

Insulino-resistenza: serve ancora misurarla? E come?

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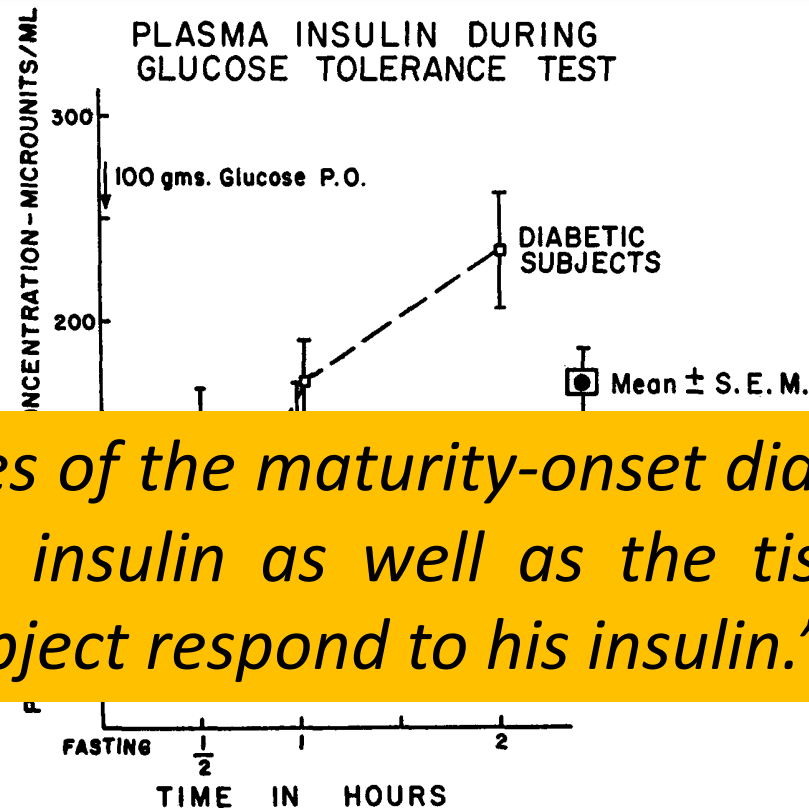


L'era dell'insulino-resistenza

Plasma Insulin Concentrations in Nondiabetic and Early Diabetic Subjects

Determinations by a New Sensitive Immuno-assay Technic

Rosalyn S. Yalow, Ph.D., and Solomon A. Berson, M.D., New York City



“that the tissues of the maturity-onset diabetic do not respond to his insulin as well as the tissues of the nondiabetic subject respond to his insulin.”



I padri dell'insulino-resistenza

Variations in Insulin-Stimulated Glucose Uptake in Healthy Individuals with Normal Glucose Tolerance*

CLARIE HOLLENBECK AND GERALD M. REAVEN

Hollembeck C, Reaven GM J Clin Endocrinol Metab 1987



RALPH A. DEFRONZO, MD

Lilly Lecture 1987

The Triumvirate: β -Cell, Muscle, Liver A Collusion Responsible for NIDDM

RALPH A. DEFRONZO

DeFronzo RA. Diabetes 1988

A Muscle-Specific Insulin Receptor Knockout Exhibits Features of the Metabolic Syndrome of NIDDM without Altering Glucose Tolerance

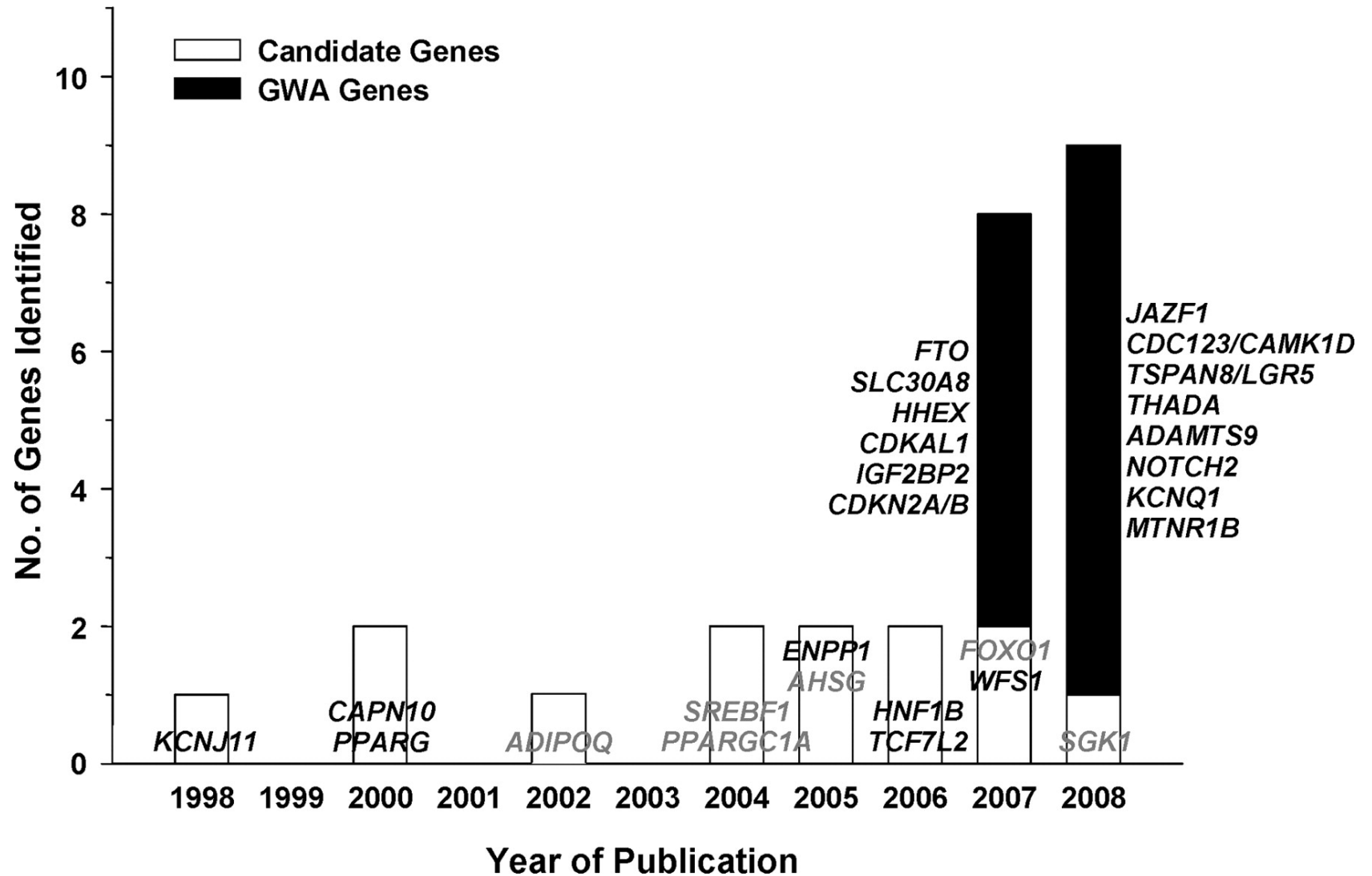
Jens C. Brüning,*§# M. Dodson Michael,*#
Jonathon N. Winnay,*# Tatsuya Hayashi,*
Dieter Hörsch,*|| Domenico Accili,†
Laurie J. Goodyear,* and C. Ronald Kahn*‡

Brüning JC, [...], Kahn CR. Molecular Cell 1998



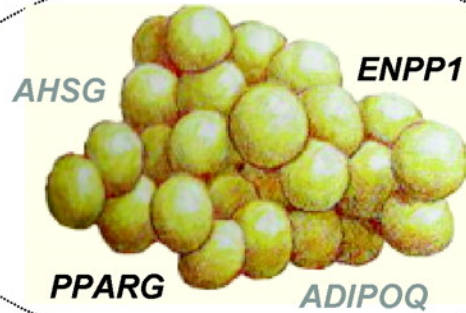
C. Ronald Kahn

GWAS

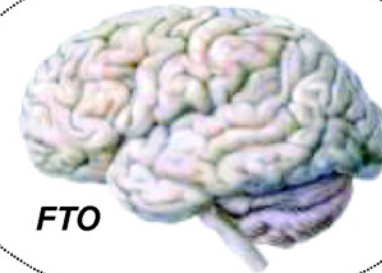


GWAS

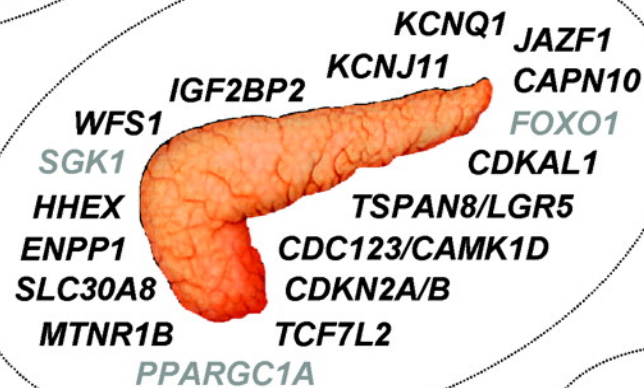
Adipose tissue



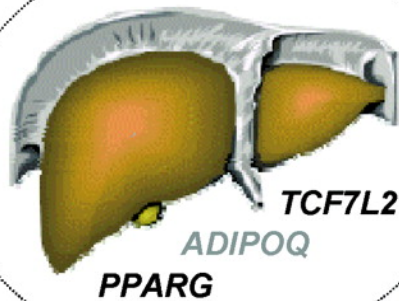
Brain



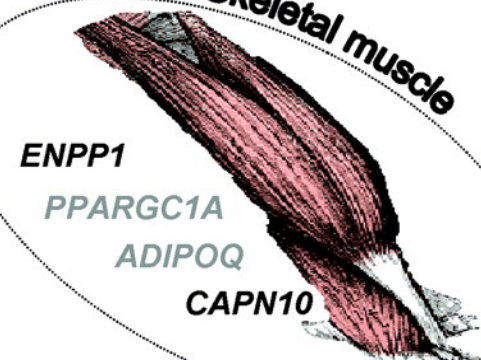
Pancreas



Liver

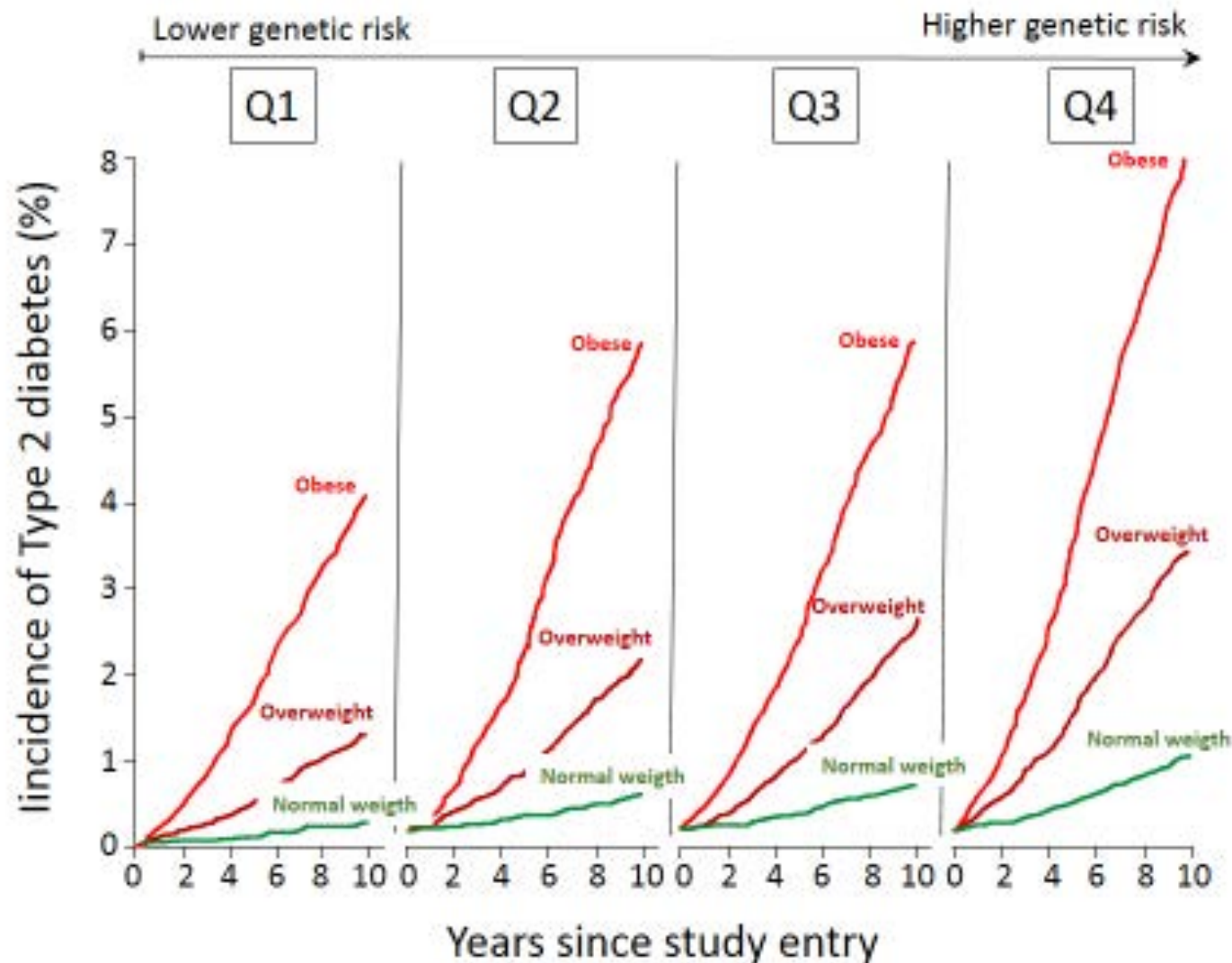


Skeletal muscle



A single puzzle piece with a blue outline, featuring a tab on the right side and a blank on the bottom side. It is positioned on a light gray background.

