DALLA MEDICINA
DELLE PATOLOGIE
ALLA SFIDA DELLE
COMPLESSITÀ:

evoluzione e prospettive nella gestione della malattia diabetica

Dalla steatosi epatica al diabete e viceversa: una pericolosa associazione

Ilaria Barchetta

Dipartimento Medicina Sperimentale

Università Sapienza, Roma

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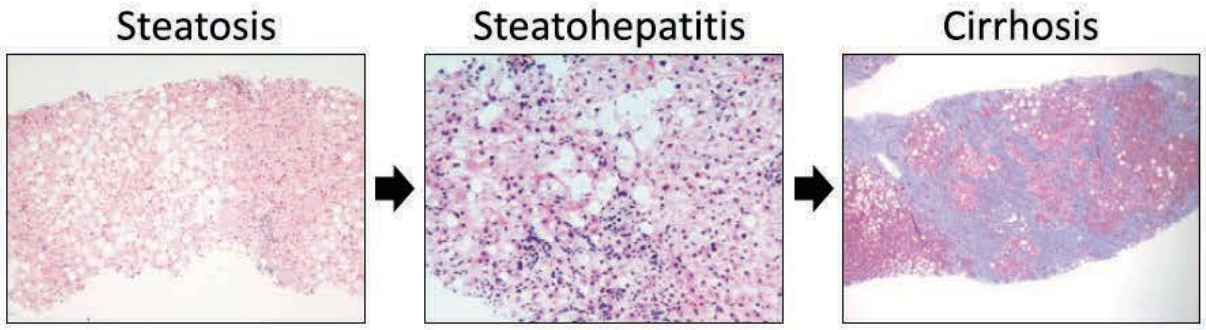
Steatosi epatica non alcolica (NAFLD):

Presenza di steatosi epatica in assenza di introito significativo di alcol o altre cause identificabili



The histologic spectrum of NAFLD. Left: Steatosis without inflammation, hepatocyte ballooning, or fibrosis. Middle: Steatohepatitis with hepatocyte ballooning, Mallory-Denk bodies, lobular inflammation, and perisinusoidal fibrosis. Right: Cirrhosis with residual steatosis. Pictures were kindly provided by Dr. Elizabeth Brunt (Washington University School of Medicine in St. Louis).

- **Hepatic steatosis can occur when there is more than 5% fat in hepatocytes**, progression can ensue if these fatty hepatocytes are exposed to insults or stress, which can then cause cell death, apoptosis, inflammation, and fibrosis, leading to **NASH**.
- As NASH progresses, hepatic fibrosis develops, the liver becomes stiff and functionally impaired, which can lead to **cirrhosis, HCC, decompensated cirrhosis, death, and/or liver transplantation.**

Finck BN. Diabetes, 2018

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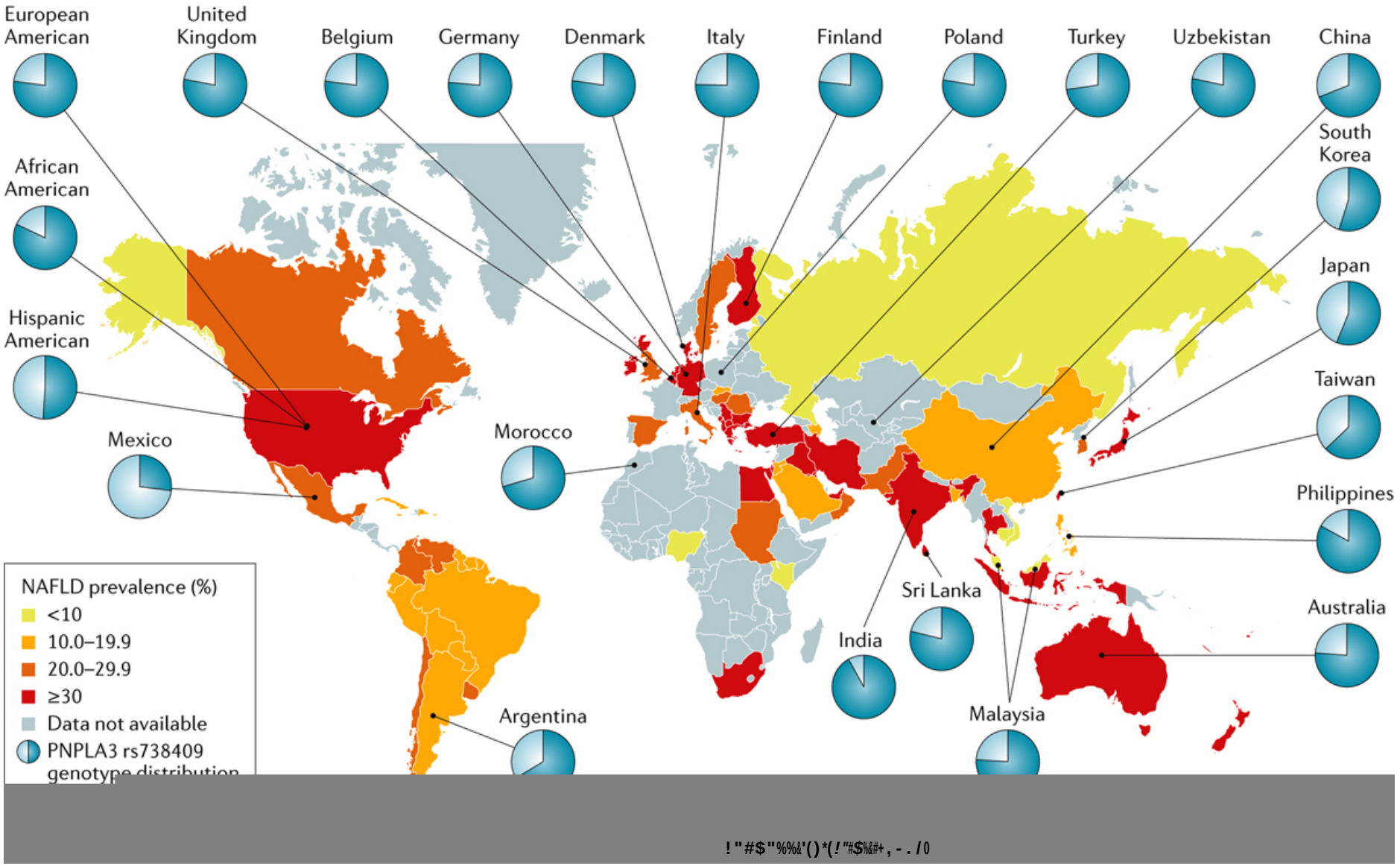
European American
United Kingdom
Belgium
Germany
Denmark
Italy
Finland
Poland
Turkey
Uzbekistan
China
South Korea
African American
Japan
Hispanic American
Taiwan
Mexico
Morocco
Philippines
Sri Lanka
Australia
India
Argentina
Malaysia
NAFLD prevalence (%)
<10
10.0–19.9
20.0–29.9
≥30
Data not available
PNPLA3 rs738409 genotype distribution

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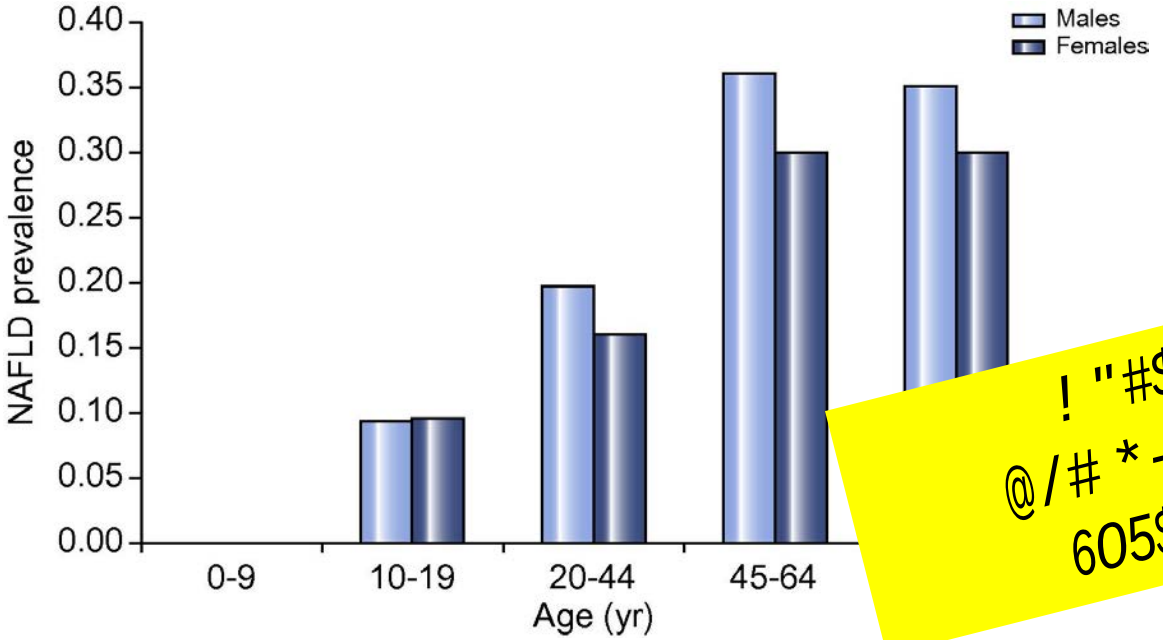

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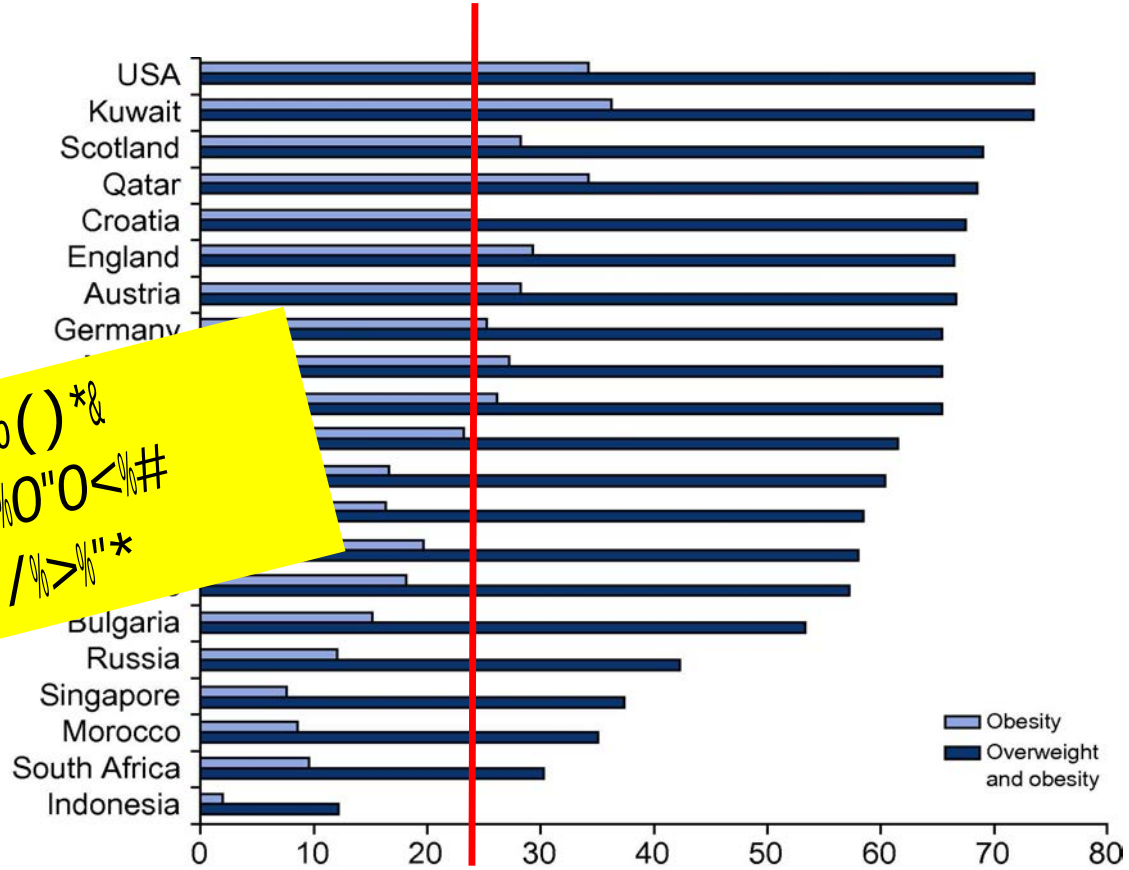

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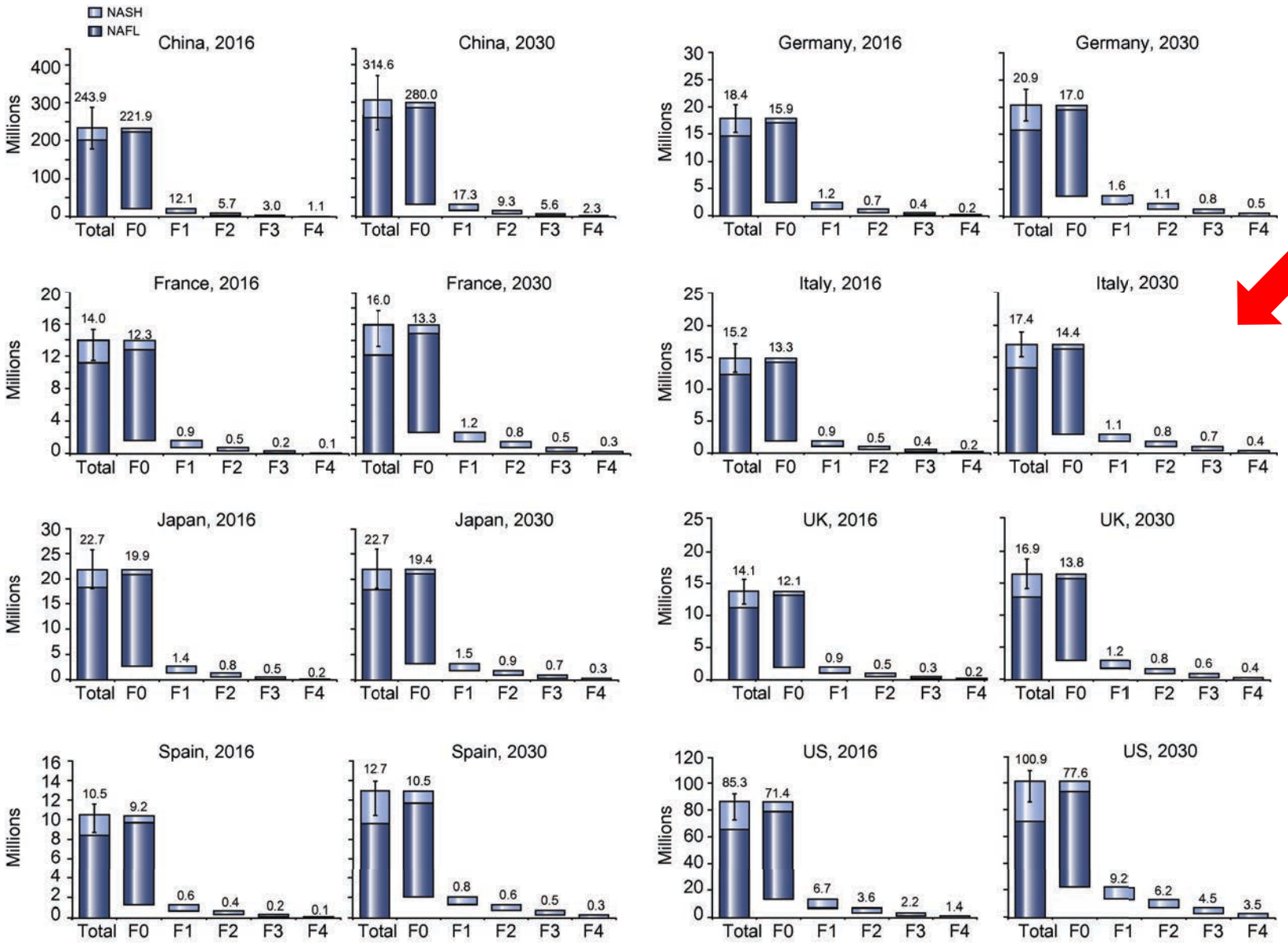
NAFLD: prevalenza in relazione al grado di fibrosi 2016 -> 2030



