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Centro de Investigación Biomédica en Red
Enfermedades Hepáticas y Digestivas

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INSTITUTO DE BIOMEDICINA DE SEVILLA



HOSPITALES UNIVERSITARIOS
Virgen del Rocío



XVIII

ASISTENCIA
LIBRE

JORNADAS DE AVANCES EN
HEPATOLOGIA

23-24 de MAYO 2019 | MÁLAGA
AULA MAGNA | Facultad de Medicina

Healthy liver



NAFLD



NASH



Cirrhosis



Enfermedad hepática grasa no alcohólica ¿son todos los obesos iguales?



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ÁLBUM

El top de los 25 'fofisanos' más atractivos

ANA CAMPUZANO

Actualizado: 15/05/2015 11:51 horas

Los músculos ya no se llevan. El tipo de hombre que triunfa actualmente es el que luce una barriguita sana durante las vacaciones de verano, y al que se le ha catalogado como 'fofisano'. A continuación, repasamos a [los 'fofisanos' más atractivos](#) del panorama nacional e internacional.

< 1 2 3 4 5 6 7 8 9 10 > >

1. Leonardo DiCaprio (40): El actor estadounidense hace tiempo que se dejó de preocupar por el físico y trata de disfrutar cada momento que le ofrece la vida. Leonardo es uno de los 'vips' a los que no les importa lucir barriguita durante sus vacaciones de verano. (FOTOS GTRES/CORDON)



¿Qué tipos de obesidad existen según el estado metabólico?

Definiendo conceptos

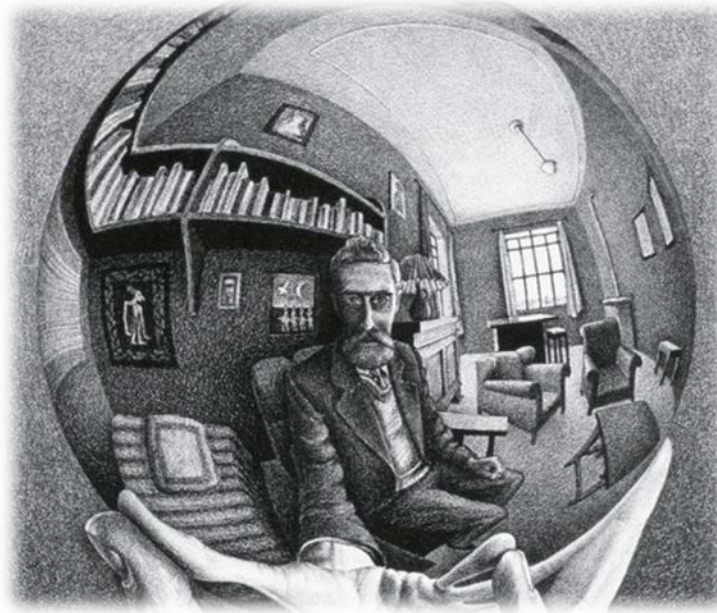


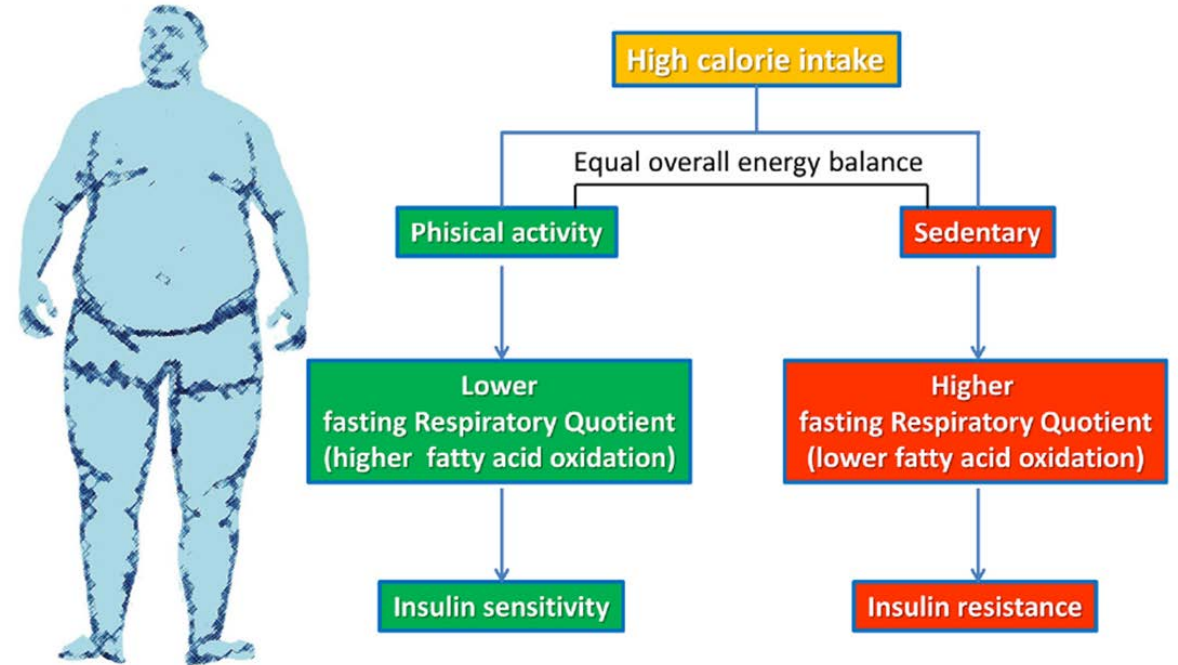
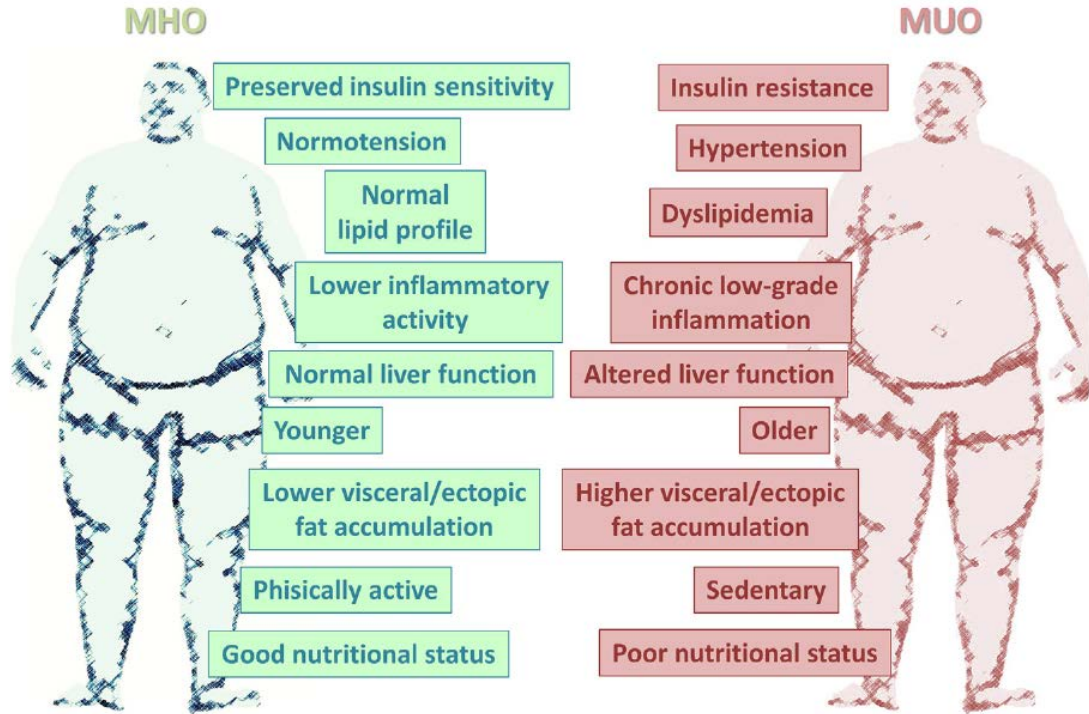
TABLE 2 Proposal of a Harmonized Definition of MHO and MUHO or MUO in Adults

Definition of MHO	
Based on the 7 fundamental points and recommendations discussed elsewhere (8) (see Online Table 1 for more detailed information), a person would be classified as MHO if they are obese (BMI ≥ 30 kg/m ²) plus they meet 0 of the 4 MetS criteria (WC excluded), which are the following (34):	
Elevated triglycerides (Drug treatment for elevated triglycerides is an alternate indicator.*)	≥ 150 mg/dl (1.7 mmol/l)
Reduced high-density lipoprotein cholesterol (Drug treatment for reduced HDL-C is an alternate indicator.*)	<40 mg/dl (1.0 mmol/l) in men <50 mg/dl (1.3 mmol/l) in women
Elevated blood pressure (Antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator.)	Systolic ≥ 130 and/or diastolic ≥ 85 mm Hg
Elevated fasting glucose [†] (Drug treatment of elevated glucose is an alternate indicator.)	≥ 100 mg/dl (5.6 mmol/l)
Definition of MUHO or MUO	
A person would be classified as MUHO or MUO if they are obese (BMI ≥ 30 kg/m ²) plus they meet 1 to 4 of the MetS criteria indicated (WC excluded).	
*The most commonly used drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking 1 of these drugs can be presumed to have high triglycerides and low HDL-C. High dose of omega-3 fatty acids presumes high triglycerides. [†] Most patients with type 2 diabetes mellitus will have the MetS by the proposed criteria. BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; MetS = metabolic syndrome; MHO = metabolically healthy obesity; MUHO = metabolically unhealthy obesity; MUO = metabolically unhealthy obesity; WC = waist circumference.	