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dall'ambiente

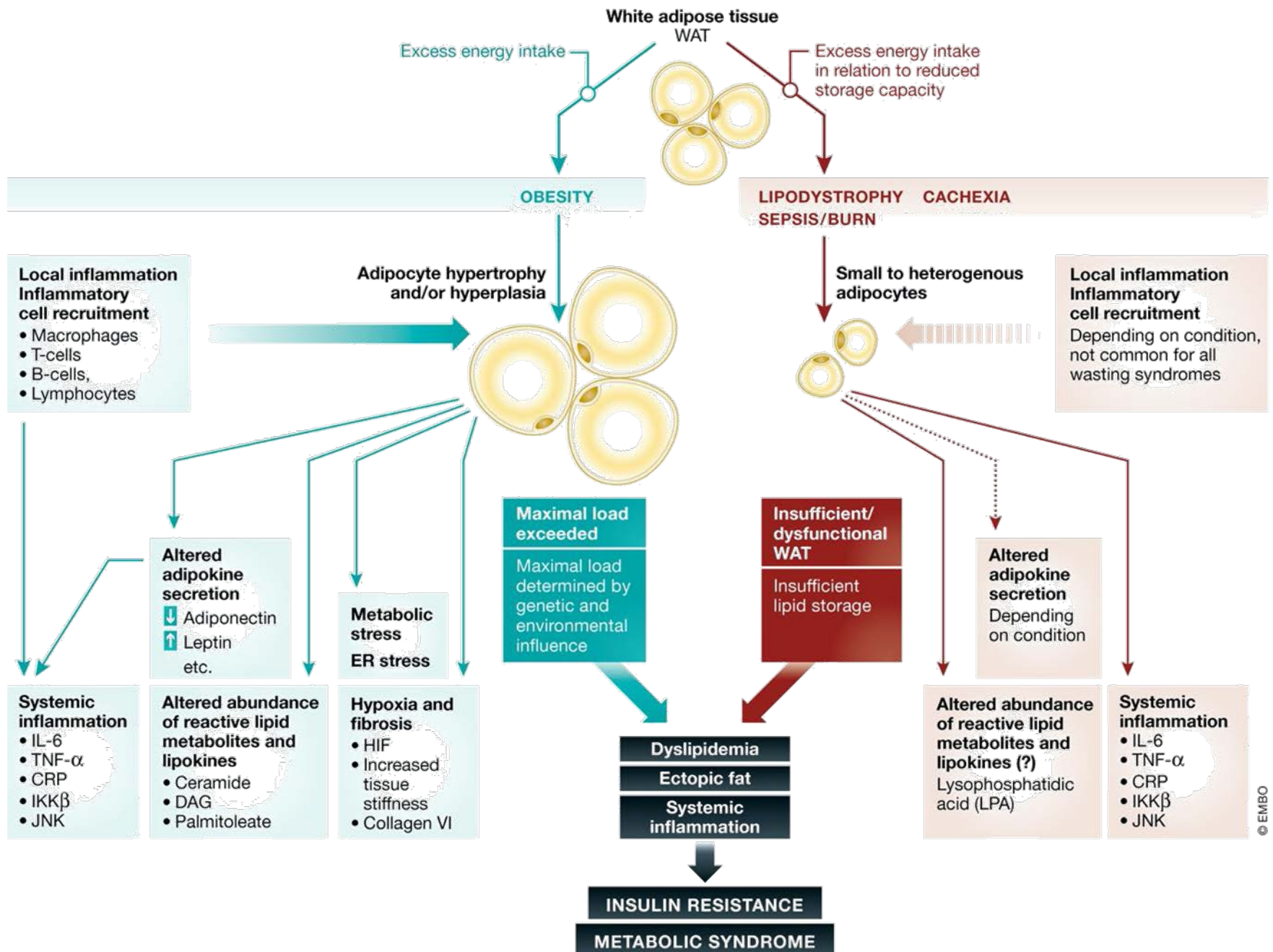


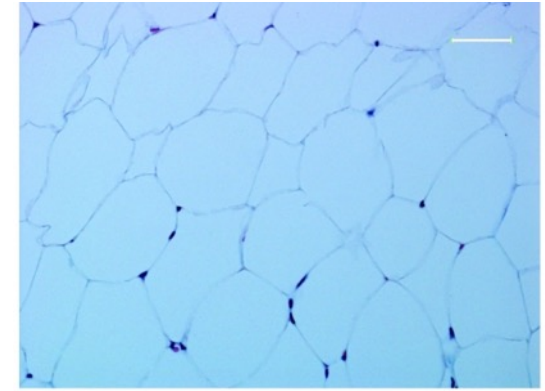
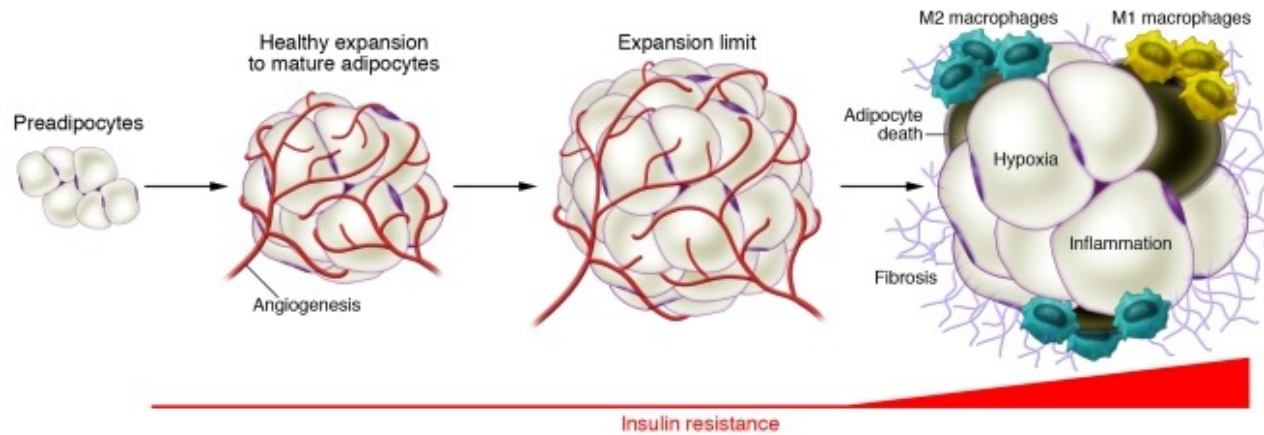
EPIC InterAct Case-Cohort Study (12,403 incident type 2 diabetes cases from a cohort of 340,234 European participants with 3.99 million person-years of follow-up).

Lezioni dalle sindromi lipodistrofiche

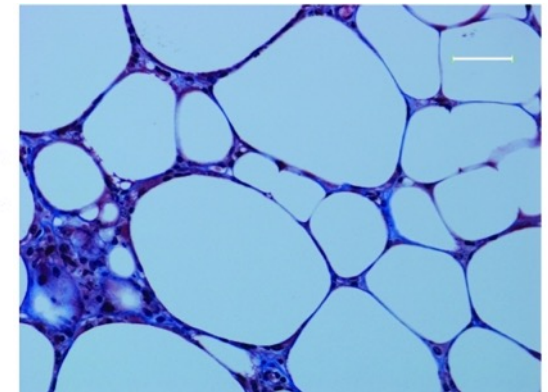
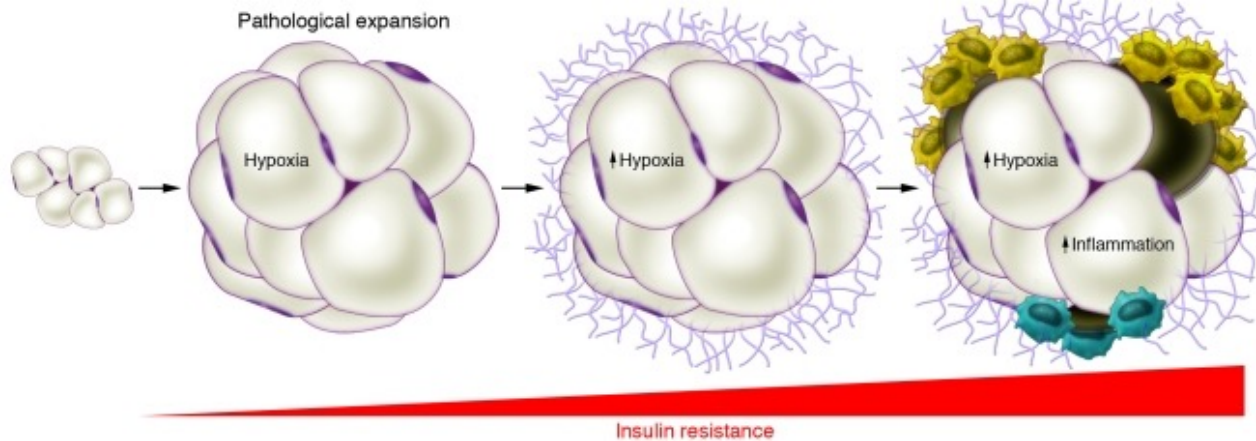
Subtype	Gene	Molecular Basis	Prevalence
CGL1	AGPAT2	AGPAT enzymes play a key role in biosynthesis of triglycerides and phospholipids in various organs. AGPAT isoform 2 is highly expressed in the adipose tissue.	Most common subtype ^{7,8,10}
CGL2	BSCL2	Seipin, encoded by <i>BSCL2</i> , plays a key role in fusion of small lipid droplets in the adipocytes and in adipocyte differentiation.	Second most common subtype ⁷⁻⁹
CGL3	CAV1	Caveolin 1 is an integral component of caveolae, which are present on adipocyte membranes. Caveolae translocate fatty acids and other lipids to lipid droplets.	Only one patient reported ¹¹
CGL4	PTRF	PTRF (also known as cavin-1) is involved in biogenesis of caveolae and regulates expression of caveolins 1 and 3.	About 20 patients reported ^{12,43,44}
FPLD1 (Kobberling-type)		Molecular basis unknown	Rare ¹⁶
FPLD2 (Dunnigan-type)		Missense mutations in <i>LMNA</i>	Most common subtype; more than 500 patients reported ¹⁷⁻¹⁹
FPLD3		Heterozygous mutations in <i>PPARG</i>	Second most common subtype; about 30-50 patients reported ^{20,21}
FPLD4		Heterozygous mutations in <i>PLIN1</i>	Reported in three families ²²
FPLD5		Homozygous nonsense mutation in <i>CIDEA</i> (autosomal recessive)	One patient reported ²³
FPLD6		Homozygous mutation in <i>LIPE</i> (autosomal recessive)	Six patients reported ^{24,25}
FPLD7		Heterozygous mutation in <i>ADRA2A</i>	Reported in one family ²⁷
AKT2-linked lipodystrophy		Heterozygous mutation in <i>AKT2</i>	Reported in one family ²⁶

Lipodystrophy Type	Gene	Molecular Basis	Clinical Features
MAD type A	<i>LMNA</i>	Mutations may disrupt nuclear function resulting in premature cell death in many tissues.	Mandibular and clavicular hypoplasia, acro-osteolysis. Partial lipodystrophy affecting the extremities and trunk. ^{45,46}
MAD type B	<i>ZMPSTE24</i>	Mutations result in accumulation of farnesylated prelamin A that can disrupt nuclear function in several tissues.	Mandibular and clavicular hypoplasia, acro-osteolysis. More generalized loss of fat, premature renal failure, progeroid features. ⁴⁷
JMP/CANDLE	<i>PSMB8</i>	<i>PSMB8</i> encodes subunit of immunoproteasomes that degrade abnormal/excess proteins in cells.	Joint contractures, muscle atrophy, microcytic anemia and panniculitis-induced lipodystrophy. Recurrent fevers, annular erythematous skin lesions, violaceous eyelid swelling, partial lipodystrophy. ^{48,49}
SHORT syndrome	<i>PIK3R1</i>	<i>PIK3R1</i> plays a role in metabolic actions of insulin, mutations associated with insulin resistance.	Variable loss of subcutaneous fat, short stature, hyperextensibility, ocular depression, teething delay. ⁵⁰
MDP syndrome	<i>POLD1</i>	Critical for DNA replication and repair.	Mandibular hypoplasia, deafness, and progeroid features. ^{51,52}
Neonatal progeroid syndrome, type A	<i>FBN1</i>	Fibrillin 1	Generalized loss of body fat and muscle mass, and progeroid appearance at birth. Marfanoid habitus. ^{53,54}
Neonatal progeroid syndrome, type B	<i>CAV1</i>	Caveolin 1, present on adipocyte membranes, binds fatty acids and translocates them to lipid droplets.	Generalized loss of body fat and muscle mass, and progeroid appearance at birth. ⁵⁵
Atypical progeroid syndrome	<i>LMNA</i>	Different heterozygous, mostly de novo mutations cause nuclear dysfunction.	Partial or generalized loss of subcutaneous fat, progeroid features. ⁵⁶
Hutchinson-Gilford progeria	<i>LMNA</i>	Specific de novo mutations induce abnormal splicing and accumulation of truncated farnesylated prelamin A.	Generalized loss of subcutaneous fat, progeroid features. ⁵⁷

