NAFLD and diabetes – causal association or epiphenomenon?

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- Prevalence of NAFLD in patients with diabetes; vice versa
- Risk for T2DM in NAFLD
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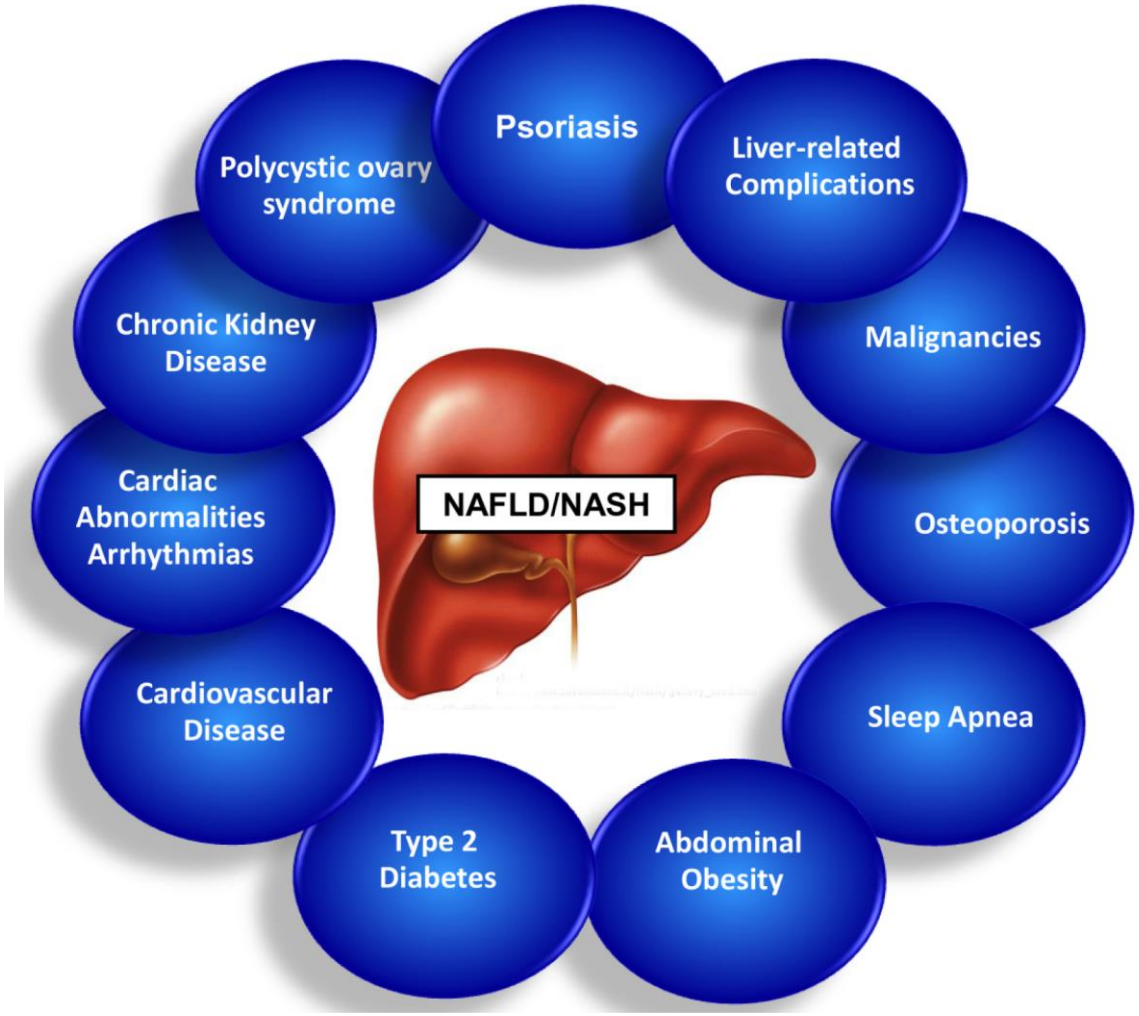
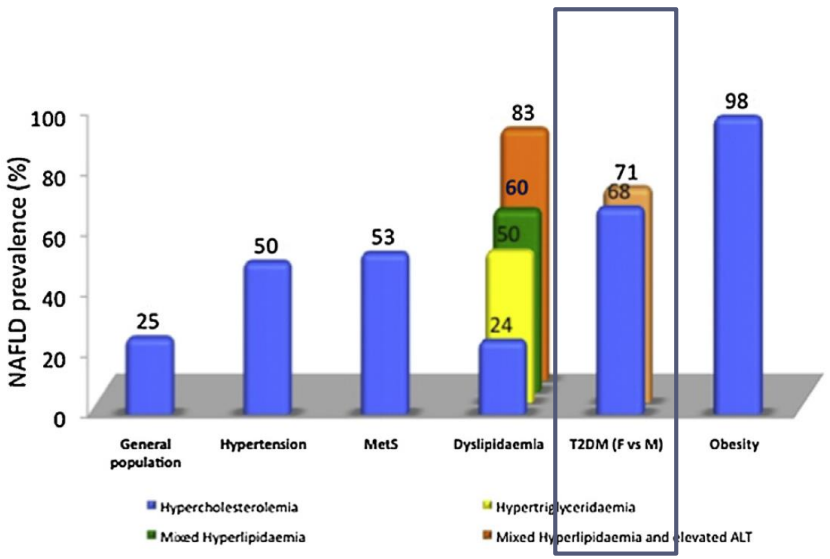
NAFLD: a multisystem disease



Adams LA et al. Gut, 2017

Prevalence of NAFLD in patients with diabetes

Known to be 50~75% in different ethnic groups



533/939 (56.9%) patients with type 2 diabetes

Table 2—*Comparison of participant characteristics across gradings of steatosis*

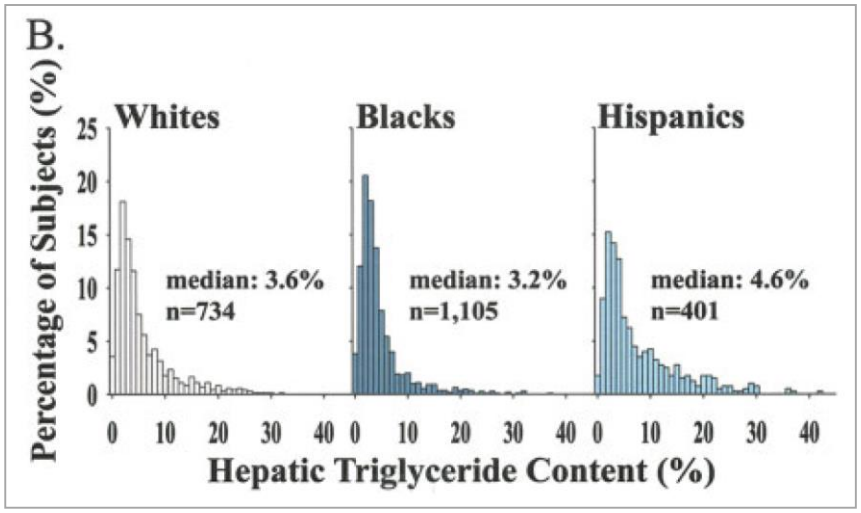
Characteristic	Steatosis grade			
	Grade 0 (n = 220)	Grade 1 (n = 22)	Grade 2 (n = 158)	Grade 3 (n = 533)
Age (years)	69.4 ± 4.2	68.5 ± 4.8	69.5 ± 4.4	68.5 ± 4.0*
Sex, % (n) male	59.9 (132)	40.9 (9)	49.4 (78)	50.1 (267)
BMI measured at baseline clinic (kg/m^2)	28.8 ± 5.18	35.1 ± 8.4	30.7 ± 4.9	32.4 ± 5.5*
Waist circumference (cm)	102.4 ± 13.5	112.6 ± 18.7	104.7 ± 11.6	108.9 ± 12.0*
Duration of diabetes (years)	9.6 ± 7.6	10.5 ± 6.0	9.8 ± 6.5	8.4 ± 5.8*
HbA_{1c} (%)	7.02 ± 0.97	7.15 ± 0.93	6.99 ± 0.98	7.33 ± 1.12*
Systolic blood pressure (mmHg)	140.1 ± 21.5	141.2 ± 22.4	135.9 ± 18.6	137.9 ± 16.7
Diastolic blood pressure (mmHg)	73.4 ± 9.5	76.3 ± 11.2	72.1 ± 9.5	74.9 ± 9.4*
Total cholesterol (mmol/L)	4.14 ± 0.81	4.53 ± 0.81	4.01 ± 0.75	4.17 ± 0.82
HDL cholesterol (mmol/L)	1.28 ± 0.69	1.16 ± 0.27	1.30 ± 0.35	1.19 ± 0.32*
LDL cholesterol (mmol/L)	2.24 ± 0.70	2.57 ± 0.72	2.08 ± 0.65	2.14 ± 0.67
Triglyceride (mmol/L)	1.37 ± 0.69	1.76 ± 0.67	1.37 ± 0.63	1.86 ± 1.00*
Metabolic syndrome, % (n) present	70.2 (153)	86.4 (19)	78.3 (123)	91.2 (485)*
Alcohol intake, % (n) over 14 units/week	6.4 (14)	0.0 (0)	7.6 (12)	12.9 (69)*
Metformin use, % (n)	48.2 (106)	50.0 (11)	63.3 (100)	70.9 (378)*

Data are mean ± SD unless otherwise indicated. *Significant difference grade 3 vs. grade 0/1/2 by t test or χ^2 test, $P < 0.05$.

Lonardo A et al. Dig Liver Dis, 2015

Prevalence of diabetes in subjects with hepatic steatosis in an urban population in USA:

- In 2287 subjects from Dallas Heart Study
- Hepatic TG content measured by H-NMR spectroscopy



Prevalence of T2DM or IFG is 18~33% in patients with NAFLD

Table 3. Comparison of Subjects with Normal and Elevated Hepatic Triglyceride Content in the DHS Population

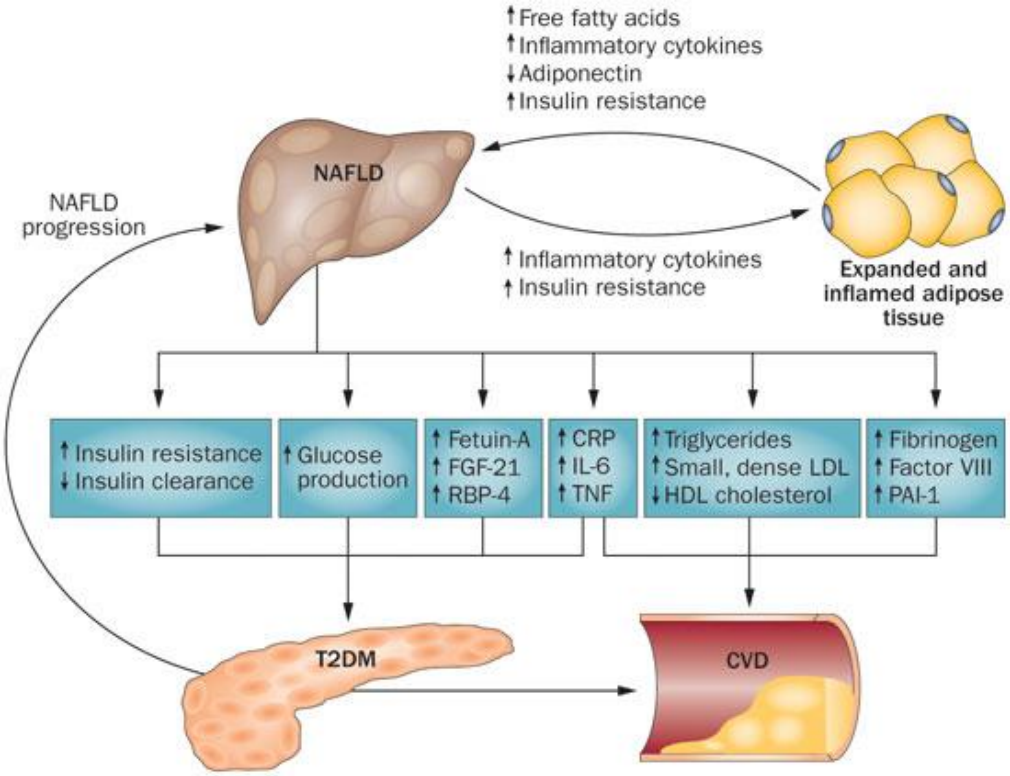
Characteristic	Normal Hepatic Triglyceride Content (<5.5%) (n = 1,579)	Elevated Hepatic Triglyceride Content (>5.5%) (n = 708)	*P* Value
Age (yr)	45 ± 9	46 ± 10	.003
Sex (M/F ratio)	0.8:1	1.1:1	.003
Obesity (%) BMI > 30 kg/m^2	33	67	<.001
DM and/or IFG (%) Glucose > 110 mg/dL	11	18	<.001
Insulin resistance IR_{HOMA} ≥ 4.04 (%)	23	58	<.001
Lipid abnormalities (%) TG > 150 mg/dL; HDL: M < 40 mg/dL, F < 50	40	64	<.001
Metabolic syndrome* (%)	8	30	<.001
Ethnicity (%)			
White	67	33	<.001
Black	76	24	<.001
Hispanic	55	45	.003
Elevated ALT (%) M > 40 U/L; W > 31 U/L	9	21	<.001
Ethanol use (g/d)	6.3 ± 15.6	6.6 ± 15.3	NS

18%

Browning JD et al. Hepatology, 2004

NAFLD as the risk factor for T2DM

NAFLD and diabetes: bad but intimate friends to each other?