¿Qué distingue la obesidad metabólicamente sana de la enferma?

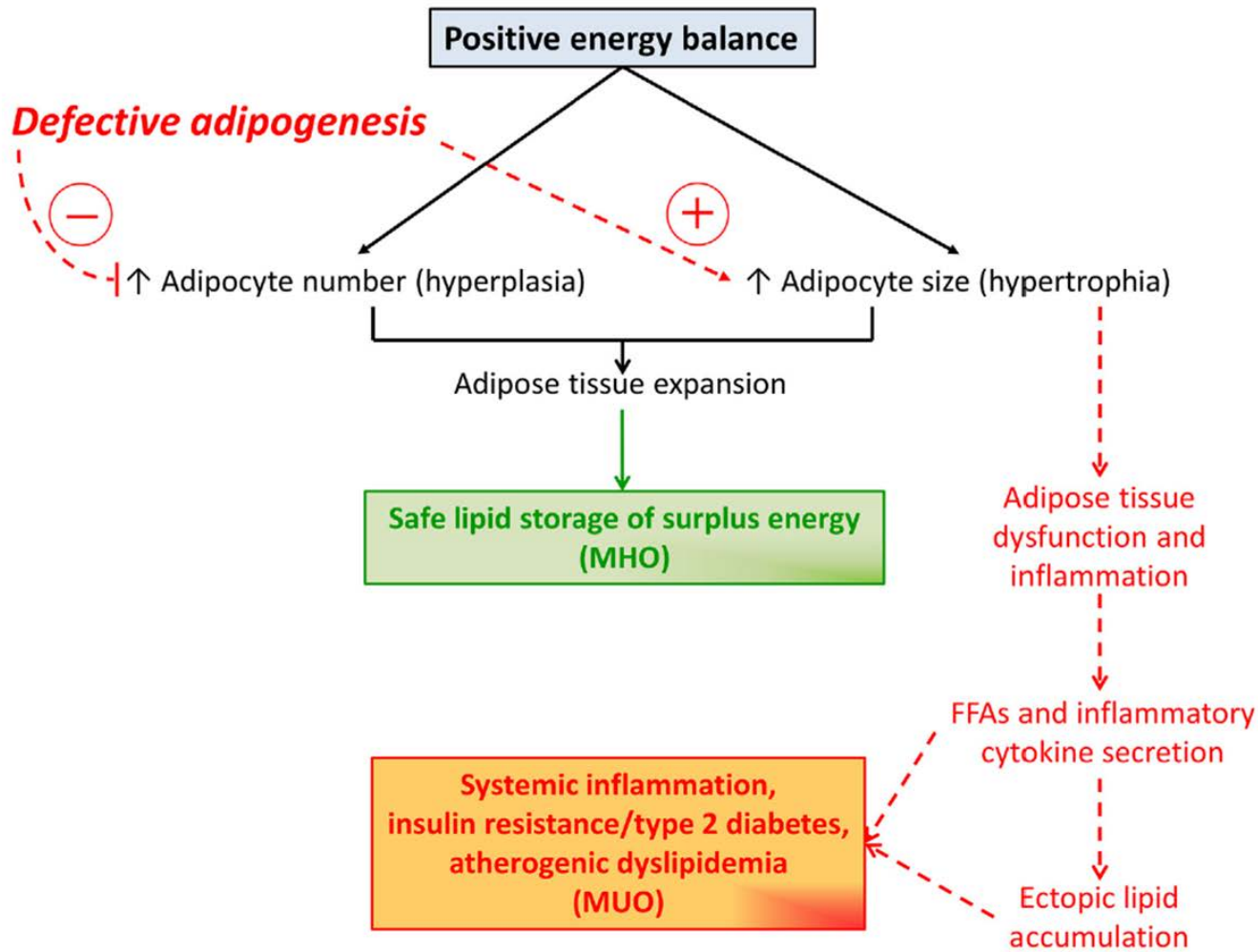
Estableciendo diferencias





No olvidar!!!





Circulating markers		MHO	MUO
Inflammatory markers	IL-6, TNF α , complement component 3, C-reactive protein, plasminogen activator inhibitor-1	Low	High
Adipokines	Leptin, chemerin, orosomucoid, resistin, progranulin, retinol-binding protein 4	Low	High
	Adiponectin	High	Low
Amino acid and derivatives	BCAA, acylcarnitines, aromatic amino acids	Low	High
Organic acids	Uric acid	Low	High
Vitamin	Vitamin D	High	Low
White Adipose Tissue		MHO	MUO
Immune cell infiltration	Macrophages, Crown-like structures	Low	High
	CD4+ T cells (Th22 and Th17)	Low	High
	T regulatory (Tregs) cells	High	Low
Biological Pathways	β -oxidation	High	Low
	TCA cycle	High	Low
	Oxidative phosphorylation	High	Low
	BCAA catabolism	High	Low
	Inflammation (IL-8, CCL5)	Low	High
	Biosynthesis of unsaturated fatty acids	High	Low
Amino acid and derivatives	Aspartate	High	Low

