NAFLD and Cardiovascular Risk

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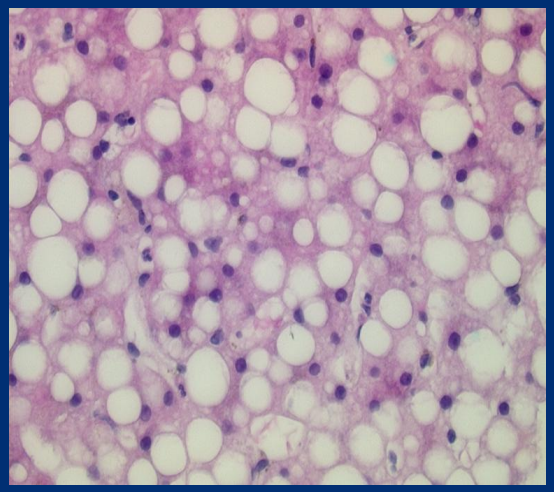
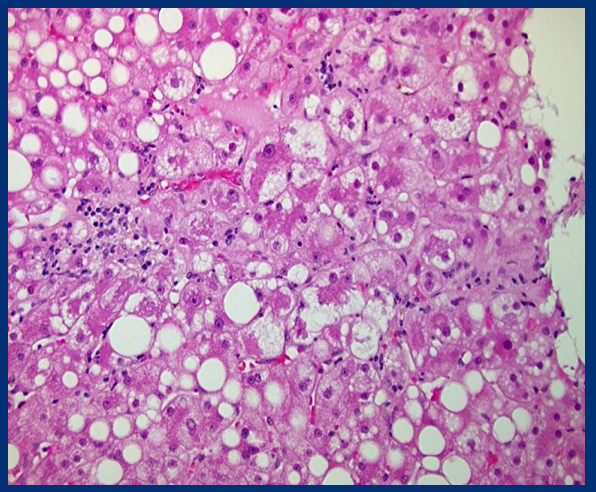
NAFLD

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





Selected studies on prevalence of NAFLD and NASH
Population-based series

Author (year)	Diagnostic method	Country	N	Prevalence of NAFLD (%)	Prevalence of NASH (%)
Clark (2003)	Aminotransferases	Unites States	15676	5.4	ND
Ruhl (2003)	Aminotransferases	United States	5724	2.8	ND
Bedogni (2005)	Ultrasonography	Italy	598	23	ND
Fan (2005)	Ultrasonography	China	3175	15	ND
Nomura (1988)	Ultrasonography	Japan	2574	14	ND
Browing (2004)	RMN	Unites States	2287	31	ND

Angulo P et al, Aliment Pharmacol Ther 2007

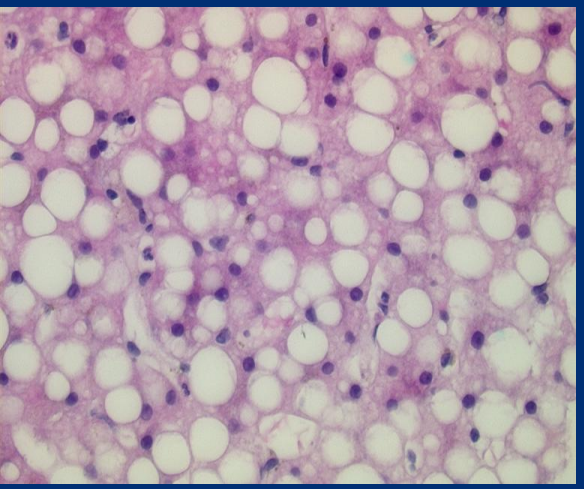
NAFLD and Metabolic Syndrome

Table 2. Clinical syndromes associated with insulin resistance.

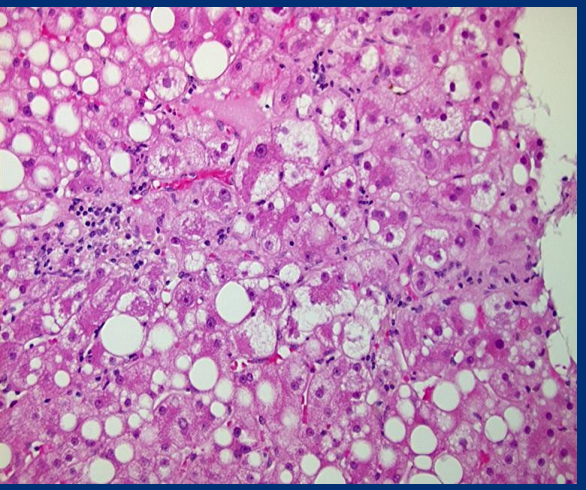
- Type 2 diabetes
- CVD
- Essential hypertension
- Polycystic ovary syndrome
- Nonalcoholic fatty liver disease
- Certain forms of cancer
- Sleep apnea

Reaven GM, Clin Chem 2005

NAFLD



Simple fatty liver: the only histologic finding is the presence of steatosis



Non-alcoholic steatohepatitis (NASH): steatosis associated with hepatocellular injury/inflammation with or without fibrosis

Non Alcoholic Fatty Liver Disease

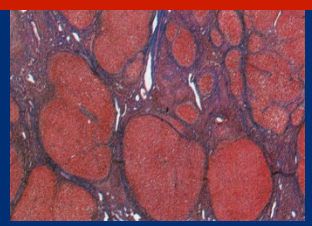
Normal

Increased cardiovascular risk

Increased kidney disease

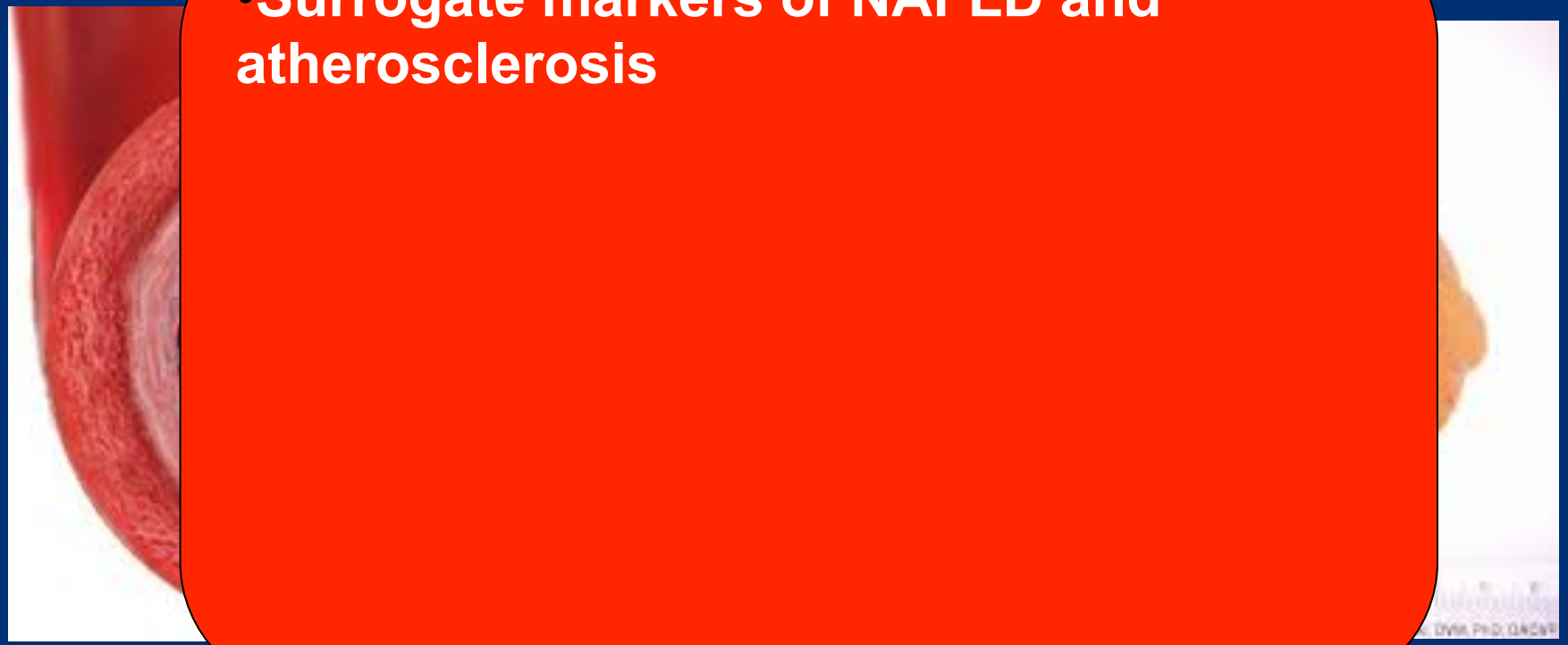
Increased diabetes risk

Increased cancer incidence



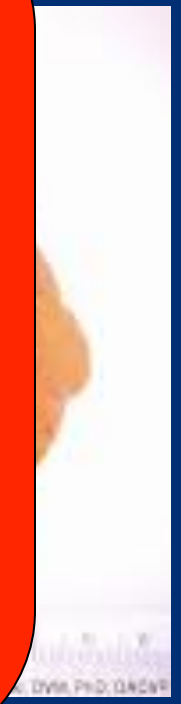
What Evidences?

- Surrogate markers of NAFLD and atherosclerosis



What Evidences?

- Surrogate markers of NAFLD and atherosclerosis
- NAFLD and both carotid and coronary atherosclerosys: cross-sectional studies



What Evidences?

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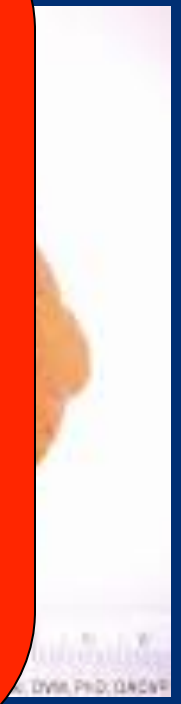
- NAFLD and both carotid and coronary atherosclerosys: cross-sectional studies
- NAFLD and heart dysfunction:cross-sectional studies

What Evidences?

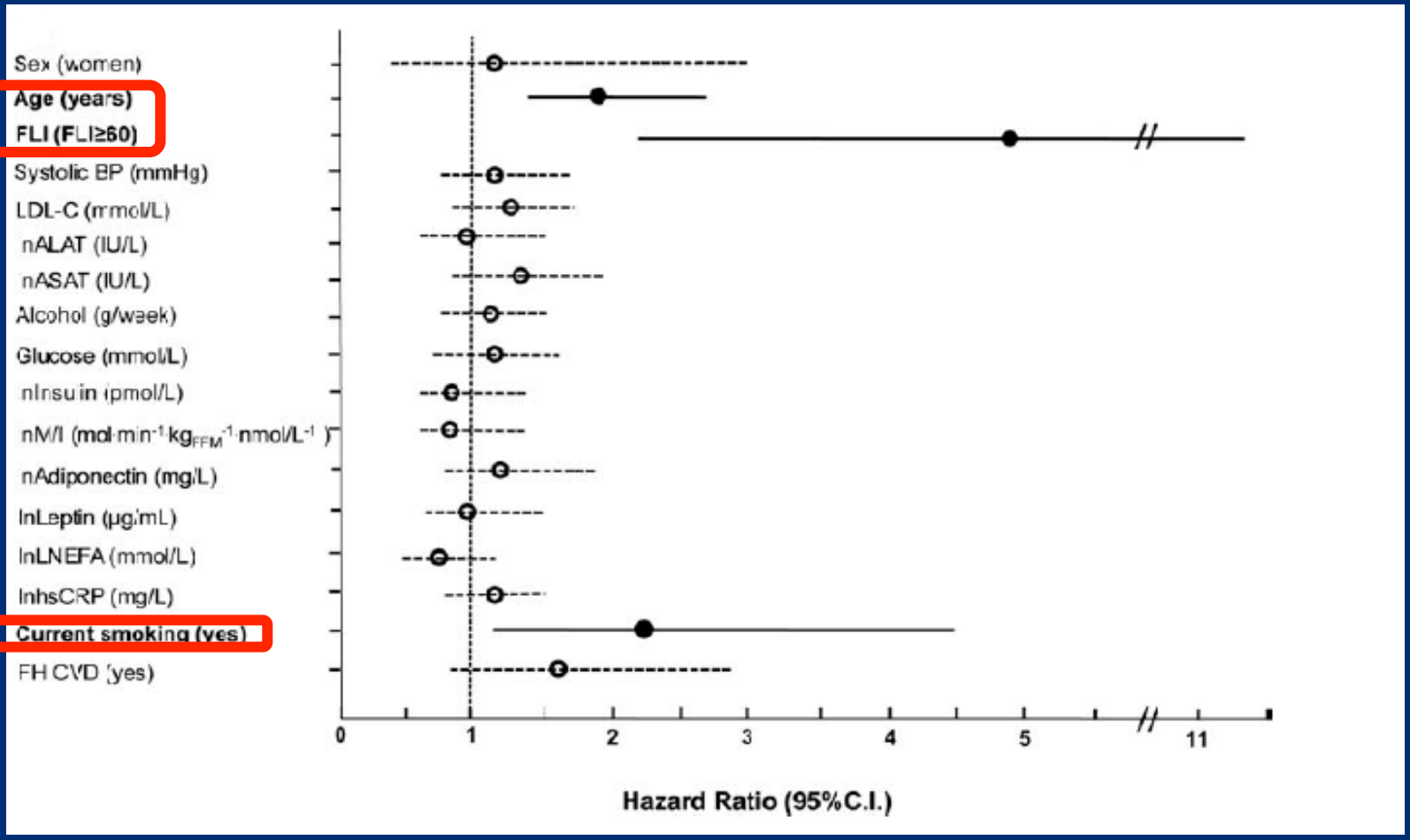
- Surrogate markers of NAFLD and atherosclerosis
- NAFLD and both carotid and coronary atherosclerosys: cross-sectional studies
- NAFLD and heart dysfunction:cross-sectional studies
- NAFLD and CVD: prospective studies



NAFLD and CVD

Evidences using liver tests as surrogate markers of steatosis

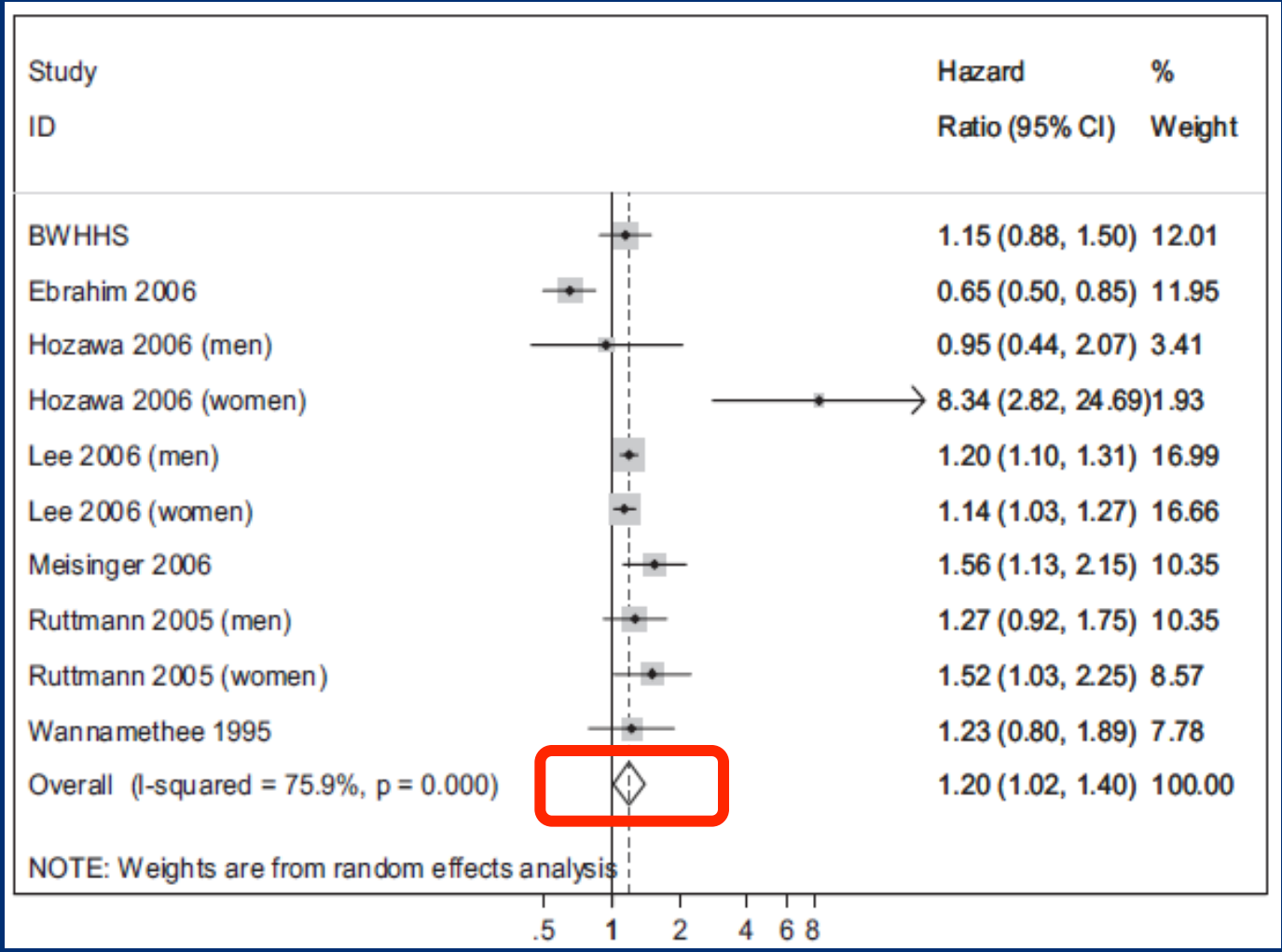
Fatty Liver Index and Early Carotid Atherosclerosis