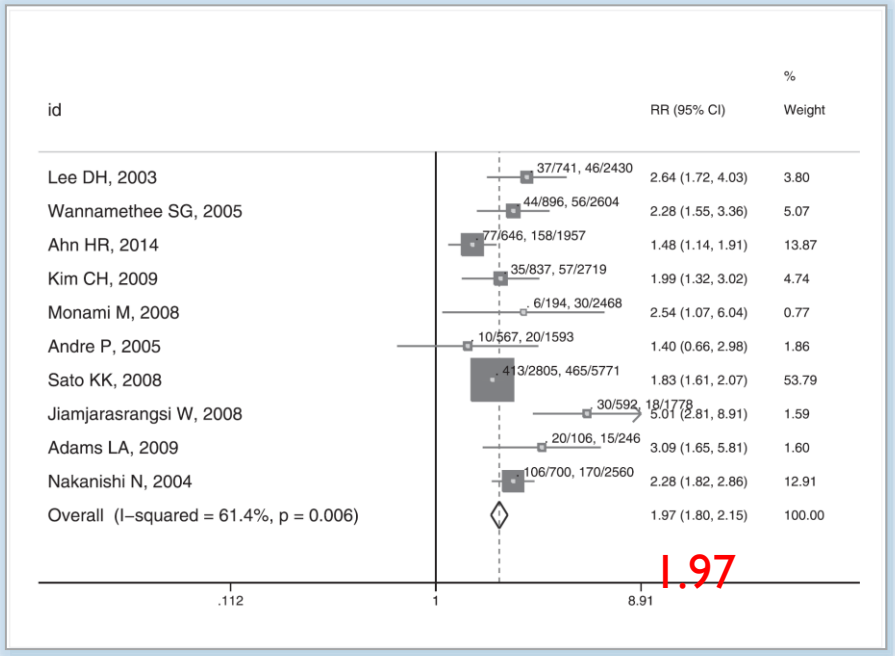


- Convincing evidence suggesting that NAFLD often precede the development of T2DM
- Conventional paradigm of NAFLD representing as the simple "hepatic manifestation" of MS is outdated..
- NAFLD regarded as an early predictor and determinant for development of diabetes

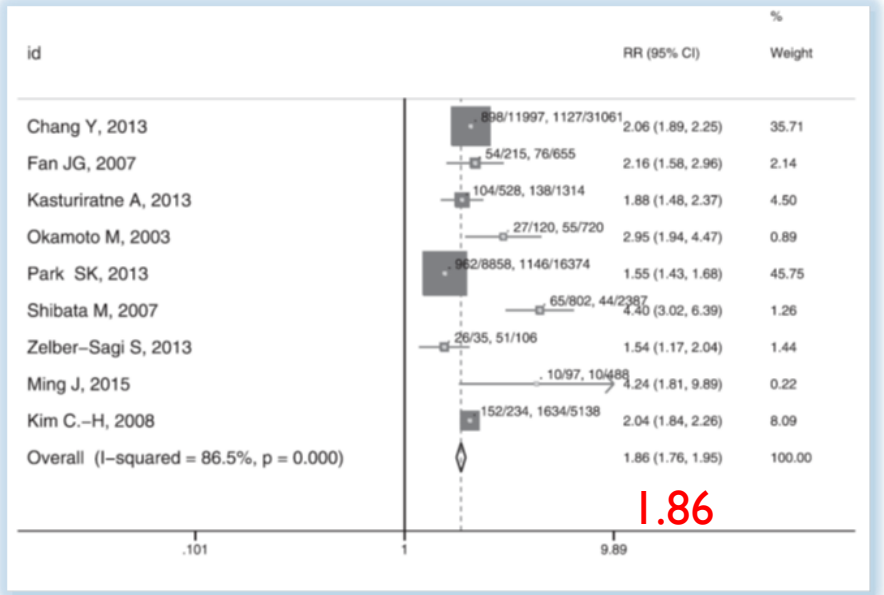
Anstee et al. Nat Rev Gastroenterol Hepatol, 2013

Risk of diabetes in NAFLD: Meta-analysis result

NAFLD defined by ALT elevation



NAFLD defined by USG



2-fold increase in diabetes risk in subjects with NAFLD

Ballestri S et al. J Gastroenterol Hepatol, 2016

Retrospective or prospective cohort studies examining NAFLD as a risk factor for incident type 2 diabetes

1.6~6.8-fold increase

Table 2 Retrospective or prospective cohort studies examining NAFLD (as detected either by ultrasonography or by CT) as a risk factor for incident T2DM

Authors, year (ref.)	Country	Sample size	Follow-up (median, years)	T2DM diagnosis	T2DM% at follow-up	Adjusted OR(s) (±95% CI)	Adjusted variables
Okamoto *et al*, 2003[124]	Japan	840	10.0	FBG ≥140 mg/dL (≥7.8 mmol/L) or HbA1c ≥6.5% or T2DM medications	14.1% (men) 4.3% (women)	1.8 (0.9 to 3.5)	Age, sex, BMI, weight gain, FBG, HbA1c, alcohol intake, family history of diabetes
Kim *et al*, 2008[122]	South Korea	5372	5.0	FBG ≥126 mg/dL (≥7.0 mmol/L) or T2DM medications or past history	4.3%	1.5 (1.1 to 2.2)	Age, sex, BMI, smoking, family history of diabetes, ALT, FBG, triglycerides, HDL-cholesterol
Yamada *et al*, 2010[128]	Japan	12 375	5.0	FBG ≥126 mg/dL or T2DM medications	1% (men) 0.5% (women)	1.9 (1.9 to 2.8) men 2.1 (2.5 to 4.7) women	Age, BMI, blood pressure, alcohol intake, smoking
Sung and Kim, 2011[127]	South Korea	11 091	5.0	Not reported	1.6%	2.05 (1.35 to 3.12)	Age, sex, BMI, alcohol, education, smoking, exercise
Chang *et al*, 2013[119]	South Korea	38 291	5.1	FBG ≥126 mg/dL or HbA1c ≥6.5% or T2DM medications	1.1% annual incidence	2.0 (1.8 to 2.2) for low NFS 4.7 (3.7 to 6.1) for intermediate/high NFS	Sex, smoking, alcohol intake, exercise, family history of diabetes, total cholesterol, triglycerides, HDL-cholesterol, CRP, HOMA-insulin resistance
Park *et al*, 2013[125]	South Korea	25 232 (men)	5.0	FBG ≥126 mg/dL or HbA1c ≥6.5% or T2DM medications or past history	8.4%	1.73 (1.00 to 3.01)	Age, waist circumference, triglycerides, HDL-cholesterol, CRP, HOMA-insulin resistance, creatinine, blood pressure, family history of diabetes, exercise, MetS
Shah *et al*, 2015[126]	USA	3153	9.1	FBG ≥126 mg/dL or T2DM medications or past history	6.9%	2.06 (1.52 to 2.79)*	Age, sex, race, BMI, waist circumference, family history of diabetes, blood pressure, FBG, HDL-cholesterol, triglycerides, exercise, CRP, statin use
Yamazaki *et al*, 2015[129]	Japan	4604	11.3	FBG ≥126 mg/dL or HbA1c ≥6.5% or T2DM medications or past history	6.1%	2.37 (1.60 to 3.52)	Age, sex, BMI, impaired fasting glycaemia, family history, dyslipidaemia, blood pressure, exercise
Ming *et al*, 2015[123]	China	508	5.0	FBG ≥126 mg/dL or 2-hour OGTT ≥200 mg/dL or T2DM medications	3.9%	4.46 (1.86 to 10.73)	Age, sex, BMI, education, smoking, alcohol intake, exercise, family history, blood pressure, FBG, HDL-cholesterol, triglycerides
Chen *et al*, 2016[120]	China	6542	6.0	FBG ≥126 mg/dL or T2DM medications or past history	5.6%	2.17 (1.53 to 3.01)*	Age, BMI, triglycerides, impaired fasting glycaemia status
Fukada *et al*, 2016[121]	Japan	4629	12.8	FBG ≥126 mg/dL or HbA1c ≥6.5% or T2DM medications	7.6%	3.6 (2.1 to 5.8) for lean 6.8 (5.2 to 8.9) for obese	Age, sex, smoking, alcohol intake, exercise, HbA1c, family history of diabetes

Adams LA et al. Gut, 2017

Fatty live as an independent risk factor ofr development of T2DM in Korean adults

In5,372 non-diabetic participants in health promotion center in Asan Medical Center in whom health checkup performed in 5 years' interval

	All patients			Excluding frequent drinkers		
	Relative risk	95% CI	*P*-value	Relative risk	95% CI	*P*-value
Model 1*						
Fatty liver, mild	2.78	2.03–3.81	< 0.001	3.21	1.88–5.45	< 0.001
Fatty liver, moderate to severe	5.04	3.56–7.12	< 0.001	8.47	4.93–14.58	< 0.001
Model 2†						
Fatty liver, mild	2.03	1.40–2.95	< 0.001	1.87	1.03–3.38	0.039
Fatty liver, moderate to severe	3.09	2.04–4.67	< 0.001	3.72	2.04–6.81	< 0.001
Model 3‡						
Fatty liver, mild	1.55	1.05–2.31	0.028	1.49	0.82–2.71	0.19
Fatty liver, moderate to severe	1.97	1.23–3.16	0.011	2.29	1.13–4.63	0.021

CI, confidence interval.
*Model 1: adjusted for sex, age.
†Model 2: adjusted for the factors in Model 1 + family history of diabetes, smoking, blood pressure, fasting glucose.
‡Model 3: adjusted for the factors in Model 2 + body mass index, serum alanine aminotransferase, high-density lipoprotein cholesterol, triglyceride levels.

Kim CH et al. Diab Med, 2008

Interrelationship between fatty liver and insulin resistance in development of T2DM

In 11,091 Koreans in KSHS in whom health checkup performed in 5 years' interval

TABLE 2. OR for T2DM at 5-yr follow-up

	T2DM [no./total no. (%)]		OR (95% confidence interval)		
	No fatty liver	Fatty liver	Unadjusted	Adjusted[a]	Adjusted[a] + baseline glucose
All	54/8120 (0.7%)	120/2971 (4%)	6.29 (4.55-8.69)	3.24 (2.19-4.78)	2.05 (1.35-3.12)
Insulin					
Quartile 1	13/2468 (0.5%)	8/307 (2.6%)	5.05 (2.08-12.29)	3.47 (1.23-9.79)	1.96 (0.63-6.13)
Quartile 2	16/2262 (0.7%)	6/511 (1.2%)	1.67 (0.65-4.28)	1.34 (0.46-3.87)	0.71 (0.22-2.26)
Quartile 3	11/2002 (0.6%)	22/768 (2.9%)	5.34 (2.58-11.06)	3.74 (1.59-8.84)	2.92 (1.12-7.62)
Quartile 4	14/1388 (1.0%)	84/1385 (6.1%)	6.34 (3.58-11.21)	3.31 (1.76-6.20)	2.42 (1.23-4.75)

[a] Adjusted for age, gender, BMI, alcohol (grams per day), education (<16 yr, ≥ 16 yr), smoking (never or past, current), and exercise (<1 time/wk, ≥1 time/wk).

Sung KC et al. JCEM, 2011

Resolution of fatty liver and risk for incident diabetes

- In 13,218 non-diabetic participants in KSHS
- Incident diabetes assessed 5 years follow-up
- Divided into groups according to FL status at baseline and 5 years after

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

Sung KC et al. JCEM, 2013

Incident association between improvement of NAFLD and reduced incidence of T2DM

In 4,604 participants in health checkup twice with > 10 years interval

Table 3—ORs and 95% CIs for the association between NAFLD improvement and T2DM incidence among participants with NAFLD at the first examination, stratified by BMI change

	Participants with NAFLD at baseline (*n* = 728)				BMI increase (*n* = 438)		BMI decrease (*n* = 290)	
	Crude		Multivariate adjusted		Multivariate adjusted		Multivariate adjusted	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
NAFLD improvement	0.31 (0.14–0.69)	0.0042	0.27 (0.12–0.61)	0.0017	0.40 (0.051–3.10)	0.38	0.18 (0.069–0.46)	<0.001
Age (continuous)*	—	—	1.03 (1.00–1.07)	0.040	1.06 (1.02–1.11)	0.0053	1.00 (0.95–1.05)	0.91
Women*	—	—	1.00 (0.54–1.87)	1.00	1.15 (0.50–2.61)	0.74	0.71 (0.25–1.98)	0.51
BMI (continuous)*	—	—	1.06 (0.98–1.15)	0.13	1.07 (0.97–1.18)	0.19	1.05 (0.93–1.19)	0.46
IFG*	—	—	3.25 (2.08–5.07)	<0.001	2.24 (1.25–4.01)	0.0069	6.21 (2.84–13.58)	<0.001
Family history of diabetes*	—	—	2.28 (1.40–3.71)	0.0010	2.19 (1.13–4.26)	0.021	2.27 (1.05–4.92)	0.038
DL*	—	—	1.77 (1.08–2.89)	0.024	2.06 (1.04–4.07)	0.038	1.63 (0.77–3.45)	0.20
HT*	—	—	0.99 (0.59–1.65)	0.96	1.14 (0.59–2.20)	0.71	0.79 (0.33–1.88)	0.59
Physical exercise*	—	—	0.92 (0.44–1.93)	0.82	0.90 (0.32–2.51)	0.84	1.38 (0.44–4.34)	0.58
Physical exercise at follow-up	—	—	0.64 (0.36–1.16)	0.14	0.73 (0.31–1.70)	0.46	0.48 (0.20–1.11)	0.087

The risk of NOD diminish over time following the improvement or resolution of NAFLD

Yamazaki H et al. Diabetes Care, 2015

Combined influence of IR, overweight/obesity and fatty liver as risk factor for type 2 diabetes

In 12,853 non-diabetic participants in KSHS; IR, weight and fatty liver by USG

Table 3—*OR for incident diabetes at follow-up for different combinations of IR, overweight/obesity, and fatty liver*

	n/proportions with incident diabetes (%)	OR [95% CI] *P*		
		Model 1	Model 2	Model 3
Whole cohort	223/12,853 (1.7)			
No risk factors	26/6,324 (0.4)	1	1	1
IR alone	14/945 (1.5)	3.95 [2.05–7.61] <0.001	4.06 [2.10–7.82] <0.001	3.66 [1.89–7.08] <0.001
Overweight/obesity alone	10/1,434 (0.7)	1.46 [0.70–3.05] 0.310	1.39 [0.67–2.90] 0.382	1.29 [0.62–2.71] 0.50
Fatty liver alone	13/850 (1.5)	3.28 [1.67–6.44] <0.001	3.36 [1.71–6.60] <0.001	2.73 [1.38–5.41] 0.004
IR and overweight/obesity	21/595 (3.5)	7.78 [4.33–13.96] <0.001	7.51 [4.18–13.50] <0.001	6.16 [3.38–11.22] <0.001
IR and fatty liver	15/388 (3.9)	8.42 [4.40–16.09] <0.001	8.73 [4.56–16.71] <0.001	6.73 [3.49–12.97] <0.001
Overweight/obesity and fatty liver	20/1,032 (1.9)	4.07 [2.25–7.38] <0.001	4.03 [2.22–7.30] <0.001	3.23 [1.78–5.89] <0.001
IR, overweight/obesity, and fatty liver	104/1,285 (8.1)	18.27 [11.72–28.46] <0.001	18.27 [12.00–29.21] <0.001	14.13 [8.99–22.2] <0.001

Model 1 adjusted for age and sex. Model 2 adjusted for age, sex, alcohol, smoking status, exercise, and educational status. Model 3 adjusted for age, sex, alcohol, smoking status, exercise, educational status, triglyceride, and ALT.

- Those with **IR, overweight/obesity and fatty liver** separately doubled the risk of type 2 diabetes
- When these three occurred together, the risk increased 14-fold!!!

Sung KC et al. Diabetes Care, 2012

Combined effect of NAFLD and IFG on development of T2DM

In 7,849 subjects without diabetes; annual check-up for 5 years

Table 1—*HRs of incident diabetes for the NAFLD and non-NAFLD groups according to the presence of IFG and combined effects of NAFLD with IFG on the development of diabetes*

	NFG (n = 5,800)			IFG (n = 2,049)		
Variable	Non-NAFLD	NAFLD	*P*	Non-NAFLD	NAFLD	*P*
Subjects (*N*)	4,353	1,447		1,204	845	
Subjects who developed diabetes, *n* (%)	66 (1.5)	47 (3.2)		142 (11.8)	180 (21.3)	
Person-years of follow-up	17,363	5,773		4,646	3,155	
Incident case of diabetes per 100 person-years (*n*)	0.4	0.8		3.1	5.7	
Adjusted HR (95% CI)*						
Age and sex	1 (reference)	2.01 (1.35–2.98)	0.001	1 (reference)	1.86 (1.48–2.33)	<0.001
Age, sex, BMI, TG, HDL-C, and systolic BP	1 (reference)	1.37 (0.87–2.18)	0.167	1 (reference)	1.31 (1.02–1.69)	0.035
Multivariate†	1 (reference)	1.39 (0.88–2.23)	0.148	1 (reference)	1.30 (1.02–1.68)	0.037
Adjusted HR (95% CI)*						
Age and sex	1 (reference)	2.03 (1.39–2.97)		7.52 (5.60–10.09)	13.97 (10.43–18.71)	
Age, sex, BMI, TG, HDL-C, and systolic BP	1 (reference)	1.37 (0.92–2.04)		6.68 (4.95–9.00)	8.83 (6.41–12.16)	
Multivariate†	1 (reference)	1.39 (0.93–2.08)		6.79 (5.03–9.16)	8.95 (6.49–12.35)	

Compared with those without IFG and NAFLD, those with IFG and NAFLD showed 9-fold increased risk for T2DM !!