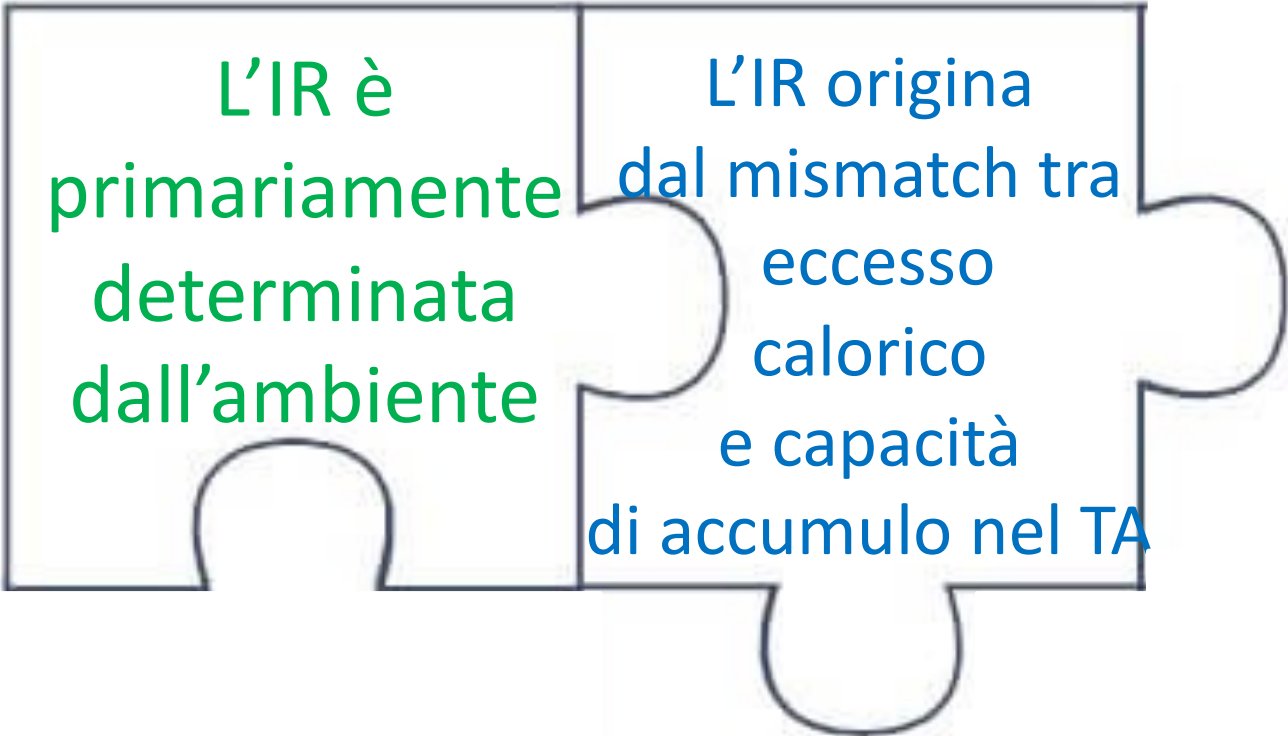




- Reclutamento di precursori adipocitari (piccoli adipociti)
- Reclutamento in appropriate proporzioni di cellule della FVS
- Adeguata vascolarizzazione
- Minima fibrosi
- Minima infiammazione



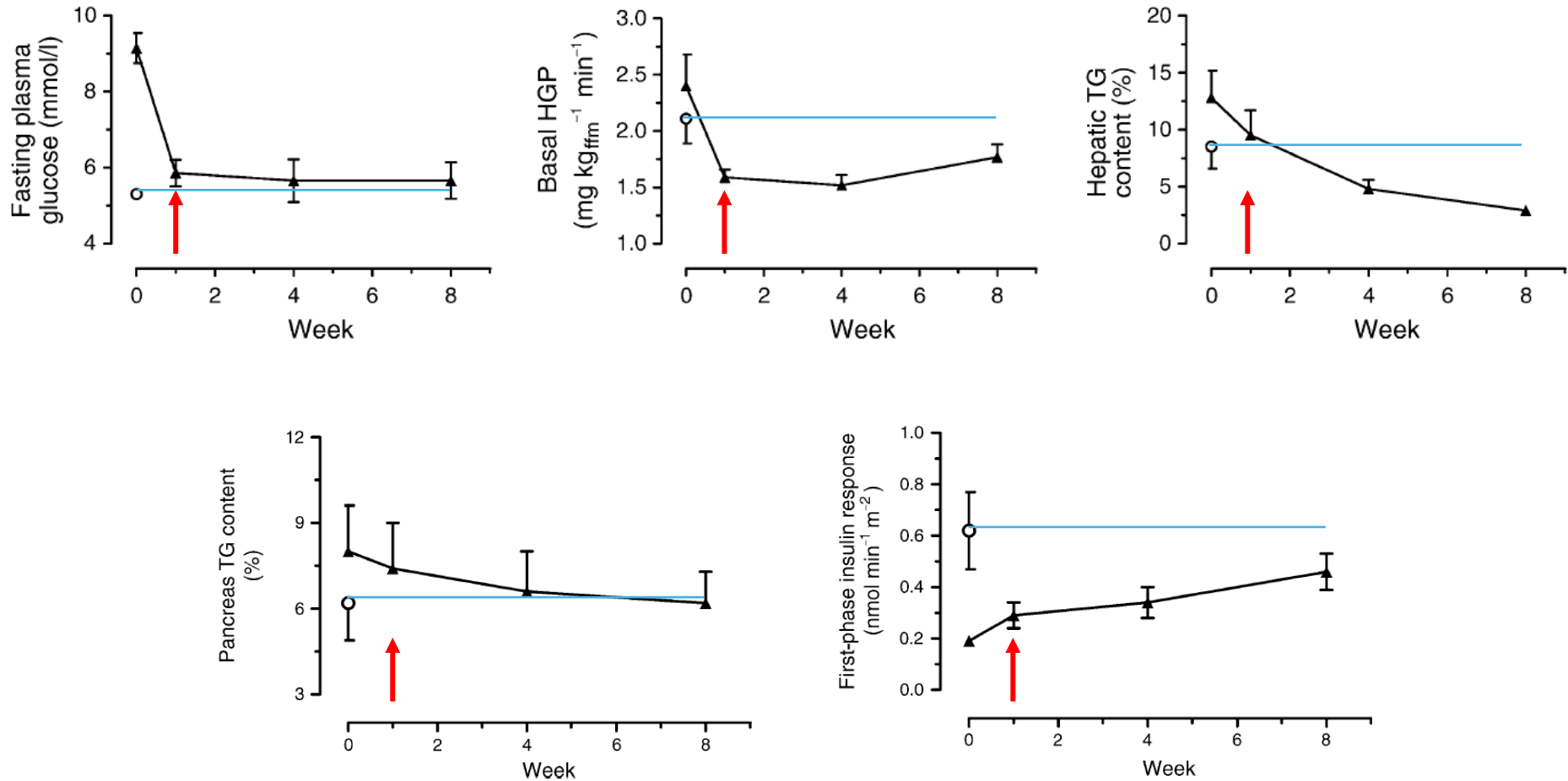
Characteristics	Obesity (with Metabolic Syndrome)	Lipodystrophies	Insulin receptoropathy
BMI	↑	↓	↔
Body fat %	↑	↓↓↓	↔
Waist (cm)	↑	↔ ↓	↔
Hip (cm)	Relative ↓	↓↓	↔
Waist/hip ratio	↑↑	↑↑	↔
Insulin resistance	↑	↑↑	↑↑↑
Triglycerides	↑	↑↑	↔
HDL cholesterol	↓	↓	↔
Leptin	↑↑	↓↓↓/↓	↔
NAFLD	↑	↑↑	Absent
PCOS	↑	↑↑	↑↑
Atherosclerosis	↑	↑↑	Unknown



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La riduzione dell'intake calorico è in grado di ripristinare l'insulino-sensibilità epatica



Subjects: 11 individuals with type 2 diabetes (age 35–65 years, HbA1c 6.5–9.0% [48–75 mmol/mol], diabetes duration <4 years, stable BMI 25–45 kg/m²) and 9 controls. **Intervention:** liquid diet (formula 600 kcal/day) for 8 weeks.

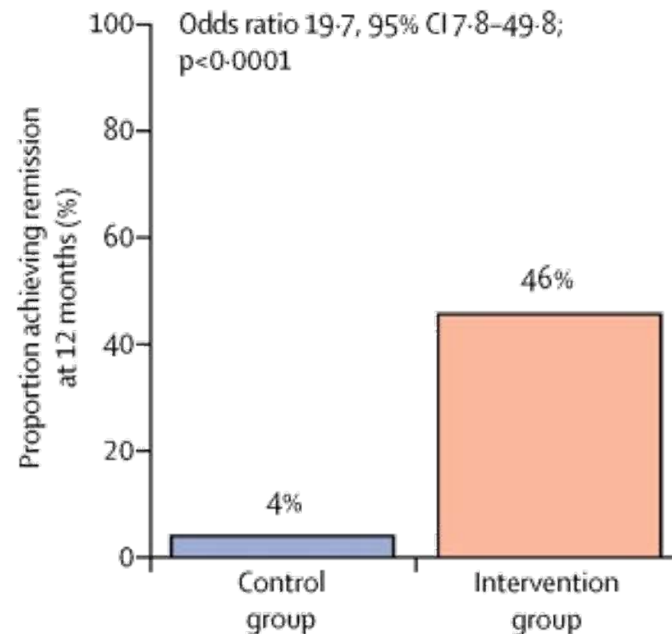
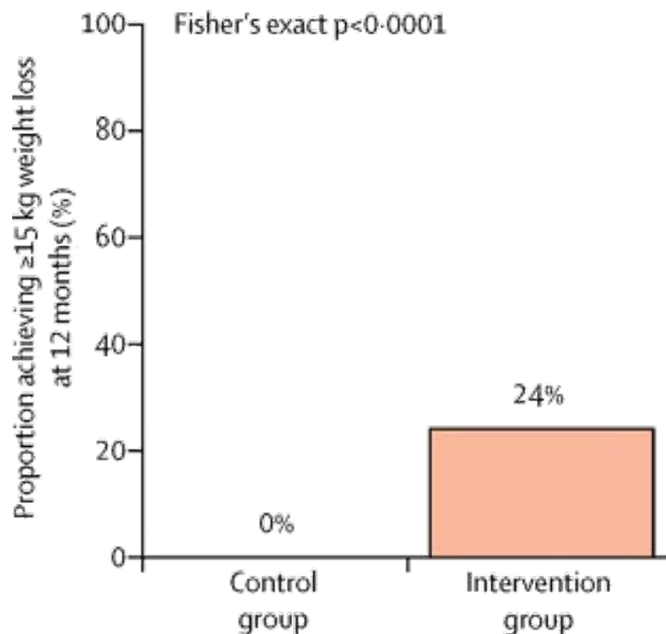
La gestione intensiva del peso può portare a remissione del diabete tipo 2

Diabetes Remission Clinical Trial (DiRECT)

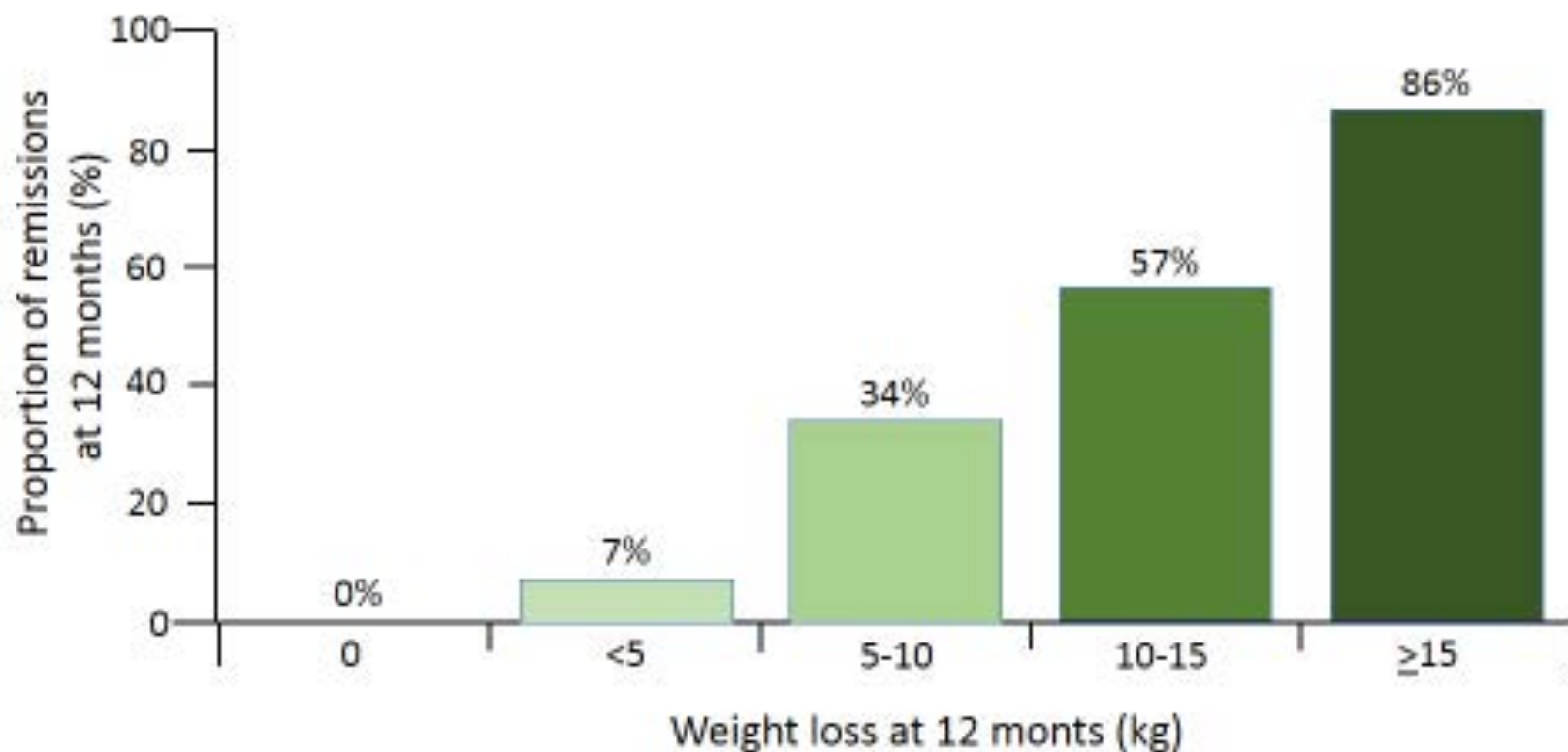
Soggetti: 298 pazienti con DM2 da meno di 6 anni, non trattati con insulina e BMI 27-45 Kg/m².