1,012 subjects without hypertension, diabetes, CVD, and dyslipidemia

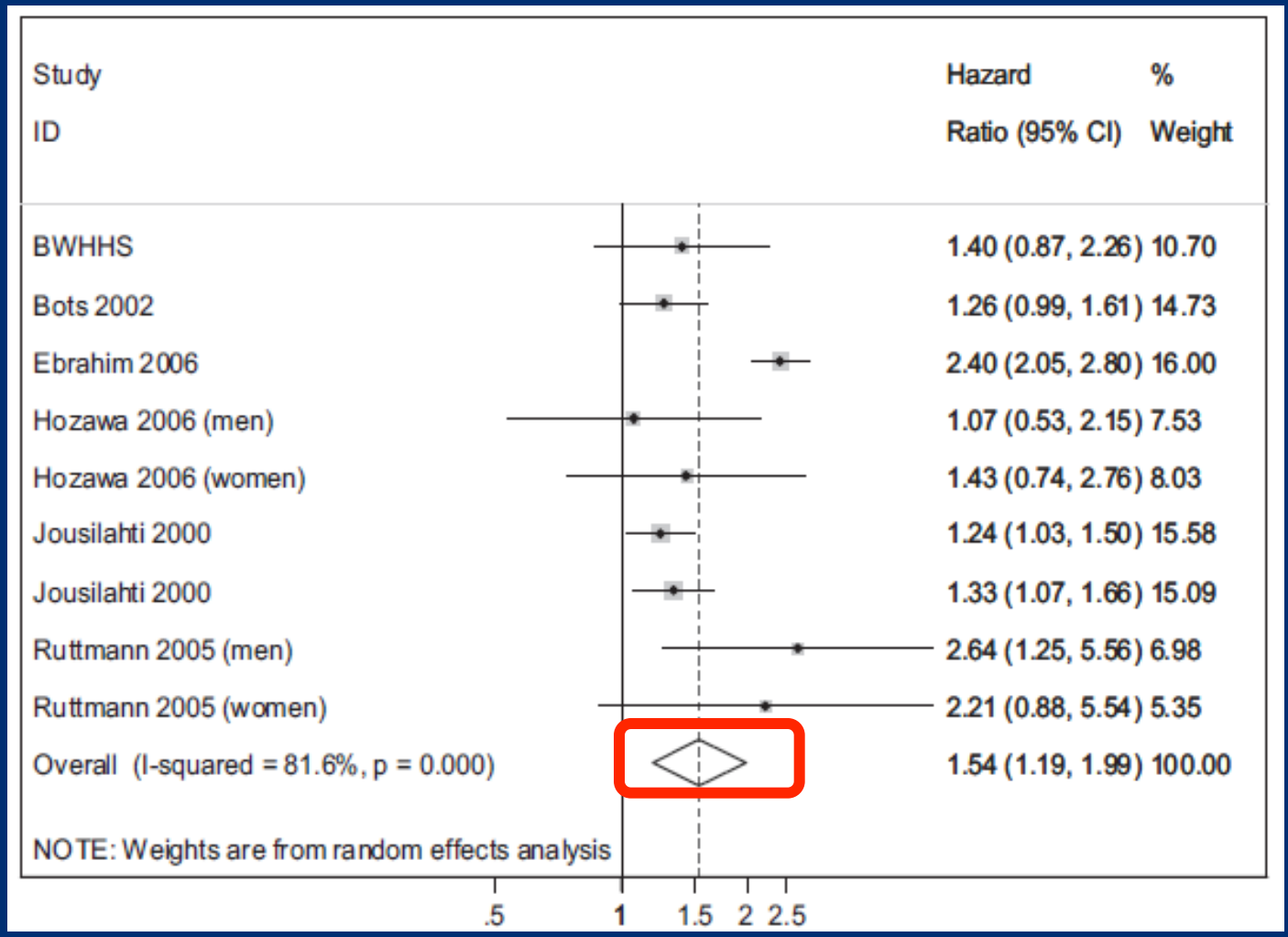
Kozakova et al, Hepatology 2012

GGT Levels and Incident Coronary Heart Disease



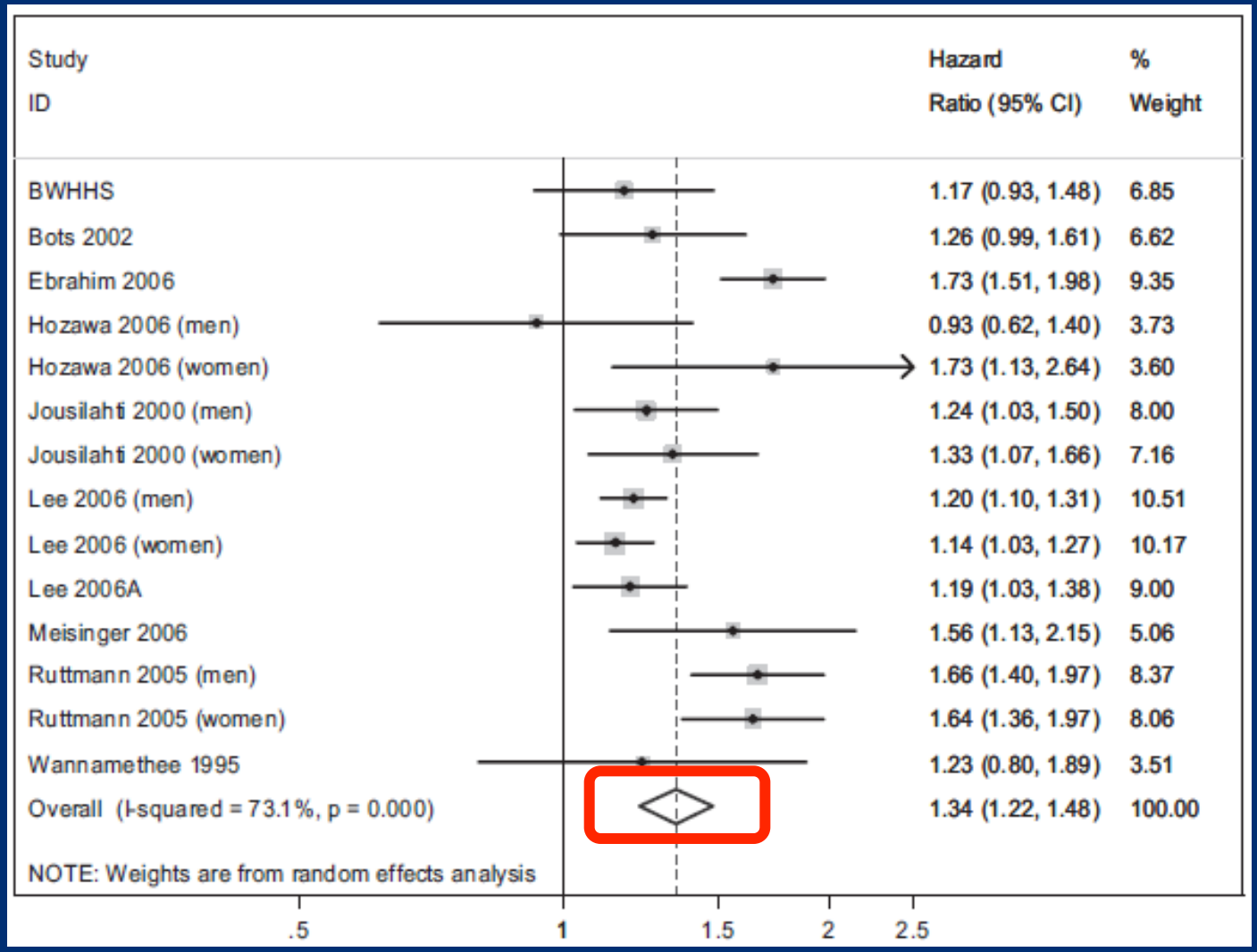
Fraser et al, Art Tromb Vasc Biol 2007

GGT Levels and Incident Stroke



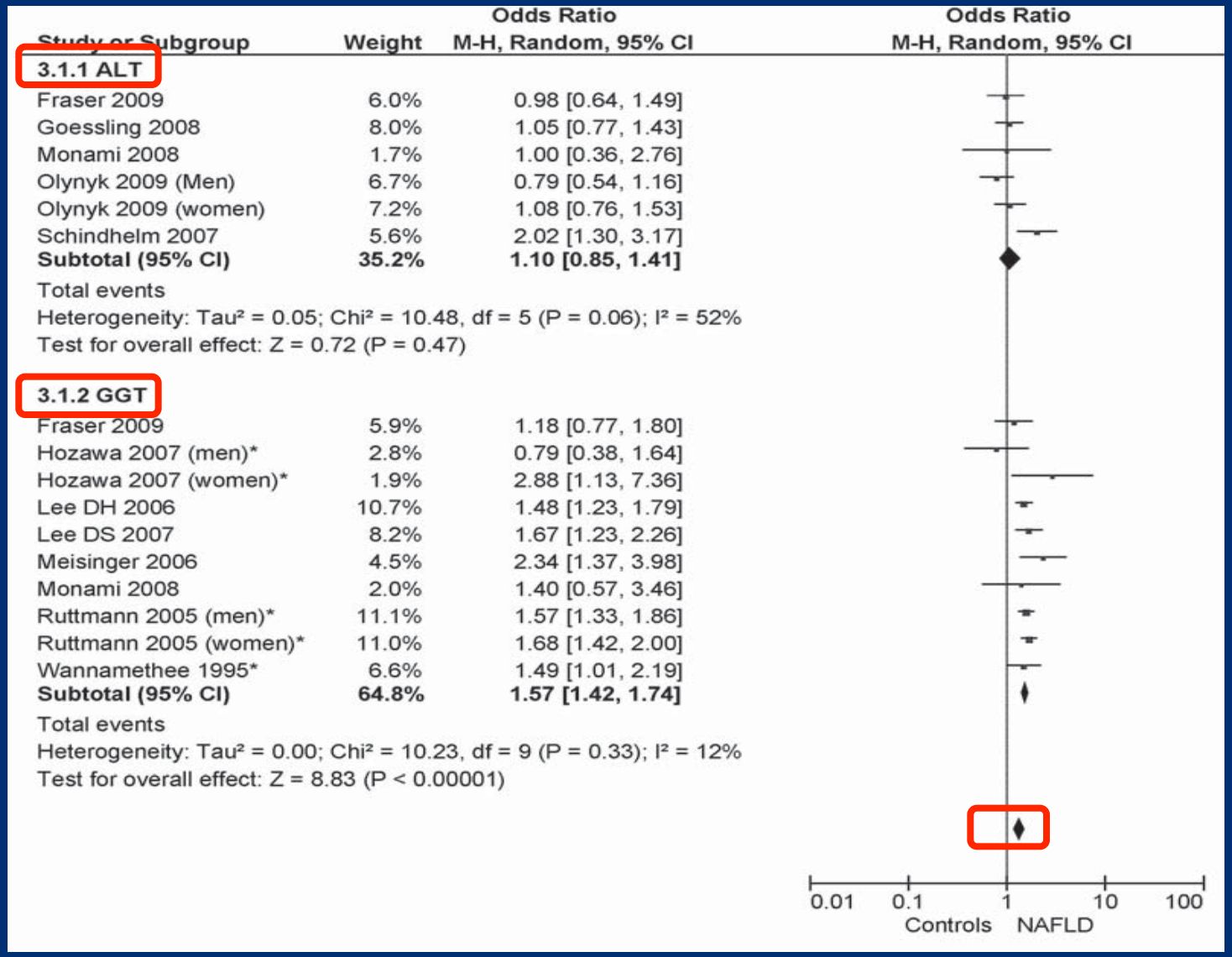
Fraser et al, Art Tromb Vasc Biol 2007

GGT Levels and Incident CHD or Stroke



Fraser et al, Art Tromb Vasc Biol 2007

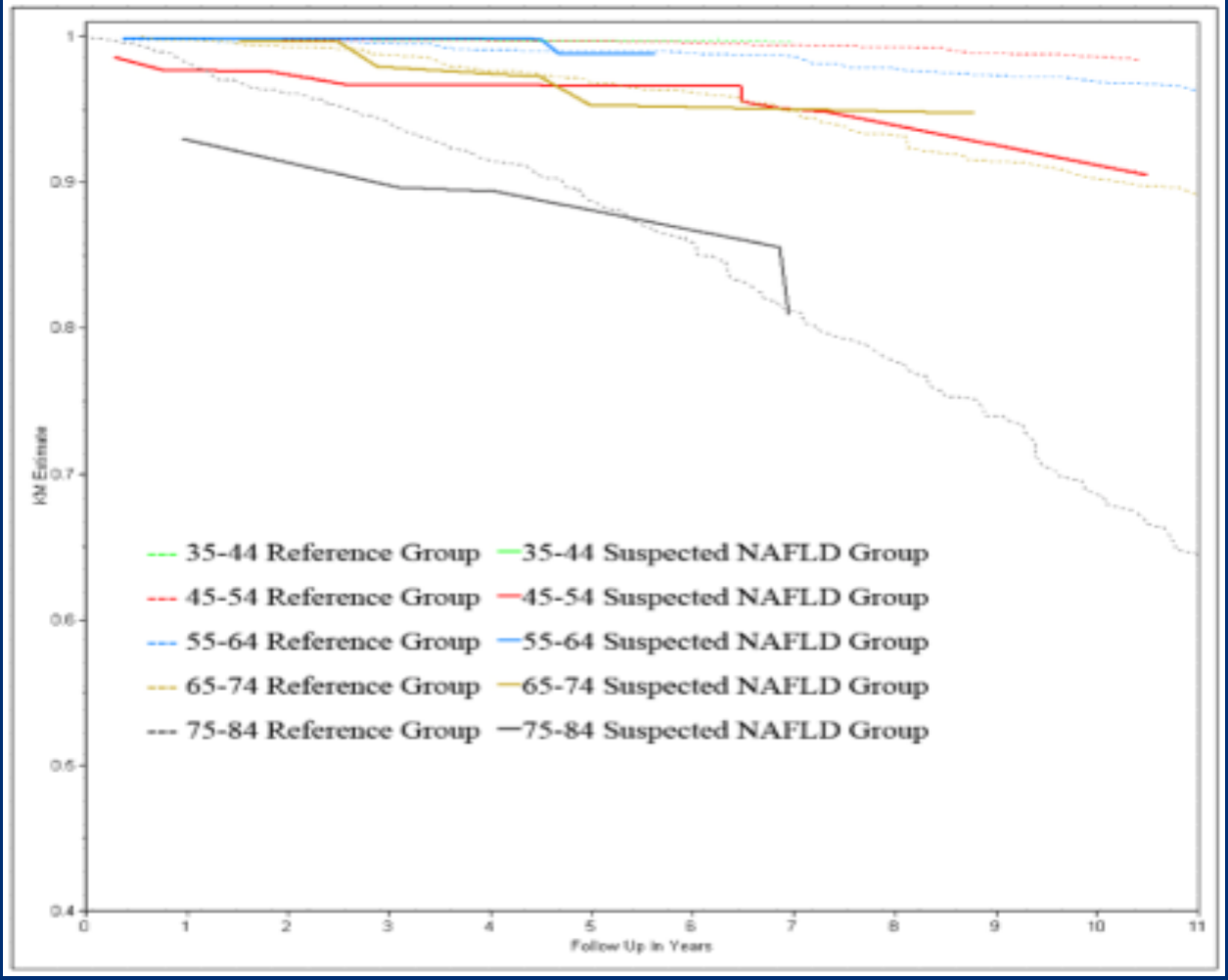
NAFLD as Risk Factor for Incident CVD Events



Study or Subgroup	Weight	Odds Ratio M-H, Random, 95% CI
3.1.1 ALT		
Fraser 2009	6.0%	0.98 [0.64, 1.49]
Goessling 2008	8.0%	1.05 [0.77, 1.43]
Monami 2008	1.7%	1.00 [0.36, 2.76]
Olynyk 2009 (Men)	6.7%	0.79 [0.54, 1.16]
Olynyk 2009 (women)	7.2%	1.08 [0.76, 1.53]
Schindhelm 2007	5.6%	2.02 [1.30, 3.17]
Subtotal (95% CI)	**35.2%**	**1.10 [0.85, 1.41]**
Total events		
Heterogeneity: Tau² = 0.05; Chi² = 10.48, df = 5 (P = 0.06); I² = 52%		
Test for overall effect: Z = 0.72 (P = 0.47)		
3.1.2 GGT		
Fraser 2009	5.9%	1.18 [0.77, 1.80]
Hozawa 2007 (men)*	2.8%	0.79 [0.38, 1.64]
Hozawa 2007 (women)*	1.9%	2.88 [1.13, 7.36]
Lee DH 2006	10.7%	1.48 [1.23, 1.79]
Lee DS 2007	8.2%	1.67 [1.23, 2.26]
Meisinger 2006	4.5%	2.34 [1.37, 3.98]
Monami 2008	2.0%	1.40 [0.57, 3.46]
Ruttmann 2005 (men)*	11.1%	1.57 [1.33, 1.86]
Ruttmann 2005 (women)*	11.0%	1.68 [1.42, 2.00]
Wannamethee 1995*	6.6%	1.49 [1.01, 2.19]
Subtotal (95% CI)	**64.8%**	**1.57 [1.42, 1.74]**
Total events		
Heterogeneity: Tau² = 0.00; Chi² = 10.23, df = 9 (P = 0.33); I² = 12%		
Test for overall effect: Z = 8.83 (P < 0.00001)		