Bae JC et al. Diabetes care, 2011

Additive effect of NAFLD on the development of diabetes in individuals with MetS

In7,849 participants in KSHS in whom health checkup was performed in 5 consecutive years

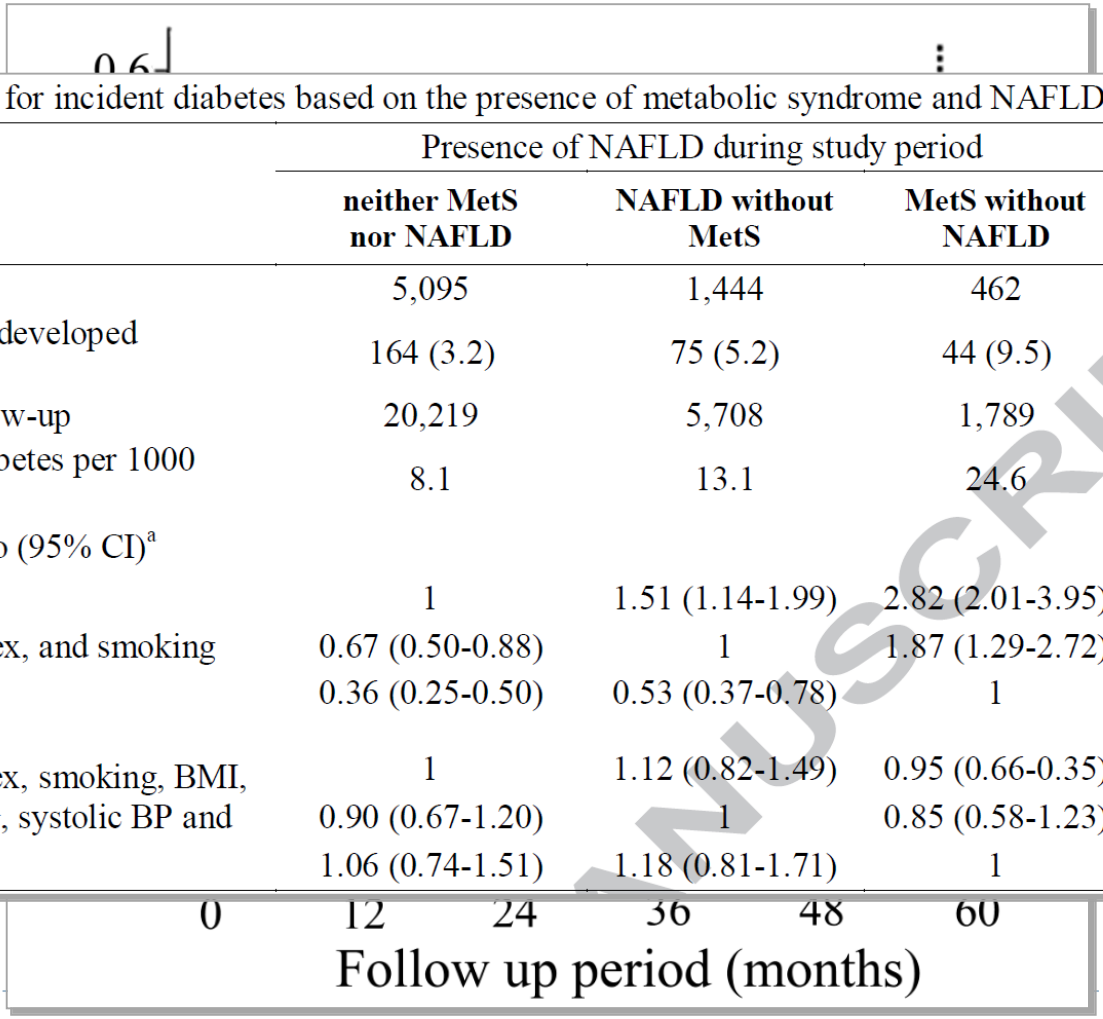


Table 2 Hazard ratio for incident diabetes based on the presence of metabolic syndrome and NAFLD

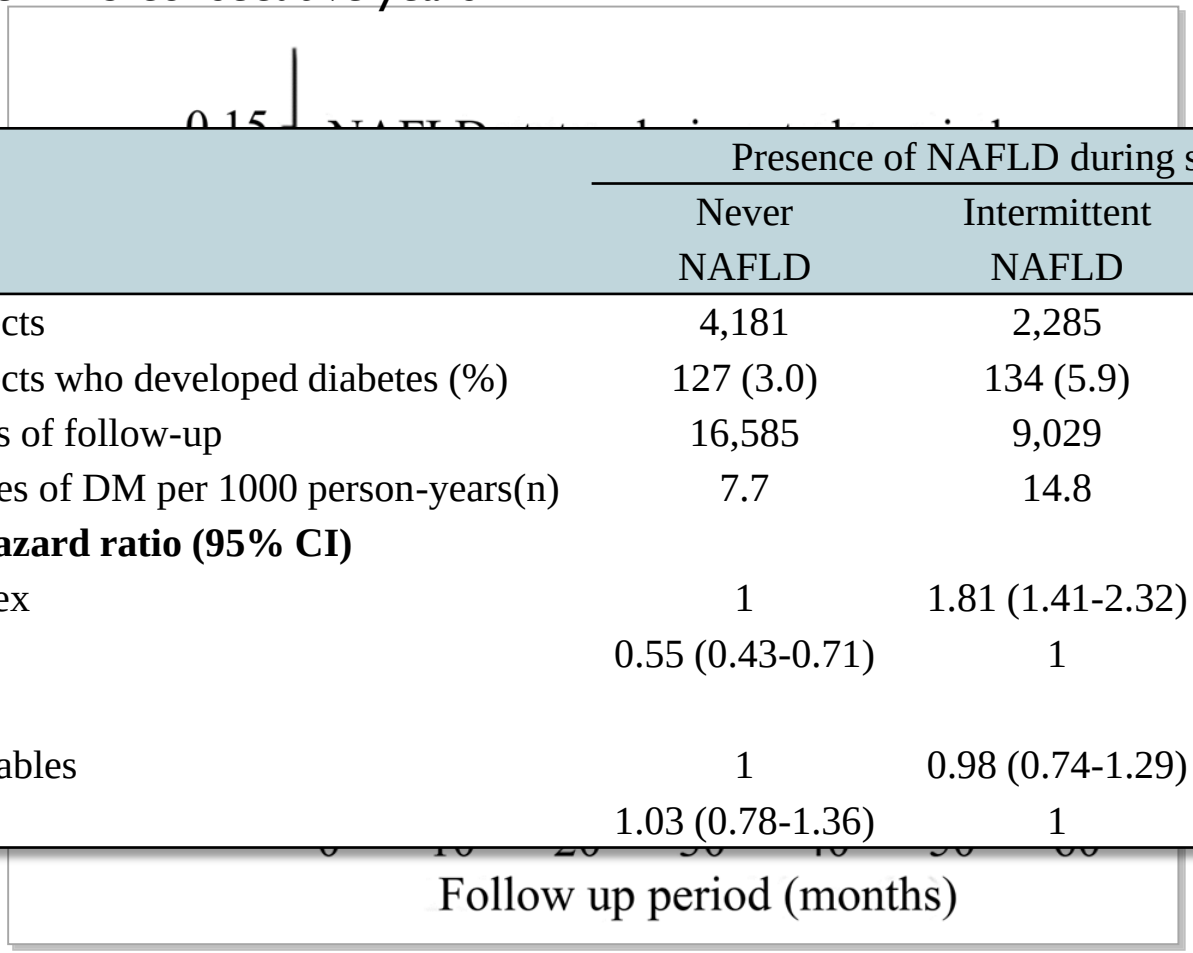
Variable	Presence of NAFLD during study period			
	neither MetS nor NAFLD	**NAFLD without MetS**	**MetS without NAFLD**	**Both MetS and NAFLD**
No. of subjects	5,095	1,444	462	848
No. of subjects who developed diabetes (%)	164 (3.2)	75 (5.2)	44 (9.5)	152 (17.9)
Person-years of follow-up	20,219	5,708	1,789	3,219
Incident cases of diabetes per 1000 person-years (n)	8.1	13.1	24.6	47.2
Adjusted hazard ratio (95% CI)[a]				
	1	1.51 (1.14-1.99)	2.82 (2.01-3.95)	5.45 (4.32-6.82)
Adjusted for age, sex, and smoking	0.67 (0.50-0.88)	1	1.87 (1.29-2.72)	3.62 (2.74-4.77)
	0.36 (0.25-0.50)	0.53 (0.37-0.78)	1	1.93 (1.38-2.71)
	1	1.12 (0.82-1.49)	0.95 (0.66-0.35)	1.45 (1.08-1.95)
Adjusted for age, sex, smoking, BMI, fasting glucose, TG, systolic BP and HDL-C	0.90 (0.67-1.20)	1	0.85 (0.58-1.23)	1.30 (0.97-1.75)
	1.06 (0.74-1.51)	1.18 (0.81-1.71)	1	1.53 (1.09-2.16)

MANUSCRIPT

Bae JC et al. DRCP, in press

The persistence of fatty liver status is important factor for an independent association between NAFLD and incident diabetes

In 7,849 on-diabetic participants in KSHS in whom annual health checkup was performed in 5 consecutive years



Variable	Presence of NAFLD during study period[a]		
	Never NAFLD	Intermittent NAFLD	Continuous NAFLD
No. of subjects	4,181	2,285	1,383
No. of subjects who developed diabetes (%)	127 (3.0)	134 (5.9)	174 (12.6)
Person-years of follow-up	16,585	9,029	5,321
Incident cases of DM per 1000 person-years(n)	7.7	14.8	32.7
Adjusted hazard ratio (95% CI)			
Age and sex	1	1.81 (1.41-2.32)	3.98 (3.12-5.02)
	0.55 (0.43-0.71)	1	2.18 (1.74-2.74)
Multi variables	1	0.98 (0.74-1.29)	1.55 (1.16-2.01)
	1.03 (0.78-1.36)	1	1.58 (1.25-1.99)

Bae JC et al. Metabolism, in review

Incidence rate of T2DM increased with severity of NAFLD

In 25,232 Korean men in KSHS without diabetes; followed up for 5 years

Table 2. Hazard ratios (HRs) and 95% confidence intervals (CI) for the incidence of type 2 DM according to NAFLD categories

	Person-year	Incidence cases	Incidence density (per 1,000 person-year)	Hazard ratios (95% Confidence Interval)		
				Unadjusted	Model 1	Model 2
NAFLD						
Normal	61,936.4	1,146	18.5	1.00 (reference)	1.00 (reference)	1.00 (reference)
Mild	28,942.3	758	26.2	1.42 (1.30-1.56)	1.30 (1.04-1.62)	1.09 (0.81-1.48)
Moderate to severe	4,291.6	204	47.5	2.58 (2.22-2.99)	1.64 (1.06-2.53)	1.73 (1.00-3.01)
P for trend				<0.001	<0.001	<0.001
Age					1.03 (1.02-1.04)	1.03 (1.01-1.05)
WC					1.00 (0.98-1.01)	0.99 (0.97-1.01)
Triglyceride					1.00 (1.00-1.01)	1.00 (1.00-1.01)
HDL-cholesterol					1.00 (0.99-1.01)	1.01 (0.99-1.02)
Systolic BP					1.01 (1.00-1.01)	1.00 (1.00-1.01)
Log(hsCRP)					1.10 (1.00-1.21)	1.03 (0.90-1.17)
Log(HOMA-IR)					3.26 (2.48-4.30)	2.63 (1.78-3.88)
Serum creatinine					1.38 (0.61-3.13)	2.33 (0.75-7.31)
Family history of diabetes						1.76 (1.35-2.29)
Regular exercise						0.88 (0.63-1.23)
MetS						1.79 (1.26-2.54)

Model 1 was adjusted for age, WC, triglyceride, HDL-cholesterol, systolic BP, log(hsCRP), log(HOMA-IR) and serum creatinine.
Model 2 was adjusted for model 1 plus family history of diabetes, regular exercise and MetS.