Italia

Prevalenza NAFLD
25% popolazione generale
28% negli individui ≥15 anni

La più alta prevalenza stimata di NAFLD nel 2030: Italia, **29.5%**

Estes C et al, J Hepatol. 2018 Oct;69(4):896-904

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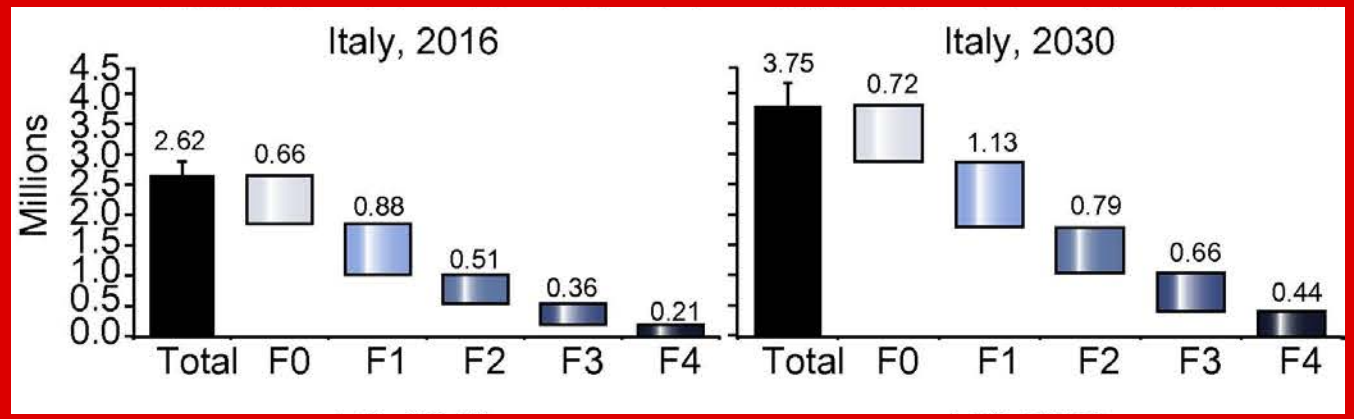

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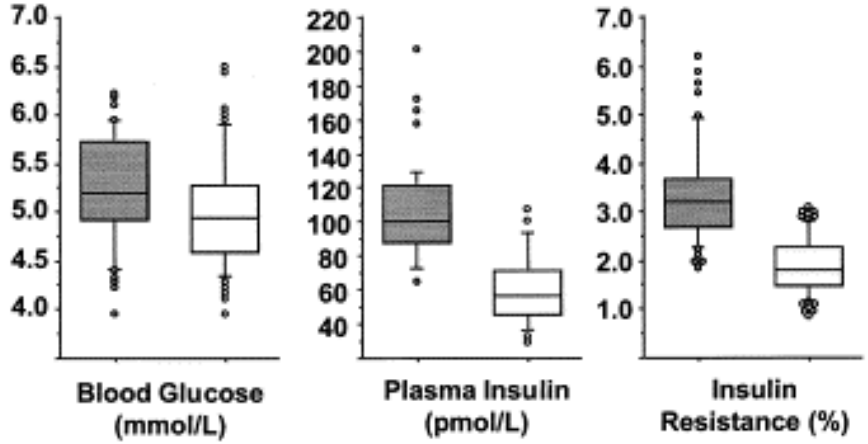

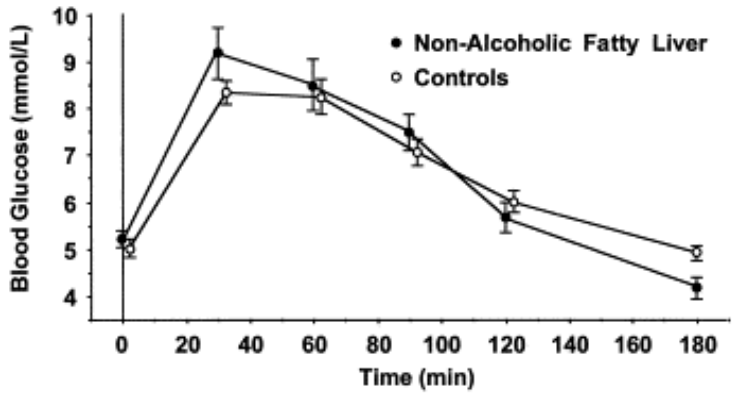

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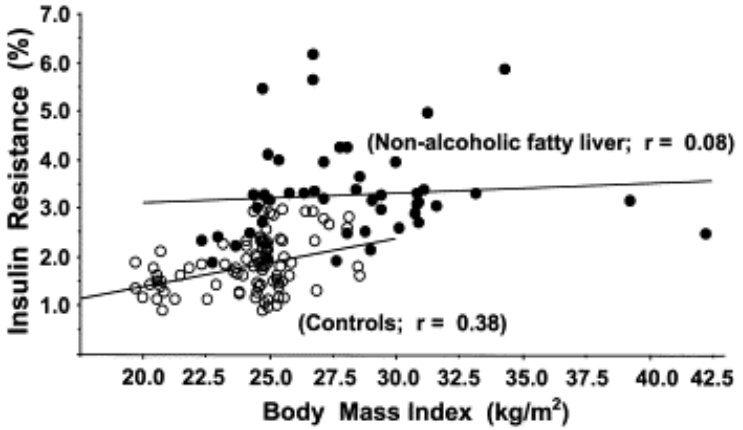

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Insulin Resistance, the Metabolic Syndrome, and Nonalcoholic Fatty Liver Disease

F. Angelico, M. Del Ben, R. Conti, S. Francioso, K. Feole, S. Fiorello, M. G. Cavallo, B. Zalunardo, F. Lirussi, C. Alessandri, and F. Violi

IR and prevalence of severe liver steatosis in 308 nondiabetic subjects with different clustering of risk factors

	No. of associated risk factors[a]			
	0 (n = 23)	1–2 (n = 113)	3–5 (n = 100)	*P*
Age (yr)	55.3 ± 14.8	53.6 ± 14.6	52.4 ± 12.6	0.647
Mean HOMA-IR	2.2 ± 0.7	3.6 ± 2.2	5.2 ± 3.2	<0.001
ALT (U/liter)	24.0 ± 13.6	37.5 ± 25.6	41.2 ± 24.4	<0.02
Severe liver steatosis (%)	19.0	34.8	41.0	<0.01
Mild/absent liver steatosis (%)	38.1	30.1	26.5	0.554
Increased waist circumference (%)		65.8	84.6	<0.001
Hypertriglyceridemia (%)		33.8	75.3	<0.001
Low HDL-cholesterol (%)		26.4	71.0	<0.001
Fasting hyperglycemia (%)		18.0	50.3	<0.001
High blood pressure (%)		58.5	88.7	<0.001

[a] As defined in *Patients and Methods* on the basis of the ATPIII criteria.

*Subjects with the **metabolic syndrome** with a **more pronounced insulin resistance had a higher prevalence of severe steatosis** ($P < 0.01$) compared with those with homeostasis model of insulin resistance below the median*

Angelico F […] Cavallo MG et al, JCEM 2004

Sviluppo e progressione di NAFLD sono strettamente correlati a **insulino-resistenza, obesità** e **diabete mellito di tipo 2**

Abnormal Lipid and Glucose Metabolism in Obesity: Implications for Nonalcoholic Fatty Liver Disease

Frank Anania, MD, FACP, AGAF

SAMIR PAREKH and FRANK A. ANANIA

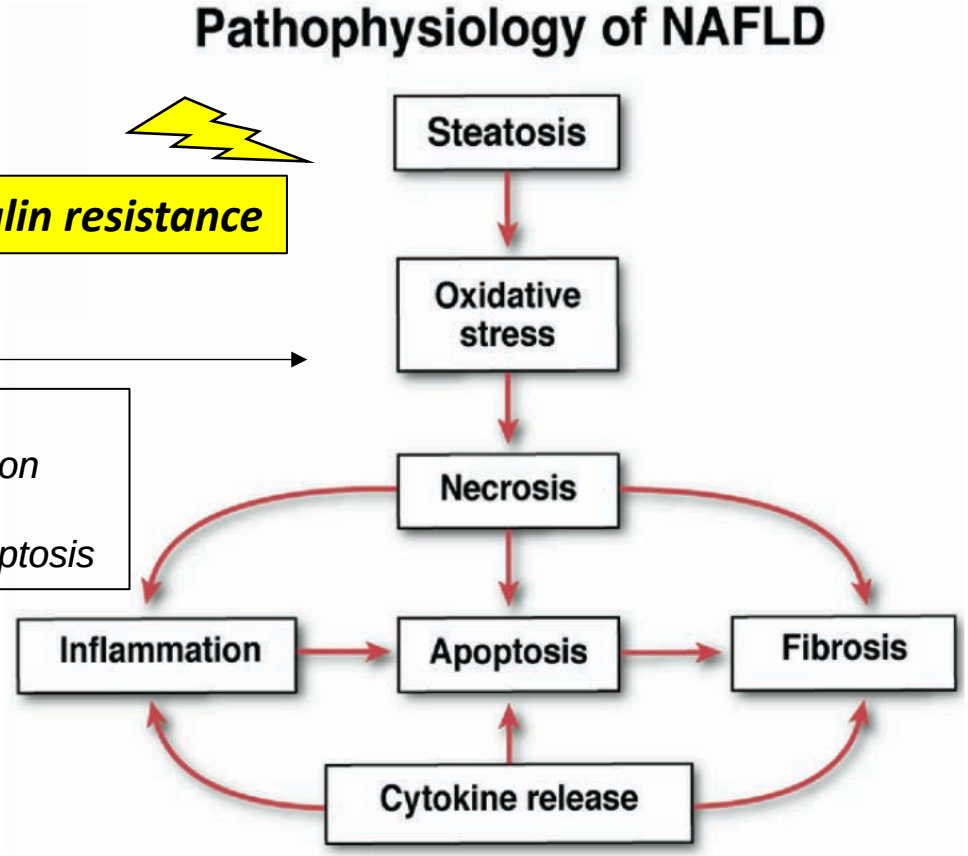
Emory University School of Medicine, Department of Medicine, Division of Digestive Diseases, Atlanta, Georgia

The two hits hypothesis

1. Insulin resistance

2.

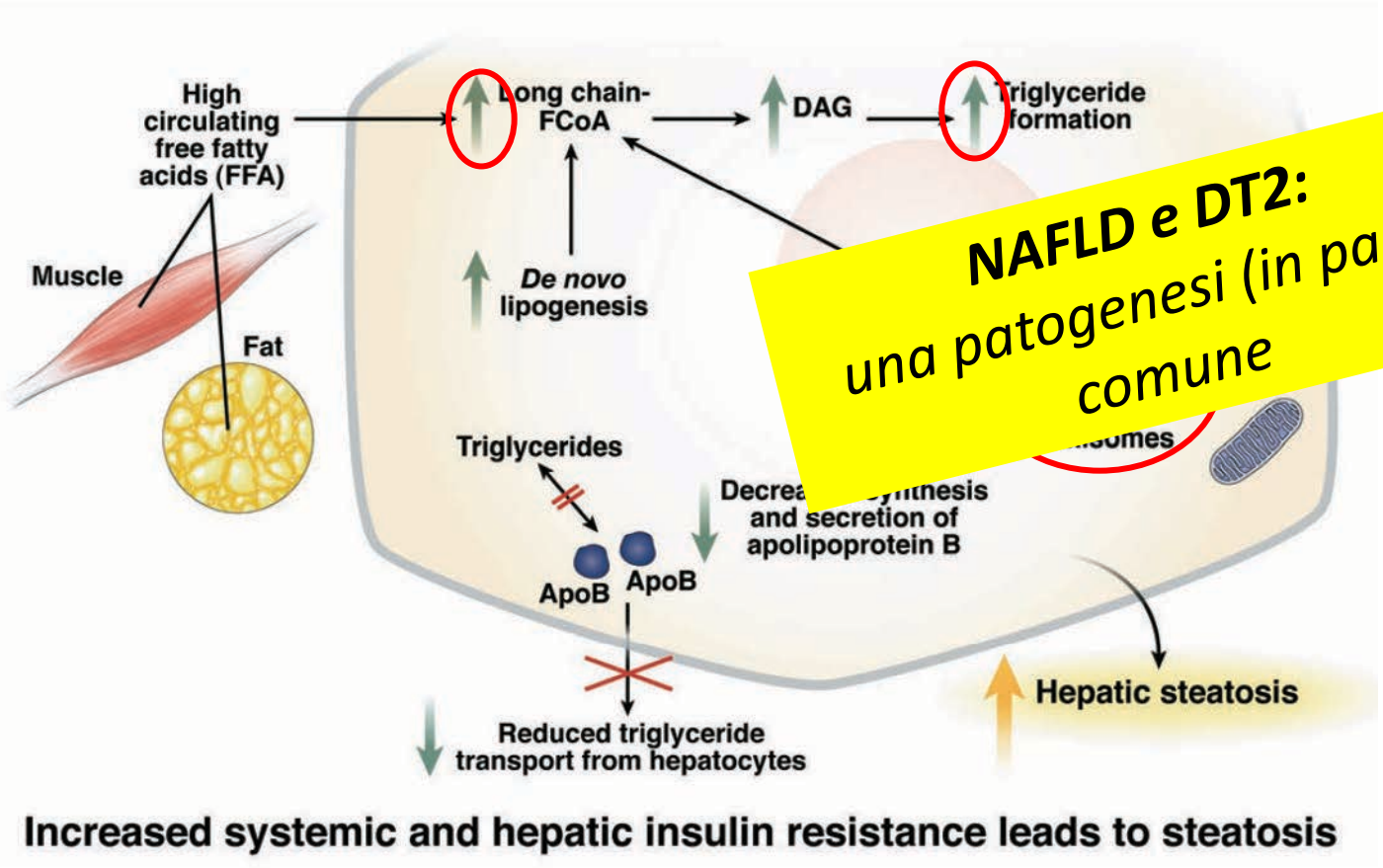
Lipid peroxidation
Impaired mitochondrial and FAs peroxisomal oxidation
Release of cytokines, chemokines and adipokines
Lobular inflammation, hepatocyte necrosis, and apoptosis



