THE EUROPEAN SOCIETY FOR CLINICAL NUTRITION AND METABOLISM

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Lifelong Learning Programme

Obesity
Aetiopathogenesis and Complications

Module 23.1

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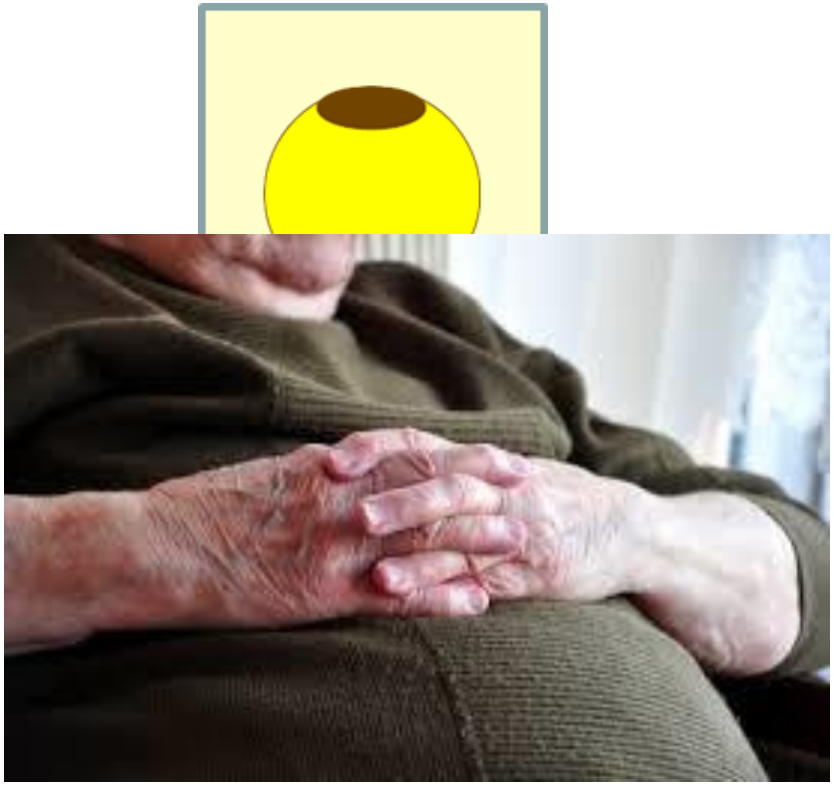

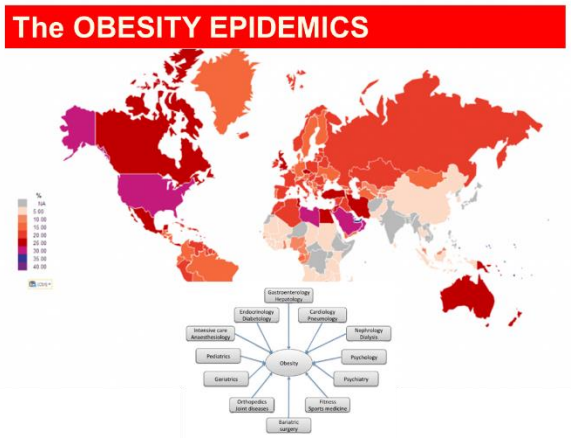

OVERWEIGHT and OBESITY

"Chronic conditions characterized by abnormal-excess fat accumulation leading to excess morbidity" (WHO)

Clinical = BMI > 30 kg/m^2

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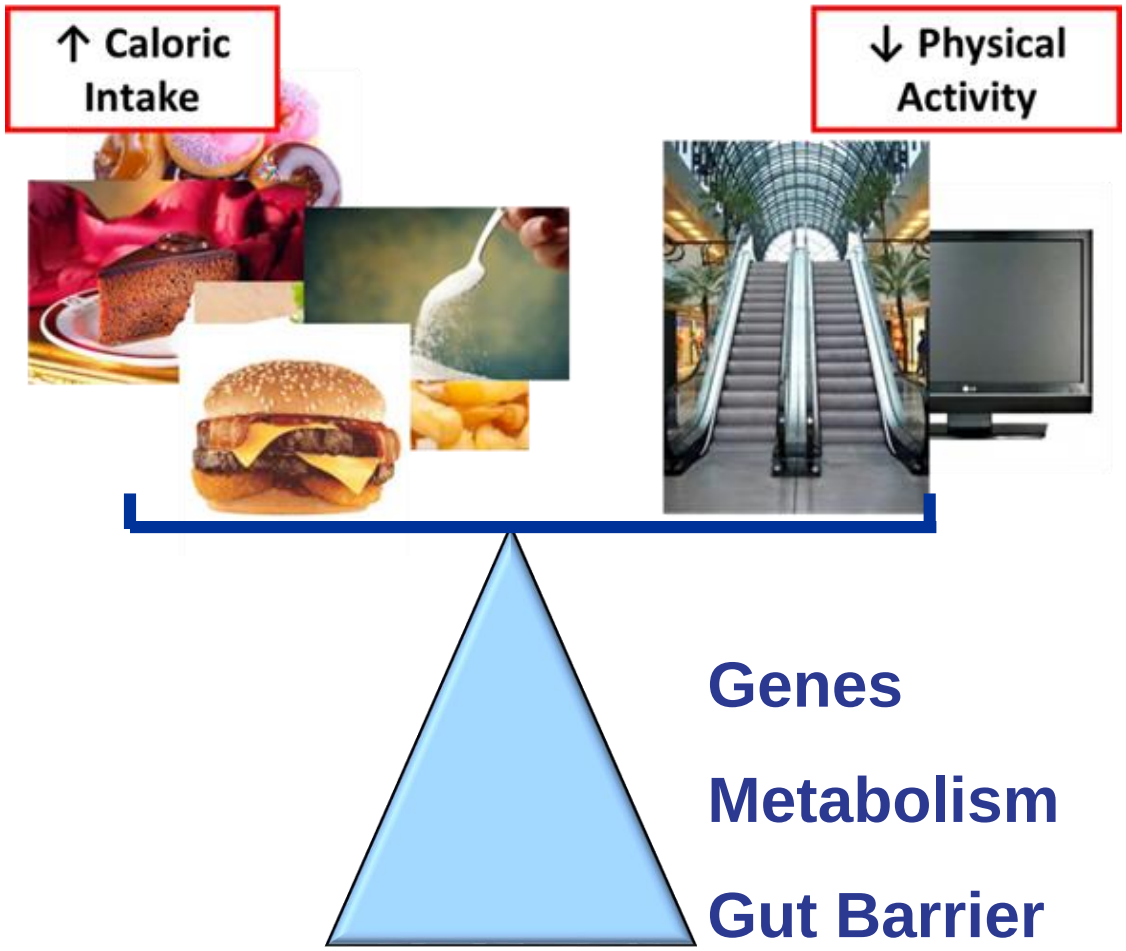

Outline

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- **Energy intake (Appetite regulation)**
- **Energy expenditure (Intermediate metabolism)**
- **Clinical impact of obesity**
- **Malnutrition in obesity (?)**

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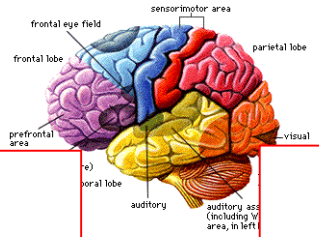
REFLECTIVE

Cognition

Cortex

REFLEXIVE



REFLEXIVE

Homeostasis

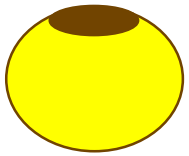
Hypothalamus

Reward

Limbic - Paralimbic

Food Intake

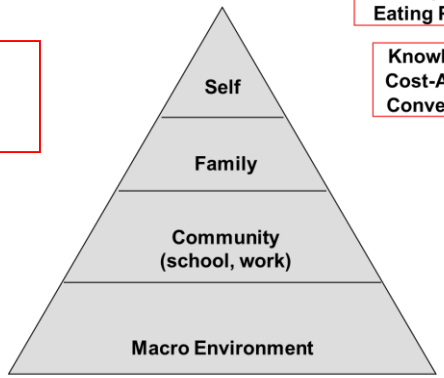
Feed-Back



Influences on Food Choices

Taste (GENETICS)
Eating PATTERNS

Knowledge
Cost-Access
Convenience



(public policies, media, industry, technology, transportation)