Park SK et al. Hepatology, 2013

Increased risk of T2DM in subjects with both elevated liver enzyme and NAFLD

In 7,849 subjects without diabetes; annual check-up for 5 years

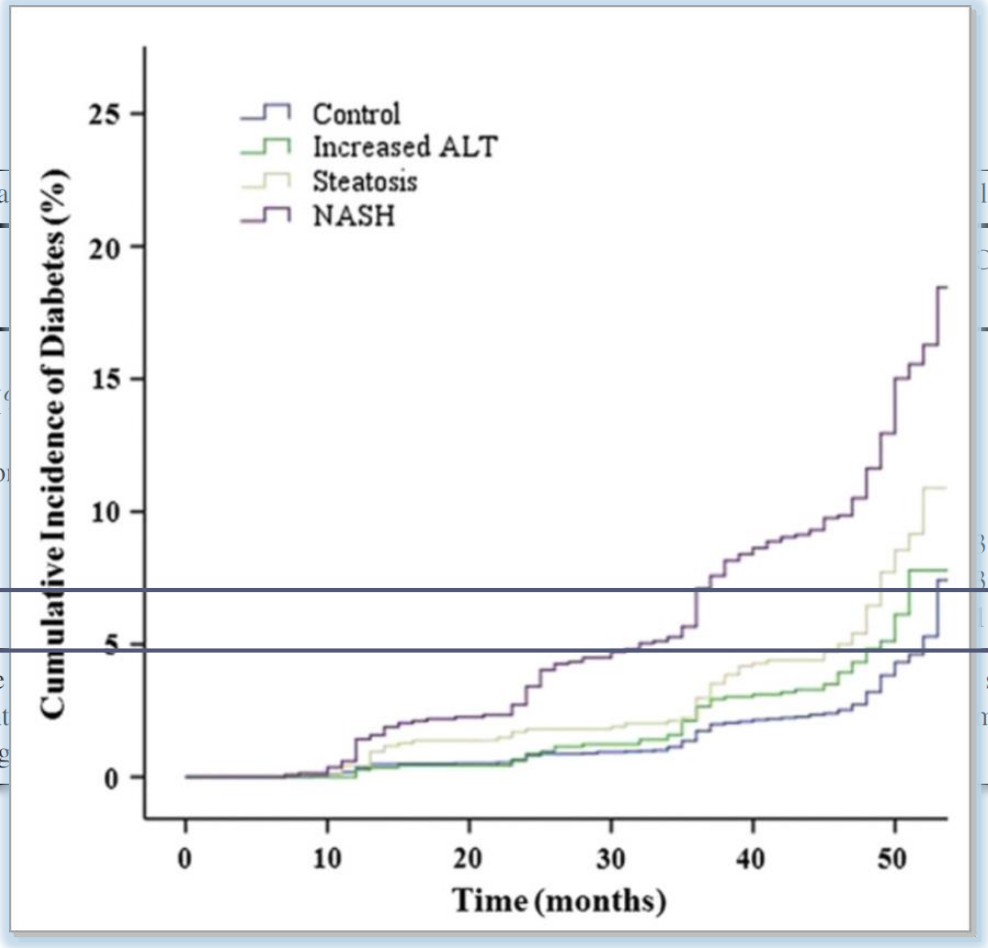


Table 2. Risk of incidence of dia ... ltrasonographic steatosis at baseline

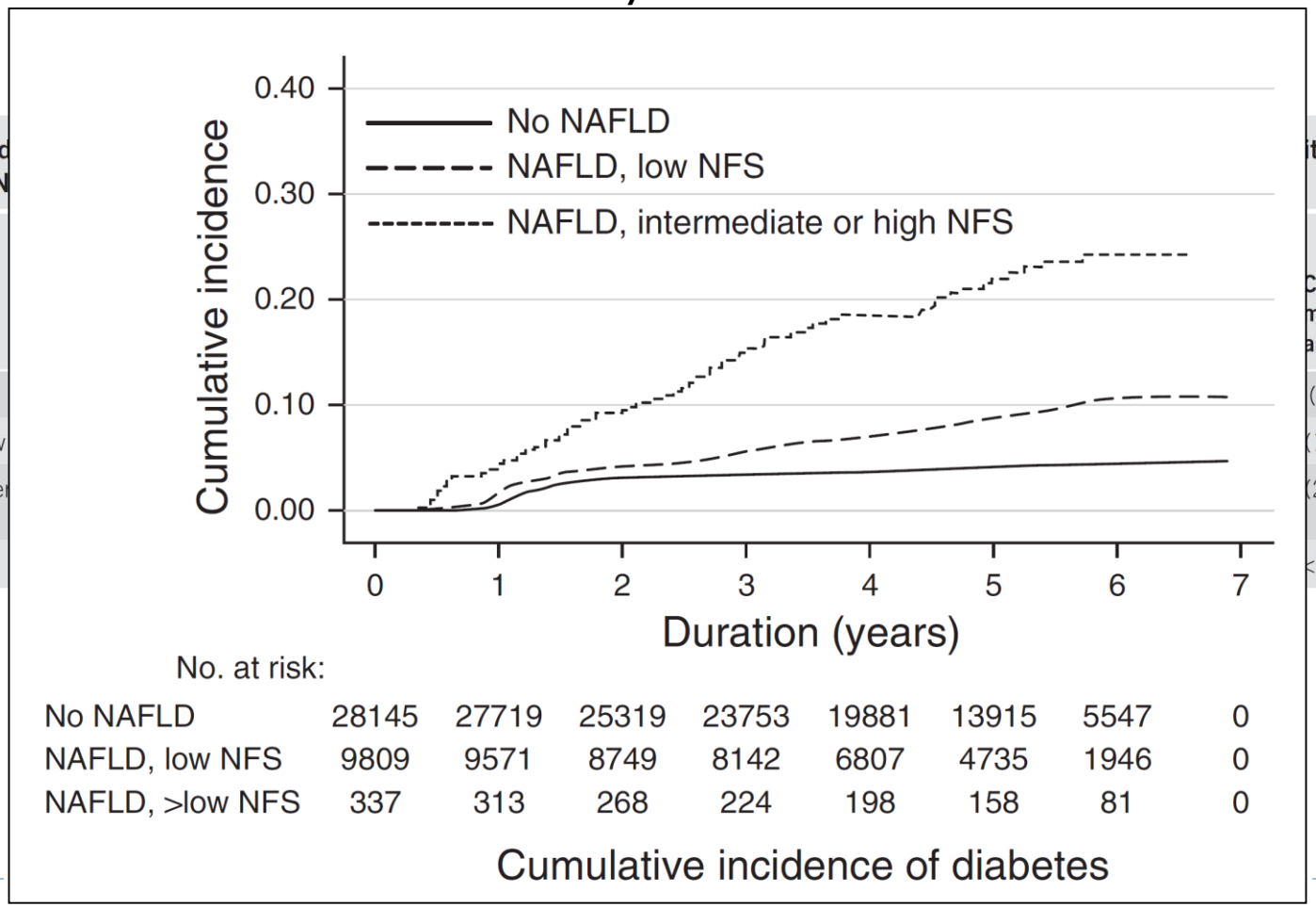
		Combined abnormality (n = 1341)	p for trend
No. of incident diabetes		158	
Proportion of incident diabetes (%		11.8	
Case/person−years		5159	
Incidence density (per 100 perso		3.06	
Adjusted hazard ratio (95% CI)			
Model 1		3.33 (2.65−4.18)	<0.001
Model 2		3.33 (2.65−4.19)	<0.001
Model 3		1.64 (1.27−2.13)	<0.001

Model 1, after adjustment for age ... smoking status and alcohol intake); and model 3, after further adjustment ... mass index; TG, triglyceride; BP, blood pressure; IFG, impaired fasting g

Choi JH et al. Arch Med Res, 2013

NAFLD and its severity by NFS independently associated with incident diabetes

- In 38,291 participants in KSHS (175,996 person-year F/U)
- NAFLD fibrosis score calculated, analyzed in association with NAFLD



Chang Y et al. Am J Gastroenterol, 2013

Fatty liver and incident diabetes: MESA study

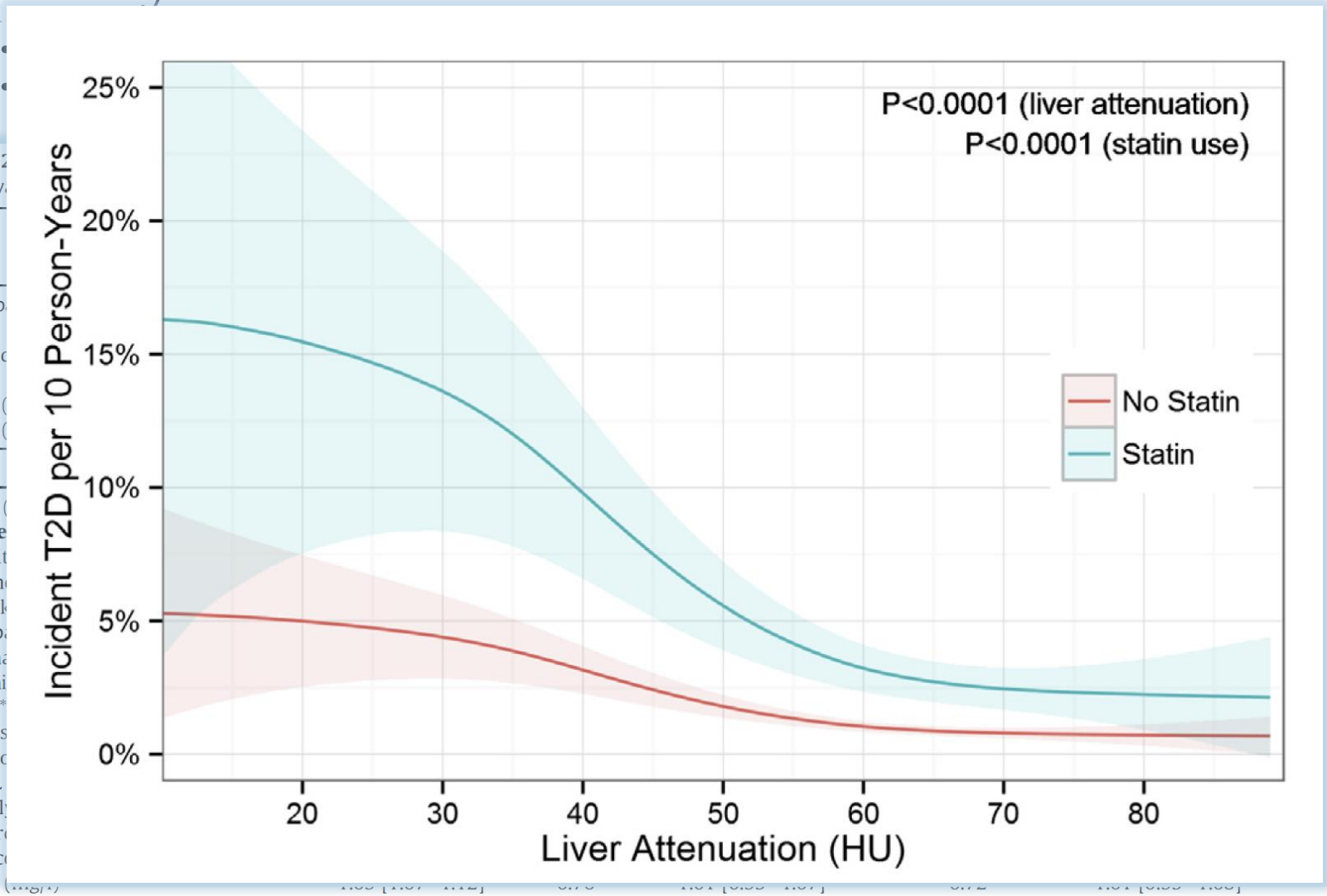


Table 2
Multiv

Glob					P
AIC					<0.0001
C-inc					<0.0001
NRI					0.7
NRI (					<0.05
NRI (					>0.05
					<0.05
					P
Age (					0.02
Race					
Whit					Ref
Chin					0.03
Black					0.0001
Hisp					0.06
Fema					0.02
Fami					0.01
BMI*					0.78
Wais					0.009
Syst					0.51
HDL					0.23
Trigl					0.52
Exer					0.66
Gluc					0.44
CRP					0.66
Statin initiation*			2.05 [1.49–2.82]	<0.0001	2.01 [1.46–2.77]	<0.0001
Fatty liver (Q1 attenuation)					2.06 [1.52–2.79]	<0.0001

Shah RV et al. Atherosclerosis, 2015

Risk for NASH and fibrosis

Longterm F/U of patients with NAFLD and elevated liver enzyme

129 biopsy-proven subjects with NAFLD; mean F/U 13.7 yrs

Table 1. Clinical and Biochemical Features of Cohort at Baseline and at Follow-Up [Mean ± SD or n (%)]

	At Baseline (n = 129)	At Follow-Up (n = 88)
Age (years)	51.0 ± 12.9	61.0 ± 11.0
Sex (male)	87 (67%)	62 (70%)
BMI (kg/m^2)	28.3 ± 3.8	29.1 ± 4.7
Overweight	72 (56%)	49 (56%)
Obese	37 (29%)	29 (33%)
Previously diagnosed diabetes	11 (8.5%)	37 (42%)
Diabetes diagnosed at consultation visit	NA	14 (16%)
IGT diagnosed at consultation visit	NA	18 (20%)
Hypertensive	93 (72%)	83 (94%)
Manifest cardiovascular disease	14 (11%)	16 (18%)
Hypertriglyceridemia	74 (57%)	35 (40%)
Metabolic syndrome	NA	52 (59%)
ALT (U/L)	76 ± 43	60 ± 35
AST (U/L)	45 ± 23	35 ± 15
AST/ALT ratio	0.6 ± 0.2	0.7 ± 0.3
ALP (U/L)	61 ± 33	65 ± 37
Bilirubin (mg/dL)	0.64 ± 0.30	0.78 ± 0.33
Albumin (g/dL)	4.1 ± 0.3	4.2 ± 0.4
Platelet count (× 10^9/L)	235 ± 67	194 ± 94
Prothrombin (INR)	1.0 ± 0.1	1.0 ± 0.2
Ferritin (μg/L)	232 ± 317	192 ± 159
Glucose (mg/dL)	NA	125 ± 38
IR_{HOMA}	NA	3.8 ± 3.5
Triglycerides (mg/dL)	190 ± 134	157 ± 89
Cholesterol (mg/dL)	236 ± 59	202 ± 43
HDL (mg/dL)	NA	51 ± 19
LDL (mg/dL)	NA	123 ± 37
Negative for HBsAg/anti-HCV	129/129	88/88
Negative for HBV DNA/HCV RNA	NA/NA	88/88
Positive for ANA/SMA/AMA	37/23/0	12/8/0
Positive for transglutaminase antibodies	NA	0
Mutation in the *HFE* gene* (C282Y homozygosity/C282Y compound heterozygosity)	NA	2/0
Mutation in the *Pi* gene† (ZZ/SZ/MZ/MS)	NA	0/0/10/3
Ceruloplasmin < 0.20 g/L	0	0

78%

Table 3. Clinical, Biochemical, and Histological Features at Follow-Up of Patients With Progressive Fibrosis and Patients With Nonprogressive Fibrosis [Mean ± SD or n (%)]

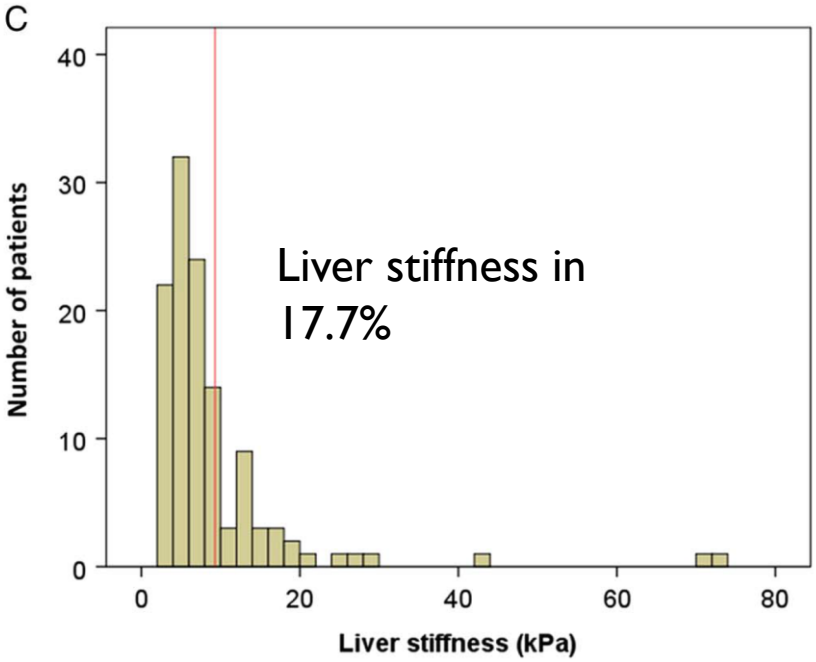
	Progressive Fibrosis (n = 29)	Nonprogressive Fibrosis (n = 41)	P
Age (years)	61.1 ± 11.0	60.1 ± 11.1	NS
Follow-up time (years)	14.0 ± 1.0	13.7 ± 1.3	NS
Sex (male)	21 (72%)	29 (71%)	NS
BMI (kg/m^2)	29.6 ± 3.3	28.3 ± 5.3	NS
BMI > 25	28 (97%)	34 (83%)	NS
Weight gain > 5 kg	16 (55%)	10 (24%)	.02
IGT	7 (24%)	7 (17%)	NS
Diabetes	15 (52%)	24 (58%)	NS
Hypertension	28 (97%)	38 (93%)	NS
Metabolic syndrome	18 (62%)	21 (51%)	NS
Alcohol consumption (g/week)	46 ± 44	28 ± 36	NS
ALT (U/L)	75 ± 44	51 ± 25	.005
AST (U/L)	42 ± 17	31 ± 13	.003
AST/ALT ratio	0.6 ± 0.2	0.7 ± 0.4	NS
ALP (U/L)	61 ± 21	67 ± 51	NS
Bilirubin (mg/dL)	0.8 ± 0.4	0.7 ± 0.2	NS
Albumin (g/dL)	4.2 ± 0.4	4.1 ± 0.4	NS
Platelet count (× 10^9/L)	205 ± 59	252 ± 62	.003
Prothrombin (INR)	1.0 ± 0.1	1.0 ± 0.09	NS
Ferritin (μg/L)	207 ± 193	174 ± 125	NS
Glucose (mg/dL)	124 ± 32	127 ± 44	NS
IR_{HOMA}	5.2 ± 5.3	2.9 ± 1.5	.04
Triglycerides (mg/dL)	167 ± 96	144 ± 84	NS
Cholesterol (mg/dL)	201 ± 44	205 ± 43	NS
HDL (mg/dL)	48 ± 11	55 ± 25	NS
LDL (mg/dL)	123 ± 38	127 ± 35	NS
Mutation in the *HFE* gene*	6 (21%)	16 (39%)	NS
Mutation in the *Pi* gene†	5 (17%)	4 (10%)	NS
Quantitative steatosis (%)	11.3 ± 8.3	7.3 ± 6.6	0.03

