Is type 2 diabetes and NASH the same disease affecting different organs?

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DISCLOSURES

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Investigators in clinical trials: Abbott, Amgen, Astra-Zeneca, Bayer, Biose, Boerhinger-Ingelheim, BMS, Genfit, GSK, Janssen, Imcyse, Isis, Lexicon, Eli-Lilly, Novo-Nordisk, Sanofi, Regeneron

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NAFLD = T2D? What does it mean?

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AGENDA

1. EPIDEMIOLOGICAL DATA
2. PATHOPHYSIOLOGICAL DATA
3. GENETIC DATA
4. THERAPEUTIC DATA
5. CONCLUDING REMARKS

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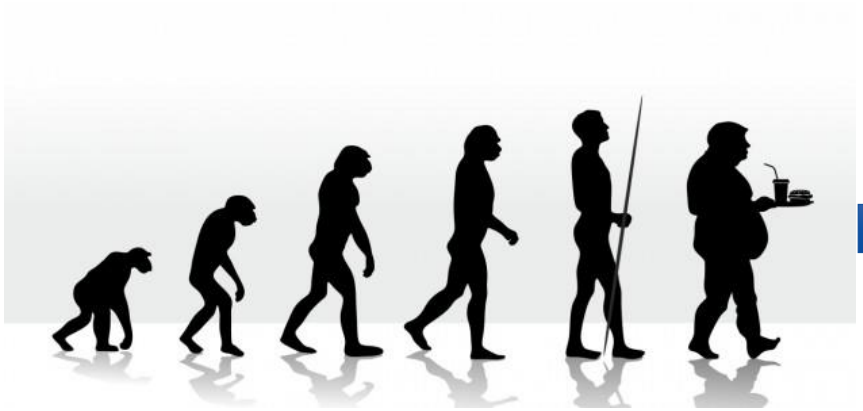
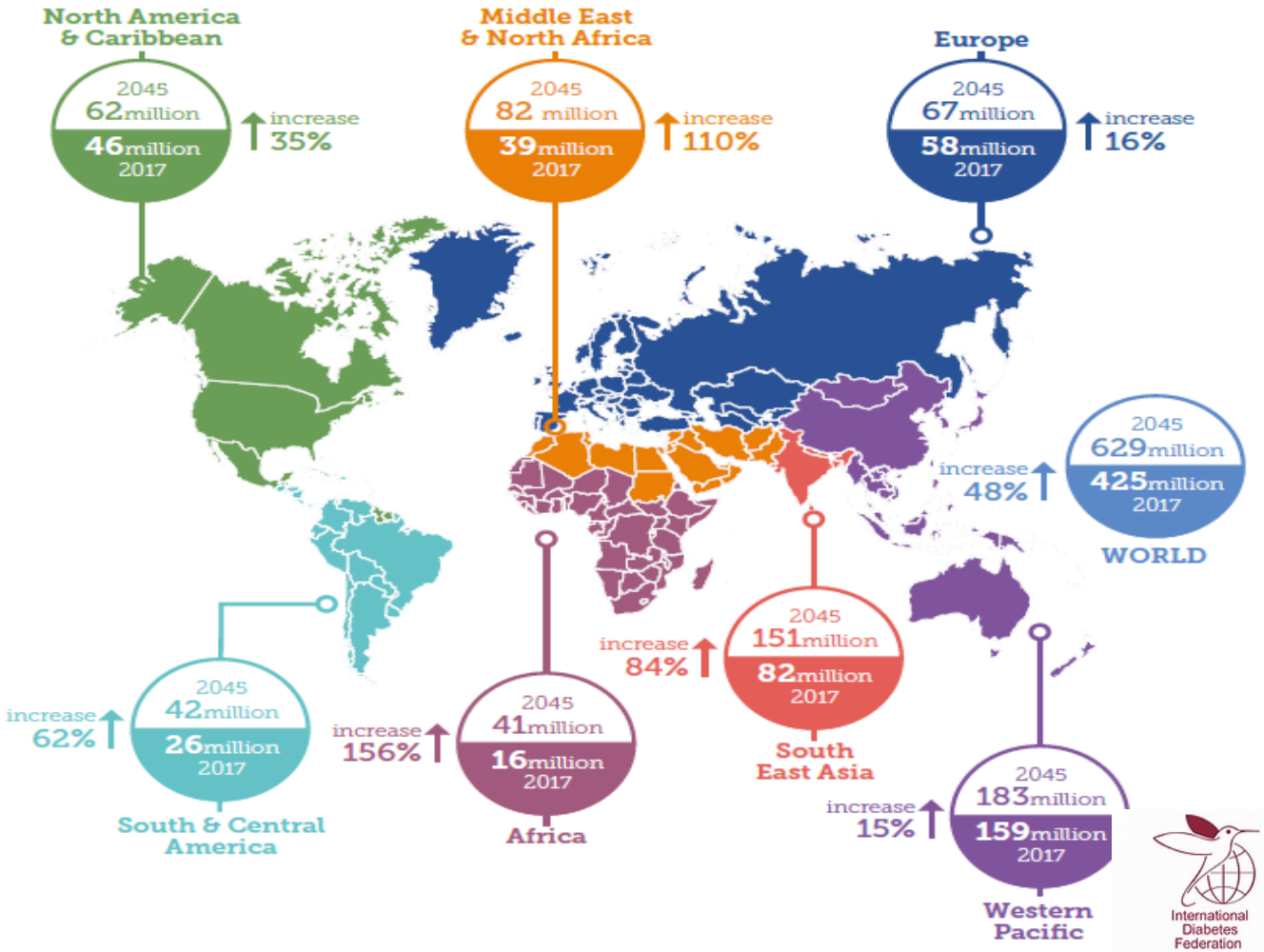
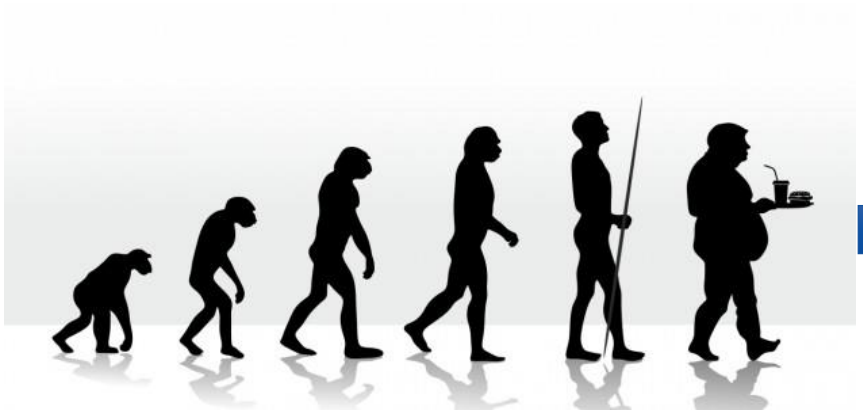
EPIDEMIOLOGY:
the same world-wide metabolic pandemia for T2D and NAFLD

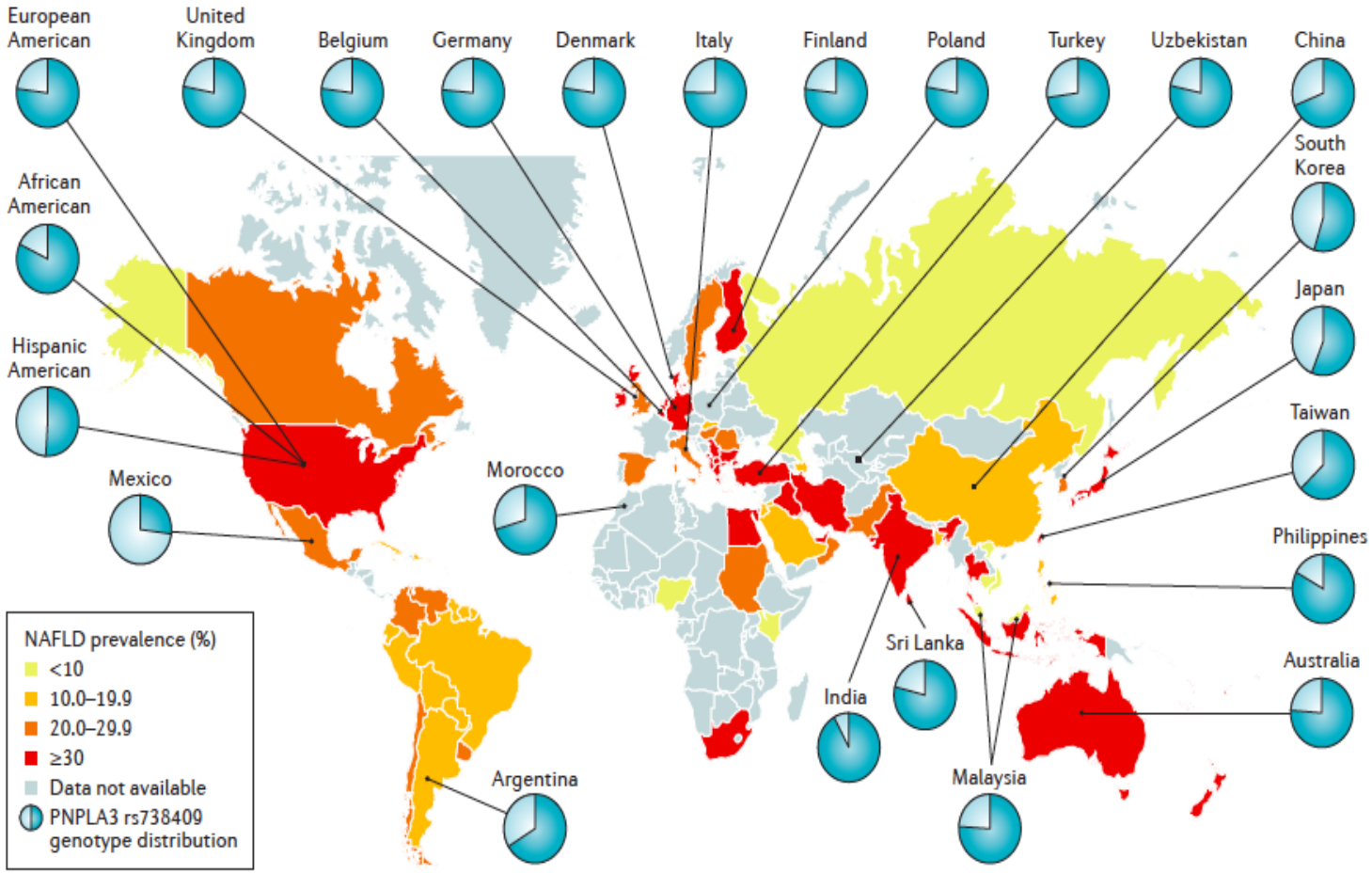
Number of people with diabetes worldwide and per region in 2017 and 2045 (20-79 years)