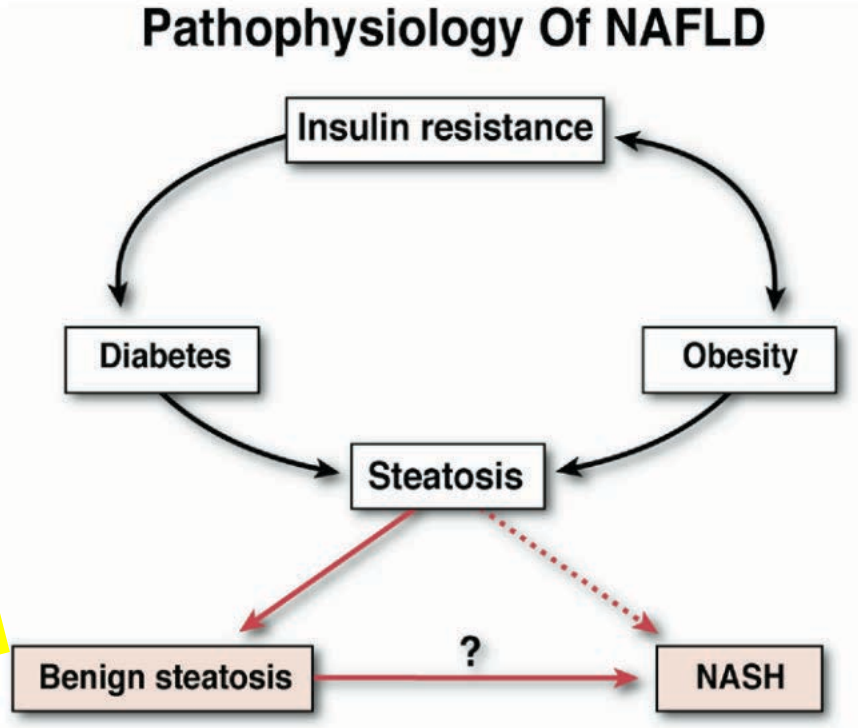
GASTROENTEROLOGY 2007;132:2191–2207

Evolution of inflammation in nonalcoholic fatty liver disease:
The two hits hypothesis

Sovraccarico cronico FFAs e iperglicemia --> alterato metabolismo epatico



NAFLD e DT2:
una patogenesi (in parte) comune



GASTROENTEROLOGY 2007;132:2191–2207

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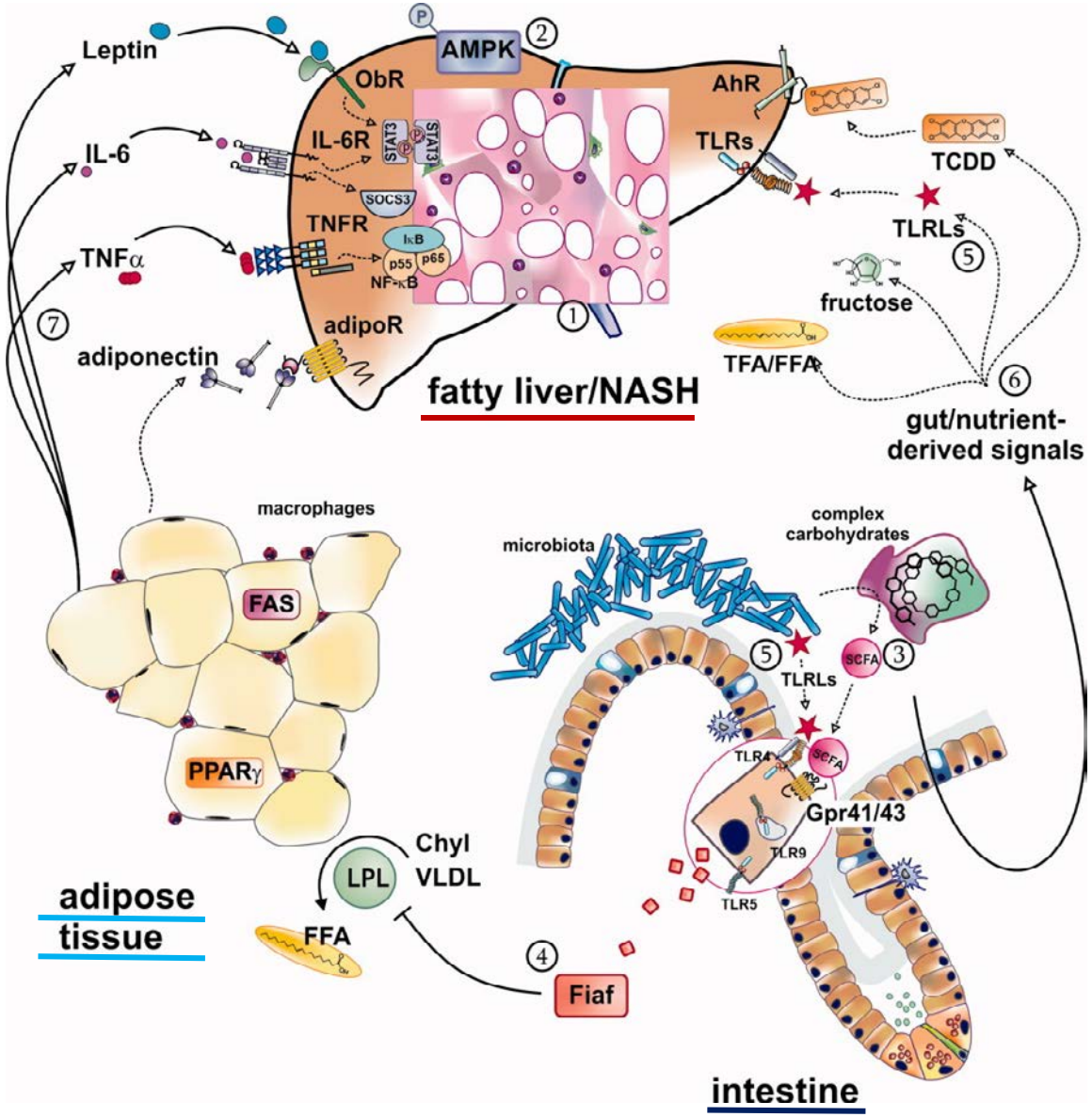

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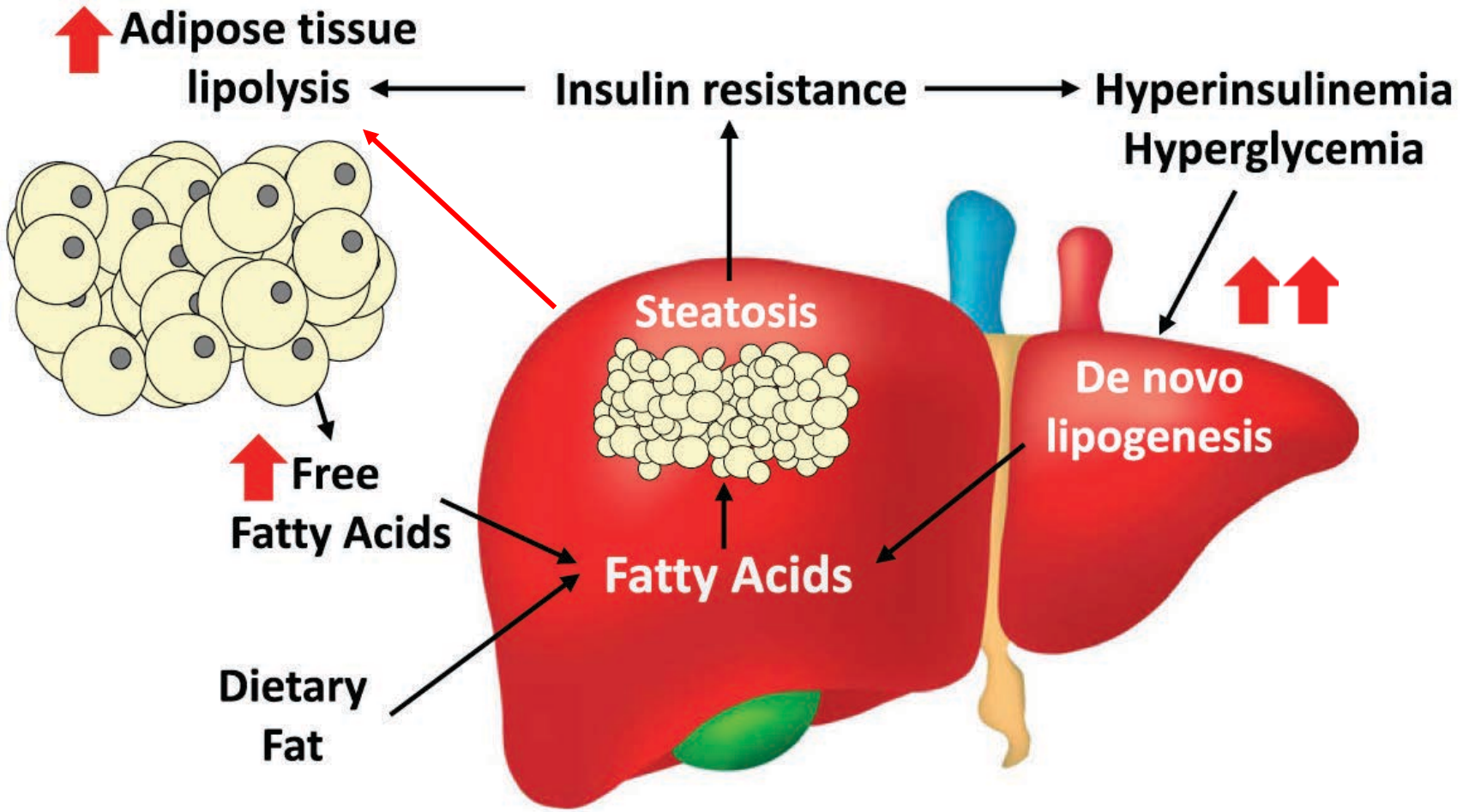
Interazione tra insulino-resistenza, diabete tipo 2 e NAFLD

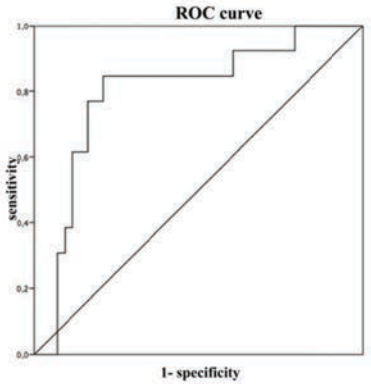


Modificato da Finck BN. Diabetes, 2018

Phenotypical heterogeneity linked to adipose tissue dysfunction in patients with Type 2 diabetes

Ilaria Barchetta*, Francesco Angelico*, Maria Del Ben*, Michele Di Martino†, Flavia Agata Cimini*, Laura Bertoccini†, Licia Polimeni*, Carlo Catalano†, Antonio Fraioli*, Riccardo Del Vescovo§, Sergio Morini§, Marco Giorgio Baroni† and Maria Gisella Cavallo*

- **55.4% of T2D patients had NAFLD**
- **Younger and more insulin-resistant** than non-NAFLD subjects
- Adipose tissue-associated insulin resistance (ADIPO-IR) was the main determinant of NAFLD in T2D



Area under the curve

Area	Standard error[a]	Asintotic significance[b]	Asintotic 95%Confidence Interval	
			Lower limit	Upper limit
0.796	0.073	0.001	0.653	0.939

	NAFLD ($n=36$)	Non-NAFLD ($n=29$)	*P*-value
Age (years)	**56.2±9.7**	**61.7±8.8**	**0.010**
Sex (males/females)	26/10	21/8	n.s.*
BMI (kg/m^2)	30.4±4.4	29.4±4.2	n.s.
Waist circumference (cm)	106.2±14.2	100.4±10.2	n.s.
T2D duration (years)	6±5	8.3±8	n.s.
SBP (mmHg)	127.5±16.3	133.9±16.6	n.s.
DBP (mmHg)	81±9.6	81.8±10.4	n.s.
Total cholesterol (mg/dl)	176.2±36.9	176.4±38.1	n.s.
HDL-C (mg/dl)	48.4±15.1	49.9±12.9	n.s.
LDL-C (mg/dl)	100.7±35.1	98.9±31.4	n.s.
Triacylglycerols (mg/dl)	135±65.8	137.3±59	n.s.
FBG (mg/dl)	130.4±32.3	134.8±46	n.s.
HbA_{1c} (%/mmol/mol)	6.7±1/50±10	6.5±0.9/48±8	n.s.
AST (IU/l)	26.9±13.3	20.8±11.5	0.012
ALT (IU/l)	39.6±25.2	24.3±12.1	0.001
γ-GT (IU/l)	51.2±61.7	32.3±33.2	n.s.
AST/ALT	0.74±0.2	0.92±0.3	0.005
FFAs (μmol/l)	549.2±281	484.8±215.5	n.s.
FBI (μ-units/l)	14±5.1	10.2±5.3	0.004
FLI	70.2±23.3	59.3±26.1	n.s.
HOMA-IR	4.4±1.6	3.2±1.9	0.025
HOMA-β%	103.3±72.2	70.8±48.8	n.s.
Quantitative insulin sensitivity check index (QUICKI)	0.31±0.02	0.33±0.03	0.025
ADIPO-IR	7.3±3.9	5±4.6	0.008
CRP	4.2±5	2.1±2.7	0.05
Adiponectin (μg/ml)	6.5±3	6.1±3.8	n.s.
Insulin treatment (*n* patients/%)	4/9	7/28	n.s.*
Number of oral anti-diabetic agents (% patients)			
0	12	15	n.s.†
1	47	43	
2	32	27	
3	9	15	
Statin treatment (*n* patients/%)	18/52	18/64	n.s.*
Anti-hypertensive treatment (*n* patients/%)	29/80	21/72	n.s.*

Clinical Science (2016) **130**, 1753–1762 doi: 10.1042/CS20160348

nutrients

MDPI

Brief Report

Neurotensin Is a Lipid-Induced Gastrointestinal Peptide Associated with Visceral Adipose Tissue Inflammation in Obesity

Ilaria Barchetta [1], Flavia Agata Cimini [1], Danila Capoccia [1], Laura Bertoccini [1], Valentina Ceccarelli [1], Caterina Chiappetta [2], Frida Leonetti [1], Claudio Di Cristofano [2], Gianfranco Silecchia [2], Marju Orho-Melander [3], Olle Melander [3] and Maria Gisella Cavallo [1,*]

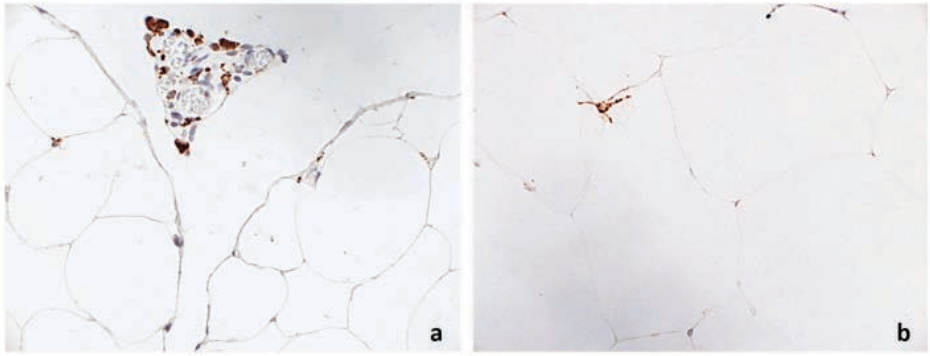


Figure 1. Immunohistochemical expression of CD68 in: VAT of a patient with high proNT ((**a**), 400×), and VAT of a patient with low proNT ((**b**), 400×).