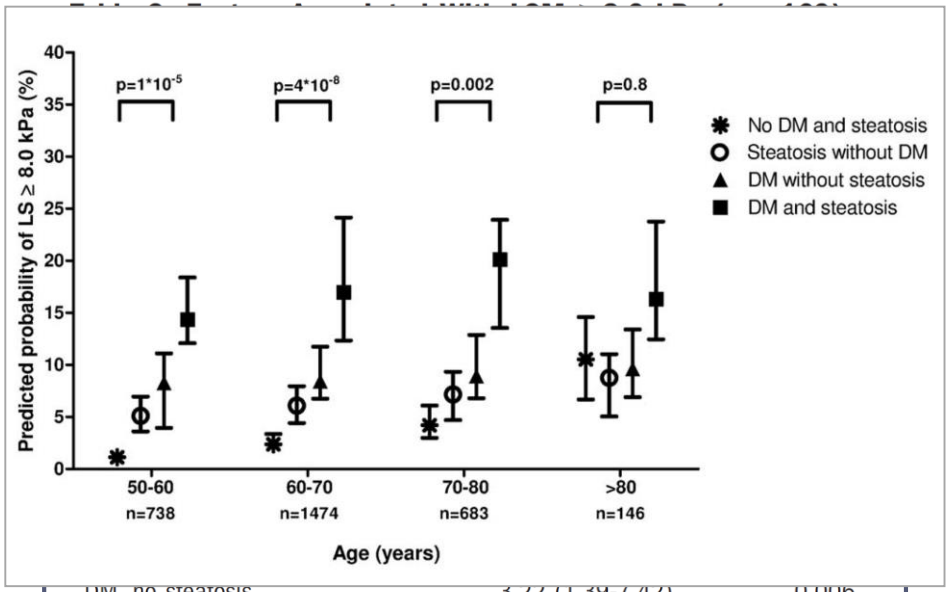
Ekstedt et al. Hepatology, 2006

Presence of diabetes and steatosis is associated with liver stiffness

- **In 1918 patients with diabetes in Hong Kong**
- **FibroScan performed**

In 3041 participants in Rotterdam study





DM, no steatosis	3.22 (1.39-7.42)	0.006
DM and steatosis	5.20 (3.01-8.98)	<0.001

Aging, diabetes and NAFLD aggrevate liver fibrosis

Kwok R et al. Hepatology, 2016
Koehler et al. Hepatology, 2016

Evidence of NAFLD progression to NASH using paired biopsy

In 108 patients with two liver biopsy

Characteristic	All patients (n = 108)	No progression of fibrosis (n = 63)	Progression of fibrosis (n = 45)	*p* value
Results at follow up biopsy				
BMI (kg/m^2)	34.9 ± 5.2	34.4 ± 4.7	35.6 ± 5.9	0.27*
T2DM	65%	51%	84%	<0.001
ALT (IU/L)	79 ± 66	82 ± 77	76 ± 48	0.63*
AST (IU/L)	57 ± 35	52 ± 34	63 ± 36	0.13*
GGT (IU/L)	148 ± 195	109 ± 143	202 ± 239	0.03*
Platelets (x10^9/L)	230 ± 62	248 ± 51	208 ± 69	0.001*
IgA (g/L)	3.26 ± 1.50	2.95 ± 1.32	3.7 ± 1.65	0.05*
IgG (g/L)	10.9 ± 3.1	11.2 ± 3.3	10.5 ± 2.7	0.4*
Ferritin	194 ± 218	199 ± 205	187 ± 237	0.81*
AST/ALT ratio	0.81 ± 0.30	0.74 ± 0.29	0.89 ± 0.29	0.01*
FIB-4 score	1.79 ± 1.39	1.36 ± 0.62	2.33 ± 1.69	0.001*
NAFLD score	-0.77 ± 1.38	-1.35 ± 1.08	-0.07 ± 1.40	<0.001*
NAS	4 (1-7)	3 (1-6)	5 (3-7)	<0.001
Fibrosis stage	2 (0-4)	1 (0-3)	3 (1-4)	<0.001^
0	23 (21%)	23 (37%)	0 (0%)	
1	19 (18%)	16 (25%)	4 (9%)	
2	19 (18%)	15 (24%)	4 (9%)	
3	33 (31%)	9 (14%)	24 (53%)	
4	13 (12%)	0 (0%)	13 (29%)	
Steatosis/NASH	25 (23%)/83 (77%)	21 (33%)/42 (67%)	0 (0%)/44 (100%)	<0.001#
Time between biopsy (yr)		6.7 ± 3.5	7.5 ± 5	0.35

McPherson S et al. J Hepatol, 2015

High prevalence of fibrosis in patients with diabetes

In 503 biopsy proven NAFLD patients (48% diabetes)

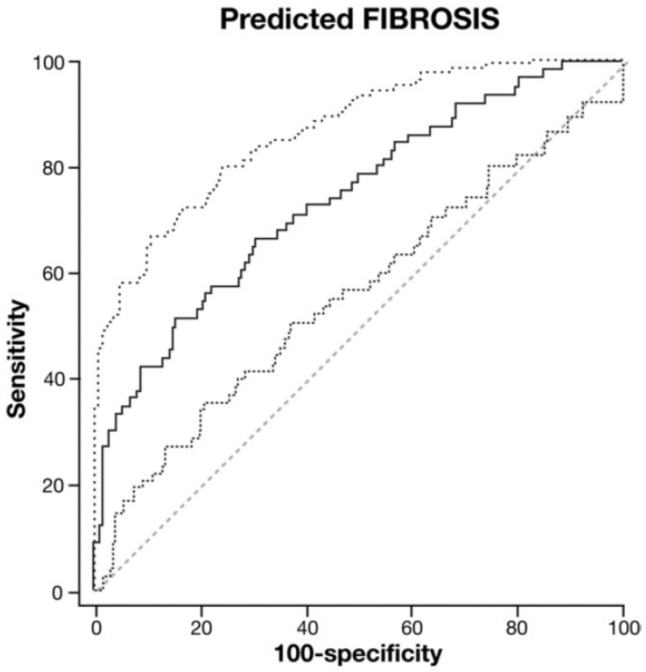
Table 2
Comparison of liver histology between DM and non-DM patients.

Histology feature	Presence of DM		p value*
	Yes (n = 238)	No (n = 263)	
Grade of steatosis			0.500
0	5 (2.1%)	6 (2.3%)	
1	85 (36.0%)	81 (30.9%)	
2	79 (33.5%)	104 (39.7%)	
3	67 (28.4%)	71 (27.1%)	
Lobular inflammation			0.017
0	8 (3.4%)	28 (10.7%)	
1	104 (44.1%)	113 (43.1%)	
2	111 (47.0%)	109 (41.6%)	
3	13 (5.5%)	12 (4.6%)	
Ballooning			<0.001
0	39 (16.6%)	70 (26.7%)	
1	98 (41.7%)	129 (49.2%)	
2	98 (41.7%)	63 (24.0%)	
NAFLD activity score			0.200
NAS < 5	108 (46.0%)	136 (51.7%)	
NAS ≥ 5	127 (54.0%)	127 (48.3%)	
Median NAS (interquartile range)	5 (3)	4 (3)	0.022
Stage of fibrosis			<0.001
0	40 (16.8%)	98 (37.3%)	
1	55 (23.1%)	79 (30.0%)	
2	47 (19.7%)	41 (15.6%)	
3	47 (19.7%)	30 (11.4%)	
4	49 (20.6%)	15 (5.7%)	

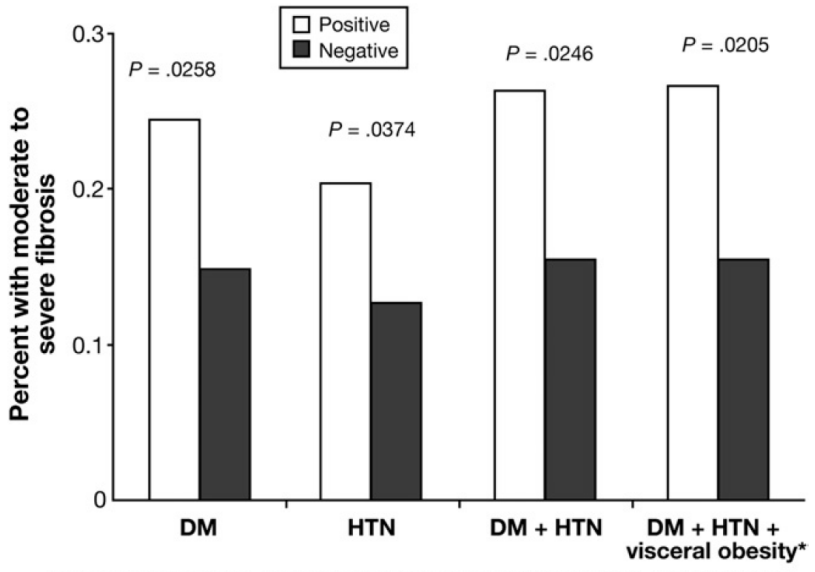
Goh GB et al. BBA Clin, 2015

Diabetes is the significant predictor for fibrosis in biopsy proven NAFLD patients

- In 432 patients with biopsy-proven NAFLD



	Beta
(Intercept)	-0.1696 +/- 0.0467
MALE	0.0964 +/- 0.0436
CAUCASIAN	0.1170+/- 0.0402
TYPE II DIABETES	0.1065 +/- 0.0405
ALT	0.0039 +/- 0.0013
AST	0.0130 +/- 0.0019



Hossain N et al. Clin Gastroenterol Hepatol, 2009

Clinical model for NASH and advanced fibrosis in patients with diabetes and NAFLD: Guideline for referral in NAFLD

- **In 346 patients with diabetes and biopsy proven NAFLD (NASH Clinical Research Network)**
- **NASH in 69.2%, advanced fibrosis in 41%**

Table 2—Clinical model for NASH in adult patients with diabetes and NAFLD

	Clinical model*		
Characteristics (n = 346)	OR	95% CI	P
Demographics			
White versus nonwhite	1.76	0.86–3.60	0.12
Obesity measures			
BMI (kg/m^2)	1.11	1.03–1.20	0.006
Waist (cm)	0.97	0.93–0.999	0.04
Laboratory measures			
AST (units/L)	1.07	1.04–1.10	<0.001
ALT (units/L)	0.98	0.97–0.998	0.03
Albumin (g/dL)	2.03	0.96–4.30	0.06
HbA_{1c} (%)	1.27	0.93–1.64	0.06
HOMA-IR (mg/dL × μU/mL/405)	1.06	1.01–1.09	0.18
Ferritin (ng/mL)	1.001	1.000–1.003	0.04
Model performance			
Cross-validated AUROC	0.80	0.75–0.84	
PPV	93.2%		
NPV	47.7%		
Correctly classified	67.0%		
Sensitivity	56.8%		
Specificity (fixed at 90%)	90.0%		
AIC	342.2		
Population prevalence of NASH	70%		
Probability cutoff for NASH†	≥0.77		

Clinical model for P (probability of NASH). Coefficients and SEs shown as b(SE): log(P/1 − P) = −7.00(2.47) + 0.106(0.039) × BMI (kg/m^2) − 0.035(0.017) × waist (cm) + 0.068(0.012) × AST (units/L) − 0.016(0.007) × ALT (units/L) + 0.71(0.38) × albumin (g/dL) + 0.24(0.13) × HbA_{1c} (%) + 0.057(0.024) × HOMA-IR (mg/dL × μU/mL/405) + 0.0014(0.0007) × ferritin (ng/dL) + 0.57 (0.36) if white. PPV: probability that the disease is present when the test is positive; NPV:

Table 3—Clinical model for advanced fibrosis in adult patients with diabetes and NAFLD

	Clinical model*		
Characteristics (n = 346)	OR	95% CI	P
Demographics			
Age (years)	1.04	1.01–1.07	0.007
Hispanic versus non-Hispanic	0.46	0.16–1.27	0.13
Clinical status			
Hypertension	1.56	0.89–2.73	0.12
Obesity measures			
BMI (kg/m^2)	1.04	0.998–1.090	0.06
Waist-to-hip ratio	21.2	0.55–821	0.10
Laboratory measures			
AST-to-ALT ratio	3.54	1.27–9.88	0.02
Alkaline phosphatase (units/L)	1.014	1.005–1.024	0.003
Isolated abnormal alkaline phosphatase	0.26	0.05–1.35	0.11
Globulin (g/dL)	2.27	1.26–4.07	0.006
Albumin (g/dL)	3.42	1.44–8.10	0.005
Total bilirubin (mg/dL)	0.44	0.16–1.24	0.12
Direct bilirubin (mg/dL)	24.4	0.47–1.254	0.11
INR	4.74	0.96–23.5	0.06
Hematology and other laboratory studies			
Hematocrit (%)	0.902	0.83–0.98	0.01
Platelet count (1,000/mm^3)	0.987	0.982–0.991	<0.001
Serum insulin (μU/mL)	1.013	1.002–1.024	0.02
Model performance			
Cross-validated AUROC	0.803	0.756–0.850	
PPV	80.2%		
NPV	75.1%		
Correctly classified	76.6%		
Sensitivity	57.0%		
Specificity (fixed at 90%)	90.0%		
AIC	368.4		
Probability cutoff for advanced fibrosis†	≥0.60		

Clinical model for P (probability of advanced fibrosis). Coefficients and SEs shown as b(se): log(P/1 − P) = −11.8(3.8) + 0.04(0.015) × age (years) + 0.042(0.023) × BMI (kg/m^2) + 3.05(1.87) × waist-to-hip ratio + 0.014(0.005) × ALK (units/L) + 1.26(0.52) × AST-to-ALT ratio + 1.23(0.44) × albumin (g/dL) + 0.82(0.30) × globulin (g/dL) − 0.103(0.041) × hematocrit (%) − 0.0133 (0.0024) × platelet count (1,000/mm^3) + 3.19(2.01) × direct bilirubin (mg/dL) − 0.81(0.52) × total bilirubin (mg/dL) − 1.33(0.83) if abnormal alkaline phosphatase + 1.56(0.82) × INR + 0.0131 (0.0056 × serum insulin (μU/mL) − 0.79(0.52) if Hispanic + 0.44(0.28) if hypertensive. ALK:

Bazick J et al. Diabetes Care, 2015

Clinical model for NASH and advanced fibrosis in patients with diabetes and NAFLD: Guideline for referral in NAFLD

- In 346 patients with diabetes and biopsy proven NAFLD (NASH Clinical Research Network)
- NASH in 69.2%, advanced fibrosis in 41%