EPIDEMIOLOGY:
the same world-wide metabolic pandemia for T2D and NAFLD





Younossi Z. et al. *Nat Rev Gastroenterol Hepatol* 2018; 15: 11-20

EPIDEMIOLOGY: a link between obesity and T2D and NAFLD

T2D

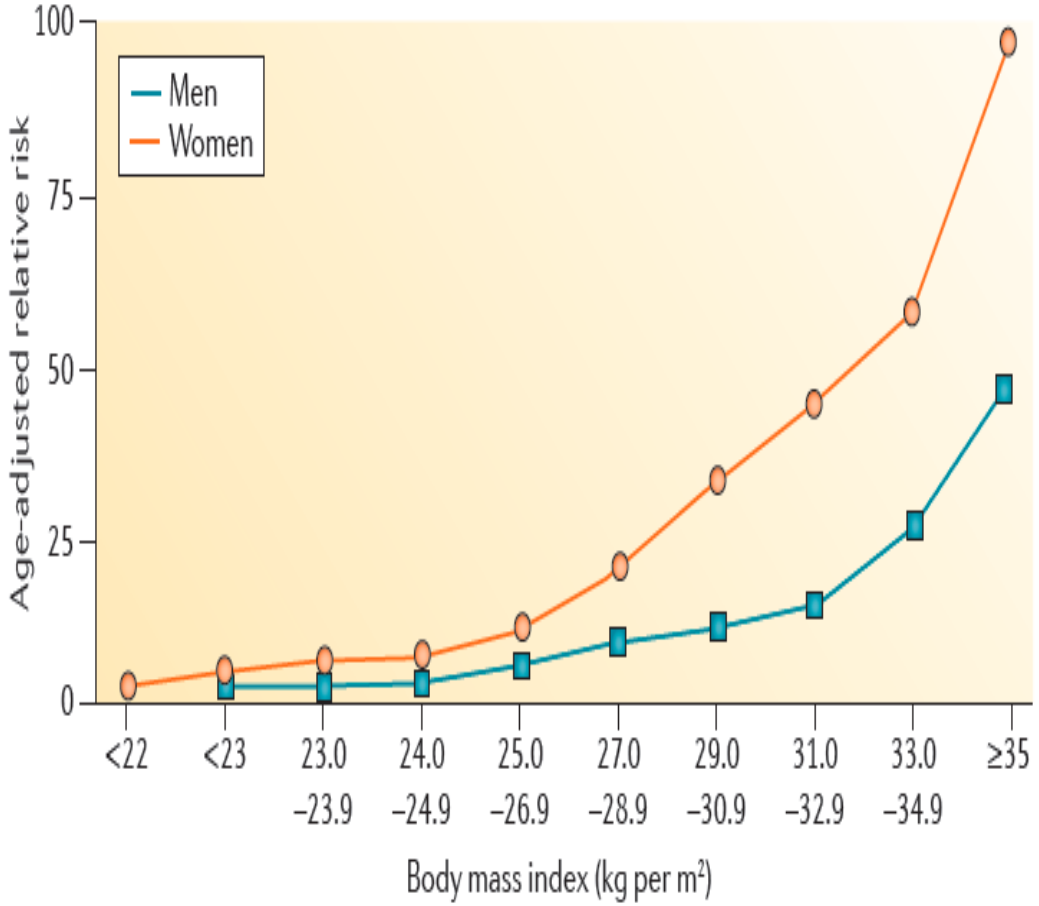


Figure 2 | **Association between BMI and T2DM.**

DeFronzo RA. et al. *Nat Rev Dis Primers* 2015; 1: 15019

NAFLD

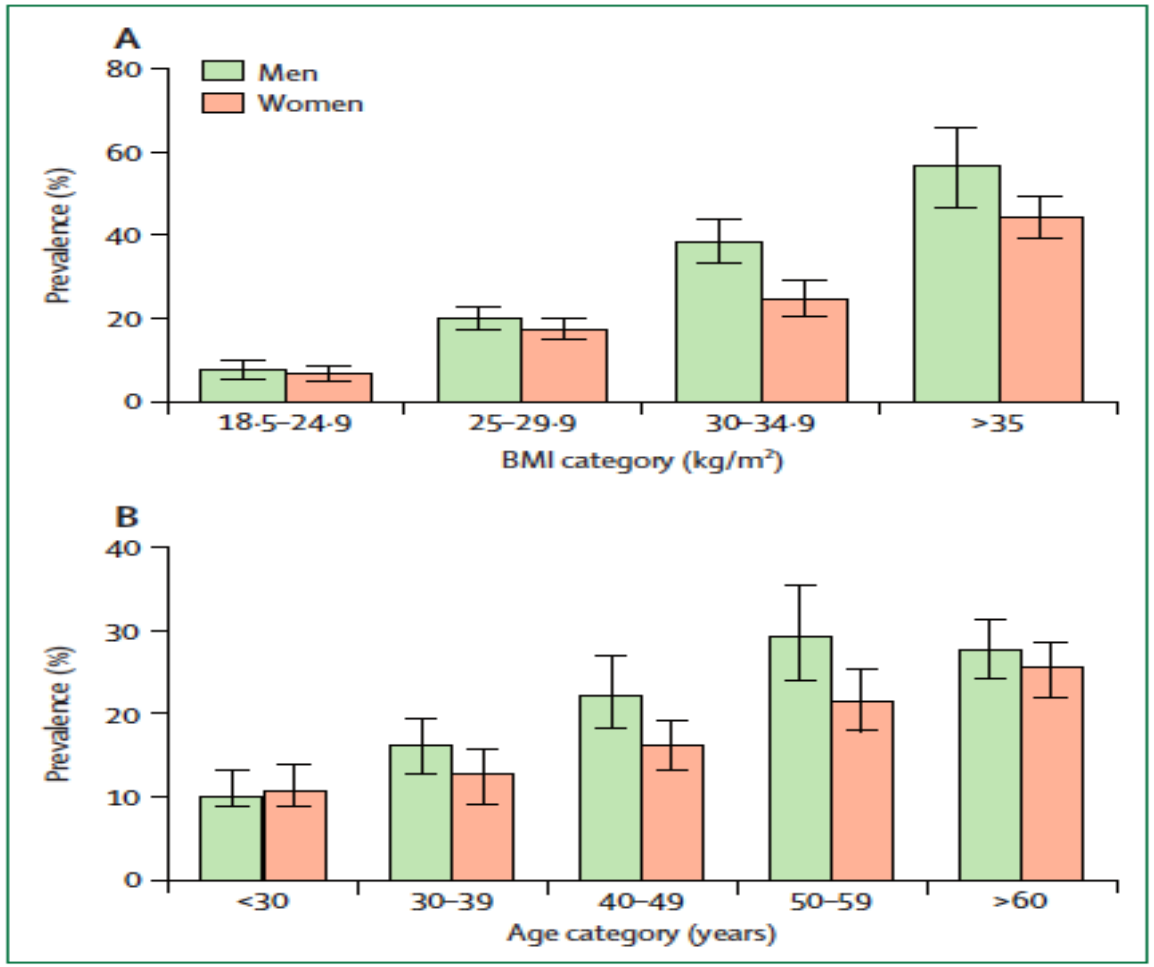


***Figure 3*: Prevalence of NAFLD according to BMI, age, and sex**

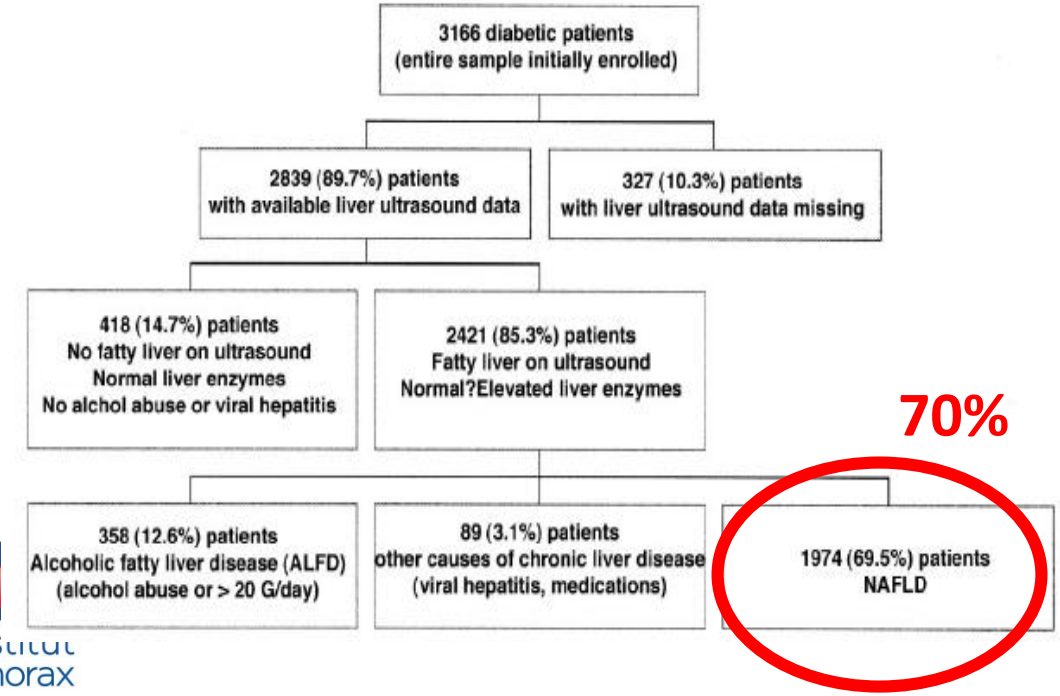
Yki-Järvinen H. et al. *Lancet Diabetes Endocrinol* 2014; 2: 901-10.

WHAT IT IS THE PREVALENCE OF NAFLD in T2D?

Prevalence of Nonalcoholic Fatty Liver Disease and Its Association With Cardiovascular Disease Among Type 2 Diabetic Patients

GIOVANNI TARGHER, MD[1,2]
LORENZO BERTOLINI, MD[1]
ROBERTO PADOVANI, MD[1]
STEFANO RODELLA, MD[3]
ROBERTO TESSARI, MD[1]
LUCIANO ZENARI, MD[1]
CHRISTOPHER DAY, MD[4]
GUIDO ARCARO, MD[1]

Diabetes Care 30:1212–1218, 2007



70%

Epidemiology/Health Services Research
ORIGINAL ARTICLE

Prevalence of and Risk Factors for Hepatic Steatosis and Nonalcoholic Fatty Liver Disease in People With Type 2 Diabetes: the Edinburgh Type 2 Diabetes Study

RACHEL M. WILLIAMSON, MRCP[1]
JACKIE F. PRICE, MD, FFPH[2]
STEPHEN GLANCY, FRCR[3]
ELISA PERRY, MRCP, FRCR[3]
LISA D. NEE, GRADDIPPAPPSCI[3]
PETER C. HAYES, PHD, MD[4]
BRIAN M. FRIER, MD, FRCPE[5]
LIESBETH A.F. VAN LOOK, MRCP[1]
GEOFFREY I. JOHNSTON, PHD[6]
REBECCA M. REYNOLDS, PHD, FRCPE[7]
MARK W.J. STRACHAN, MD, FRCPE[1]
ON BEHALF OF THE EDINBURGH TYPE 2 DIABETES STUDY INVESTIGATORS

Diabetes Care 34:1139–1144, 2011

N=939 patients with T2

43%

RESULTS—Hepatic steatosis was present in 56.9% of participants. After excluding those with a secondary cause for steatosis, the prevalence of NAFLD in the study population was 42.6%. Independent predictors of NAFLD were BMI, lesser duration of diabetes, HbA_{1c}, triglycerides, and metformin use. These remained unchanged after exclusion of participants with evidence of hepatic fibrosis from the group with no hepatic steatosis.

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…AND IN PRIMARY CARE?

AP&T Alimentary Pharmacology and Therapeutics

Non-invasive screening of diabetics in primary care for NAFLD and advanced fibrosis by MRI and MRE

I. Doycheva*, J. Cui*, P. Nguyen*,†, E. A. Costa‡, J. Hooker‡, H. Hofflich§, R. Bettencourt¶, S. Brouha**, C. B. Sirlin‡ & R. Loomba*,†,¶

N= 100

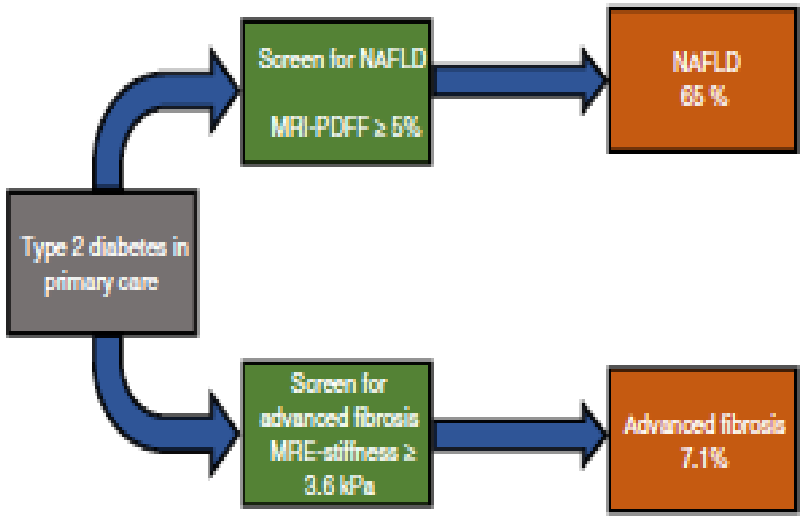

Figure 1 | Prevalence of NAFLD and advanced fibrosis among patients with type 2 diabetes in primary care. Patients with type 2 diabetes in the primary care setting were screened for NAFLD with magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF). NAFLD was defined by the presence of hepatic steatosis ≥5% on MRI-PDFF. Screening for advanced fibrosis was performed using magnetic resonance elastography (MRE) with a threshold of 3.6 kPa to identify those with advanced fibrosis.

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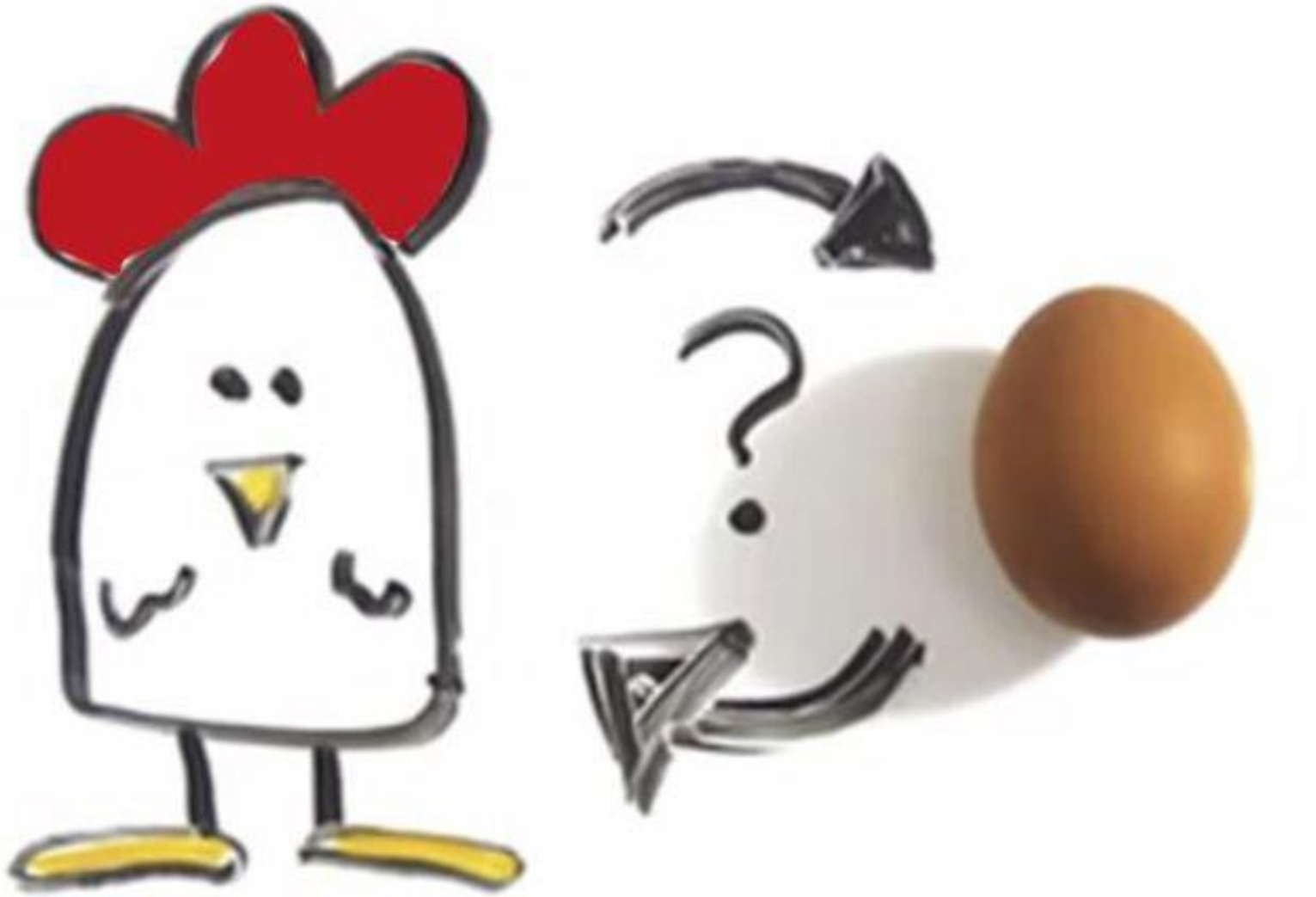