Table 2. Pro-NT-Bivariate correlation analyses (Pearson's coefficient, * Spearman's coefficient, pro-NT is considered a continuous variable).

Parameter	Correlation Coefficient	*p*-Value
Age	0.43	0.004
Gender (M/F)	0.02 *	0.89
BMI	0.31	−0.16
Waist circumference	−0.16	0.31
FBG	0.07	0.67
FBI	0.38	0.02
HbA1c	0.40	0.012
Total Cholesterol	0.02	0.89
HDL	−0.04	0.78
LDL	0.02	0.88
Triglycerides	0.39	0.012
AST	−0.08	0.61
ALT	0.04	0.80
T2D yes/no	0.33 *	0.039
NAFLD yes/no	0.41 *	0.01
NAS score	0.36 *	0.023

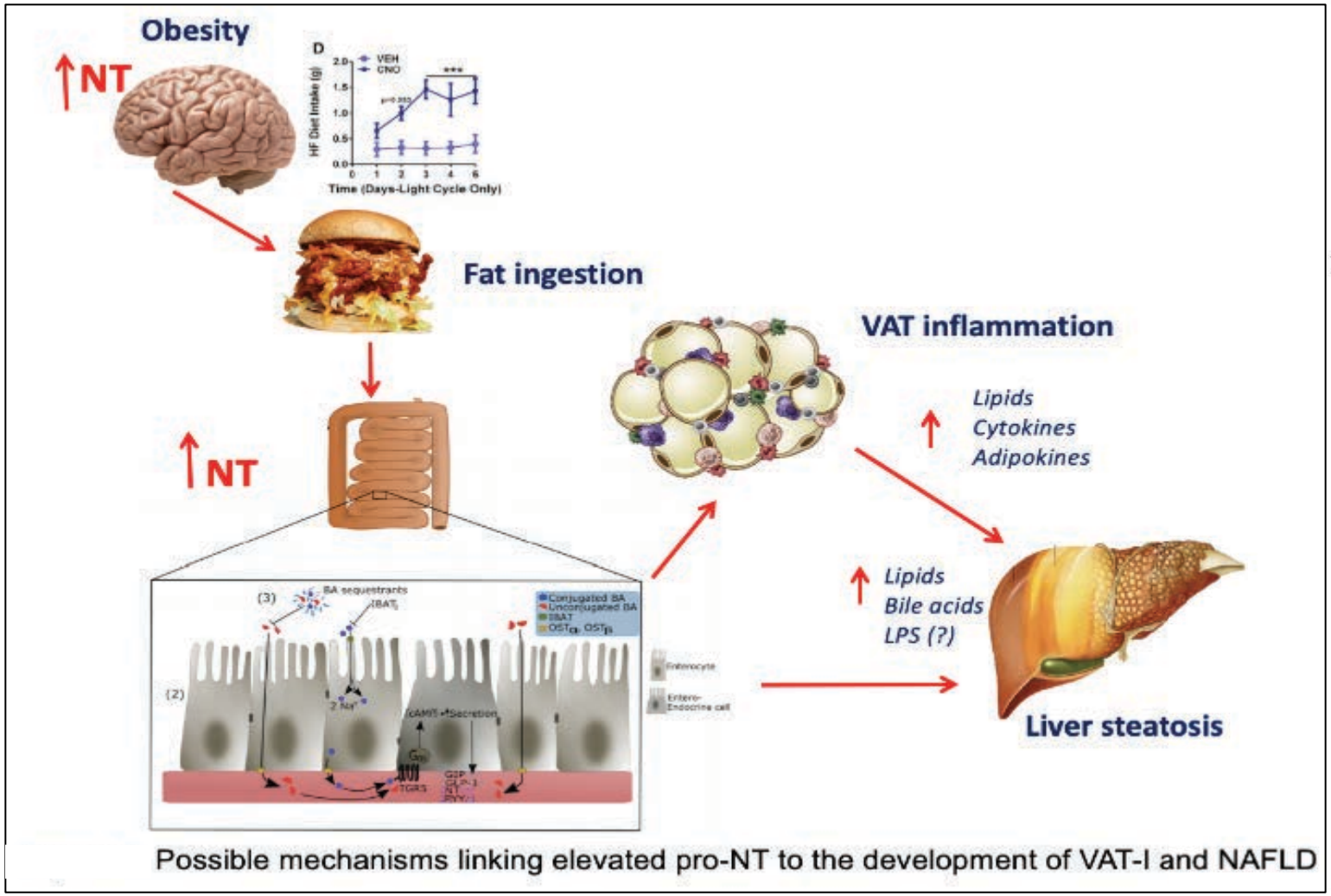
Table 3. Bivariate correlation analyses between circulating pro-NT levels and VAT gene expression (Spearman's coefficient).

Gene	Correlation Coefficient	*p*-Value
NTN1	−0.11	0.50
UNC5B	0.42	0.009
CAV1	0.11	0.50
IL8	−0.08	0.61
MIP1A	0.08	0.61
MIP2	0.11	0.50
TIMP1	0.15	0.38
GZMB	−0.13	0.43
CASP3	−0.02	0.9
CASP7	0.09	0.58
PARP1	0.16	0.43
HIF-1α	0.41	0.011
WISP1	0.37	0.022

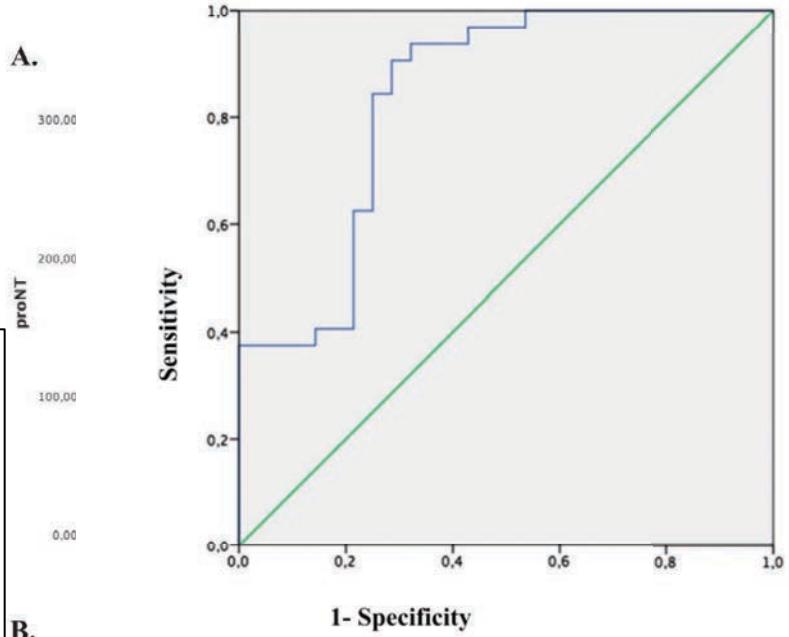
Barchetta I et al, Nutrients 2018

Increased Plasma Proneurotensin Levels Identify NAFLD in Adults With and Without Type 2 Diabetes

Ilaria Barchetta,[1] Flavia Agata Cimini,[1] Frida Leonetti,[1] Danila Capoccia,[1] Claudio Di Cristofano,[2] Gianfranco Silecchia,[2] Marju Orho-Melander,[3] Olle Melander,[3] and Maria Gisella Cavallo[1]



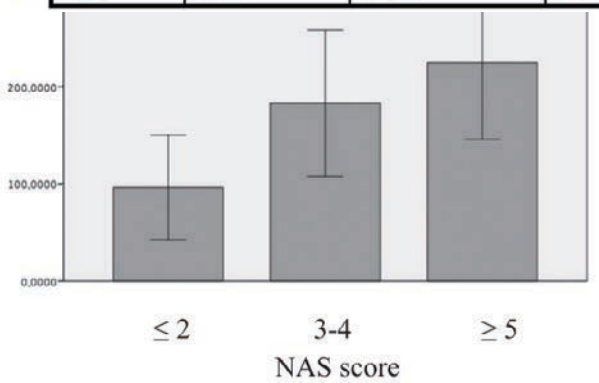
A.



B.

Area under the curve

Area	Standard error[a]	Asintotic significance[b]	Asintotic 95%Confidence Interval	
			Lower limit	Upper limit
0.836	**0.054**	**<0.001**	**0.731**	**0.941**



NAS score	n. of subjects	Pro-NT (pmol/L)	P value
≤ 2	37	92.3 ± 53.8	#0.001; ^<0.001
3-4	11	182.8 ± 75	#0.001; °0.39
≥ 5	12	224.6 ± 79.1	^<0.001; °0.39

Barchetta I et al, JCEM 2018

RESEARCH ARTICLE BMC Medicine

Elevated plasma copeptin levels identify the presence and severity of non-alcoholic fatty liver disease in obesity

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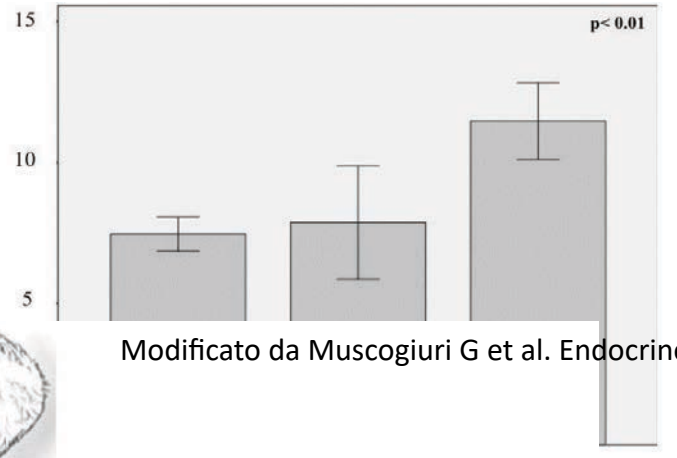


Modificato da Muscogiuri G et al. Endocrine 2018

NAFLD e DT2:
una patogenesi complessa che identifica alcune noxae comuni

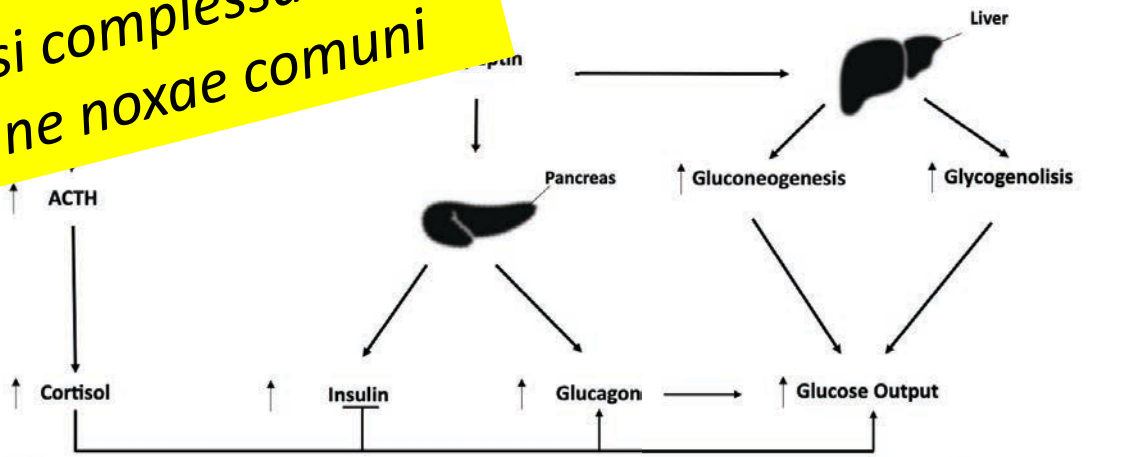


Fig. 1 Mechanism of action of copeptin. Low water intake stimulates the secretion of copeptin that in turn potentiates CRH action resulting in an increased ACTH and cortisol secretion. Copeptin acts on liver stimulating glycogenolysis and gluconeogenesis. Further, pancreas is another target of copeptin, which contributes to the regulation of insulin and glucagon secretion

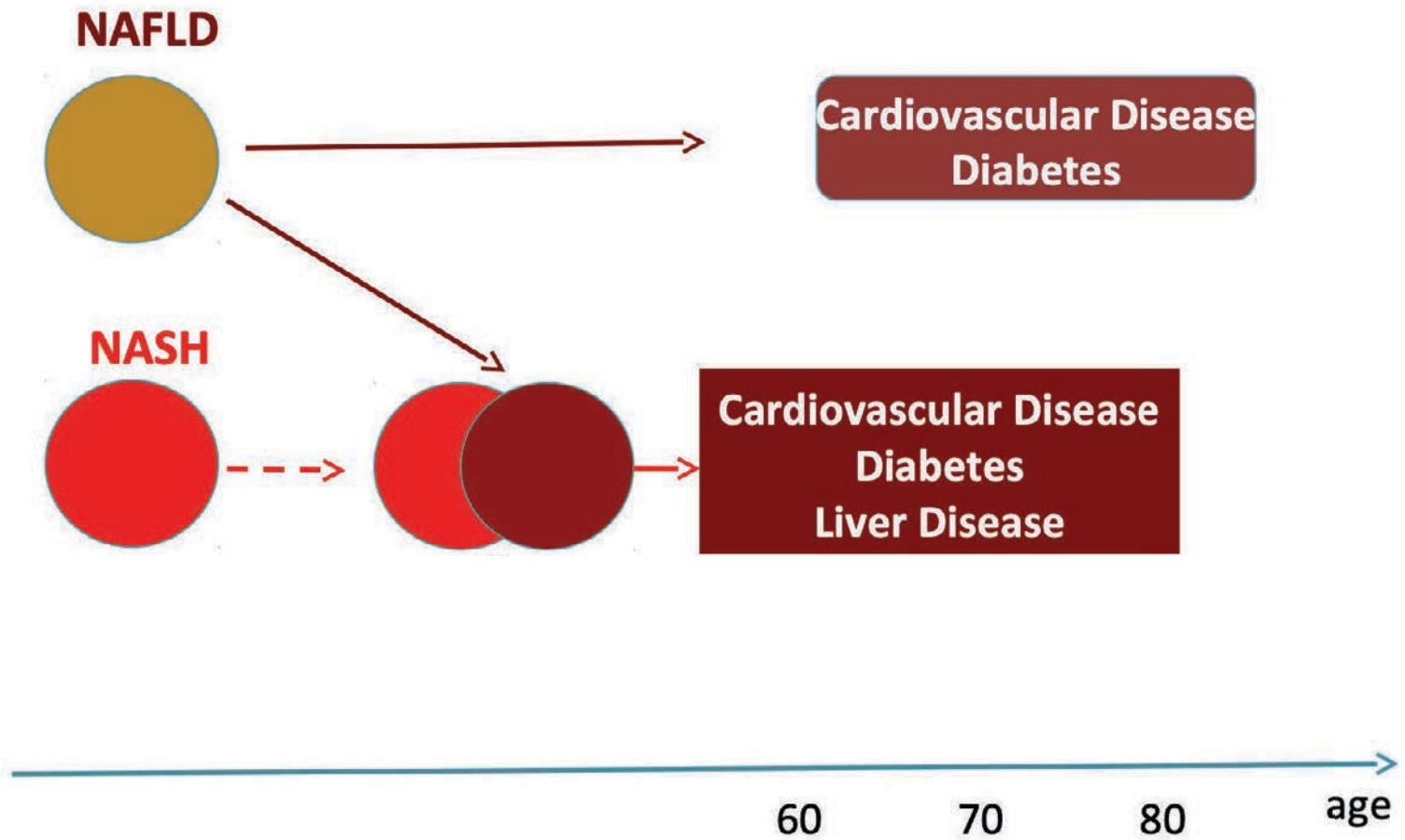
Multivariate logistic regression analysis. The p
continuous variable