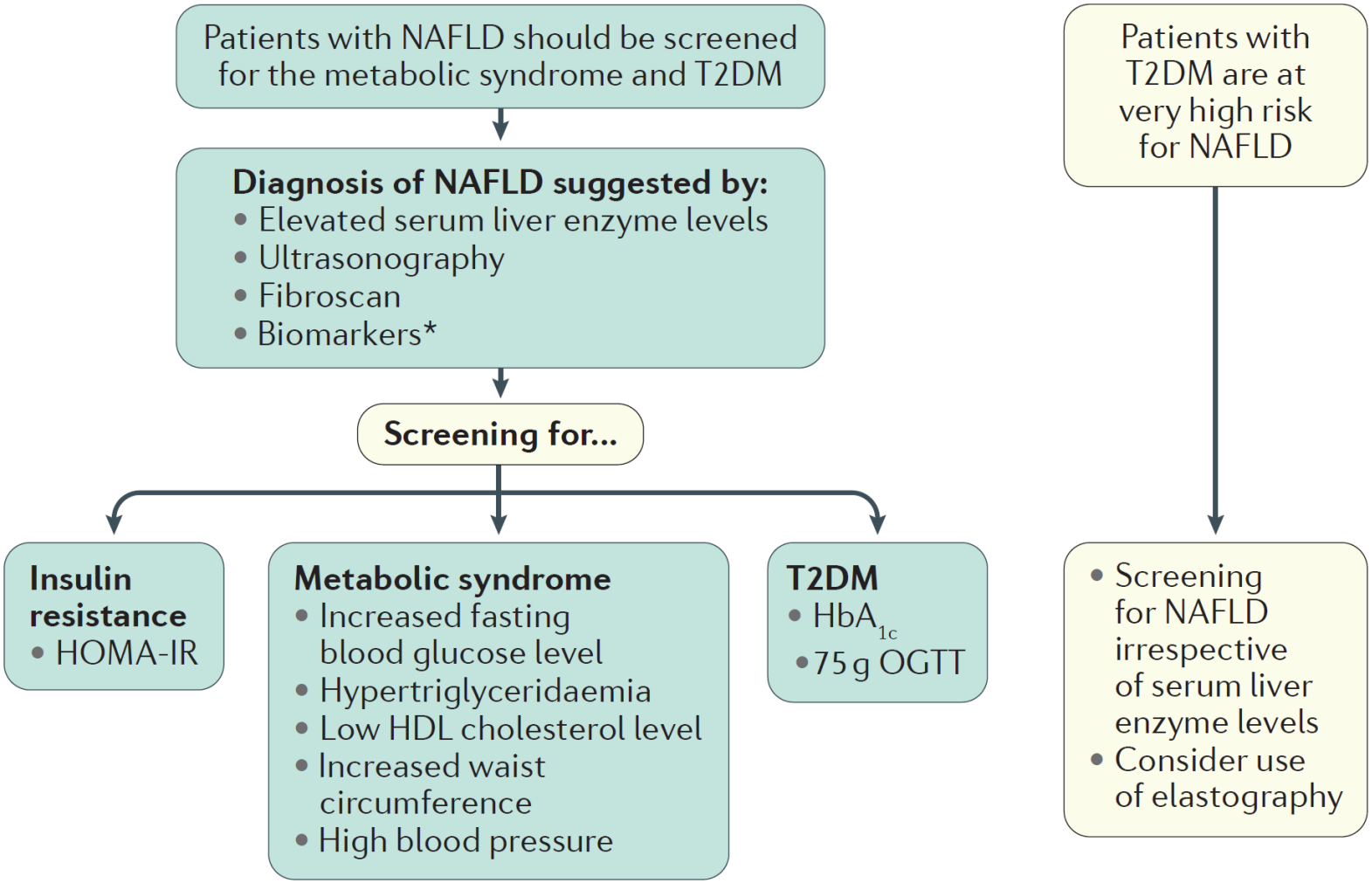
Supplementary Table 1. Comparison of clinical model for advanced fibrosis to NAFLD Fibrosis Score model for predicting advanced fibrosis

	NASH CRN Cohort	NAFLD Fibrosis Score Model*
AUROC (95% CI)	0.84 (0.80 - 0.88)	0.77 (0.67 – 0.87)
Positive predictive value (PPV)	80.2%	68.0%
Negative predictive value (NPV)	75.1%	72.0%
Specificity	90.0%	87.1%
Sensitivity	57.0%	44.7%
Correctly classified	76.6%	71.0%

*NAFLD Fibrosis Score model for P = probability of advanced fibrosis b(SE): log(P/1-P)= 2.06(3.72) + 0.03(0.02)*age(years) + 0.05(0.04)*BMI(kg/m2) + 1.43(0.78)*ALT/AST - 0.13(0.60)*albumin (g/dL) + 0.01(0.004)*Platelet count (100/mm2) - 0.036(.48)*hyperglycemia

Bazick J et al. Diabetes Care, 2015

Clinical algorithms in management of NASH and diabetes



Tilg H et al. Nat Rev Gastroenterol Hepatol, 2017

NAFLD and diabetic complications

NAFLD is independently associated with an increased prevalence of macrovascular complications in T2DM

In 2,839 T2DM patients

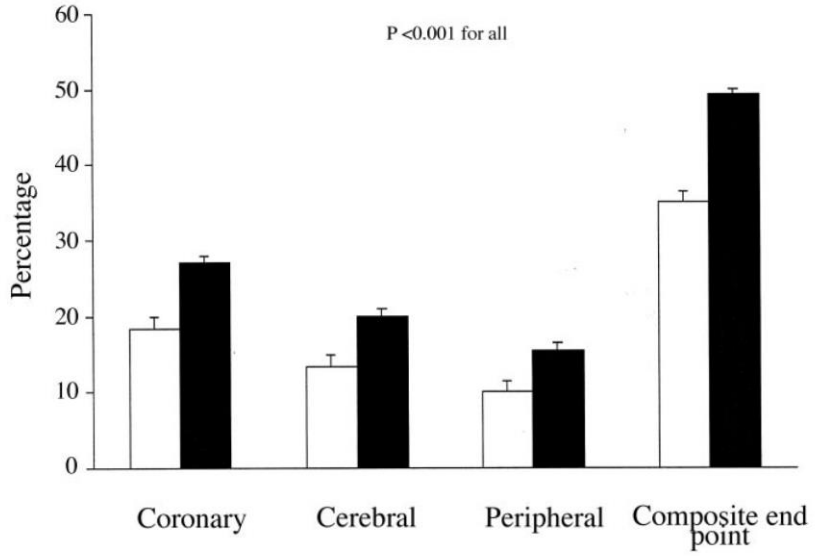


Figure 2—*Age- and sex-adjusted prevalence of CVD in type 2 diabetic adults with (■) and without (□) NAFLD. Data are expressed as percentages ± SE. P < 0.001 for differences between the groups.*

■ NAFLD

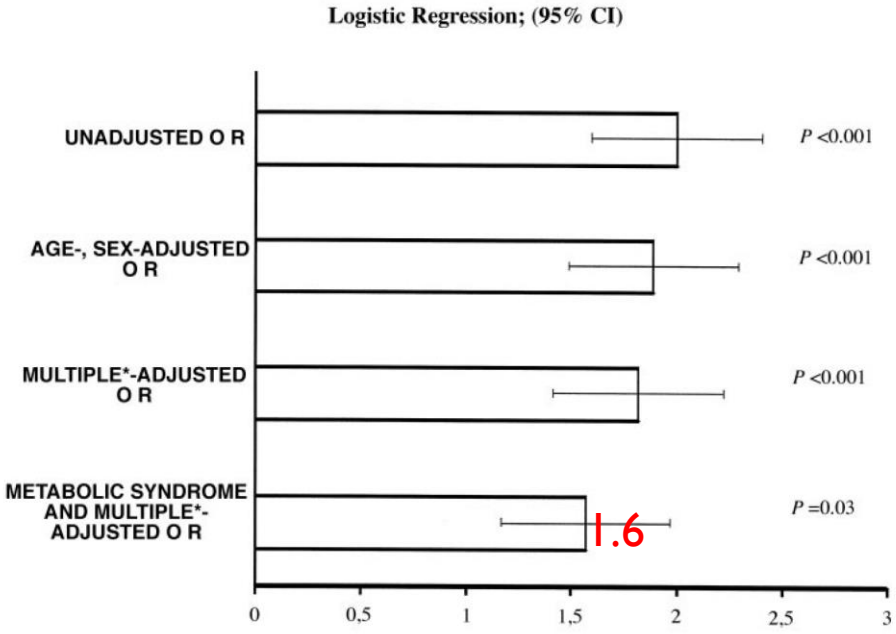


Figure 3—*Association between NAFLD and prevalent CVD in type 2 diabetic adults with and without NAFLD (n = 2,392). Data are expressed as ORs ± 95% CI. *The multiple adjustment reported in the third and fourth bars was as follows: age, sex, BMI, smoking status, diabetes duration, A1C, LDL cholesterol, and current use of medications (hypoglycemic, antihypertensive, lipid-lowering, or antiplatelet drugs).*

Targher G et al. Diabetes Care, 2007

NAFLD is independently associated with an increased prevalence of microvascular complications in T2DM

In 2103 T2DM patients

Table 1 Clinical and bi

Variable		1,421)	*p* value
Sex (% men)			0.001
Age (years)			0.001
BMI (kg/m^2)			0.001
Waist circumference (cm			0.001
Duration of diabetes (ye			0.001
Oral hypoglycaemic drug			0.30
Insulin only (%)			0.001
Anti-hypertensive users			0.001
Aspirin users (%)			0.20
Lipid-lowering users (%			0.50
Current smokers (%)			0.70
Systolic blood pressure			0.001
Diastolic blood pressure			0.001
HbA_{1c} (%)			0.001
Triacylglycerol (mmol/l)			0.001
HDL-cholesterol (mmol/			0.001
LDL-cholesterol (mmol/l			0.70
e-GFR (ml min^{-1} 1.73 m			0.001
AST (U/l)			0.001
ALT (U/l)			0.001
GGT (U/l)			0.001
Elevated ALT[a] (%)			0.001
Non-proliferative retinop			0.001
Proliferative/laser-treated			0.001
Microalbuminuria alone			0.001
CKD (%)			0.001

Table 2 Univariate and multivariate logistic regression analyses showing associations of NAFLD with prevalent retinopathy and chronic kidney disease among type 2 diabetic patients

Variable	Univariate	Multivariate model 1	Multivariate model 2
Non-proliferative retinopathy			
OR	1.6	1.5	1.19
95% CI	1.1–2.3	1.03–2.2	0.8–1.7
p value	0.001	0.01	0.50
Proliferative/laser-treated retinopathy			
OR	2.2	2.0	1.75
95% CI	1.2–4.2	1.1–4.2	1.1–3.7
p value	0.001	0.001	0.031
Chronic kidney disease			
OR	2.4	2.2	1.87
95% CI	1.6–4.7	1.3–4.5	1.3–4.1
p value	0.001	0.001	0.020

Cohort size: n=2,103

Model 1: adjustment for age, sex, BMI, waist circumference, smoking, LDL-cholesterol, triacylglycerol, HbA_{1c}, diabetes duration and medications use

Model 2: further adjustment for hypertension and chronic kidney disease (for the first and second variable of the table) or for hypertension and proliferative/laser-treated retinopathy (for the last variable of the table)

Targher G et al. Diabetologia, 2008

NAFLD increases risk of death among patients with diabetes

In 337 patients with diabetes, followed up for 10.9 years

Table 2. Causes of death

	Total cohort (n=337)	DM + NAFLD (n=116)	DM – NAFLD (n=221)
Overall	99	27	72
Heart disease	31 (31%)	5 (19%)	26 (36%)
Cerebrovascular	5 (5%)	0	5 (7%)
Malignancy	23 (23%)	9 (33%)	13 (18%)
Infection	15 (15%)	3 (11%)	12 (17%)
Liver related	5 (5%)	5 (19%)	0
Others	18 (18%)	4 (15%)	14 (20%)
Unknown	2 (2%)	1 (3%)	1 (2%)

DM, diabetes mellitus; NALFD, nonalcoholic fatty liver disease.

More liver-related death in NAFLD pt
Death due to malignancy

Table 4. Multivariate Cox proportional hazard modeling for predictors of death in patients with diabetes mellitus

Variable	*P* value	HR	95% CI
Age (years)			
<50		1.0 (reference)	
50–60	0.22	2.2	0.6–7.9
60–70	0.005	5.8	1.7–19.7
>70	<0.001	12.9	3.6–46.3
Gender	0.96	1.0	0.6–1.8
Date of DM diagnosis	0.01	1.1	1.03–1.2
Smoker	0.45	1.2	0.7–2.2
Hypertension	0.61	1.2	0.7–2.0
Obesity	0.65	0.9	0.5–1.5
Hyperlipidemia	0.14	0.5	0.2–1.3
Earlier malignancy	0.03	2.4	1.1–5.3
CVD	0.02	2.8	1.2–6.7
IHD	0.01	2.3	1.2–4.4
NAFLD	0.03	2.2	1.1–4.2

Adams LA et al. Am J Gastroenterol, 2010

Risk for liver-related mortality directly related to severity of diabetes

In 7148 T2DM patients

Table 4—*Relative risk of dying according to therapeutic regimens for some specific causes of death, after adjusting for sex, age, and time since diagnosis (in tertiles)*

	OHD (vs. diet)	Insulin (vs. diet)
All causes	1.68 (1.36–2.1)*	2.95 (2.2–3.9)*
Ischemic heart disease	1.80 (1.02–3.20)†	1.55 (0.65–3.67)
Cerebrovascular disease	1.35 (0.72–2.5)	1.41 (0.5–3.7)
Cirrhosis	4.93 (1.19–20.4)†	6.84 (1.2–38.0)†

Data are relative risks (95% CI). *$P < 0.001$; †$P < 0.05$.

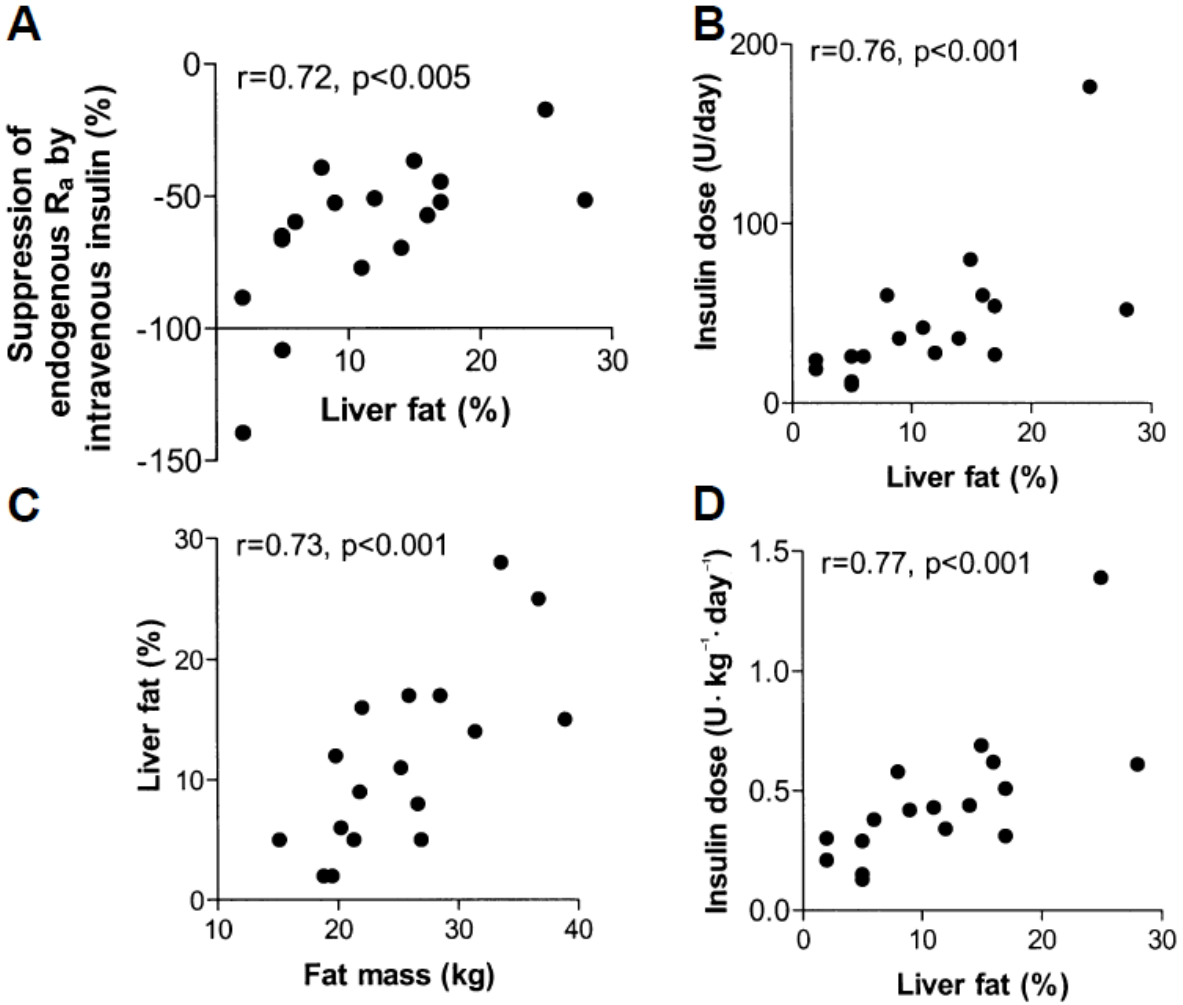
Injury and poisoning 1.20 (0.84–1.80) 0.82 (0.91–1.24) 1.02 (0.76–1.34)

Data are SMRs (95% CI).