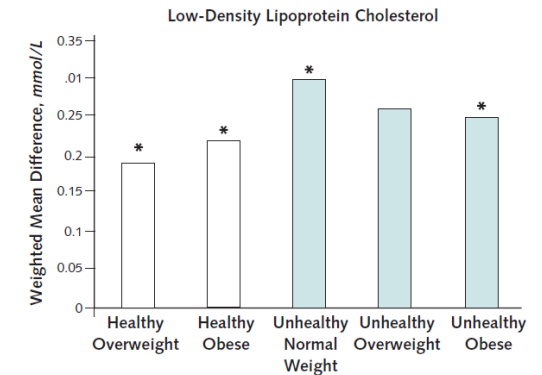
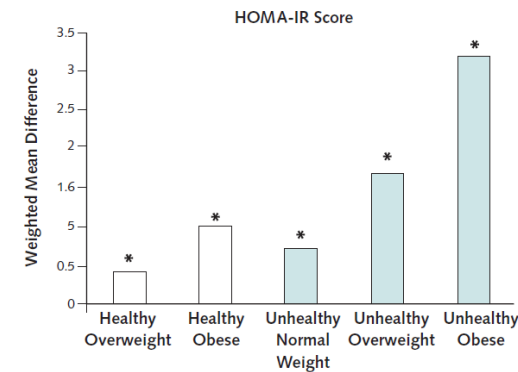
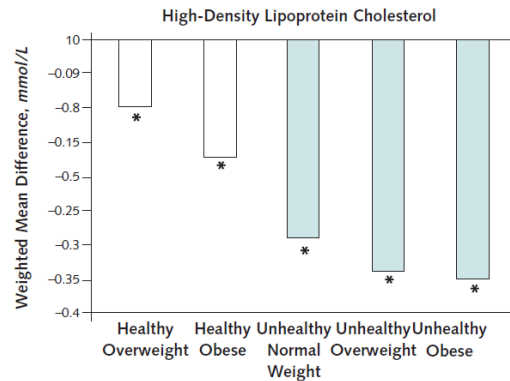
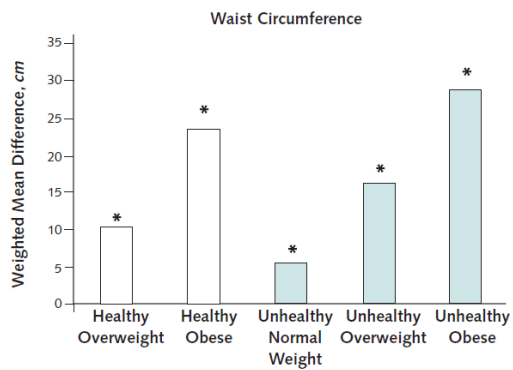
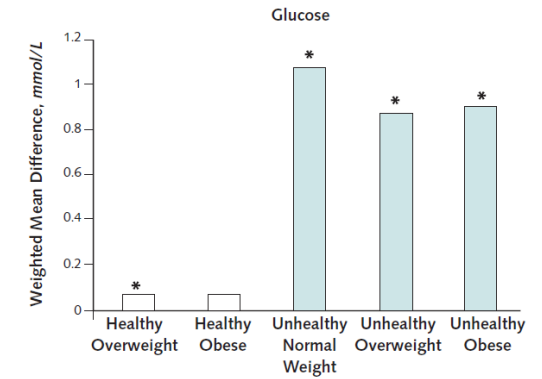
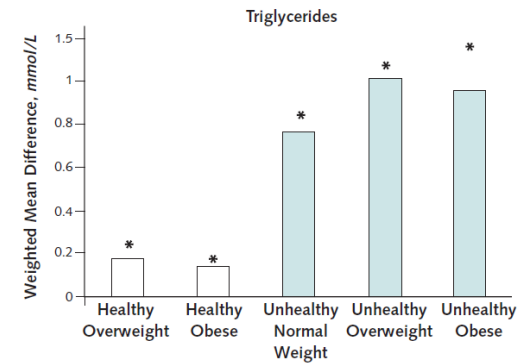
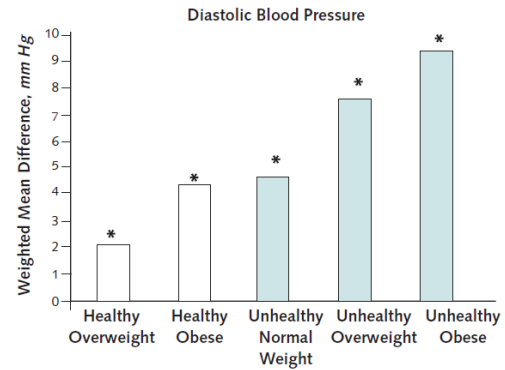
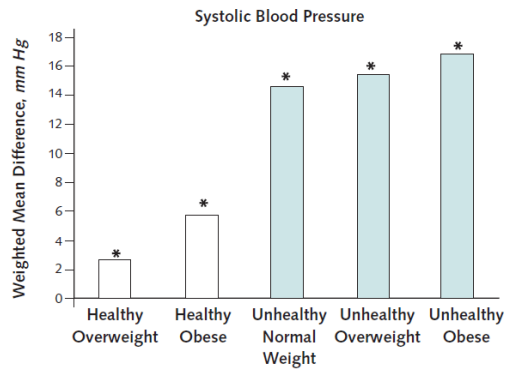
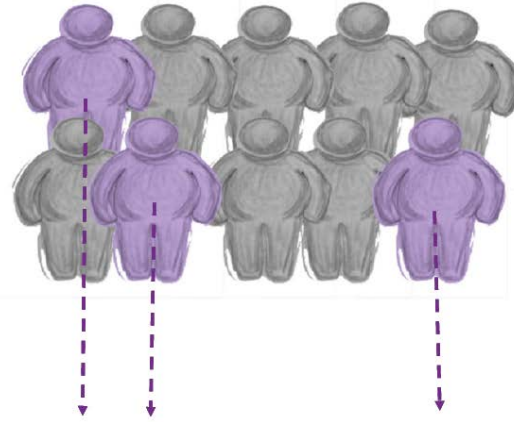
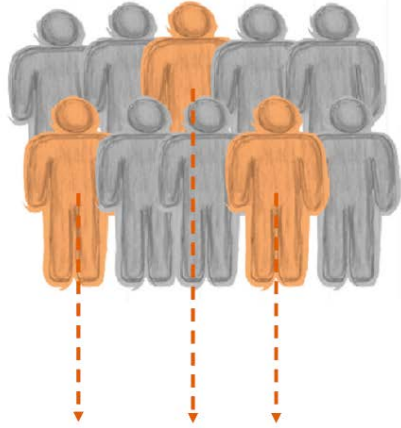


Table 2. Absolute Incidence of Events per Year of Follow-up, by Body Mass Index Category and Metabolic Status

Study, Year (Reference)	Normal Weight, %		Overweight, %		Obese, %	
	Metabolically Healthy	Metabolically Unhealthy	Metabolically Healthy	Metabolically Unhealthy	Metabolically Healthy	Metabolically Unhealthy
Kip et al, 2004 (47)	1.51	4.48	0.55	2.68	0.43	2.53
Meigs et al, 2006 (8)	0.43	1.94	0.71	1.25	0.73	1.27
Song et al, 2007 (48)	0.21	0.79	0.24	0.70	0.26	0.61
Kuk and Arden, 2009 (49)	0.32	0.80	0.30	0.99	0.40	0.96
Arnlöv et al, 2010 (9)	1.46	1.77	1.58	2.02	2.00	2.52
Hosseini et al, 2011 (50)	0.50	1.66	0.43	1.55	0.39	1.20
Vouglari et al, 2011 (10)	2.45	10.54	2.36	7.78	1.55	9.02
Ogorodnikova et al, 2011 (53)	0.39	1.13	Not available	Not available	0.39	1.13

ESTADO METABÓLICO: MÁS ALLÁ DE LA OBESIDAD

Healthy vs. Unhealthy Met.



MUNW

- ~10-27% of lean individuals
- BMI < 25 kg/m²
- Insulin resistance
- Dyslipidemia (elevated TG and LDL-c, reduced HDL-c)
- Higher % body fat

MHO

- ~13-29 % of obese individuals
- BMI > 30 kg/m²
- Normal insulin sensitivity
- Normal fasting glucose
- Normal blood lipid (reduced TG, total-cholesterol and LDL-c, elevated HDL-c)

Metabolically unhealthy

Normal weight

Leg fat mass (%) ↓↓

Fatty Liver ↑

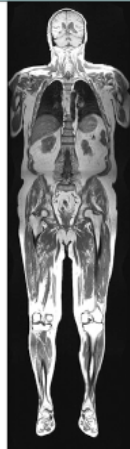
Visceral Obesity ↑

Imp. insulin secr. capacity ↑↑

Insulin resistance ↑

Cardioresp. fitness ↓

cIMT ↑



Obesity

Leg fat mass (%) ↓

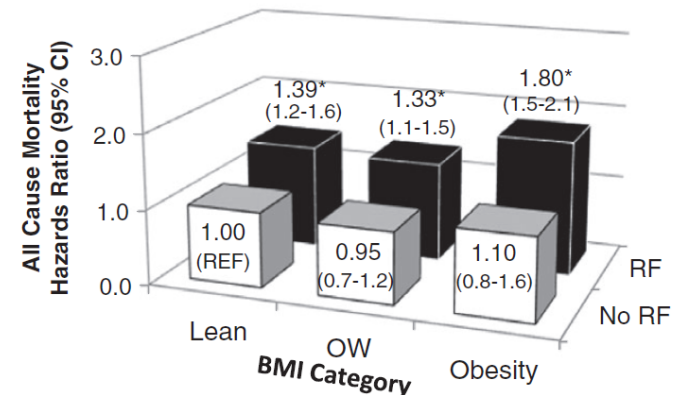
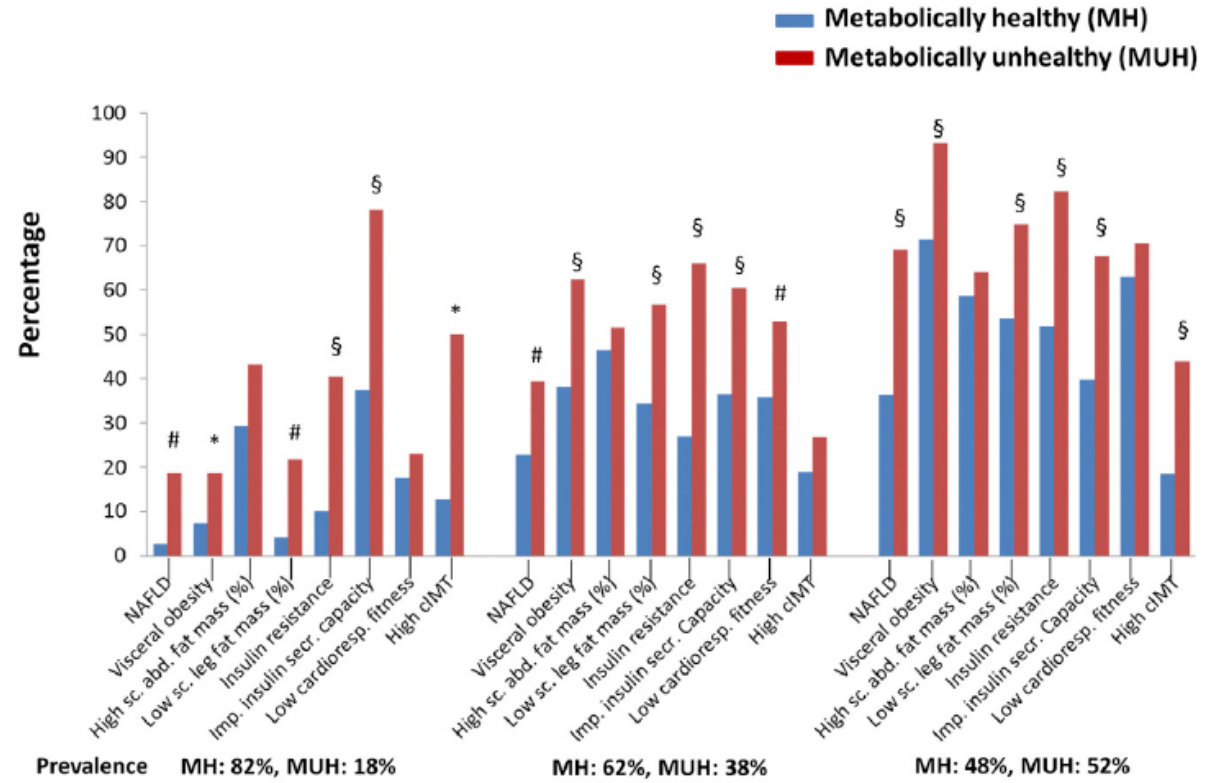
Fatty Liver ↑↑