	β	S.E.	Wald	β-standardized
Age	0.33	0.17	3.47	0.63
Sex (M/F)	− 1.08	1.88	0.33	− 0.11
Copeptin	0.547	0.27	4.09	0.54
T2DM (yes/no)	1.65	1.85	0.79	0.13
Serum creatinine	0.57	5.4	0.01	− 0.02
Dyslipidemia (yes/no)	0.43	2.80	2.41	0.03
Number of MS components	3.46	1.71	4.09	0.36
	0.92	1.77	0.000	7420
	0.12	0.013	0.000	3.12
	0.043	31.8	1.11	909.1

Cox and Snell $R^2 = 0.408$
Abbreviations: *S.E.* standard error, *CI* confidence interval, *T2DM* type 2 diabetes mellitus, *MS* metabolic syndrome

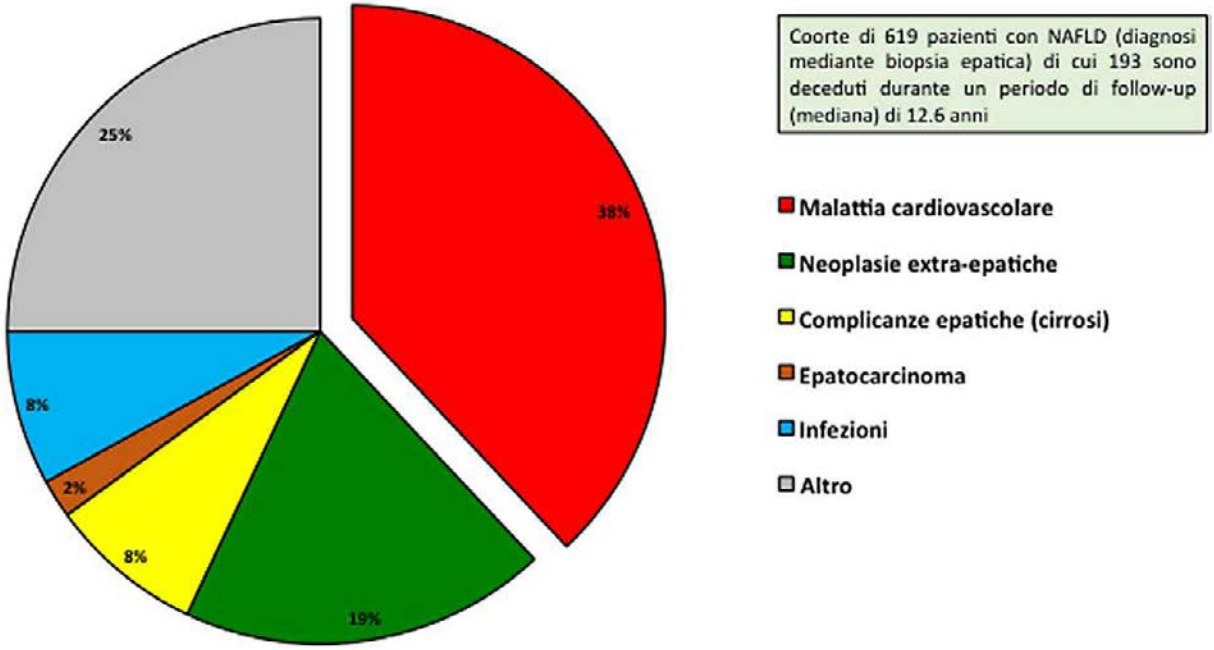
Barchetta *et al. BMC Medicine* (2019) 17:85
https://doi.org/10.1186/s12916-019-1319-4

NAFLD e mortalità



Armstrong et al, Hepatology 2013, modificato da Bellentani S

Principali cause di morte nei pazienti con NAFLD



Mantovani A et al, L'Endocrinologo 2018

Cause of death	*N* (% of all deaths)
Coronary artery disease [ICD-9: 404 (hypertensive heart disease), 410–414 (ischemic heart disease), 427-429 (cardiac dysrhythmias, heart failure), 440 (atherosclerosis); ICD-10: I20–I25 (ischemic heart diseases), I46 (cardiac arrest), I50 (heart failure)]	32 (27.8 %)
Liver-related [ICD-9: 571–572 (chronic liver disease, cirrhosis, sequelae of CLD), 155.0 (primary liver cancer); ICD-10: K72–K74 (hepatic failure, chronic hepatitis, fibrosis and cirrhosis of liver), C22.0 (liver cell carcinoma)]	30 (26.1 %)
Malignancy [ICD-9: 151–153 (gastrointestinal), 157 (pancreas), 189 (kidney), 199 (other), 201 (Hodgkin's disease), 202 (other lymphoma); ICD-10: C18 (colon), C34 (lung), C64 (kidney), C81 (Hodgkin's disease), C97 (multiple)]	18 (15.7 %)
Other (diabetes, infection, pulmonary, accident, unknown)	35 (30.4 %)
Total (% of the studied cohort)	115 (39.8 %)

NAFLD e NASH: il cuore del problema

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

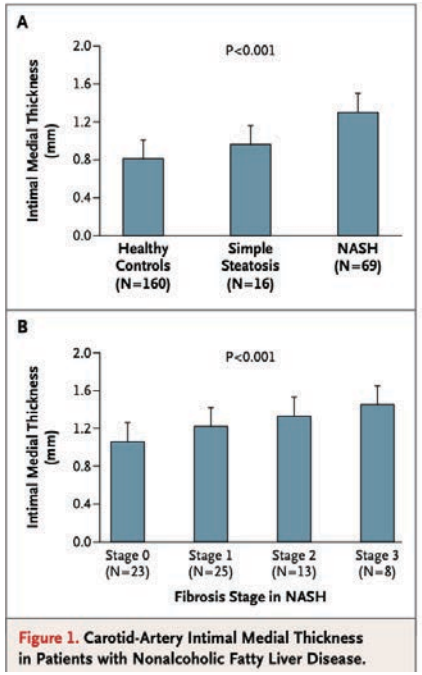


Figure 1. Carotid-Artery Intimal Medial Thickness in Patients with Nonalcoholic Fatty Liver Disease.

CURRENT CONCEPTS

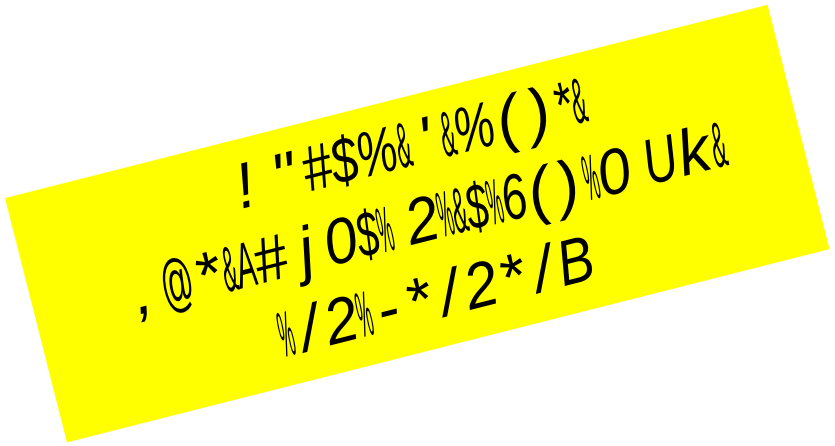
Risk of Cardiovascular Disease in Patients with Nonalcoholic Fatty Liver Disease

Giovanni Targher, M.D., Christopher P. Day, M.D., Ph.D., and Enzo Bonora, M.D., Ph.D.

Table 1. Principal Prospective Studies of the Association between Nonalcoholic Fatty Liver Disease and the Incidence of Major Cardiovascular Events.*

Investigators	Study Population	Age	Length of Follow-up	Outcomes	Main Results
			years		
Hamaguchi et al.[40]	Community-based cohort of 1637 healthy subjects in Japan	22–83	5	Nonfatal coronary heart disease, ischemic stroke, and cerebral hemorrhage events	Increased risk of nonfatal CVD events associated with NAFLD independently of age, sex, BMI, smoking status, alcohol consumption, blood pressure, LDL cholesterol, triglycerides, and HDL cholesterol
Targher et al.[41]	Nested case–control study in an outpatient cohort of patients with type 2 diabetes in Italy; 248 patients and 496 control subjects matched for age and sex, who did not have CVD or viral hepatitis at baseline	40–79	5	Death from CVD and nonfatal myocardial infarction, ischemic stroke, and revascularization procedures	Increased risk of fatal and nonfatal CVD events associated with NAFLD independently of age, sex, BMI, waist circumference, smoking status, medication use (lipid-lowering, hypoglycemic, antihypertensive, and antiplatelet drugs), alcohol consumption, duration of diabetes, and levels of blood pressure, glycated hemoglobin, LDL cholesterol, triglycerides, HDL cholesterol, and GGT activity
Targher et al.[42]	Valpolicella Heart Diabetes Study: outpatient cohort of 2103 patients with type 2 diabetes in Italy who did not have CVD or viral hepatitis at baseline	40–79	6.5	Death from CVD and nonfatal myocardial infarction, ischemic stroke, and revascularization procedures	Increased risk of fatal and nonfatal CVD events associated with NAFLD independently of age, sex, BMI, waist circumference, smoking status, medication use, alcohol consumption, blood pressure, diabetes duration, glycated hemoglobin, LDL cholesterol, triglycerides, HDL cholesterol, and GGT
Haring et al.[43]	Study of Health in Pomerania: population-based study of 4160 men and women in Germany who did not have viral hepatitis or cirrhosis at baseline	20–79	7.3	Death from any cause and death from CVD	Increased risk of death from any cause and death from CVD among men with NAFLD, independent of age, sex, waist circumference, alcohol consumption, physical activity, educational level, civil status (living alone vs. living with a spouse or partner), blood pressure, status with respect to diabetes, and Groll functional comorbidity index[44]

* Nonalcoholic fatty liver disease (NAFLD) was diagnosed on the basis of ultrasonographic findings in all the studies, with one exception: in the Study of Health in Pomerania, NAFLD was diagnosed on the basis of ultrasonographic findings, an elevated γ-glutamyltransferase (GGT) level, or both. BMI denotes body-mass index, CVD cardiovascular disease, HDL high-density lipoprotein, and LDL low-density lipoprotein.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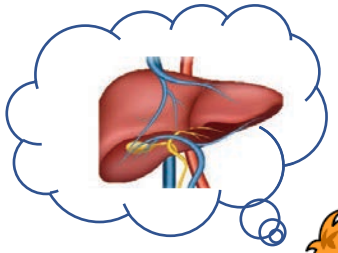

NAFLD nei pazienti con DT2

DT2 nei pazienti con NAFLD

Considerazioni cliniche

NAFLD nei pazienti con DT2

1. Va sospettata ed indagata
2. Peggiora l’insulino-resistenza
3. Peggiora il compenso glicemico

High Prevalence of Nonalcoholic Fatty Liver Disease in Patients With Type 2 Diabetes Mellitus and Normal Plasma Aminotransferase Levels

Prevalence of NAFLD: 50% → 56% NASH

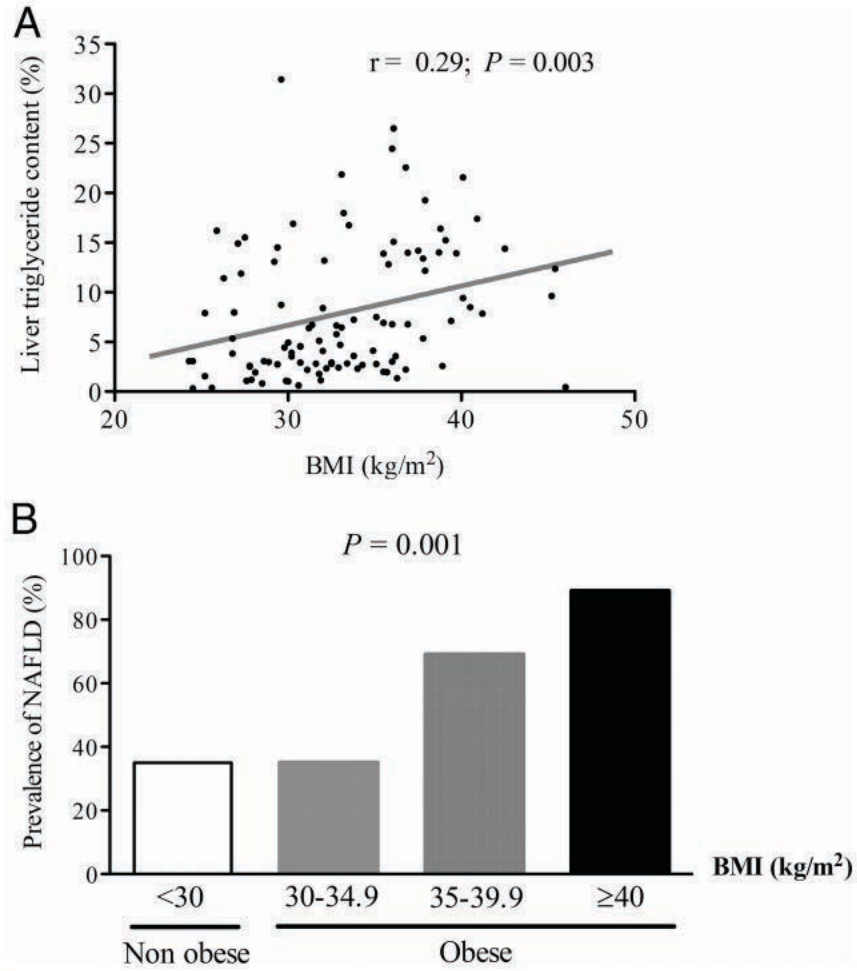

Figure 1. Relationship between BMI and liver triglyceride content measured by ^{1}H-MRS. A, Correlation between BMI and liver triglyceride content. B, Prevalence of NAFLD according to different BMI groups (n = 31, 34, 29, and 9, respectively).