De Marco et al. Diabetes Care, 1999

Hepatic fat content and insulin action associated with insulin requirement in T2DM patients

In 20 T2DM patients on insulin therapy



Ryysy L et al. Diabetes, 2000

Increased CVD risk in T1DM patients with NAFLD

In 250 T1DM patients; prevalence of NAFLD 44.4%

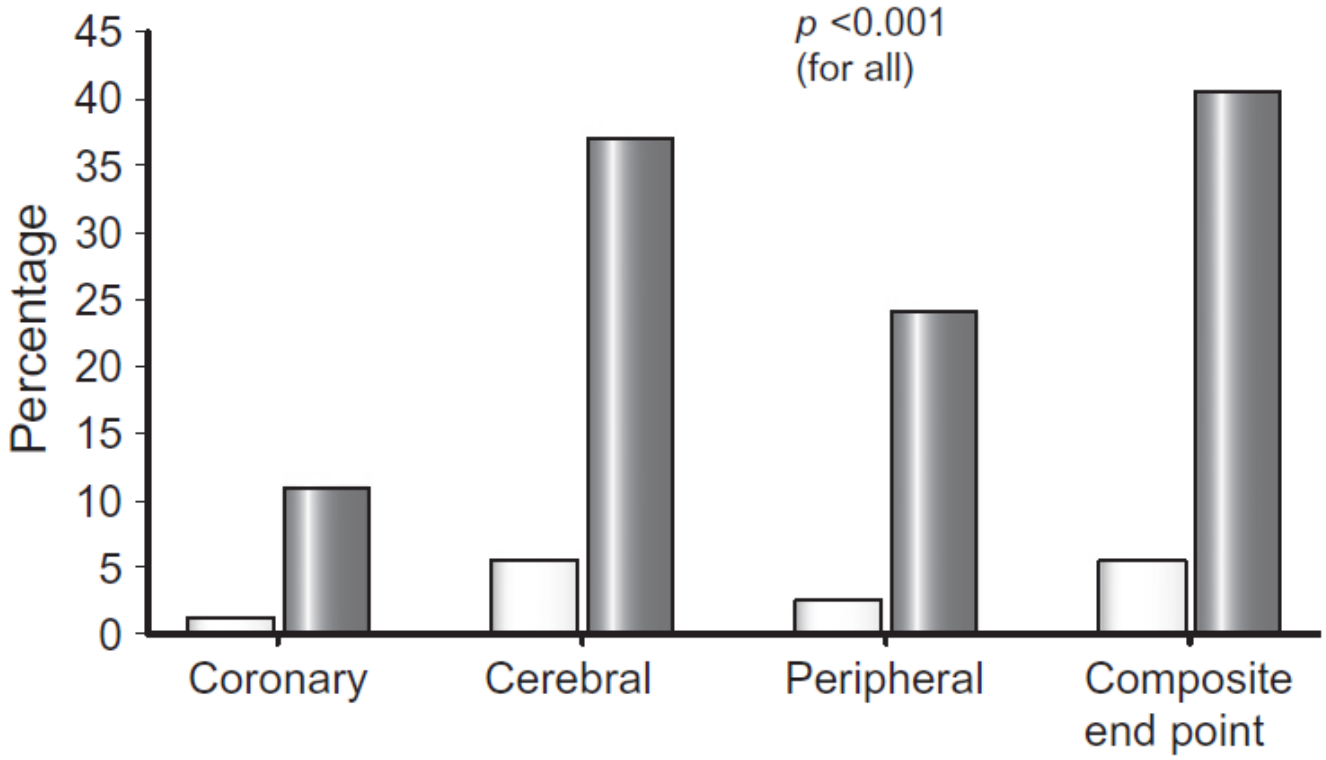
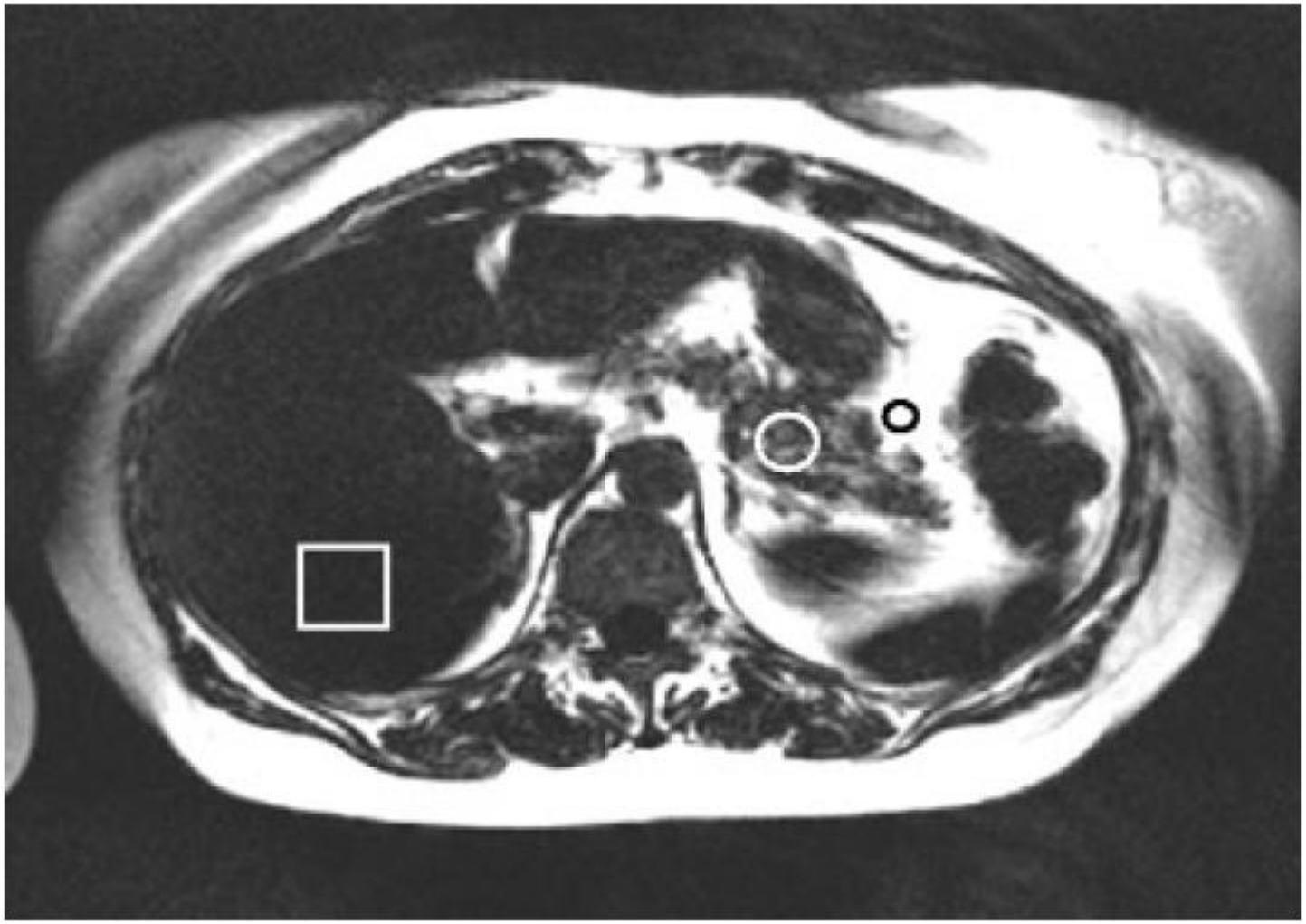


Fig. 2. Age and sex-adjusted prevalence of symptomatic/asymptomatic CVD in type 1 diabetic adults with (black columns) and without (white columns) ultrasound-diagnosed NAFLD. $p < 0.001$ for differences between those with vs. those without NAFLD.

Targher G et al. J Hepatol, 2010

Non-alcoholic fatty pancreatic disease



Non-alcoholic fatty pancreatic disease

- First described in 1933 by Oligvie – presence of pancreatic fat to be higher in obese individuals (17% vs. 9%) as compared to lean individuals
- Olsen – in 394 autopsies, observed pancreatic fat increased with age
- Stamm showed that pancreatic fat > 25% associated with increased risk of T2DM and severe generalized atherosclerosis

Imaging modalities for diagnosis of pancreatic steatosis

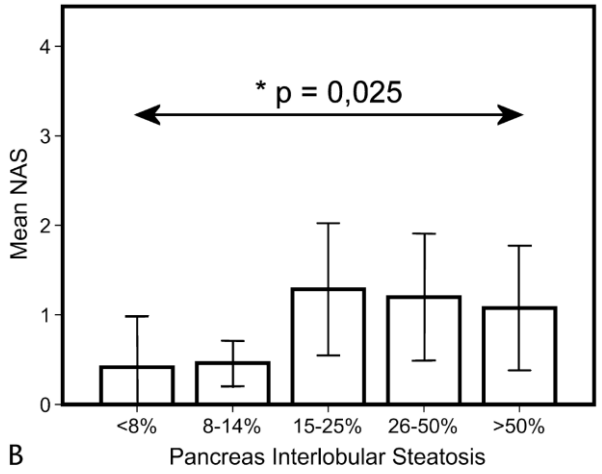
Table 3. Imaging Modalities for Diagnosis of Pancreatic Steatosis [11, 28-31]

Imaging modality	Advantage	Disadvantage
Ultrasonography (USG)	Widely available	Pancreas may not be visible in obese patients. Pancreatic fibrosis also appears hyperechogenic similar to fat deposition. Pancreas echogenicity has been traditionally compared with liver echogenicity. Liver is metabolically very active and its echogenicity exhibits high variance.
Endoscopic ultrasound (EUS)	The close proximity of the ultrasound probe to the pancreas results in superior spatial resolution compared with CT and MRI.	Invasive procedure. Requires sedation. Carries risk of complications.
Computed tomography (CT)	Easily available. Can be performed without intravenous contrast for diagnosis of pancreatic steatosis.	No cut-off points for pancreatic steatosis on CT have been defined. Exposure to radiation. Mild degree of focal fatty replacement of pancreas cannot be diagnosed with CT alone.
Magnetic resonance imaging (MRI)	Quantify pancreatic fat content with high accuracy.	Lack of research. The detection limit for pancreatic steatosis is unknown.

Tariq et al. Gastroenterol Res, 2016

NAFPD is related to NAFLD

In 80 autopsied patients



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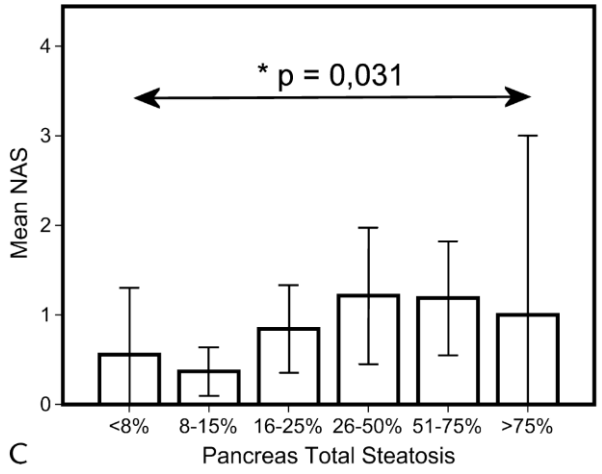

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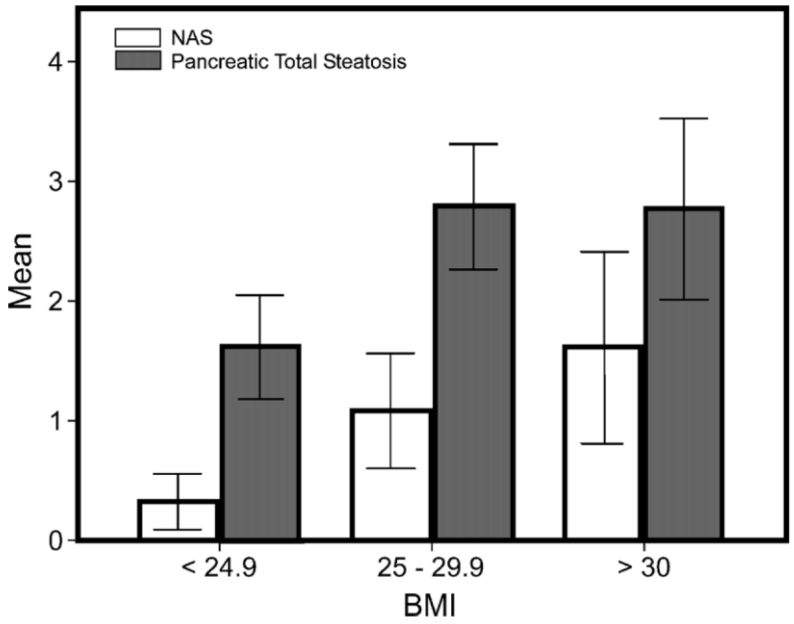


Van Geenen EM et al. Pancreas 39:2010

NAFPD associated with diabetes

- In 8097 subjects in health checkup
- NAFLD and fatty pancreas diagnosed with USG
- Prevalence of fatty pancreas: 16%

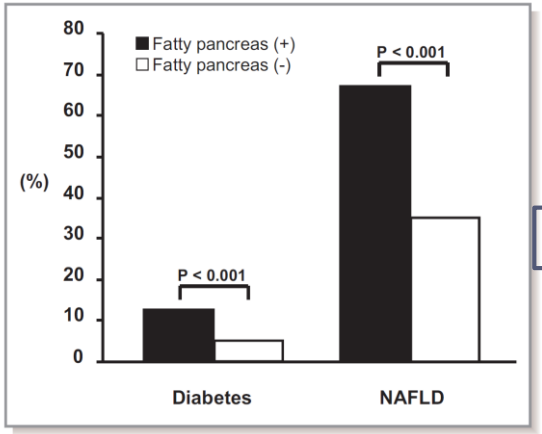


Table 4. Logistic Regression Analysis for Factors Associated With Diabetes

	Diabetes		
	OR	95% CI	*P* Value
Age, y	1.087	1.076 to 1.099	<0.001
Creatinine	1.071	0.509 to 2.255	0.856
ALT/AST ratio	2.103	1.602 to 2.760	<0.001
Hypertension, yes vs no	1.413	1.098 to 1.819	0.007
Sex, female vs male	1.1282	0.957 to 1.718	0.096
NAFLD, yes vs no	2.235	1.783 to 2.801	<0.001
Fatty pancreas, yes vs no	1.593	1.300 to 1.953	<0.010
Low-HDL cholesterol, yes vs no	1.4567	1.201 to 1.792	<0.001
Hypertriglyceridemia, yes vs no	1.471	1.196 to 1.808	<0.001
Central obesity, yes vs no	1.216	0.982 to 1.506	0.073
Current smoking, yes vs no	1.281	0.947 to 1.733	0.108
Current alcohol drinking, yes vs no	0.954	0.696 to 1.309	0.772
Regular physical exercise, yes vs no	1.108	0.907 to 1.353	0.314

ALT indicates alanine transaminase; AST, aspartate transaminase; HDL, high-density lipoprotein; NAFLD, nonalcoholic fatty liver disease.

