Il dr. Ciro Celsa dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

III Congresso Congiunto
SID-AMD Sicilia
Palermo 29-30 Novembre 2018

PREDIABETE E FEGATO

Dr. Ciro Celsa
Dr. Salvatore Petta
Sezione di Gastroenterologia ed Epatologia
Dipartimento di Medicina Interna e Specialistica
AOUP «P. Giaccone», Palermo

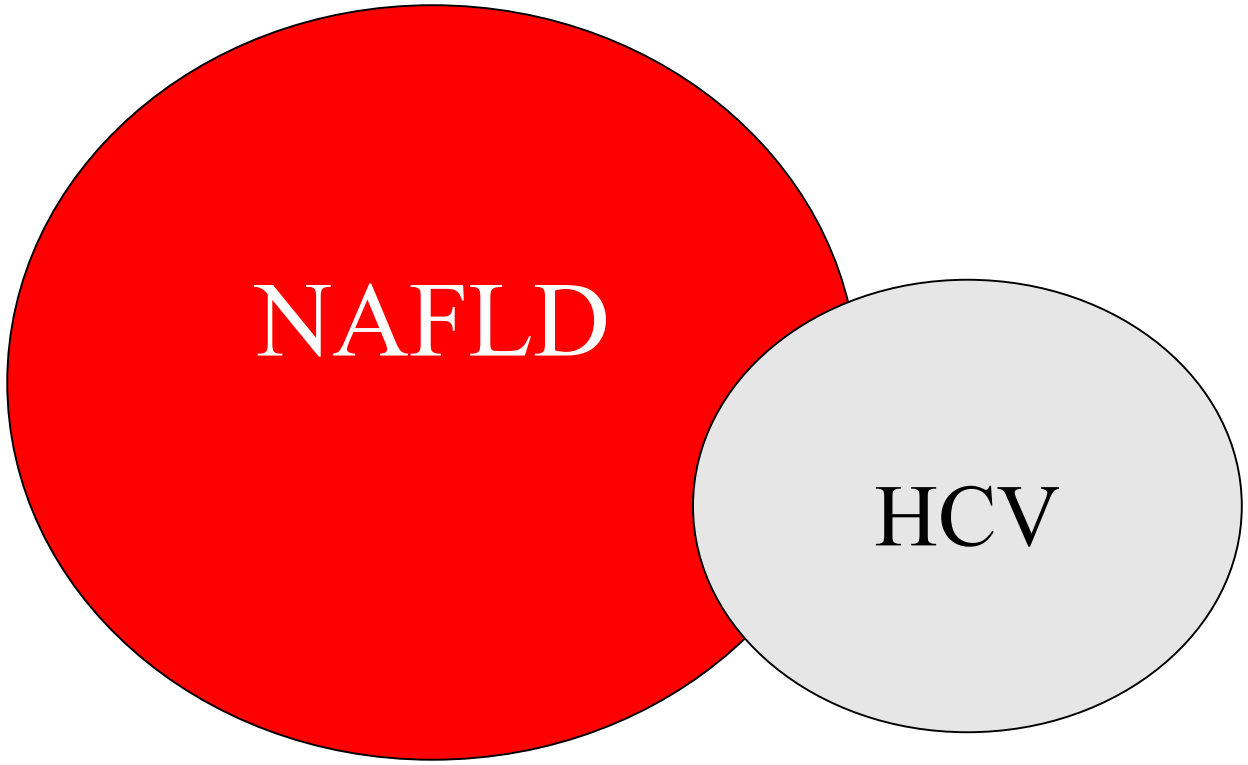
SID Società Italiana di Diabetologia

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AMD 1974 ANNO DI FONDAZIONE ASSOCIAZIONE MEDICI DIABETOLOGI

Liver and Diabetes



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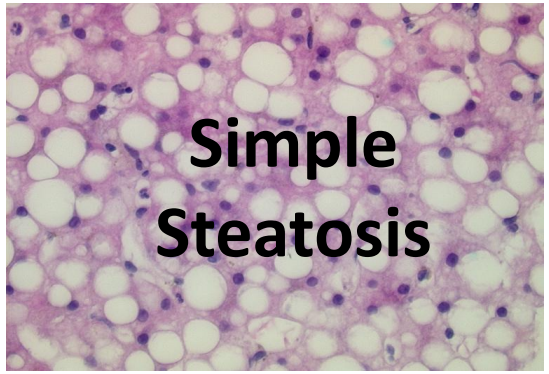
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NAFLD

Nonalcoholic fatty liver disease (NAFLD) represents a spectrum of disorders characterized by predominantly macrovesicular hepatic steatosis that occurs in individuals in the absence of significant alcohol consumption

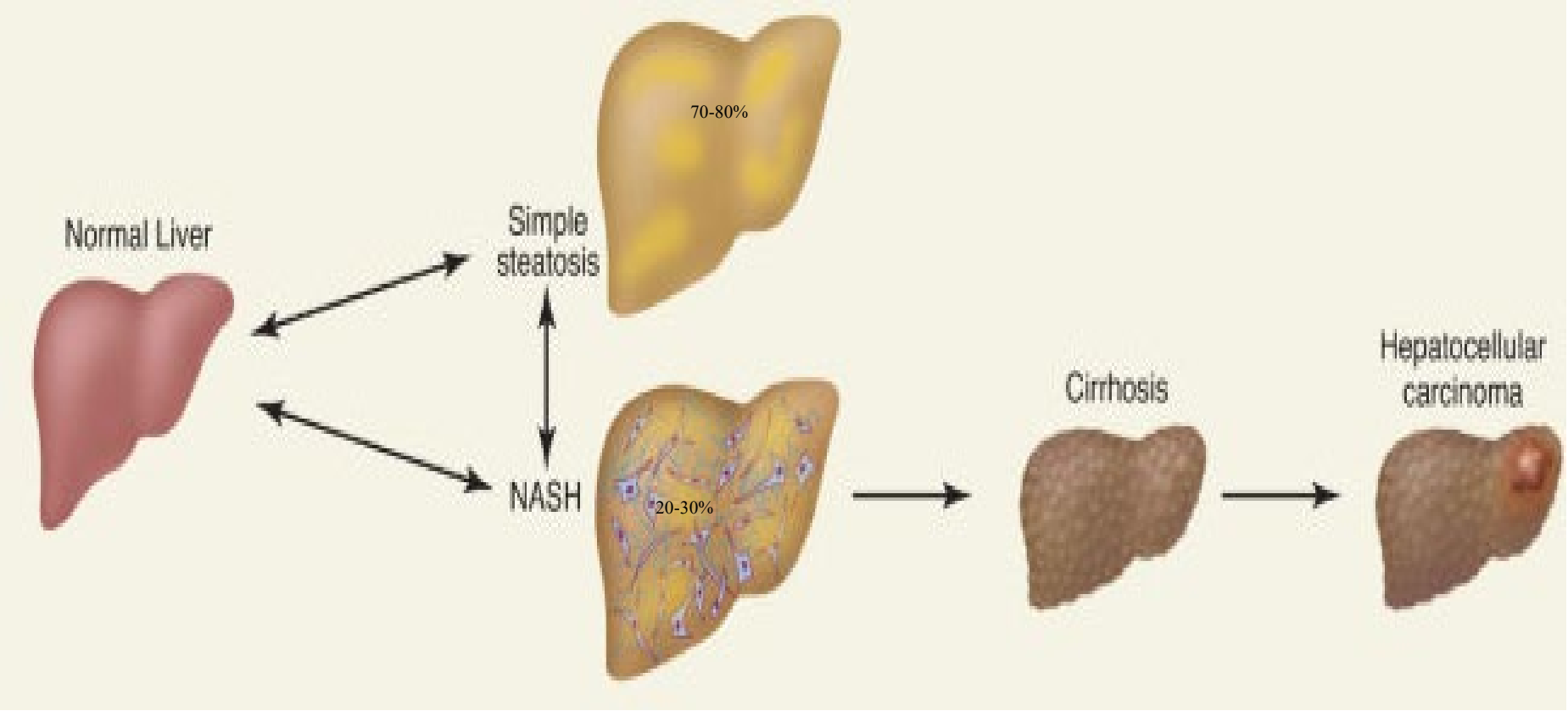
NAFLD prevalence is about 20%-30% in the general population