Intervento: sospensione dei farmaci antidiabetici e antipertensivi, la sostituzione totale della dieta (dieta liquida 825-853 kcal/giorno per 16 settimane), reintroduzione graduale del cibo (2-8 settimane) e supporto strutturato per il mantenimento a lungo termine della perdita di peso.

Outcome primario: perdita di peso ≥ 15 kg e la remissione del diabete (HbA1c < 6,5% dopo almeno 2 mesi senza farmaci antidiabetici).



La gestione intensiva del peso può portare a remissione del diabete tipo 2



I benefici metabolici della chirurgia bariatrica e della dieta sono simili e dipendenti dalla perdita di peso

Table 3. Multiorgan Insulin Sensitivity and Beta-cell Function before and after Weight Loss.*

	Diet Group			Surgery Group			Difference between Groups (95% CI)
	Before	After	Difference (95% CI)	Before	After	Difference (95% CI)	
Glucose RA (Stage 1) — $\mu\text{mol/kg FFM/min}$	17.07 $\pm$ 2.36	10.03 $\pm$ 3.08	−7.04 (−9.33 to −4.74)	17.44 $\pm$ 4.99	10.42 $\pm$ 4.30	−7.02 (−10.84 to −3.21)	0.25 (−3.08 to 3.59)
Glucose RA (Stage 2) — $\mu\text{mol/kg FFM/min}$	8.84 $\pm$ 3.91	3.45 $\pm$ 2.74	−5.39 (−8.34 to −2.44)	8.84 $\pm$ 4.08	3.47 $\pm$ 0.77	−5.37 (−8.33 to −2.41)	0.02 (−2.00 to 2.04)
Glucose RD (Stage 3) — $\mu\text{mol/kg FFM/min}$	30.5 $\pm$ 15.9	61.6 $\pm$ 13.0	31.0 (22.5 to 39.6)	29.4 $\pm$ 12.6	54.5 $\pm$ 10.4	25.1 (16.4 to 33.8)	−6.5 (−15.7 to 2.7)
Palmitate RA (Stage 1) — $\mu\text{mol/kg FFM/min}$	1.78 $\pm$ 0.55	0.81 $\pm$ 0.41	−0.97 (−1.30 to −0.64)	2.24 $\pm$ 1.13	1.17 $\pm$ 0.74	−1.07 (−2.11 to −0.03)	0.33 (−0.26 to 0.91)
Palmitate RA (Stage 2) — $\mu\text{mol/kg FFM/min}$	1.14 $\pm$ 0.76	0.65 $\pm$ 0.40	−0.49 (−1.06 to 0.08)	1.41 $\pm$ 0.75	0.64 $\pm$ 0.31	−0.77 (−1.23 to −0.31)	−0.04 (−0.39 to 0.31)
Beta-cell function†	0.93 $\pm$ 0.94	2.76 $\pm$ 1.20	1.83 (1.22 to 2.44)	0.99 $\pm$ 0.82	2.10 $\pm$ 1.24	1.11 (0.08 to 2.15)	−0.71 (−1.75 to 0.34)

OUTCOME PRIMARIO: variazione della sensibilità insulinica epatica

OUTCOME SECONDARI: variazione della sensibilità all'insulina nei tessuti muscolare e adiposo; funzione delle cellule beta; risposta metabolica all'ingestione di pasti misti; concentrazione nelle 24 ore del glucosio e acidi grassi liberi, profili di insulina e composizione corporea.

Come misurare l'insulino-resistenza?

Table 1. Methods for Assessing Insulin Sensitivity and Resistance In Humans

Method	Measure of Insulin sensitivity
Direct Measures	
Hyperinsulinemic Euglycemic Glucose Clamp	Average glucose infusion rate (GIR) = glucose disposal rate (M). $SI_{Clamp} = M/(G \times \Delta I)$, where M is normalized for G (steady-state blood glucose concentration) and ΔI (difference between fasting and steady-state plasma insulin concentrations)
Insulin-suppression Test (IST)	Steady-state plasma glucose (SSPG) concentrations during constant infusions of insulin and glucose with suppressed endogenous insulin secretion
Indirect Measures	
Minimal Model Analysis of Frequently Sampled Intravenous Glucose Tolerance Test (FSIVGTT)	Minimal model uniquely identifies model parameters that determine a best fit to glucose disappearance during the modified FSIVGTT. S_I : fractional glucose disappearance per insulin concentration unit; S_G (glucose effectiveness): ability of glucose <i>per se</i> to promote its own disposal and inhibit HGP in the absence of an incremental insulin effect (i.e., when insulin is at basal levels).

Method	Formula	Normal level	Advantage	Disadvantage	Correlation coefficients with HEC
Belfiore index	$2/ISI_{\text{Belfiore}} = \frac{G_s}{G_N} \times \frac{I_s}{I_N} + 1$	Values above 1.27 indicate pathological IR	Showed normal value for basal glucose and insulin concentrations and for mean nor-mal value for glucose and insulin areas during OGTT	Multiple blood sampling	0.65; $P < 0.01$ in subjects with normal glucose tolerance, 0.54; $P < 0.01$ in subjects with impaired glucose tolerance, and 0.48; $P < 0.01$ in subjects with diabetes type 2
Avignon index	$Sib = 10^8 / \left(\frac{I_0 \text{ (mU/L)} \times G_0}{\text{(mmol/L)} \times VD} \right)$ $Si2h = 10^8 / \left(\frac{I_{120} \text{ (mU/L)} \times G_{120}}{\text{(mmol/L)} \times VD} \right)$	-	Determines glucose tolerance and insulin sensitivity in single test	Its correlation is very weak in diabetic patients	Normal glucose tolerance (0.89; $P \leq 0.0001$), with impaired glucose tolerance (0.96; $P \leq 0.0001$), and in patients with diabetes mellitus type 2 (0.69-0.83; $P \leq 0.05$)
Stumvoll index	$0.156 - 0.0000459 \times I_{120} \text{ (pmol/L)}$ $- 0.000321 \times I_0 \text{ (pmol/L)}$ $- 0.00541 \times G_{120} \text{ (mmol/L)}$	-	Utilizes demographic data like age, sex and BMI along with plasma glucose and insulin to predict insulin sensitivity	Very robust and weekly correlate in diabetic patients	Correlation coefficients with HEC were in the range between 0.62 and 0.79 ($P < 0.001$)
Gutt index	$75,000 + (G_0 - G_{120}) \text{ (mg/dl)}$ $\times 0.19 \times BW / 120 \times G_{\text{mean}}$ $(0, 120) \text{ (mmol/L)} \times \text{Log}$ $[I_{\text{mean}}(0, 120)] \text{ (mU/L)}$	<45 predict IR	Good to predict onset of type 2 diabetes	Suitable for epidemiological studies	Correlation coefficients with HEC 0.63; $P < 0.001$

HOMA-IR	$(I_0 \times G_0) / 22.5$	<2.5	Simple, minimally invasive, predicts fasting steady-state G and I levels	Insulin sensitivity in subjects treated with insulin needs further validation	Normal glucose tolerance (0.65; $P < 0.0001$), impaired glucose tolerance (0.56; $P < 0.0001$) and with type 2 diabetes (0.51; $P < 0.0001$)
QUICKI	$1 / \left[\log(I_{\mu\text{U/mL}}) + \log(G_{\text{mg/dl}}) \right]$	0.382±0.007 for nonobese, 0.331±0.010 for obese and 0.304±0.007 for diabetic individuals	Consistent, precise index of insulin sensitivity, minimally invasive	Normal range to be established for each laboratory due to significant inter laboratory variations in insulin assay	Correlation coefficient 0.78; $P < 2 \times 10^{-12}$
Matsuda index	$10,000 / \sqrt{(\text{fasting G} \times \text{fasting I}) (\text{mean G} \times \text{mean I})}$	<4.3 predict IR	Represents both hepatic and peripheral tissue sensitivity to insulin	Its correlation is very weak in diabetic patients	0.73 ($P < 0.0001$) in subjects with normal glucose tolerance, 0.66 ($P < 0.0001$) in subjects with impaired glucose tolerance, and 0.60 ($P < 0.0005$) in nondiabetic subjects, and in subjects with type 2 diabetes mellitus the correlation proved to be weaker 0.54 ($P < 0.0001$)

HOMA-IR

General Use of the HOMA-IR

Epidemiological studies

In individuals (to track changes longitudinally, or to indicate if insulin resistance or β cell failure predominates) → triplicate insulin samples should be used

Caveat

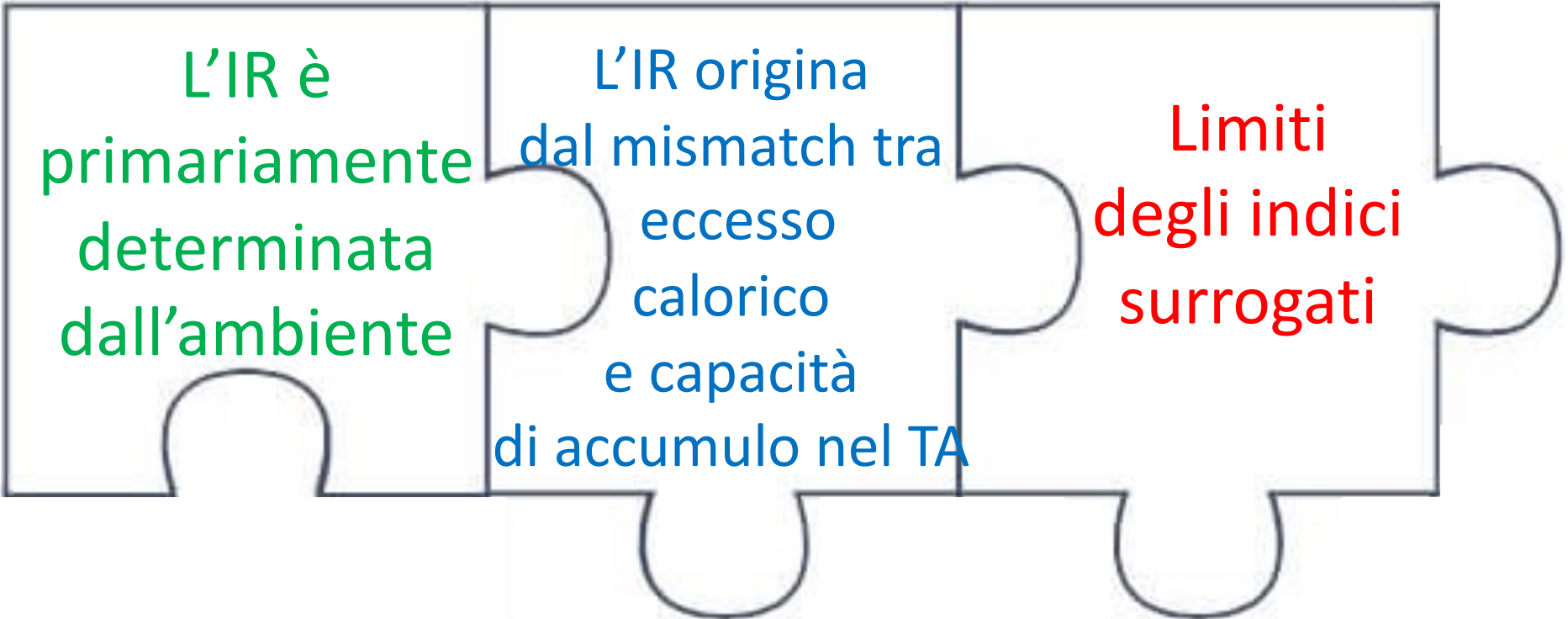
Diabetics; use in patients treated with insulin

Insulin independent mechanisms of plasma glucose regulation (e.g., glucose uptake by non-insulin sensitive vital organs and tissues, glucose-mediated suppression of glucose production and stimulation of muscle glucose uptake)

Cross-cultural comparisons

No distinction is made between hepatic insulin sensitivity and peripheral insulin sensitivity

Insulin sensitivity method	Correlation with HOMA-%S	Comments
Euglycemic clamp	$R_s = 0.88$	NGT ($n = 12$), diabetes ($n = 11$)
Euglycemic clamp	$R_s = 0.82$	NGT ($n = 62$), diabetes ($n = 53$)
Euglycemic clamp	$r = 0.73$	Diabetes ($n = 80$)
Euglycemic clamp	$r = 0.73$	Diabetes ($n = 55$)
Euglycemic clamp	$r = 0.58$	NGT ($n = 104$)
Euglycemic clamp	$r = 0.78$	Diabetes ($n = 30$)
Minimal model	$r = 0.7$	NGT ($n = 87$)
Minimal model	$r = 0.88$	NGT ($n = 7$), IGT ($n = 5$), diabetes ($n = 1$)



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Limiti
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surrogati

La misurazione dell'insulino-resistenza per la stima del rischio di malattie cardio-metaboliche

	Oms (1999)	Egir (1999)	Ncep-Atplll (2001)	Idf (2005)	Aha/Nhlbi (2005)
Definizione	Diabete,lfg, lgt oppure insulino-resistenza + due o più tra i seguenti:	Insulino-resistenza + due o più tra i seguenti:	Tre o più tra i seguenti:	Circonferenza vita: ≥ 94 cm (M) ≥ 80 cm (F) + due o più tra i seguenti:	Tre o più tra i seguenti:
Obesità	Bmi > 30 oppure rapporto vita/fianchi > 0,9 (M) >0,85 (F)	Circonferenza vita: ≥ 94 cm (M) ≥ 80 cm (F)	Circonferenza vita: ≥ 94 cm (M) ≥ 80 cm (F)		Circonferenza vita: ≥ 94 cm (M) ≥ 80 cm (F)
Glicemia		≥110 mg/dl ma <126 mg/dl	≥110 mg/dl	≥100 mg/dl	≥100 mg/dl
Pressione arteriosa	≥ 140/≥90 mmHg	≥140/ ≥90 mmHg	≥130/ ≥85 mmHg	≥130/ ≥85 mmHg	≥130/ ≥85 mmHg
Trigliceridi	≥ 150 mg/dl	≥ 175 mg/dl	≥ 150 mg/dl	≥ 150 mg/dl	≥ 150 mg/dl
Colesterolo Hdl	<35 mg/dl (M) <39 mg/dl (F)	<39 mg/dl	<40 mg/dl (M) <50 mg/dl (F)	<40 mg/dl (M) <50 mg/dl (F)	<40 mg/dl (M) <50 mg/dl (F)
M: maschi; F: femmine.					