Visceral Obesity ↑↑

Imp. insulin secr. capacity ↑↑

Insulin resistance ↑↑

cIMT ↑



La obesidad metabólica sana ¿es realmente sana?

¿Podemos estar tranquilos?

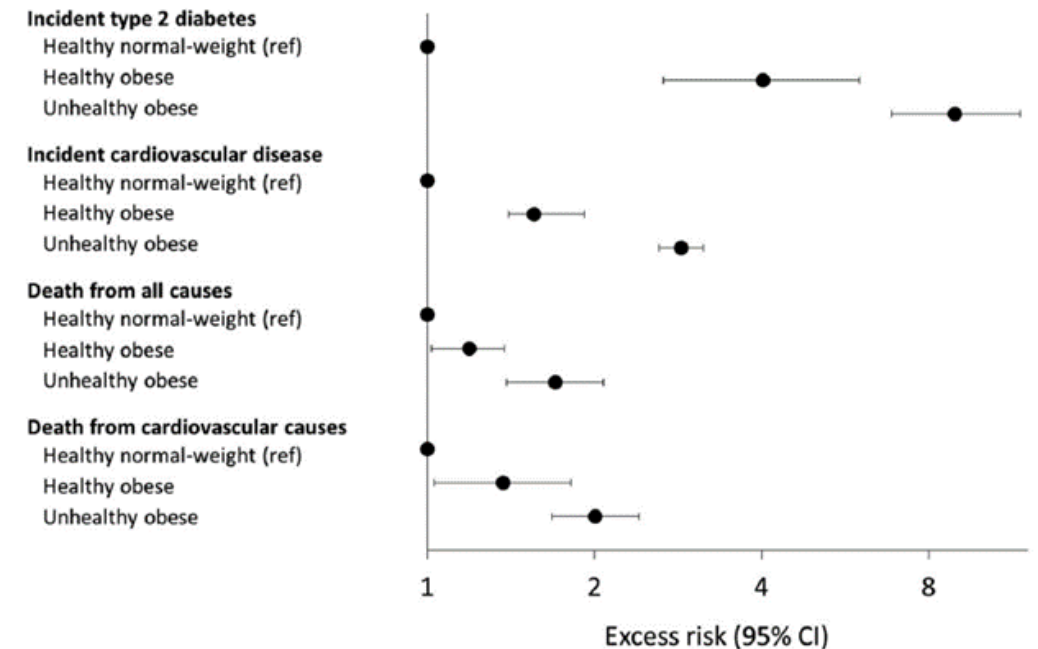
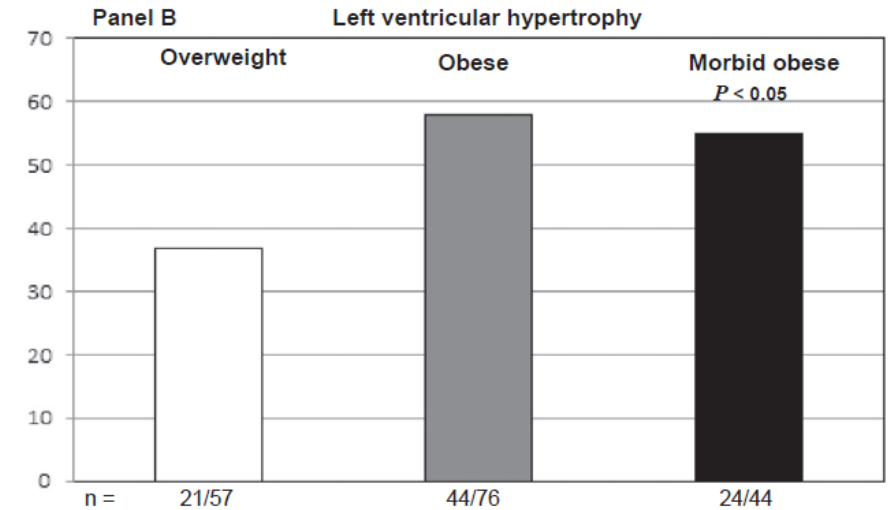


Table 3. Development of nonalcoholic fatty liver disease (NAFLD) by body mass index categories in men and women

BMI category (kg/m ²)	Person-years	Number of incident cases	Incidence rate (per 1,000 person-years)	Multivariable-adjusted HR* (95% CI)
<i>Men (n=30,502)</i>				
<18.5	6,287.8	74	11.8	0.31 (0.24–0.39)
18.5–22.9	79,765.0	2,924	36.7	1.00 (reference)
23.0–24.9	37,666.2	2,437	64.7	1.82 (1.73–1.92)
≥25.0	17,216.5	1,690	98.2	2.87 (2.70–3.05)
<i>P</i> for trend				<0.001
Per 1 kg/m ² increase in BMI				1.25 (1.23–1.26)
<i>Women (n=46,923)</i>				
<18.5	26,014.9	83	3.2	0.28 (0.22–0.35)
18.5–22.9	147,666.5	1,703	11.5	1.00 (reference)
23.0–24.9	24,221.2	836	34.5	3.03 (2.79–3.30)
≥25.0	9,355.5	593	63.4	5.76 (5.23–6.34)
<i>P</i> for trend				<0.001
Per 1 kg/m ² increase in BMI				1.38 (1.36–1.39)

Table 4. Logistic Regression Analysis for the Risk of Nonalcoholic Fatty Liver Disease over 4 Years of Follow-up according to Groups Divided by Baseline Metabolic Health and Obesity Status

Variable	<i>P</i> value	Exp (B)	95% CI	
			Lower	Upper
Age	0.262	0.991	0.976	1.007
Gender	0.618	1.069	0.823	1.388
ALT	0.015	1.013	1.003	1.023
Total cholesterol	0.006	1.005	1.001	1.008
Waist circumference	<0.01	1.068	1.048	1.089
Exercise status ^a	0.837	1.025	0.809	1.299
MHNO	-	-	-	-
MHO	0.010	1.731	1.239	2.419
MUHNO	<0.01	1.877	1.412	2.494
MUHO	<0.01	2.501	1.699	3.681



¿El estado metabólico de la obesidad es estático o dinámico?