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Orexigenic

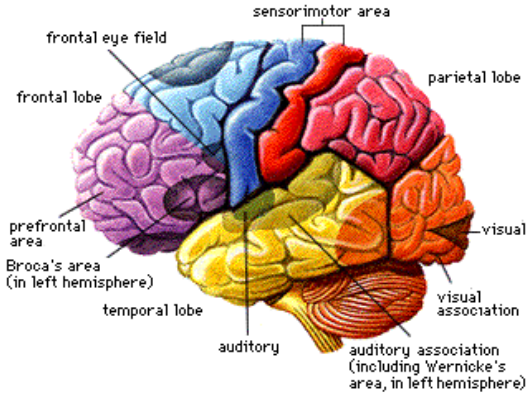
Ghrelin

Anorexigenic

Leptin

Homeostasis

Hypothalamus



NPY-AgRP

POMC alpha MSH

Appetito

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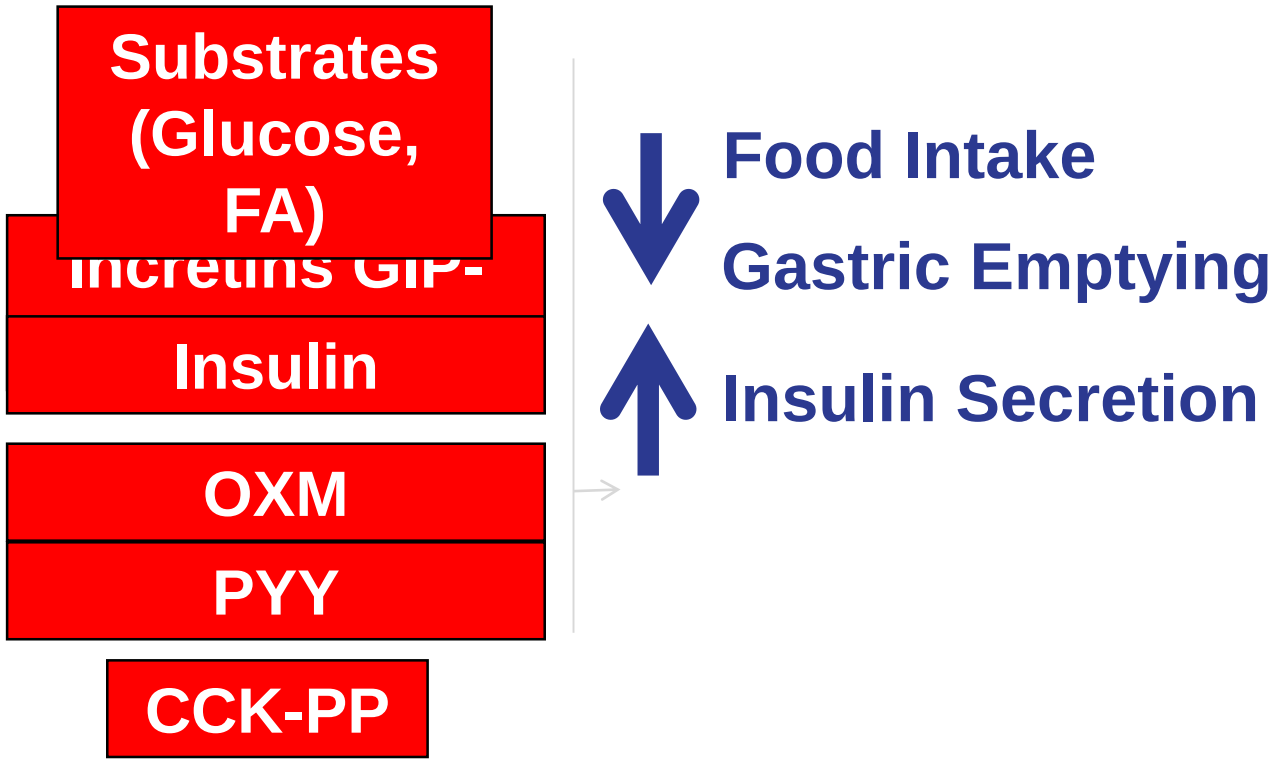
GUT ENDOCRINE SYSTEM

Nutrient-Triggered SATIETY Signalling



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GUT ENDOCRINE SYSTEM

Nutrient-Triggered SATIETY Signalling

- Substrates (Glucose, FA)
- Incretins GIP-GLP1
- Insulin
- OXM
- PYY
- CCK-PP

↓ Food Intake

↓ Gastric Emptying

↑ Insulin Secretion

HIGH-FAT DIET SATIETY RESISTANCE

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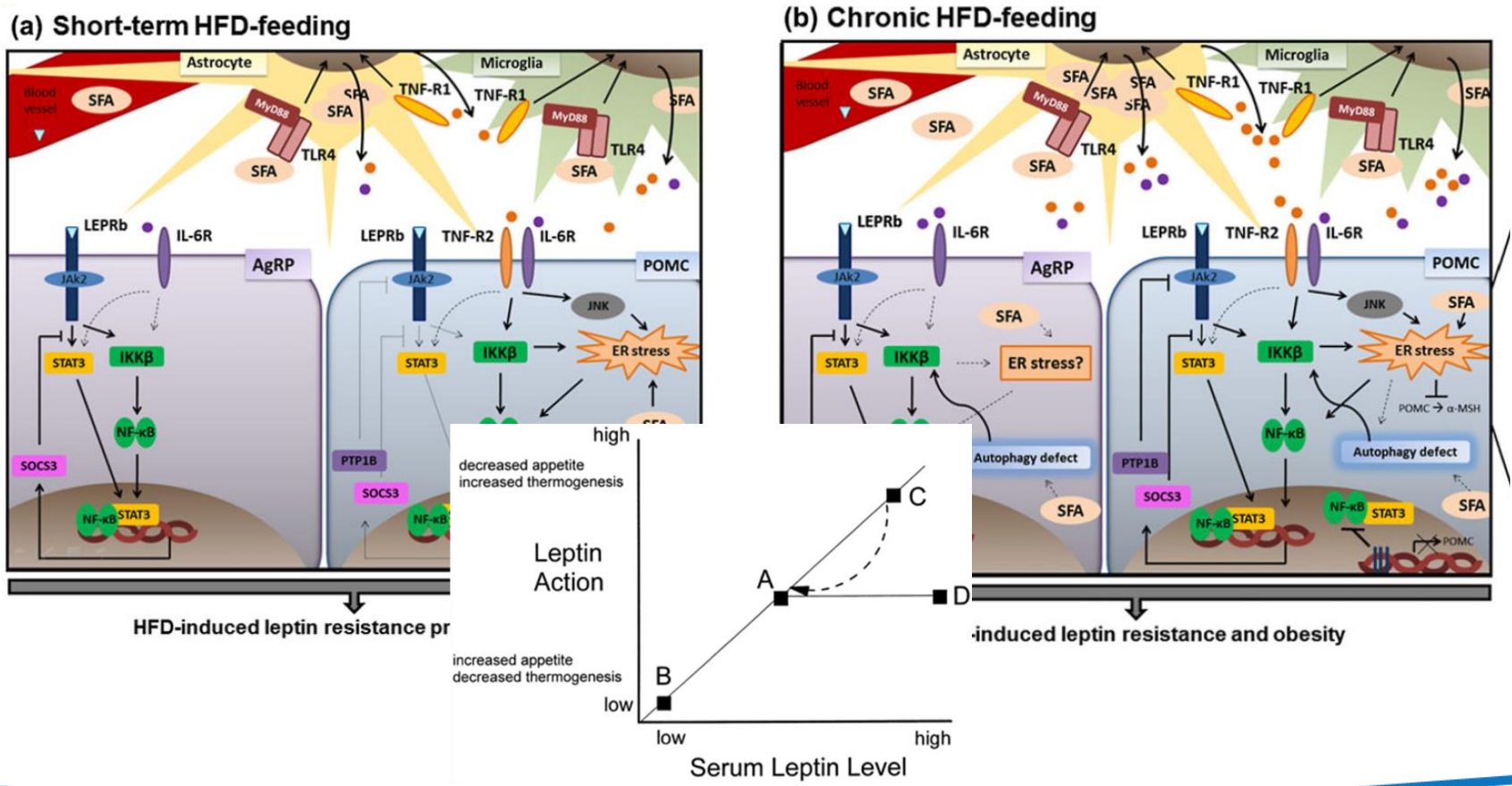
Leptin resistance in diet-induced obesity: the role of hypothalamic inflammation