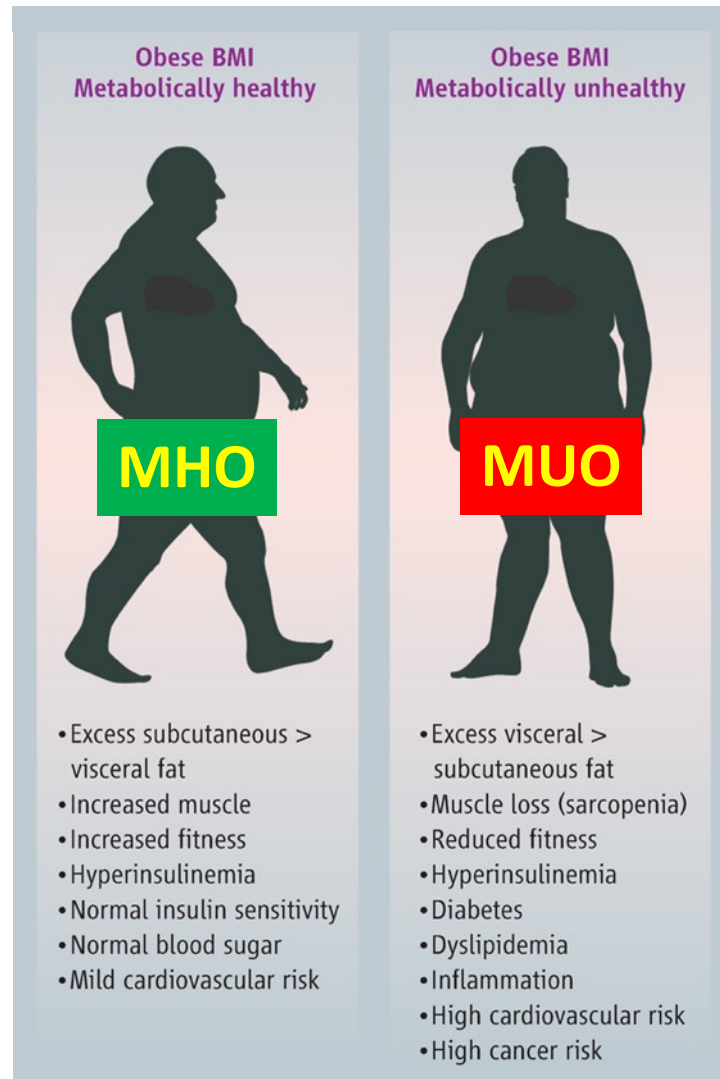
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La CFR vita è un
valido indice
surrogato di
IR sistemica

Lezioni dall'obesità metabolicamente sana (MHO)



Caratterizzazione e determinanti di MHO

Preserved insulin sensitivity

Normotension

Normal lipid profile

Normal
intrahepatic TG

BMI < 35

Women

Younger

European ancestry

Physically active

Good nutritional status

Insulin resistance

Hypertension

Dyslipidemia

Increased
intrahepatic TG

BMI ≥ 35

Men

Older

African, South American, Indian

Sedentary

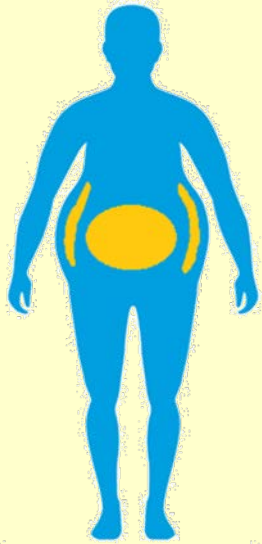
Poor nutritional status

≠

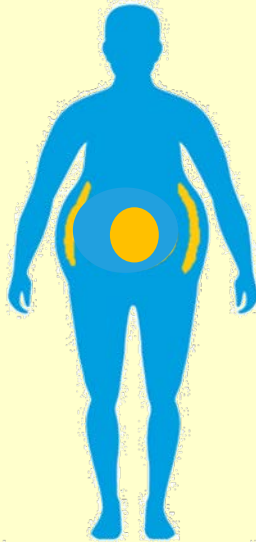


Body composition

MUO

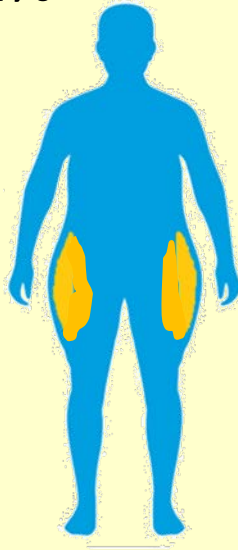
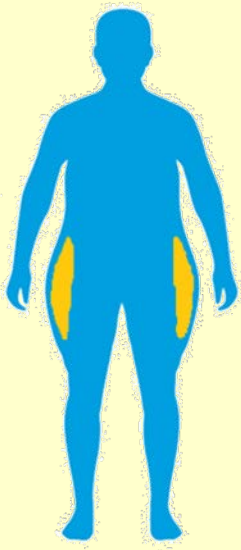


MHO



= FM%

♀



MHO



WAT expansion

↓ Cell size

Lipid metabolism

↑ Lipogenesis (SAAT)

Inflammation

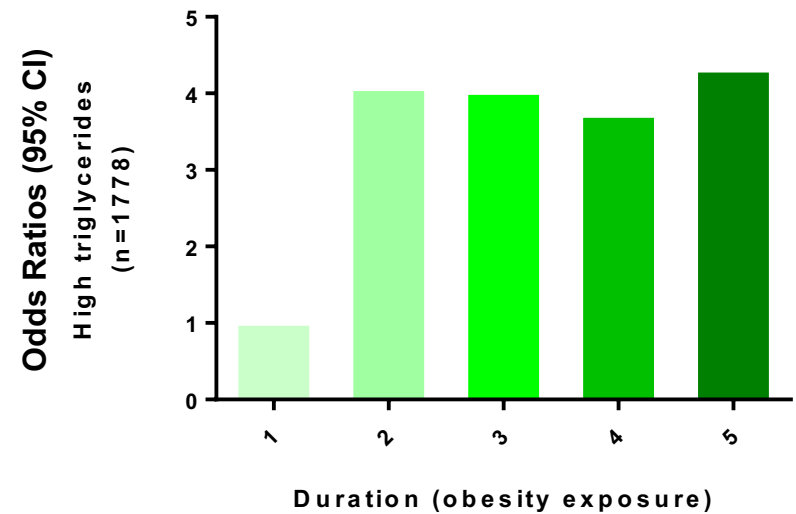
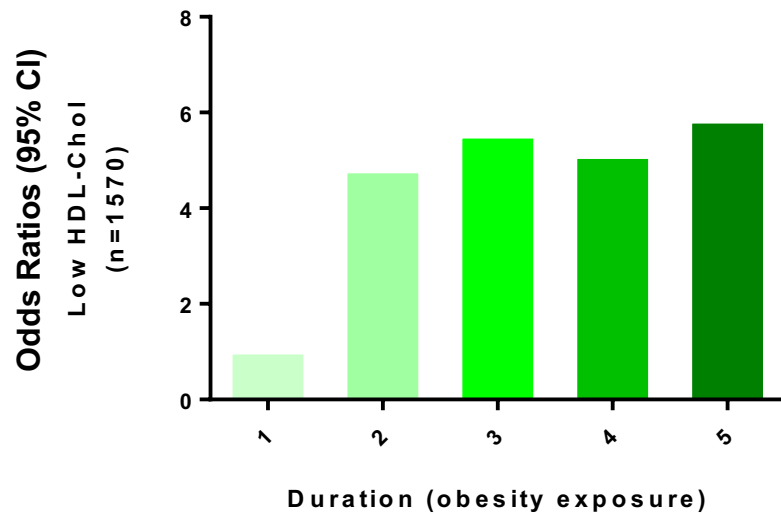
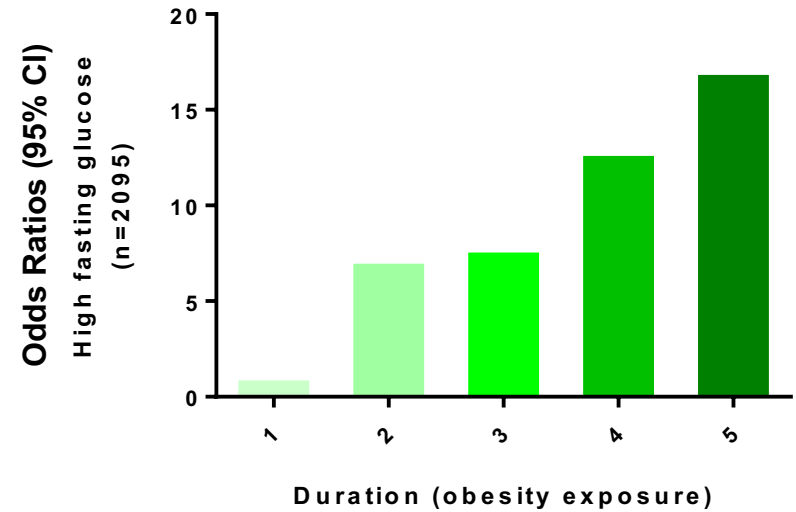
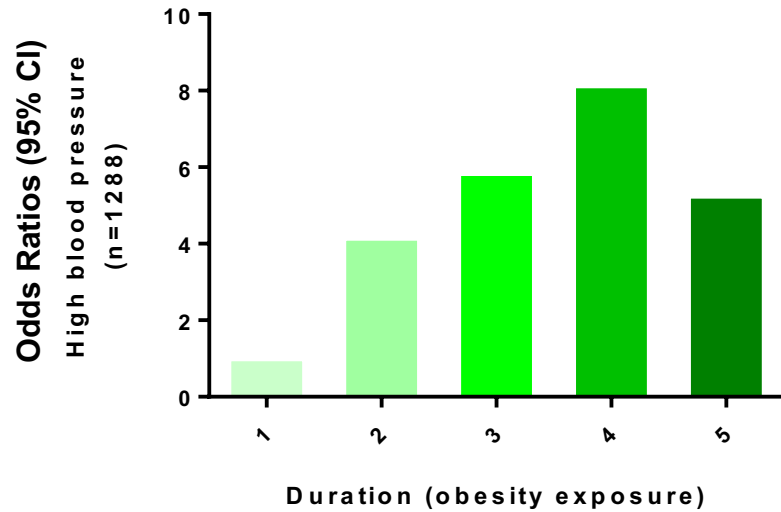
↓ Pro-inflammatory adipokine secretion pattern

↓ Inflammatory cell infiltration (SAAT, IAAT)