Musso et al, Ann of Med 2010

Cardiovascular Disease Survival in NHANES III Cohort



n=7574

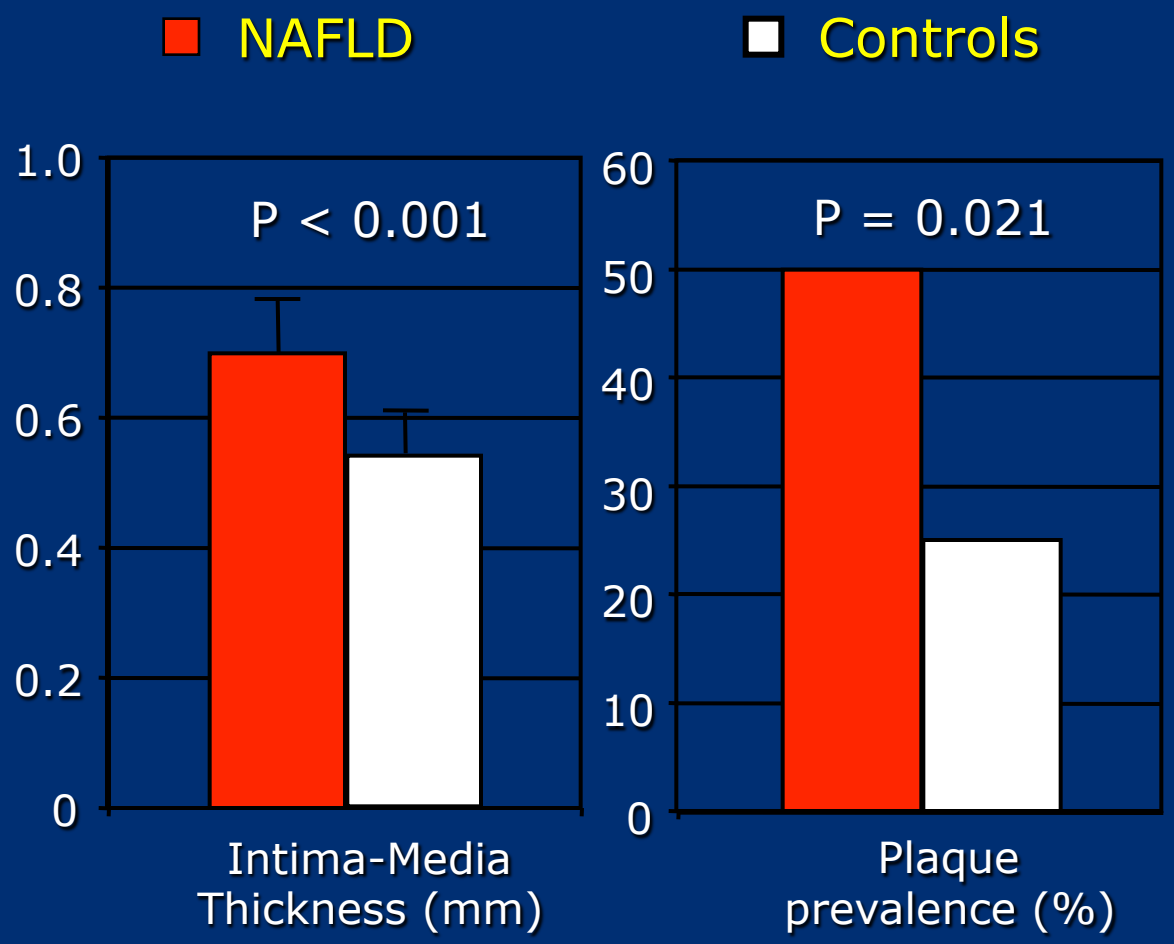
Suspected NAFLD according to ALT levels

Dunn W et al, AJG 2008

NAFLD and CVD

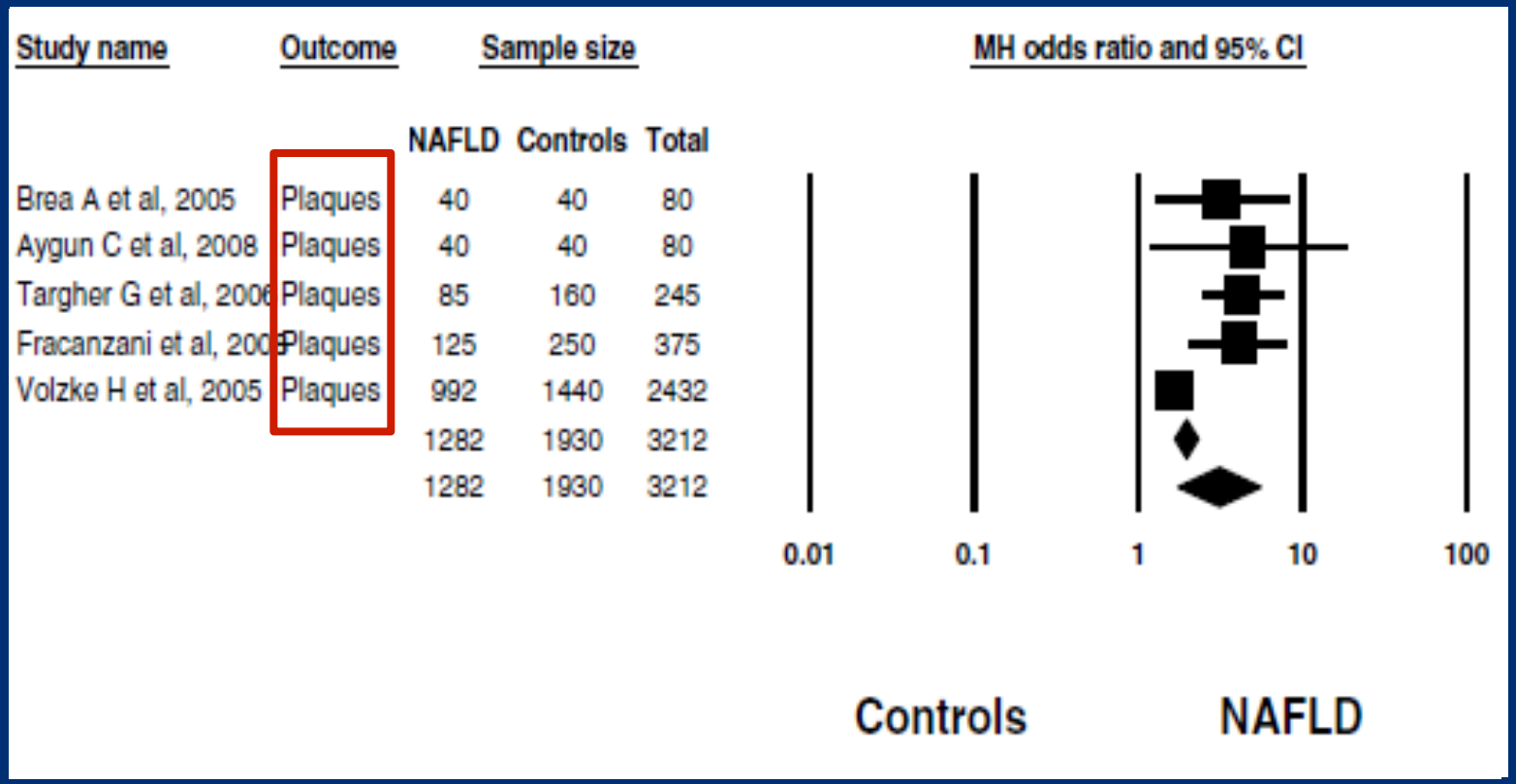
Association between NAFLD and Carotid Atherosclerosis: cross-sectional studies

Carotid Atherosclerosis and NAFLD



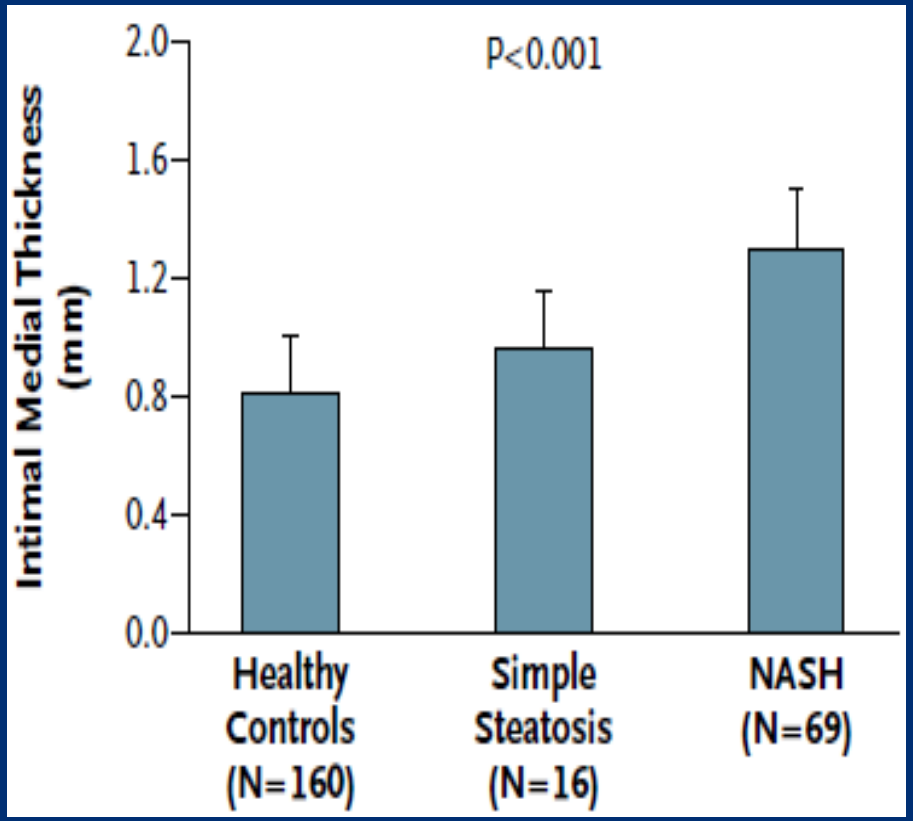
Brea, Arterioscler Thromb Vasc Biol 2005

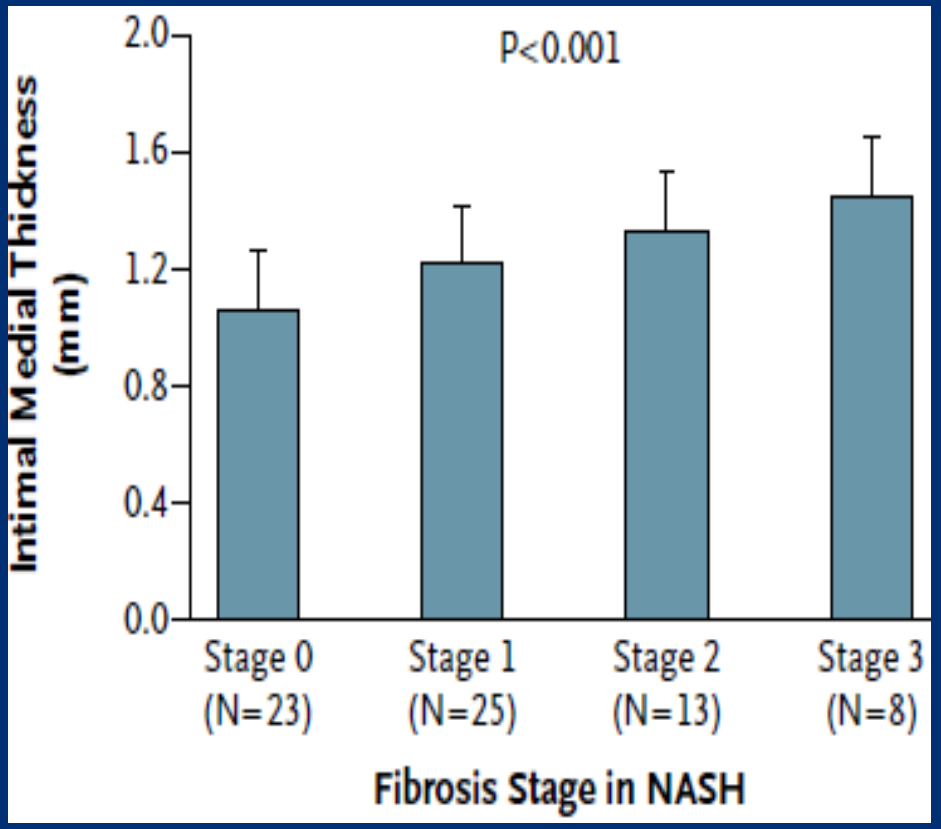
Carotid Atherosclerosis and NAFLD



Sookoian et al, J Hep 2008

Carotid Atherosclerosis and NAFLD





Targher G, Diabetes Care 2006

BUT!!

Nonalcoholic Fatty Liver Is Not Associated with Carotid Intima-Media Thickness in Type 2 Diabetic Patients

JCEM 2009

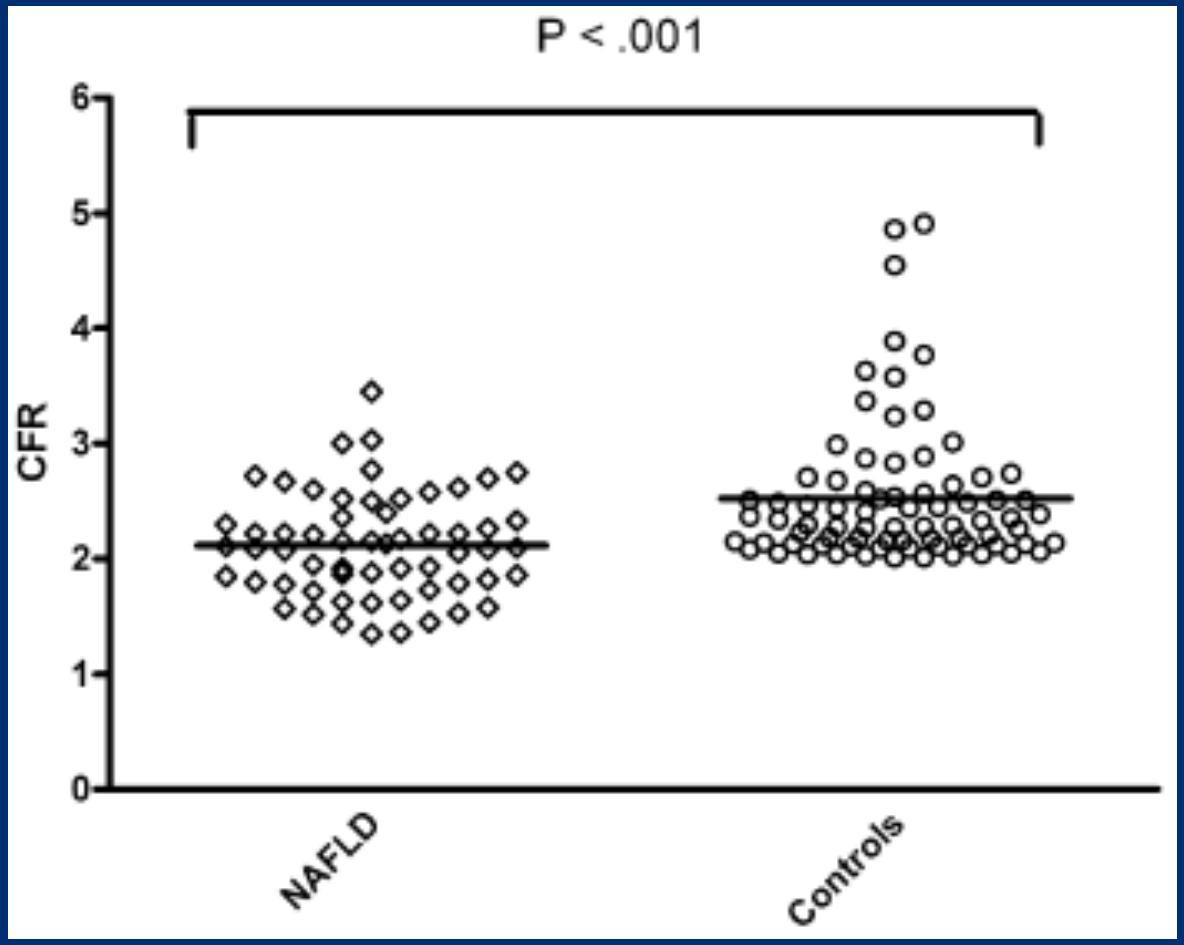
Jean Michel Petit, Boris Guiu, Beatrice Terriat, Romaric Loffroy, Isabelle Robin, Vincent Petit, Benjamin Bouillet, Marie-Claude Brindisi, Laurence Duvillard, Patrick Hillon, Jean-Pierre Cercueil, and Bruno Verges

No Association between NAFLD evaluated ma MR spectroscopy, and carotid intima-media thickness in 101 diabetic patients

NAFLD and CVD

Association between NAFLD and Coronary Atherosclerosis: cross-sectional studies

Coronary Flow Reserve by Doppler Echocardiography in NAFLD Patients



Coronary flow reserve was lower in 59 NAFLD compared to 77 controls, and inversely related to the severity of liver fibrosis.