NAFLD is the hepatic expression of metabolic syndrome



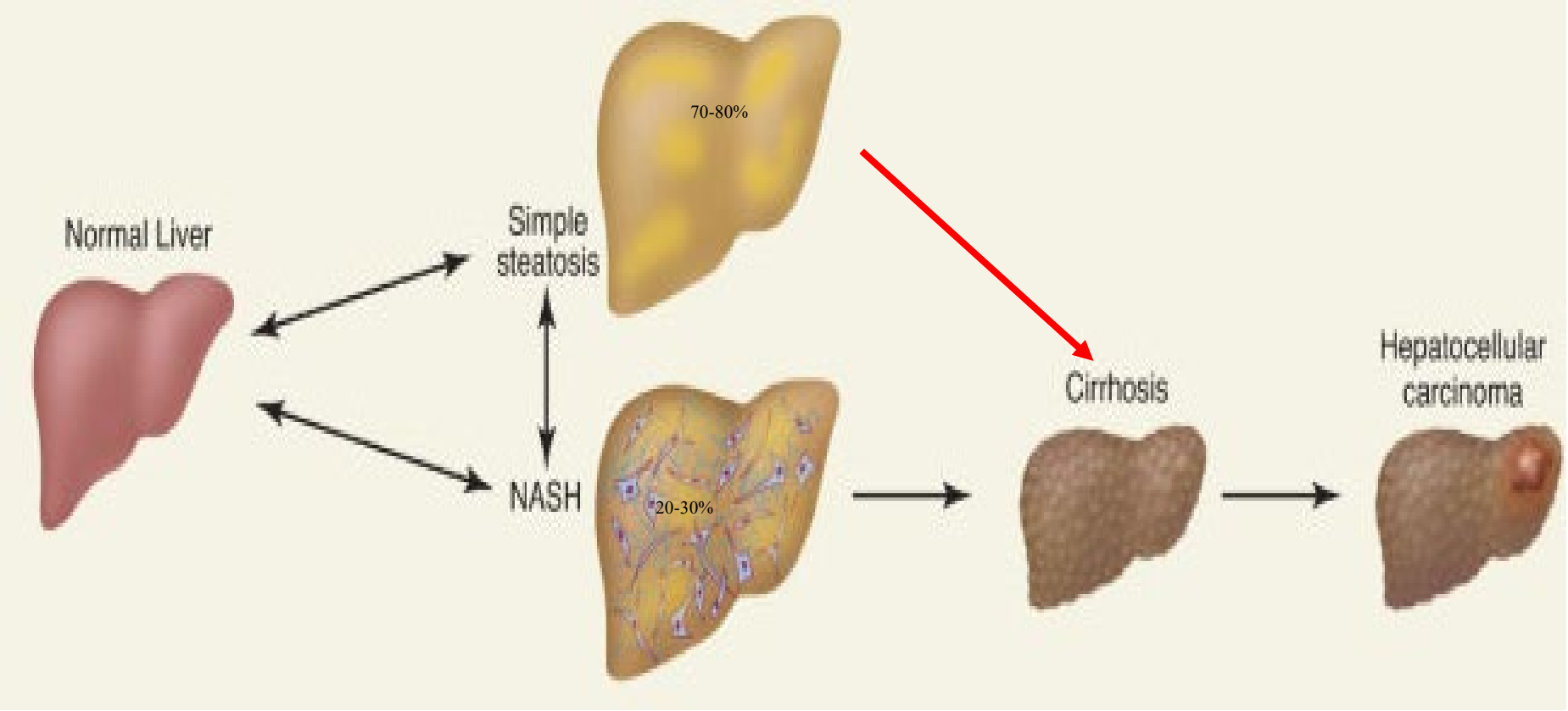


NAFLD



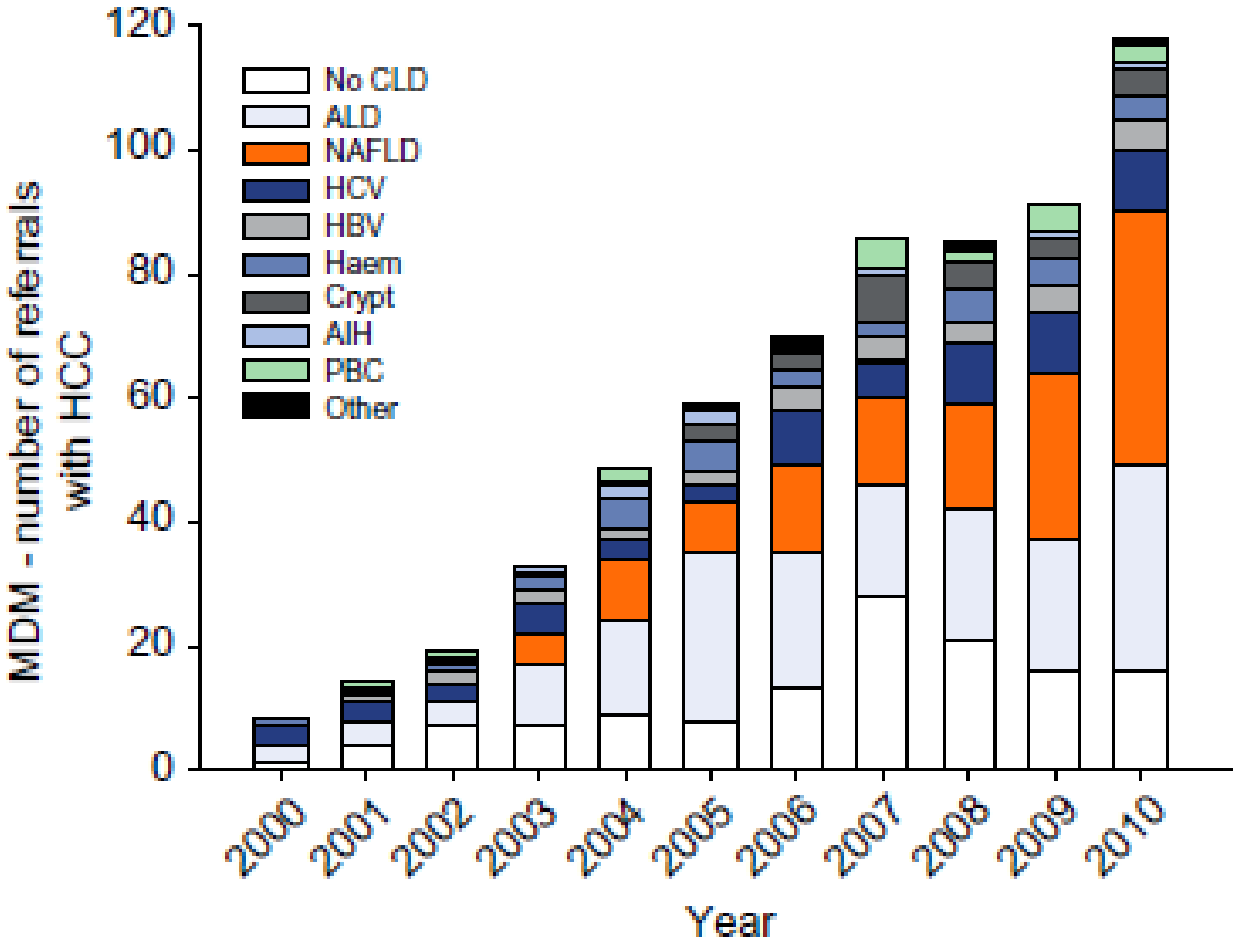
Cohen et al, Science 2011

NAFLD



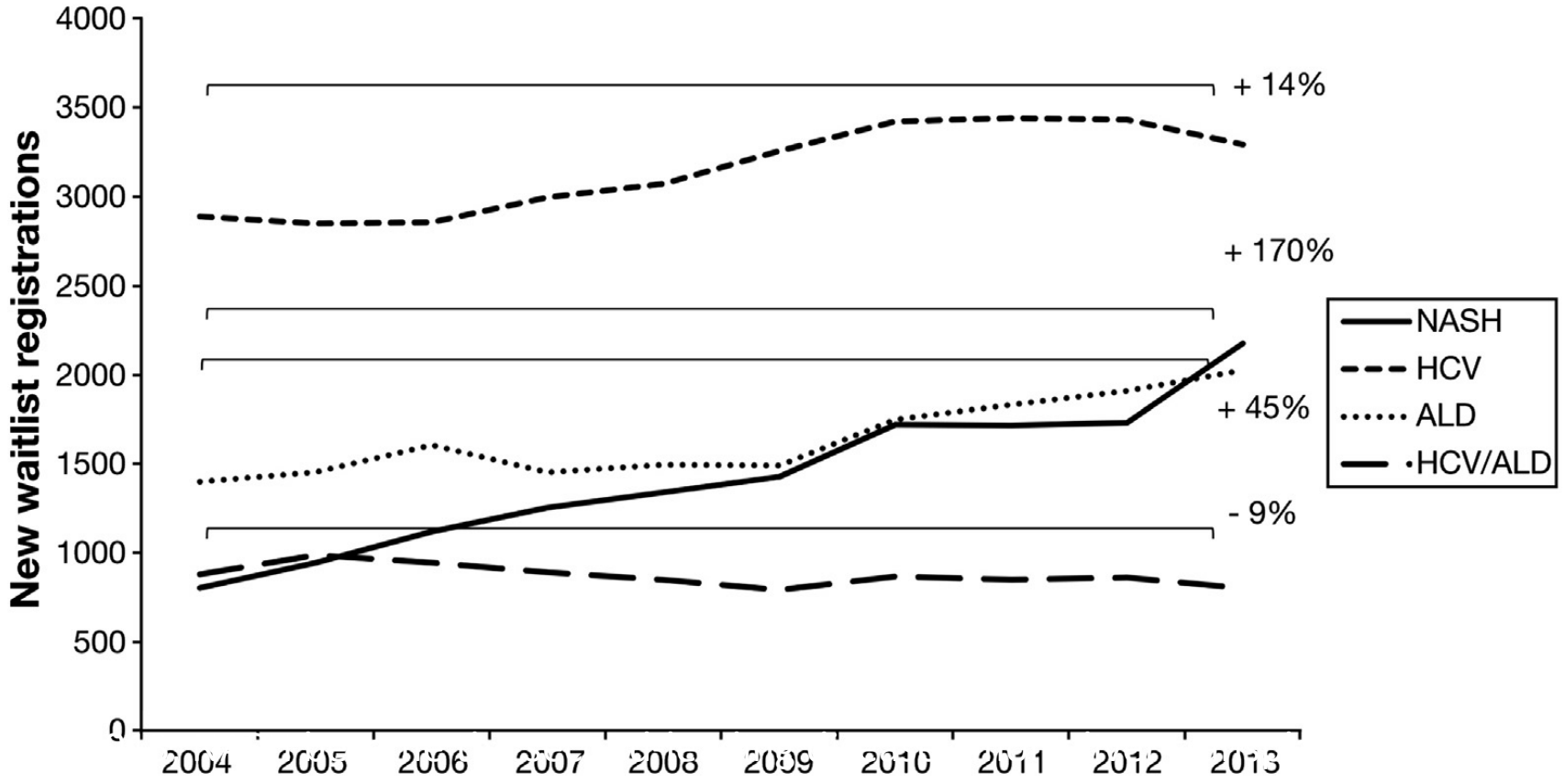
Cohen et al, Science 2011

Etiologies of chronic liver disease associated with HCC



Dyson et al, JHEP 2013

Causes of Liver Transplantation in USA



Wong et al, Gastroenterology 2015

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Does NAFLD Affect Diabetes occurrence and Severity?

What is the Burden of NAFLD/NASH in Diabetic Patients?

Does Diabetes Affect NAFLD Severity?

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Does NAFLD Affect Diabetes occurrence and Severity?

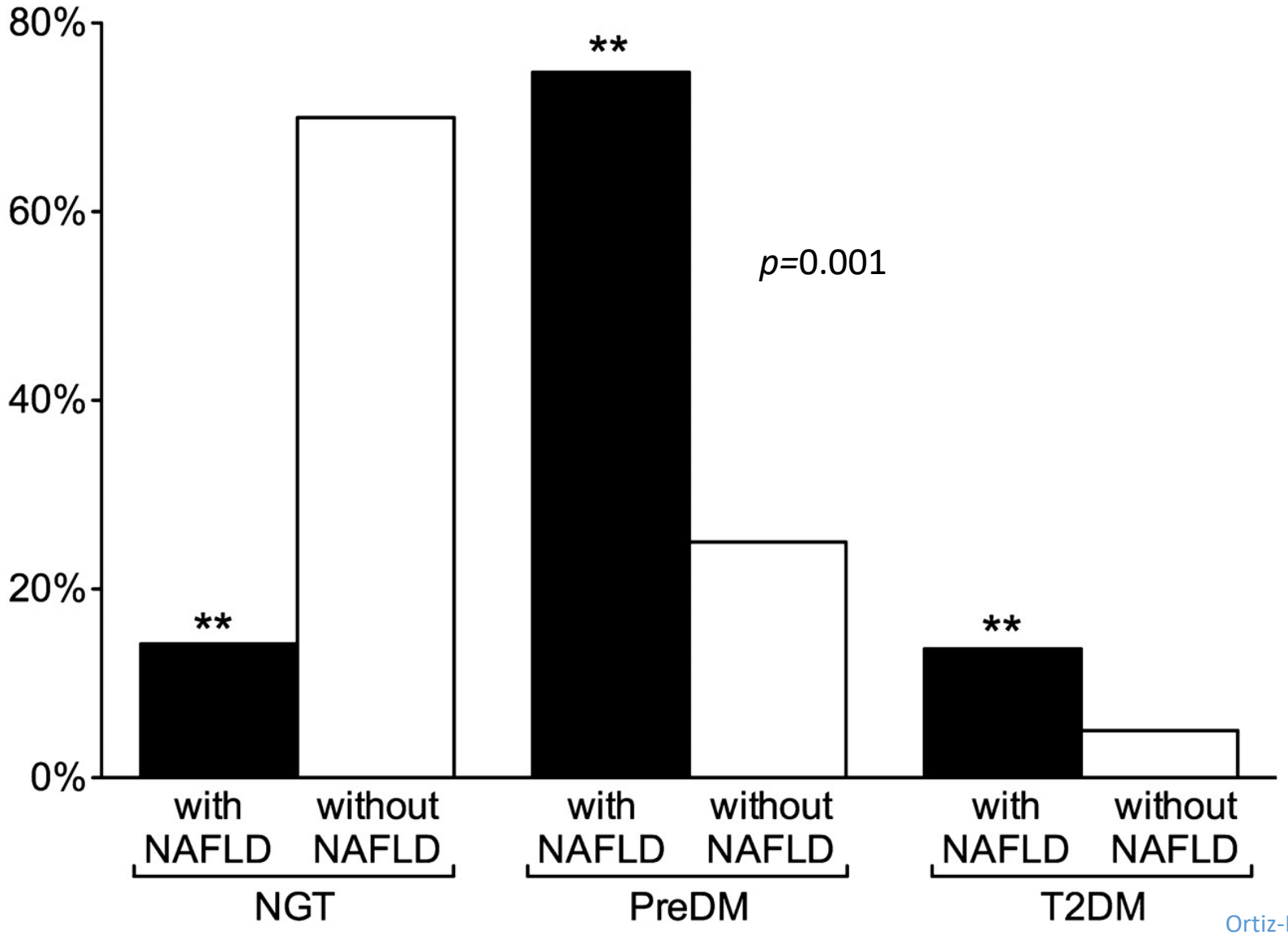
What is the Burden of NAFLD/NASH in Diabetic Patients?

Does Diabetes Affect NAFLD Severity?

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Prediabetes and NAFLD



Ortiz-Lopez et al. Diabetes Care 2012

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Prediabetes in NAFLD

Table 3. Baseline metabolic syndrome vs. NAFLD on US or HRI as predictors f

	Model 1	
Parameter	OR (95% CI)	*P* value
NAFLD on US	3.51 (1.29–9.54)	0.014
Age (years)	1.05 (1.01–1.09)	0.024
Male gender	0.59 (0.28–1.24)	0.165
BMI (kg/m^2)	1.04 (0.93–1.16)	0.538
Family history of DM	1.24 (0.55–2.79)	0.612
Metabolic syndrome	1.13 (0.32–3.99)	0.845

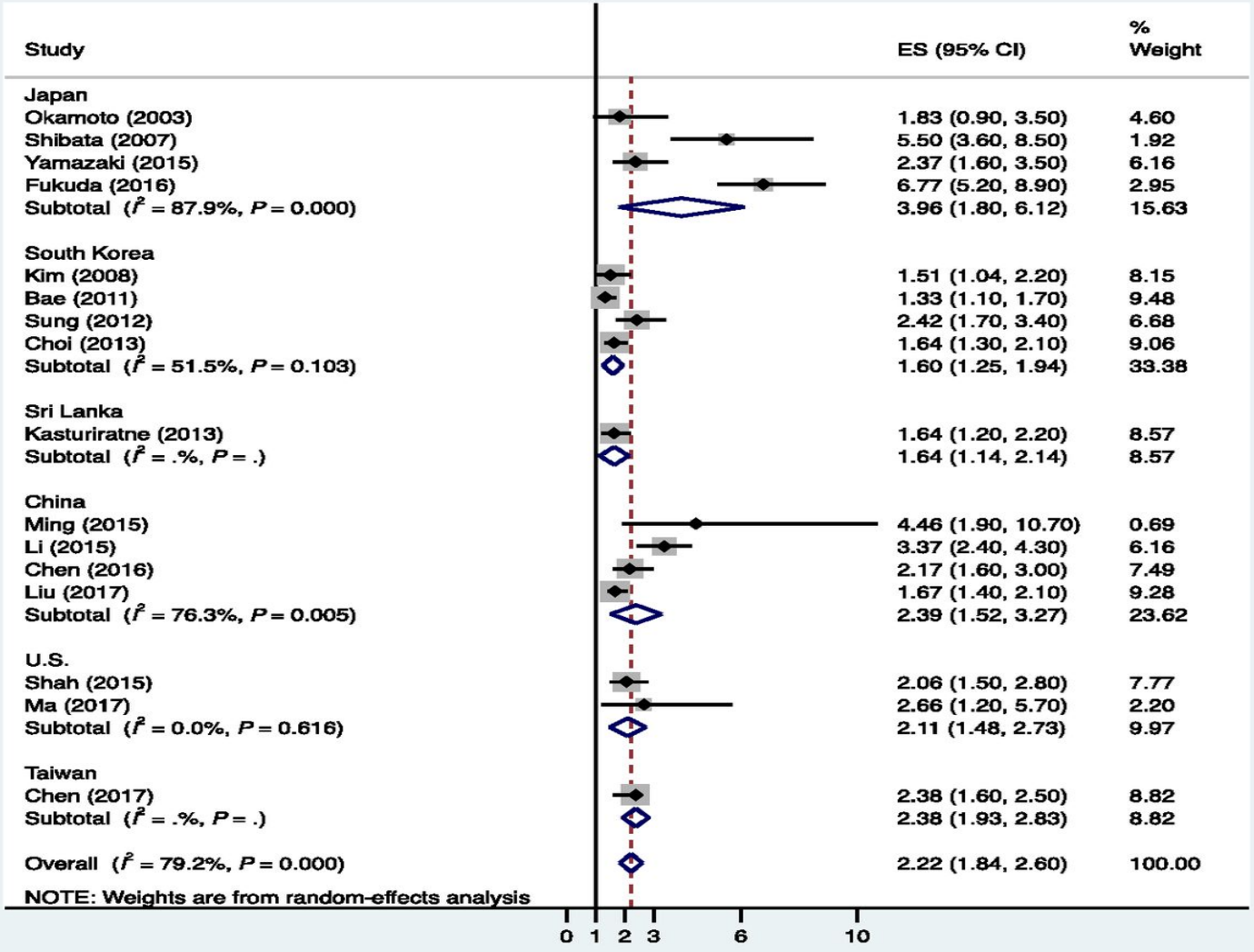
Zelber-Sagi et al. Liver Int. 2013

Table 3. Multivariate analysis of non-alcoholic fatty liver disease in predicting type 2 diabetes mellitus and prediabetes

