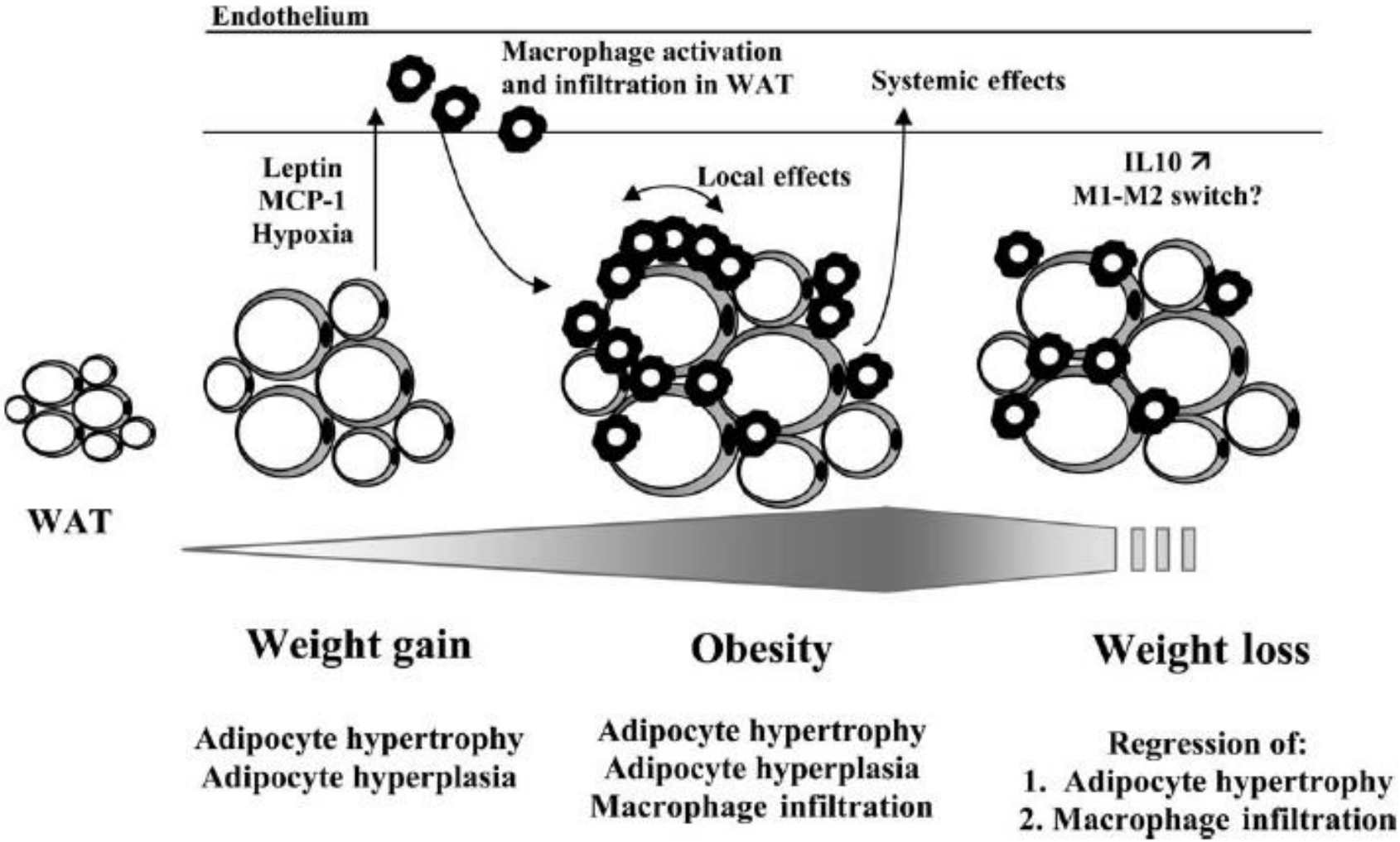


20X

100X

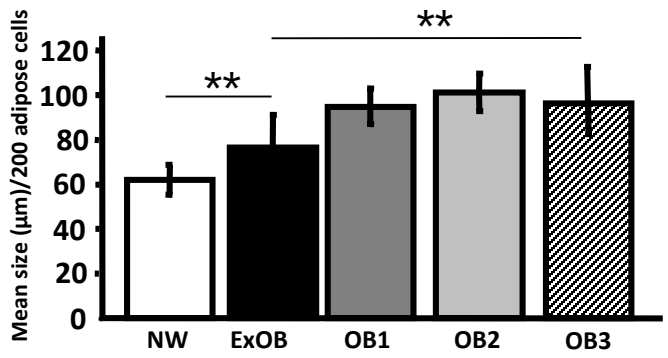
Cancello R. et al., Diabetes 2005

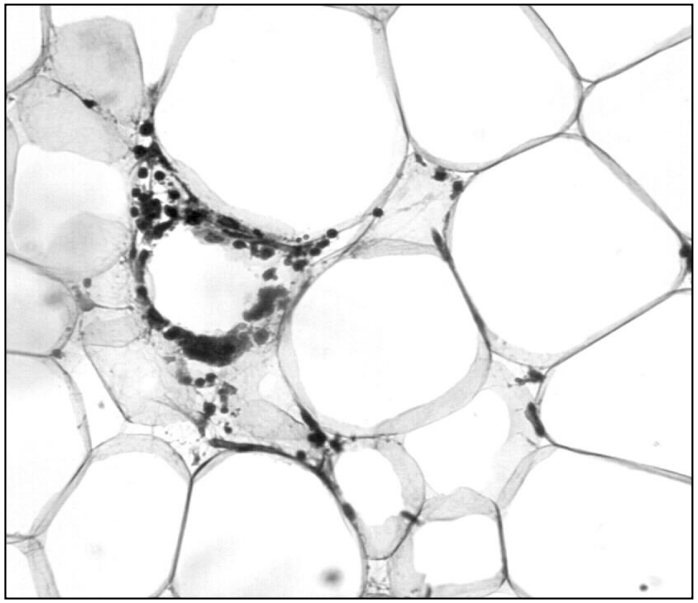
Obesità: patologia d'organo

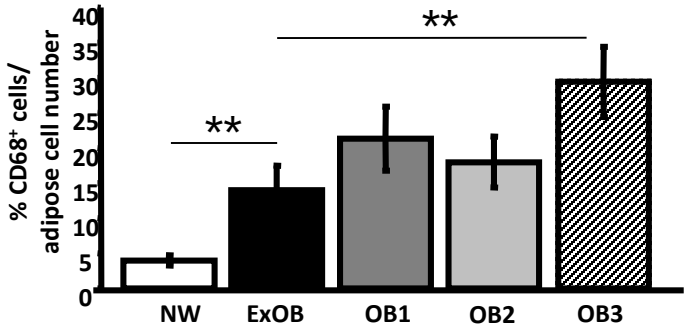


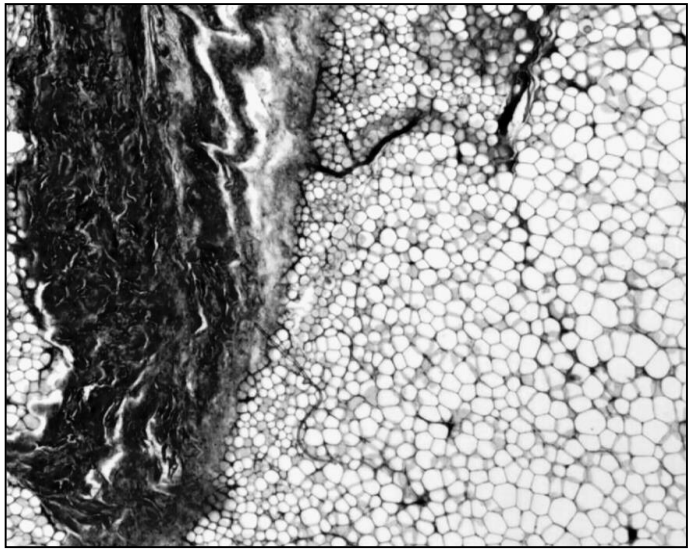
Cancello R BJOG 2006

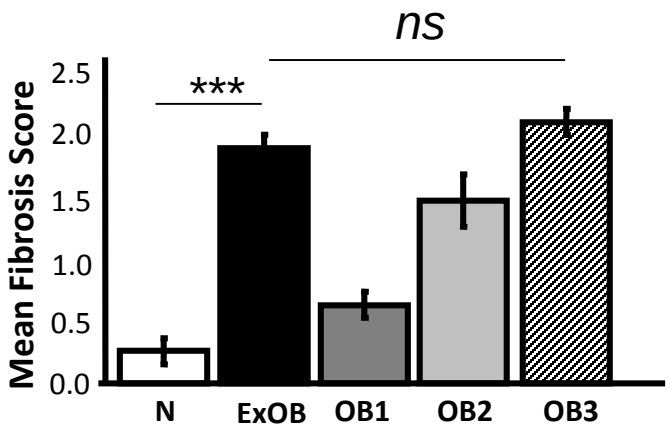
Modulazione dell'infiammazione dopo il calo ponderale