NAFLD / NASH **INSULIN RESISTANCE / T2D**

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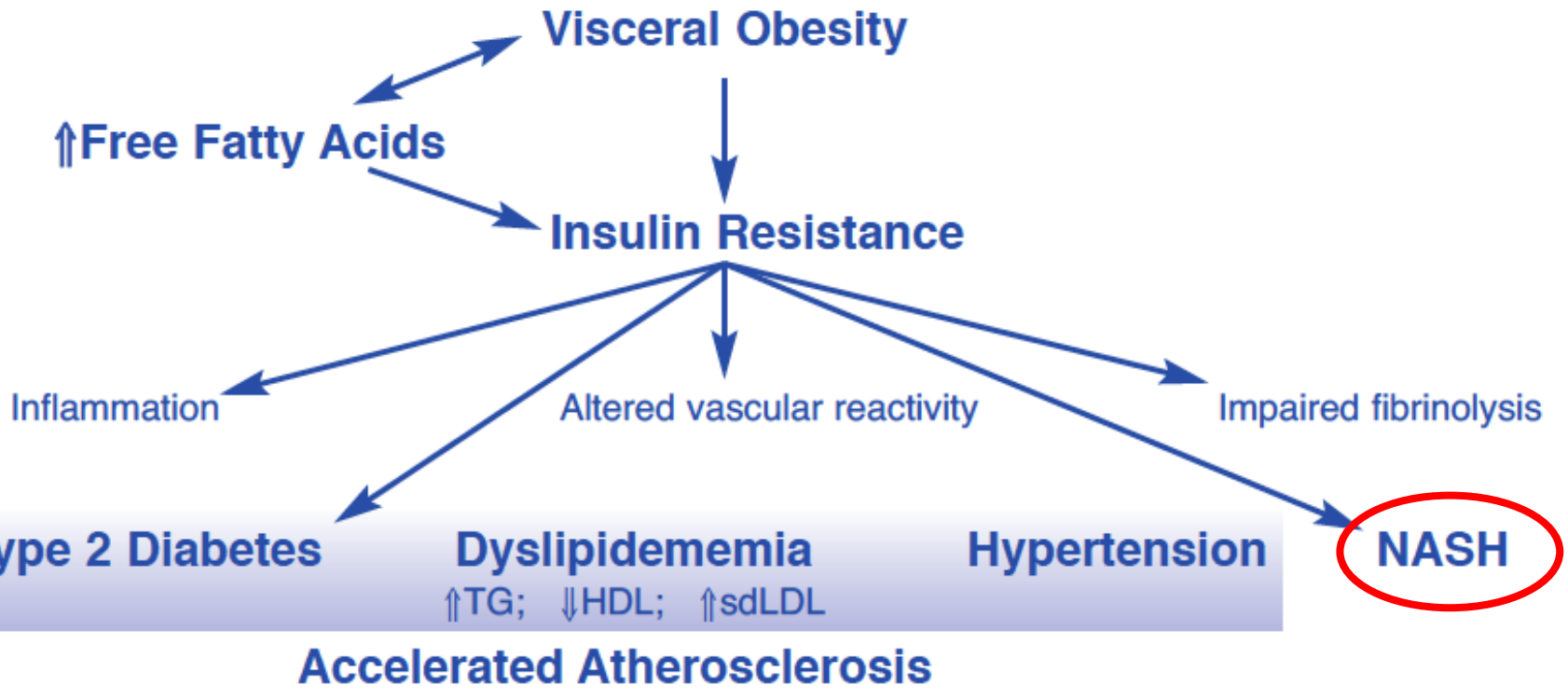
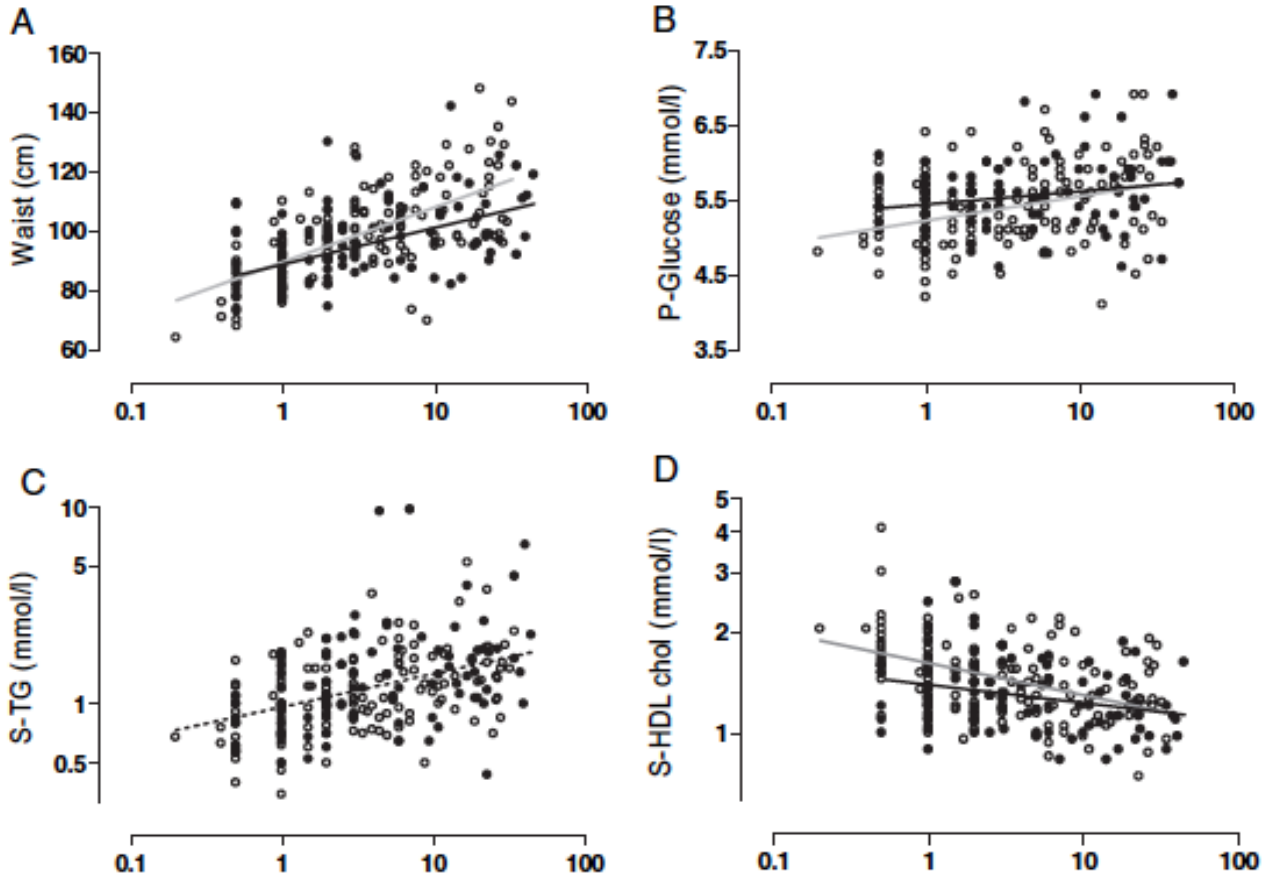
Insulin Resistance and Metabolic Syndrome

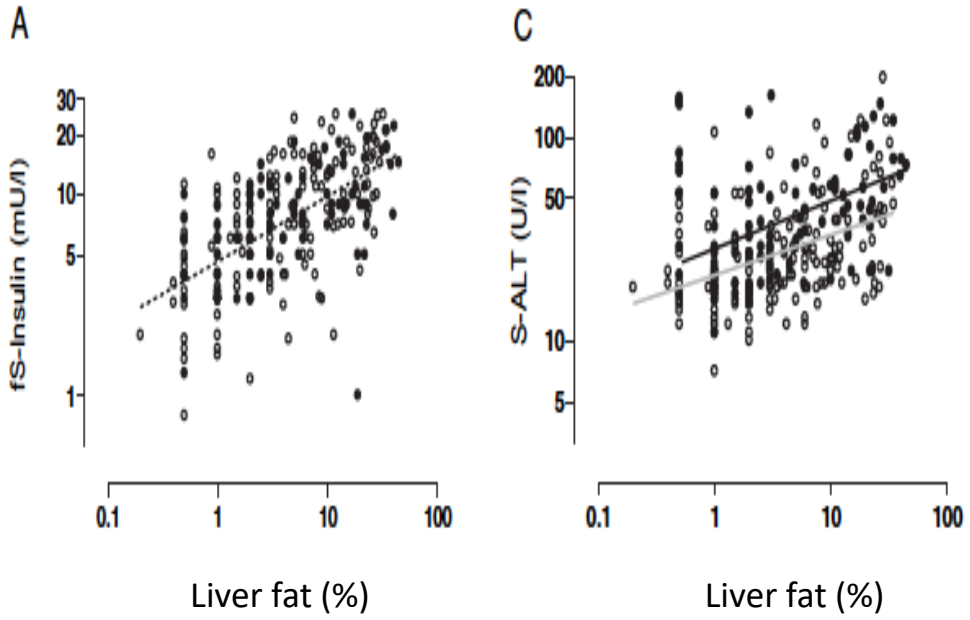


NASH = Nonalcoholic steatohepatitis
TG = Triglycerides; HDL = high-density lipoprotein; sdLDL = small dense LDL

RELATION BETWEEN LIVER FAT AND COMPONENTS OF METABOLIC SYNDROME

271 non-diabetic subjects (162 women, 109 men)
Liver fat assessed by proton MRI (spectroscopy)





Kotronen A. et al. *J Clin Endocrinol Metab* 2007; 92: 3490-97

RELATION BETWEEN LIVER FAT AND HEPATIC INSULIN RESISTANCE

45 non-diabetic men; hyperinsulinemic-euglycemic clamps

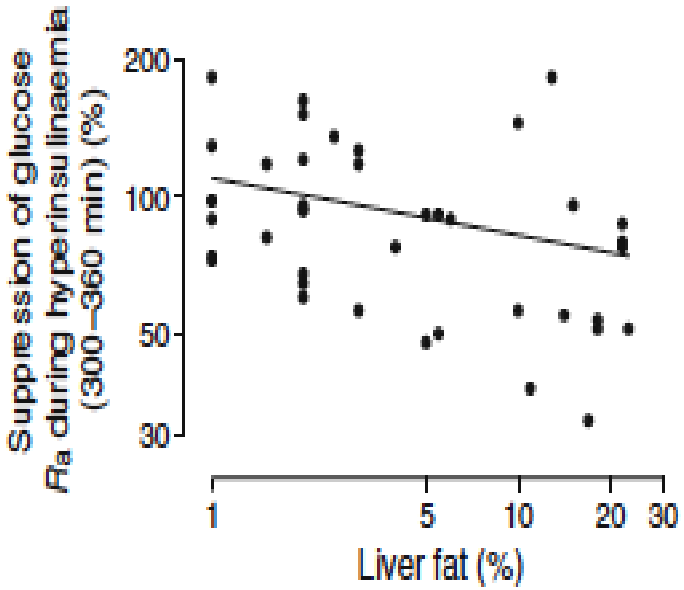


Fig. 4 Graph showing the relationship between percentage suppression of endogenous glucose production during the last hour of hyperinsulinaemia (300–360 min, log scale) and liver fat content (log scale) in individual participants (circles). $r=-0.30$, $p<0.05$

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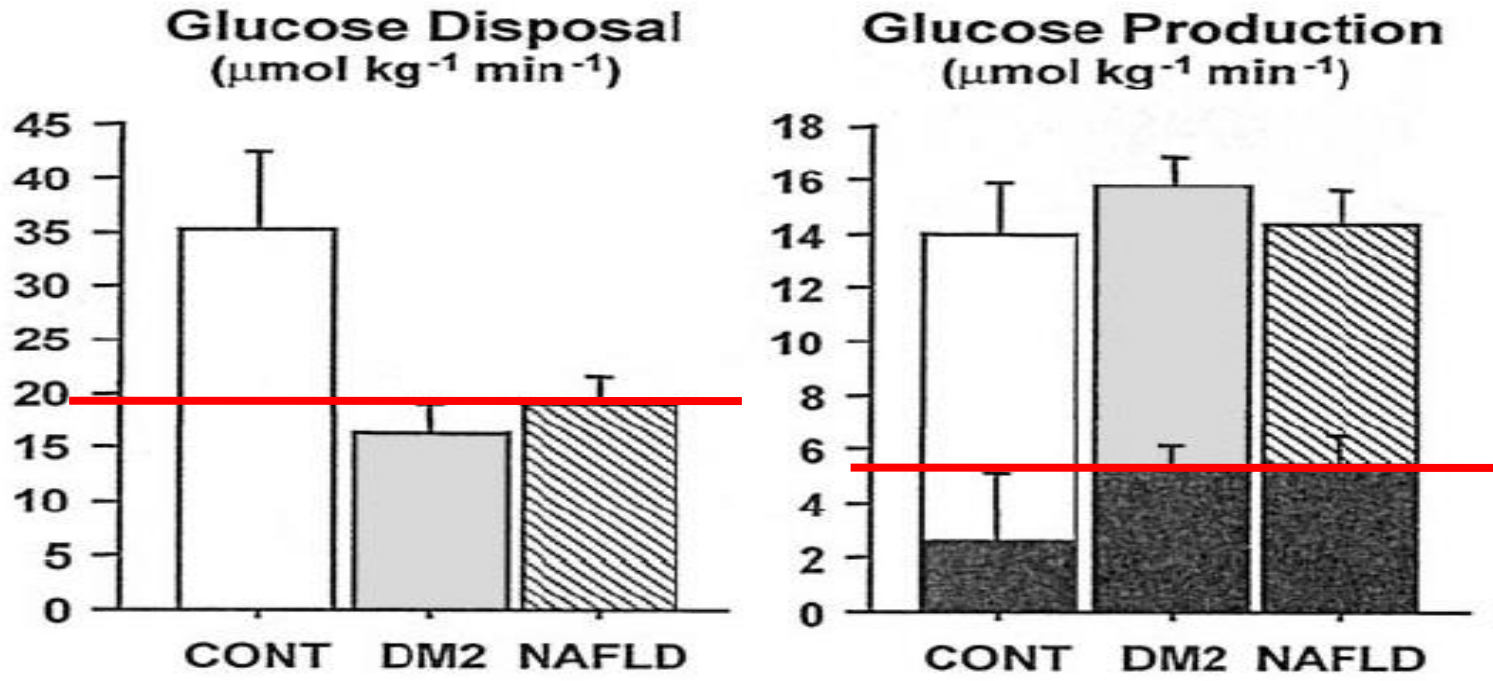
Kotronen A. et al. *Diabetologia 2008; 51: 130-38*

PATIENTS WITH NAFLD DISPLAY INSULIN RESISTANCE AS IN T2D

Peripheral insulin resistance



Hepatic insulin resistance

FIG. 3. Glucose disposal in the course of the clamp and hepatic glucose production in the subgroup of subjects infused with [6,6-$^{2}H_{2}$]glucose. The subgroups—control subjects (CONT; open columns; $n = 5$), type 2 diabetic patients (DM2; shaded columns; $n = 5$), and NAFLD subjects (hatched columns; $n = 10$)—are representative of the whole population. Black bars represent hepatic glucose production at the end of the clamp study. Data are presented as means and 95% CI.