	Crude		Adjusted*	
Variable	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Diabetes				
Non-NAFLD	1.000		1.000	
NAFLD	4.247 (1.768–10.204)	<0.001	4.462 (1.855–10.734)	<0.001
Prediabetes				
Non-NAFLD	1.000		1.000	
NAFLD	1.788 (1.110–2.881)	0.017	1.642 (0.965–2.793)	0.067

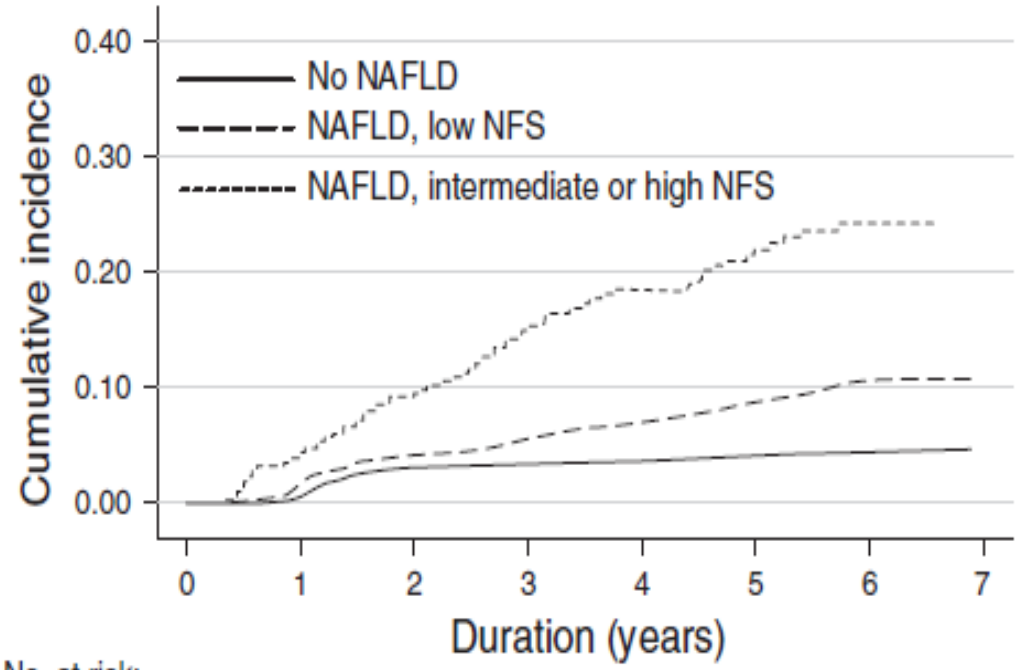
Ming et al. Liver Int. 2015

Diabetes Development and NAFLD



Mantovani et al. Diabetes Care 2018

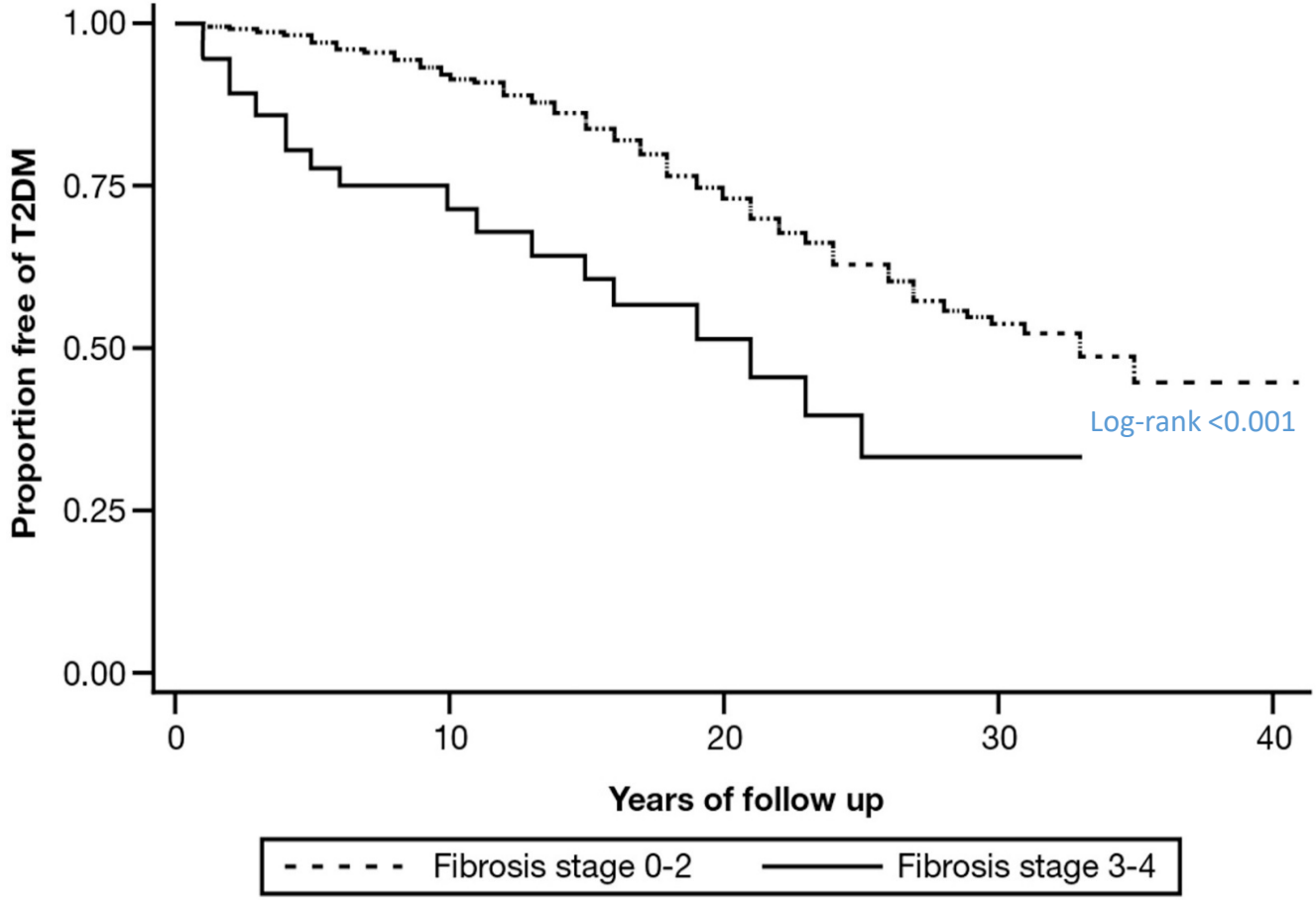
Diabetes Incidence according to NAFLD severity



No. at risk:

No NAFLD	28145	27719	25319	23753	19881	13915	5547	0
NAFLD, low NFS	9809	9571	8749	8142	6807	4735	1946	0
NAFLD, >low NFS	337	313	268	224	198	158	81	0

Chang Y et al, AJG 2013



Björkström et al. Clin Gastroenterol Hepatol 2017

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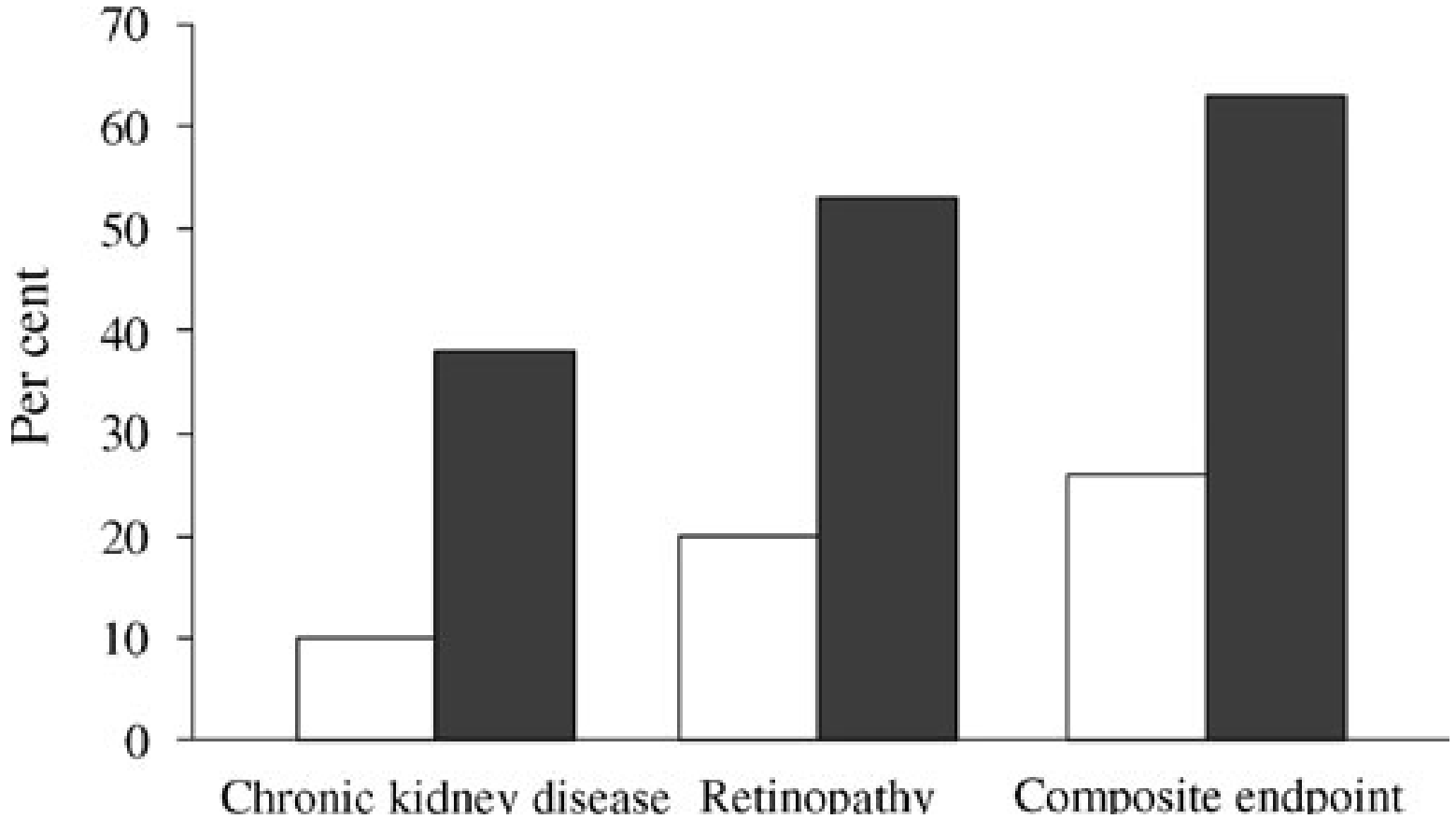
NAFLD and Diabetes Complications

Table 3 Univariate and multivatiate logistic regression analyses of the presence of microalbuninuria as the dependent variable in subjects with prediabetes

Variable	Odds ratio of microalbuminuria (95% confidence interval)			
	Univariate	*P*-value	Multivariate	*P*-value
NAFLD	3.51 (1.60–7.70)	0.002	3.42 (1.23–9.55)	0.019
MS	3.56 (1.72–7.38)	0.001	1.45 (0.54–3.88)	0.464
Hypertension	2.42 (1.17–5.03)	0.018	1.97 (0.82–4.71)	0.127
HOMA-IR (>2.5)	2.38 (1.11–5.10)	0.026	1.09 (0.45–2.67)	0.846
HbA1c	2.06 (0.78–5.48)	0.147	1.71 (0.50–5.85)	0.396
Sex	0.68 (0.35–1.35)	0.271	0.44 (0.14–1.38)	0.157
Age	1.02 (0.99–1.05)	0.291	1.00 (0.96–1.04)	0.966
BMI	1.28 (1.12–1.46)	<0.001	1.10 (0.84–1.44)	0.492
WC	1.05 (1.00–1.10)	0.044	1.02 (0.91–1.15)	0.694
Triglyceride	1.00 (1.00–1.01)	0.044	1.00 (1.00–1.00)	0.595
LDL-cholesterol	1.00 (0.99–1.01)	0.486	1.00 (0.98–1.00)	0.091
AST	1.01 (0.99–1.02)	0.419	1.01 (0.94–1.09)	0.746
ALT	1.00 (1.00–1.02)	0.043	0.98 (0.93–1.03)	0.365
GGT	1.00 (1.00–1.01)	0.049	1.00 (1.00–1.01)	0.265
Smoking	1.65 (0.54–2.02)	0.322	1.04 (0.84–1.31)	0.752