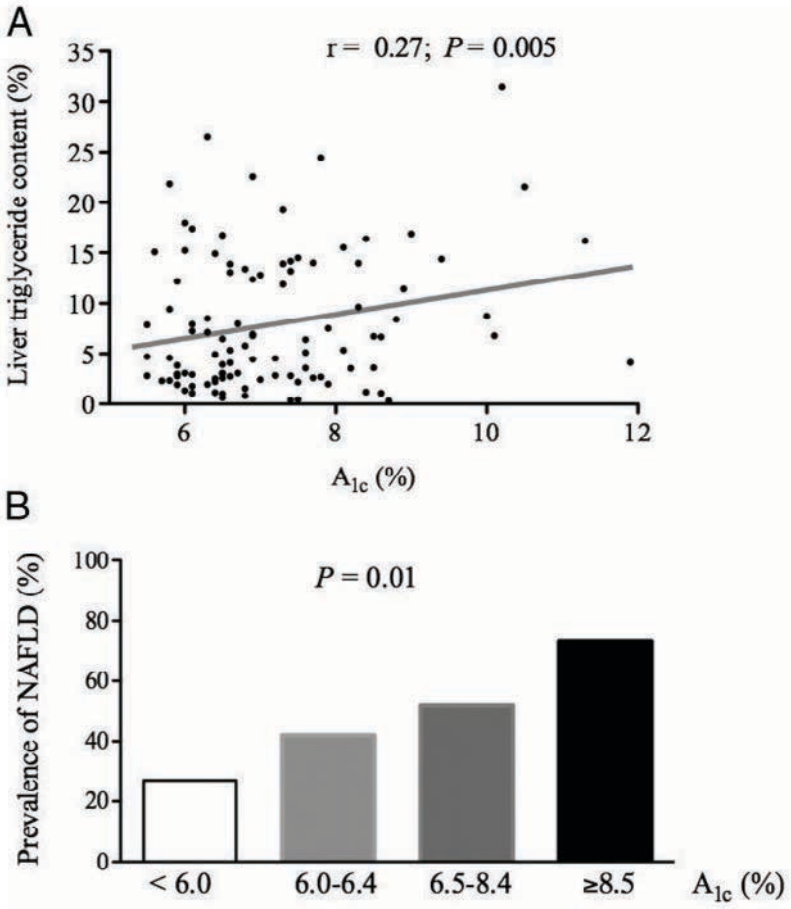

Figure 3. Relationship between glycemic control on liver triglyceride content measured by ^{1}H-MRS. A, Correlation between plasma A_{1c} levels and liver triglyceride content. B, Prevalence of NAFLD among patients with a broad spectrum of plasma A_{1c} levels (n = 15, 19, 54, and 15, respectively).

Portillo-Sanchez P et al, JCEM 2015

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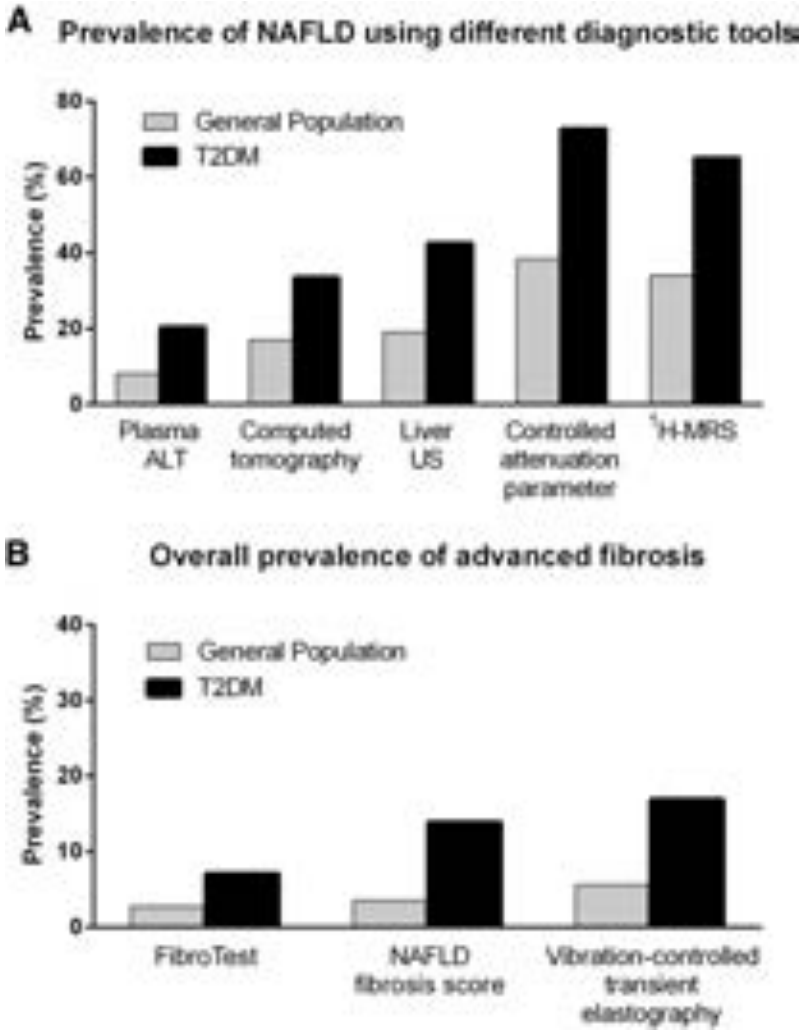

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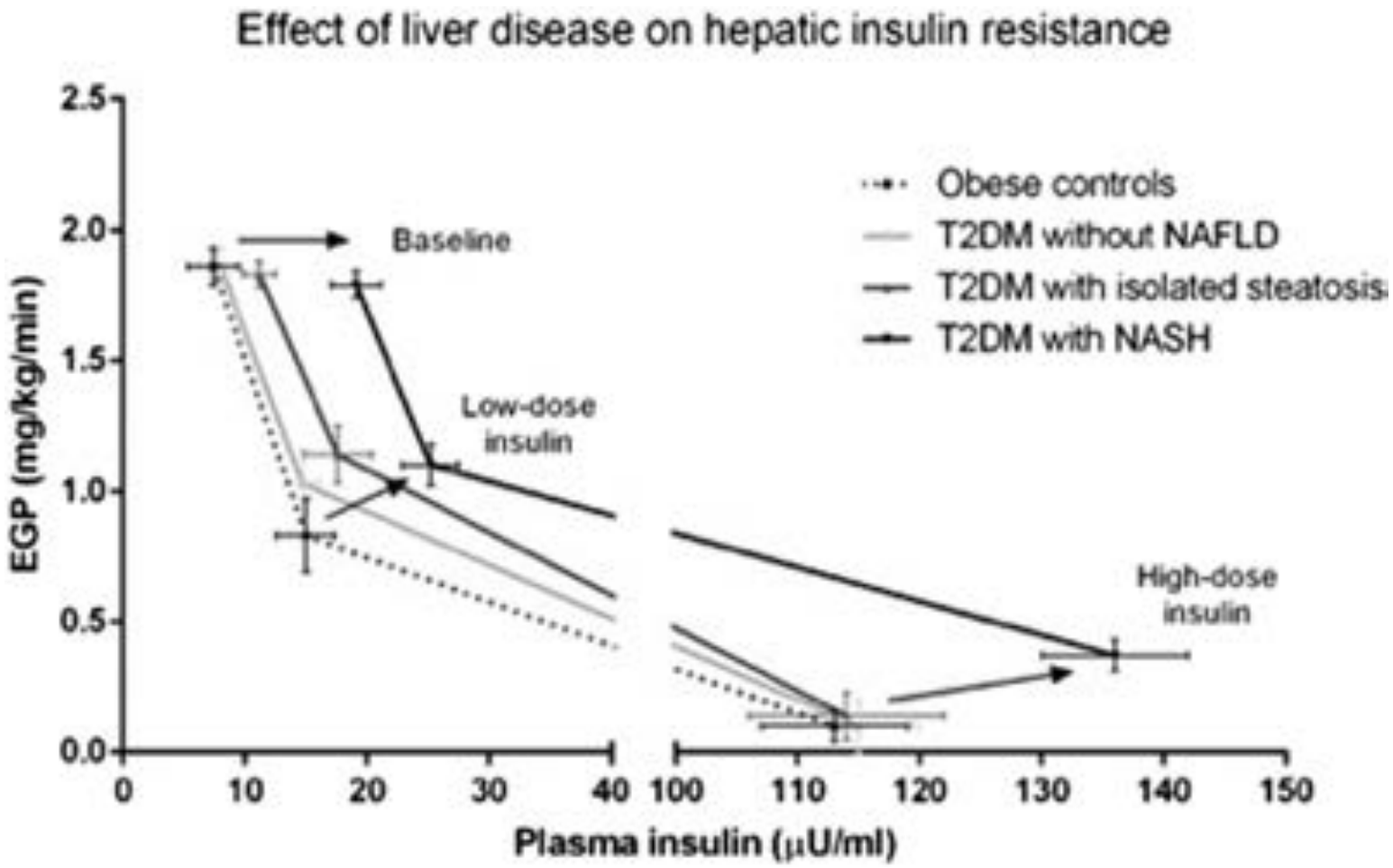

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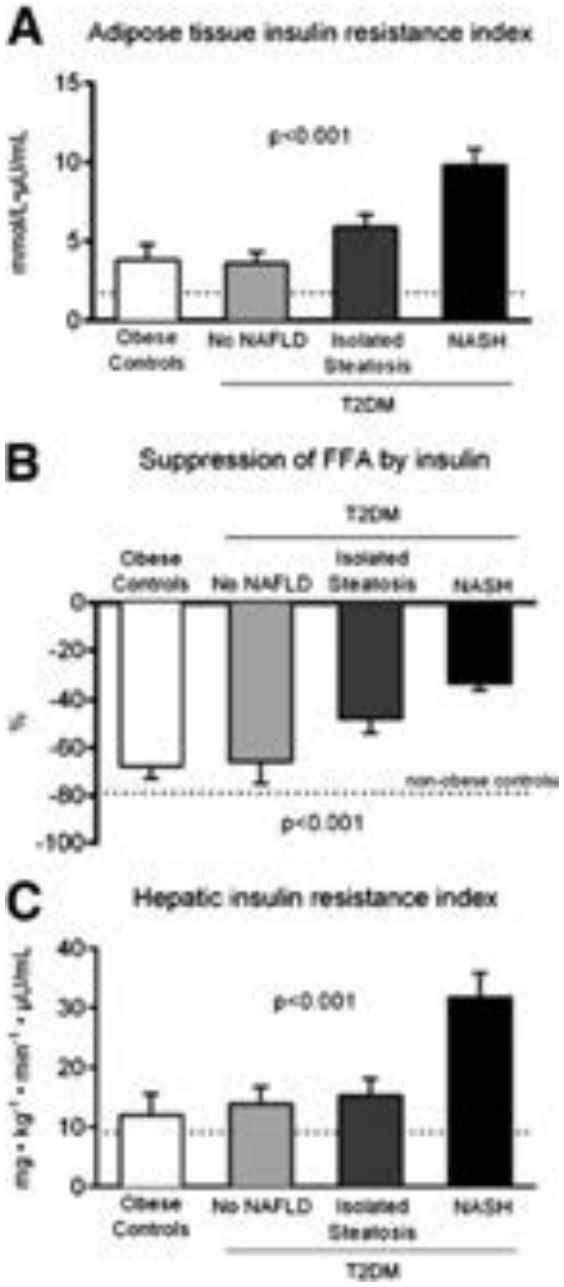

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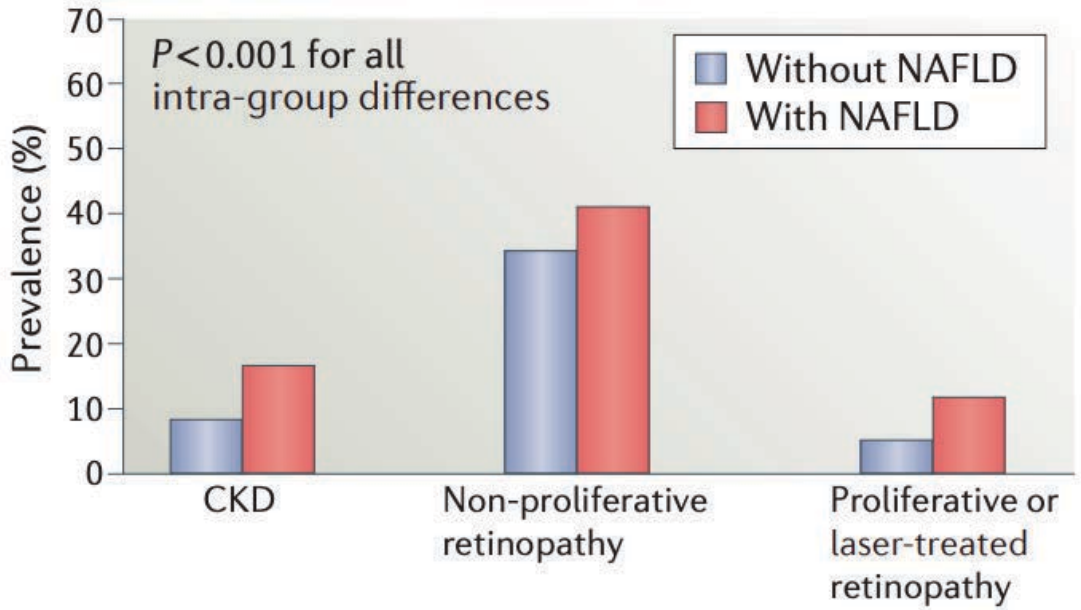
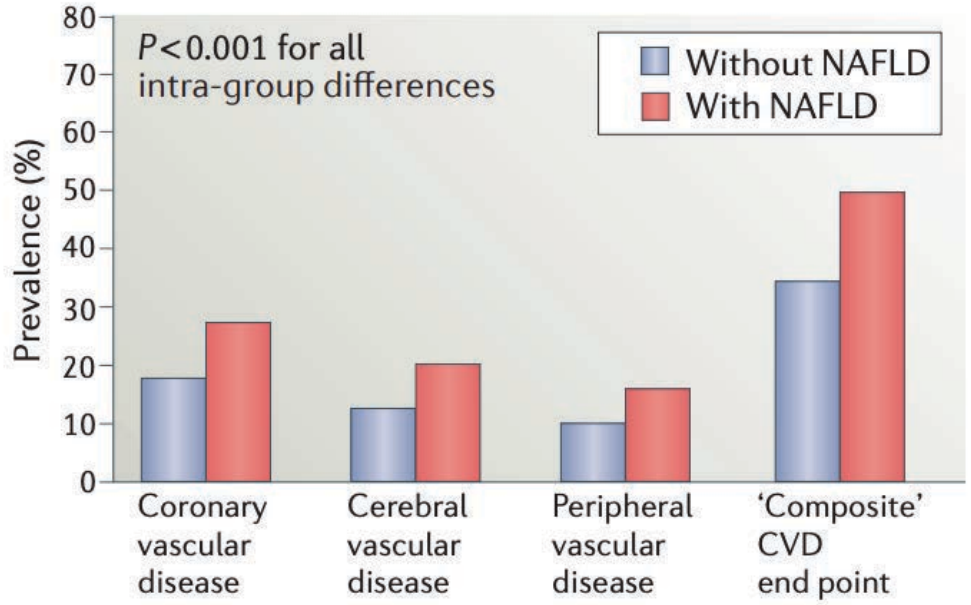
Prevalenza delle complicanze micro e macrovascolari del DT2 in relazione alla NAFLD