Marchesini G. et al. *Diabetes* 2001; 50: 1844-50

Hepatic rather than intramyocellular fat content is associated with features of Met-S

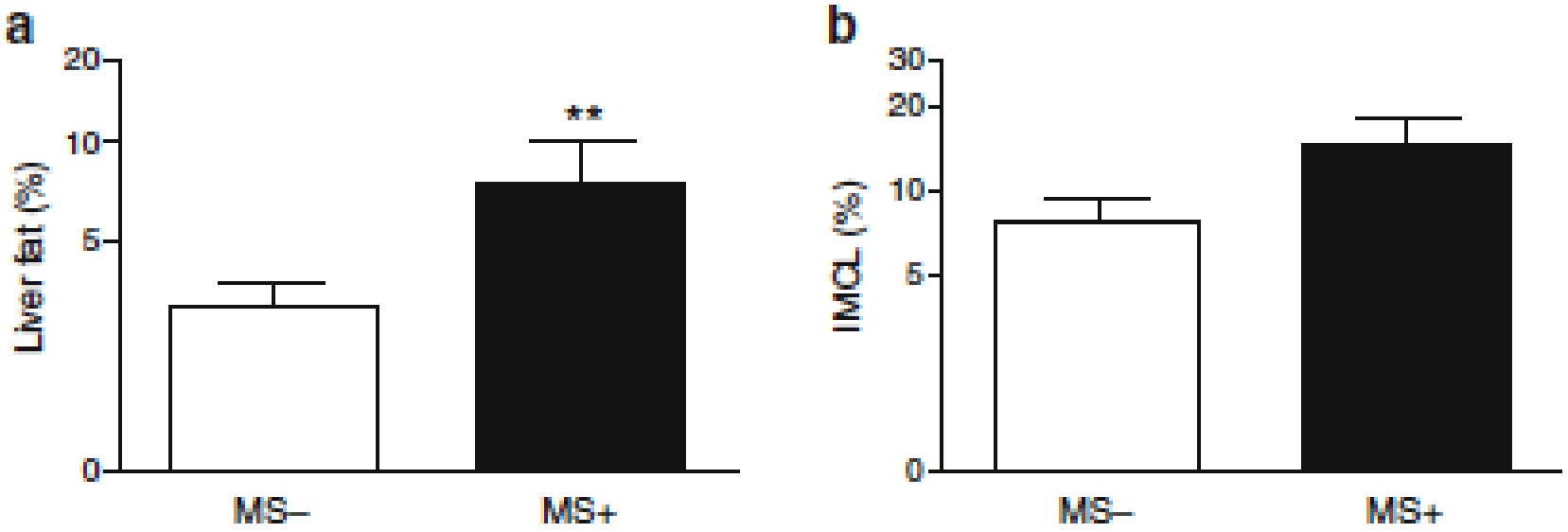
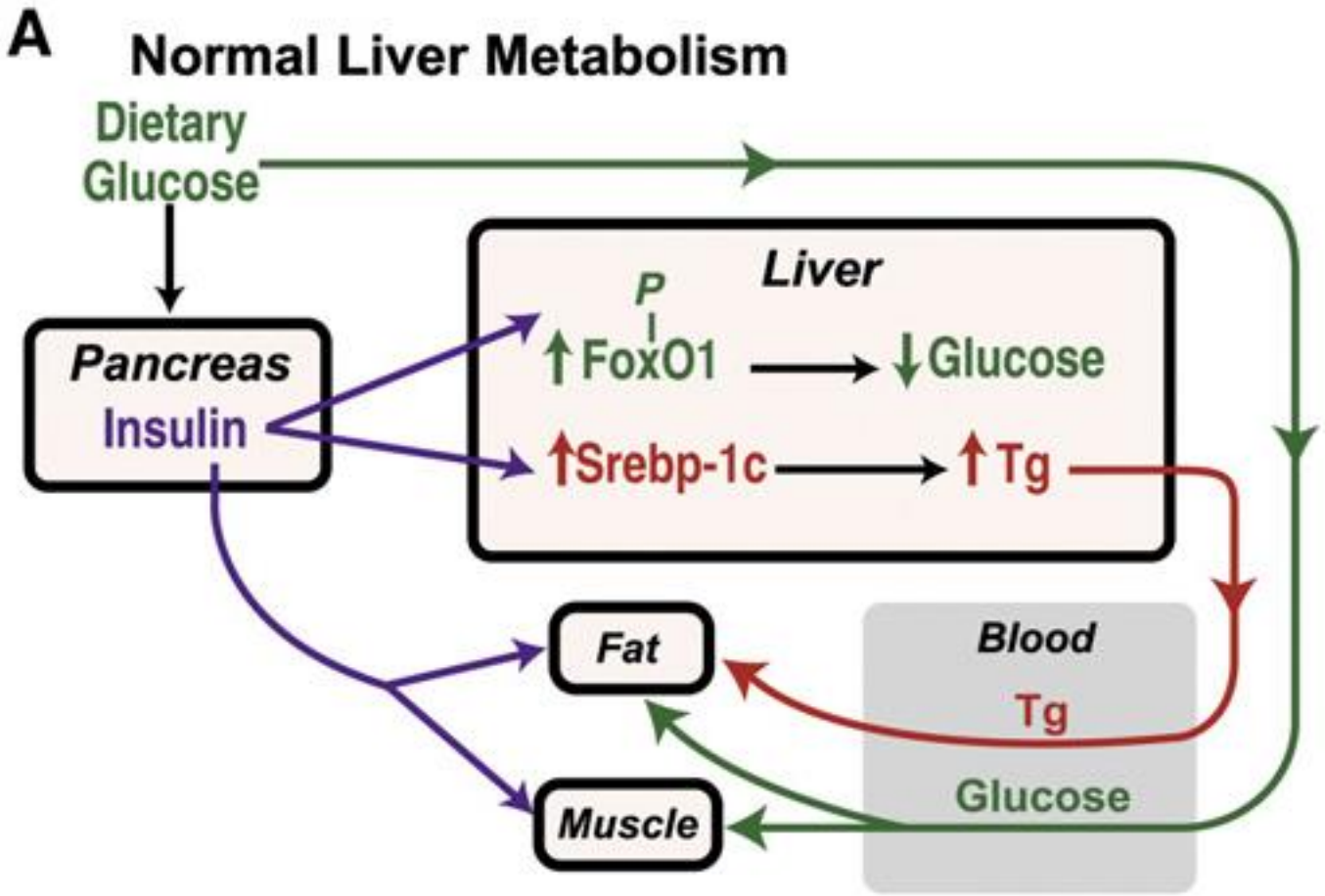


Fig. 3 Bar graphs (log scale) showing liver fat (a) and IMCL (b) in participants without (–) and with (+) the metabolic syndrome (MS). $^{**}p<0.01$ vs individuals without the metabolic syndrome

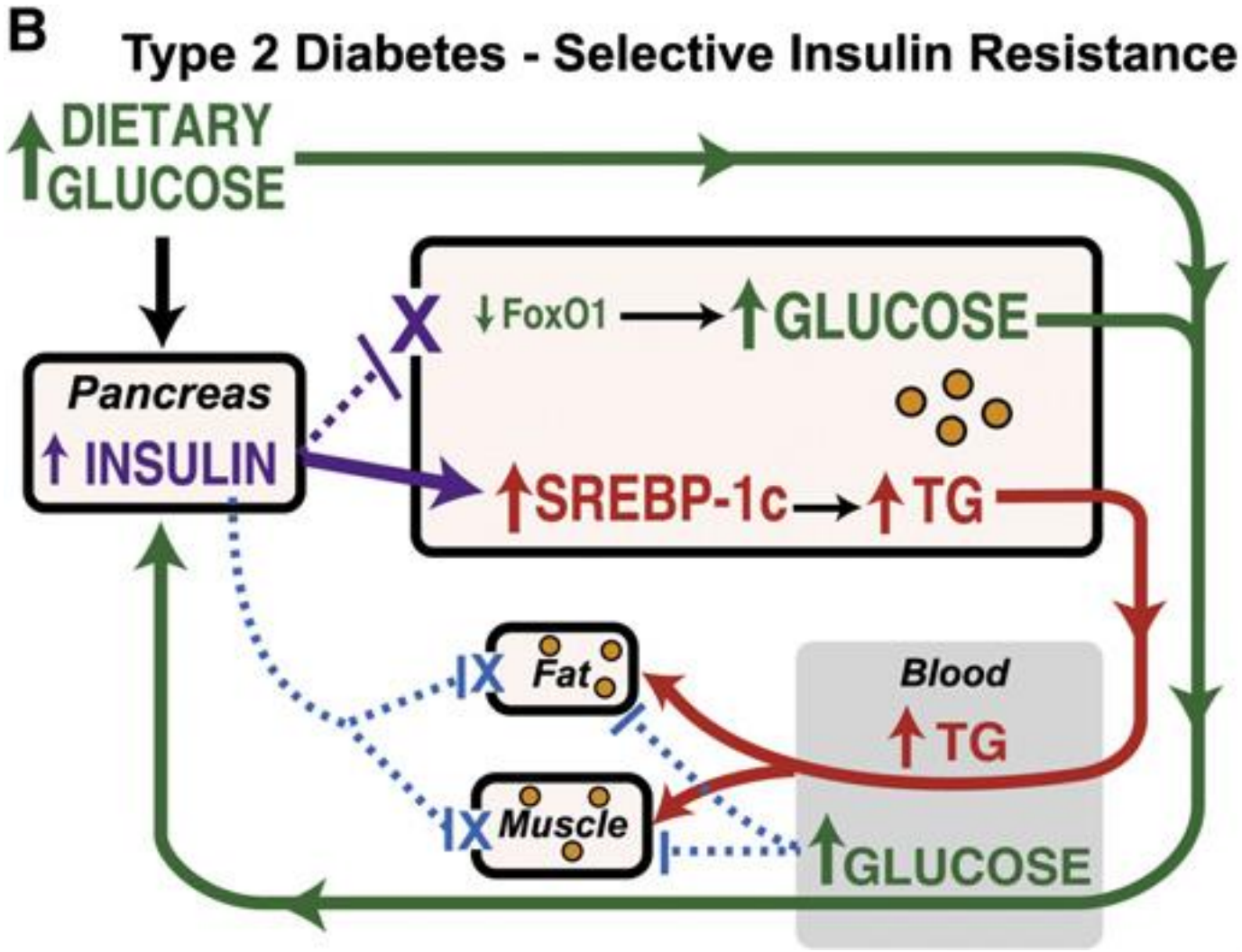
Kotronen A. et al. *Diabetologia 2008; 51: 130-38*

SELECTIVE HEPATIC INSULIN RESISTANCE: A molecular basis for T2D



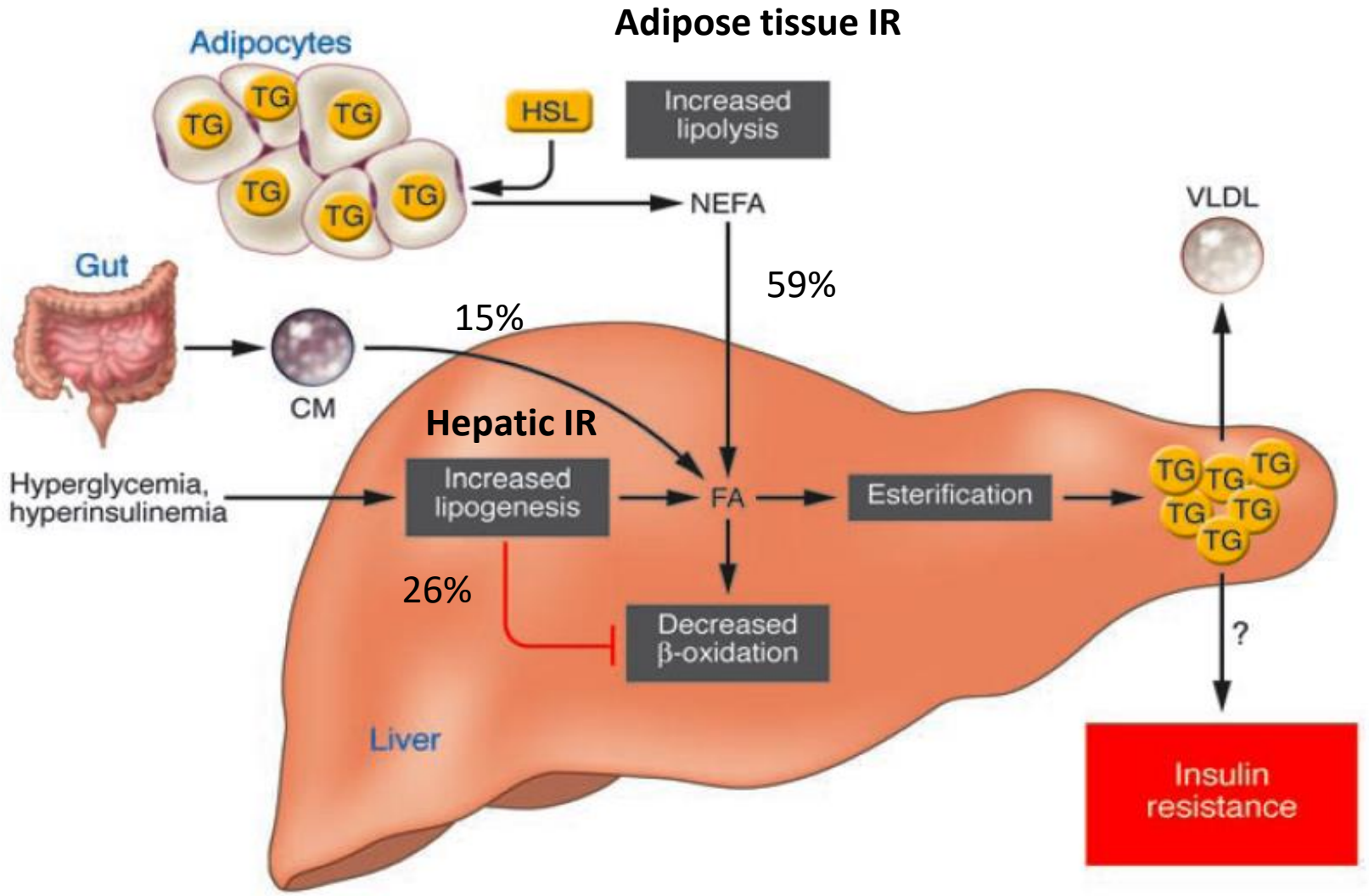
Brown MS & Goldstein JS. *Cell Metab* 2008; 7: 95-96

SELECTIVE HEPATIC INSULIN RESISTANCE: A molecular basis for T2D

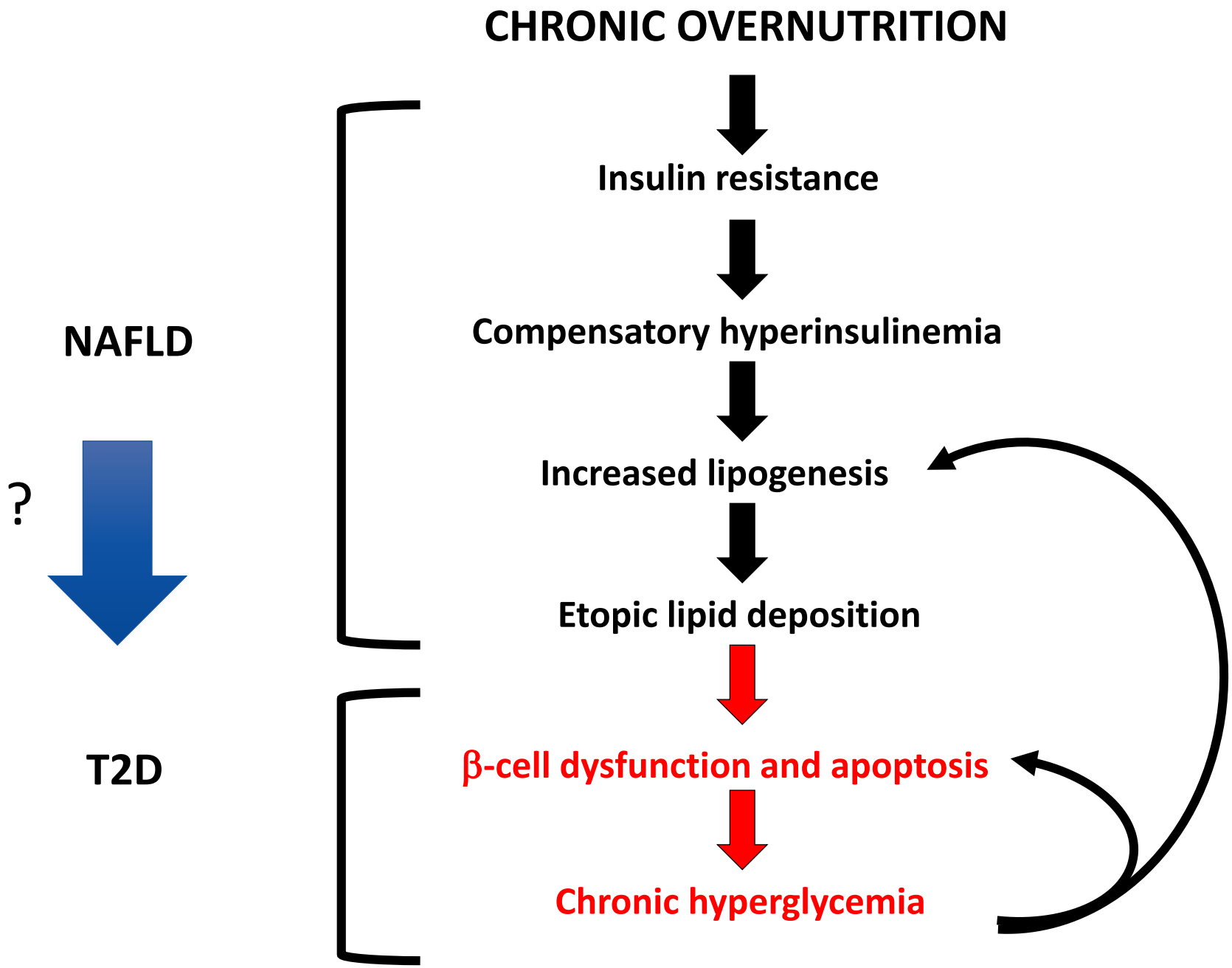


Brown MS & Goldstein JS. *Cell Metab* 2008; 7: 95-96

NAFLD/NASH: PATHOPHYSIOLOGY



Postic C & Girard J. *J Clin Invest* 2008; 118: 829-38.