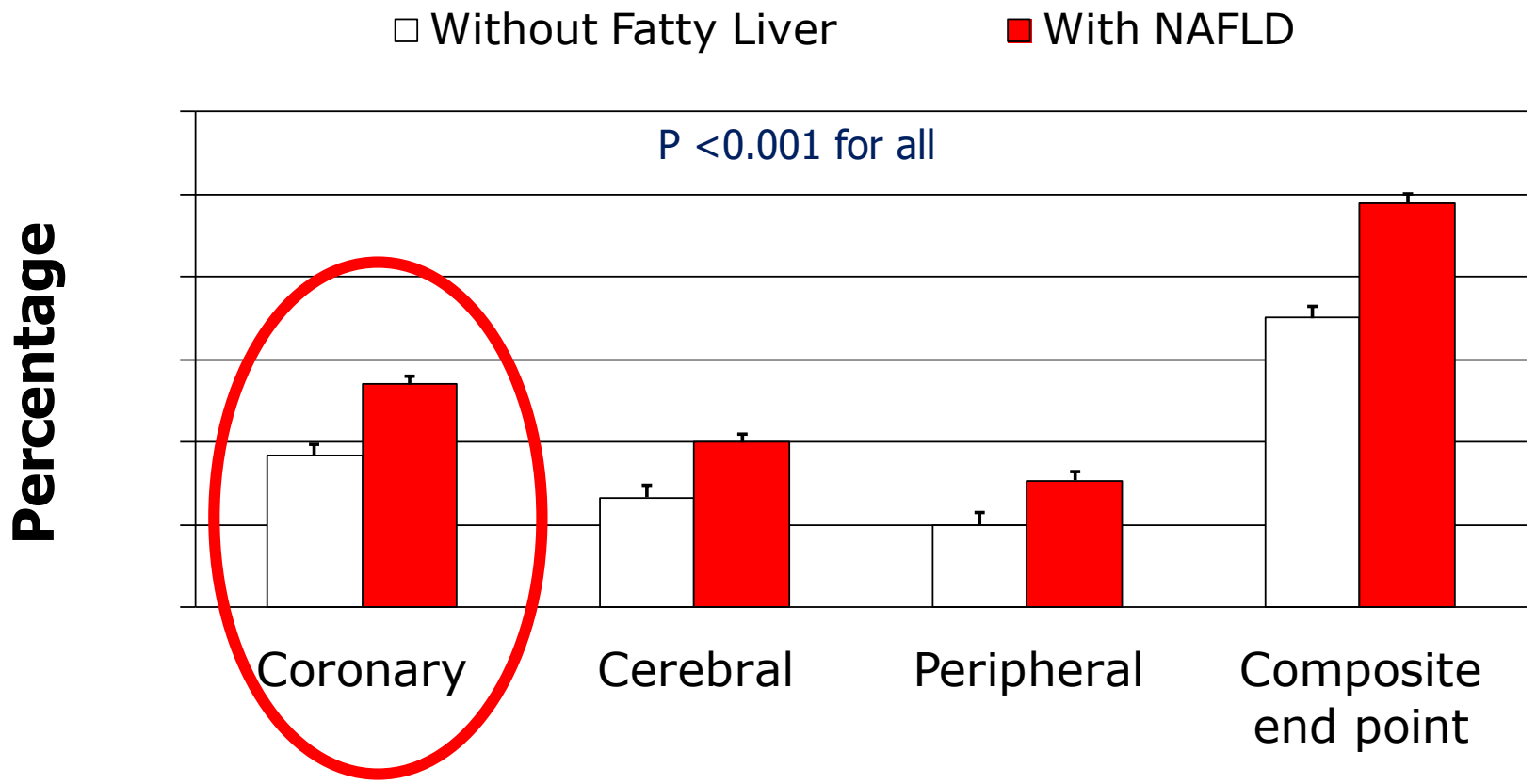
Hwang et al, Internal Medicine Journal 2010

NAFLD and Diabetes Complications



Targher et al, Diabetologia 2010

Prevalence of CVD among 2,392 T2DM patients (*Valpolicella Heart Diabetes Study*)



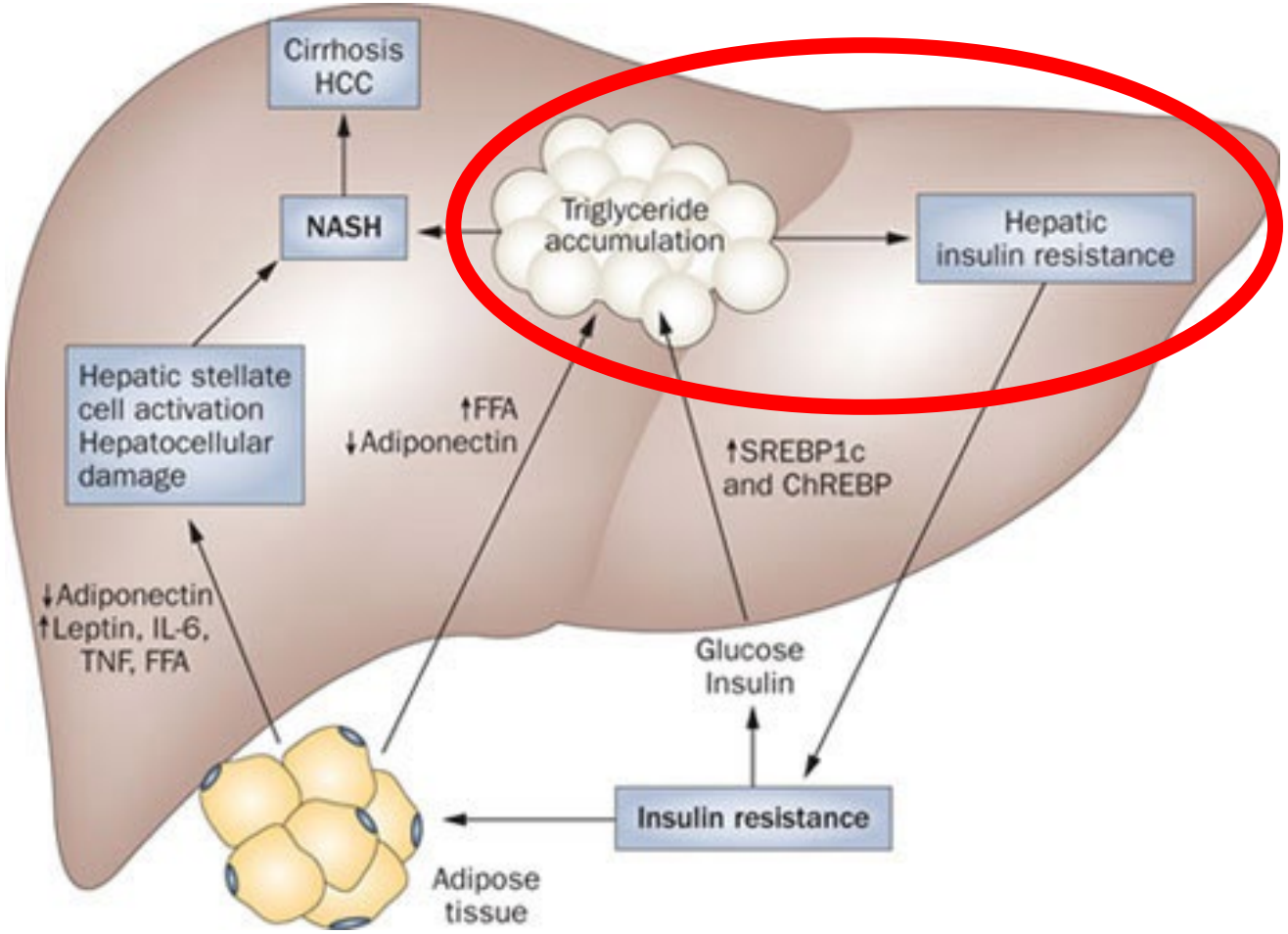
In a mean follow-up of 6.5 yrs 384 cases were observed (myocardial infarction, ischemic stroke, coronary revascularization, or cardiovascular death) and were indepedently associated with NAFLD presence

Targher, Diabetes Care 2007

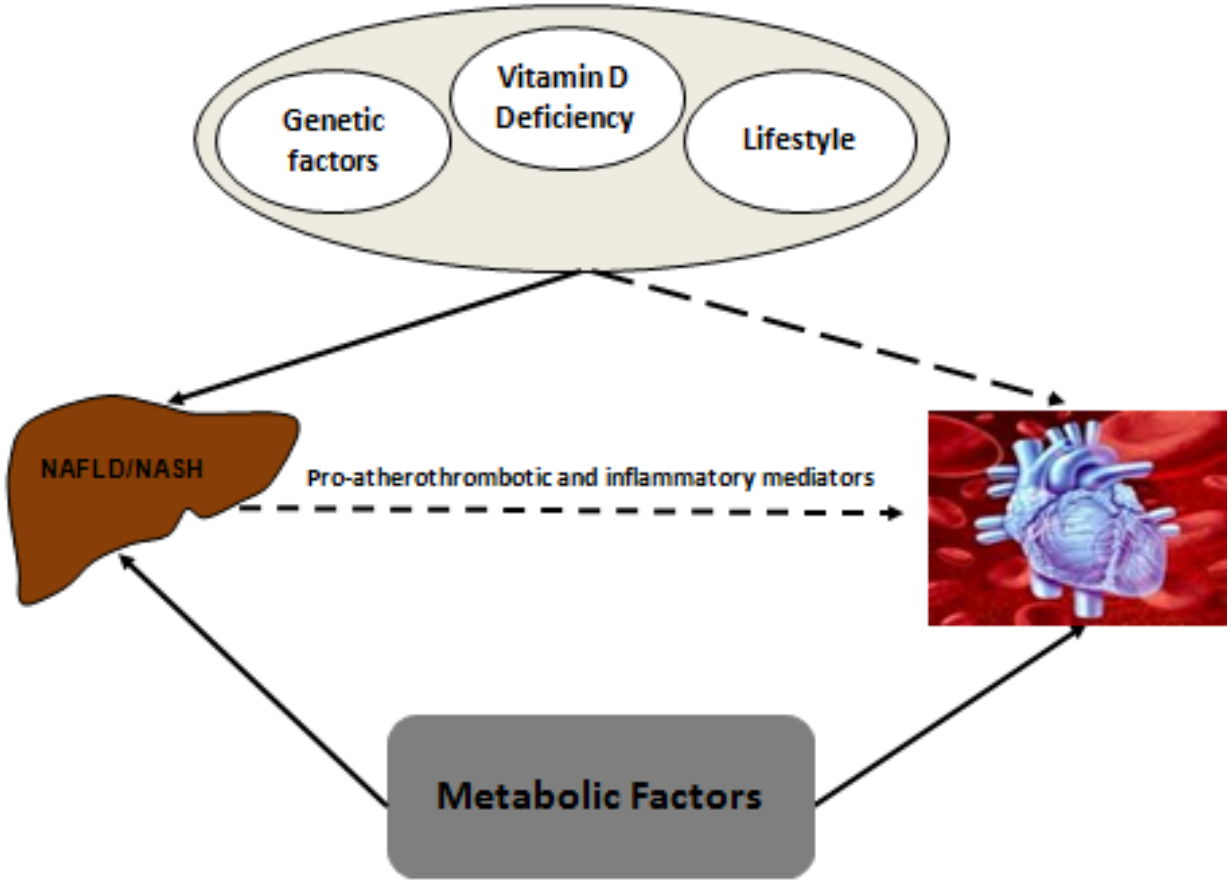
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How NAFLD Prompts to IR and Diabetes?



NAFLD and extrahepatic complications: A plausible Hypothesis



Petta S et al, in press

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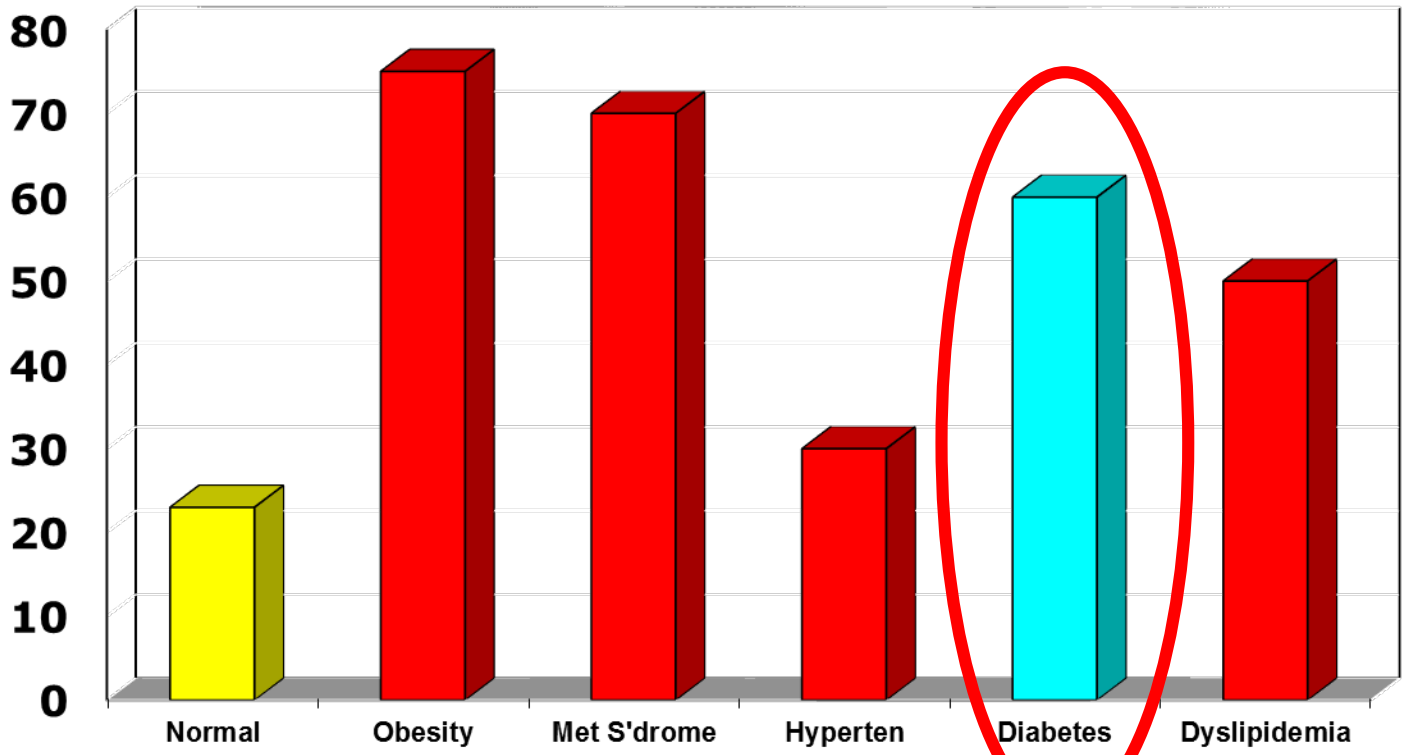
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Does NAFLD Affect Diabetes occurrence and Severity?