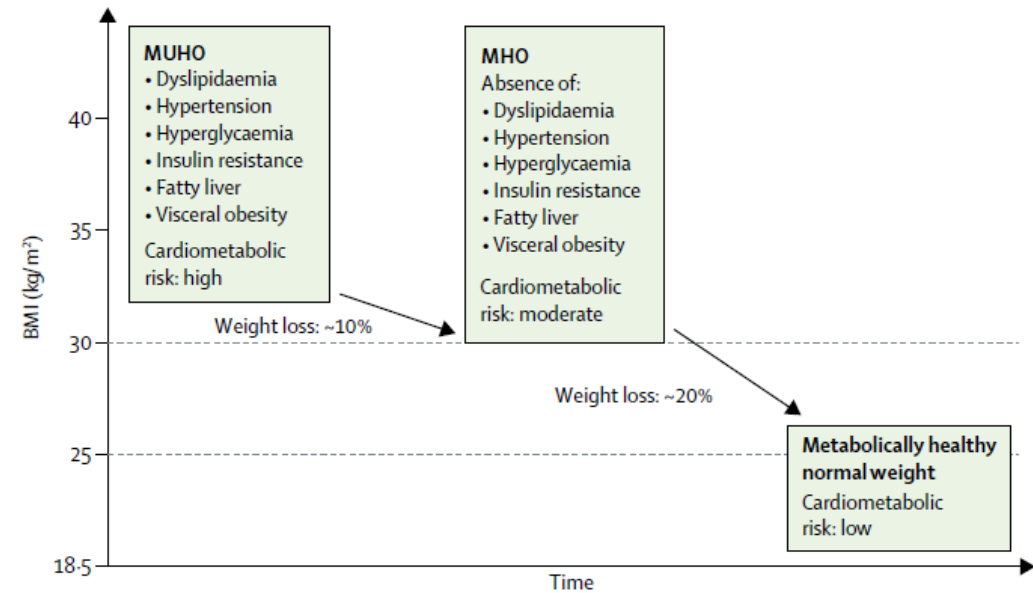
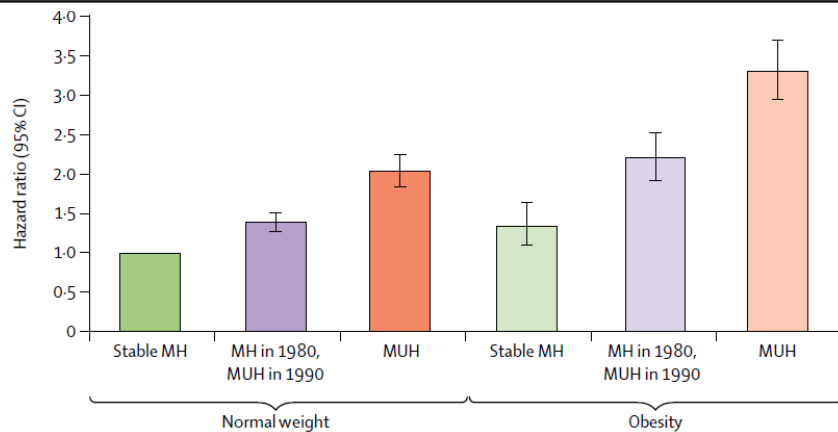
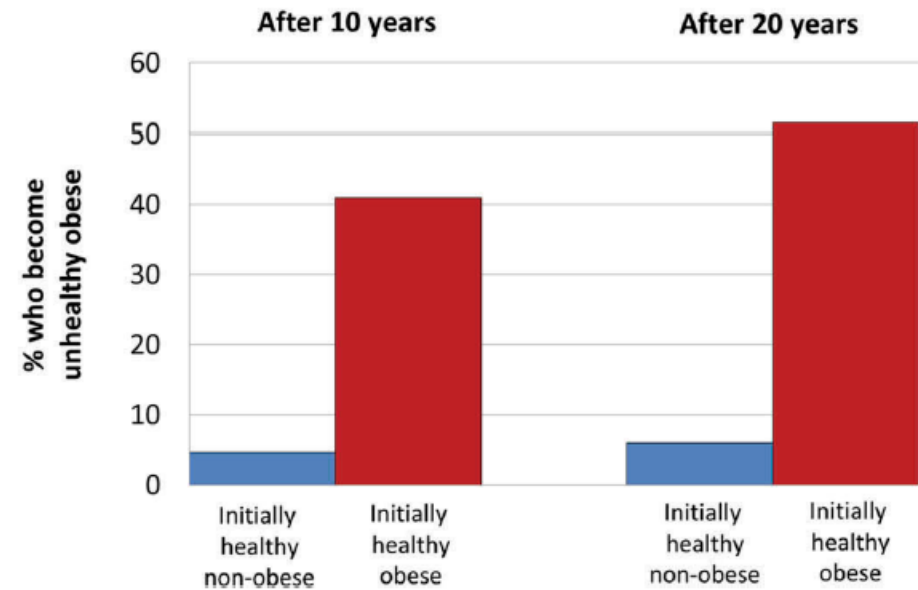
Atentos al cambio



TRANSICIÓN ENTRE ESTADÍOS

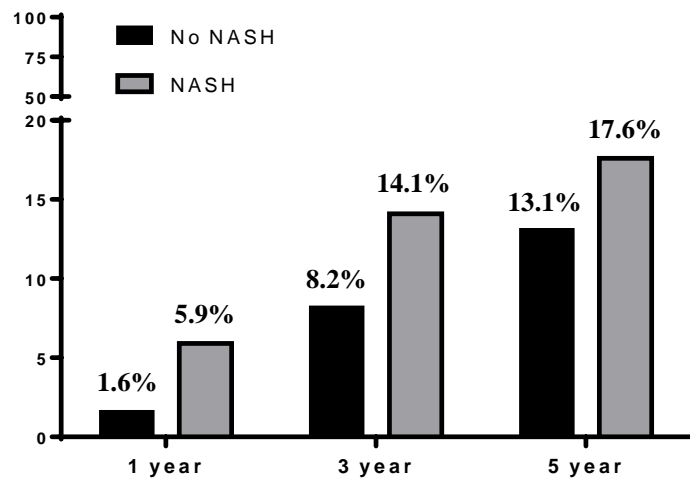
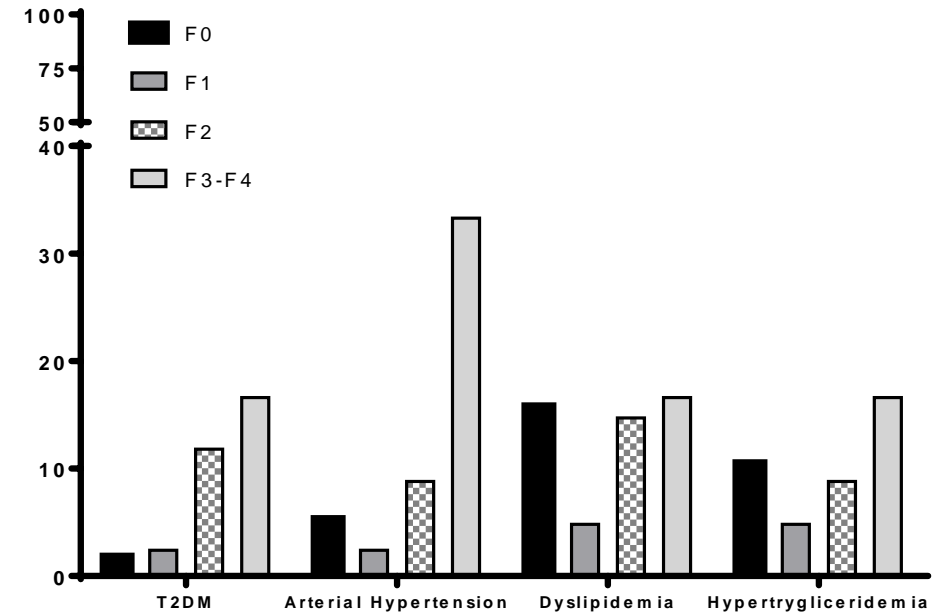
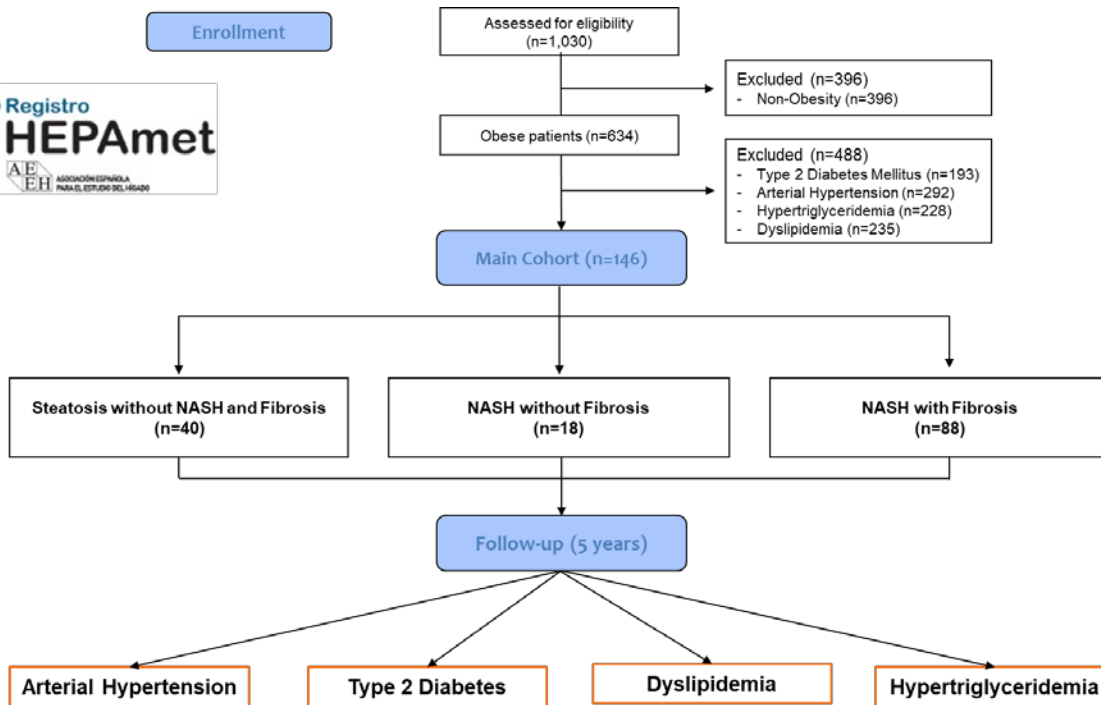
MHO → MUHO