CHRONIC OVERNUTRITION
Insulin resistance
Compensatory hyperinsulinemia
Increased lipogenesis
Etopic lipid deposition
β-cell dysfunction and apoptosis
Chronic hyperglycemia
NAFLD
?
T2D

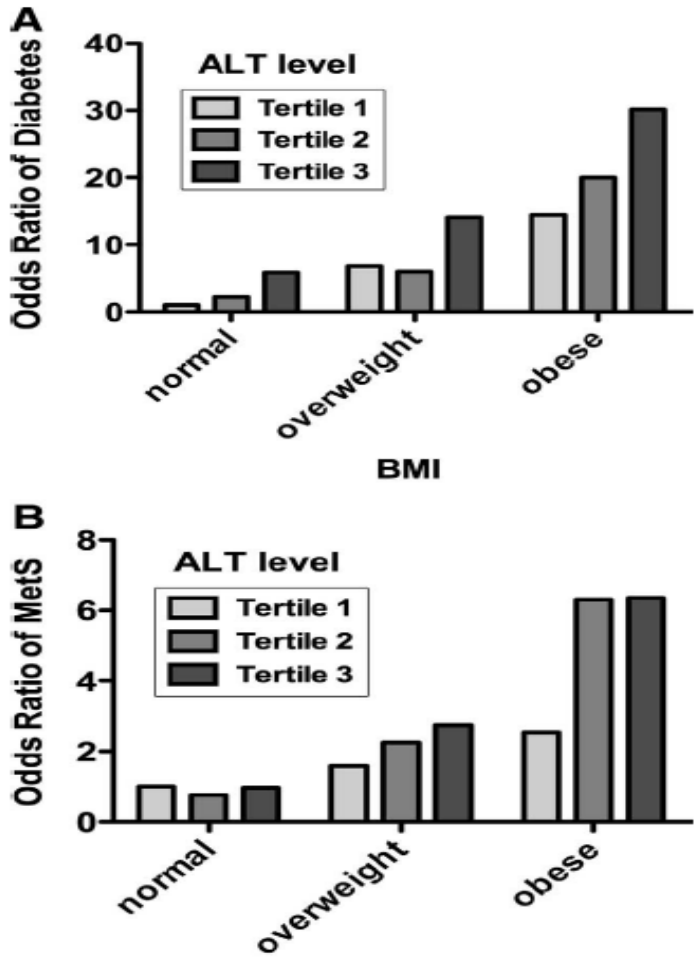
NAFLD is a risk factor for new onset type 2 diabetes

Framingham cohort – 20 years follow-up

Table 4. Baseline ALT and AST and the OR of Developing Incident DM Over 20 Years of Follow-Up

	Overall sample		AST or ALT in the normal range	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
AST				
Age/gender adjusted	1.41 (1.25–1.60)	< .0001	1.32 (1.12–1.55)	.001
MV adjusted[a]	1.33 (1.16–1.52)	< .0001	1.24 (1.04–1.48)	.02
+ glucose adjusted	1.25 (1.08–1.45)	.002	1.15 (0.96–1.39)	.13
+ interim weight change	1.33 (1.17–1.53)	< .0001	1.24 (1.04–1.48)	.02
ALT				
Age/gender adjusted	1.72 (1.51–1.94)	< .0001	1.62 (1.36–1.94)	.0001
MV adjusted[a]	1.48 (1.30–1.69)	< .0001	1.34 (1.11–1.61)	.002
+ glucose adjusted	1.42 (1.23–1.63)	< .0001	1.28 (1.05–1.55)	.01
+ interim weight change	1.48 (1.30–1.69)	< .0001	1.34 (1.11–1.61)	.002

NOTE. The OR of developing incident DM was calculated per 1 gender-specific SD increase in log-transformed aminotransferase levels.
AST, aspartate aminotransferase; ALT, alanine aminotransferase; OR, odds ratio; CI, confidence interval; MV, multivariable.
[a]Adjusted for age, gender, smoking, menopause, alcohol use (g/day), BMI.



Goessling W et al. *Gastroenterology* 2008; 135: 1935-44

NAFLD is a risk factor for type 2 diabetes

13 218 non-diabetic Korean subjects followed during 5 years

Table 4. Odds Ratios for Incident Diabetes at Follow-Up According to Fatty Liver Status at Baseline and at Follow-Up

	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 *J Clin Endocrinol Metab* 2013; 98: 3637-43

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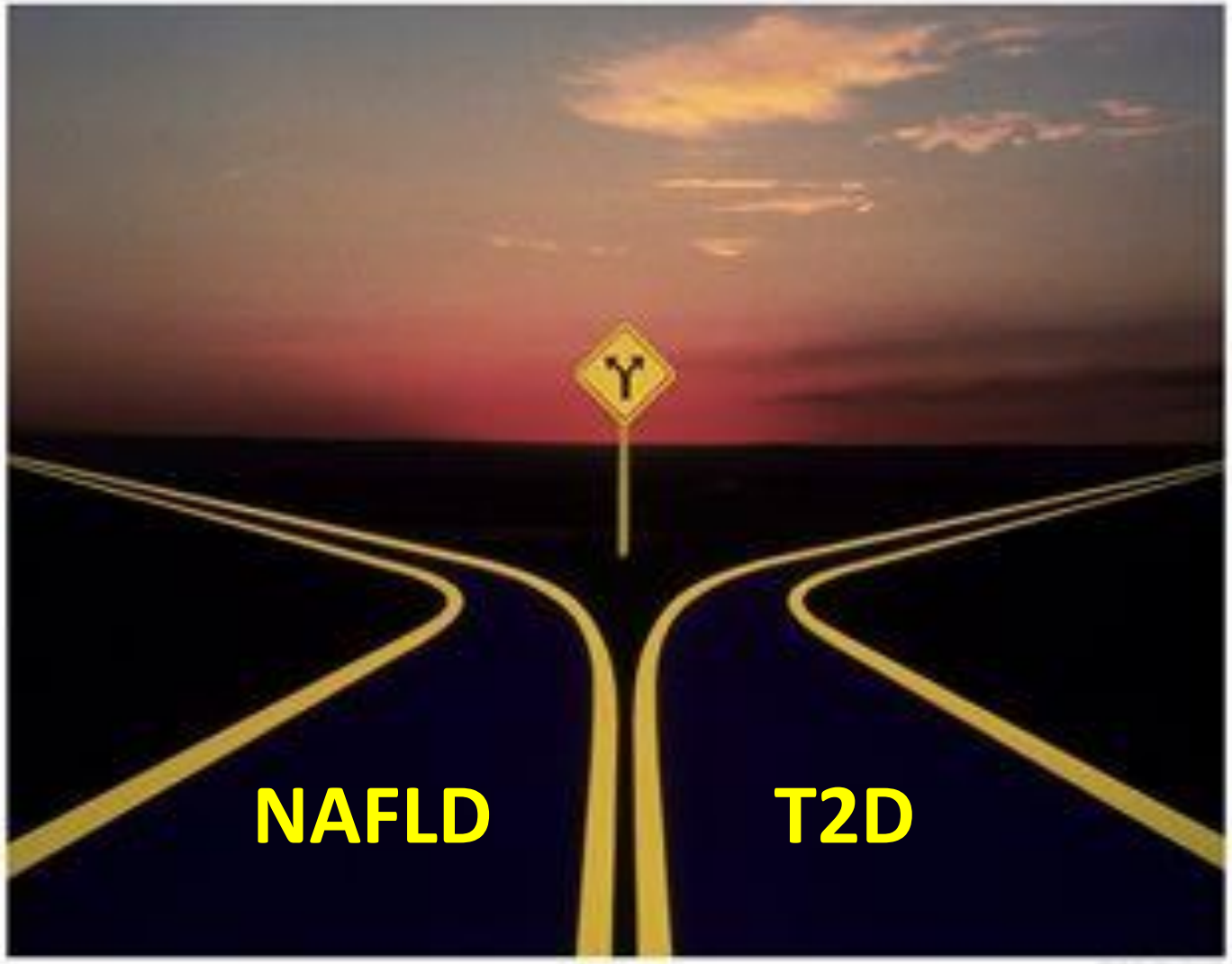
NAFLD and T2D: a same disease? The dilemna of genetics



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GENETICS OF T2D: THE GWAS ERA

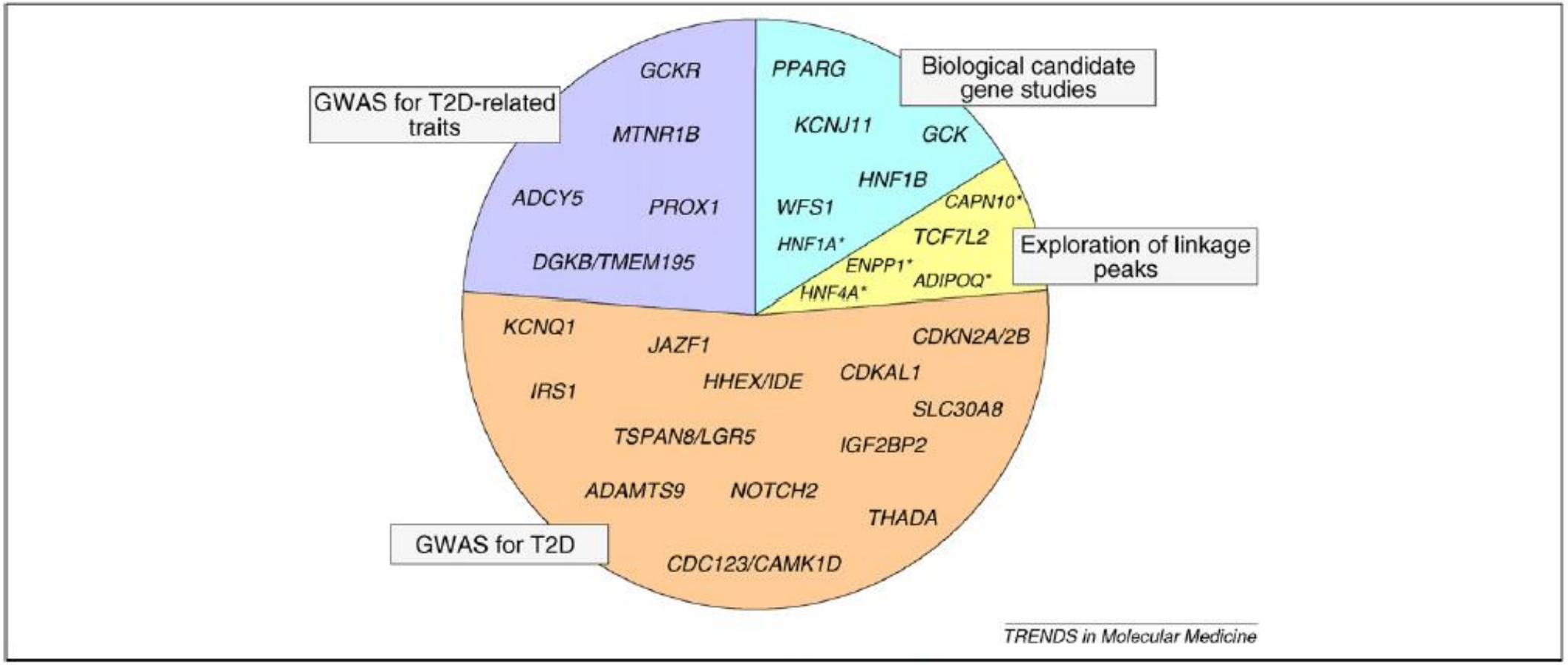
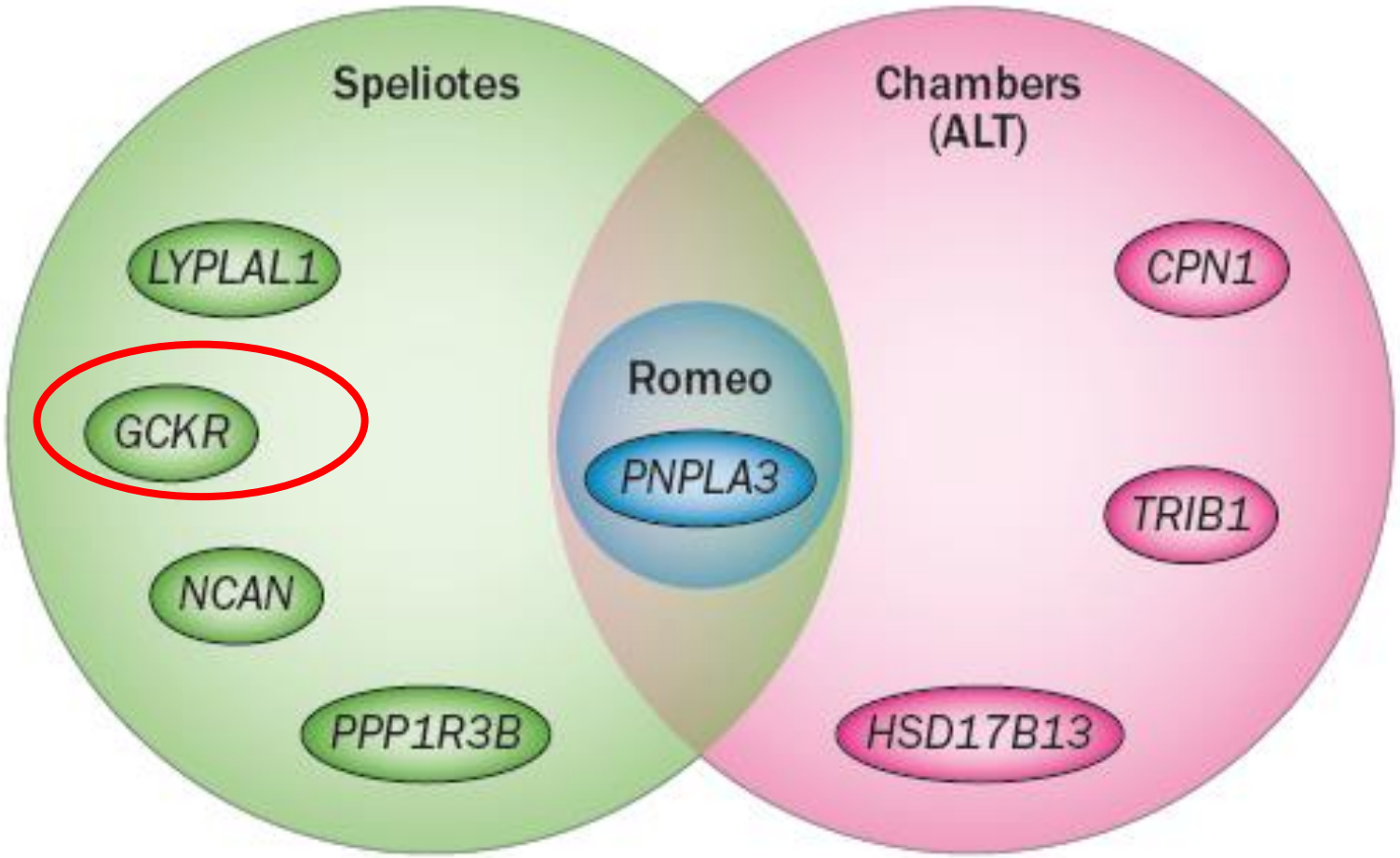