What is the Burden of NAFLD/NASH in Diabetic Patients?

Does Diabetes Affect NAFLD Severity?

Association of NAFLD with features of Metabolic Syndrome

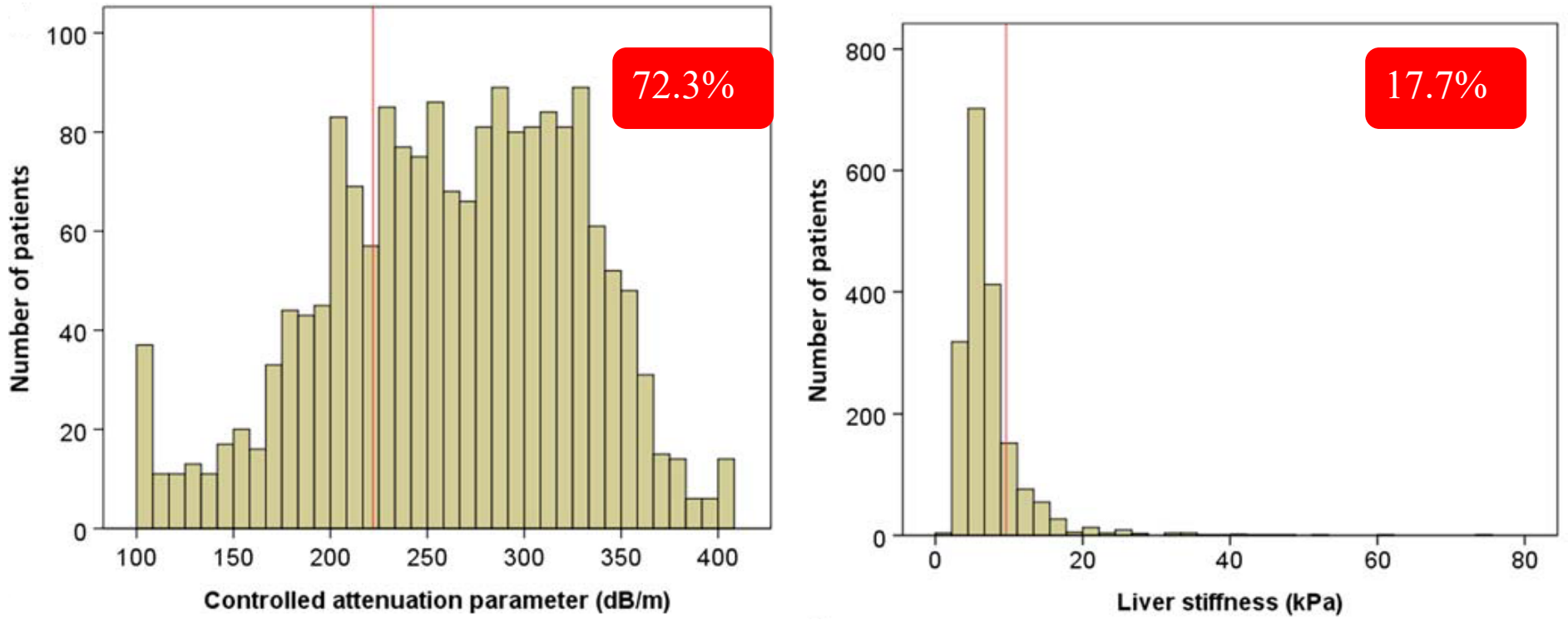


NAFLD as liver expression of Insulin Resistance syndrome

Marchesini G et al, Hepatology 2006

NAFLD and Severe Fibrosis in Diabetes

1799 Diabetic Patients with Reliable Liver Stiffness and CAP

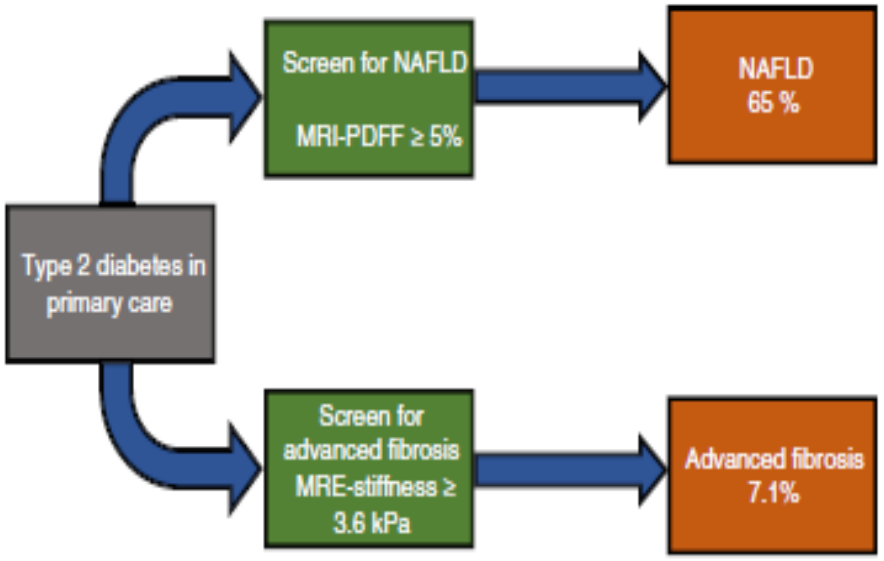


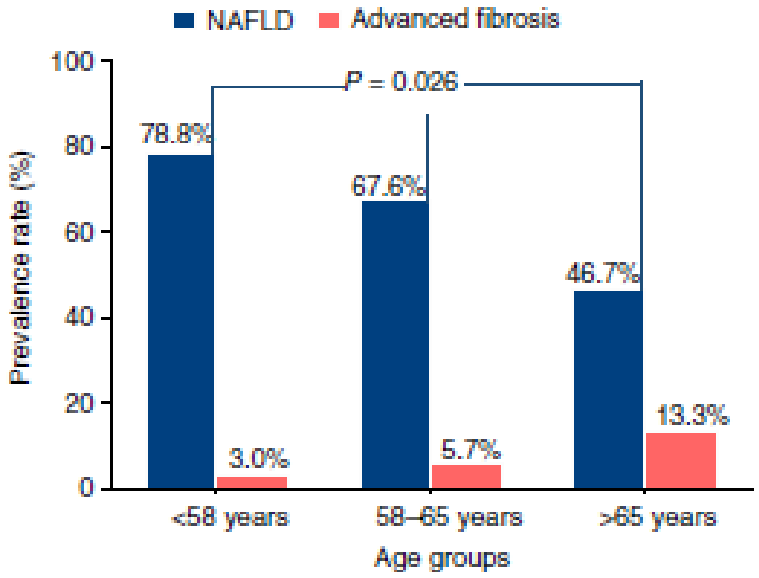
Longer duration of diabetes, higher BMI, increased ALT and spot urine albumin/creatinine ratio and lower HDL were associated with increased LSM.

Kwok et al, GUT 2015

NAFLD and Severe Fibrosis in Diabetes

100 Diabetic Patients



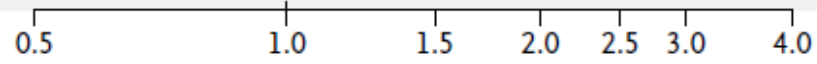


Doycheva APT 2015 et al, GUT 2015

Type 2 Diabetes and Cause of Death

Cancer Death

Subgroup	No. of Deaths	Hazard Ratio with Diabetes (95% CI)
Liver	533	2.16 (1.62–2.88)
Pancreas	2189	1.51 (1.24–1.83)
Ovary	1149	1.45 (1.03–2.02)
Colorectum	3876	1.40 (1.20–1.63)
Bladder	834	1.40 (1.01–1.96)
Oral	475	1.38 (0.90–2.12)
Melanoma	547	1.36 (0.83–2.23)
Kidney	815	1.28 (0.89–1.85)
Lung	7823	1.27 (1.13–1.43)
Breast	3338	1.25 (1.02–1.52)
Esophagus	795	1.21 (0.86–1.69)
Stomach	1531	1.16 (0.92–1.46)
Connective tissue	310	1.11 (0.58–2.11)
Hematologic	3425	0.93 (0.77–1.13)
Prostate	2217	0.89 (0.71–1.10)
Endocrine and nervous	1209	0.88 (0.60–1.27)
Site unspecified or other	8680	1.17 (1.07–1.27)



HR for cause-specific death, according to baseline diabetes status, from individual-participant data on 123,205 deaths among 820,900 people in 97 prospective studies

NEJM 2011

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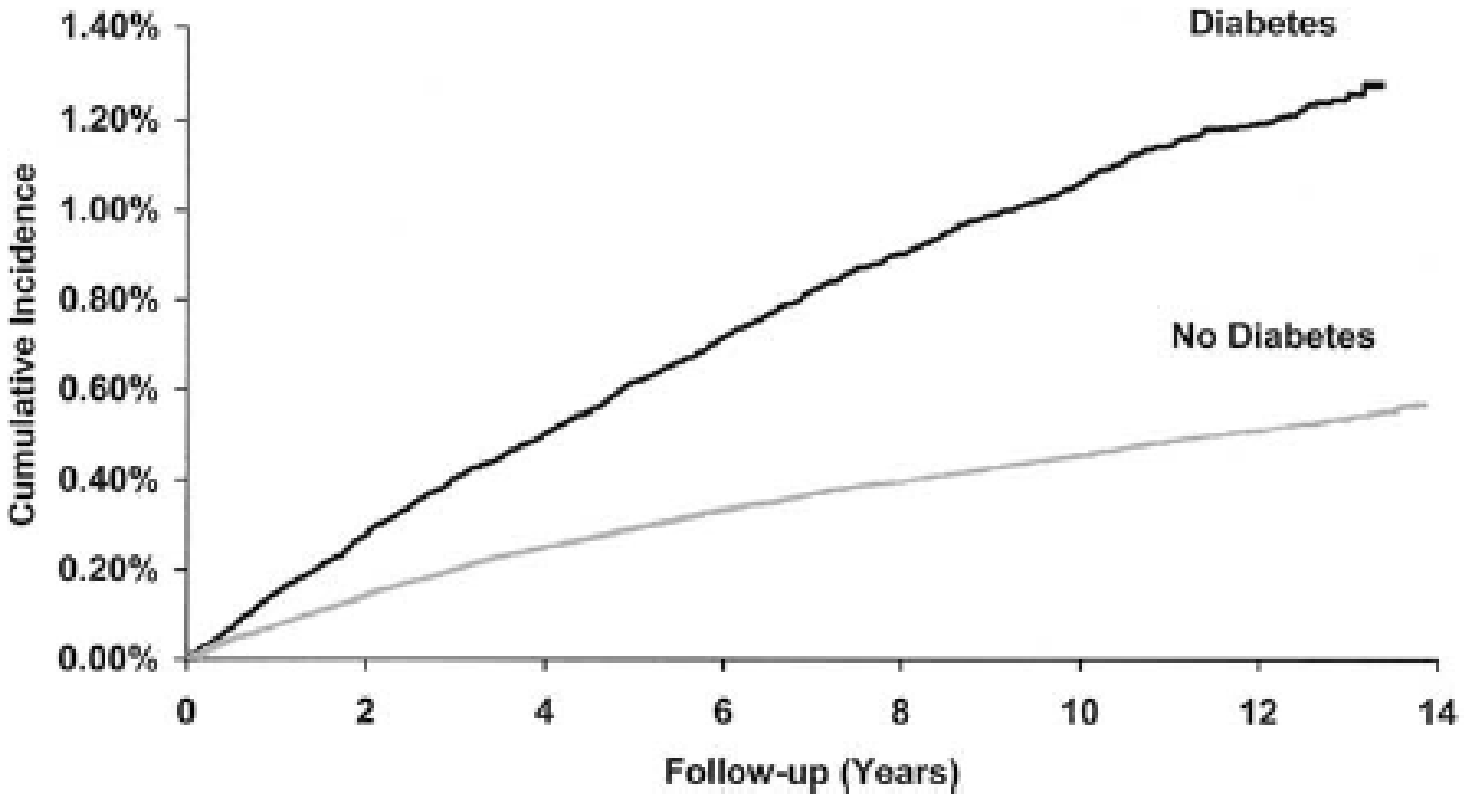
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Diabetes and CLD Incidence