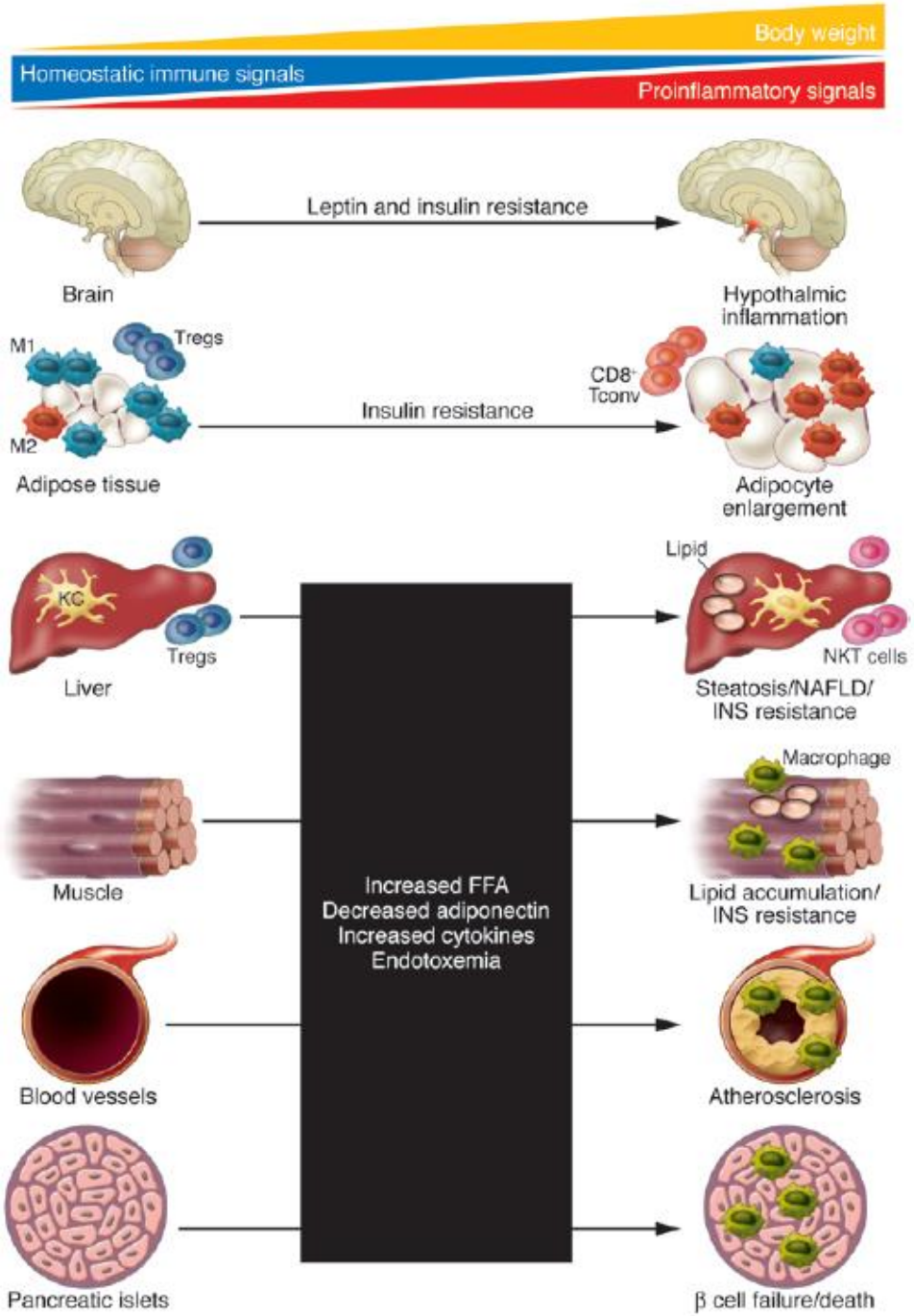








Cancello R. et al. Obesity, 2012



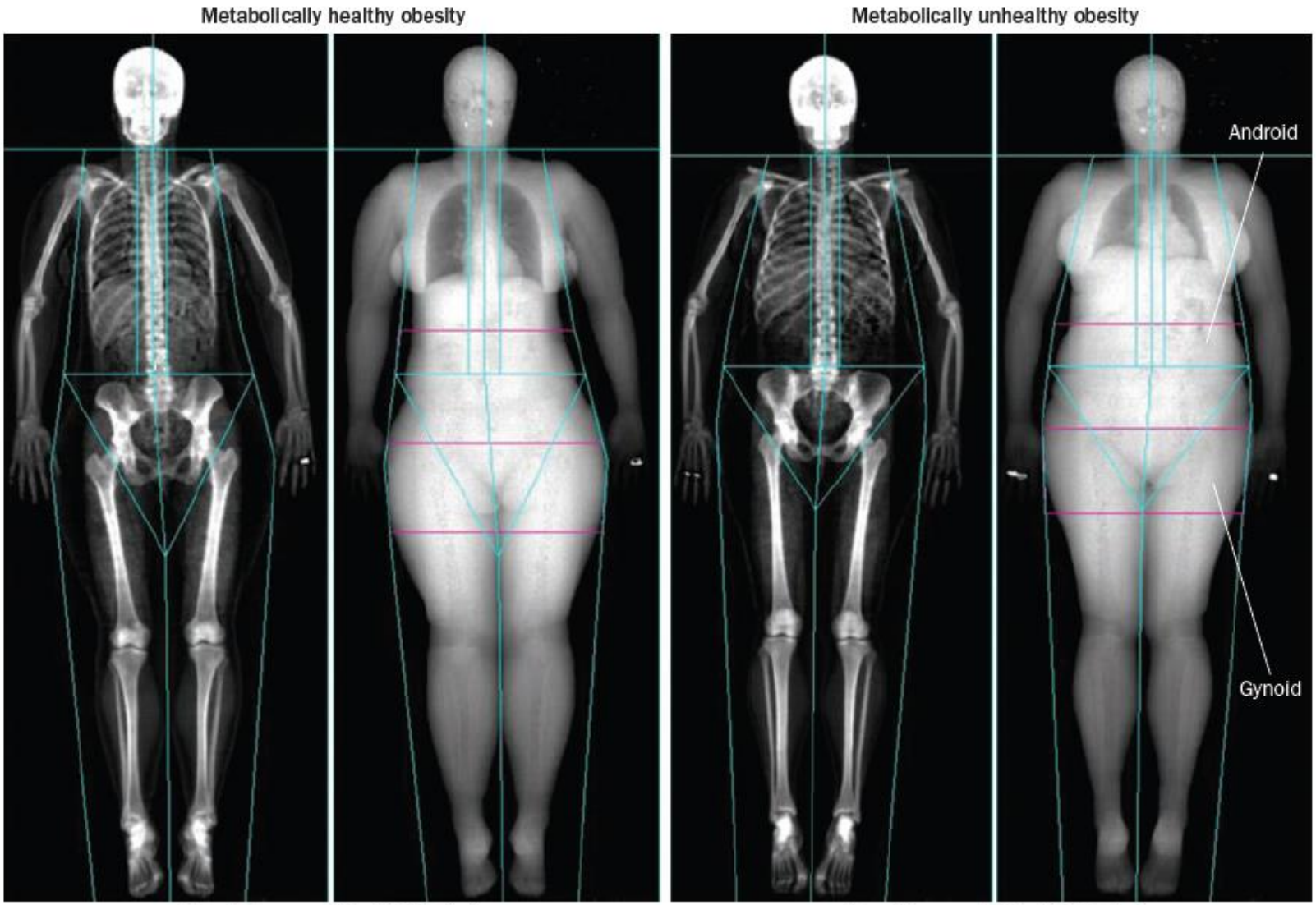
Obesità Patologia sistemica

Endotossemia Metabolica
=low grade inflammation

↑PCR
↑IL6
↑TNF alfa
↑Leptin
↑FFA
↑Colesterolo
↑LDL

Lumeng C.N., JCI 2006

I depositi adiposi non sono tutti uguali…….



Age: 34 years; BMI: 30.2 kg/m²;
lean body mass: 44.4 kg; fat mass: 30.8 kg

Age: 39 years; BMI: 30.7 kg/m²;
lean body mass: 44.0 kg; fat mass: 31.1 kg

Karpe F., 2014 Nature Rev Endo

Obesità e Fertilità: una questione aperta

Pregnancy in a Woman with a Leptin-Receptor Mutation

TO THE EDITOR: Leptin is considered to have an important role in reproductive functions, including menstrual-cycle regulation, pregnancy, and lactation.[1,2] The absence of leptin action caused by functional mutations in the leptin gene (*LEP*) or the leptin receptor gene (*LEPR*) has been linked to infertility in rodents and humans.[3-5] We report a pregnancy in a woman despite absent leptin signaling.

In 1998, we reported the case of a morbidly obese patient with a rare homozygous *LEPR* mutation, which was shared by several affected siblings.[4] The mutation was found in the patient's blood and adipose tissue, indicating no evidence of chimerism. She had been followed for morbid obesity since early childhood, with abnormal compulsive-feeding behaviors and reduced levels of growth hormone and thyrotropin.[4] She entered puberty late, with irregular cycles after the age of 17 years. Repeated evaluations of sex-hormone levels were considered to be normal after the age of 18 years. The patient underwent abdominoplasty at the age of 16 years and gastric-bypass surgery at the age of 24 years. Six months after gastric bypass, her weight had decreased from 220 kg (485 lb) to 170 kg (375 lb), with a concurrent decrease in the body-mass index (the weight in kilograms divided by the square of the height in meters) from 81 to 62. She was counseled regarding contraception and was prescribed oral contraceptives. Two years after gastric bypass, just before an unplanned pregnancy, she had no diabetes, hypertension, respiratory disorders, or other recognized complications of obesity.

Ultrasonographic examinations during pregnancy were considered normal except for suspected macrosomia in the third trimester. The patient's total weight gain during pregnancy was 50 kg (110 lb) from a prepregnancy weight of 180 kg (397 lb). Routine screening for gestational diabetes was normal. Although occasional elevated blood sugar levels were documented during the pregnancy, the glycated hemoglobin level in the third trimester was 5.6%. At 37 weeks 5 days of gestation (on the basis of first-trimester ultrasonography), the patient delivered a son by elective cesarean section, which was performed because of breech presentation and suspected macrosomia under epidural anesthe-