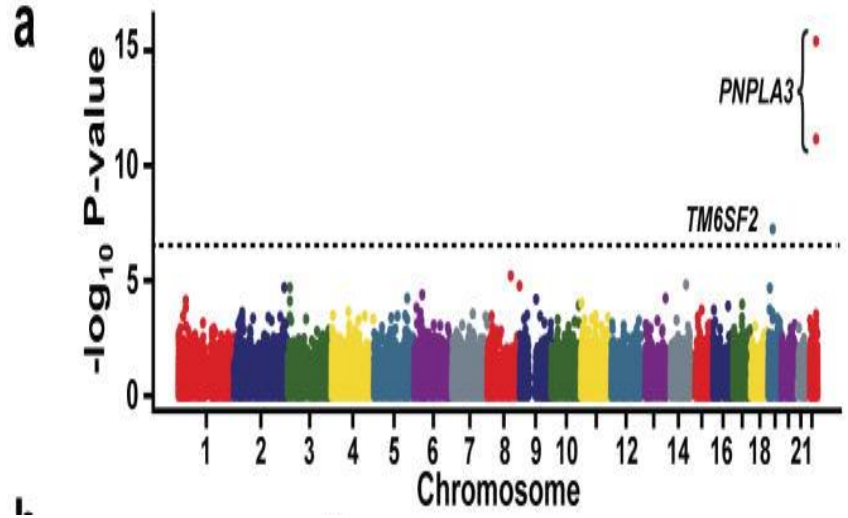
Figure 1. Identification of T2D susceptibility genes.

Bonnefond A. et al. *Trends Mol Med* 2010; 16: 407-16

GENETICS OF NAFLD: THE PREDOMINANT ROLE OF PNPLA3



+ TSM6SF2

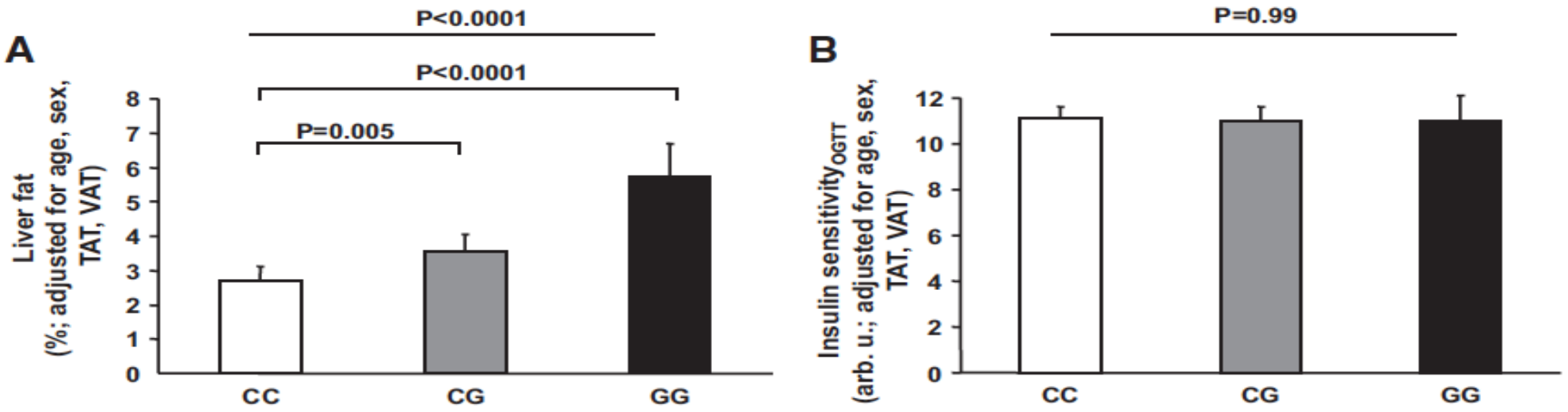


Exome-wide association study with hepatic TG content in the *Dallas Heart study* (n=2736)

Anstee QM et al. *Nat Rev Gastroenterol Hepatol 2013; 10: 645-55*

NAFLD does not always correlates with insulin resistance…

1. The SNPs rs738409 of PNPLA3 correlates with liver fat content BUT NOT with insulin sensitivity[1]



2. PNPLA3 (Ile148 Met) impairs hepatic TG hydrolysis but does not associate with insulin resistance

3. A similar dissociation between liver fat content and insulin sensitivity is also observed with the E167K variant in TM6SF2[2] and in familial hypobetalipopproteinemia[3]

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[1] Kantartzis K et al. Diabetes 2009; 58: 2616-23; [2] He S. et al. *J Biol Chem 2010; 285: 6706-15;*
[3] Zhou Y. et al. *J Hepatol* 2015: 62: 657-63; [4] Amaro A. et al. Gastroenterology 2010; 139: 149-53.

…and cardiovascular diseases

PNPLA3 genotypes

100 patients with MetS and CC genotype (Gpe M)
100 patients with NAFLD and GG genotype (Gpe G)
100 controls with CC genotype

CIMT as primary endpoint

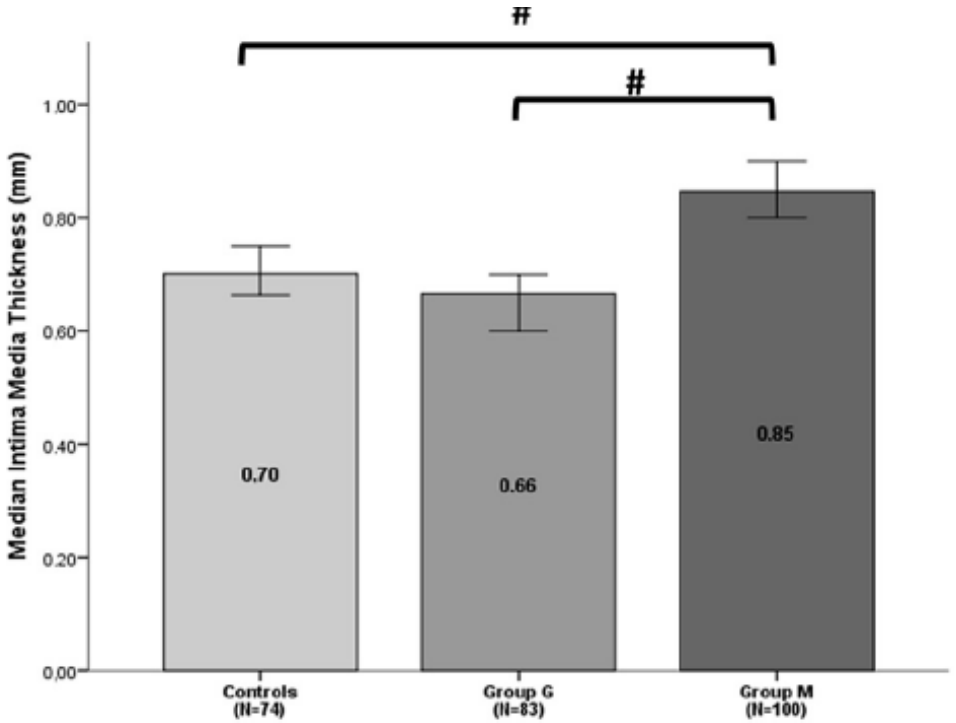

Fig. 1. Comparison of CIMT between study groups. (A) Median CIMTs for the three study status and steatosis severity reflected by the Hamaguchi score, General Lineal Model (G
#*adjusted p* < 0.05 for age, sex, smoking status and HFF, General Lineal Model (GLM) tes
resonance spectroscopy.

Di Costanzo A. et al. *Atherosclerosis* 2017; 257: 232-39.

NAFLD is associated with an increased burden of subclinical atherosclerosis only when it is linked to MetS traits rather than when it occurs owing to the PNPLA3 rs738409 gene polymorphism

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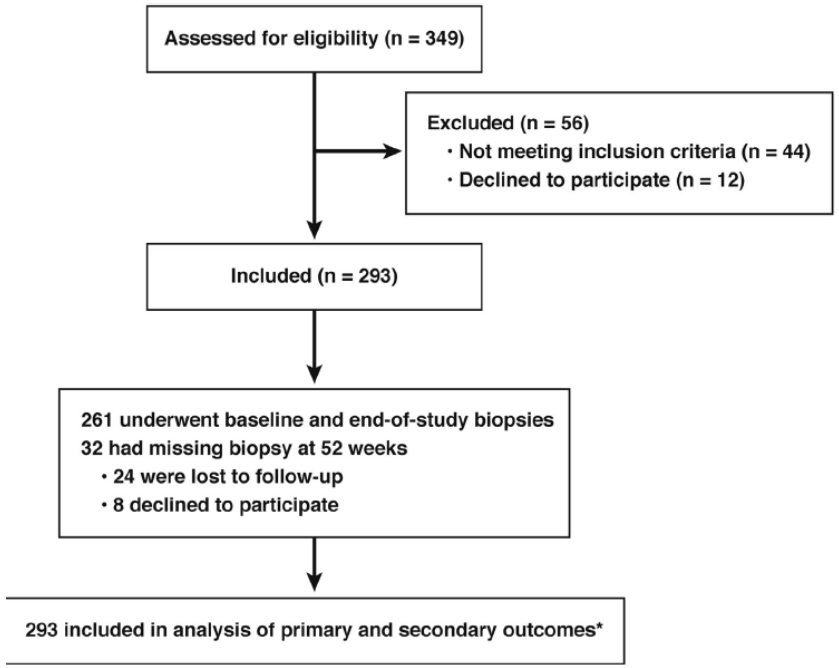
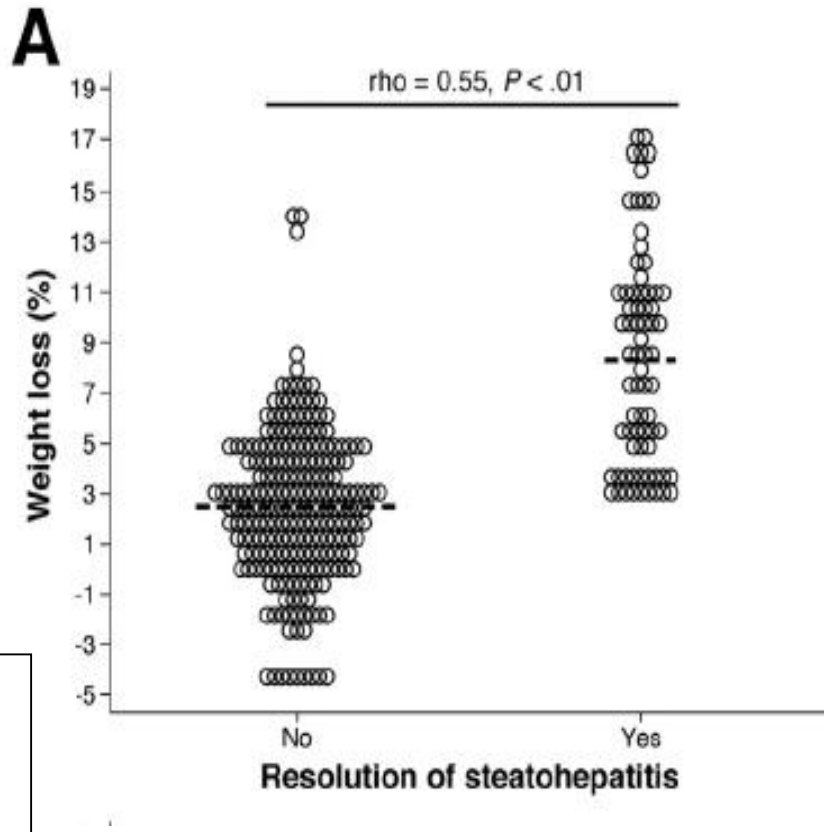
Life style changes improve both T2D and NAFLD



Intervention

🡻750 kcal/day less than daily energy need
64% carbohydrates, 22% fat (< 10% SFA), 14% Prot
Physical activity: 200 min walk /week



Vilar-Gomez E. et al. *Gastroenterology* 2015; 49: 367-78

BARIATRIC SURGERY

362 patients who underwent bariatric surgery
(gastric banding of RYGB)

Table 5. Effects of Bariatric Surgery on Histologic Parameters at 1 and 5 Years

Variables	Before surgery (n = 362)	1 Year (n = 267)	5 Years (n = 211)	*P* value, paired *t* test: Before vs 1 year	Before vs 5 years	1 Year vs 5 years
Amount of steatosis, mean ± SD, (%)	37.4 ± 25.5	15.3 ± 19.8	16 ± 27.3	.00001	.00001	.5
Severe steatosis, n (%)	106 (29)	15 (5.6)	18 (8.5)	.00001	.00001	.5
NAS, mean ± SD	1.97 ± 1.33	1.07 ± 1.26	1 ± 1.33	.00001	.00001	.07
NAS inflammation, mean ± SD	0.18 ± 0.41	0.196 ± 0.45	0.23 ± 0.45	.7	.1	.7
NAS ballooning, mean ± SD	0.20 ± 0.47	0.12 ± 0.36	0.1 ± 0.33	.001	.001	.07
Extent of fibrosis, mean ± SD	0.27 ± 0.55	0.41 ± 0.69	0.36 ± 0.59	.002	.001	.9
Fibrosis score						
F0	280 (77.4)	181 (67.8)	147 (69.7)			
F1	67 (18.5)	69 (25.8)	55 (26)			
F2	13 (3.6)	10 (3.7)	6 (2.8)			
F3	2 (0.5)	7 (2.6)	2 (1)			
F4	—	—	1 (0.5)			

NAS, nonalcoholic fatty liver disease score.