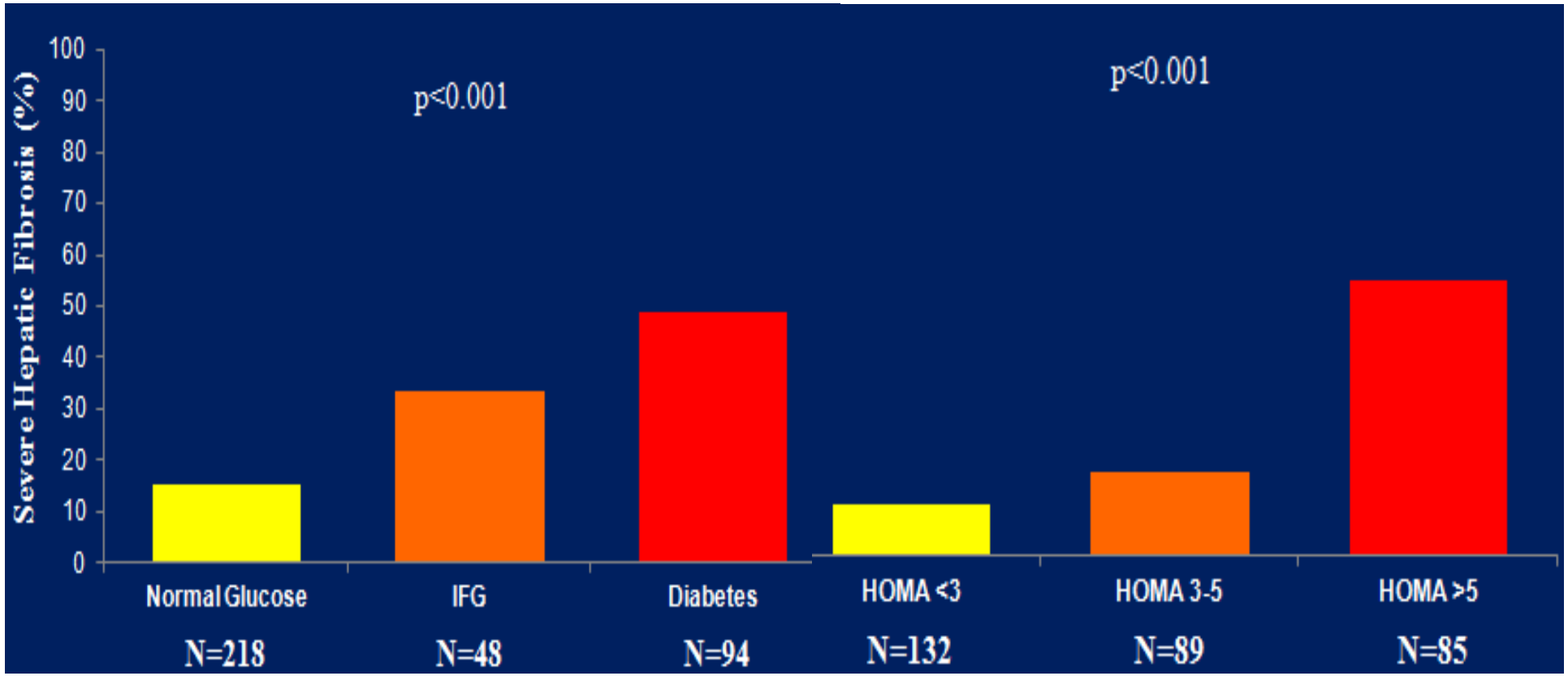
Cumulative risk (Kaplan–Meier) of chronic nonalcoholic liver disease among veteran patients hospitalized during 1985 to 1990 and followed until 2002.

El Serag et al, GASTROENTEROLOGY 2004

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Severity of Fibrosis in NAFLD According to Blood Glucose Status



Petta S et al, UNPUBLISHED DATA

Prediabetes and Hepatic Fibrosis

Multivariate analysis of PD and T2D to severity of histological features in patients with NAFLD.

	Steatosis	Lobular inflammation	Ballooning	Portal inflammation	Fibrosis
Normal glucose tolerance	-	-	-	-	-
PD	OR, 1.3 [95% CI, 0.8–1.7]	OR, 1.2 [95% CI, 0.7–1.6]	OR, 1.5 [95% CI, 0.8–1.9]	OR, 1.8 [95% CI, 1.1–3.2]	OR, 2.4 [95% CI, 1.3–3.7]
T2D	OR, 1.5 [95% CI, 0.7–2.1]	OR, 1.4 [95% CI, 0.8–1.5]	OR, 1.6 [95% CI, 0.7–1.6]	OR, 2.6 [95% CI, 1.3–5.8]	OR, 3.8 [95% CI, 1.9–6.1]
P value	0.67	0.48	0.89	< 0.01	< 0.001

Yilmaz et al, Journal of Diabete and its complications, 2014

Fibrosis Progression in NAFLD

Table 5. Independent associations between baseline-selected clinicopathological variables and the worsening of fibrosis in the follow-up.

Baseline variable	*P* (adjusted) [a]	Odds ratio (OR) [b]	95% Confidence interval
Amount of fibronectin (>1)	<0.001	14.1	6.9–32.3
% Incidence of hypertension	0.028	4.8	2.7–18.2
HOMA-IR score (>10)	0.004	1.9	1.6–12.1

Sorrentino et al, AJG 2010

Independent predictors of FPR in 118 Italian patients with NAFLD (including 10 with F4 fibrosis at baseline).

FPR predictor	Estimate±SE	p value
APRI at f-up, per unit	+0.04±0.01	0.005
RAS inhibitors at baseline or f-up	-0.012±0.004	0.009
T2D at baseline, yes	+0.010±0.004	0.025
Beta-blockers at baseline or f-up	-0.008±0.005	0.14
BMI variation, Kg/m^2	+0.001±0.001	0.14
Hypertension at baseline or f-up	+0.006±0.005	0.24

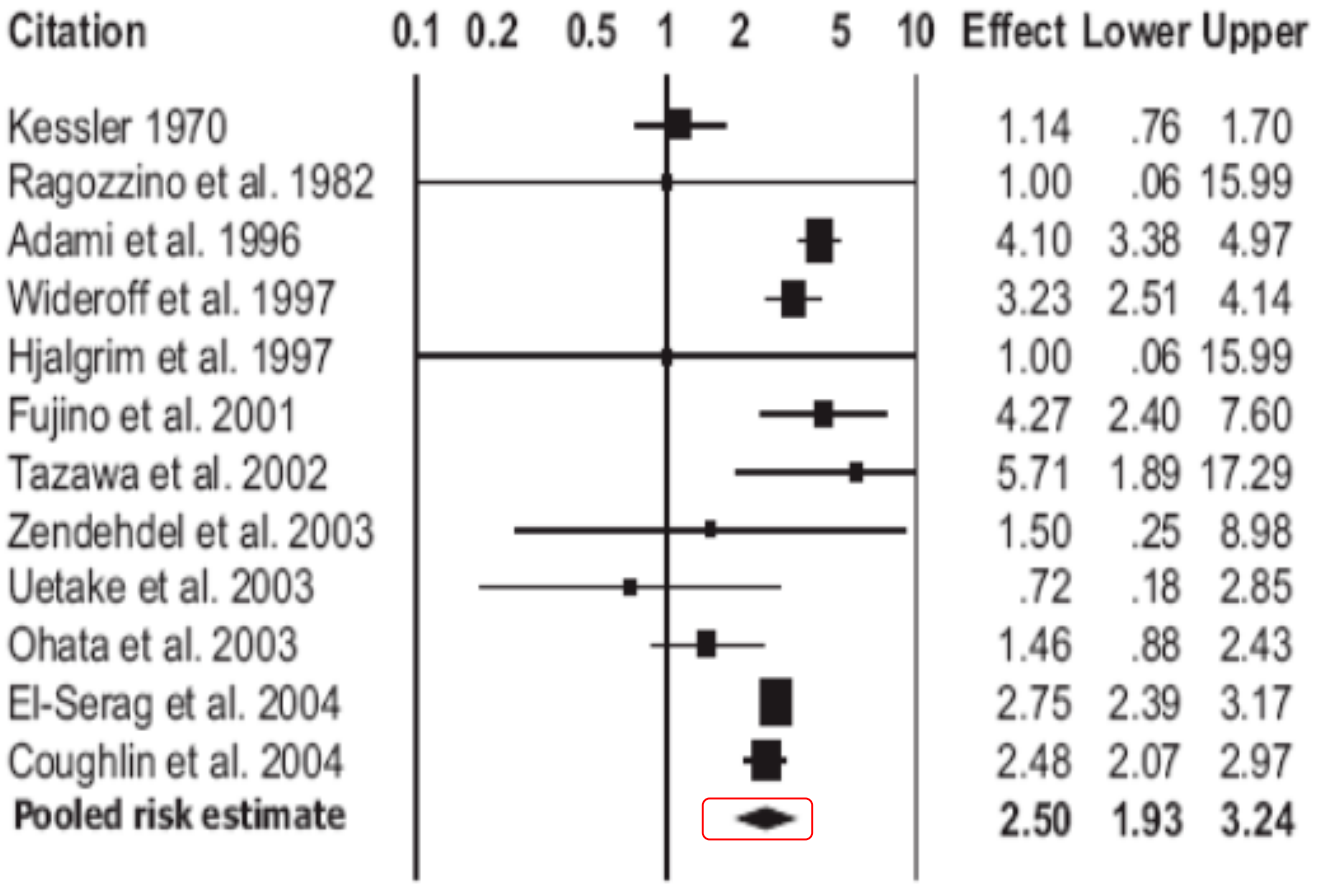
Pelusi et al, Plos One 2016

Hepatocellular Carcinoma Development in NAFLD: Is there a role for Diabetes?

Variable	HCC on NAFLD (n = 145)	HCC on HCV (n = 611)	P*
Demographic and clinical			
Age in years (mean, SD)	67.8 (9.0)	71.1 (9.5)	<0.0001
Male gender (n and percent of patients)	115 (79.3%)	374 (61.2%)	<0.0001
Body mass index (mean, SD)	29.1 (5.0)	27.6 (4.4)	0.430
Alcohol (n and percent of drinkers)	66 (45.5%)	41(8.6%)	<0.0001
Tobacco (n and percent of smokers)	84 (60.9%)	108 (23.8%)	<0.0001
Metabolic risk factors†			
Diabetes (n and percent of patients)	106 (73.1%)	148 (24.9%)	<0.0001
Hypertension (n and percent of patients)	106 (73.1%)	204 (37.1%)	<0.0001
Hypertriglyceridemia (n and percent of patients)	37 (25.7%)	17 (3.8%)	<0.0001
Hypercholesterolemia (n and percent of patients)	47 (32.9%)	34 (7.3%)	<0.0001
Atherosclerosis (n and percent of patients)	44 (31.0%)	89 (19.1%)	0.004
Ischemic cardiomyopathy (n and percent of patients)	18 (12.4%)	47 (8.5%)	0.151
Blood glucose (mg/dL; mean and SD)	124.3 (61.2)	108.0 (39.6)	<0.0001
LDL cholesterol (mg/dL; mean and SD)	90.1 (44.79)	94.5 (43.0)	0.516
HDL cholesterol (mg/dL; mean and SD)	46.9 (24.9)	43.3 (16.5)	0.204
Triglycerides (mg/dL; mean and SD)	150.3 (163.2)	104.4 (48.5)	<0.0001