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IMC=62 Kg/m^2

Sospetta Macrosomia Ecografica al terzo trimestre

Aumento gravidico di 50Kg

No GDM, Iperglicemia

Parto distocico

Infezione della ferita

Neonato: Ipoglicemia, ipocalcemia, itterizia

NEJM, 2012

Obesità e Gravidanza

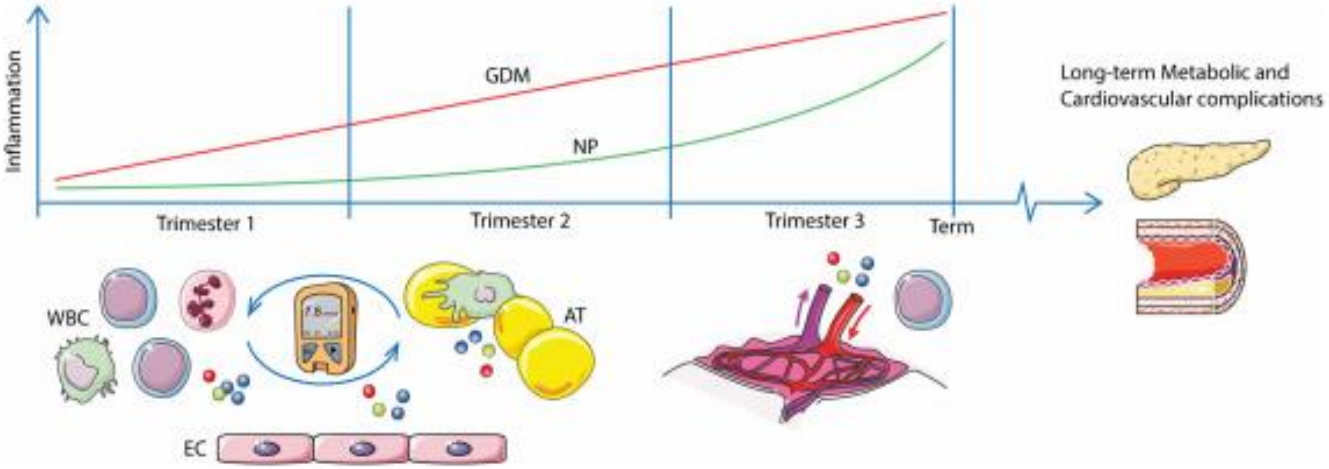


Tabella II. *Griteri ADA per la valutazione del grado di rischio per GDM*

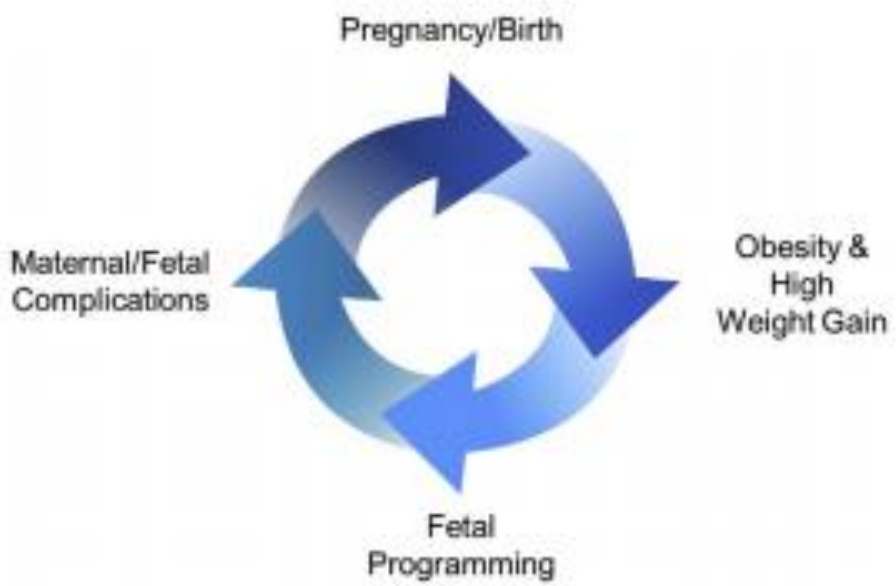
Basso rischio Screening non indicato	Medio Screening fra 24a -28a s.g.	Alto Screening appena possibile
Appartenenza a gruppo etnico con bassa prevalenza GDM		Familiarità positiva per diabete in parenti di 1° grado
Familiarità negativa per diabete mellito		Pregresso riscontro di intolleranza glucidica
Anamnesi ostetrica priva di esiti sfavorevoli	Caratteristiche intermedie tra basso e alto rischio	Pregresso riscontro di intolleranza glucidica
Nessun precedente di anormale tolleranza al glucosio		Obesità
Età inferiore a 25 aa		Glicosuria marcata nella gravidanza in corso
Normopeso		

Tabella I. *Fattori di rischio per Diabete Gestazionale (Linee guida SID)*

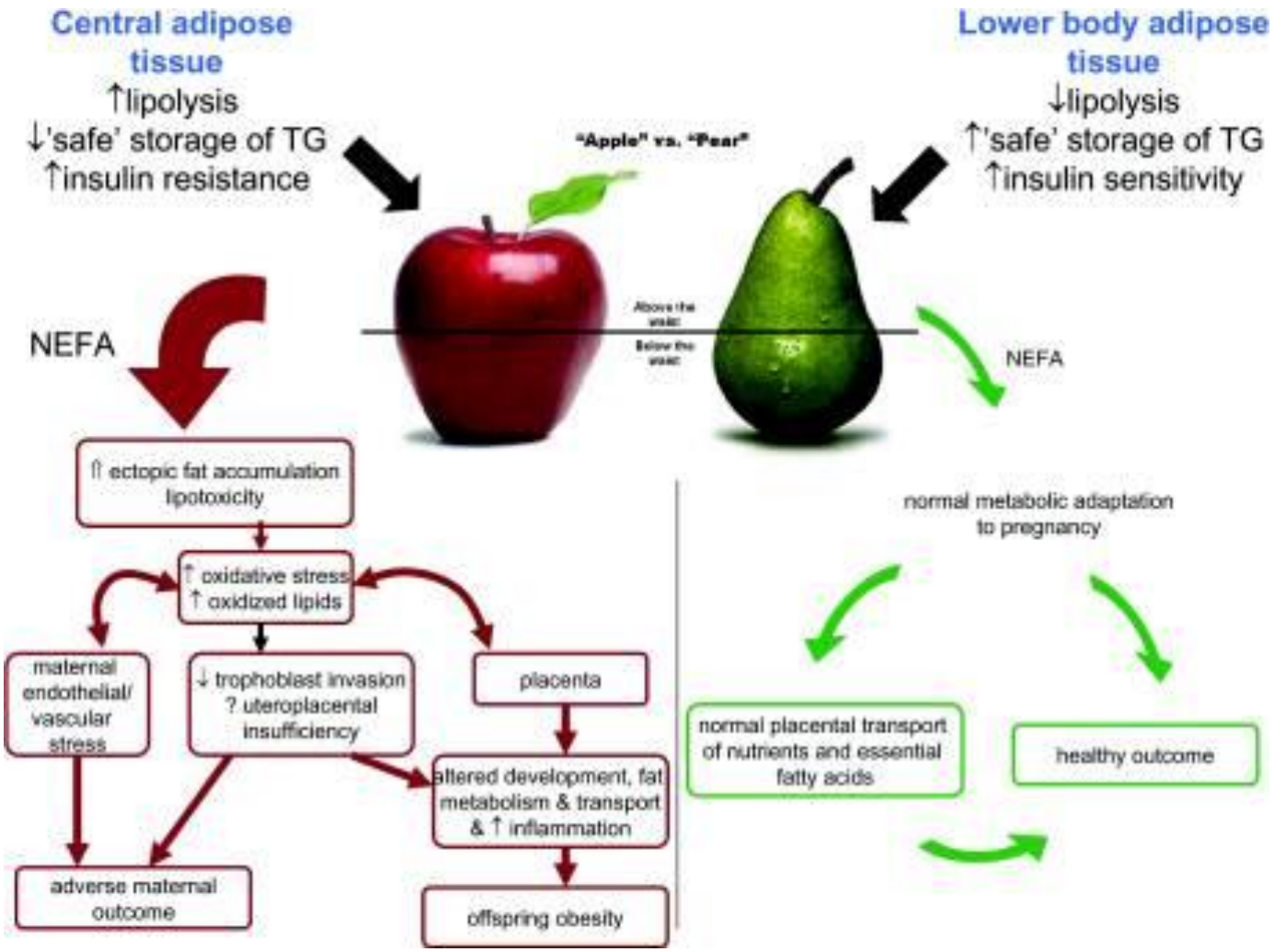
Anamnestici Maggiori 1 solo criterio	Anamnestici Minori Almeno 2 criteri	Attuali 1 solo criterio
Pregresso GDM o IGT	Sovrappeso	Incremento ponderale >1,2 kg nel 1° trimestre e/o 400 gr/settimana nel 2°-3° trimestre
Familiarità di 1°grado per diabete	Ipertensione arteriosa	Ricorrente glicosuria a digiuno
Età >30 anni	Due o più aborti	Poliidramnios
Obesità (BMI>28)	Poliidramnios	Crescita fetale accelerata e dismorfica
Pregressa macrosomia (≥ 4kg) o LGA (>90°C)	Gestosi	
Mortalità perinatale da causa ignota	Elevata parità	
	Parti pre-termine	