➔ significant decrease of steatosis and ballooning
➔ maximal effect at 1 year
➔ **early improvement of insulin resistance (QUICKI) is the best predictor of the long-term outcome**

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Mathurin P, Gastroenterology 2009; 137: 532-540

THE DISCREPANT EFFECT OF METFORMINE IN T2D & NASH

- Metformin is the first choice therapy in T2D regarding its hypoglycaemic efficacy and potential cardiovascular benefit (UKPDS 34)

- Metformin failed to demonstrate some clinical efficacy in NAFLD

TONIC trial

Table 3. Change From Baseline to End of Treatment in Liver Histology by Treatment Group

	Vitamin E (n = 50)	Metformin (n = 50)	Placebo (n = 47)	*P* Value[a] Vitamin E vs Placebo	*P* Value[a] Metformin vs Placebo
Fibrosis score					
No. (%) improved [95% CI]	18 (37) [23 to 52]	22 (44) [30 to 59]	19 (40) [26 to 56]	.71	.72
Mean change (95% CI)	−0.3 (−0.6 to 0.0)	−0.4 (−0.7 to −0.0)	−0.2 (−0.6 to 0.1)	.48	.60
Steatosis score					
No. (%) improved [95% CI]	27 (54) [39 to 68]	26 (52) [37 to 66]	19 (40) [26 to 56]	.18	.25
Mean change (95% CI)	−0.8 (−1.1 to −0.5)	−0.6 (−0.9 to −0.2)	−0.4 (−0.8 to −0.1)	.24	.50
Lobular inflammation score					
No. (%) improved [95% CI]	22 (44) [30 to 59]	23 (46) [32 to 61]	20 (43) [28 to 59]	.89	.73
Mean change (95% CI)	−0.4 (−0.6 to −0.2)	−0.3 (−0.5 to −0.0)	−0.3 (−0.6 to −0.1)	.14	.97
Ballooning degeneration score					
No. (%) improved [95% CI]	22 (44) [30 to 59]	22 (44) [30 to 59]	10 (21) [11 to 36]	.02	.02
Mean change (95% CI)	−0.5 (−0.8 to −0.3)	−0.3 (−0.6 to −0.0)	0.1 (−0.2 to 0.3)	.006	.04
Change in NAFLD activity score, mean (95% CI)	−1.8 (−2.4 to −1.2)	−1.1 (−1.7 to −0.5)	−0.7 (−1.3 to −0.2)	.02	.25
Resolution of NASH, No. (%) [95% CI][b]	25 (58) [42 to 73]	16 (41) [26 to 58]	11 (28) [15 to 45]	.006	.23

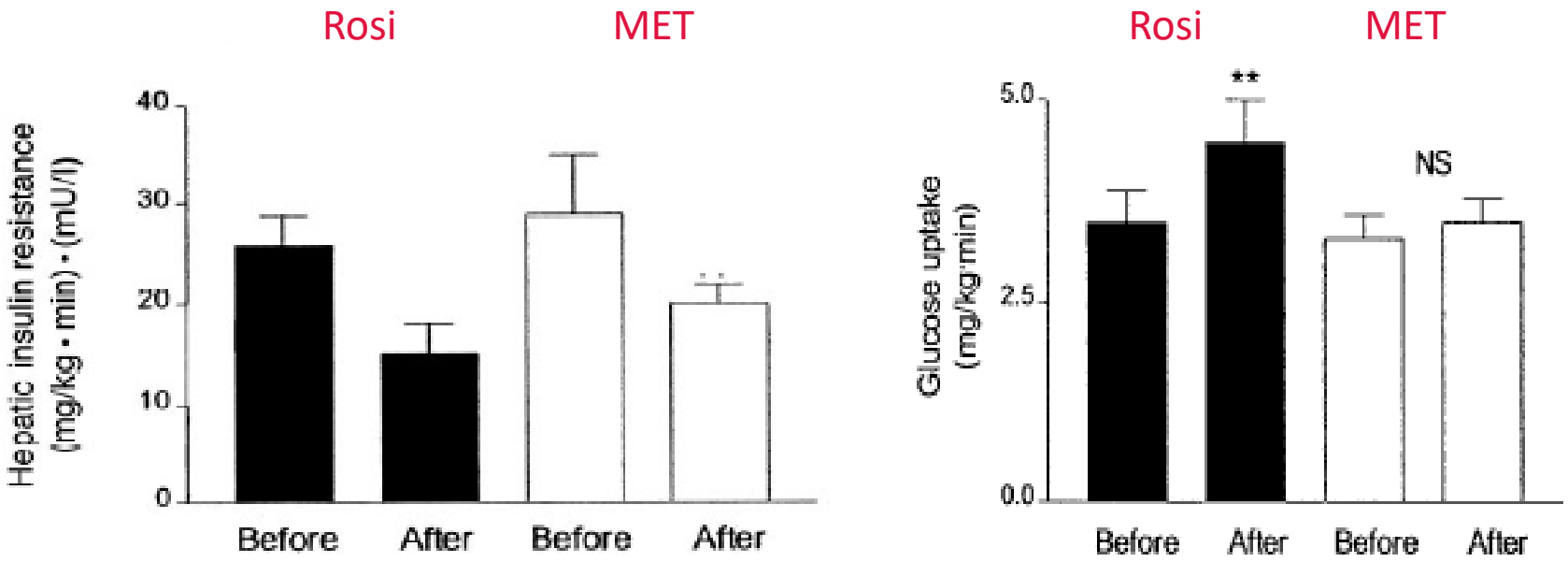
Abbreviations: CI, confidence interval; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.
[a] *P* values derived from either χ^2 test for binary outcomes or analysis-of-covariance model regressing change from baseline to 96 weeks on treatment group and baseline value of the outcome for continuous outcomes.
[b] Defined as number of patients with no NASH at week 96 among patients with borderline or definite NASH at baseline. Excludes 7, 11, and 8 patients with no NASH at baseline in vitamin E, metformin, and placebo groups, respectively.

Lavine JE et al. JAMA 2011

DIFFERENCES BETWEEN METFORMIN AND GLITAZONES MECHANISMS OF ACTION

Double-blind, randomized study in 20 drug-naïve T2DM patients, comparing metformin, 2g/j and Rosiglitazone 8g/j for 16 weeks

Hyperinsulinemic-Euglycemic clamps



⇒ Glitazones improve both hepatic and peripheral insulin sensitivity

Tiikkainen M. et al. Diabetes 2004; 53: 2169-2176.

Meta-analysis: insulin sensitizers for the treatment of non-alcoholic steatohepatitis

M. O. Rakoski*, A. G. Singal*, M. A. M. Rogers† & H. Conjeevaram*

Table 2 | Summary of effect sizes (weighted mean difference) for all insulin sensitizers, glitazones and metformin compared with controls

	All insulin sensitizers			Glitazones			Metformin		
Outcomes	WMD*	95% CI	*P*-value	WMD*	95% CI	*P*-value	WMD*	95% CI	*P*-value
Primary outcome: histological response									
Steatosis	0.40	0.14, 0.65	0.003	0.57	0.36, 0.77	<0.001	−0.19	−0.69, 0.31	0.45
Ballooning	0.16	−0.031, 0.35	0.10	0.36	0.24, 0.49	<0.001	−0.037	−0.19, 0.12	0.64
Inflammation	0.17	−0.15, 0.48	0.29	0.29	−0.05, 0.63	0.09	−0.19	−0.55, 0.17	0.31
Fibrosis	0.24	0.053, 0.42	0.011	0.21	−0.046, 0.46	0.11	0.22	−0.37, 0.81	0.46
Secondary outcome: biochemical and anthropometric response									
ALT	11.9	2.4, 21.5	0.004	16.4	7.70, 25.0	<0.001	13.6	−2.7, 29.9	0.10
BMI	−1.23	−1.61, −0.85	<0.001	−0.90	−1.59, −0.22	0.010	0.75	−0.97, 2.48	0.39

WMD, weighted mean difference; CI, confidence interval; DM, diabetes mellitus; ALT, alanine aminotransferase; BMI, body mass index.

* WMD: a positive WMD indicates greater improvement in the treatment group compared with controls.

Pioglitazone > Rosiglitazone on ballooning and fibrosis

Aliment Pharmacol Ther 2010; 32: 1211–1221

GLP-1 R agonists and liver steatosis: molecular mechanisms

- It is unclear whether or not GLP-1 R is expressed in hepatocytes

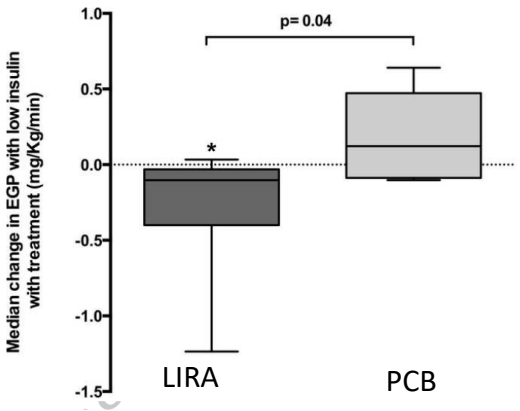
Samson SL et al. *J Diabetes Complic* 2013; 27: 401-406

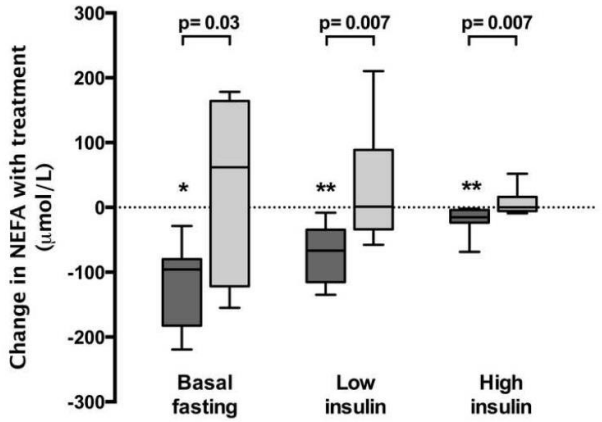
- GLP-1 R agonists can improve steatosis in an indirect manner through body weight loss

- Pilot mechanistic study with liraglutide 1.8 mg/d (n=7) or PCB (n=7) in patients with liver biopsy-proven NASH

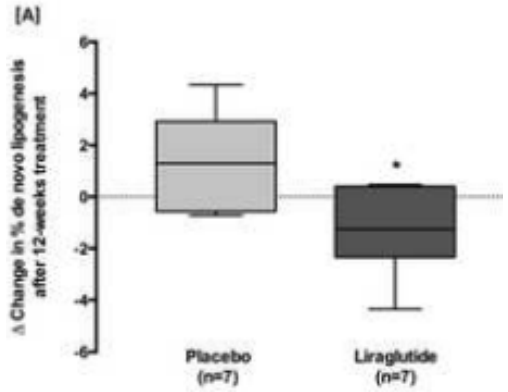
Armastrong ME et al. J Hepatol 2016; 64: 399-408

Hyperinsulinemic-euglycemic clamps





Human hepatocytes



Improved hepatic IR

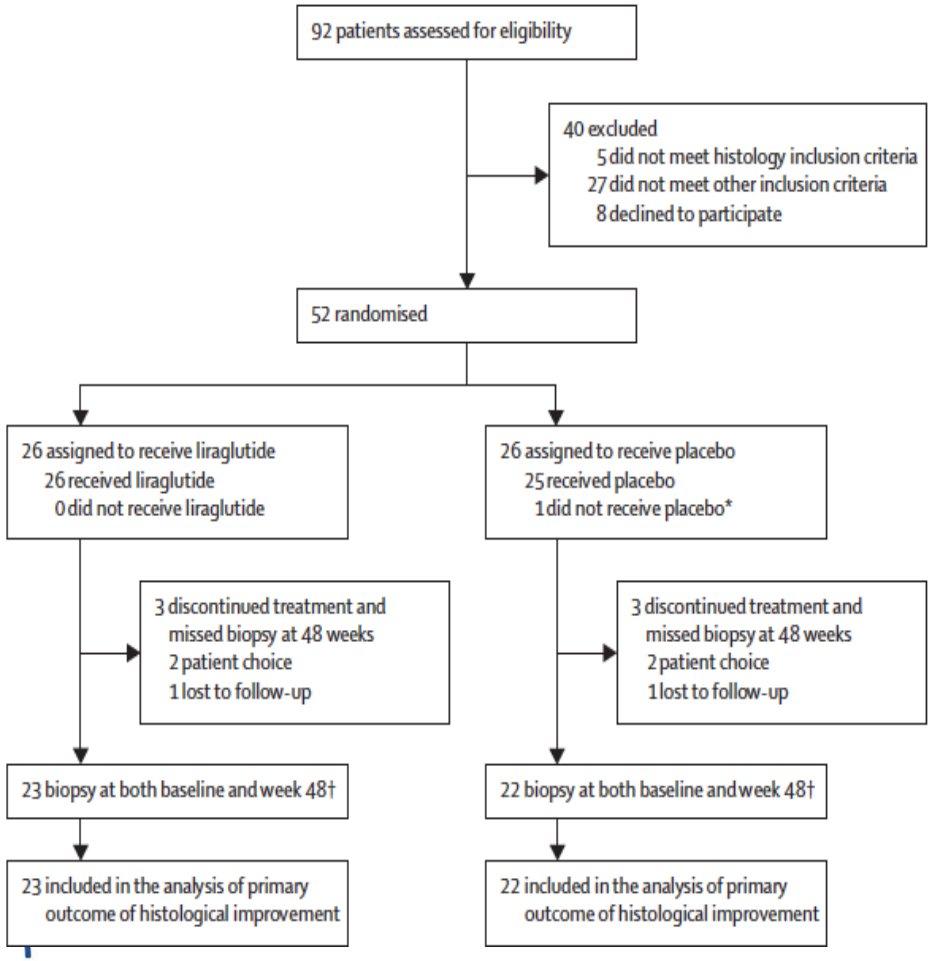
Reduced lipolysis

Reduced hepatic DNL

Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study

Matthew James Armstrong, Piers Gaunt, Guruprasad P Aithal, Darren Barton, Diana Hull, Richard Parker, Jonathan M Hazlehurst, Kathy Guo, LEAN trial team, George Abouda, Mark A Aldersley, Deborah Stocken, Stephen C Gough, Jeremy W Tomlinson, Rachel M Brown, Stefan G Hübscher, Philip N Newsome*

Lancet 2016; 387: 679–90



Disappearance of ballooning without worsening of fibrosis

	Liraglutide	Placebo	Relative risks or mean changes (95% CI) from baseline to 48 weeks (liraglutide vs placebo)	p value*
Primary outcome				
Number of patients with paired liver biopsies	23	22	..	..
Patients with resolution of non-alcoholic steatohepatitis	9 (39%)	2 (9%)	4·3 (1·0 to 17·7)	0·019
Changes from baseline in histopathological parameters				
Total NAFLD activity score				
Change in score	−1·3 (1·6)	−0·8 (1·2)	−0·5 (−1·3 to 0·3)	0·24
Patients with improvement	17 (74%)	14 (64%)	1·2 (0·8 to 1·7)	0·46
Hepatocyte ballooning score				
Mean change	−0·5 (0·7)	−0·2 (0·6)	−0·3 (−0·7 to 0·1)	0·15
Patients with improvement	14 (61%)	7 (32%)	1·9 (1·0 to 3·8)	0·05
Steatosis				
Change in score	−0·7 (0·8)	−0·4 (0·8)	−0·2 (−0·6 to 0·2)	0·32
Patients with improvement	19 (83%)	10 (45%)	1·8 (1·1 to 3·0)	0·009
Lobular inflammation				
Change in score	−0·2 (0·6)	−0·2 (0·5)	−0·01 (−0·3 to 0·3)	0·97
Patients with improvement	11 (48%)	12 (55%)	0·9 (0·5 to 1·6)	0·65
Kleiner fibrosis stage				
Change in score	−0·2 (0·8)	0·2 (1·0)	−0·4 (−0·8 to 0·1)	0·11
Patients with improvement	6 (26%)	3 (14%)	1·9 (0·5 to 6·7)	0·46†
Patients with worsening	2 (9%)	8 (36%)	0·2 (0·1 to 1·0)	0·04†

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≅ 35% of patients with T2DM

Table 1 | **Medical treatment modalities in NASH and T2DM**

Intervention	Metformin	GLP-1	Thiazolidinediones	SGLT2 inhibitors	DPP4 inhibitors	Sulphonylurea	Insulin
Glucose lowering efficacy	++	++	+ or ++	+ or ++	+	+++	+++
Hypoglycaemia risk	Low	Low	Low	Low	Low	High	High
Effect on body weight	Loss	Loss	Gain	Loss	Neutral	Gain	Gain
Adverse effects	Gastrointestinal	Gastrointestinal	• Oedema • Heart failure • Fractures	• Genitourinary infections • Dehydration	Pancreatic	Hypoglycaemia	Hypoglycaemia
Liver-specific effects							
Steatosis	NE	↓	↓	?	?	NE	↑
Inflammation	NE	↓	↓	?	?	?	?
Hepatocyte ballooning	NE	↓	↓	?	?	?	?
Fibrosis	NE	NE	?	?	?	?	?
RCTs showing effectiveness in NAFLD	NE	Liraglutide	Pioglitazone (Rosiglitazone)	ND	ND	ND	ND

Diet and exercise should be advised for all patients, and continued throughout medical treatments. DPP4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; ND, not done; NE, no effect; RCT, randomized controlled trial; SGLT2, sodium glucose co-transporter 2.