Piscaglia et al, Hepatology 2016

Association between diabetes and HCC in cohort studies



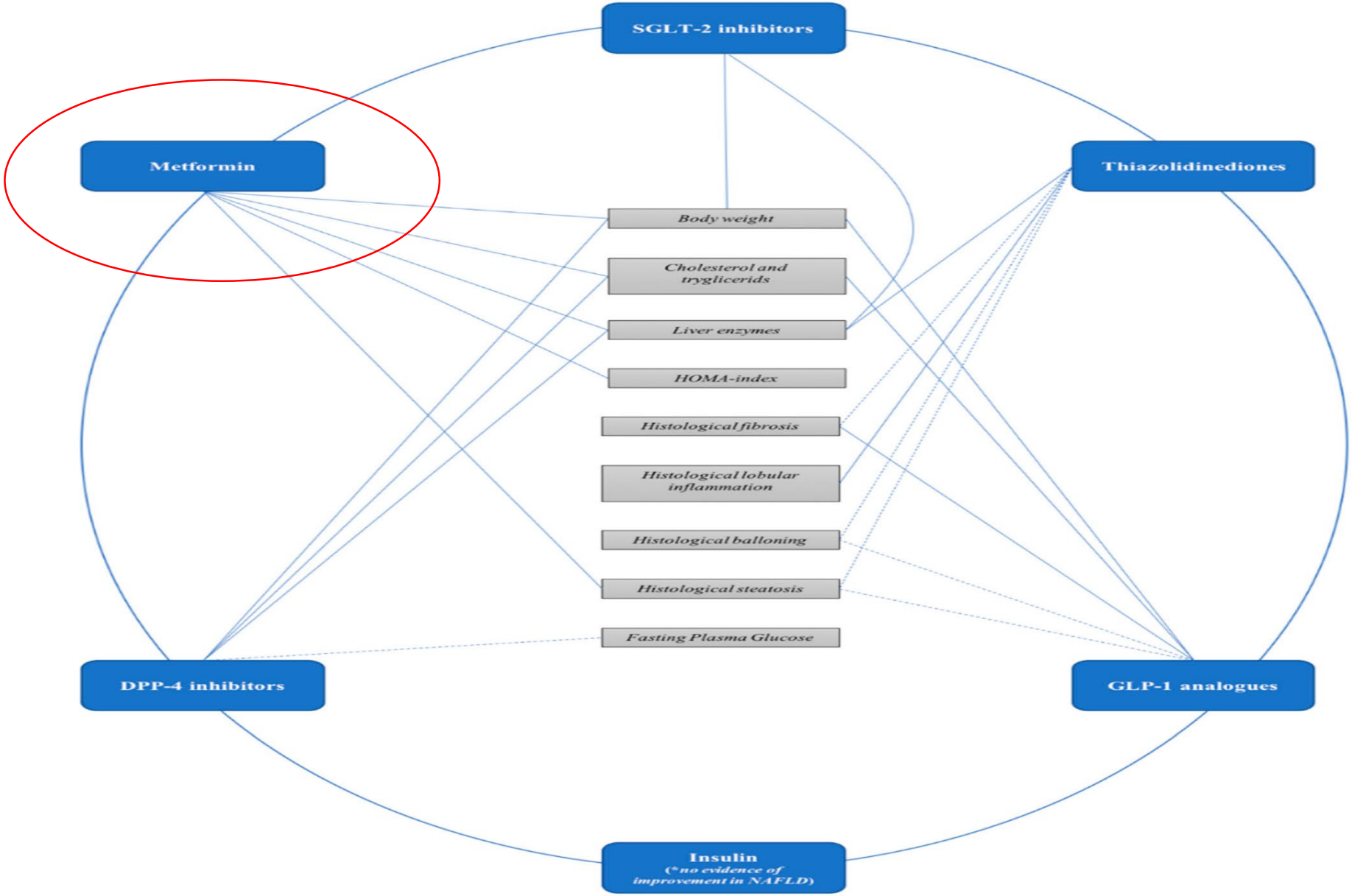
El Serag HB et al, CGH 2006

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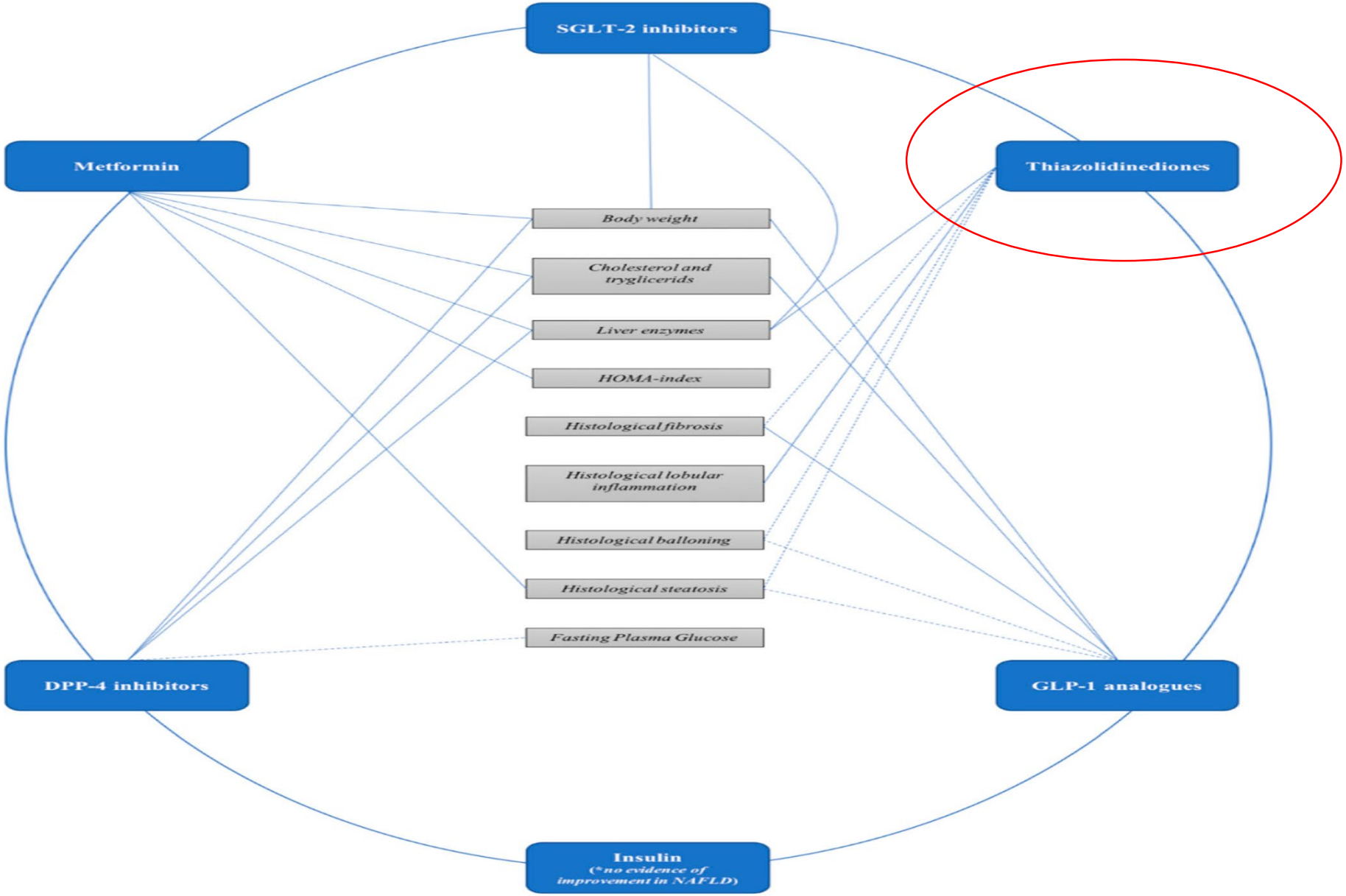
What Interplay between Diabetes Treatment and NAFLD?

Effects of Antidiabetic Treatment



Tacelli, Celsa, et al. 2018

Effects of Antidiabetic Treatment



Tacelli, Celsa, et al. 2018

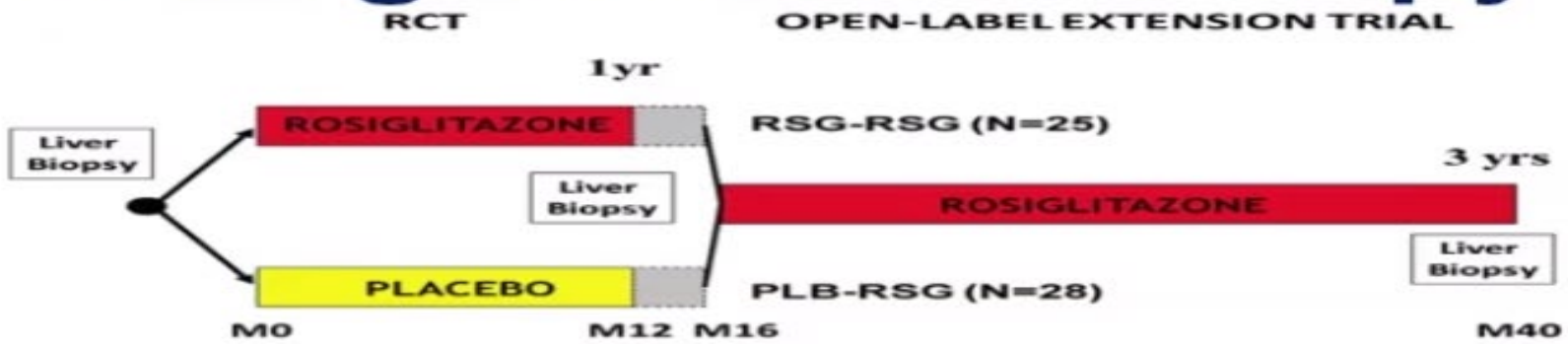
Annals of Internal Medicine

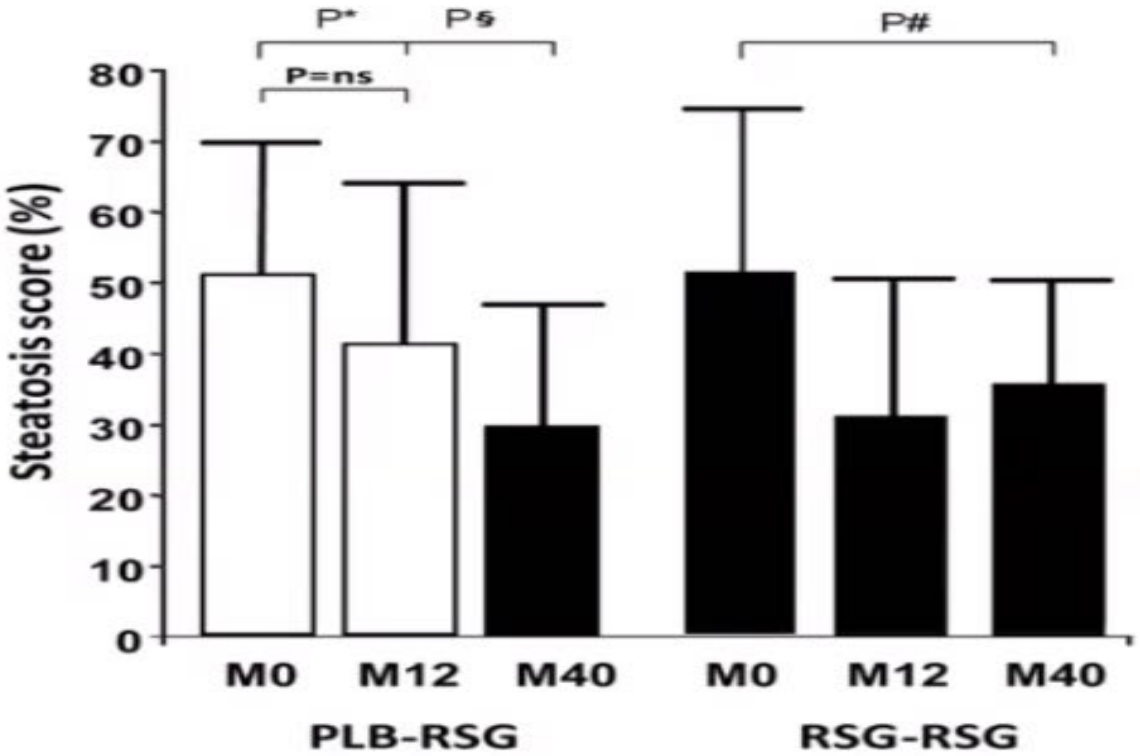
Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus

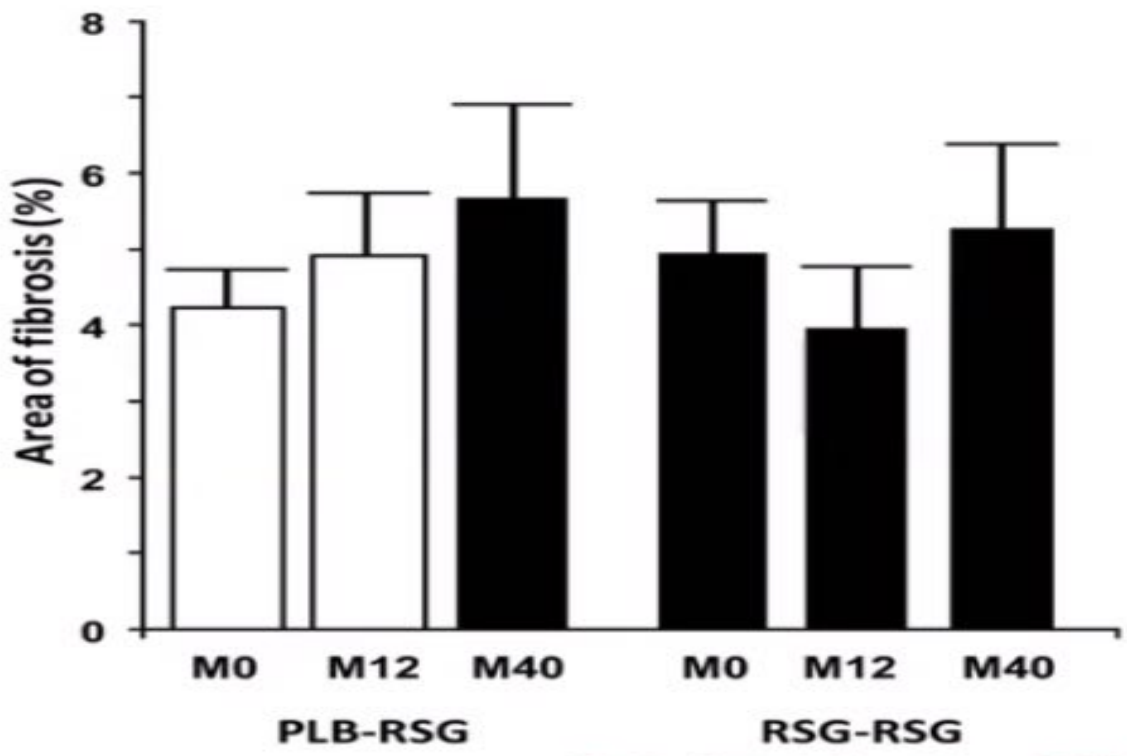
A Randomized Trial

Outcome	Placebo (n = 51)	Pioglitazone (n = 50)	Treatment Difference (95% CI)	P Value
Primary outcome				
≥2-point reduction in NAS (in 2 categories) without worsening of fibrosis, *n (%)*	9 (17)	29 (58)	41 (23 to 59)	<0.001
Secondary outcomes				
Resolution of NASH, *n (%)*†	10 (19)	26 (51)	32 (13 to 51)	<0.001
Steatosis				
≥1-point improvement, *n (%)*	13 (26)	35 (71)	44 (25 to 63)	<0.001
Mean change in score (SD)	−0.2 (0.8)	−1.1 (1.0)	−0.9 (−1.3 to −0.5)	<0.001
Inflammation				
≥1-point improvement, *n (%)*	11 (22)	25 (49)	27 (8 to 46)	0.004
Mean change in score (SD)	−0.1 (0.8)	−0.6 (0.9)	−0.6 (−0.9 to −0.2)	<0.001
Ballooning				
≥1-point improvement, *n (%)*	12 (24)	25 (51)	27 (7 to 47)	0.004
Mean change in score (SD)	−0.2 (0.7)	−0.6 (0.6)	−0.4 (−0.7 to −0.2)	0.001
Fibrosis				
≥1-point improvement, *n (%)*	13 (25)	20 (39)	14 (−6 to 34)	0.130
Mean change in score (SD)	0 (1.2)	−0.5 (1.0)	−0.5 (−0.9 to 0)	0.039