Yilmaz et al, Atherosclerosis 2010

Coronary Artery Disease and NAFLD

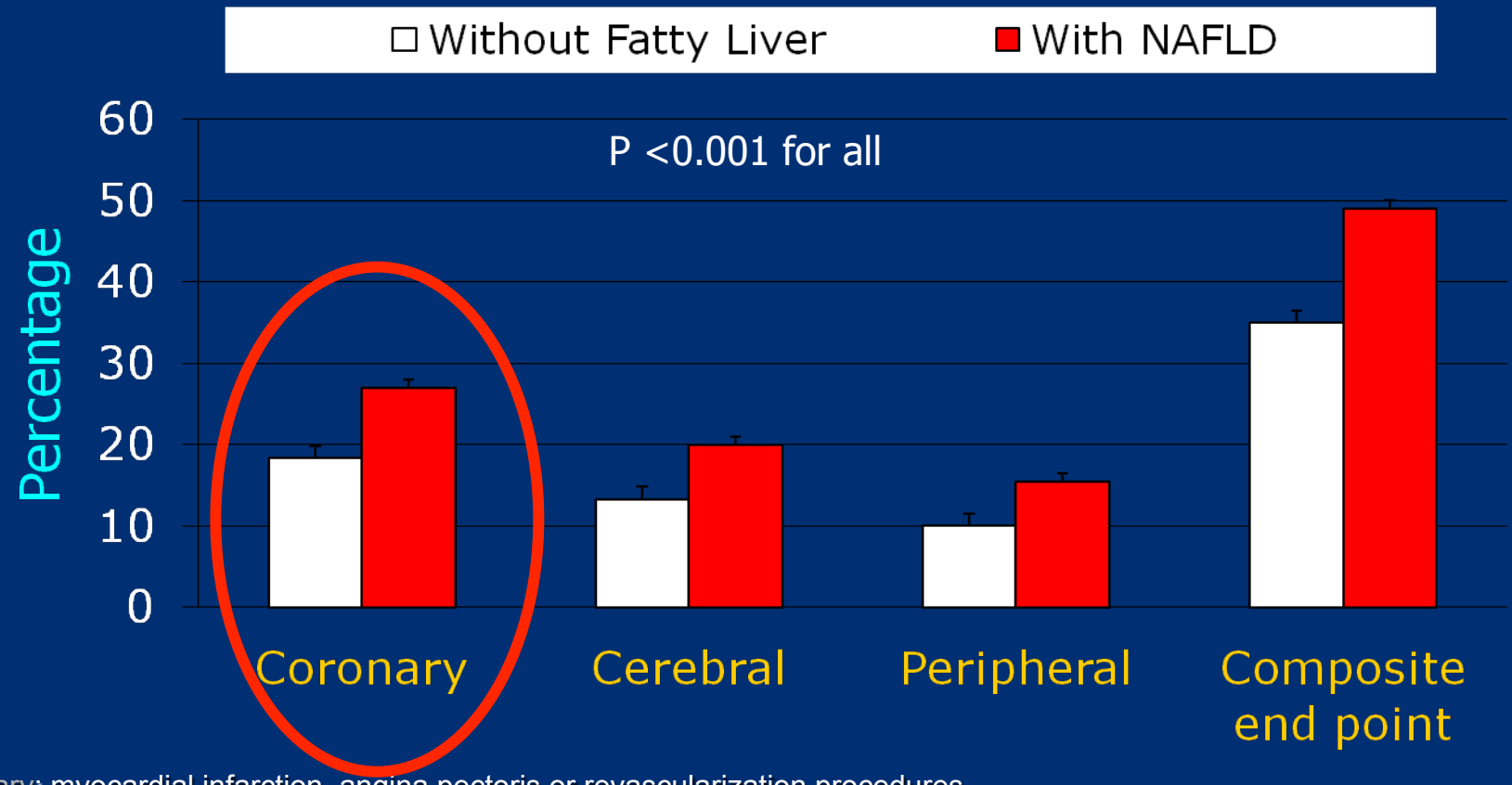
Factors associated with coronary artery disease

Factors	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Fatty liver	3.07 (2.09 to 4.51)	<0.001	2.31 (1.46 to 3.64)	<0.001
Age (years)	1.03 (1.02 to 1.05)	<0.001	1.05 (1.03 to 1.07)	<0.001
Male gender	2.44 (1.66 to 3.60)	<0.001	2.60 (1.65 to 4.09)	<0.001
Smoking	1.45 (0.96 to 2.20)	0.081		
Alcohol	0.84 (0.51 to 1.38)	0.48		
Diabetes	2.29 (1.46 to 3.61)	<0.001	1.45 (0.84 to 2.51)	0.18
Hypertension	1.38 (0.94 to 2.02)	0.098		
Systolic blood pressure (mm Hg)	1.01 (1.00 to 1.02)	0.14		
Diastolic blood pressure (mm Hg)	1.01 (1.00 to 1.03)	0.091		
Body mass index (kg/m^2)	1.02 (0.97 to 1.07)	0.54		
Waist circumference (cm)	1.03 (1.01 to 1.05)	0.004	0.99 (0.97 to 1.02)	0.56
Fasting glucose (mmol/l)	1.21 (1.07 to 1.37)	0.002	1.12 (0.98 to 1.28)	0.092
Total cholesterol (mmol/l)	0.88 (0.76 to 1.03)	0.12		
HDL-cholesterol (mmol/l)	0.20 (0.11 to 0.36)	<0.001	0.25 (0.13 to 0.48)	<0.001
LDL-cholesterol (mmol/l)	1.04 (0.84 to 1.29)	0.70		
Triglycerides (mmol/l)	0.99 (0.85 to 1.15)	0.87		
Creatinine (μmol/l)	1.00 (1.00 to 1.01)	0.16		
Alanine aminotransferase (IU/l)	1.01 (1.00 to 1.02)	0.005	1.01 (1.00 to 1.02)	0.044

The presence of NAFLD is independently associated with CAD, in 612 patients underwent coronary angiogram

Wong W et al, Gut 2012

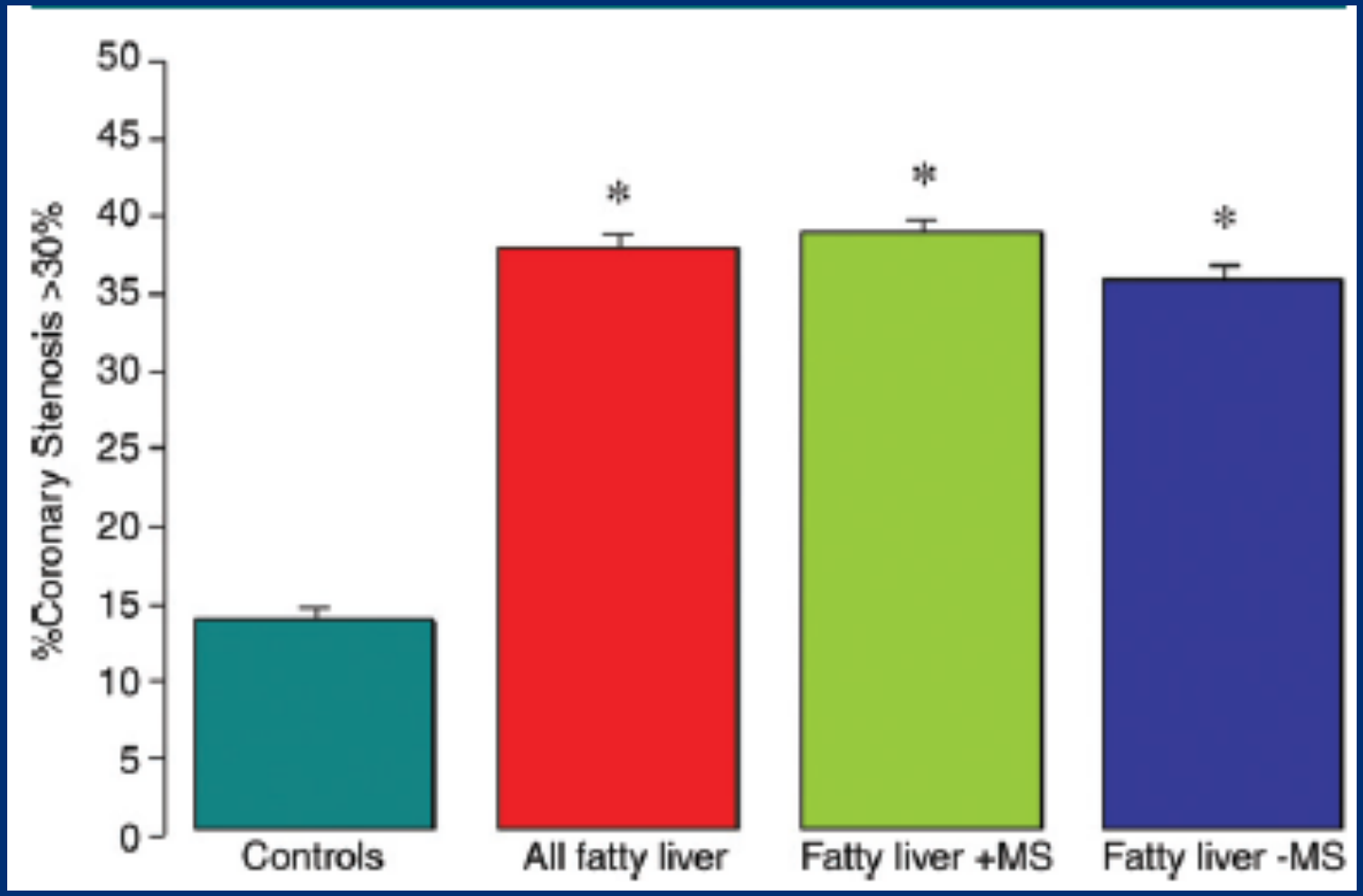
Prevalence of CVD among 2,392 T2DM patients (*Valpolicella Heart Diabetes Study*)



Coronary; myocardial infarction, angina pectoris or revascularization procedures
Cerebrovascular ; ischemic stroke, recurrent TIA, carotid endarterectomy or carotid stenosis >70% (by echo-Doppler)
Peripheral: claudication, rest pain - as confirmed by echo-Doppler - lower extremity amputation or revascularization procedures

Targher, Diabetes Care 2007

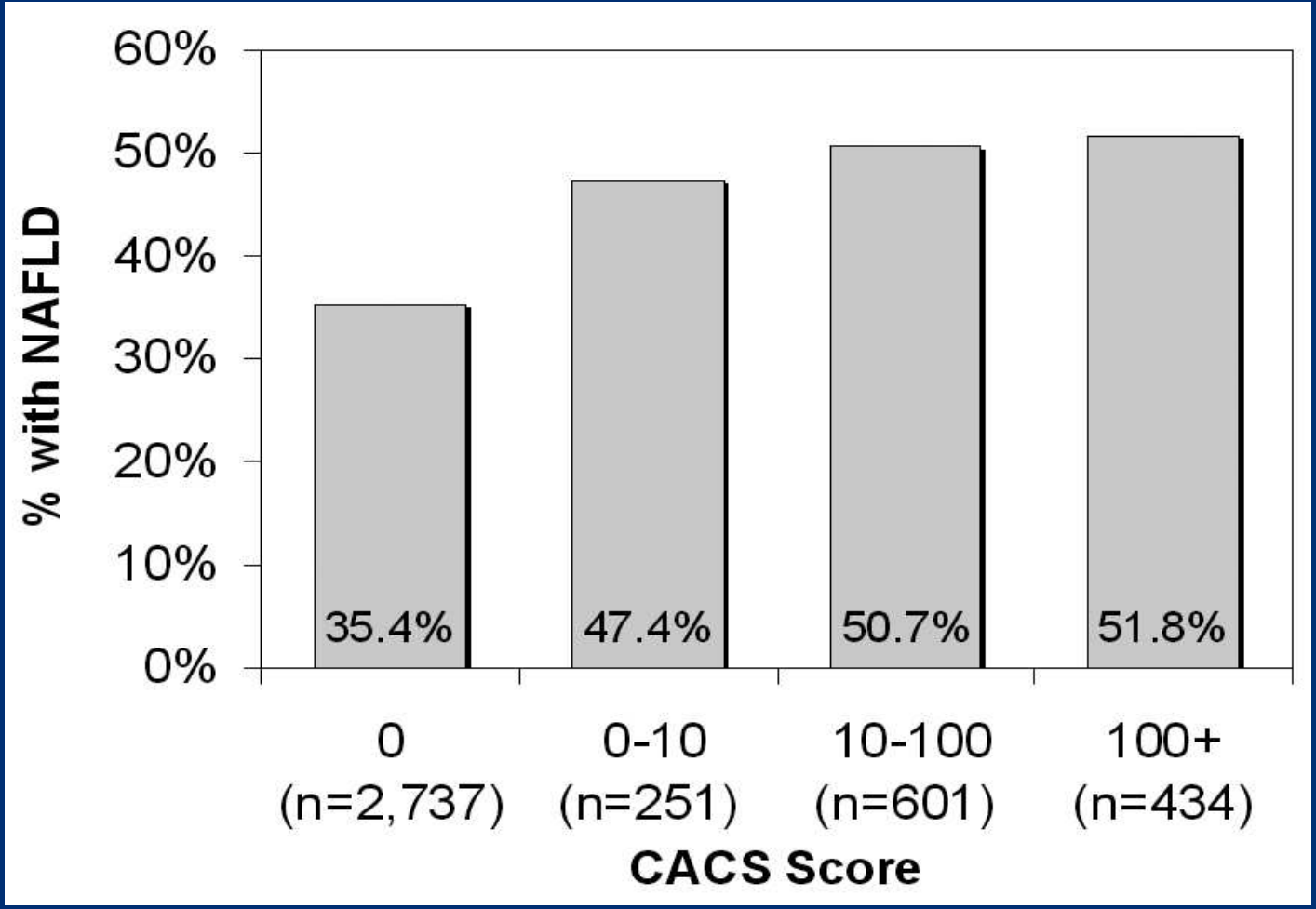
Coronary Artery Disease by TC and NAFLD in Health Subjects



29 NAFLD pts at low to intermediate CAD risk, were compared to 33 age-sex matched individuals without steatosis

Assy N, Radiology 2010

Coronary Artery Calcification by TC and NAFLD in Health Subjects



Coronary artery calcification indepedently associated with ultrasonographic NAFLD, also after correction for TC detected visceral and sub-cutaneous fat

Kim D, Hepatology 2012

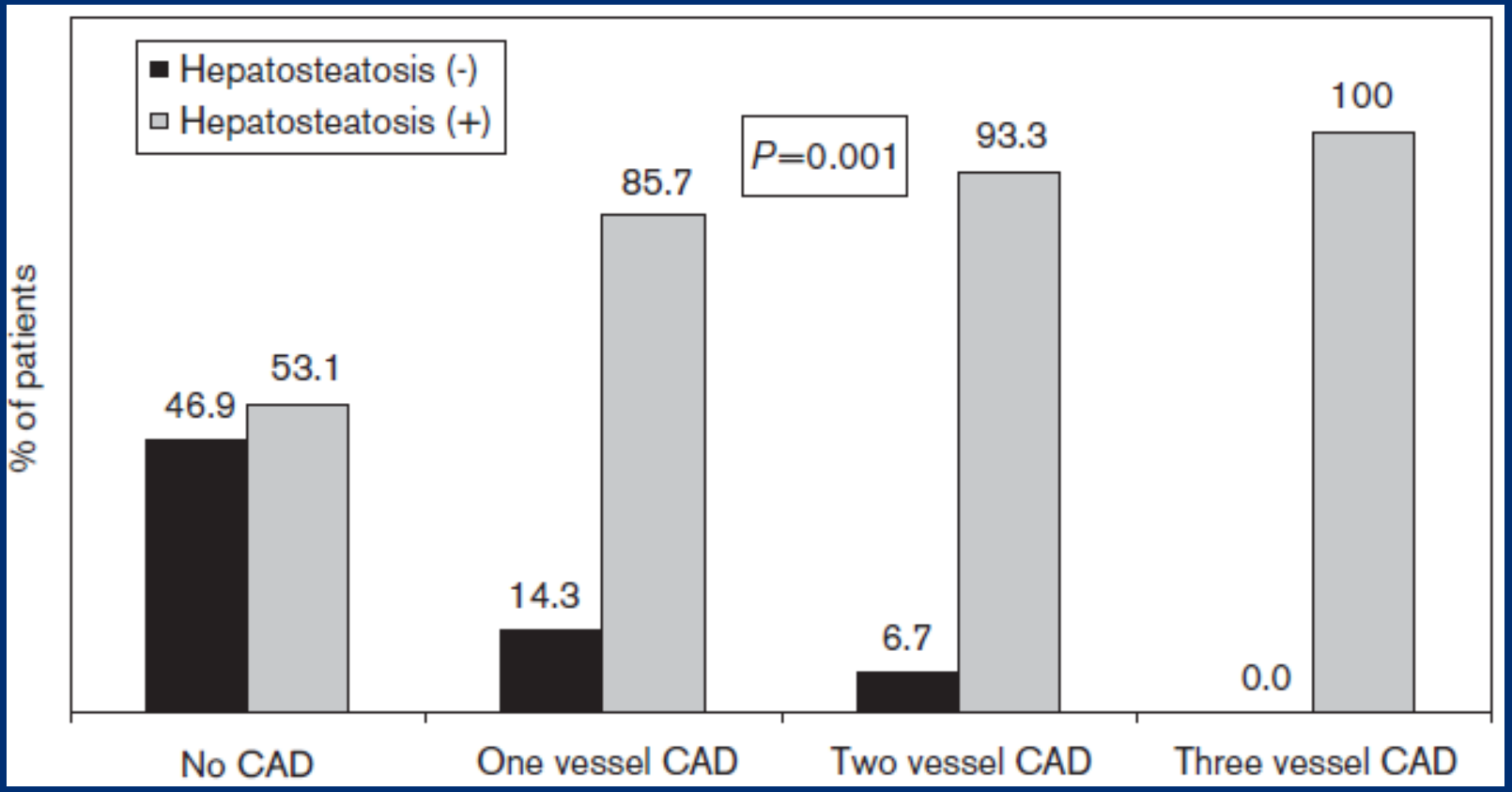
Coronary Artery Calcification by TC and NAFLD in Health Subjects