De Git et al, Obesity Rev 2015



Flier JS, J Clin Endocrinol Metab, 2000

Metabolic adaptation to nutrient intake
Thrifty genotype hypothesis

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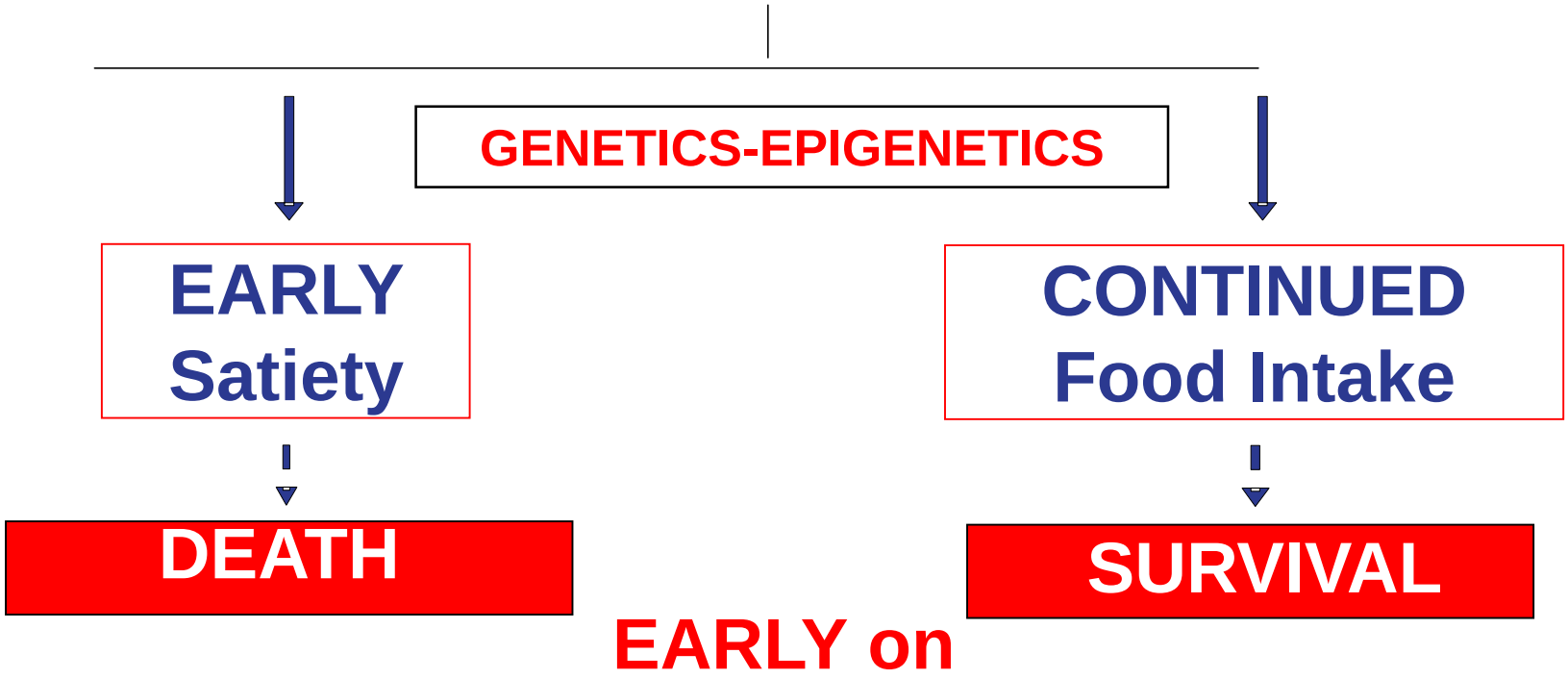
High Nutrient Availability



Metabolic adaptation to nutrient intake
Thrifty genotype hypothesis

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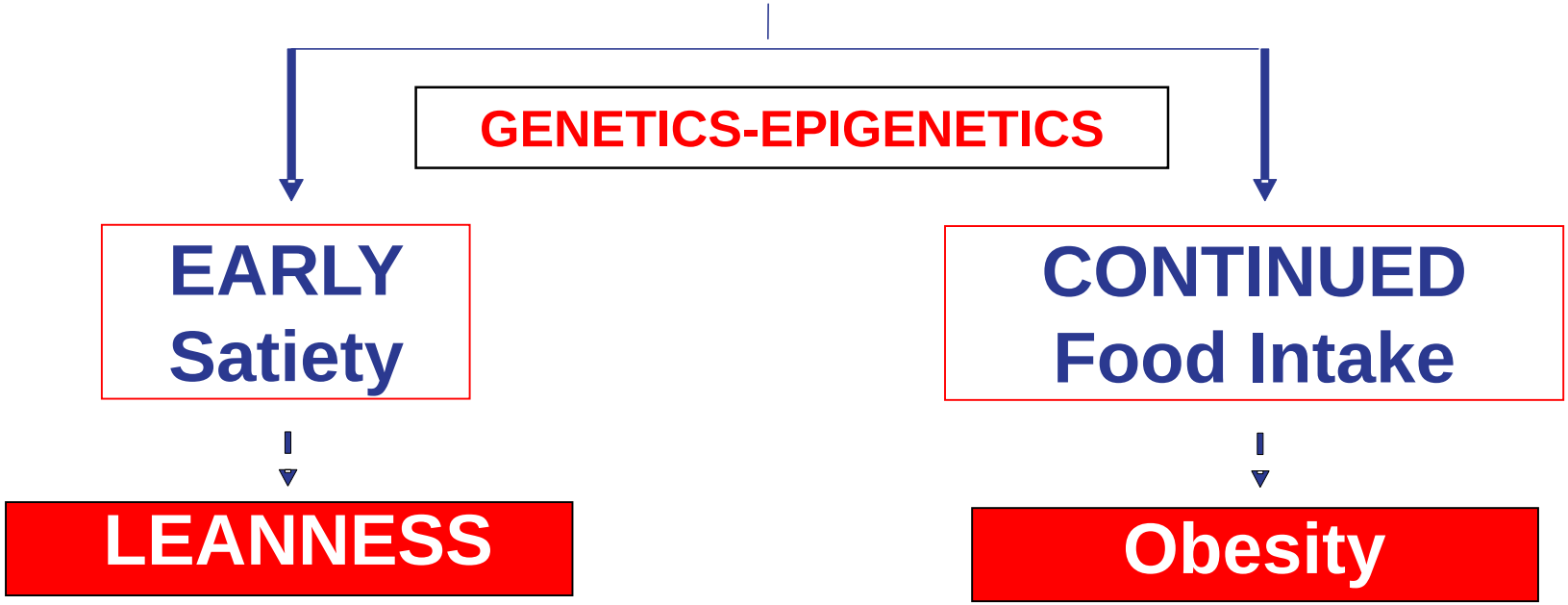
High Nutrient Availability



20-21st century

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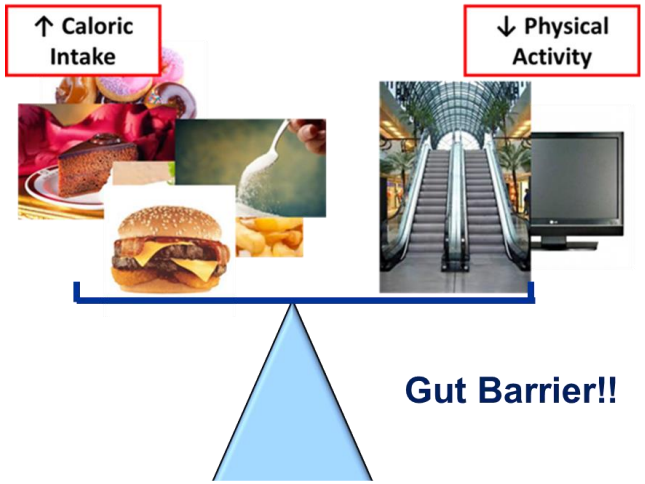