Author	Study	Definition of metabolic health	Follow-up time	Findings for the MHO phenotype
Appleton et al, 2013 [29]	North West Adelaide Health Study	Absence of the metabolic syndrome	~8 years	Transition to MUHO: 31%
Soriguer et al, 2013 [37]	Pizarra Study	Absence of the metabolic syndrome and/or insulin resistance	6 years	Transition to MUHO: 37%
Achilike et al, 2015 [28]	San Antonio Heart Study	Absence of the metabolic syndrome, including insulin resistance	~8 years	Transition to MUHO: 48%
Bell et al, 2015 [30]	Whitehall II Study	Absence of the metabolic syndrome, including insulin resistance	5, 10, 15 and 20 years	Transition to MUHO: 32% at 5 years; 41% at 10 years; 35% at 15 years; 52% at 20 years
Lee et al, 2015 [33]	Chungju Metabolic Disease Cohort	In the lower 3 quartiles for fasting glucose and triacylglycerol indexes	4 years	Transition to MUHO: 15%
Hamer et al, 2015 [34]	English Longitudinal Study of Ageing	Absence of the metabolic syndrome, including inflammation	8 years	Transition to MUHO: 45%
Hwang et al, 2015 [39]	Japanese American Community Diabetes Study	Absence of the metabolic syndrome	10 years	Transition to MUHO ^a : 65%
Kim et al, 2016 [32]	Korean Genome Epidemiology Study	Absence of the metabolic syndrome	10 years	Transition to MUHO ^a : 45%
Kabat et al, 2017 [31]	Women's Health Initiative	Absence of the metabolic syndrome	6 years	Transition to metabolically unhealthy phenotypes: 34%
Eckel et al, 2018 [13]	Nurses' Health Study	Absence of diabetes, hypertension and hypercholesterolaemia	10, 20 and 30 years	Transition to metabolically unhealthy phenotypes: 57% at 10 years; 84% at 20 years; 94% at 30 years
Mongraw-Chaffin et al, 2018 [35]	Multi-Ethnic Study of Atherosclerosis	Absence of the metabolic syndrome	10 years	Transition to MUHO: 48%
Moussa et al, 2018 [36]	UK Clinical Practice Research Datalink	Absence of diabetes, hypertension, hyperlipidaemia, CVD, cerebrovascular disease, liver disease, renal disease and obstructive sleep apnoea	~9 years	Transition to metabolically unhealthy phenotypes ^b : 44%

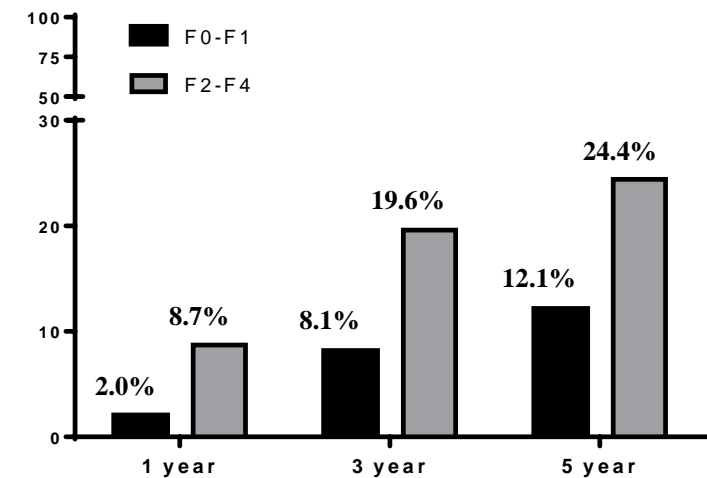


TRANSICIÓN ENTRE ESTADÍOS

MHO → MUHO



Cumulative Incidence of Metabolic Disturbances

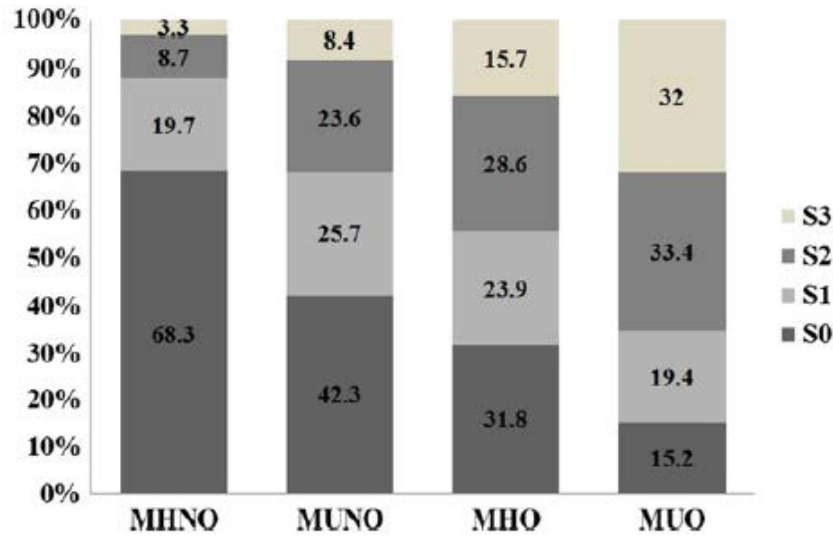


¿El estado metabólico de la obesidad influye en la EHGNA?

Cuándo y en quién estar atentos



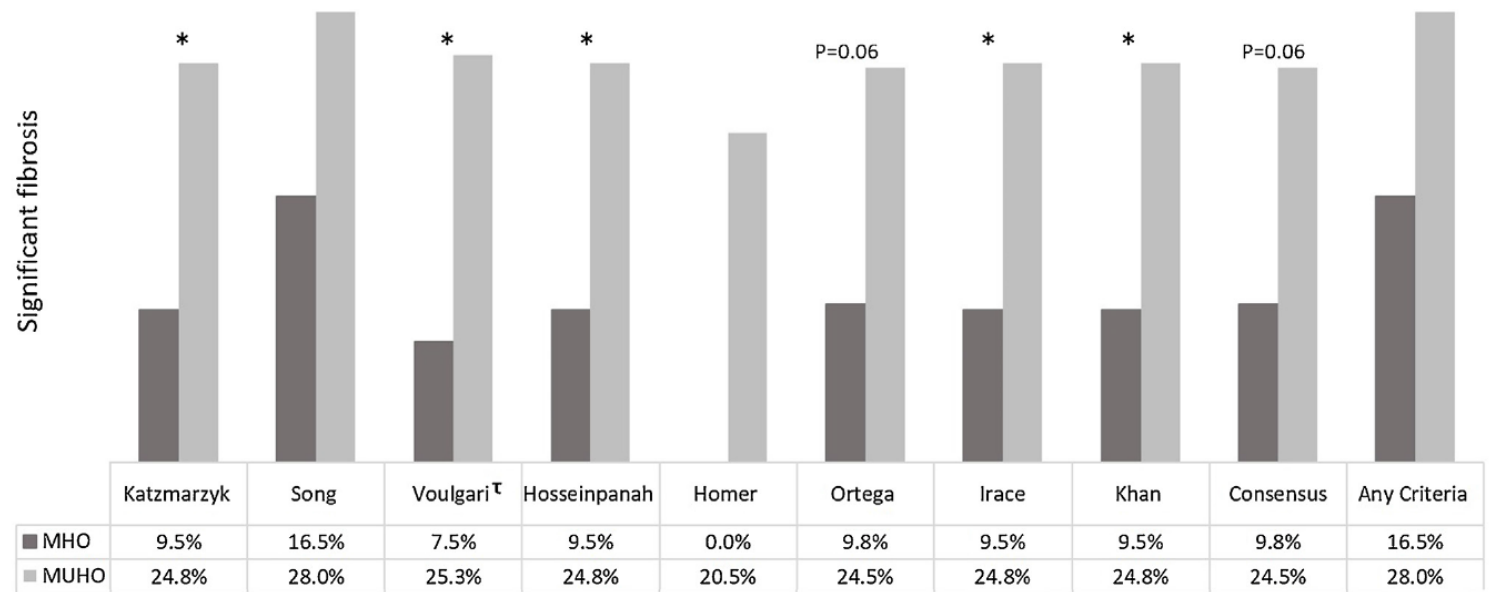
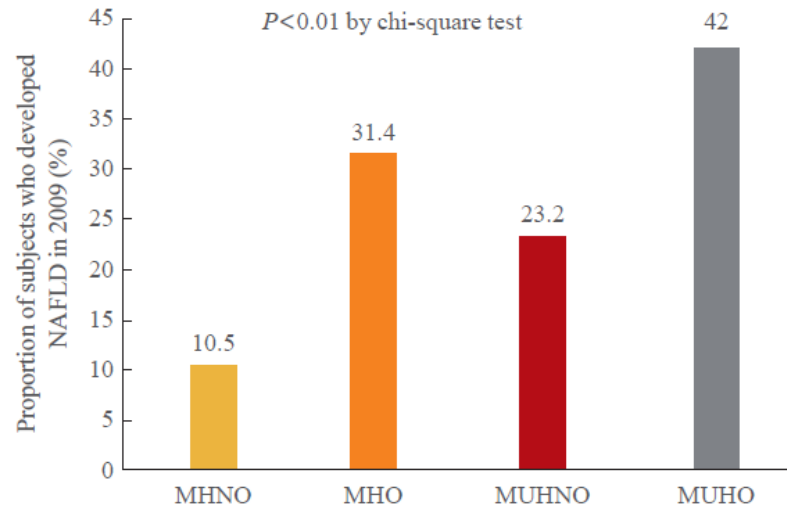
Caucásicos