Obesità e Gravidanza

- Disordini Ipertensivi
- Diabete gestazionale
- Complicanze tromboemboliche
- Alterazione Sistema Epatobiliare



Gravidanza e Obesità centrale: lipotossicità



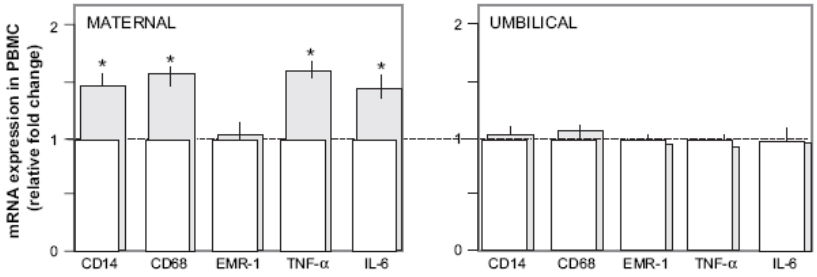
Clin Sci (Lond). 2010 Apr 28; 119(Pt 3): 123–129.
Published online 2010 Apr 28. doi: 10.1042/CS20090640

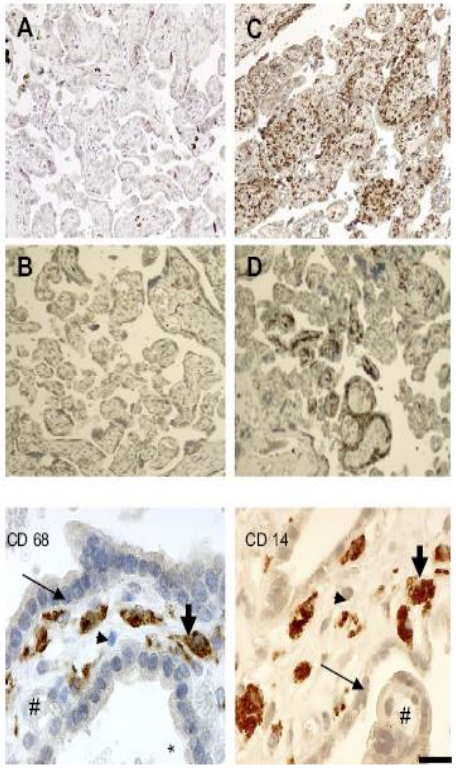
Accumulo di Macrofagi e infiammazione placentare nella donna obesa

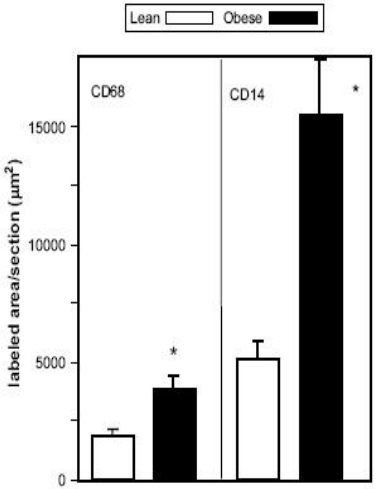
Table 2
Metabolic and inflammatory parameters in maternal plasma (mean ± SEM)

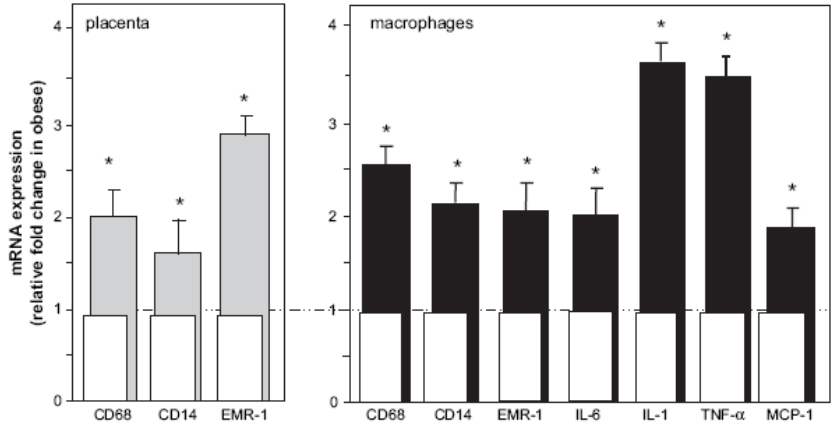
	Obese group ($n = 20$)	Lean group ($n = 15$)
Insulin (μU/ml)	26.9 ± 3.5**	10.6 ± 1.7
Insulin sensitivity at delivery (HOMA index)	4.3 ± 0.5**	1.2 ± 0.3
Leptin (ng/ml)	63.4 ± 6.2**	27.6 ± 2.6
TNF-alpha (pg/ml)	1.1 ± 0.2	1.1 ± 0.1
IL-6 (ng/ml)	4.2 ± 0.3**	2.8 ± 0.2
CRP (ng/ml)	10,453 ± 602*	8162 ± 926
% Monocytes	5.6 ± 0.5	5.3 ± 0.4
% Granulocytes	69.2 ± 1.2	65.5 ± 2.0

*: $p < 0.05$, **: $p < 0.001$.