- Diet:
Balanced
Mediterranean style
- Probiotics

- Diet:
High-fat/High-Sugar
High Calorie
- Stress response
- Antibiotic abuse

GUT Microbial BALANCE

- ↑ Energy Harvest
- ↑ Satiating Metabolites
- ↓Inflammation

GUT Microbial DYSBIOSIS

- ↓ Energy Harvest
- ↓ Satiating Metabolites
- ↑ Inflammation

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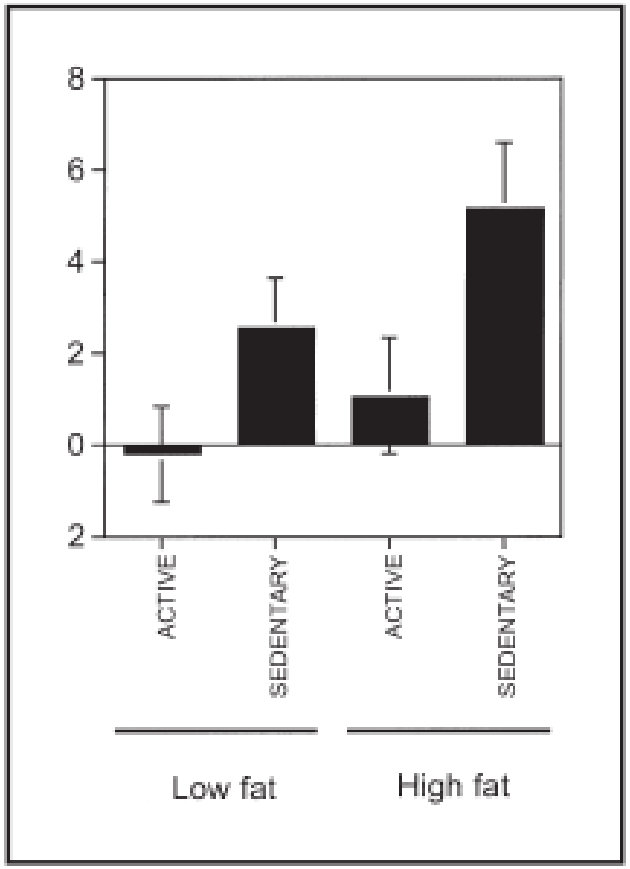
- Food intake regulation is complex and only partly understood
- Appetite regulation is at least partly beyond volitional control
- Failure of homeostatic feedback control mechanisms in the presence of food availability favours the obesity epidemic and likely reflects evolutionary processes

Outline

- Energy intake (Appetite regulation)
- Energy expenditure (Intermediate metabolism)
- Clinical impact of obesity
- Malnutrition in obesity (?)

Physical activity and weight gain during high-fat diet



Prentice et al, Nutr Rev 2004

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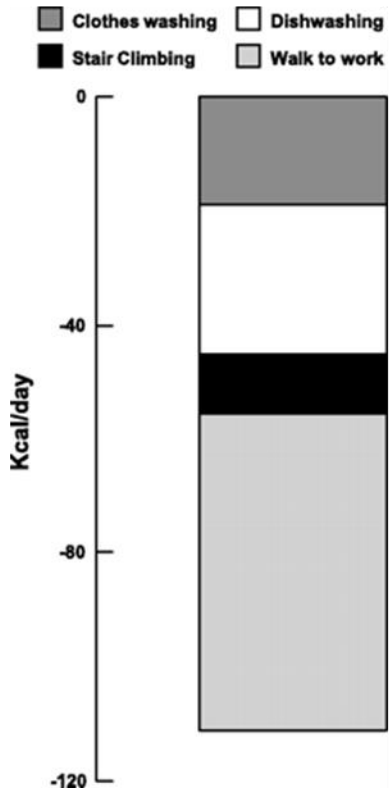
Low (?) Intensity ADLs



OBESE and Sedentary

	Walking bouts (*n*/day)	Time engaged in walking (minutes/day)	Average distance of a walking bout (miles)	Free-living walking velocity (mph)
Baseline				
Lean	46 ± 8	448 ± 111	0.22 ± 0.04	1.19 ± 0.21
Obese	47 ± 5	339 ± 74*	0.14 ± 0.04†	1.10 ± 0.20
Total	47 ± 6	389 ± 106	0.18 ± 0.06	1.14 ± 0.20
Overfed				
Lean	48 ± 11	459 ± 119	0.19 ± 0.06‡	1.09 ± 0.28
Obese	47 ± 9	334 ± 79*	0.11 ± 0.03§¶	0.96 ± 0.15‖
Total	47 ± 10	391 ± 116	0.15 ± 0.06**	1.02 ± 0.20**

Levine et al, Diabetes 2008

Being obese is associated with negative changes in QUANTITY and QUALITY of walking during overfeeding (VICIOUS CYCLING)

REGULATION LARGELY UNKNOWN!!
(GENETIC-VOLITIONAL-ENDOCRINE/METABOLIC?)

Outline

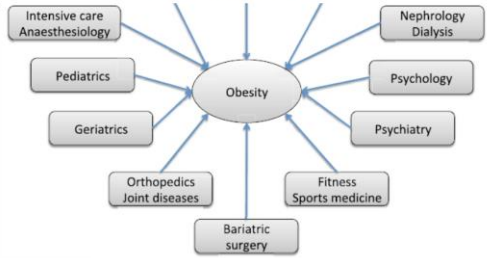
- **Clinical impact of obesity**

↑↑↑ ACUTE and CHRONIC DISEASE

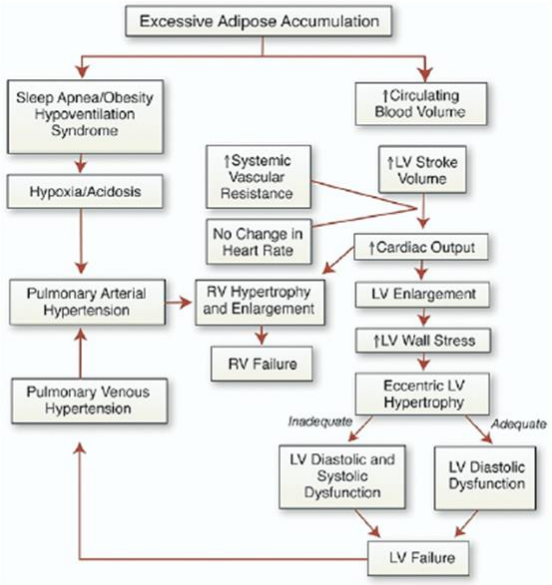
Towards a multidisciplinary approach to understand and manage obesity and related diseases☆

Stephan C. Bischoff [a,*], Yves Boirie [b], Tommy Cederholm [c], Michael Chourdakis [d], Cristina Cuerda [e], Nathalie M. Delzenne [f], Nicolaas E. Deutz [g], Denis Fouque [h], Laurence Genton [i], Carmen Gil [j], Berthold Koletzko [k], Miguel Leon-Sanz [l], Raanan Shamir [m], Joelle Singer [n,o], Pierre Singer [o,p], Nanette Stroebele-Benschop [q], Anders Thorell [r], Arved Weimann [s], Rocco Barazzoni [t]

Clin Nutr 2017

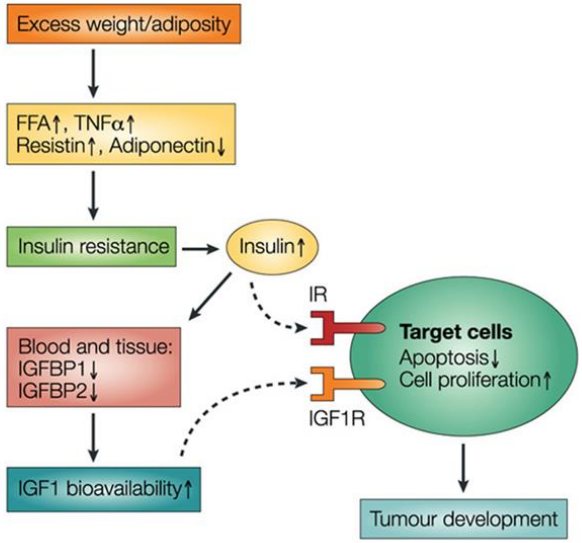


CHF



Lavie et al, JACC 2009

CANCER



Nature Reviews | Cancer

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↑↑↑ (CARDIO)METABOLIC COMPLICATIONS