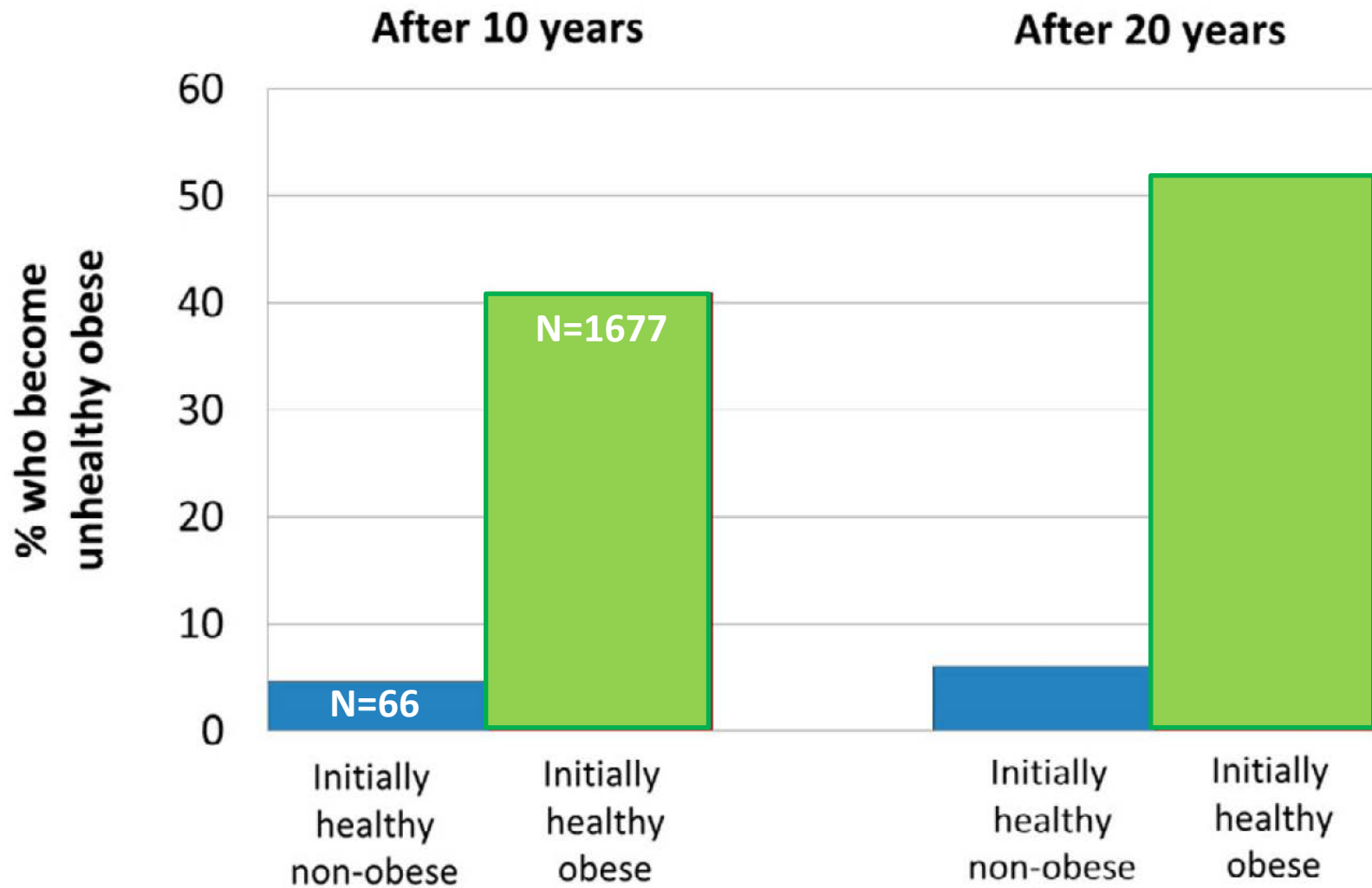
ECM remodelling

↓ Pericellular fibrosis

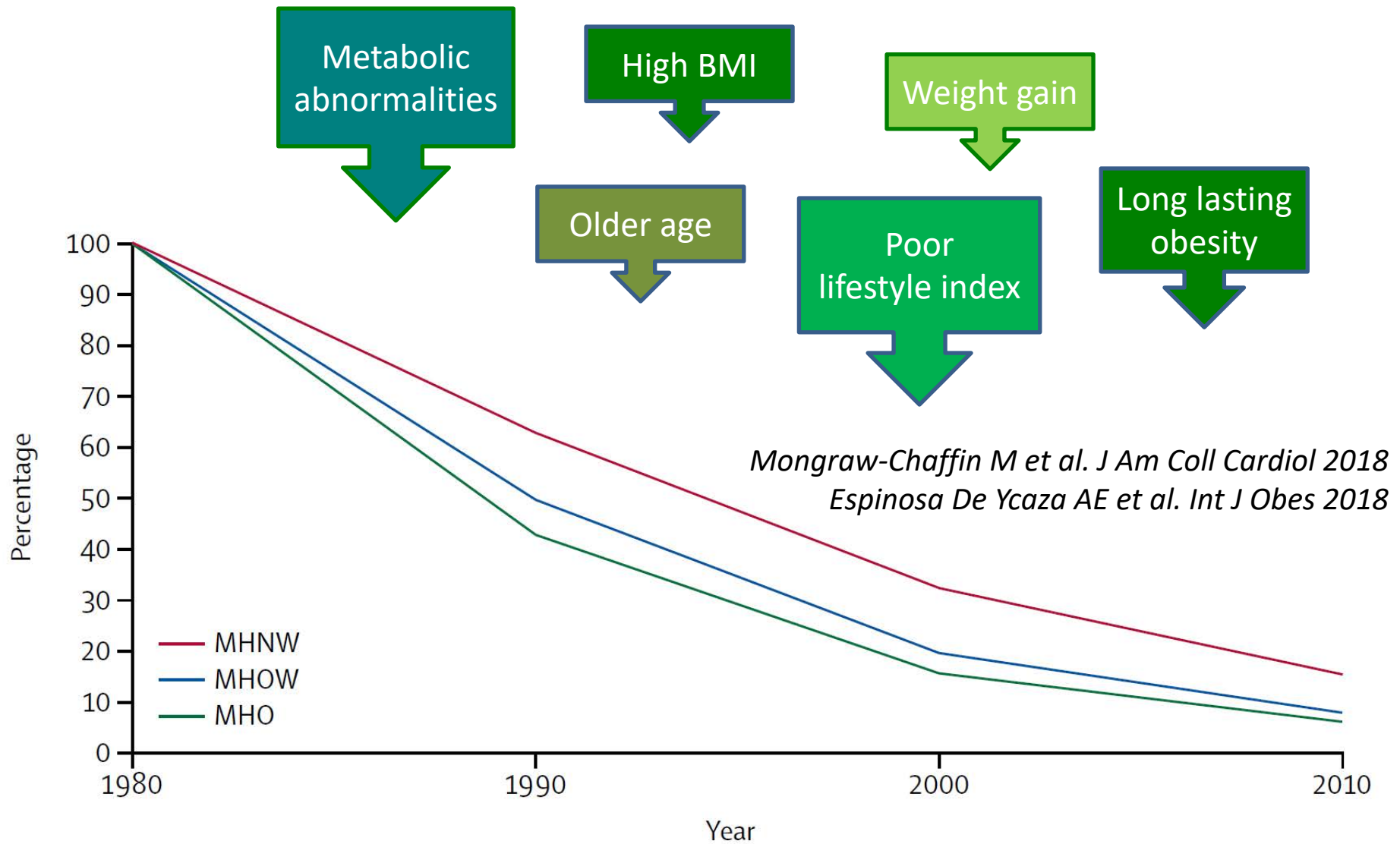
Stabilità del fenotipo MHO nel tempo



Stabilità del fenotipo MHO nel tempo

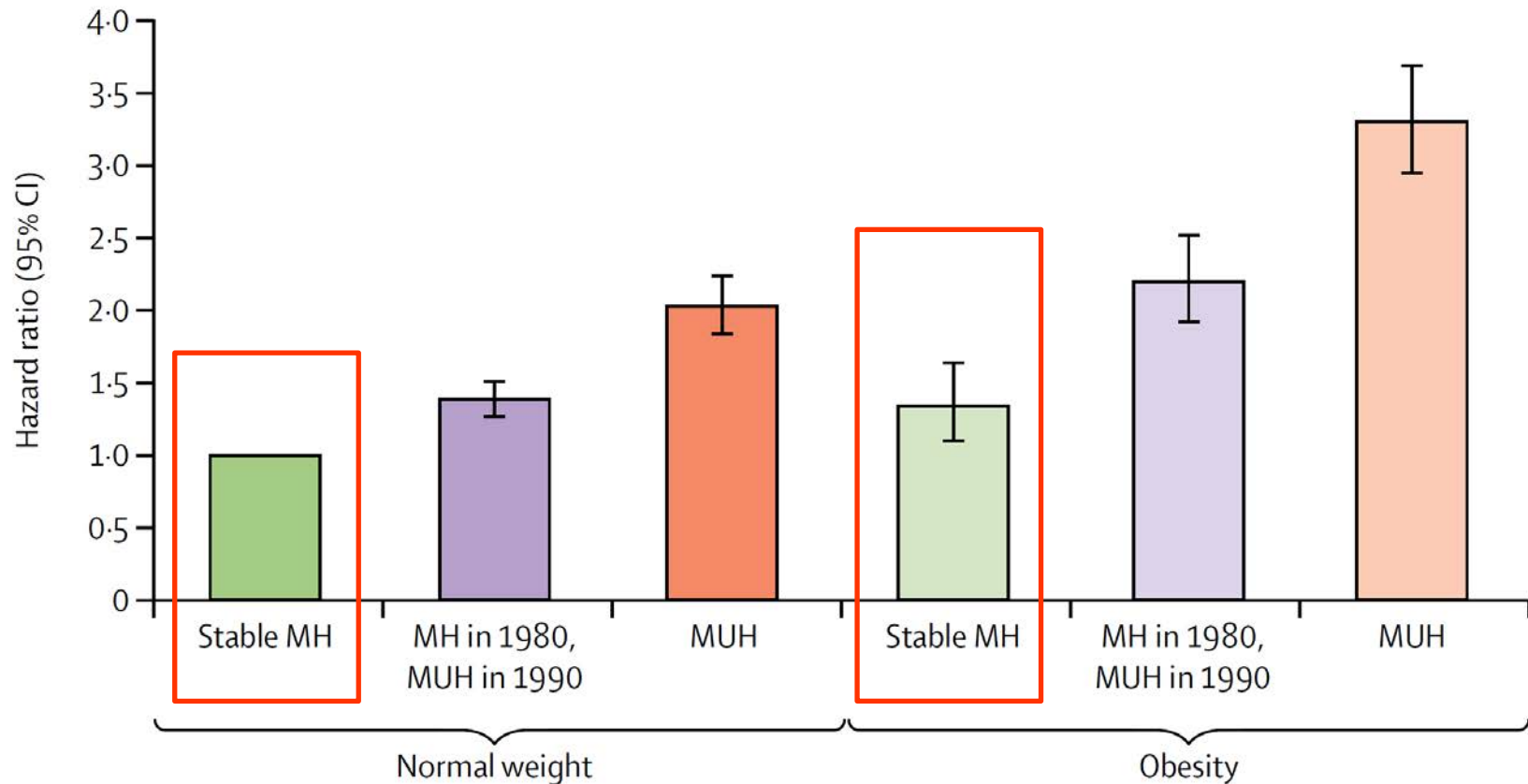


Stabilità del fenotipo MHO nel tempo



Eckel N et al. Lancet Diabetes Endocrinol 2018

Rischio cardiovascolare nei MHO



121701 female nurses recruited to the Nurses' Health Study (NHS)

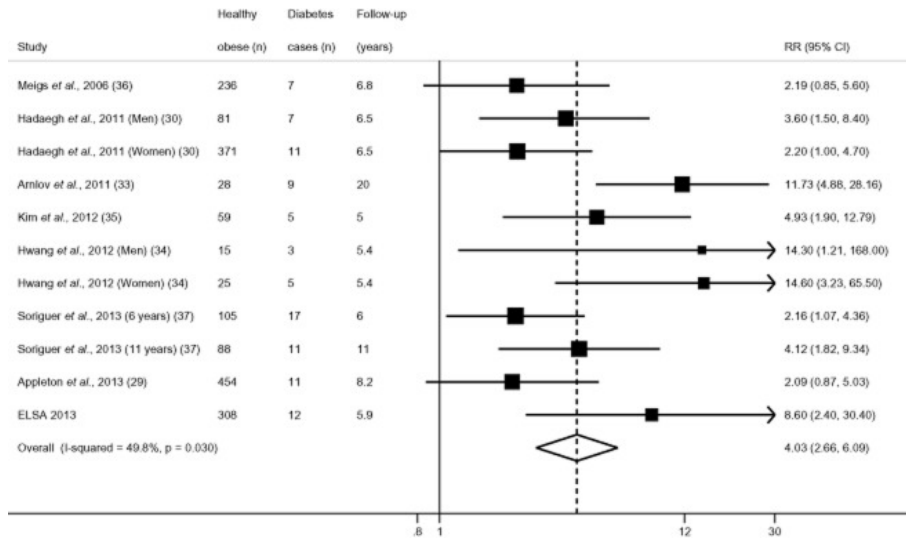
Mean follow up: 24 y

Metabolic health defined by absence of diabetes, hypertension and hypercholesterolaemia