Targher G et al. NATURE REVIEWS | ENDOCRINOLOGY 2017

Cardiovascular Disease, Cancer, and Mortality Among People With Type 2 Diabetes and Alcoholic or Nonalcoholic Fatty Liver Disease Hospital Admission

Sarah H. Wild,[1] Jeremy J. Walker,[1] Joanne R. Morling,[2] David A. McAllister,[1] Helen M. Colhoun,[3] Bassam Farran,[3] Stuart McGurnaghan,[3] Rory McCrimmon,[4] Stephanie H. Read,[1] Naveed Sattar,[5] and Christopher D. Byrne,[6,7] on behalf of the Scottish Diabetes Research Network Epidemiology Group*

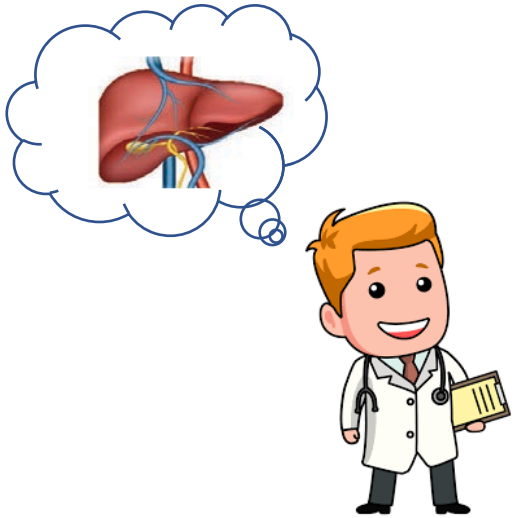
Diabetes Care 2018;41:341–347 | https://doi.org/10.2337/dc17-1590

134.368 people with T2DM (1.452 with NAFLD)

Table 4—Associations between history of hospital admission with ALD or NAFLD and incident/recurrent CVD, cancer, and mortality among people aged 40–89 years diagnosed with T2DM in Scotland between 2004 and 2013 with record of one or more hospital admission and no record of other chronic liver disease

	HR (95% CI)	
Outcome	ALD (*n* = 1,707)	NAFLD (*n* = 1,452)
Incident/recurrent CVD event*	1.59 (1.43, 1.76)	1.70 (1.52, 1.90)
Incident/recurrent HCC†	41.7 (30.0, 57.8)	19.3 (11.8, 31.4)
Incident/recurrent cancer, excluding HCC‡	1.28 (1.12, 1.47)	1.10 (0.94, 1.29)
All-cause mortality§	4.85 (4.49, 5.23)	1.60 (1.40, 1.83)
CVD mortality*	2.05 (1.63, 2.58)	1.15 (0.85, 1.57)
HCC mortality†	20.5 (13.9, 30.1)	6.16 (3.02, 12.6)
Cancer mortality, excluding HCC‡	1.24 (0.98, 1.57)	0.76 (0.55, 1.04)
Other causes of death	3.50 (3.00, 4.07)	1.60 (1.28, 1.99)

HRs are expressed relative to group with no record of any of the specified liver disease types (*n* = 131,209). See RESEARCH DESIGN AND METHODS for definitions. *Model includes prevalent CVD (i.e., CVD diagnosed before T2DM) as additional predictor. †Model includes prevalent HCC as additional predictor. ‡Model includes prevalent non-HCC as additional predictor. §Model includes prevalent CVD and prevalent cancer (any site) as additional predictors.



DT2 nei pazienti con NAFLD

1. Va sospettato: screening, prevenzione e terapia
2. Peggiora il quadro della NAFLD → fibrosi
3. Aumenta la mortalità

RESEARCH ARTICLE

Fatty liver index is a predictor of incident diabetes in patients with prediabetes: The PREDAPS study

Josep Franch-Nadal[1,2,3,4]*, Llorenç Caballeria[4,5,6], Manel Mata-Cases[1,2,3], Didac Mauricio[1,2,3,7], Carolina Giraldez-García[1,8,9], José Mancera[1,10], Albert Goday[1,11], Xavier Mundet-Tudurí[1,2,12]*, Enrique Regidor[1,9,13,14], for the PREDAPS Study Group[¶]

	Fatty Liver Index		
	<30	30–59	≥60
Incident T2D; unadjusted	1.00	2.22 (0.97–5.11)	4.52 (2.10–9.72)
Base model: Incident T2D adjusted for age, sex and educational level	1.00	2.40 (1.03–5.55)	4.97 (2.28–10.80)
Base model adjusted for family history of T2D	1.00	2.31 (1.00–5.36)	4.82 (2.22–10.48)
Base model adjusted for lifestyle*	1.00	2.26 (0.97–5.24)	4.63 (2.12–10.10)
Base model adjusted for hypertension	1.00	2.30 (0.99–5.34)	4.59 (2.10–10.03)
Base model adjusted for lipids (total and HDL cholesterol)	1.00	2.35 (1.01–5.44)	4.58 (2.09–10.01)
Base model adjusted for transaminases (AST, ALT)	1.00	2.22 (0.96–5.14)	4.13 (1.88–9.04)
Base model adjusted for family history of T2D, lifestyle* hypertension, lipids and transaminases			
All	1.00	1.96 (0.85–4.54)	3.21 (1.45–7.09)
Men	1.00	1.53 (0.43–5.40)	1.70 (0.50–5.74)
Women	1.00	1.73 (0.53–5.59)	4.95 (1.73–14.29)

*Includes tobacco consumption, alcohol intake, consumption of fruits and vegetables, breakfast and physical activity
T2D, type 2 diabetes mellitus; ALT, alanine transaminase; AST, aspartate transaminase; HDL, high density lipoprotein

DT2 nei pazienti con NAFLD

13.218 people without diabetes followed up for 5 years

	Incident DM, n (%)	Model 1 Odds Ratio 95% CIs *P* Value	Model 2 Odds Ratio 95% CIs *P* Value	Model 3 Odds Ratio 95% CIs *P* Value	Model 4 Odds Ratio 95% CIs *P* Value
Reference					
No fatty liver at both baseline and at follow-up, no fatty liver (n = 7918)	39 (0.5%)	1	1	1	1
Fatty liver at baseline but not follow-up (n = 828)	12 (1.5%)	2.63 (1.36, 5.07) .004	0.89 (0.44, 1.82) .75	0.98 (0.48, 2.02) .97	0.95 (0.46, 1.6) .89
No fatty liver at baseline, but fatty liver at follow-up (n = 1640)	35 (2.1%)	4.06 (2.55, 6.47) <.001	2.86 (1.73, 4.71) <.001	2.59 (1.56, 4.30) <.001	2.49 (1.49, 4.14) <.001
Fatty liver at baseline and at follow-up (n = 2832)	148 (5.2%)	9.93 (6.88, 14.35) <.001	3.27 (2.14, 5.02) <.001	3.13 (2.04, 4.81) <.001	2.95 (1.91, 4.54) <.001
Fatty liver at baseline and remaining static at follow-up (n = 2275)	98 (4.3%)	8.22 (5.55, 12.17) <.001	2.97 (1.83, 4.81) <.001	2.92 (1.80, 4.75) <.001	2.78 (1.70, 4.53) <.001
Fatty liver at baseline and worsening in severity at follow up (n = 324)	27 (8.3%)	15.6 (9.23, 26.18) <.001	9.28 (4.42, 19.46) <.001	7.82 (3.63, 16.86) <.001	7.38 (3.36, 16.22) <.001

Abbreviation: DM, diabetes mellitus. Model 1 was adjusted for baseline age and sex. Model 2 was adjusted for baseline age, sex, BMI, glucose, insulin, baseline triglycerides, HDL-C, systolic BP, alcohol, smoking, and physical activity. Model 3 was adjusted for baseline age, sex, BMI, glucose, insulin, baseline triglycerides, HDL-C, systolic BP, alcohol, smoking, physical activity, and change in BMI between baseline and follow-up. Model 4 was adjusted for baseline age; sex; BMI; glucose; insulin; baseline triglycerides; HDL-C; systolic BP; alcohol use; smoking; physical activity; change in BMI between baseline and follow-up; and ALT, AST, and GGT.

Sung KC et al, JCEM 98: 3637–3643, 2013

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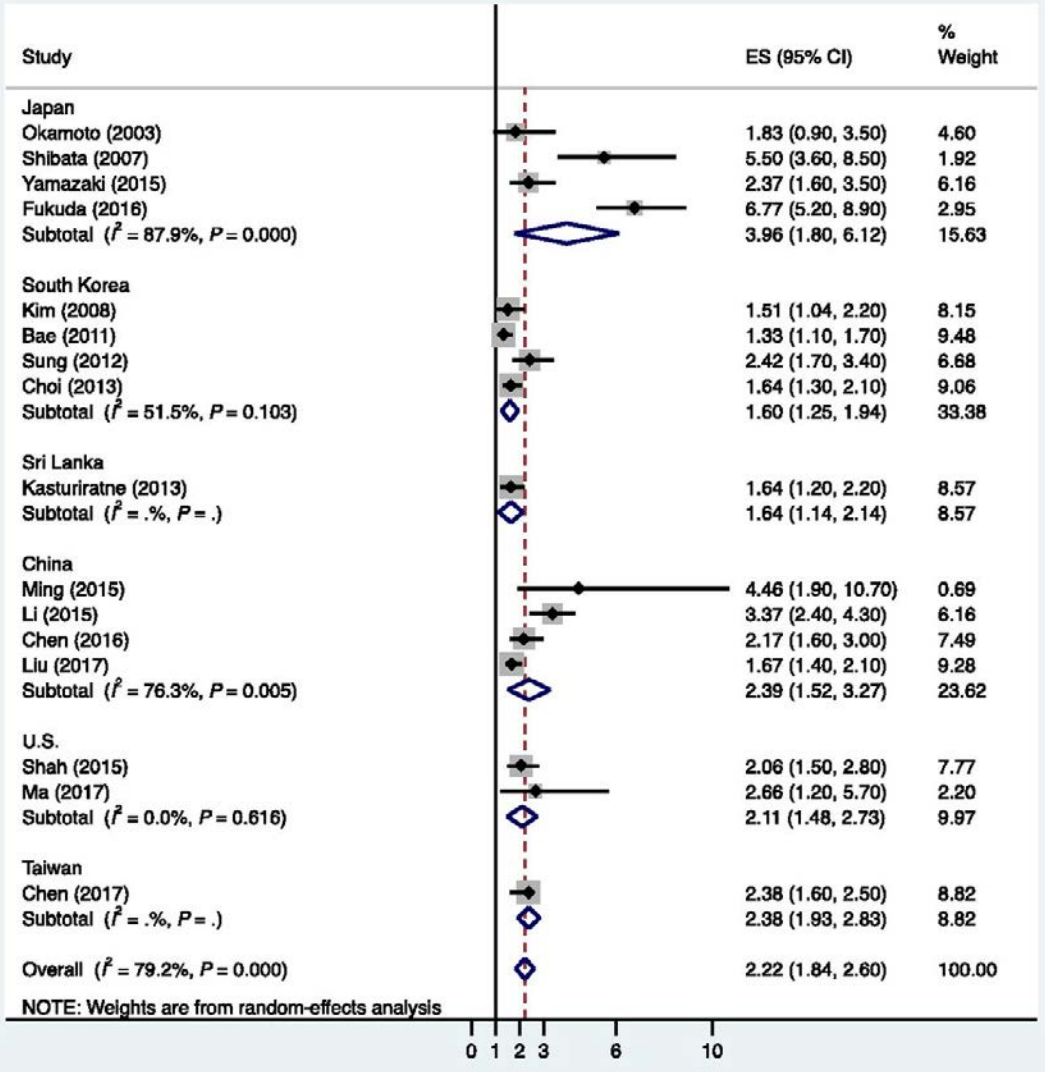