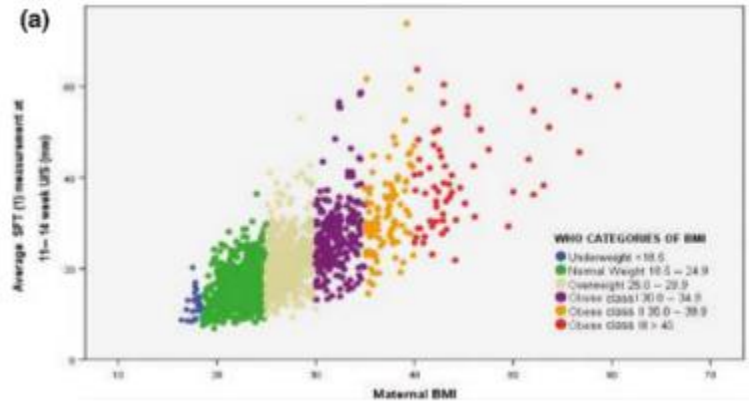


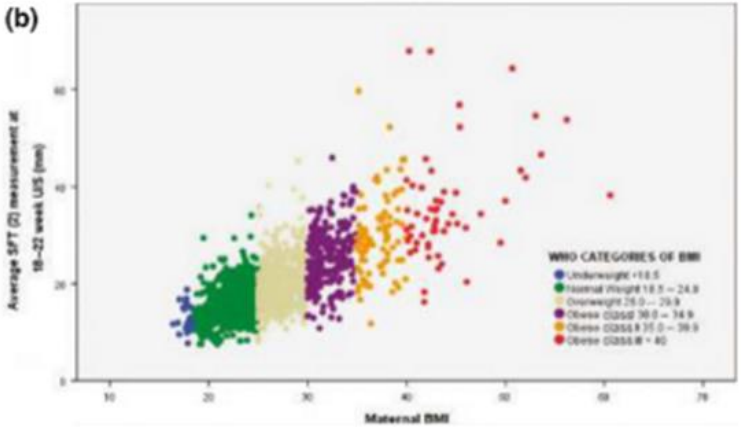
Challier JC, Placenta 2008

DOI: 10.1111/1471-0528.13758
www.bjog.org

Maternal abdominal subcutaneous fat thickness as a predictor for adverse pregnancy outcome: a longitudinal cohort study

NJ Kennedy,[a,b] MJ Peek,[a,c] AE Quinton,[a,c,d] V Lanzarone,[e] A Martin,[f] R Benzie,[a,b] R Nanan[a,c]





Conclusion

This study has demonstrated that measurement of SFT in the first and second trimester is a significant predictor for pregnancy complications such as gestational diabetes, hypertensive disease, caesarean section, preterm delivery, low birthweight, neonatal respiratory distress and NICU admissions. Ultrasound measurement of SFT can be used for obesity-related risk modelling in pregnancy. When using BMI as a reference, not all overweight/obese pregnant women develop complications during pregnancy. The increased variability and distribution of SFT in overweight/obese women may explain why SFT is a better predictor of complications than BMI, as SFT may be more representative of central obesity. Distribution of subcutaneous fat remains unchanged in underweight and normal weight women but decreases in overweight/obese women with increasing gestation. Further research about this interesting observation is required.

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RESEARCH ARTICLE

Characterization of Visceral and Subcutaneous Adipose Tissue Transcriptome and Biological Pathways in Pregnant and Non-Pregnant Women: Evidence for Pregnancy-Related Regional-Specific Differences in Adipose Tissue

Shali Mazaki-Tovi[1,2]*, Edi Vaisbuch[3], Adi L. Tarca[4,5,6], Juan Pedro Kusanovic[4,7,8], Nandor Gabor Than[4,9,10], Tinnakorn Chaiworapongsa[4,11], Zhong Dong[4], Sonia S. Hassan[4,11], Roberto Romero[4,11]*

Table 1. Demographic and clinical characteristics.

	Pregnant N = 25	Non-Pregnant N = 11	p
Maternal age (years)	34 (33–42)	32 (28–40)	0.6
BMI at Sampling (kg/m2)	30.4 (27.5–38.8)	31.1 (26.2–39.1)	0.9
Gravidity	4 (3–5)	4 (3–7)	0.7
Parity	3 (2–4)	3 (2–4)	0.6
Ethnic Origin (%)			0.5
African American	90.9	81.8	
Caucasian	9.1	18.2	
Systolic Blood Pressure (mmHg)	117 (114–120)	114 (111–117)	0.6
Diastolic Blood Pressure (mmHg)	74 (69–79)	66 (63–81)	0.4
Fasting Glucose (mg/dl)	87 (80–89)	88 (73–90)	0.3
Gestational Age at Delivery (weeks)	39.1 (38–39.3)	NA	NA
Birth Weight (grams)	3335 (2980–3555)	NA	NA

Data are presented as median and interquartile range (IQR). BMI—Body Mass Index.

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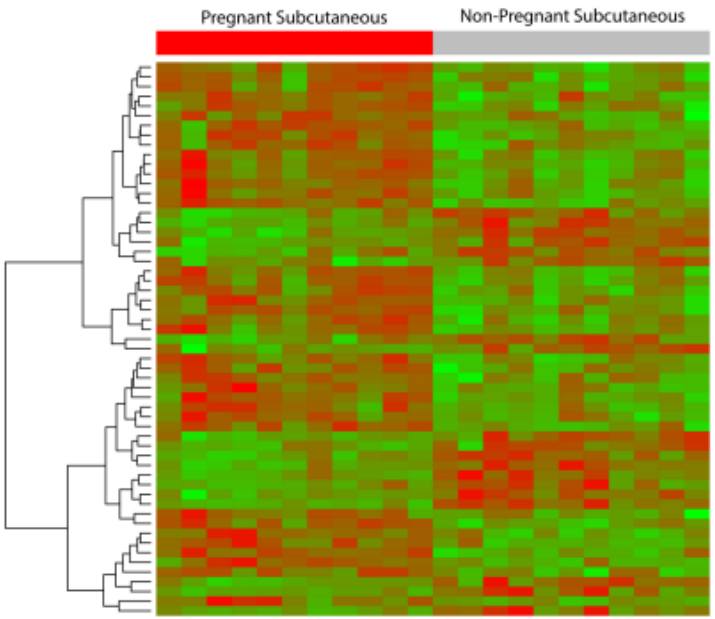