NASH: Effect of Prolonged Rosiglitazone Therapy

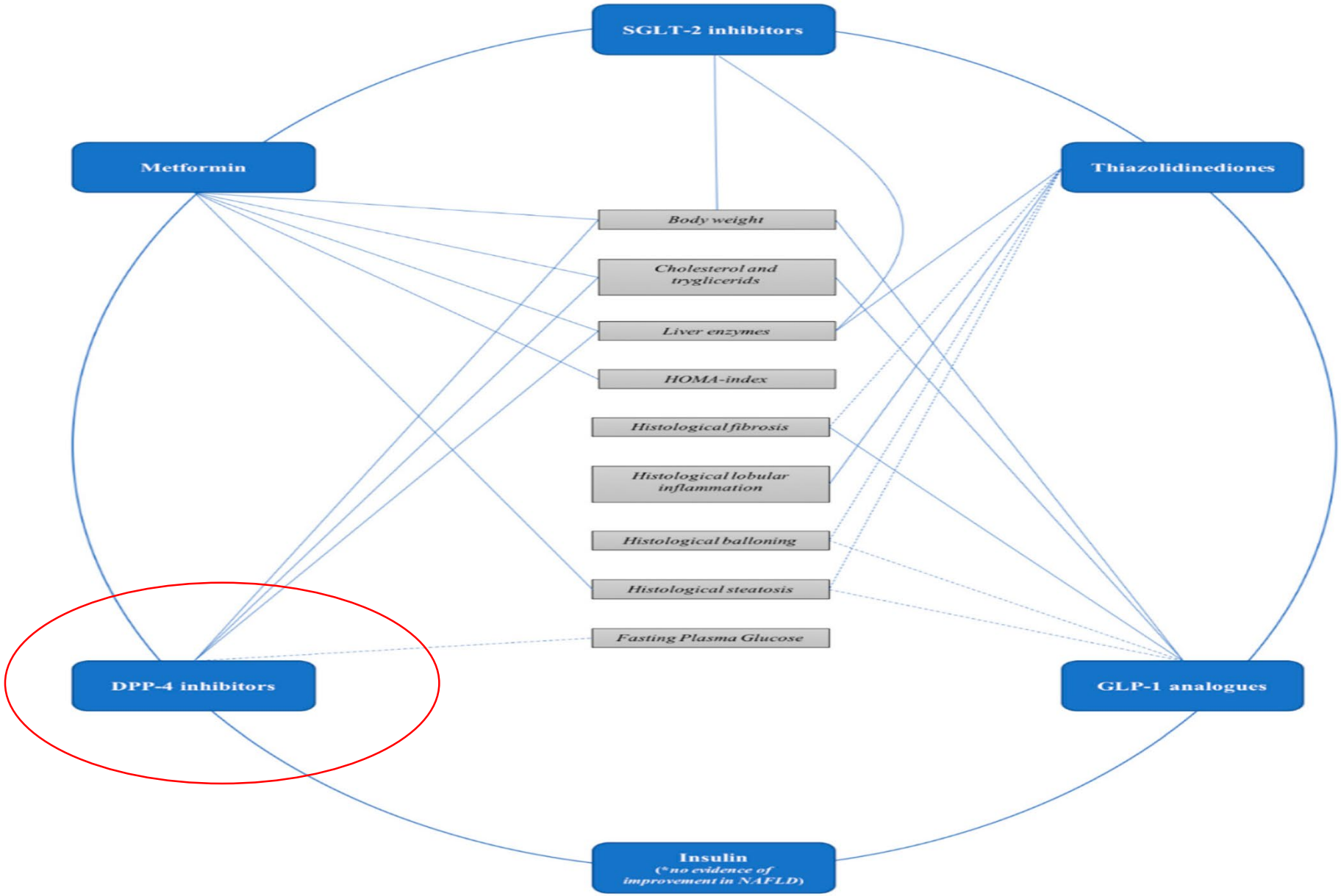






Ratziu V et al, Hepatology 2010

Effects of Antidiabetic Treatment

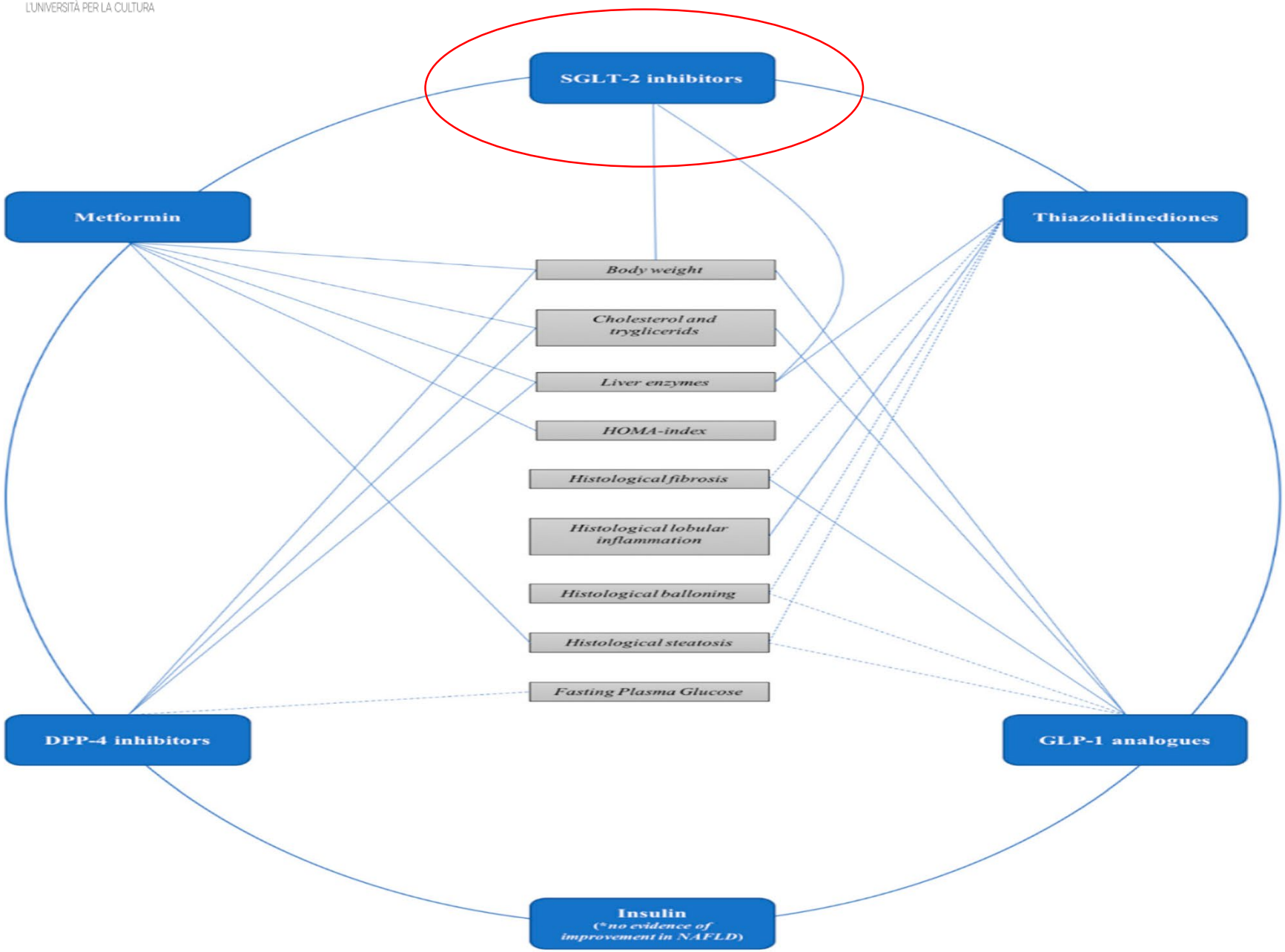


Tacelli, Celsa, et al. 2018

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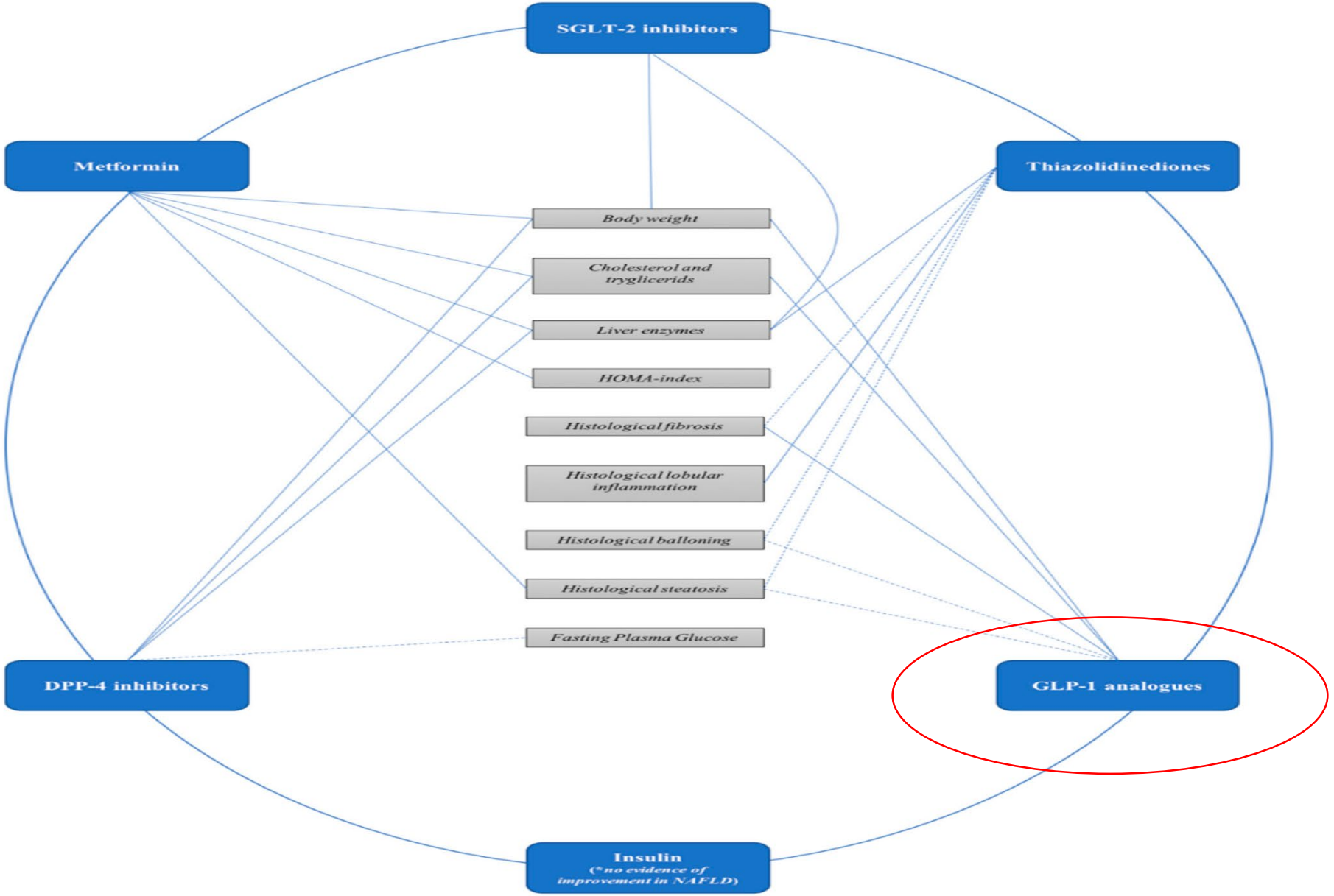
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Effects of Antidiabetic Treatment



Tacelli, Celsa, et al. 2018

Effects of Antidiabetic Treatment



Tacelli, Celsa, et al. 2018

LEAN "Liraglutide's Efficacy & Action in NASH

52 Histological NASH

Control Group N=26

Placebo 0.6 mg OD (Days 1-7)

Placebo 1.2 mg OD (Days 8-14)

Placebo 1.8 mg OD (Days 15-336)

Experimental Group N=26

Liraglutide 0.6 mg OD (Days 1-7)

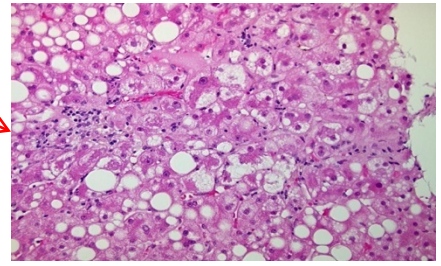
Liraglutide 1.2 mg OD (Days 8-14)

Liraglutide 1.8 mg OD (Days 15-336)

Primary Endpoint:

NASH Disappereance without impairment of Fibrosis

48 weeks



Amstrong MJ, Lancet 2016

LEAN "Liraglutide's Efficacy & Action in NASH

	Liraglutide (n = 23)	Placebo (n = 22)	p
NASH disappearence without fibrosis progression	9 (39,1 %)	2 (9,1 %)	< 0,05
Kleiner Fibrosis score **Improvement, n (%)** **Impairment, n (%)**	-0,2 6 (26,1 %) 2 (8,7 %)	0,2 3 (13,6 %) 8 (36,4 %)	ns ns < 0,05
NAS Score	-1,3	-0,8	ns
Ballooning **Improvement, n (%)**	-0,5 14 (60,9 %)	-0,2 7 (31,8 %)	ns
Steatosis **Improvement, n (%)**	-0,7 19 (82,6 %)	-0,4 10 (45,5 %)	ns < 0,05
Lobular Inflammation **Improvement, n (%)**	-0,1 11 (47,8 %)	-0,2 12 (54,5 %)	ns ns

Amstrong MJ, Lancet 2016

Take-home messages

- NAFLD predicts diabetes occurrence and increases the risk of cardiovascular complications among diabetic patients
- NAFLD is highly prevalent in diabetic patients
- Diabetic Patients with NAFLD are at high risk of severe liver damage and of progression of the liver disease
- Drugs used for diabetes treatment can affect liver damage in NAFLD