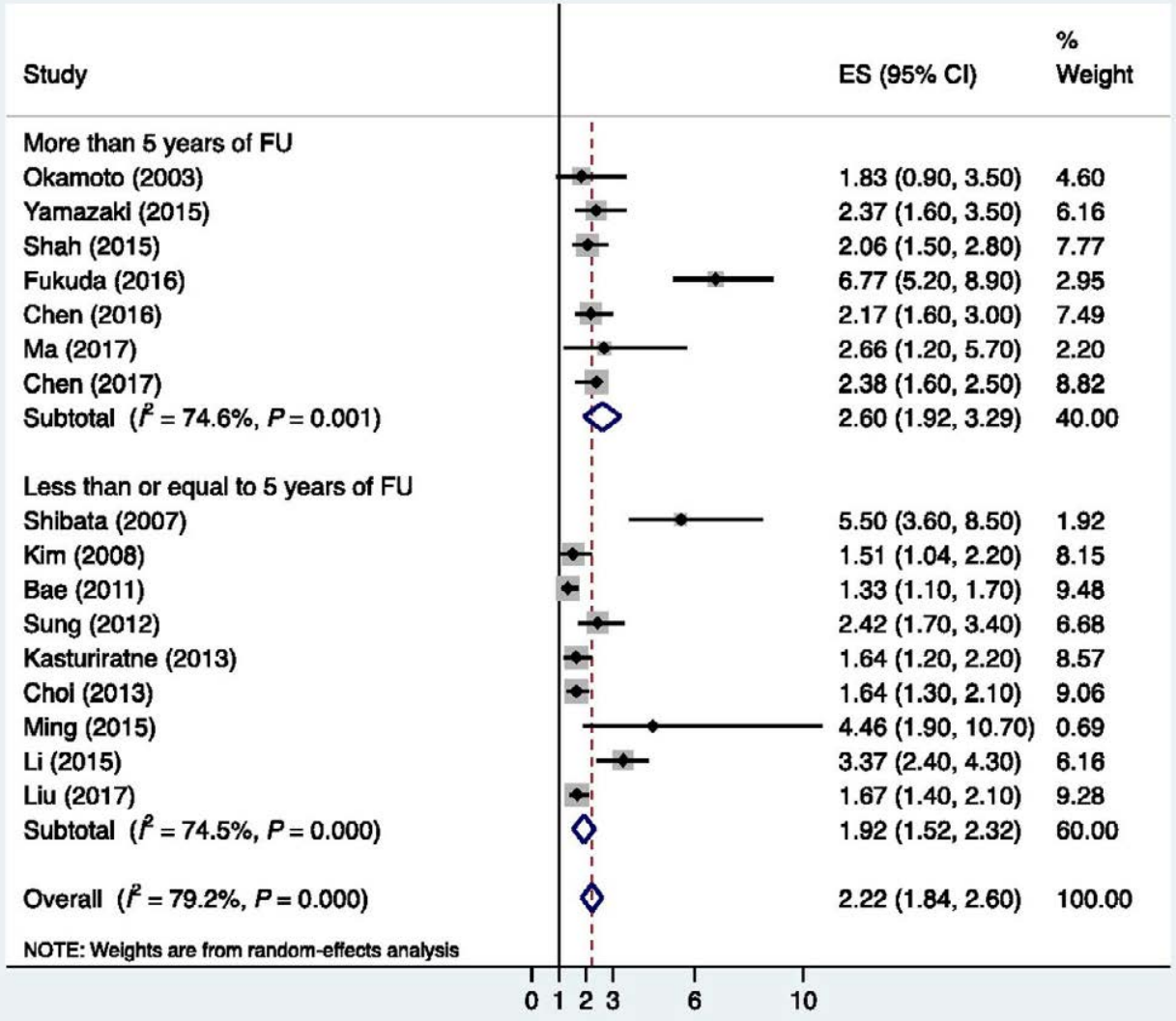

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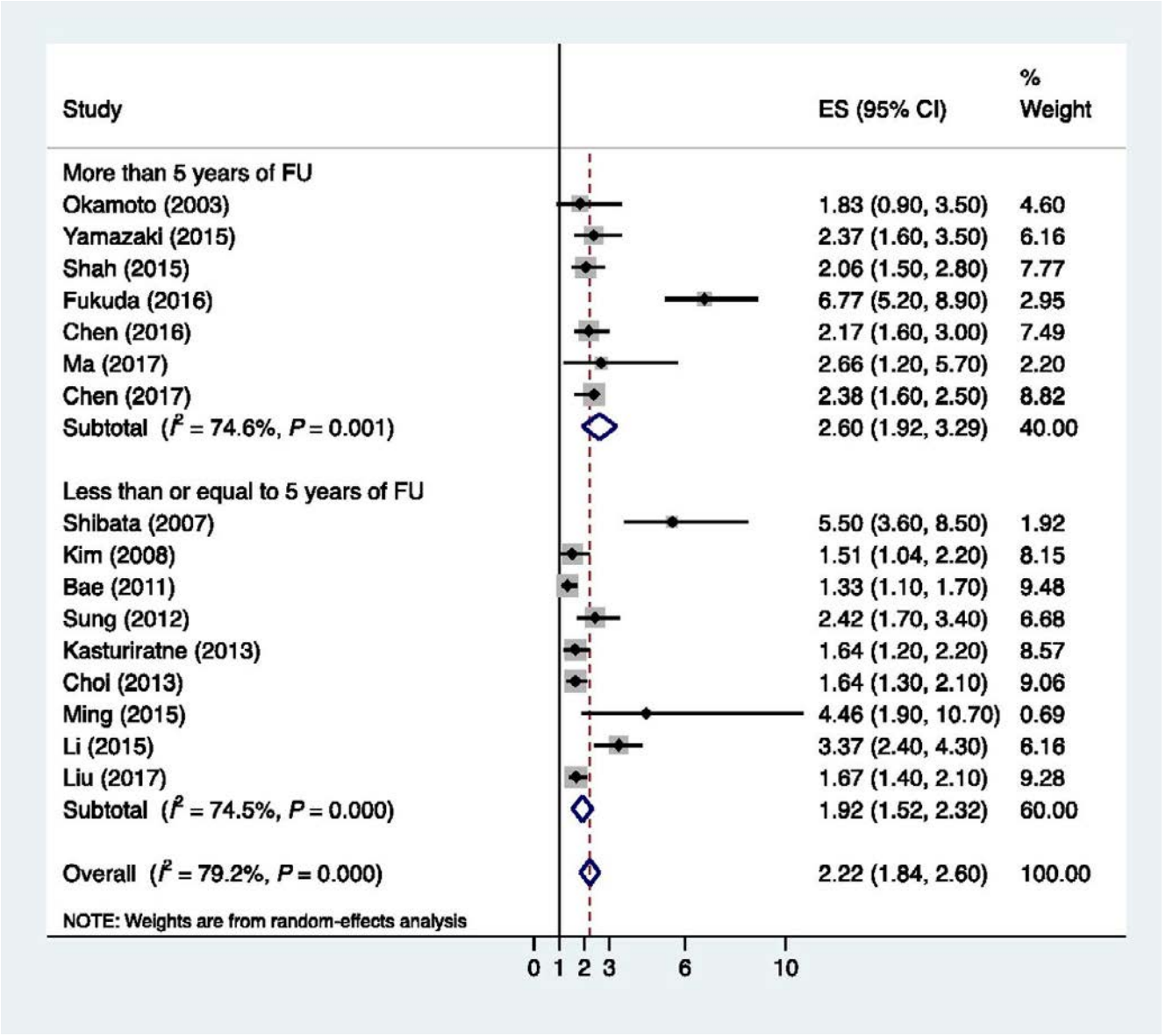

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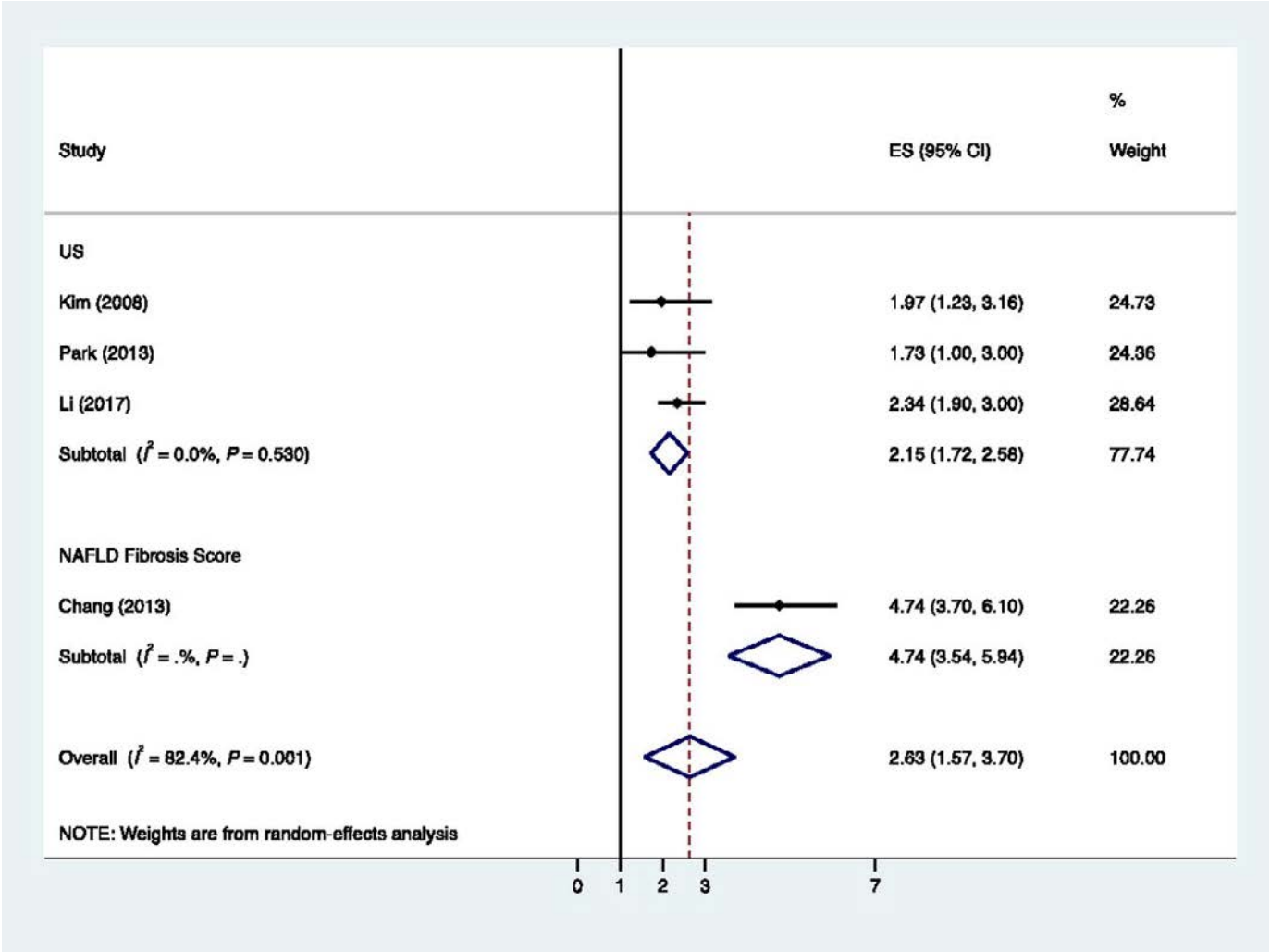

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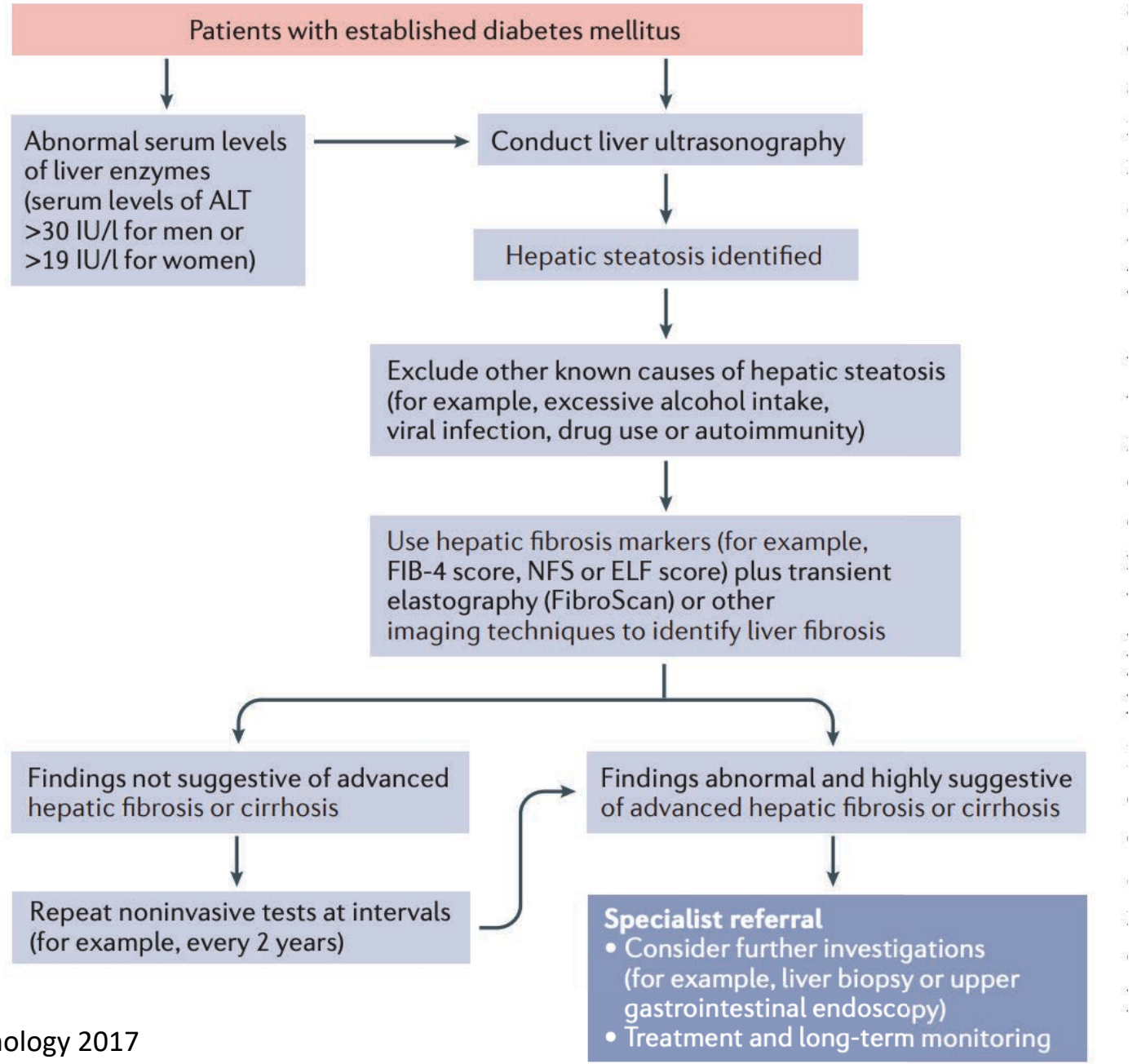
The presence of T2D increases the risk of both liver related mortality and overall mortality in NAFLD patients (280 subjects, 12.5 years median follow-up)

Risk factor	Overall mortality aHR (95 % CI)	Liver-related mortality aHR (95 % CI)	Cardiac mortality aHR (95 % CI)
NASH	1.13 (0.74–1.71)	**9.16 (2.10–9.88)**	0.51 (0.23–1.10)
Age	**1.07 (1.05–1.10)**	**1.06 (1.02–1.10)**	**1.12 (1.08–1.18)**
Male gender	0.95 (0.62–1.47)	1.44 (0.62–3.34)	0.83 (0.36–1.90)
Caucasian race	1.67 (0.92–3.06)	1.85 (0.62–5.47)	1.37 (0.39–4.83)
Obesity	0.91 (0.60–1.40)	0.88 (0.38–2.04)	1.56 (0.70–3.47)
Type II diabetes	**2.09 (1.39–3.14)**	**2.19 (1.00–4.81)**	1.71 (0.75–3.86)
Hyperlipidemia	1.01 (0.68–1.52)	0.48 (0.19–1.23)	1.68 (0.78–3.61)

Stepanova M et al, Dig Dis Sci (2013)

Importanza specifica identificazione NAFLD per il diabetologo



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Considerazioni finali e *take-home messages*

- La NAFLD è una condizione ad **elevata morbidità e mortalità**
- La prevalenza di NAFLD e NASH nei pazienti con DT2 raggiunge il **60-70%**.
- LA NAFLD si associa a **peggiori esiti metabolici** e ad una **maggiore incidenza di complicanze** del diabete mellito, inclusa morte CV.
- La presenza del **DT2 accelera la progressione della NAFLD** ed è un predittore di fibrosi aumentata e mortalità.
- Identificare la NAFLD nel DT2 permette una **migliore stratificazione del rischio**
- Strategie di screening standardizzate per la NAFLD sono auspicabili nelle popolazioni a rischio elevato come gli individui con DT2.

Grazie dell'attenzione

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