	Model dependent variable		
Coronary artery calcium score >0	ORs	95% CIs	*P* value
Age (per year)	1.13	1.12–1.14	<0.001
Female sex	0.35	0.27–0.47	<0.001
Triglyceride (per mg/dL)	1.03	0.95–1.11	0.51
HDL-C (per mg/dL)	0.71	0.53–0.95	0.02
LDL-C (per mg/dL)	1.44	1.31–1.57	<0.001
Waist (per cm)	0.99	0.98–1.00	0.06
Fatty liver	1.21	1.01–1.45	0.04
Systolic blood pressure (per mmHg)	1.01	1.00–1.02	0.02
Alcohol (per unit)	1.00	0.99–1.02	0.75
Smoking (ex/current vs. never)	1.35	1.14–1.60	<0.001
Activity (30 min/day vs. no activity)	1.14	0.98–1.33	0.08
Hx CVA	3.56	1.39–9.12	0.01
Hx CHD	2.72	1.56–4.75	0.001
Hx HTN	2.21	1.82–2.68	<0.001
Hx diabetes	2.34	1.77–3.10	<0.001
HOMA-IR (per 1.0 unit)	1.10	1.02–1.18	0.02

In a South Korean occupational cohort of 10,153 people, coronary artery calcification indepedently associated with both ultrasonographic NAFLD and IR

Sung K et al, Diab Care 2012

Coronary Artery Disease and NAFLD



The presence of NAFLD is independently associated with the presence and extent of CAD, in 92 patients with acute coronary syndrome

Arslan et al, Cor Art Dis 2007

NAFLD and CVD

Association between NAFLD and early cardiovascular alterations

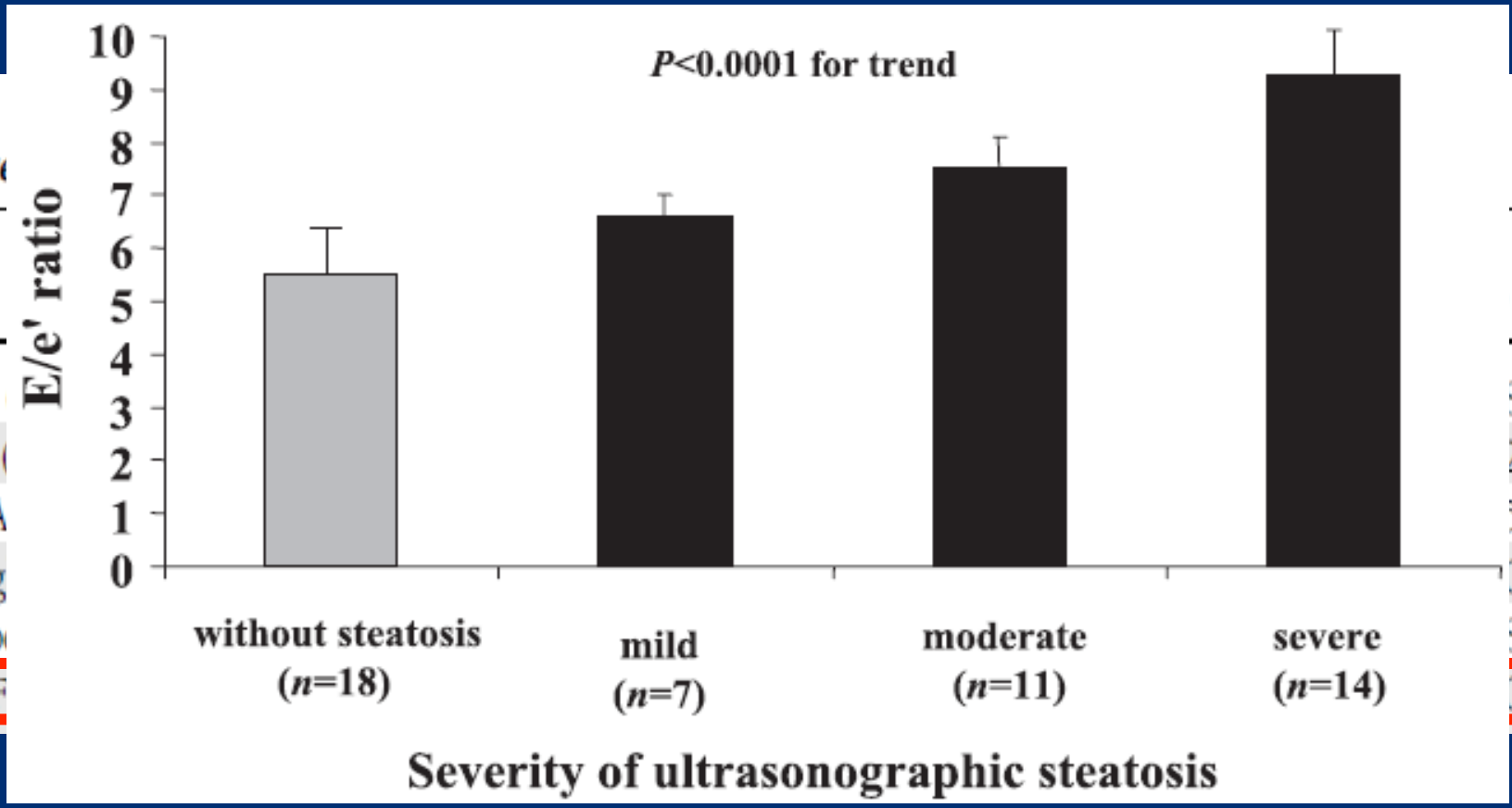
Left Ventricular Alterations in NAFLD Patients

	Control	NAFLD	*P*
Cardiac geometry			
LVDd (mm)	48.6 ± 3.9	48.8 ± 4.9	0.86
IVS (mm)	8.9 ± 2.9	11.3 ± 2.2	0.001
PWT (mm)	8.5 ± 1.7	9.7 ± 2.3	0.04
LV mass (g)	115.3 ± 35.4	160.7 ± 58.7	0.001
LVM index (g/m^2)	66.6 ± 27.8	78.5 ± 22.2	0.06
LVM/height (g/m)	69.2 ± 19.8	92.6 ± 29.5	0.001
RWT	0.36 ± 0.1	0.41 ± 0.1	0.08
Diastolic properties			
E (cm/s)	86.4 ± 20.0	73.6 ± 11.0	0.006
E/*A*	1.76 ± 0.8	1.0 ± 0.3	< 0.0001
E_p (cm/s)	74.7 ± 18.4	49.0 ± 9.7	< 0.0001
DT (ms)	148.1 ± 26.5	168.5 ± 35.8	0.01
IVRT (ms)	89 ± 10	91 ± 11	0.31
E′ of mitral annulus (cm/s)	13.8 ± 1.7	10.3 ± 2	< 0.0001
E/*E*′	7.6 ± 1.1	7.1 ± 1.7	0.19
Cardiac function			
EF (%)	65.8 ± 3.9	64.3 ± 6.5	0.33
S′ (cm/s)	6.0 ± 2.0	5.8 ± 1.5	0.12
LV Tei index	0.4 ± 0.2	0.4 ± 0.2	0.74

NAFLD patients (n=38) without morbid obesity, hypertension, and diabetes have mildly altered LV geometry and early features of left ventricular diastolic dysfunction.

Goland S et al, JCG 2007

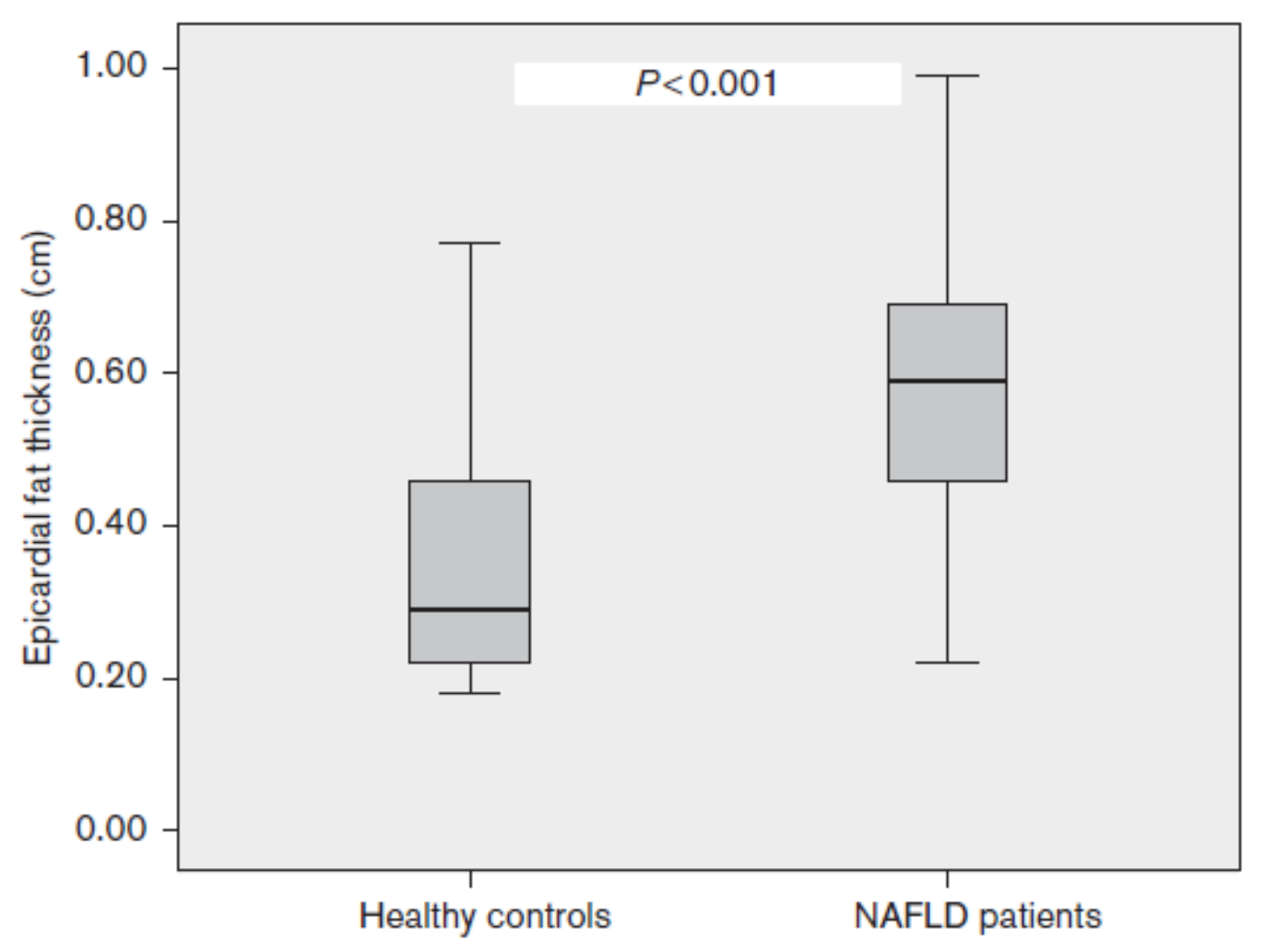
Left Ventricular Alterations in NAFLD Patients



Diabetic patients (n=50) had a greater prevalence of early diastolic dysfunction according to steatosis presence and severity

Bonapace S et al, Diab Care 2012

Epicardial Fat Thickness and NAFLD

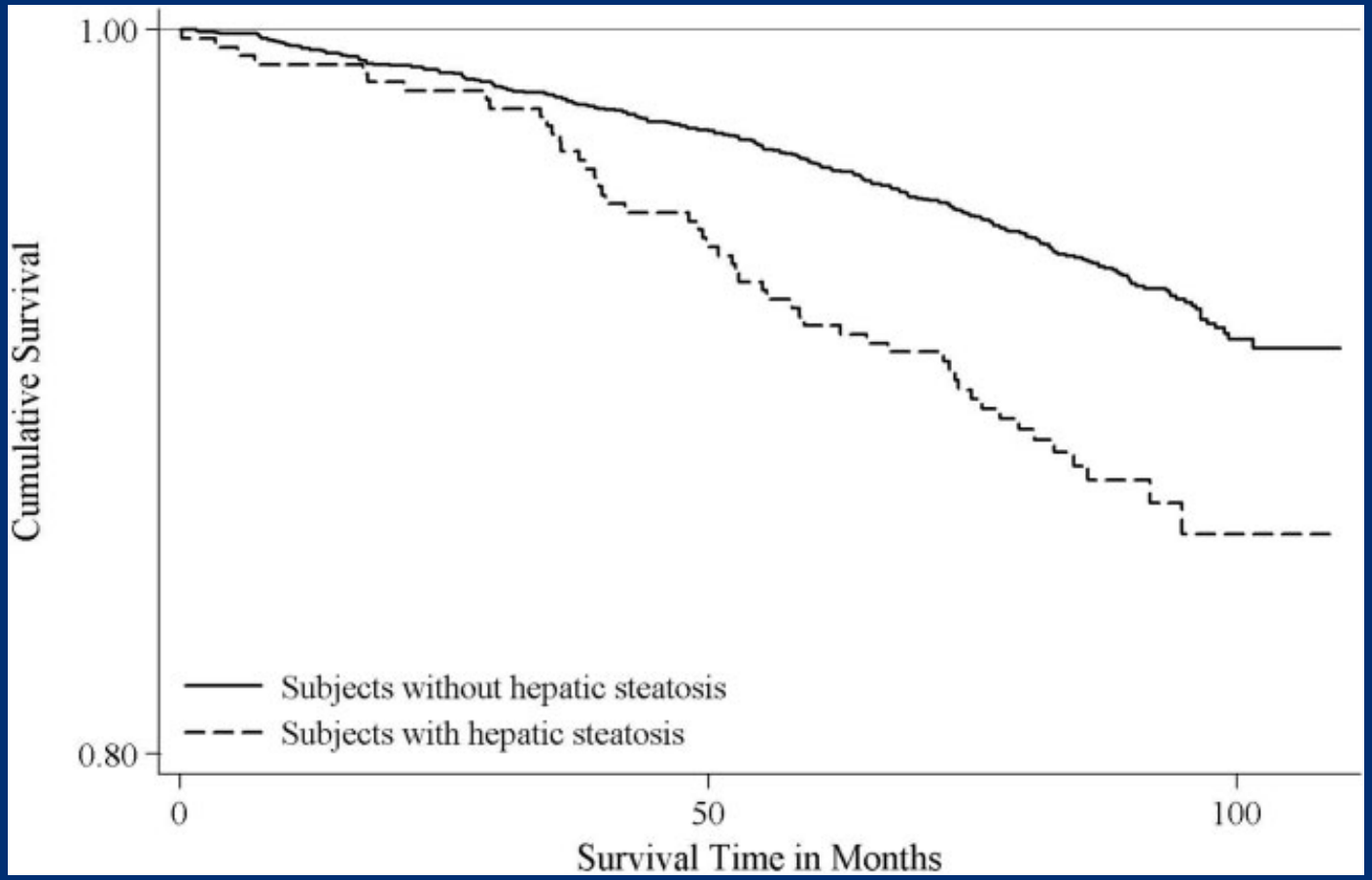


Colak J et al, EJGE 2012

NAFLD and CVD

Association between NAFLD and CVD: evidences from prospective studies

Survival in 4160 Subjects of the Study of Health in Pomerania According to Steatosis