Wang C et al. JAHA, 2014

NAFPD associated with metabolic risk factors

- In 557 participants in a health checkup program
- NAFPD assessed by abdominal USG

Table 2 Prevalence of each parameter of metabolic syndrome in the study group

Metabolic parameters	Fatty pancreas n (%)	Normal pancreas n (%)
Abdominal obesity*	52 (72.2%)	214 (44.1%)
TG*	28 (38.9%)	93 (19.2%)
HDL*	32 (44.4%)	161 (33.2%)
HTN*	24 (33.3%)	128 (26.4%)
FBG*	34 (47.2%)	95 (19.6%)

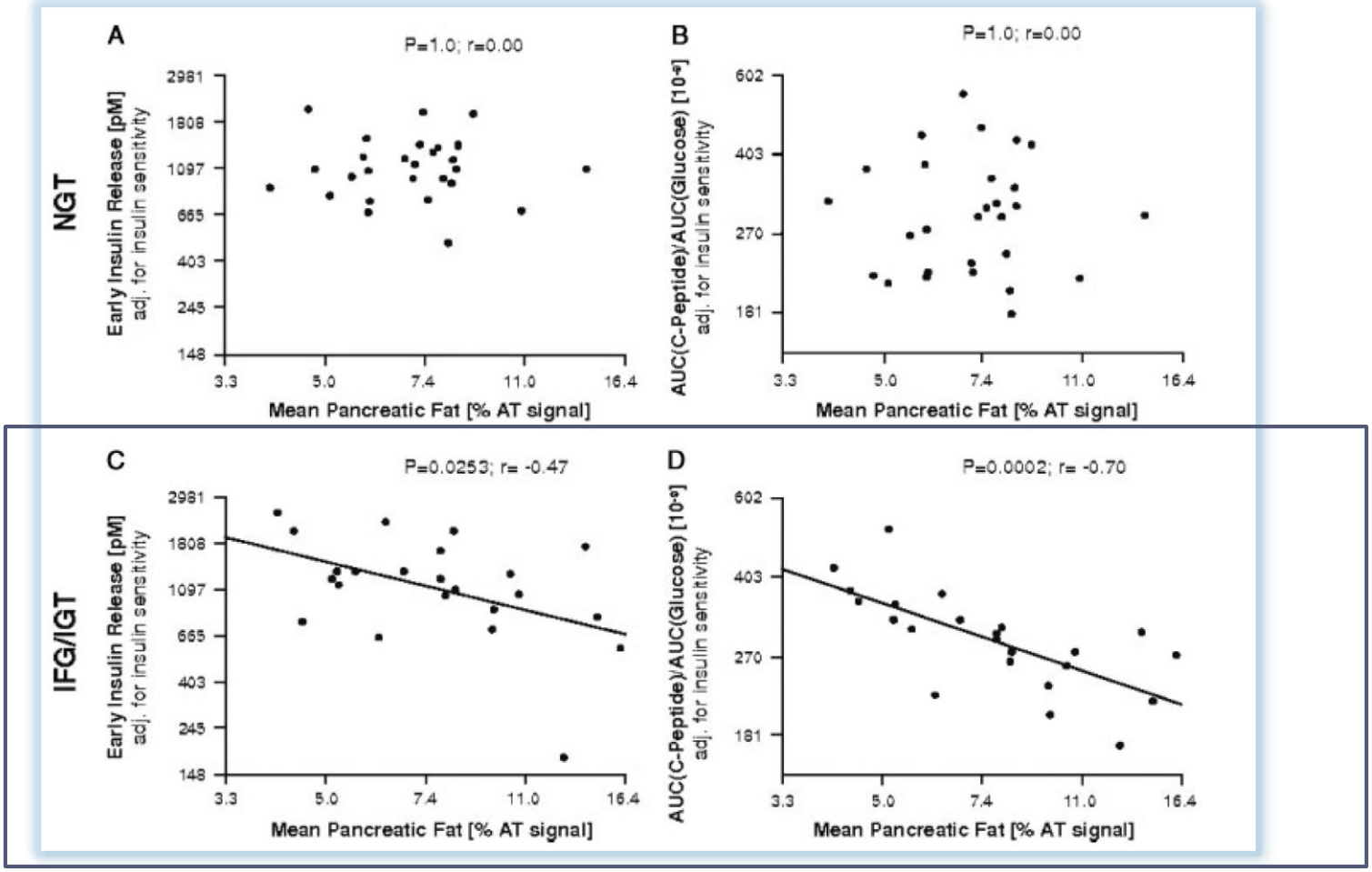
Table 3 Number of parameters of metabolic syndrome for subjects in the two groups

Number of metabolic Syndrome parameters	Fatty pancreas n (%)	Normal pancreas n (%)
0	4 (5.6%)	156 (32.2%)
1	22 (30.6%)	132 (27.2%)
2	21 (29.2%)	112 (23.1%)
3	16 (22.2%)	54 (11.1%)
4	7 (9.7%)	27 (5.6%)
5	2 (2.8%)	4 (0.8%)
Meet ≥ 3 criteria*	25 (34.7%)	85 (17.5%)
Mean number*	2.1 ± 1.2	1.3 ± 1.2

Wu WC et al. Cardiovasc Diabetol, 2013

Pancreatic fat negatively associated with insulin secretion in subjects with IFG/IGT

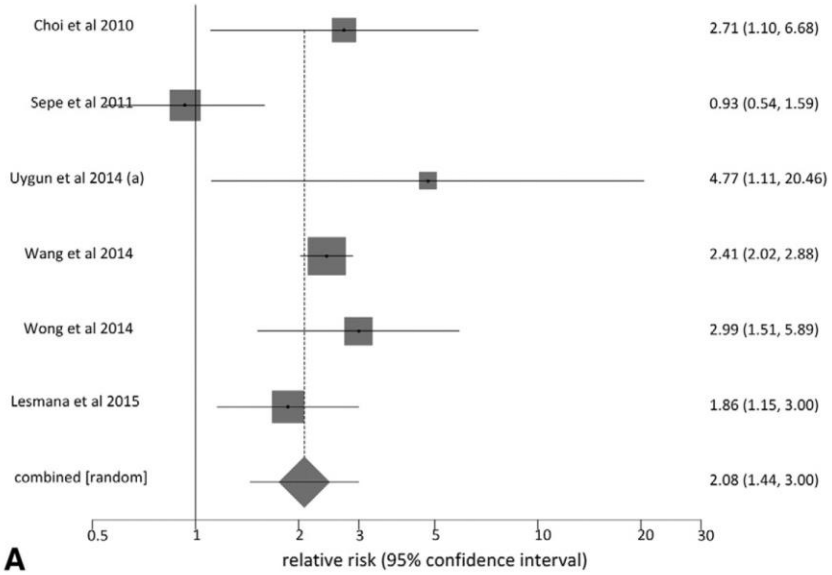
In 51 subjects (23 IFG/IGT), 28 NGT

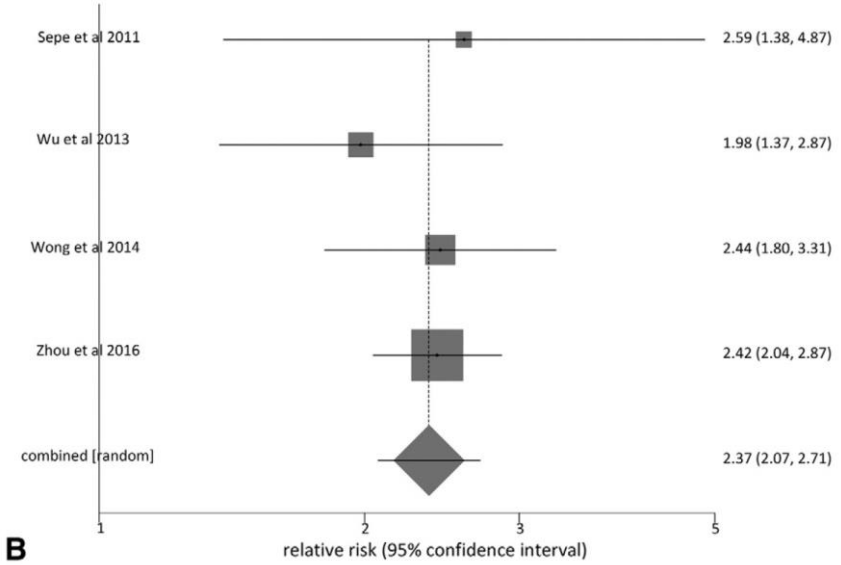


Heni M et al. Diabetes Metab Res Rev, 2010

Risk for diabetes and MetS in NAFPD

12,675 subjects from 11 studies



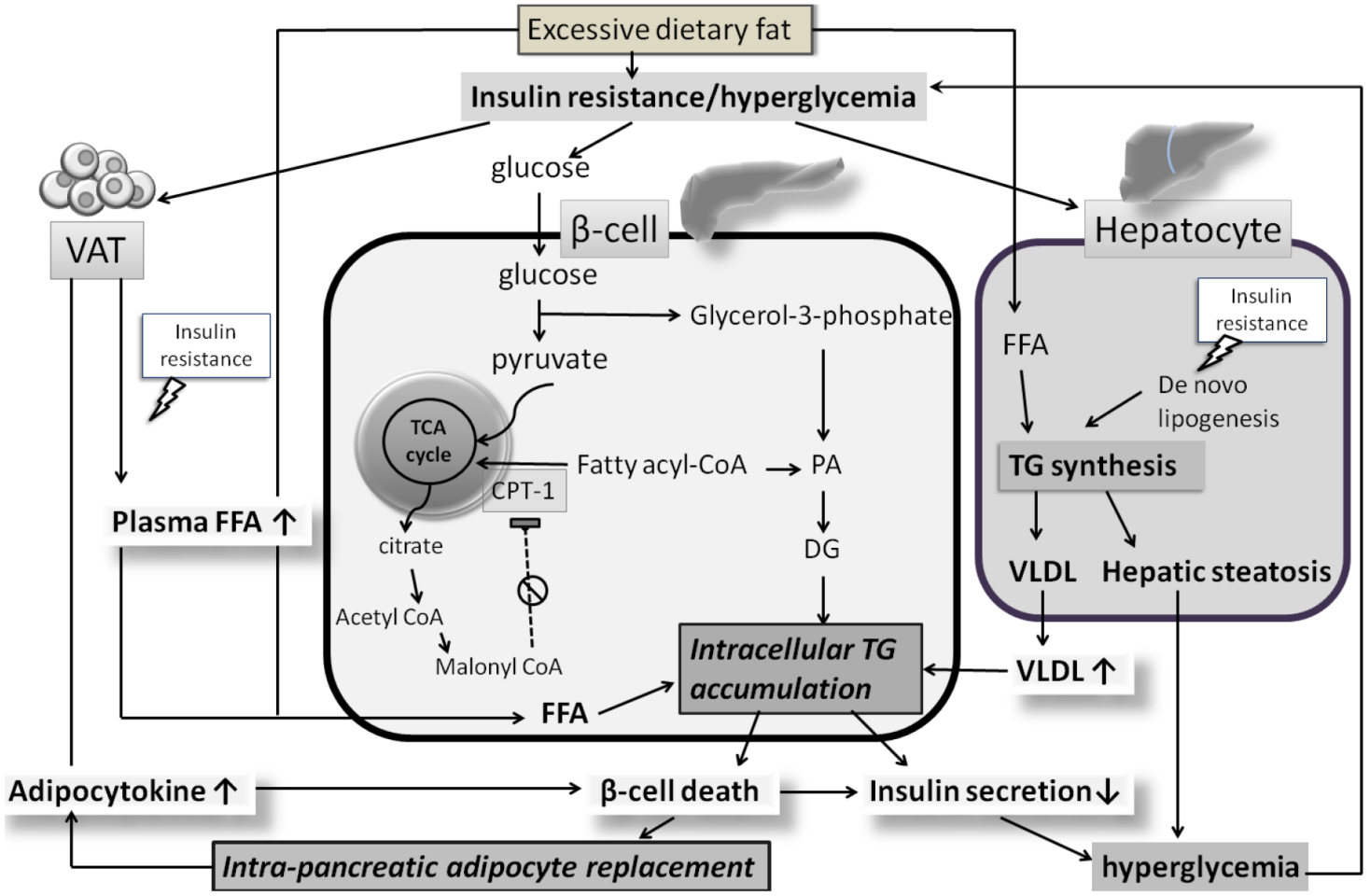


Relative risk for diabetes: 2.08

Relative risk for MetS: 2.37

Singh RG et al. Metabolism, 2017

Potential interplay between dysglycemia, NAFPD and beta-cell dysfunction



Yu TY et al. J Diabetes Invest, 2017

Recommendation of screening for diabetes in persons with NAFLD – EASL/EASD/ESO

Recommendations

- In persons with NAFLD, screening for diabetes is mandatory, by fasting or random blood glucose or HbA_{1c} (**A1**) and, if available, by the standardised 75 g OGTT in high-risk groups (**B1**)
- In patients with T2DM, the presence of NAFLD should be looked for irrespective of liver enzyme levels, since T2DM patients are at high risk of disease progression (**A2**)

Diabetologia, 2016

Interpreting the results from the literature regarding the relationship between NAFLD and diabetes…

- Retrospective
- Mostly from Asia – regular health checkup data…
- Asian and non-Asian have different adipose tissue distributions and cultural background..
- Diagnostic method of diabetes skewed..
- Unclear whether NAFLD is causally related to T2DM or simply a marker of other shared risk factors ; whether other factors in addition to hepatic steatosis are important for T2DM development..

Lessons from today's review..

- It is clear the NAFLD is a strong and important risk factor for development of diabetes
- The presence of NAFLD in patients with T2DM aggravates the natural course of NAFLD and also increases the risk of macro and microvascular complication of diabetes
- The presence of NAFLD would reflect the presence of NAFPD; this would lead to increased risk of T2DM
- Screening for NAFLD in patients with diabetes should be routinely performed in clinical setting
- Patient education is essential for resolution of NAFLD – exercise, weight control and diet control – for the prevention of liver-related morbidity and diabetes development