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Tilg H. et al. Nat Rev Gastroenterol Hepatol 2017; 14: 32-43

AGENDA

1. EPIDEMIOLOGICAL DATA

2. PATHOPHYSIOLOGICAL DATA

3. GENETIC DATA

4. THERAPEUTIC DATA

5. CONCLUDING REMARKS

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TAKE HOME MESSAGES

- NAFLD is the « liver » feature of Metabolic syndrome (Met-S)

- **Selective hepatic insulin resistance** is the main underlying molecular common driver for both NAFLD and Met-S

- Interventions should target insulin resistance (« **insulin sensitizers** »)

- A tight **collaboration between diabetologists & hepatologists** is required
  - Hepatologists for screening Met-S and T2D in patients with NAFLD
  - Diabetologists for screening NAFLD and NASH in patients with T2D

- Genetics tell us that we need **« Precision Medicine »** to stratify NAFLD (*rs738409 PNPLA3 vs other)* and optimize therapeutic management

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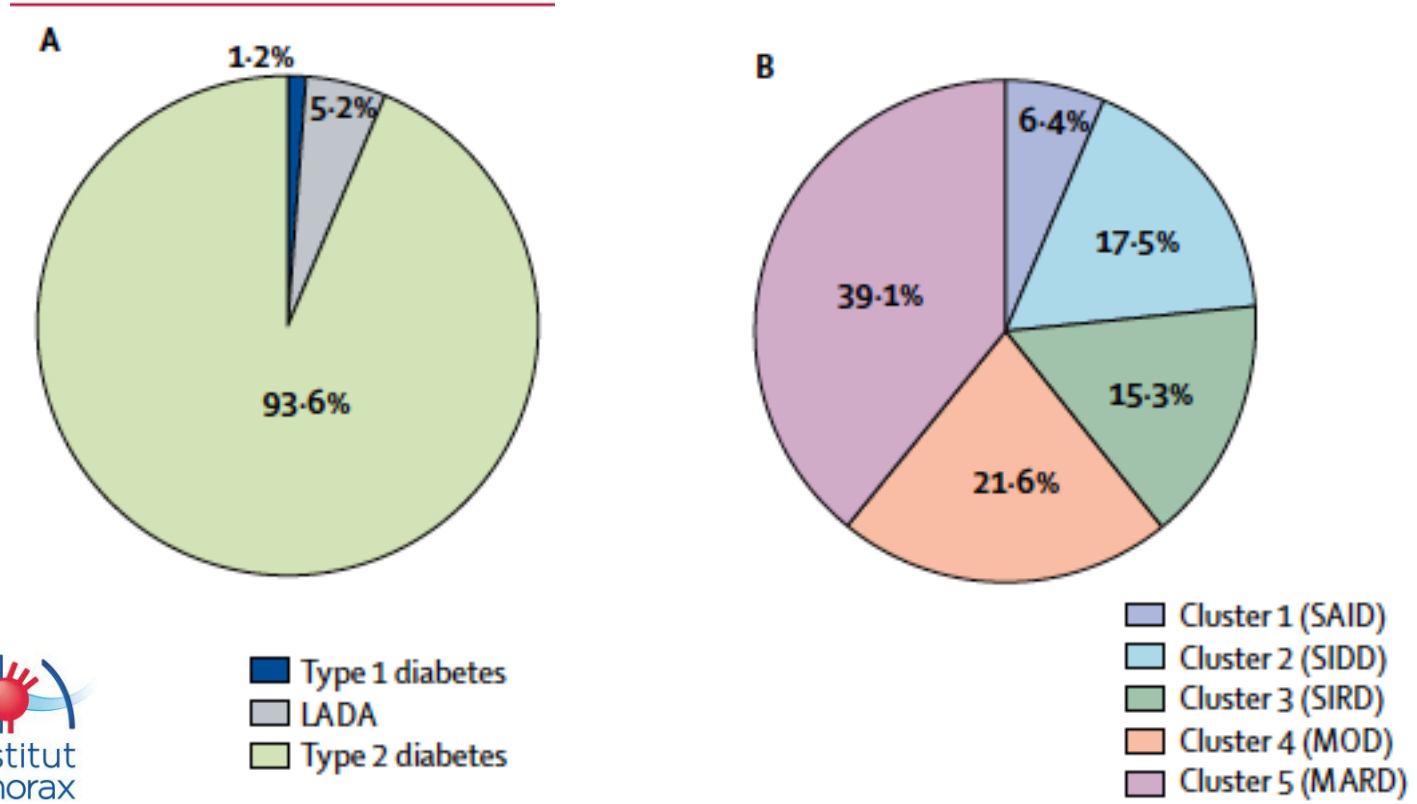
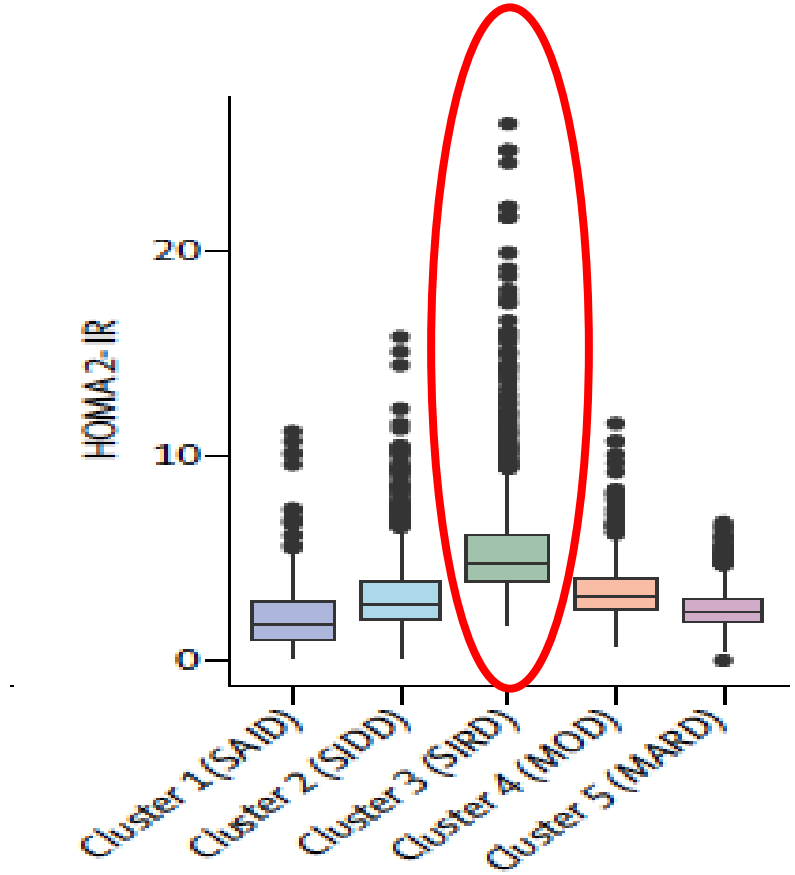
Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables

Emma Ahlqvist, Petter Storm, Annemari Käräjämäki, Mats Martinell*, Mozhgan Dorkhan, Annelie Carlsson, Petter Vikman, Rashmi B Prasad, Dina Mansour Aly, Peter Almgren, Ylva Wessman, Nael Shaat, Peter Spégel, Hindrik Mulder, Eero Lindholm, Olle Melander, Ola Hansson, Ulf Malmqvist, Åke Lernmark, Kaj Lahti, Tom Forsén, Tiinamaija Tuomi, Anders H Rosengren, Leif Groop*

Cluster-analysis with 6 variables: GAD antibodies, age at diagnosis, BMI, HbA1C, HOMA-IR & HOMA-B





Lancet Diabetes Endocrinol 2018; 6: 361–69

Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables

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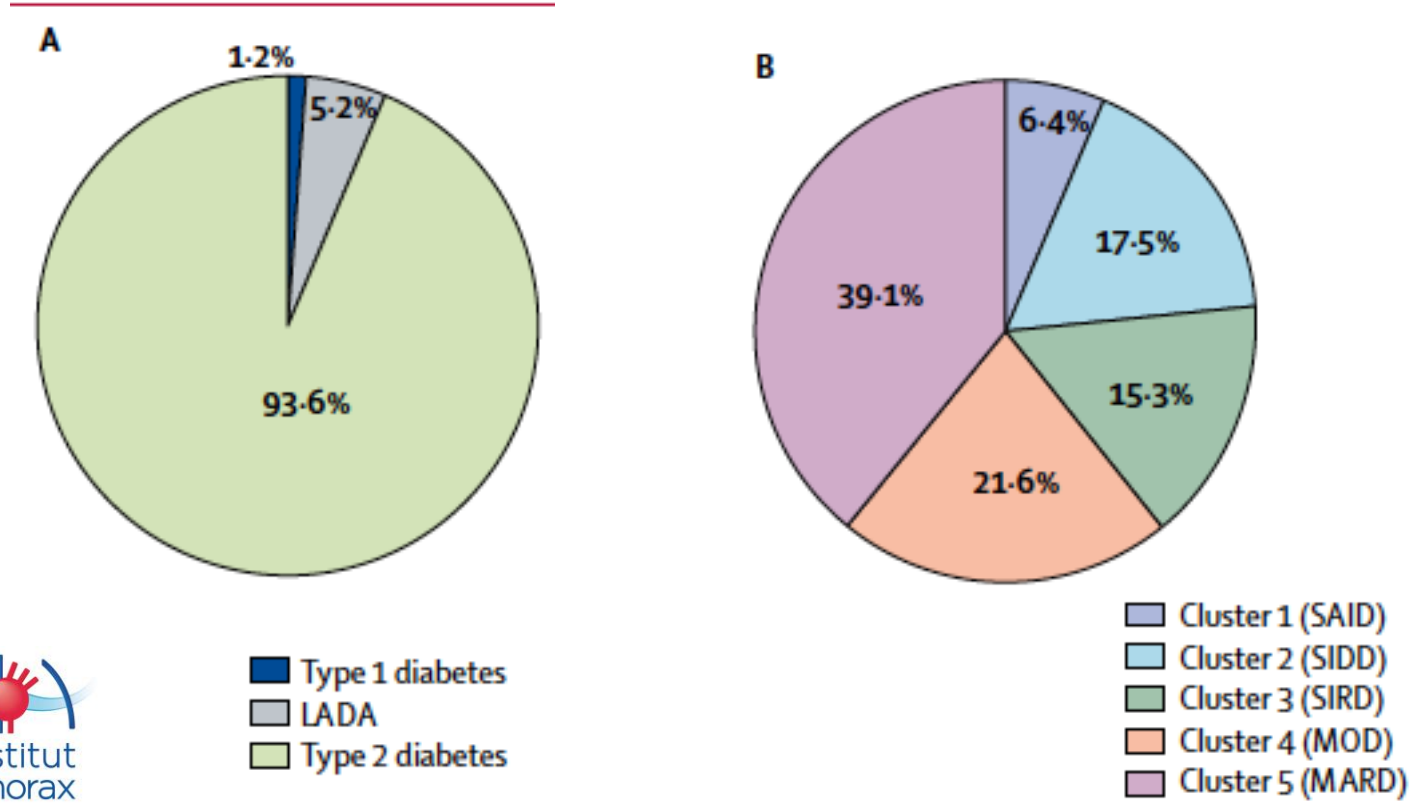
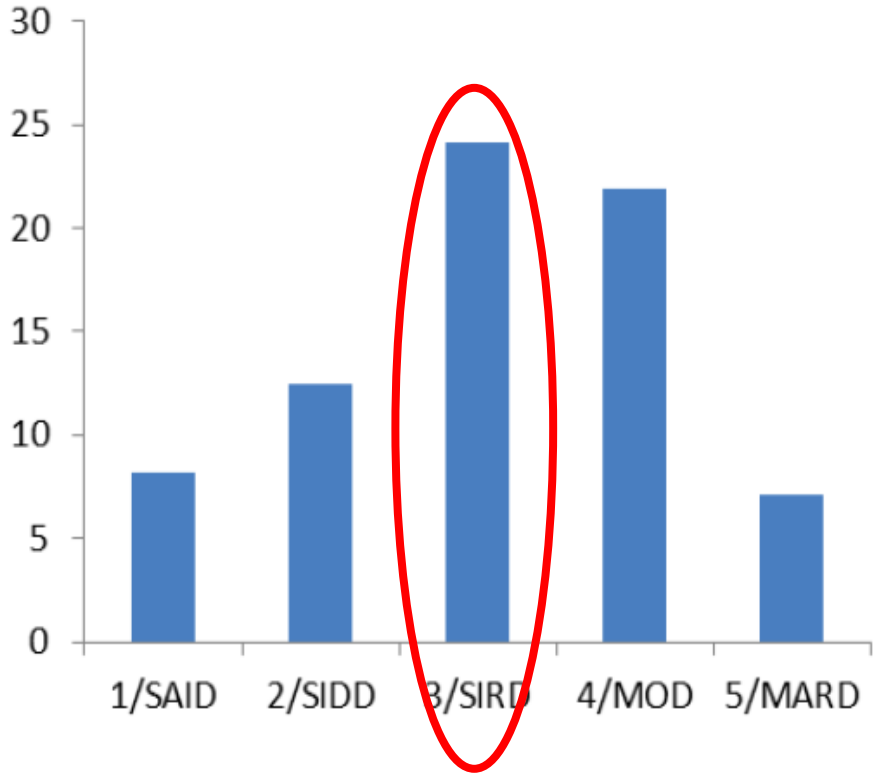
Cluster-analysis with 6 variables: GAD antibodies, age at diagnosis, BMI, HbA1C, HOMA-IR & HOMA-B



Prevalence of NAFLD in ANDIS estimated from ALT measurements



Lancet Diabetes Endocrinol 2018; 6: 361–69

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Paris NASH Meeting

International Think Tank

THANK YOU FOR YOUR ATTENTION

International Think Tank

Paris NASH Meeting

July 5 & 6, 2018
Institut Pasteur

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Arun Sanyal
Virginia Commonwealth University School of Medicine, Richmond, Virginia, USA

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