Haring, Hepatology 2009

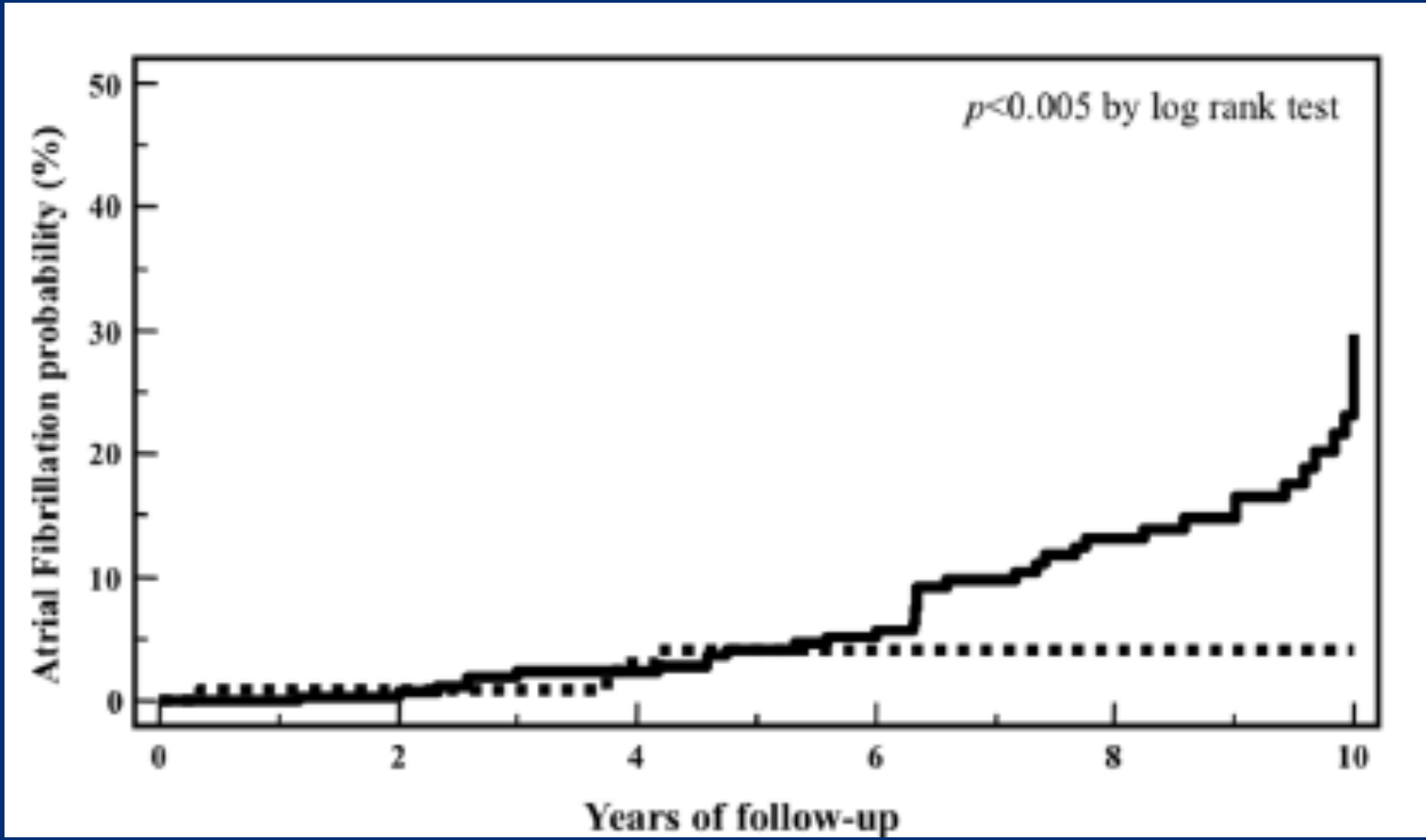
Causes of Death in NAFLD

CAUSE OF DEATH IN NAFLD	
Malignancy	28%
Ischemic heart disease	25%
Liver Disease	13%
Infection	11%
Others……	

-420 NAFLD followed for a mean period of 7.6 years (0.1-23.5)
-mortality of 12.6%
-mortality higher than expected in general population

Adams et al, Gastroenterology 2006

NAFLD as Predictor of Atrial Fibrillation in Type 2 Diabetic Patients



In a cohort of 400 diabetic patients, NAFLD predicted atrial fibrillation occurrence independently of metabolic risk factors

Targher et al, Plos One 2013

NAFLD as Predictor of Cardiovascular Events in Type 2 Diabetic Patients

Variables	Control subjects	Case subjects	P
n	1,719	384	
Sex (% men)	62%	63%	0.80
Age (years)	59 ± 3	61 ± 4	0.001
BMI (kg/m^2)	26 ± 3	28 ± 4	0.001
Waist circumference (cm)	93 ± 11	99 ± 13	0.001
Duration of diabetes (years)	14 ± 3	16 ± 3	0.60
Diabetes treatment			
Diet only	21	15	0.20
Oral hypoglycemic drugs	62	65	0.30
Insulin only	17	20	0.20
Antihypertensive users	60	73	0.001
Aspirin users	49	48	0.80
Lipid-lowering users	34	36	0.60
Current smokers	22	23	0.70
Systolic blood pressure (mmHg)	127 ± 12	131 ± 16	0.001
Diastolic blood pressure (mmHg)	80 ± 12	83 ± 14	0.001
A1C (%)	6.9 ± 0.8	7.3 ± 1.0	0.001
Triglycerides (mmol/l)	1.32 ± 0.6	1.62 ± 1.0	0.001
HDL cholesterol (mmol/l)	1.40 ± 0.3	1.32 ± 0.4	0.001
LDL cholesterol (mmol/l)	3.35 ± 0.4	3.32 ± 0.5	0.80
AST (units/l)	20 ± 6	26 ± 12	0.001
ALT (units/l)	24 ± 6	32 ± 13	0.001
GGT (units/l)	23 ± 10	34 ± 14	0.001
Metabolic syndrome	59	75	0.001
NAFLD	61	96	0.001

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 et al, Diab Care 2007

BUT!!

Non-alcoholic fatty liver disease and mortality among US adults: prospective cohort study

OPEN ACCESS

BMJ 2011

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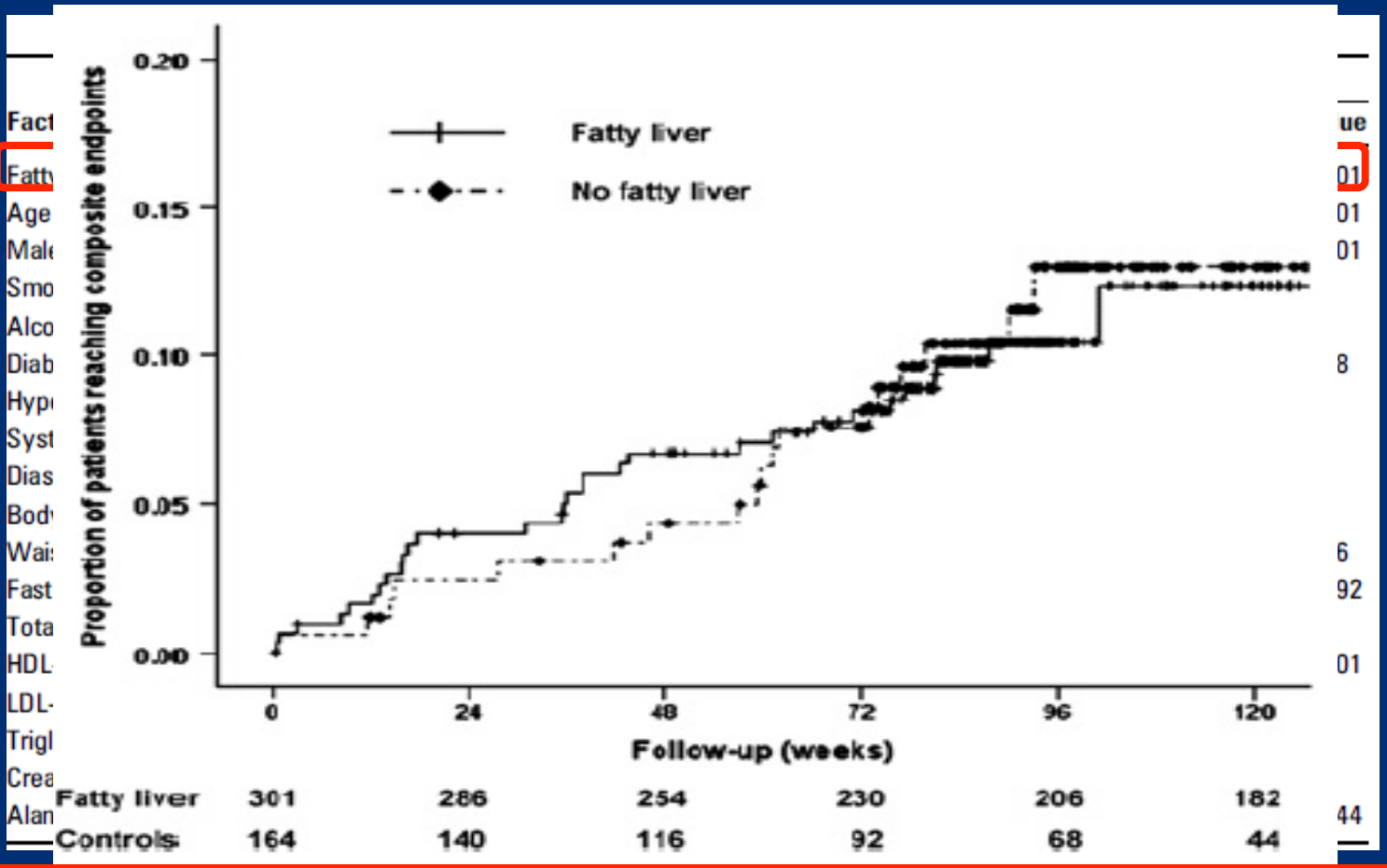
No Association between NAFLD and both all and cardiovascular mortality among 11,371 subjects

Coronary Artery Disease and NAFLD



The presence of NAFLD is independently associated with CAD, in 612 patients underwent coronary angiogram, but not with cardiovascular death/events

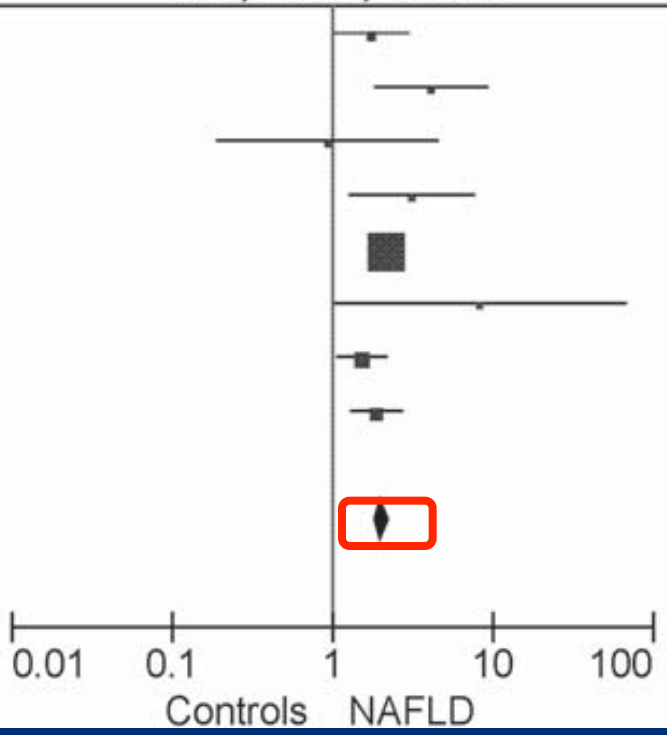
Wong W et al, Gut 2012

NAFLD as Risk Factor for Incident CVD Events

Study or Subgroup	Weight	Odds Ratio M-H, Fixed, 95% CI
Eckstedt 2006*	5.7%	1.75 [1.03, 2.95]
Hamaguchi 2007	1.6%	4.12 [1.85, 9.15]
Haring 2009 (females)*	1.1%	0.93 [0.19, 4.50]
Haring 2009 (males)*	2.5%	3.11 [1.28, 7.55]
Jepsen 2003*	58.6%	2.15 [1.86, 2.50]
Sanyal 2006*	0.3%	8.28 [1.02, 67.02]
Targher 2005	17.8%	1.53 [1.07, 2.17]
Targher 2007	12.4%	1.88 [1.30, 2.71]
Total (95% CI)	**100.0%**	**2.05 [1.81, 2.31]**
Total events		

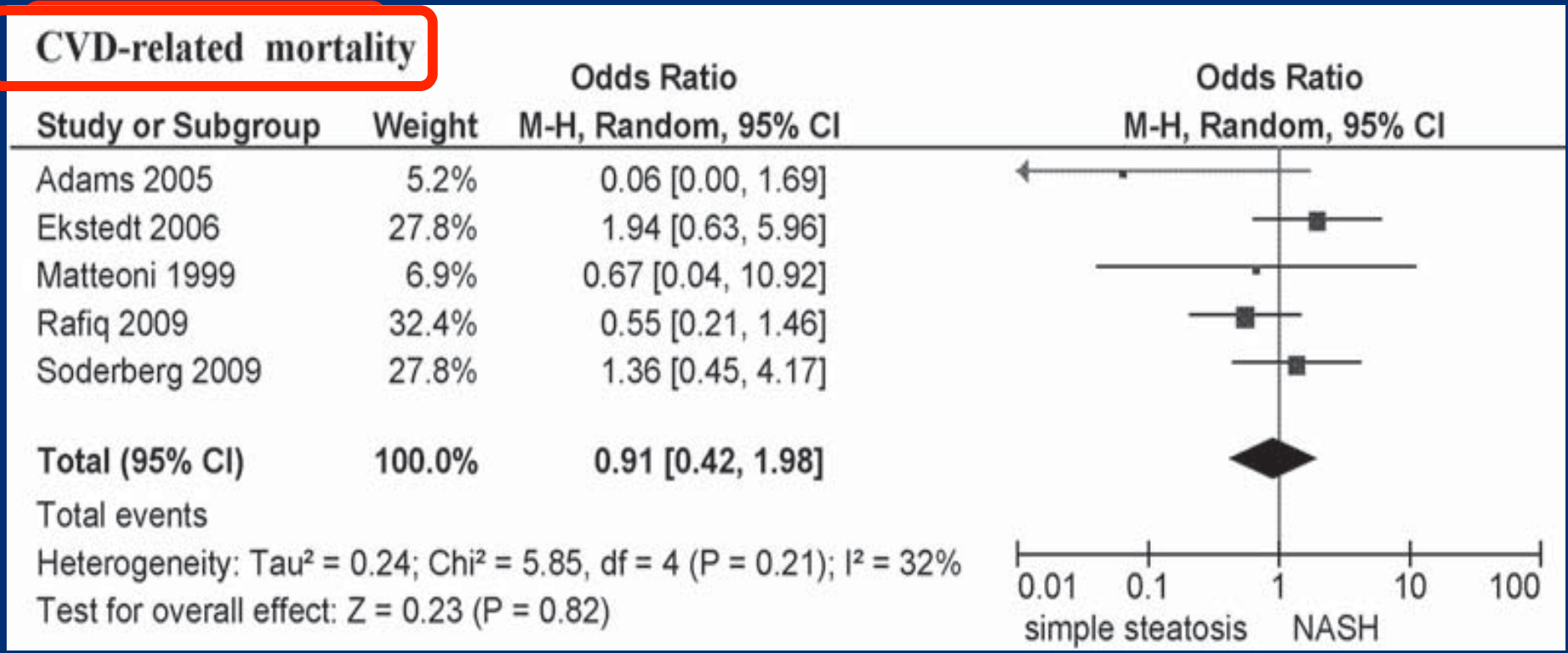
Heterogeneity: Chi² = 10.19, df = 7 (P = 0.18); I² = 31%

Test for overall effect: Z = 11.39 (P < 0.00001)