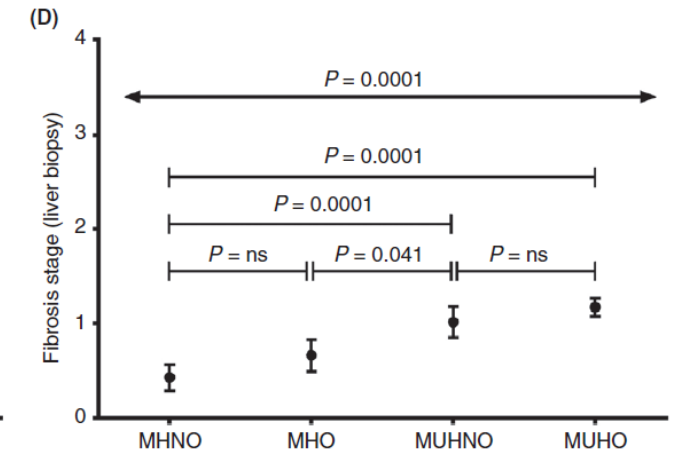
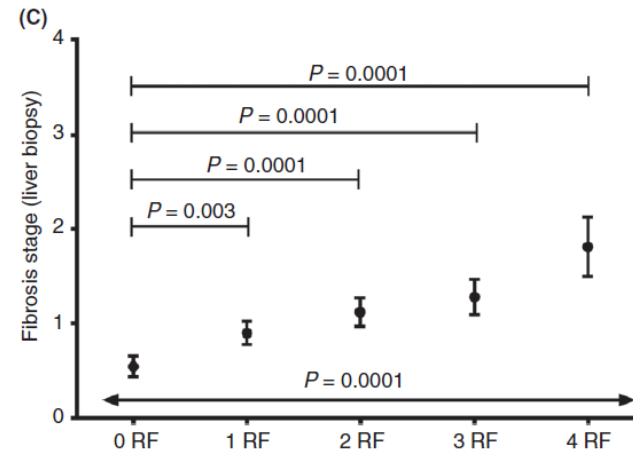
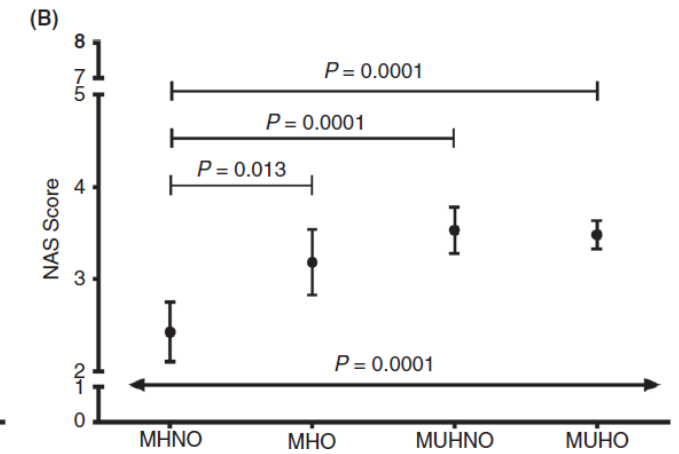
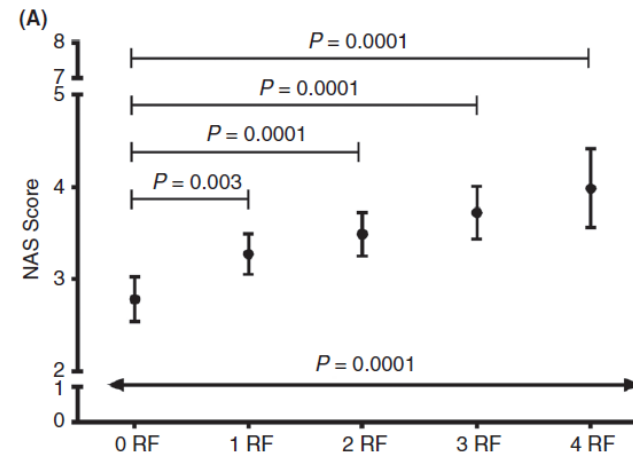
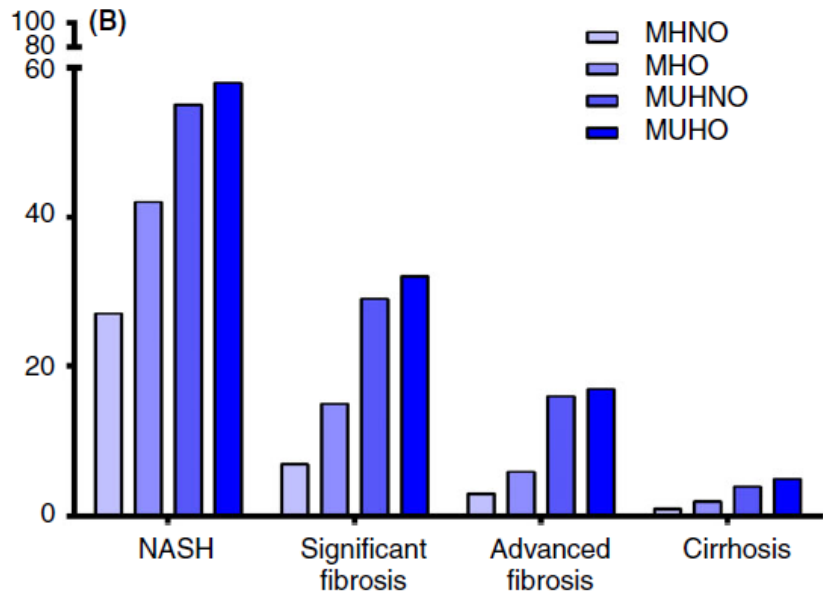
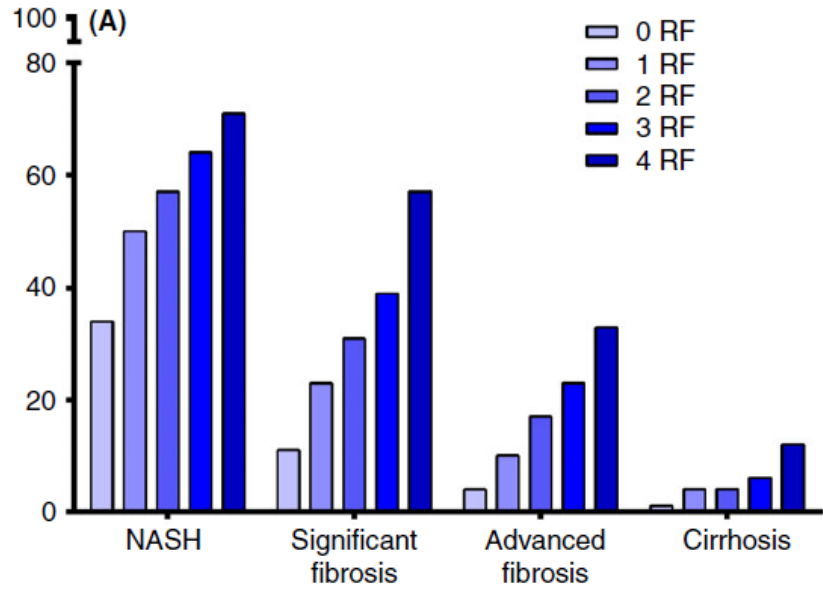


Criteria used to define metabolically healthy obese (MHO) subjects.