INSULIN RESISTANCE

METABOLIC SYNDROME

TYPE 2 DIABETES

CARDIOVASCULAR DISEASE

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OBESITY

Ox STRESS ⟷ **INFLAMMATION**

+

+

INSULIN RESISTANCE

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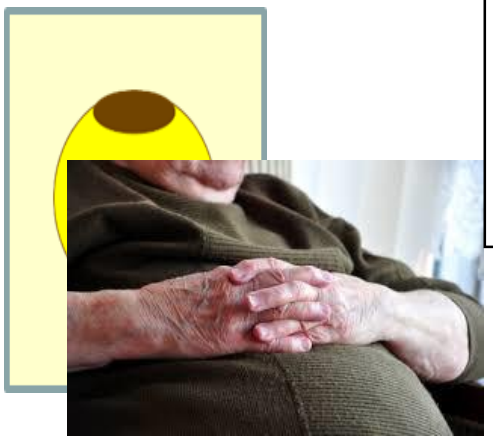
ADIPOSE TISSUE DISEASE:

Dealing with excess fat

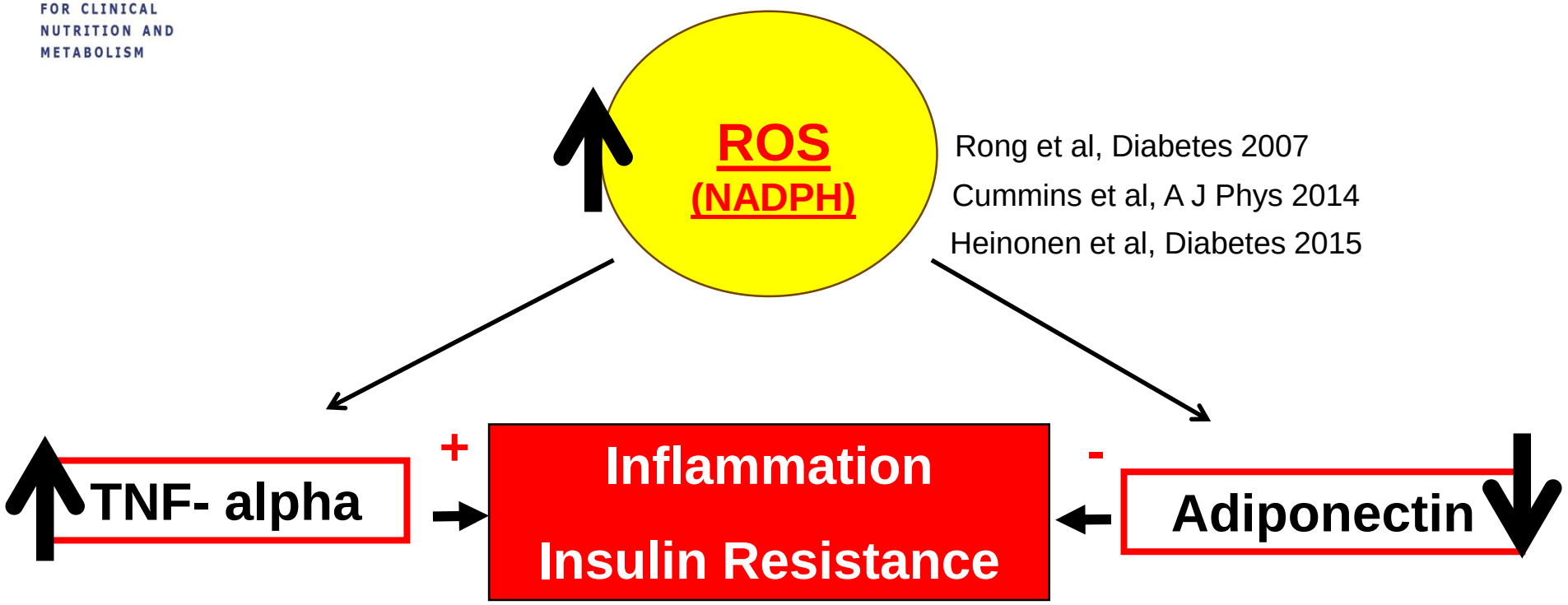
ADIPOSOPATHY



EXCESS FAT

ADIPOSE TISSUE METABOLISM

CHRONIC NUTRIENT EXCESS



Paglialunga S et al, Diabetologia 2015

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EXCESS FAT

ADIPOSE TISSUE METABOLISM

↓

Adipogenesis

AO HYPERTROPHY ↓

HYPOXIA
STRESS
DEATH → **INFLAMMATION – M2 → M1 Macrophages**
INSULIN RESISTANCE

Reilly and Saltiel, Nature Rev Endocrinol 2017

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EXCESS FAT

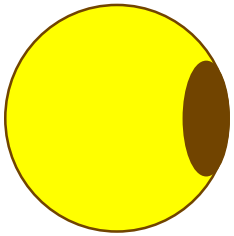
ADIPOSE TISSUE DISTRIBUTION

ADIPOGENESIS

AO HYPERTROPHY

ECTOPIC FAT

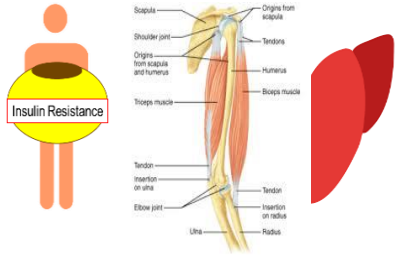
VISCERAL FAT



↓ STORAGE CAPACITY

INFLAMMATION

INSULIN RESISTANCE



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↑↑↑ (CARDIO)METABOLIC COMPLICATIONS

INSULIN RESISTANCE

METABOLIC SYNDROME

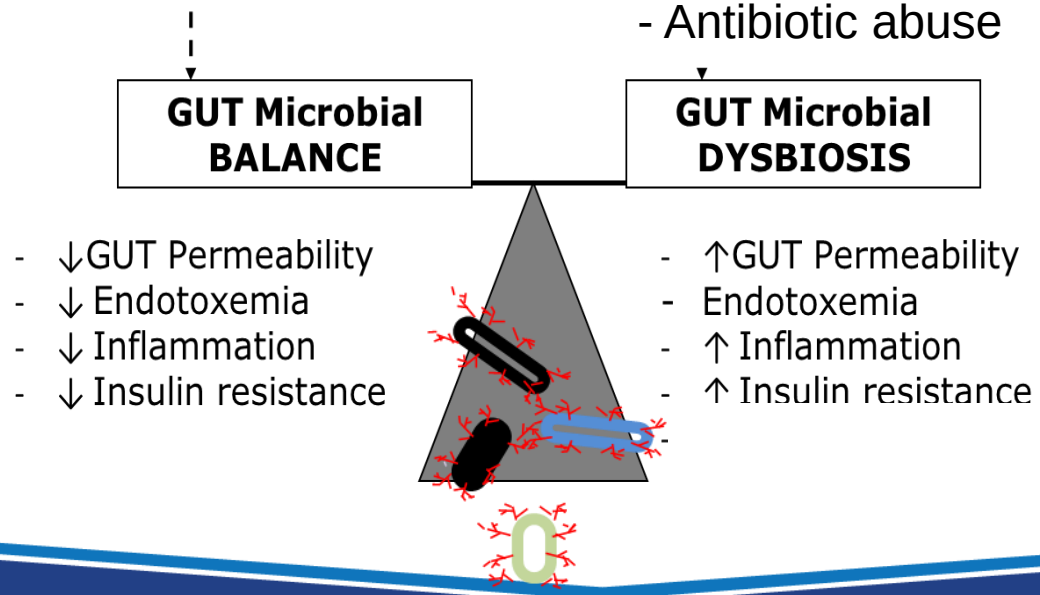
TYPE 2 DIABETES

CARDIOVASCULAR DISEASE

Gut Barrier!!