Outcomes: fatal and non-fatal myocardial infarction and stroke

Rischio di diabete tipo 2 nei MHO

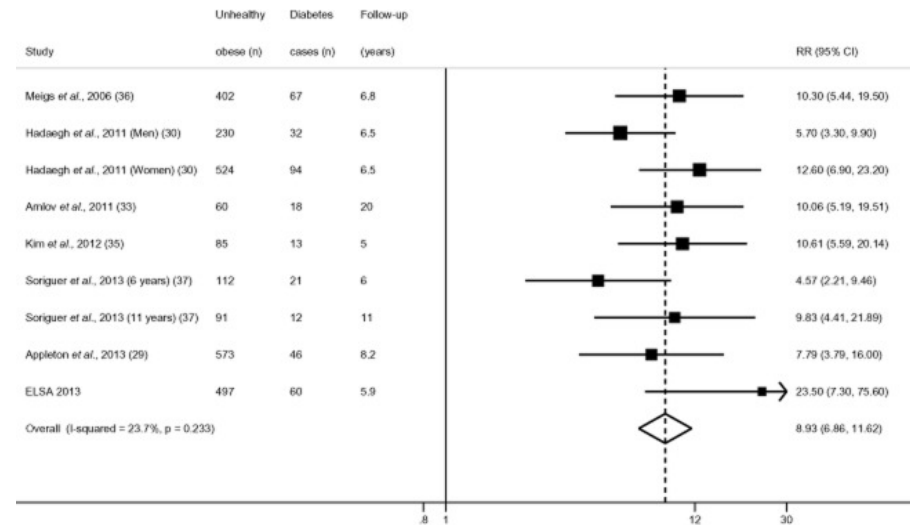
MHO



RR 4

Follow-up: 5-20 y

MUO



RR 8

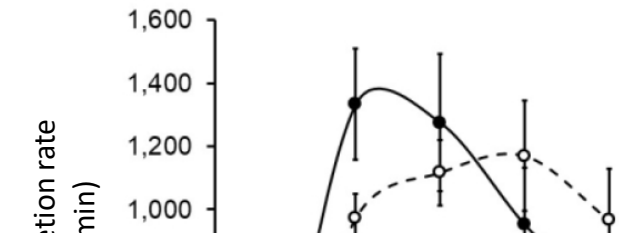
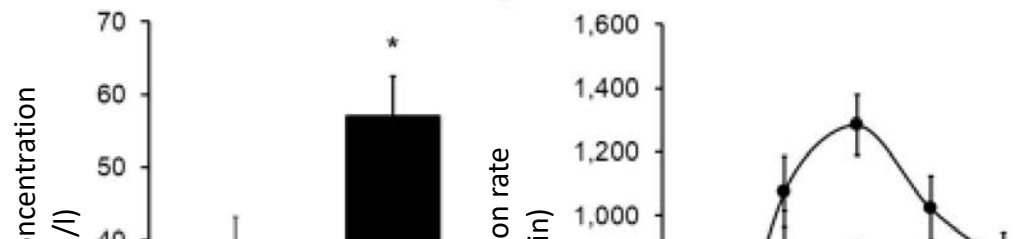
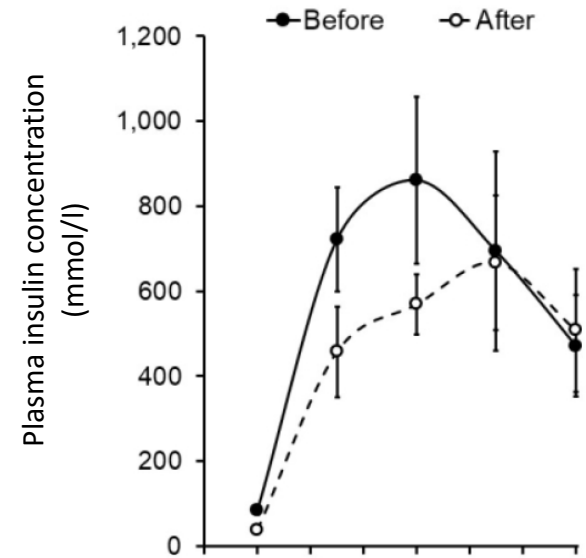
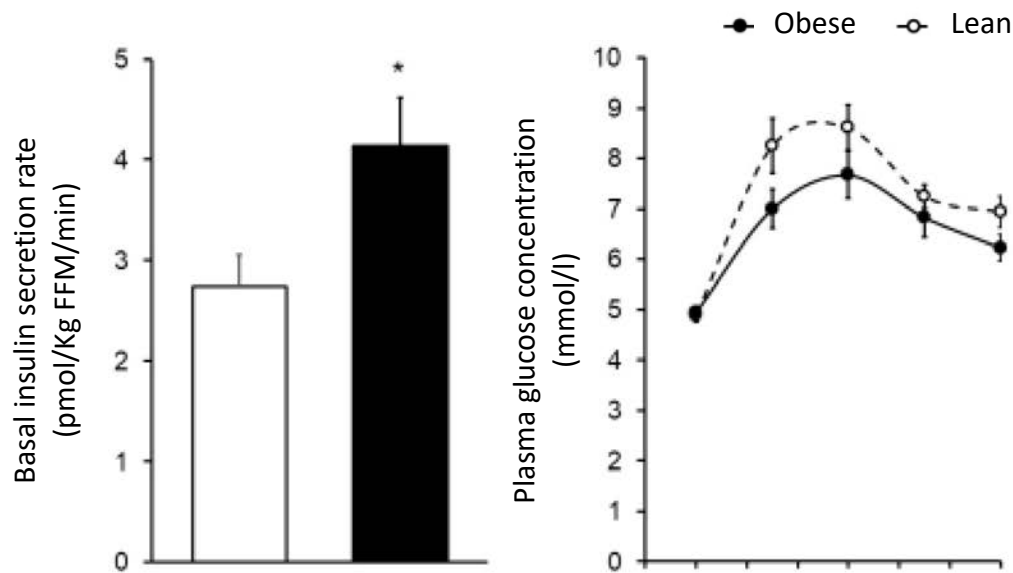
L'IR è
primariamente
determinata
dall'ambiente

L'IR origina
dal mismatch tra
eccesso
calorico
e capacità
di accumulo nel TA

Limiti
degli indici
surrogati

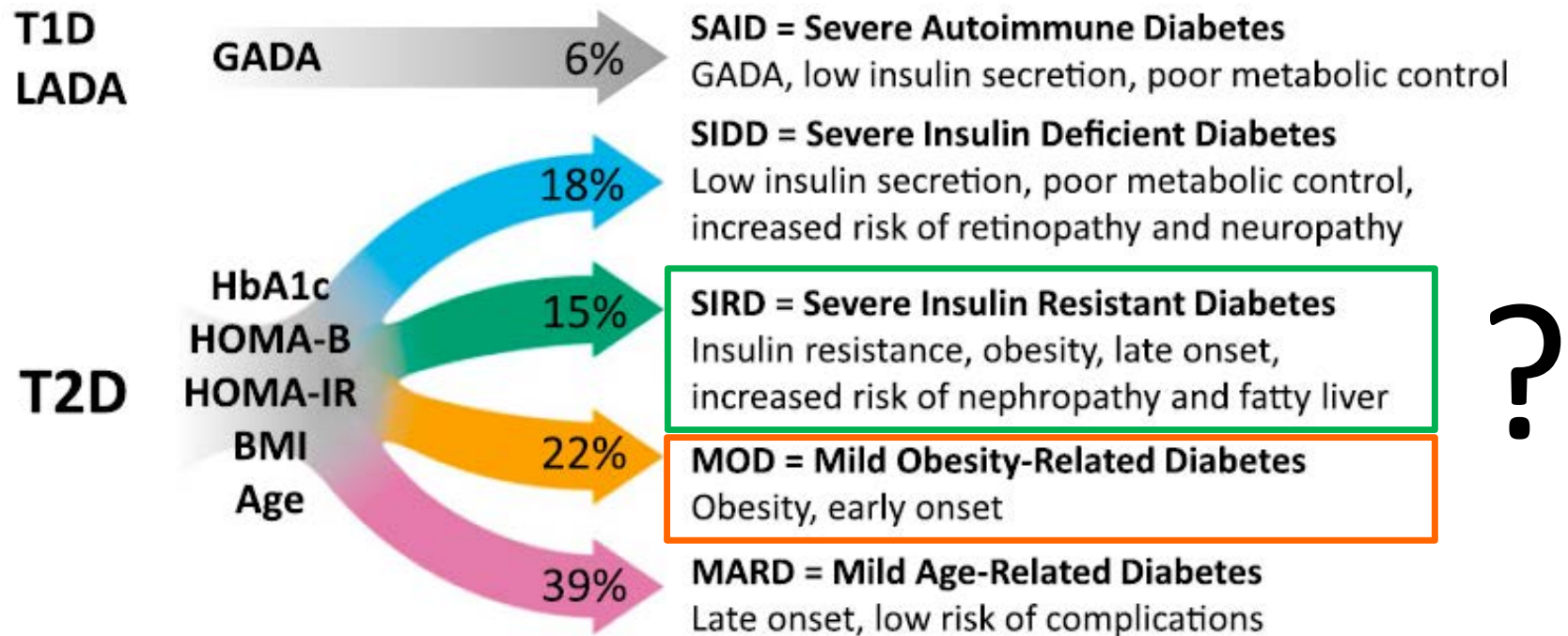
La CFR vita è un
valido indice
surrogato di
IR sistemica

Il calo
ponderale è il
primo obiettivo
nel pz obeso
indipendenteme
nte dal suo
grado di IR.

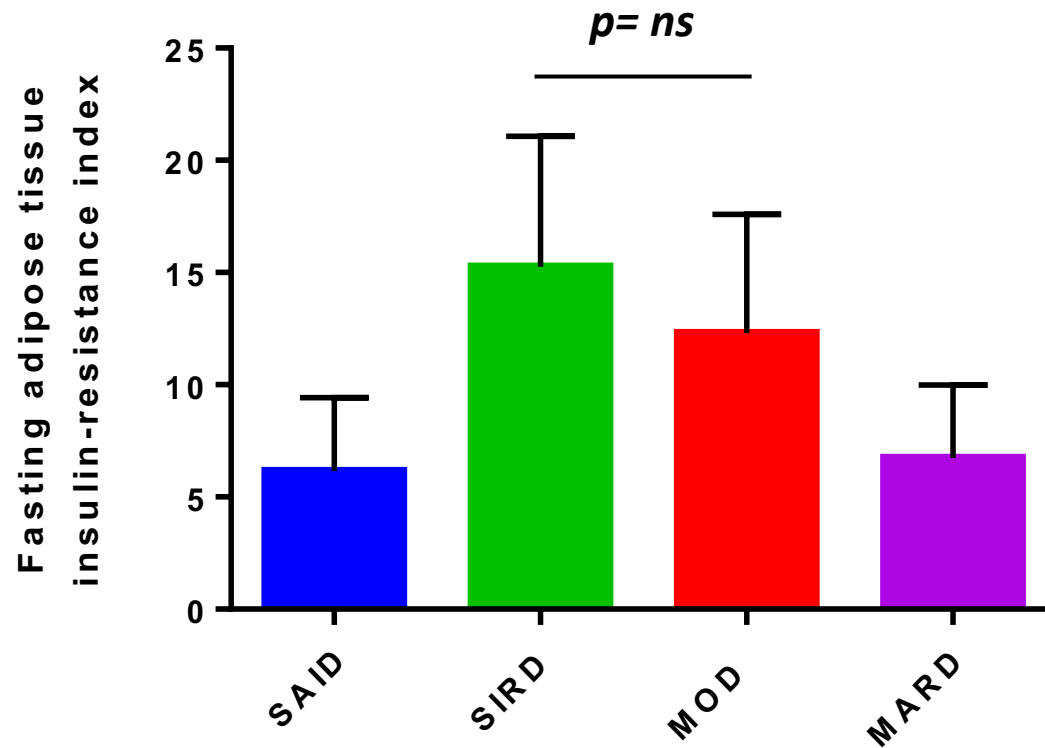


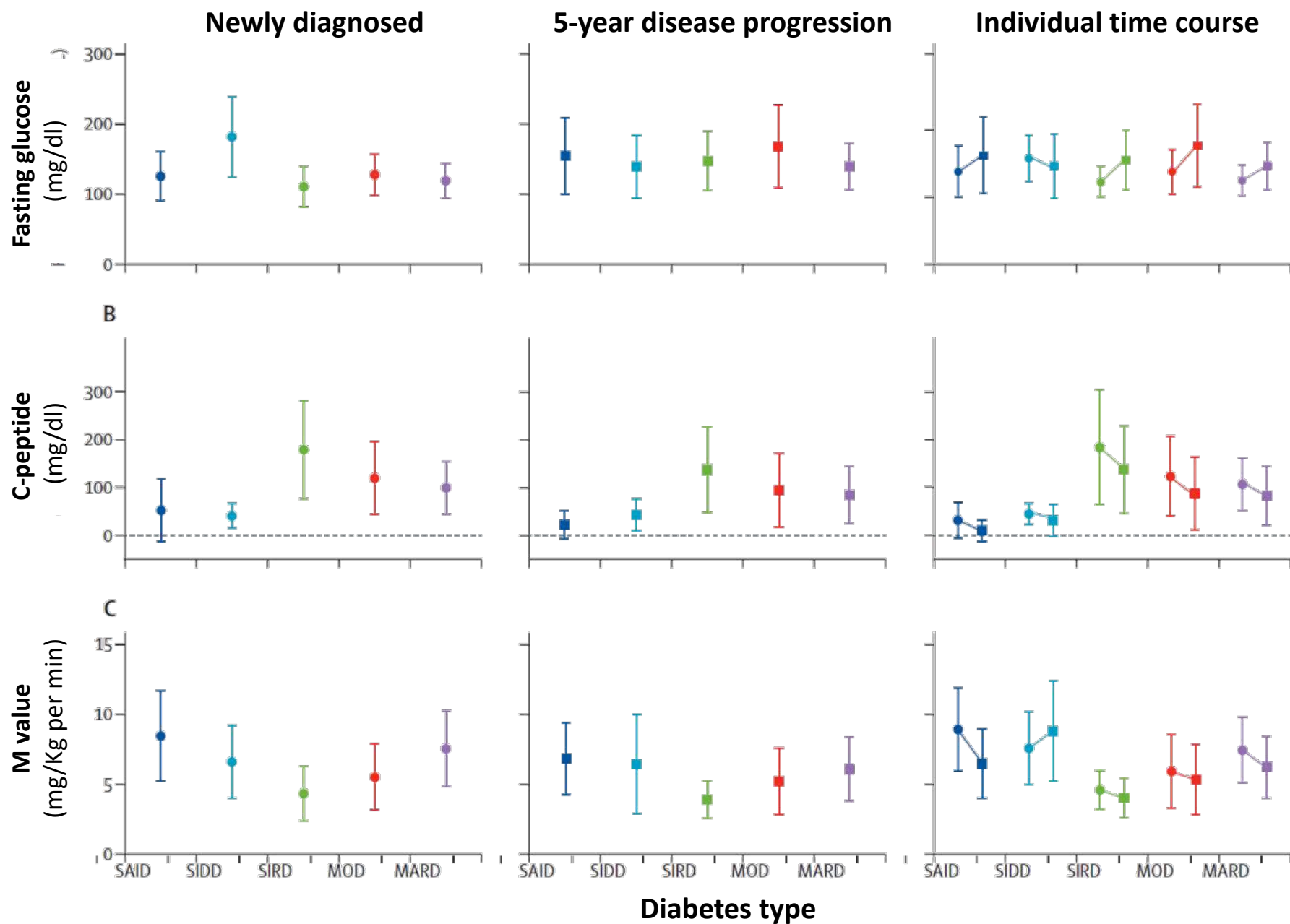
La perdita di peso potrebbe ridurre il rischio di sviluppare diabete di tipo 2 anche indipendentemente dal suo effetto sull'IR ovvero diminuendo la secrezione insulinica e quindi il carico di lavoro delle β -cellule.