Musso et al, Ann of Med 2010

NAFLD vs NASH: Overall and CVD Mortality

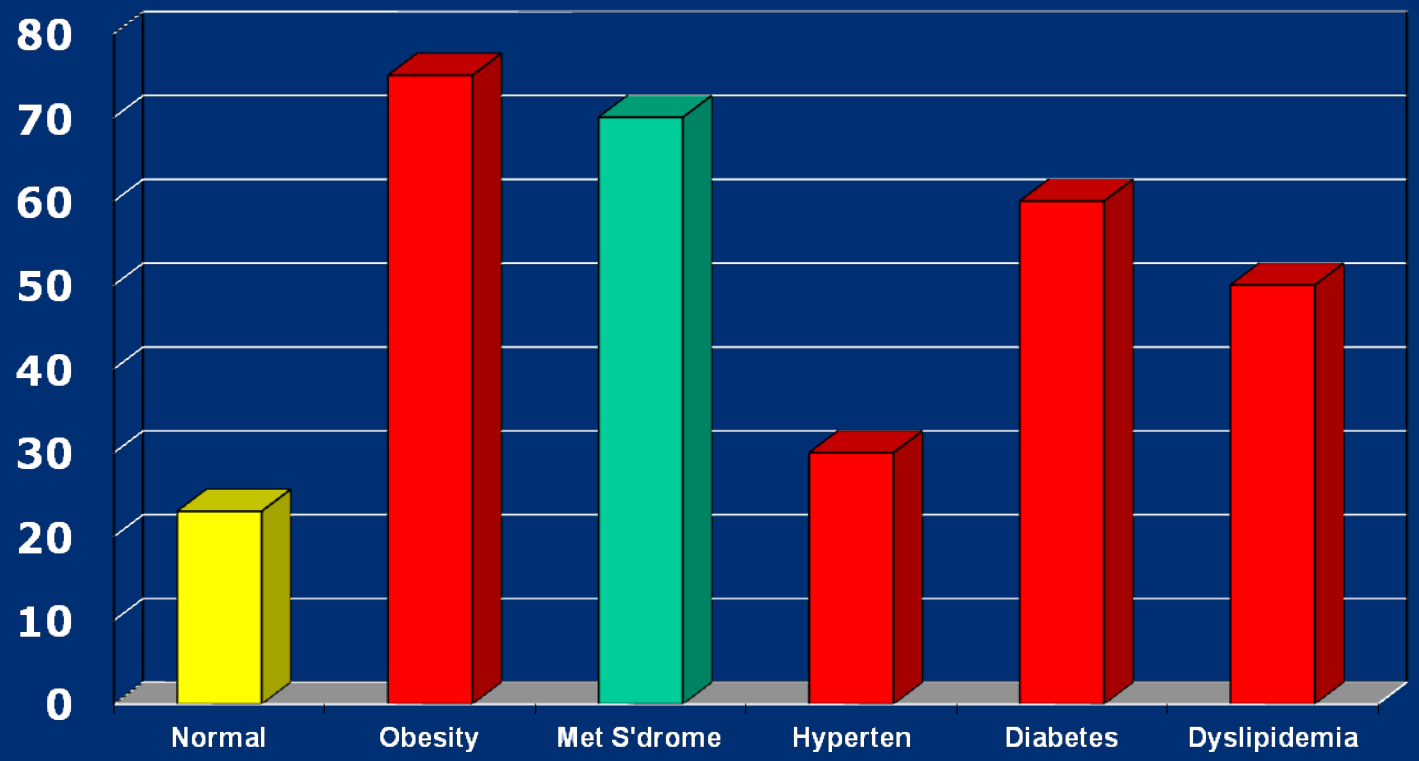


Musso et al, Ann of Med 2010

NAFLD and CVD

Mechanisms linking NAFLD to cardiovascular alterations

Association of NAFLD with features of Metabolic Syndrome



Marchesini G et al, Hepatology 2006

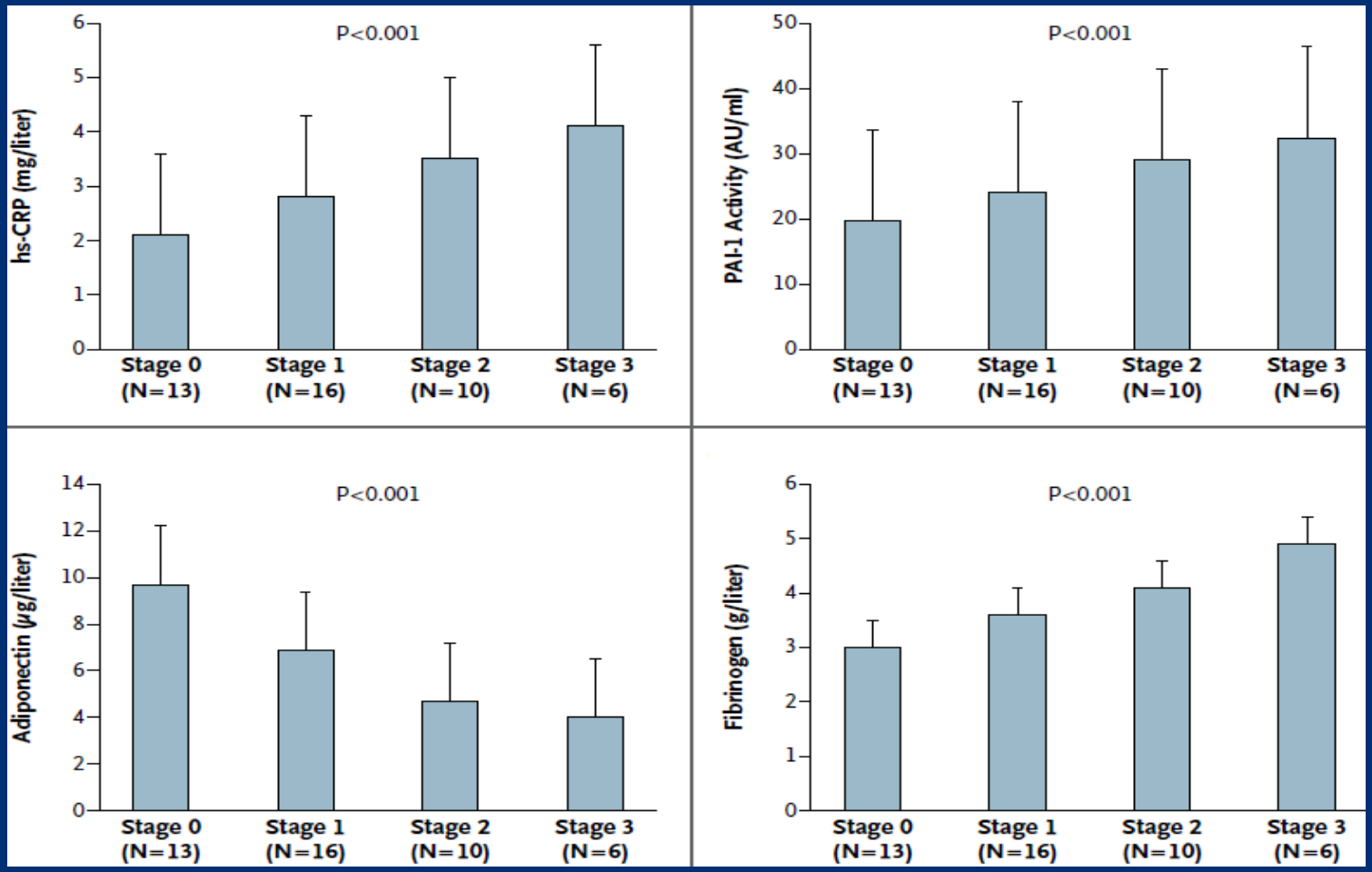
Association of NAFLD with features of Metabolic Syndrome

Prevalence odds ratio (CI) for association with atherogenic dyslipidemia[a]	Mild NAFLD L/S ratio 1.0–0.7	Moderate NAFLD L/S ratio 0.7–0.5	Severe NAFLD L/S ratio <0.5
Low HDL & high triglycerides (HDL < 40 mg/dL in men, <50 mg/dL in women, triglycerides >150 mg/dL)			
• Model 1	2.91 (2.33–3.65)	3.68 (2.39–5.68)	6.70 (3.71–12.1)
• Model 2	2.86 (2.28–5.62)	3.64 (2.35–5.62)	6.74 (3.73–12.2)
• Model 3	1.62 (1.25–2.10)	1.87 (1.15–3.03)	3.17 (1.63–6.15)
Triglyceride/HDL-C ratio >3			
• Model 1	3.17 (2.57–3.90)	4.07 (2.63–6.29)	6.56 (3.38–12.7)
• Model 2	3.17 (2.56–3.92)	4.23 (2.70–6.65)	7.44 (3.80–14.5)
• Model 3	1.87 (1.48–2.37)	2.28 (1.39–3.73)	3.08 (1.56–6.10)

3362 pts of the MESA Study, free of clinical cardiovascular disease, and assessed for steatosis by TC

DeFilippis et al, Atherosclerosis 2013

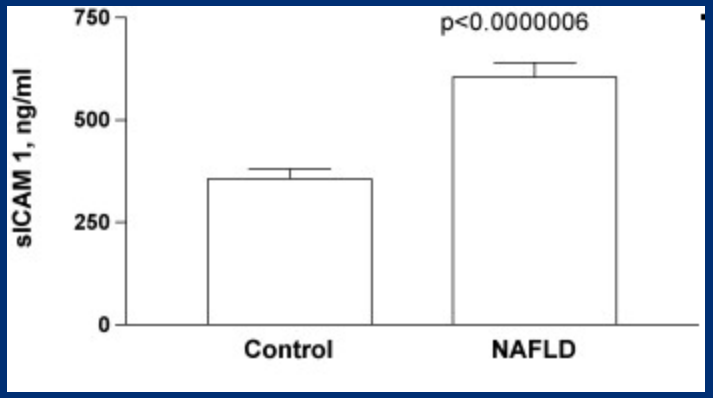
Proinflammatory Biomarkers in NAFLD Patients



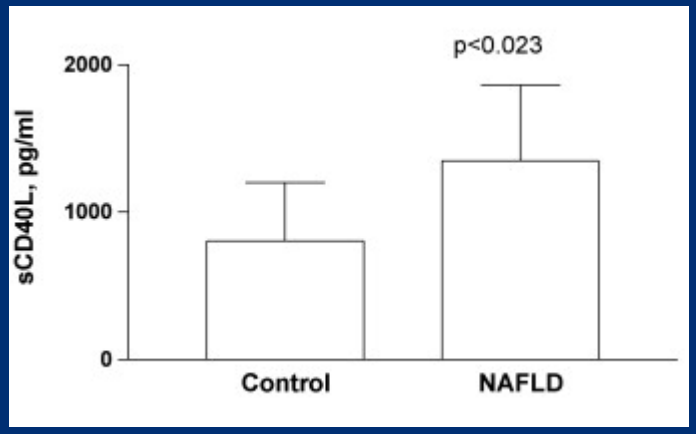
Proinflammatory biomarkers directly assocuated with fibrosis severity

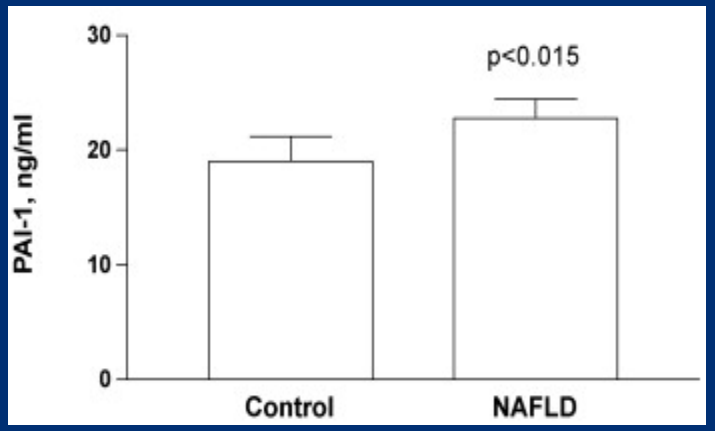
Targher, NEJM 2011

Molecular Mediators of Atherosclerosis in NAFLD



NAFLD=123
Controls=102

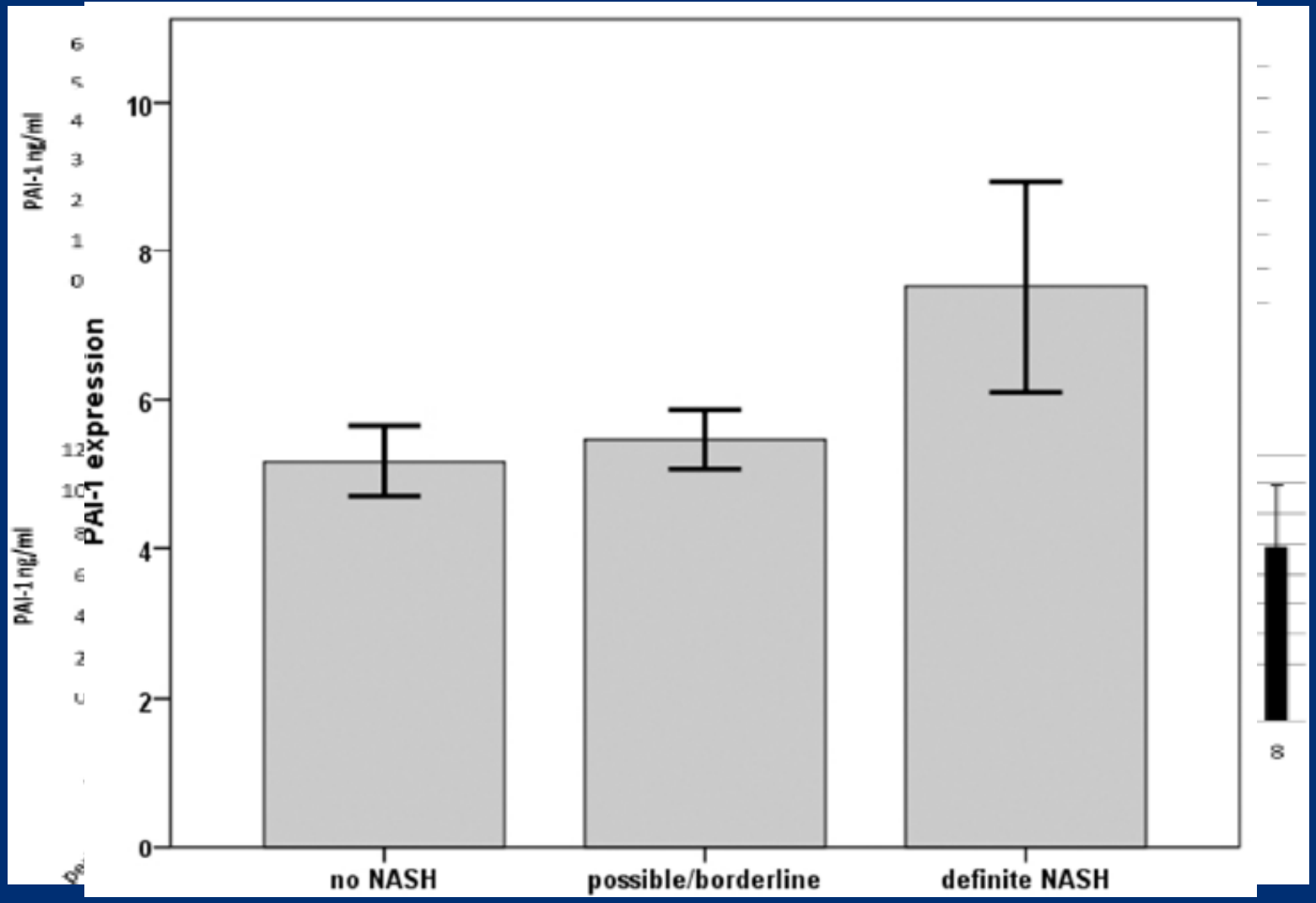




Liver ICAM-1 expression in the lobular inflammatory infiltrate was associated with the degree of liver steatosis and the the severity of necroinflammatory activity

Sookoian et al, Atherosclerosis 2010

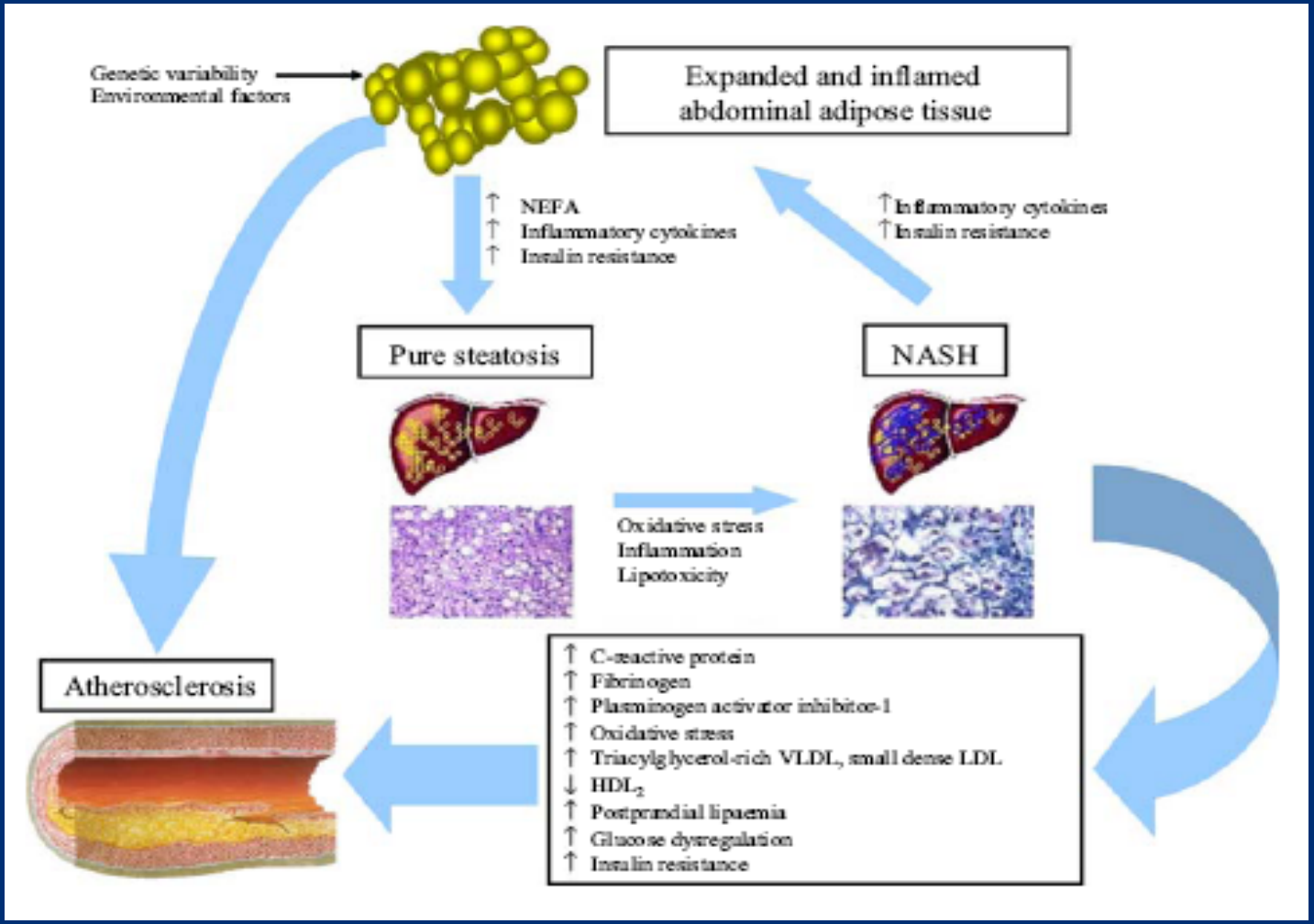
Molecular Mediators of Atherosclerosis in NAFLD



In 273 NAFLD patients PAI independently associated with steatosis, fasting C peptide and WC

Verrijken et al, Hepatology in press

NAFLD and Atherosclerosis: A plausible Hypothesis



Targher et al, Diabetologia 2008

But.....

Is NAFLD/NASH increasing Atherosclerosis risk, or are other (co)factors?

Role of Vitamin D?

Role of Fructose?

Role of Genetic?

Role of Vitamin D?

Role of Fructose?

Role of Genetic?