- Diet:
Balanced
Mediterranean style
- Probiotics

- Diet:
High-fat/High-Sugar
High Calorie
- Stress response
- Antibiotic abuse



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Consensus criteria of the Metabolic Syndrome IDF-AHA/NHLBI

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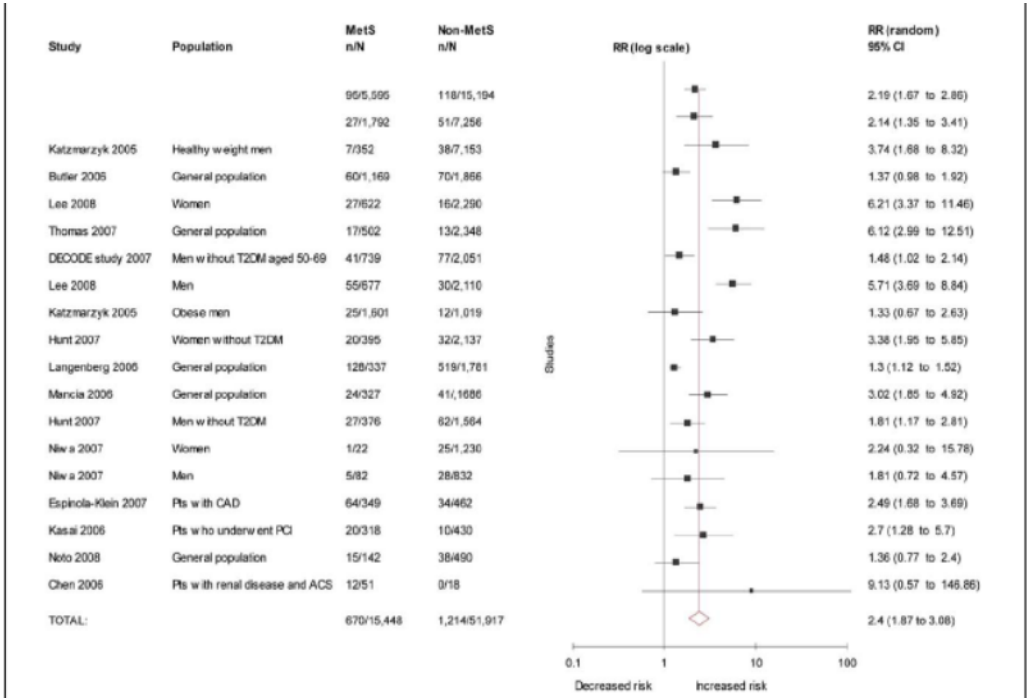
Measure	Categorical cut points
• Elevated waist circumference*	Variable according to ETHNICITY
• Elevated blood pressure**	Systolic ≥ 130 and/or diastolic ≥ 85 mm Hg
• Elevated fasting glucose**	≥ 100 mg/dl
• Elevated triglycerides**	≥ 150 mg/dl (1.7 mmol/L)
• Reduced HDL-c**	< 40 mg/dl (1.0 mmol/L) in males; < 50 mg/dl (1.3 mmol/L) in females

**or drug treatment

Any 3 of 5 risk factors constitutes a diagnosis of MS

Alberti KGMM, et al. Circulation 2009; 120: 1640-5.

MetS and CVD



Study	Population	MetS n/N	Non-MetS n/N	RR (random) 95% CI
		95/5,595	118/15,194	2.19 (1.67 to 2.86)
		27/1,792	51/7,256	2.14 (1.35 to 3.41)
Katzmarzyk 2005	Healthy weight men	7/352	38/7,153	3.74 (1.68 to 8.32)
Butler 2006	General population	60/1,169	70/1,866	1.37 (0.98 to 1.92)
Lee 2008	Women	27/622	16/2,290	6.21 (3.37 to 11.46)
Thomas 2007	General population	17/502	13/2,348	6.12 (2.99 to 12.51)
DECODE study 2007	Men without T2DM aged 50-69	41/739	77/2,051	1.48 (1.02 to 2.14)
Lee 2008	Men	55/677	30/2,110	5.71 (3.69 to 8.84)
Katzmarzyk 2005	Obese men	25/1,601	12/1,019	1.33 (0.67 to 2.63)
Hunt 2007	Women without T2DM	20/395	32/2,137	3.38 (1.95 to 5.85)
Langenberg 2006	General population	128/337	519/1,781	1.3 (1.12 to 1.52)
Mancia 2006	General population	24/327	41/1686	3.02 (1.85 to 4.92)
Hunt 2007	Men without T2DM	27/376	62/1,564	1.81 (1.17 to 2.81)
Niwa 2007	Women	1/22	25/1,230	2.24 (0.32 to 15.78)
Niwa 2007	Men	5/82	28/832	1.81 (0.72 to 4.57)
Espinola-Klein 2007	Pts with CAD	64/349	34/462	2.49 (1.68 to 3.69)
Kasai 2006	Pts who underwent PCI	20/318	10/430	2.7 (1.28 to 5.7)
Neto 2008	General population	15/142	38/490	1.36 (0.77 to 2.4)
Chen 2006	Pts with renal disease and ACS	12/51	0/18	9.13 (0.57 to 146.86)
TOTAL:		670/15,448	1,214/51,917	2.4 (1.87 to 3.08)

Figure 4 The Metabolic Syndrome and the Relative Risk for CVD Mortality

Mottillo et al, JACC 2010

Outline

- Energy intake (Appetite regulation)
- Energy expenditure (Intermediate metabolism)
- Clinical impact of obesity
- Malnutrition in obesity (?)

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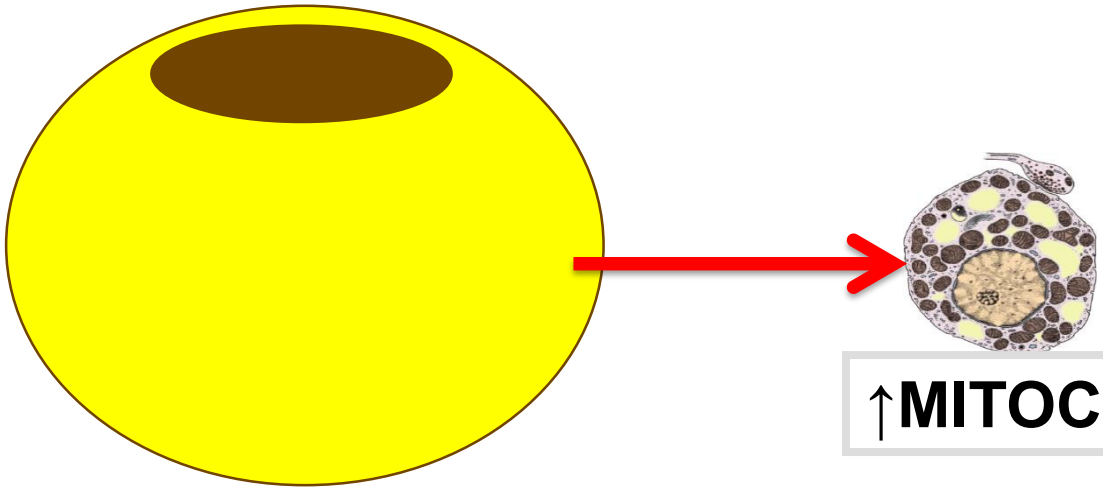
BROWN ADIPOSE TISSUE DYSFUNCTION