La misurazione dell'insulino-resistenza per individualizzare la terapia nel diabete conclamato

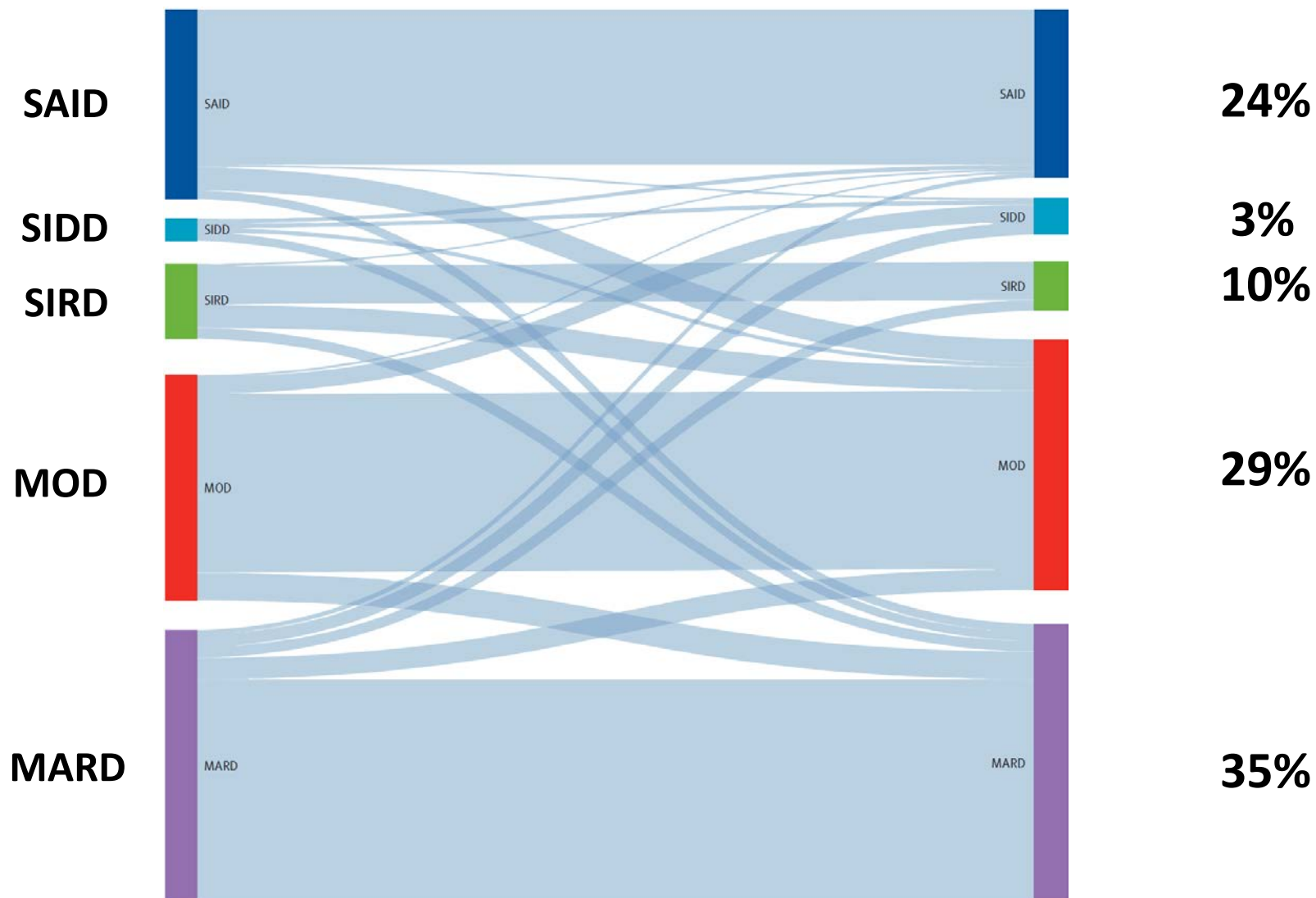


MOD = Mild obesity-Related Diabetes

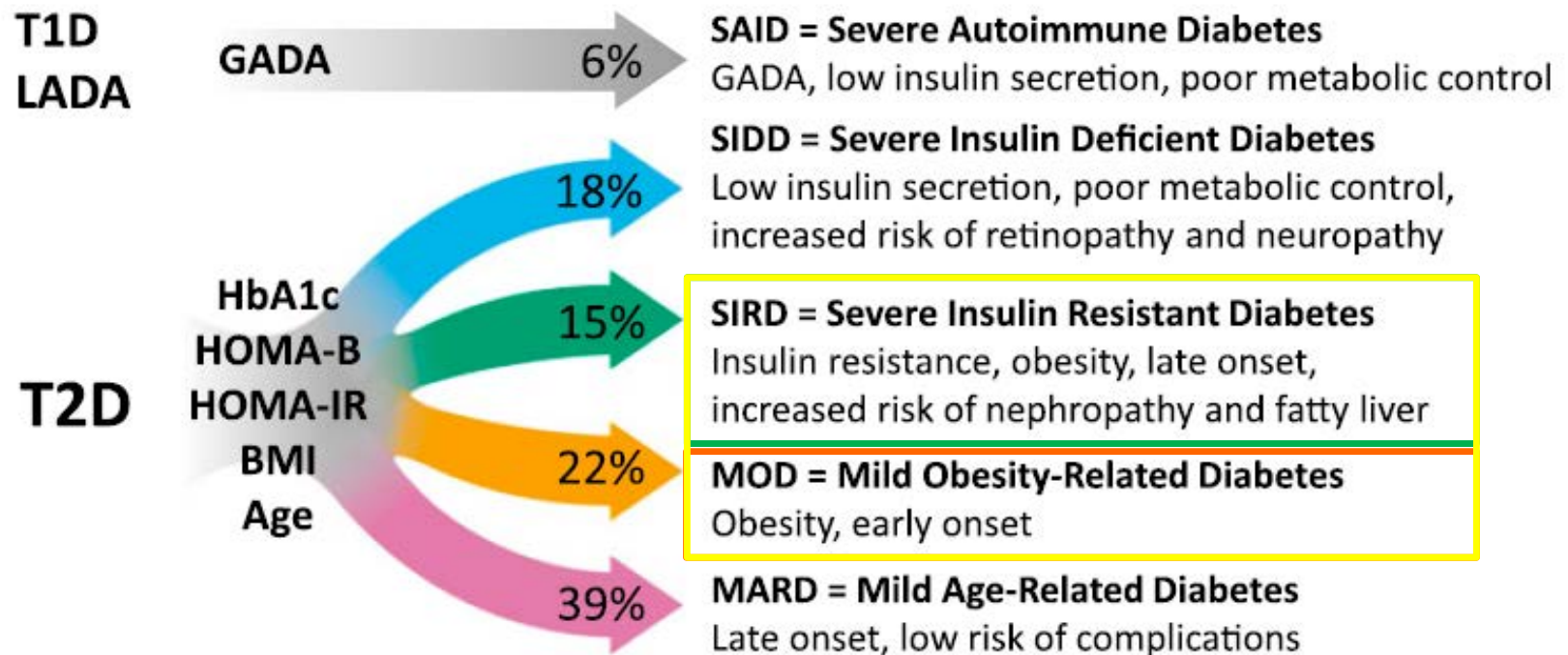




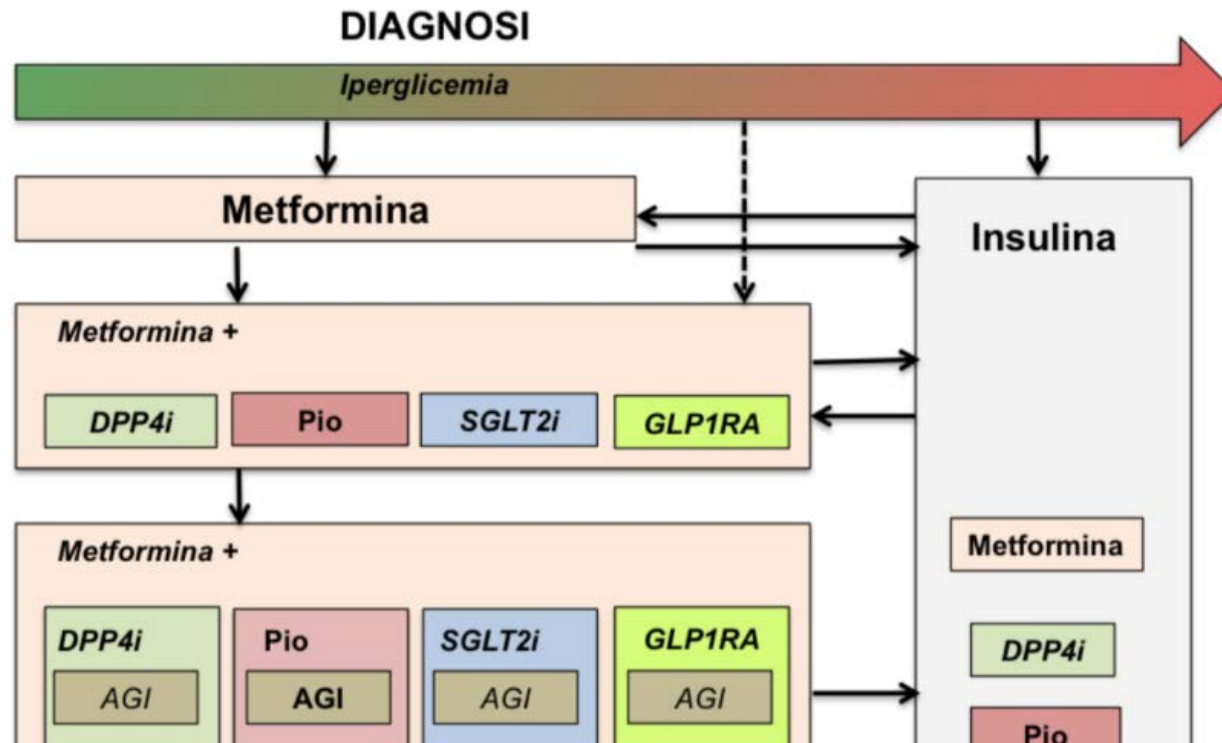
**% redistribution
at 5-year follow-up**



La misurazione dell'insulino-resistenza per individualizzare la terapia nel diabete conclamato



La terapia del paziente diabetico obeso



I **TZD** sono indicati per il trattamento del pz diabetico obeso non tanto per la loro azione insulino-sensibilizzante (peraltro indiretta) quanto piuttosto perchè in grado di contrastare l'ADIPOSOPATIA che è alla base delle complicanze metaboliche dell'obesità.

La terapia del paziente diabetico obeso

Tabella 4.H2. Benefici dei farmaci per il diabete di tipo 2.

	Metformina	Acarbose	GLP1RA	Gliflozine	Gliptine	Pioglitazone	SU/glinidi	Insulina basale	Insulina basale-bolus
Riduzione HbA1c a breve termine (3-4 mesi)*	+++	+	+++	++	++	+	+++	+++	++++
Riduzione HbA1c a medio termine (1-2 anni)*	++	+	+++	++	++	++	++	+++	++++
Riduzione HbA1c a lungo termine (oltre 2 anni)*	++	+	+++	++	ND	+++	+	+++	++++
Riduzione peso corporeo	+/-	+/-	+++	++	-	-	-	-	-
Riduzione pressione arteriosa	+/-	-	+	++	-	+	-	-	-
Riduzione morbilità e mortalità cardiovascolare**	+/-	+/-	++ ^a	+++ ^b	-	++	-	-	-

* HbA1c da 7,5% a 9,0% (158-209 mg/dl); ** dati di pazienti con diabete di tipo 2 e malattia cardiovascolare; ND, non disponibili; ^a dati di pazienti con diabete di tipo 2 e malattia cardiovascolare; ^b dati di pazienti con diabete di tipo 2 e malattia cardiovascolare.

La stima dell'IR resta giustificata da scopi di ricerca mentre nella routine clinica (mediante indici surrogati) ha progressivamente perso gran parte della sua utilità sia predittiva che classificativa.

Pertanto, gli interventi atti a prevenire e trattare il diabete di tipo 2 nelle persone con obesità non dovrebbero concentrarsi tanto sull'insulino-resistenza, quanto piuttosto avere tra i primi obiettivi il calo ponderale.