NAFLD and 25-hydroxyvitamin D3

Vitamin D inhibits proliferation and profibrotic marker expression in hepatic stellate cells and decreases thioacetamide-induced liver fibrosis in rats

Shirley Abramovitch,[1] Liora Dahan-Bachar,[1] Efrat Sharvit,[1,2] Yosef Weisman,[2,3] Amir Ben Tov,[1] Eli Brazowski,[2,4] Shimon Reif[2,3]

Gut 2012

Vitamin D Deficiency in Obese Rats Exacerbates Nonalcoholic Fatty Liver Disease and Increases Hepatic Resistin and Toll-Like Receptor Activation

Christian L. Roth,[1] Clinton T. Elfers,[1] Dianne P. Figlewicz,[2,3] Susan J. Melhorn,[2] Gregory J. Morton,[4] Andrew Hoofnagle,[4] Matthew M. Yeh,[4] James E. Nelson,[5] and Kris V. Kowdley[4,5,6]

Hep 2012

Targher G et al, Nutr Metab Cardiovasc Dis 2007

Atherosclerosis 225 (2012) 253–263

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Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review

The role of vitamin D in cardiovascular disease: From present evidence to future perspectives

Vincent M. Brandenburg [a,*], Marc G. Vervloet [b], Nikolaus Marx [a]

Role of Vitamin D?

Role of Fructose?

Role of Genetic?

Fructose Consumption and Severity of NAFLD

	Unadjusted		Adjusted (Model 1)		Adjusted (Model 2)	
	OR[95%CI]	p-value	OR[95%CI]	p-value	OR[95%CI]	p-value
Steatosis						
Fructose consumption						
0 serving	-	-	-	-	-	-
0-7 servings	0.7[0.4, 1.1]	0.09	0.6[0.4, 0.9]	0.02	0.7[0.4, 1.1]	0.10
>=7 servings	0.6[0.4, 1.0]	0.06	0.4[0.2, 0.8]	0.007	0.4[0.2, 0.9]	0.02
Lobular inflammation						
Fructose consumption						
0 serving	-	-	-	-	-	-
0-7 servings	0.8[0.5, 1.3]	0.30	0.9[0.5, 1.4]	0.55	0.8[0.5, 1.4]	0.53
>=7 servings	0.6[0.4, 1.0]	0.06	0.9[0.5, 1.8]	0.86	1.1[0.6, 2.3]	0.70
Ballooning						
Fructose consumption						
0 serving	-	-	-	-	-	-
0-7 servings	0.7[0.4, 1.1]	0.13	0.9[0.5, 1.4]	0.62	0.9[0.5, 1.5]	0.73
>=7 servings	0.7[0.4, 1.2]	0.25	1.3[0.7, 2.4]	0.44	1.4[0.7, 2.7]	0.32
Fibrosis						
Fructose consumption						
0 serving	-	-	-	-	-	-
0-7 servings	0.6[0.4, 0.9]	0.01	0.8[0.5, 1.3]	0.44	0.9[0.6, 1.5]	0.78
>=7 servings	0.7[0.4, 1.2]	0.19	1.7[1.0, 3.2]	0.07	2.6[1.4, 5.0]	0.004

Abdelmalek M et al, Hepatology 2010

Fructose Consumption and Metabolic Syndrome

The toxic truth about sugar

Added sweeteners pose dangers to health that justify controlling them like alcohol, argue **Robert H. Lustig**, **Laura A. Schmidt** and **Claire D. Brindis**.

Hypertension (uric acid)
Myocardial infarction (dyslipidaemia, insulin resistance)
Dyslipidaemia (*de novo* lipogenesis)
Pancreatitis (hypertriglyceridaemia)
Obesity (insulin resistance)
Malnutrition (obesity)
Hepatic dysfunction (non-alcoholic steatohepatitis)
Habituation, if not addiction

Lustig et al, Nature 2012

Role of Vitamin D?

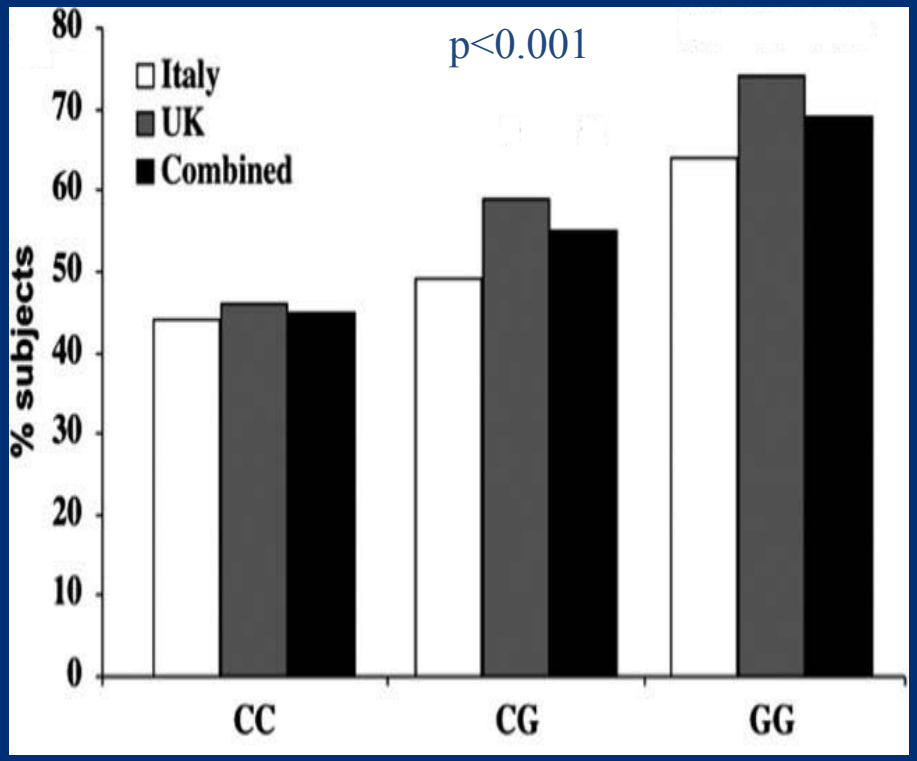
Role of Fructose?

Role of Genetic?

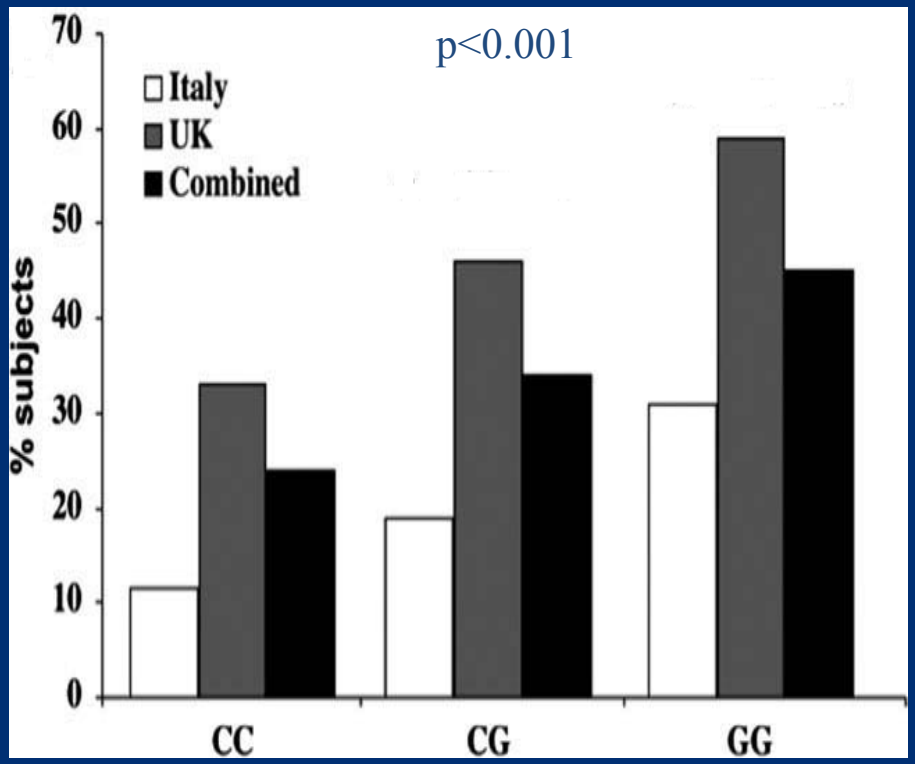
Since NAFLD is the hepatic expression of a systemic metabolic dysorder, SNPs of genes associated with NAFLD could also be linked to cardiovascular alterations in these patients?

PNPLA3 and NAFLD

- Adiponutrin/PNPLA3 is a protein involved in energy mobilization and storage in lipid droplets in the liver and adipose tissue .
- The SNP in adiponutrin rs738409 C>G, encodes the I148M adiponutrin variant protein that is a loss-of function variant that predisposing to steatosis by decreasing triglyceride hydrolysis in hepatocytes



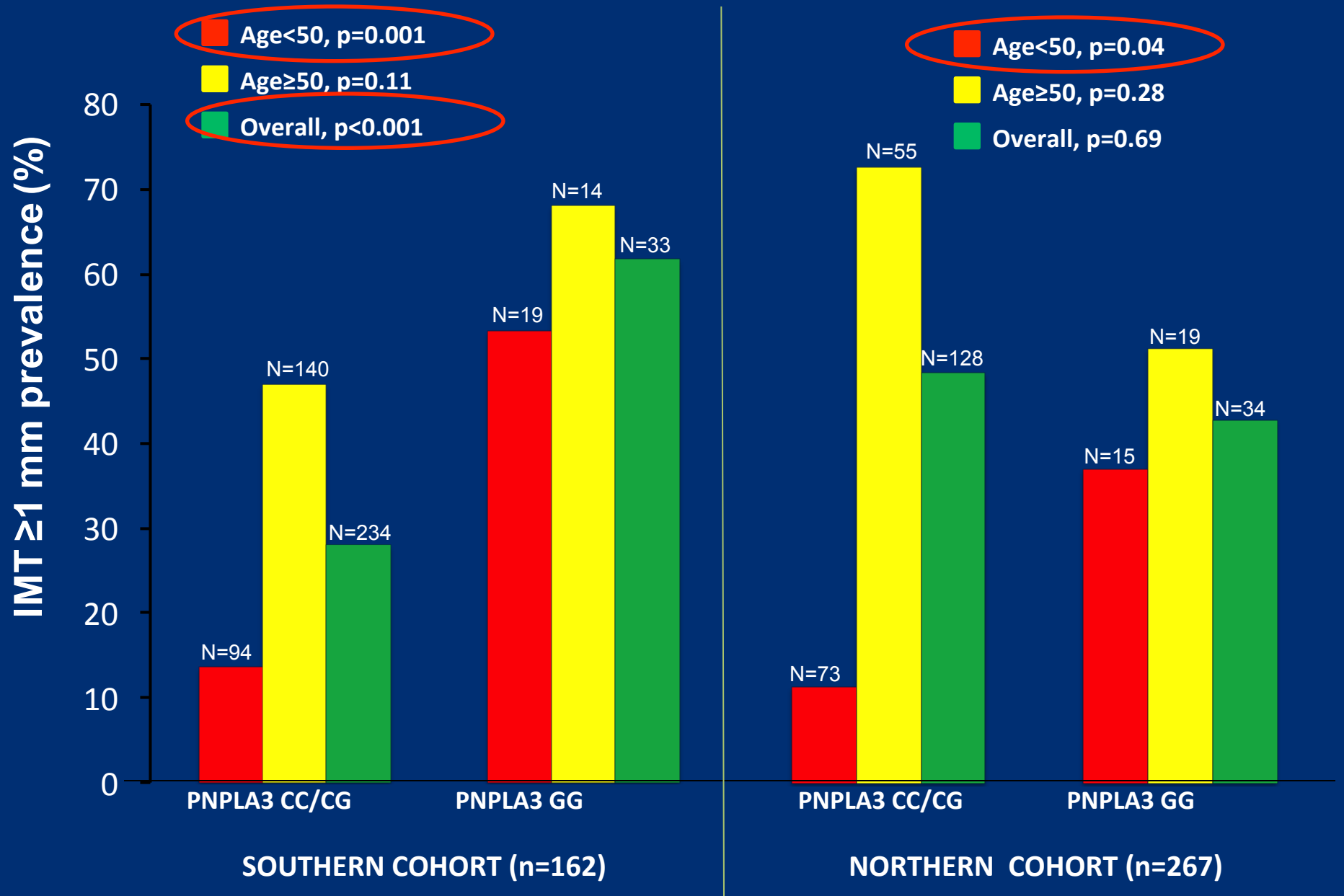
Prevalence of NASH



Prevalence of Fibrosis

Valenti L et al, Hepatology 2010

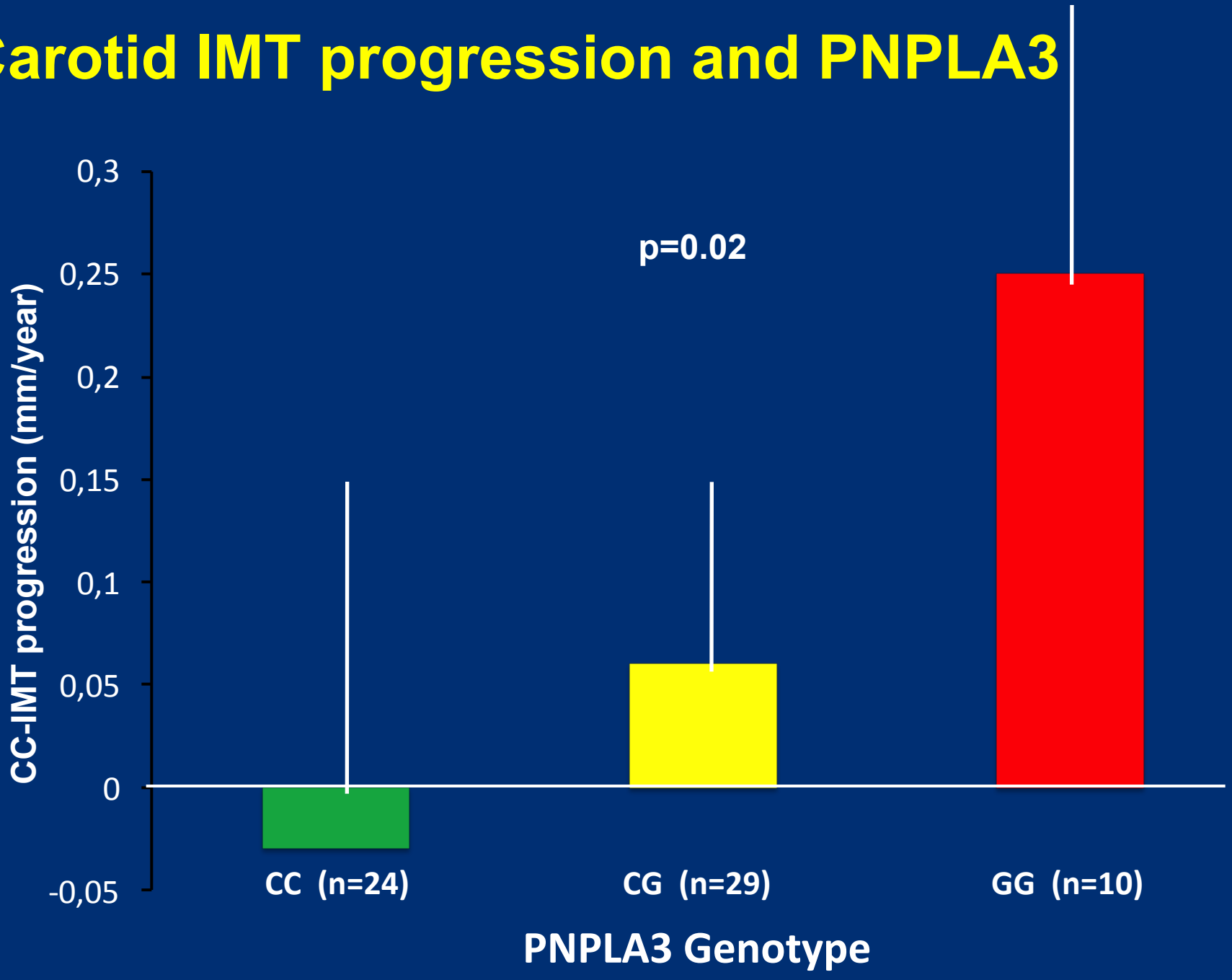
Carotid Tickening and PNPLA3



Univariate and multivariate analysis of factors associated with carotid thickening (II)

Southern Cohort <50 years (n=88)		Northern Cohort <50 years (n=113)	
Variable	Multivariate Analysis OR (95% CI) *p* value	Variable	Multivariate Analysis OR (95% CI) *p* value
Blood Glucose – mg/dL	1.00 (0.98 – 1.03) 0.41	BMI Kg/m2	0.99 (0.93 – 1.07) 0.94
LDL – mg/dL	1.02 (1.00 – 1.04) 0.01	LDL mg/dl	1.02 (1.00 – 1.04) 0.01
PNPLA3 GG	7.46 (1.96 –28.3) 0.003	PNPLA3 GG	6.00 (1.36 – 29) 0.01
		Ferritin log ng/ml	1.70 (0.90 – 2.06) 0.12
		Arterial Hypertension	1.18 (0.24 – 7.74) 0.84

Carotid IMT progression and PNPLA3



PNPLA3

Apoptosis
ICAM
Arterial lipid storage

Liver Damage

Metabolic factors

Conclusions

Mounting evidence suggests an increased rate of atherosclerosis-related alterations in patients with NAFLD

Severity of NAFLD has been associated with the severity of atherosclerosis

Further evidences are needed to establish if NAFLD is only a marker of higher metabolic dysfunctions, or a direct pathogenic trigger for cardiovascular alterations