WAT

BAT



↑MITOCHONDRIA

↑UNCOUPLING

↑THERMOGENESIS

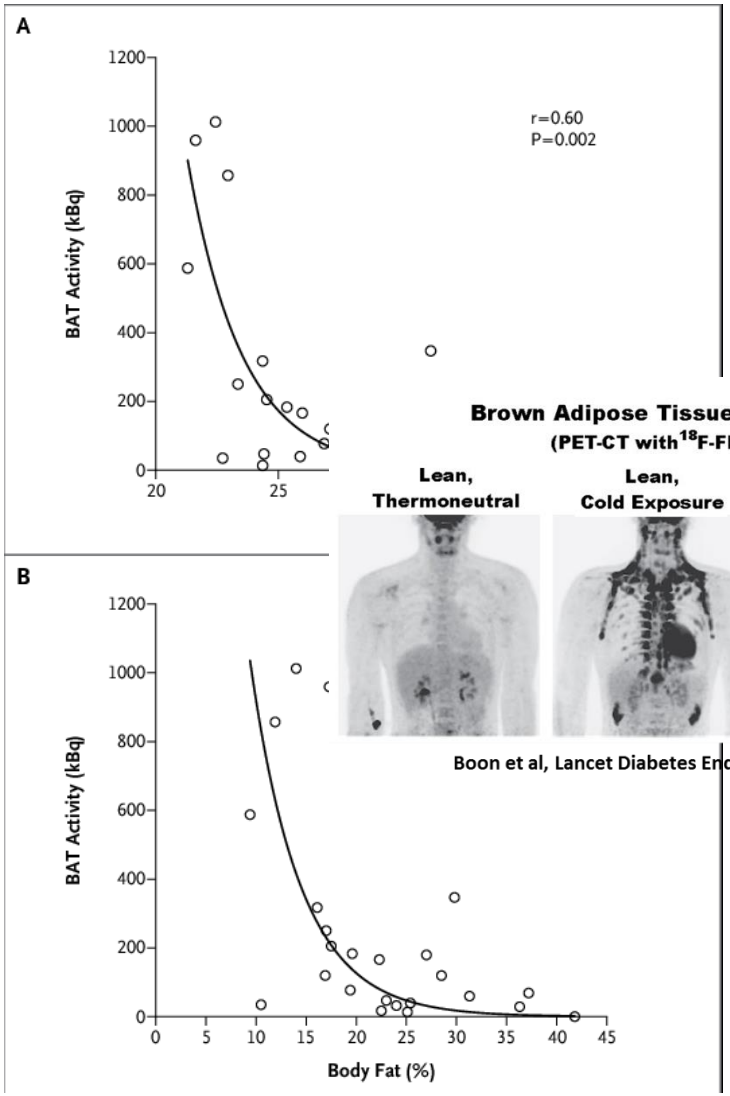
↑ENERGY EXPENDITURE

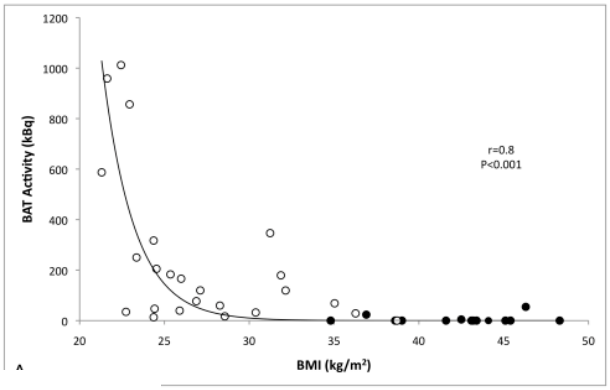
COLD

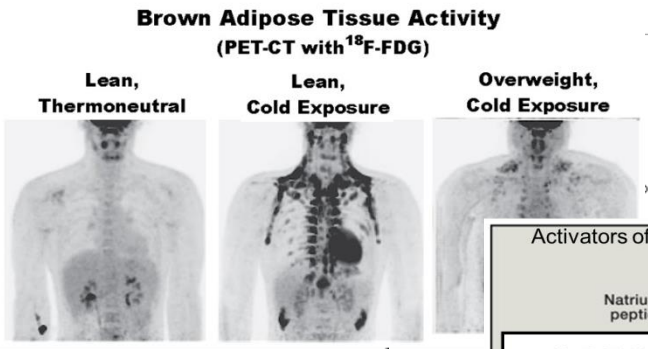
EXERCISE

NUTRITION!!

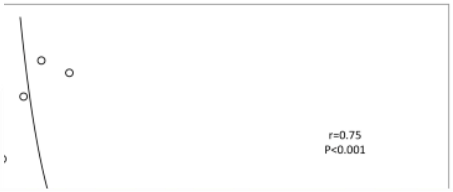
Impaired BAT activity in OBESITY!!

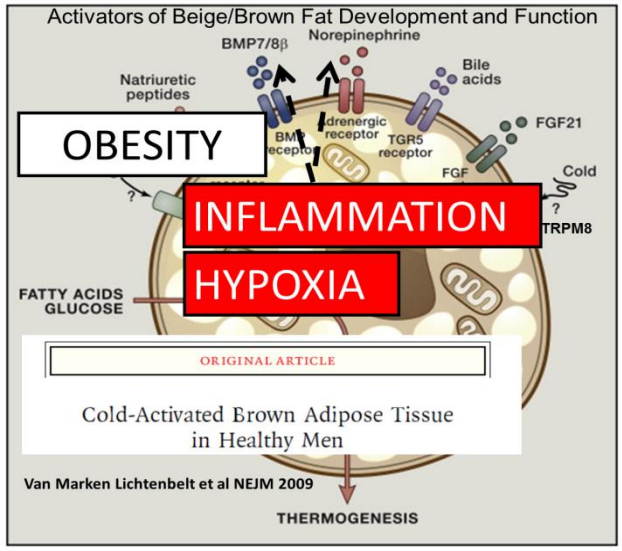






Boon et al, Lancet Diabetes Endocrinolog





Van Marken Lichtenbelt et al NEJM 2009

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MITOCHONDRIAL DYSFUNCTION

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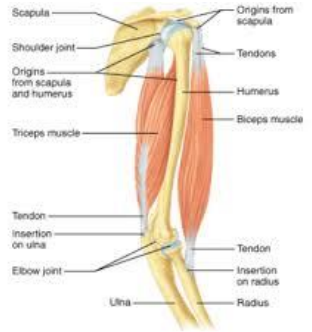
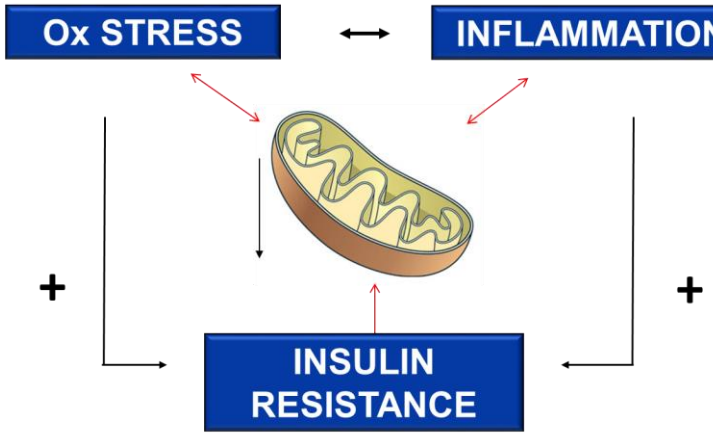


Potential CONSEQUENCES



↓ Fat-Glucose utilization

↓ Energy expenditure

Tissue Fat ACCUMULATION

Insulin Resistance

Outline

- Energy intake (Appetite regulation)
- Energy expenditure (Intermediate metabolism)
- Clinical impact of obesity
- Malnutrition in obesity (?)