Study	Year	Definition of MHO	
		Body mass index	Number of MetS criteria
Katzmarzyk	2005	$\geq 30 \text{ kg/m}^2$	< 3
Song	2007	$\geq 30 \text{ kg/m}^2$	$< 3^a$
Voulgari ^e	2011	$\geq 30 \text{ kg/m}^2$	< 3
Hosseinpanah	2011	$\geq 30 \text{ kg/m}^2$	$< 3^b$
Hamer	2012	$\geq 30 \text{ kg/m}^2$	$< 2^c$
Ortega	2013	$\geq 30 \text{ kg/m}^2$	$\leq 1^a$
Irace	2009	$> 29.9 \text{ kg/m}^2$	< 3
Khan	2011	$> 25 \text{ kg/m}^2$	$< 3^d$
Consensus	2009	$> 30 \text{ kg/m}^2$	< 3

Asiáticos

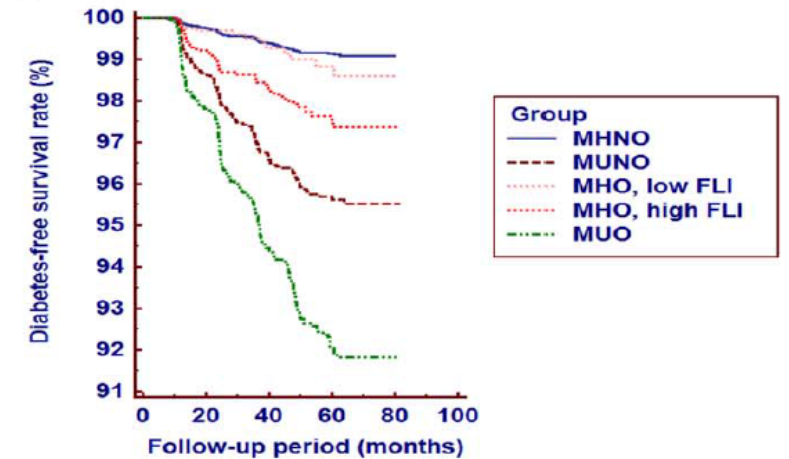
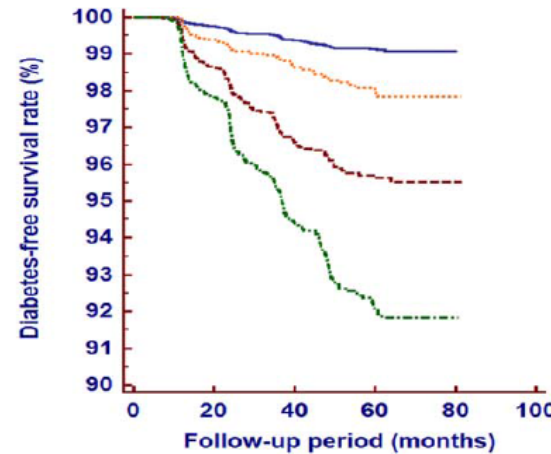
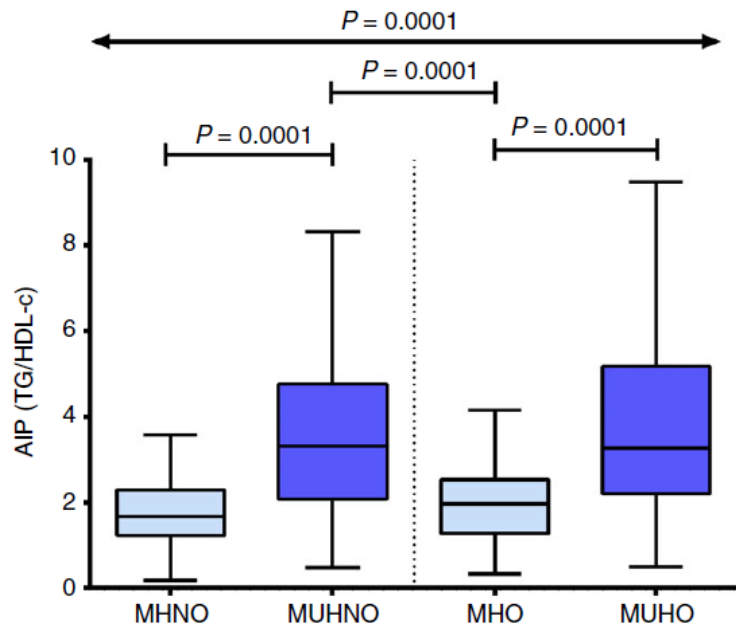
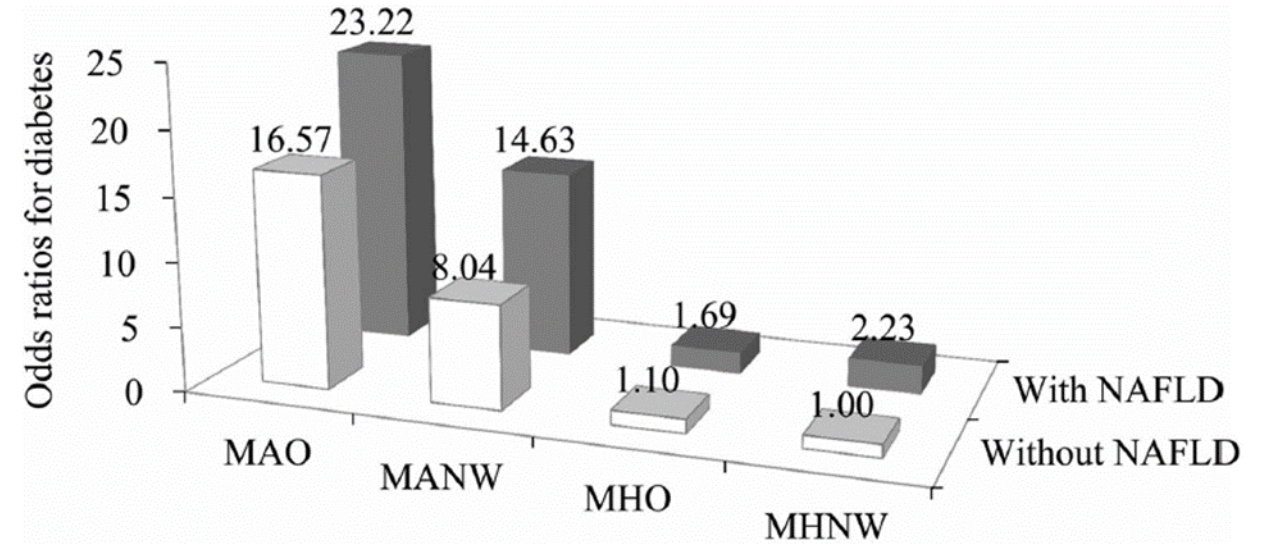
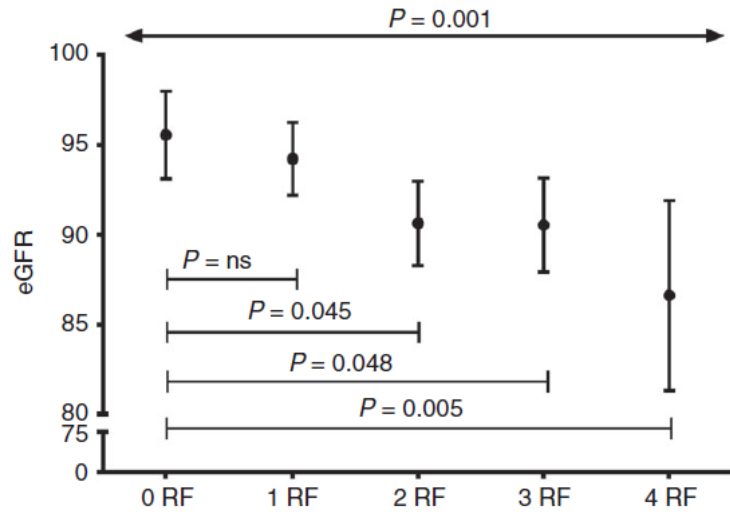




¿El estado metabólico de la obesidad determina los outcomes de la EHGNA?

Mirando más allá del hígado





- **La obesidad se puede acompañar de factores de riesgo metabólicos adicionales, que confieren peor un pronóstico.**
- **La obesidad metabólica “sana” no debería ser considerada como tal.**
 - Incrementa el riesgo de EHGNA (esteatosis, esteatohepatitis y fibrosis).
 - Incrementa el riesgo cardiovascular.
 - Incrementa el riesgo de disturbios metabólicos (ej: diabetes mellitus).
- **La obesidad metabólica sana suele ser una transición hacia el metabolismo enfermo.**
 - EHGNA determina la transición de obesidad metabólica sana a enferma (esteatohepatitis y fibrosis).
- **La obesidad metabólicamente enferma (IMC>30 más un factor de riesgo) debería obligarnos a descartar la presencia de EHGNA.**
- **En pacientes con EHGNA y obesidad metabólica enferma, debemos estar atentos:**
 - Incidencia de diabetes mellitus.
 - Deterioro de la función renal.
 - Riesgo cardiovascular.

Muchas Gracias



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