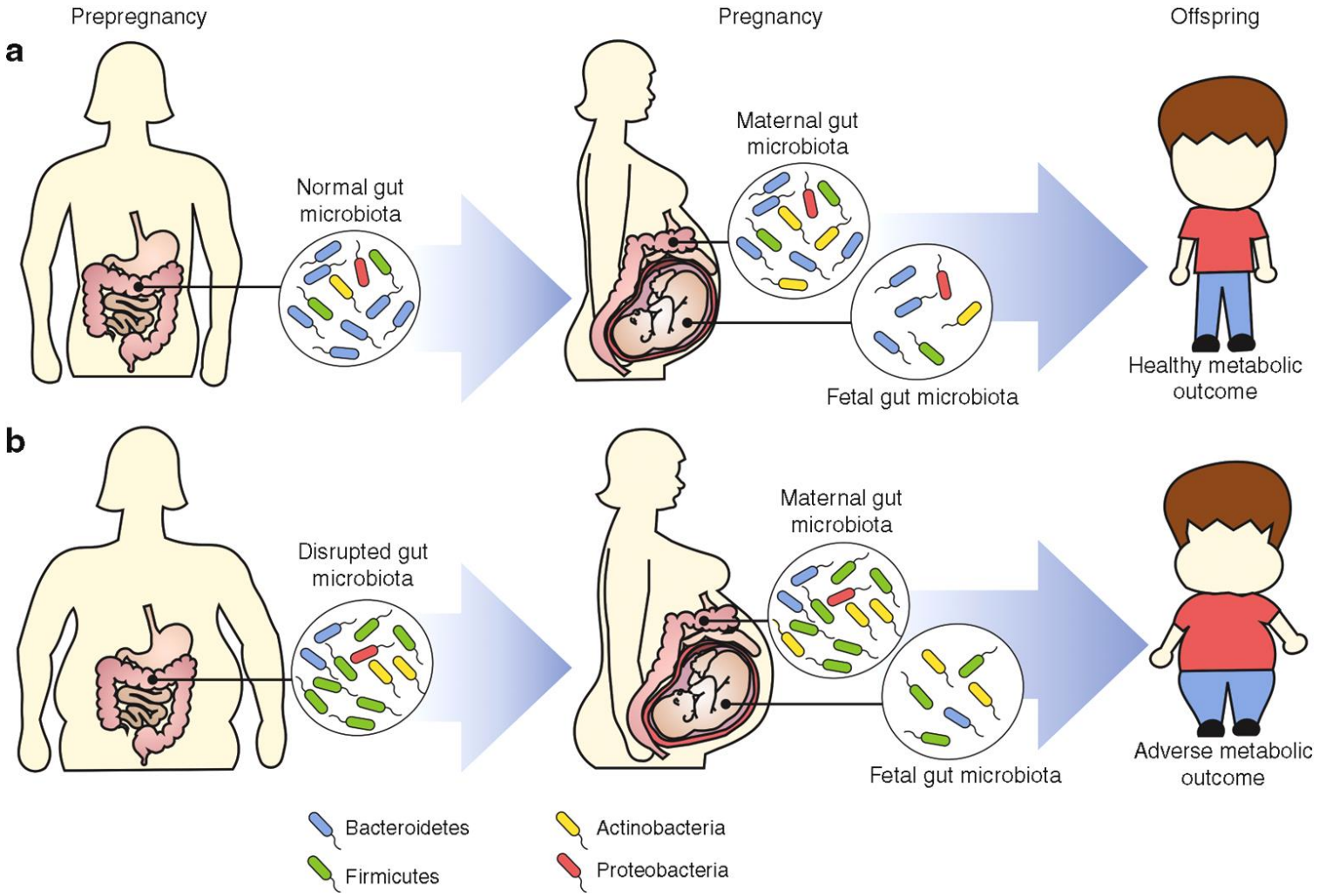
Fig 4. Heat map representing subcutaneous adipose tissue differences in gene expr pregnant vs non-pregnant women. The heat map in Fig 4 uses a color scale to show the expression levels within each group of samples as well as the differences between the gro positive test results.

Omentin
PPARs
ECM remodelling

Complement activation, classical inflammatory pathway, immunoglobulin mediated immune response and humoral immune response

GPR64 (G-coupled protein receptor 64)

Obesità, gravidanza e microbiota intestinale: un nuovo scenario



Obesità e latte materno

ORIGINAL ARTICLE

Breastmilk from obese mothers has pro-inflammatory properties and decreased neuroprotective factors

PG Panagos[1], R Vishwanathan[2], A Penfield-Cyr[3], NR Matthan[2], N Shivappa[4,5], MD Wirth[4,5], JR Hebert[4,5] and S Sen[2,3]

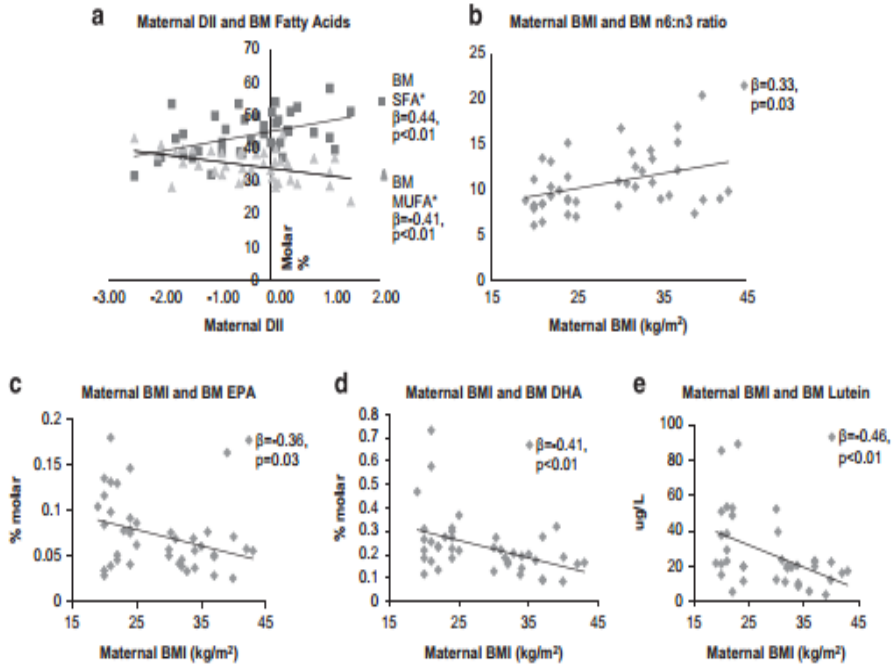


Figure 1. Associations of breastmilk fatty acid and carotenoid composition. (**a**) Maternal DII is associated with the concentration of breastmilk saturated fatty acids (SFAs) and breastmilk monounsaturated fatty acids (MUFAs). (**b–e**) Maternal BMI is associated with breastmilk concentrations of n6:n3 fatty acid ratio (**b**), EPA (**c**), DHA (**d**) and lutein (**e**). BM, breastmilk; BMI, body mass index; DHA, docosahexaenoic acid; DII, Dietary Inflammatory Index; EPA, eicosapentaenoic acid.