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OBESITY per se

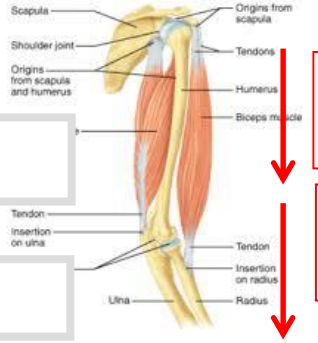
ACUTE and CHRONIC DISEASE

OX STRESS ⟷ INFLAMMATION

PROTEIN DEGRADATION

DIET

SEDENTARY LIFESTYLE



MASS

FUNCTION

+

INSULIN RESISTANCE

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THERAPEUTIC WEIGHT LOSS BARIATRIC SURGERY

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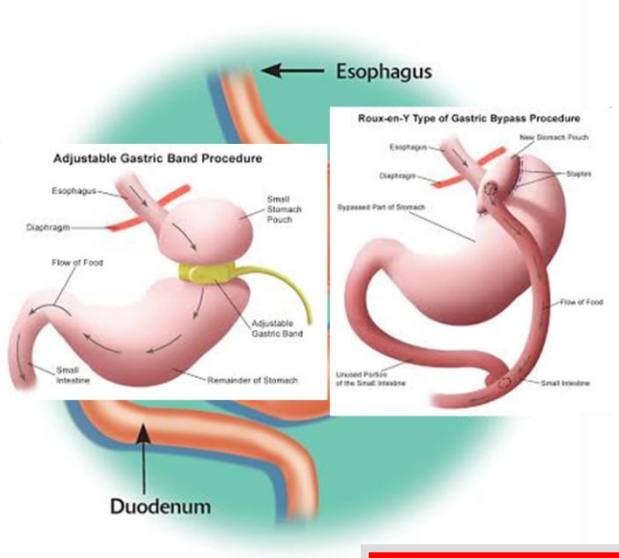
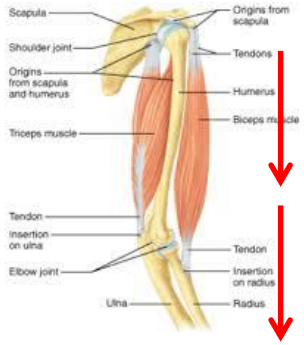


PROTEIN



MASS

FUNCTION

BEYOND BMI

ONE OBESITY SIZE does NOT FIT ALL!

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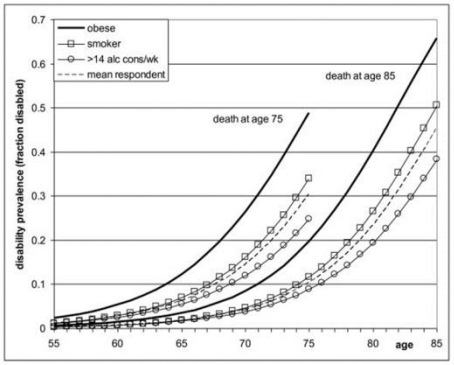
Body Composition

(FAT/MUSCLE)

- SARCOPENIC OBESITY
  - ↑ FRAILTY-MORBIDITY
  - ↑ MORTALITY

Obesity leads to higher chance of disability than other major disease risk factors



Klijs et al, BMC Pub Health 2011

ESPEN endorsed recommendation

Sarcopenic obesity: Time to meet the challenge

Rocco Barazzoni[a, b, *], Stephan C. Bischoff[c], Yves Boirie[d, e], Luca Busetto[f, g], Tommy Cederholm[h], Dror Dicker[i], Hermann Toplak[j], Andre Van Gossum[k], Volkan Yumuk[l], Roberto Vettor[f, g]

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Obese AND Malnourished

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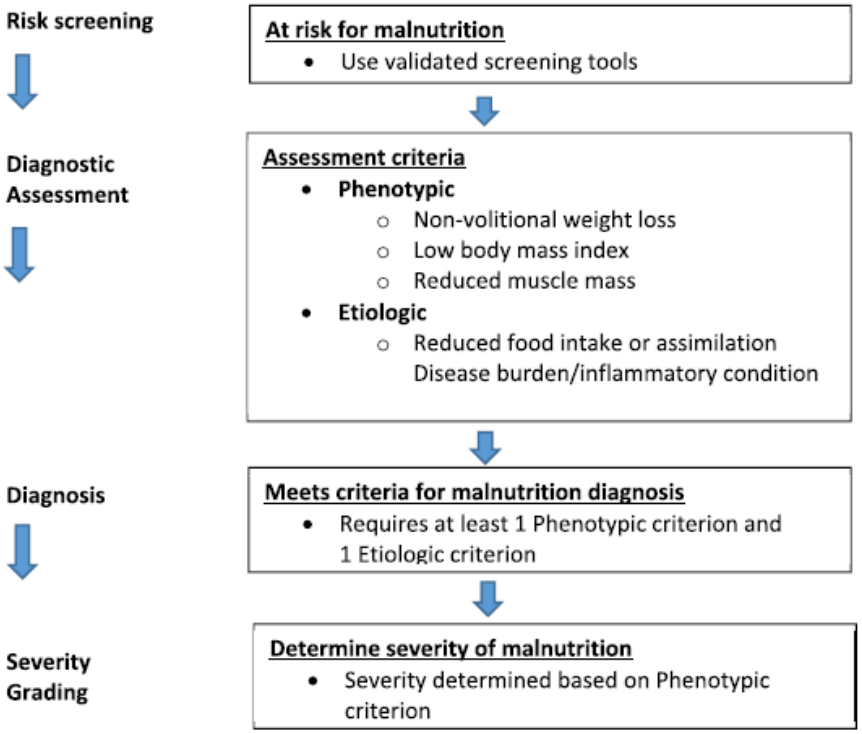
GLIM criteria for the diagnosis of malnutrition – A consensus report from the global clinical nutrition community☆

T. Cederholm [a, b, *, 1], G.L. Jensen [c, 1], M.I.T.D. Correia [d], M.C. Gonzalez [e], R. Fukushima [f], T. Higashiguchi [g], G. Baptista [h], R. Barazzoni [i], R. Blaauw [j], A. Coats [k, l], A. Crivelli [m], D.C. Evans [n], L. Gramlich [o], V. Fuchs-Tarlovsky [p], H. Keller [q], L. Llido [r], A. Malone [s, t], K.M. Mogensen [u], J.E. Morley [v], M. Muscaritoli [w], I. Nyulasi [x], M. Pirlich [y], V. Pisprasert [z], M.A.E. de van der Schueren [aa, ab], S. Siltharm [ac], P. Singer [ad, ae], K. Tappenden [af], N. Velasco [ag], D. Waitzberg [ah], P. Yamwong [ai], J. Yu [aj], A. Van Gossum [ak, 2], C. Compher [al, 2], GLIM Core Leadership Committee, GLIM Working Group[3]



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ESPEN guideline on clinical nutrition in the intensive care unit

Pierre Singer [a,*], Annika Reintam Blaser [b,c], Mette M. Berger [d], Waleed Alhazzani [e], Philip C. Calder [f], Michael P. Casaer [g], Michael Hiesmayr [h], Konstantin Mayer [i], Juan Carlos Montejo [j], Claude Pichard [k], Jean-Charles Preiser [l], Arthur R.H. van Zanten [m], Simon Oczkowski [e], Wojciech Szczeklik [n], Stephan C. Bischoff [o]

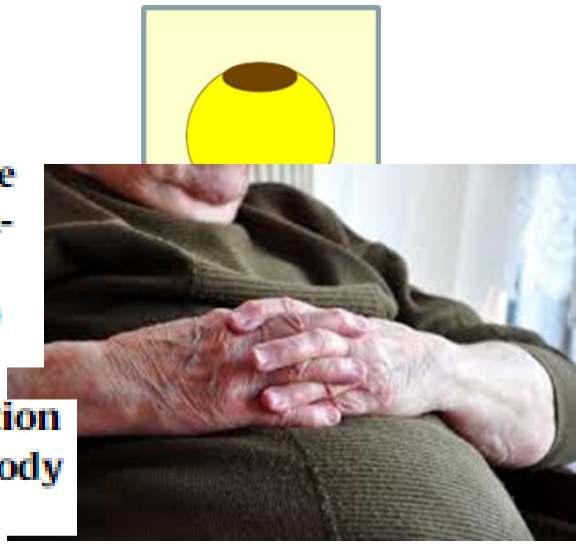
Clin Nutr 2018

Recommendations 51-52

An iso-caloric high protein diet can be administered to obese patients, preferentially guided by indirect calorimetry measurements and urinary nitrogen losses.

Grade of recommendation: 0 – consensus (89% agreement)

If urinary nitrogen losses or lean body mass determination are not available, protein intake can be 1.3 g/kg "adjusted body weight"/d.



PROTEIN: 1.3 g/kg ABW
(=1.6-1.8 g/kg IBW)

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Conclusions

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- Aetiology and pathogenesis of obesity involve lifestyle changes that however appear to be only partly under volitional control
- Their negative impact on body fat accumulation is moreover largely influenced by genetic, epigenetic and metabolic factors
- Clinical complications of obesity potentially involve all organs and systems with a relevant role for insulin resistance and its cardio-metabolic impact
- Clinical complications of obesity include malnutrition with a major role for skeletal muscle loss of mass and function (sarcopenic obesity)