Table 4. BM composition

	Lc BM	*Ob BM*	P
	Mean (s.d.)	*Mean (s.d.)*	
Energy	$n=21$	$n=21$	
Calories per ounce	19.6 (4.8)	19.6 (5.3)	0.79
Macronutrients (g per 100 ml)	$n=21$	$n=21$	
Total fat	4.0 (1.8)	3.5 (1.9)	0.32
Total protein	1.3 (0.04)	1.3 (0.1)	0.73
Total lactose	6.9 (0.3)	7.0 (0.5)	0.78
Micronutrients	$n=20$	$n=21$	
Retinol (μg dl^{-1})	4.6 (1.7)	5.5 (6.6)	0.31
Vitamin E, alpha-tocopherol (μg dl^{-1})	378.1 (171.7)	325.1 (267.9)	0.069
Vitamin E, gamma-tocopherol (μg dl^{-1})	80.0 (56.4)	109.0 (55.6)	0.054
Vitamin B12 (pg ml^{-1})	488.0 (451.8)	671.8 (933.0)	0.79
25-OH vitamin D (ng ml^{-1}) (Lc $n=14$, Ob $n=17$)	1.3 (0.6)	0.8 (0.7)	0.0025**
Total folate (ng ml^{-1})	46.4 (42.2)	41.3 (29.5)	0.63
Carotenoids (μg l^{-1})	$n=17$	$n=20$	
Lutein	36.6 (24.2)	18.5 (10.9)	0.006*
Zeaxanthin	9.1 (7.0)	5.7 (2.4)	0.048*
Cryptoxanthin	32.3 (40.5)	7.7 (5.0)	0.011*
α-Carotene	7.4 (5.9)	2.4 (1.8)	0.001*
β-Carotene	54.4 (44.9)	14.4 (7.0)	< 0.001*
Lycopene	43.1 (38.8)	29.8 (21.4)	0.196
Total FA (mol%)	$n=21$	$n=21$	
SFA	42.3 (6.7)	44.6 (5.8)	0.50
MUFA	35.4 (4.3)	34.2 (4.8)	0.36
PUFA n-6	18.1 (3.5)	18.5 (3.1)	0.72
PUFA n-3	2.0 (0.5)	1.6 (0.3)	0.0033*
Trans-FA	1.1 (0.4)	1.1 (0.4)	0.88
SFA profiles (mol%)	$n=21$	$n=21$	
8:0 (caprylic acid)	0.2 (0.1)	0.2 (0.7)	0.26
10:0 (capric acid)	2.5 (0.6)	2.3 (0.6)	0.20
12:0 (lauric acid)	8.9 (3.4)	8.5 (3.0)	0.86
14:0 (myristic acid)	7.7 (2.8)	7.7 (2.8)	0.95
16:0 (palmitic acid)	16.7 (3.1)	19.5 (2.3)	0.0001*
18:0 (stearic acid)	6.5 (1.8)	5.8 (1.0)	0.14
20:0 (arachidonic acid)	0.3 (0.2)	0.2 (0.05)	0.70
22:0 (behenic acid)	0.08 (0.003)	0.06 (0.02)	0.0025*
MUFA profiles (mol%)	$n=21$	$n=21$	
14:1n-5 (myristoleic acid)	0.3 (0.9)	0.2 (0.1)	0.29
16:1n-7 (palmitoleic acid)	2.4 (0.8)	2.5 (0.9)	0.84
18:1n-9 (oleic acid)	30.3 (3.7)	29.0 (4.6)	0.28
20:1n-9 (gondoic acid)	0.4 (0.7)	0.3 (0.08)	0.0001*
22:1n-9 (erucic acid)	0.07 (0.03)	0.05 (0.01)	0.0098*
PUFA profiles (mol%)	$n=21$	$n=21$	
PUFA n-6			
18:2n-6 (linoleic acid)	16.6 (3.4)	17.0 (3.0)	0.74
18:3n-6 (gamma-linolenic acid)	0.16 (0.06)	0.16 (0.07)	0.91
20:4n-6 (AA)	0.5 (0.08)	0.5 (0.1)	0.7
PUFA n-3			
18:3n-3 (ALA)	1.7 (0.6)	1.2 (0.3)	0.008*
20:5n-3 (EPA)	0.8 (0.04)	0.6 (0.03)	0.013*
22:5n-3 (DPA)	0.2 (0.03)	0.1 (0.05)	0.0025*
22:6n-3 (DHA)	0.3 (0.1)	0.2 (0.06)	0.001*
PUFA n-6 to PUFA n-3 ratio	9.3 (2.3)	12.0 (3.3)	0.0034*
Trans-FA profiles (mol%)	$n=21$	$n=21$	
16:1n- 9T (trans-7-hexadecenoic acid)	0.03 (0.01)	0.05 (0.02)	0.0012*
18:1T (petroselinic+elaidic+trans-vaccenic)	0.084 (0.04)	0.085 (0.03)	0.75
18:2T (linolelaidic acid)	0.09 (0.04)	0.1 (0.03)	0.23

Abbreviations: AA, arachadonic acid; BM, breastmilk; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; FA, fatty acid; Lc, lean control; MUFA, monounsaturated fatty acid; Ob, obese; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid. *$P<0.05$ by Student's *t*-test or Mann–Whitney test. Molar % is calculated based on the sum of 37 individual FAs of which 23 are reported in this table. **$P<0.05$, adjusted *P*-value, determined by multivariate linear regression models controlling for maternal race.

J Puericult, 2016

Take-home message

- **L'infiammazione di basso grado dell'obesità produce un <u>effetto additivo</u> all'infiammazione della gravidanza**
- **Rischio per lo stato di salute sia materno sia fetale e alterazione del «programming» fetale**
- **Rischio anche durante la fase di allattamento al seno**
- **Un calo ponderale del 3-5% risulta in un miglioramento dell'infiammazione di basso grado nell'obeso**
- **Controllo qualitativo-quantitativo dell'alimentazione!**

Ospedale San Giuseppe Piancavallo

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