Diabetes and NAFLD: a vicious spiral affecting both diseases

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Declaration of interests

- Abbott/Pronova providing Omacor (DHA+EPA) for WELCOME study

(**Wessex Evaluation of fatty Liver and Cardiovascular markers in NAFLD (non alcoholic fatty liver disease) with OMacor thErapy**)

www.clinicaltrials.gov registration number NCT00760513

- Chr Hansen providing synbiotic and placebo for INSYTE study

(**Investigation of synbiotic treatment in NAFLD)**

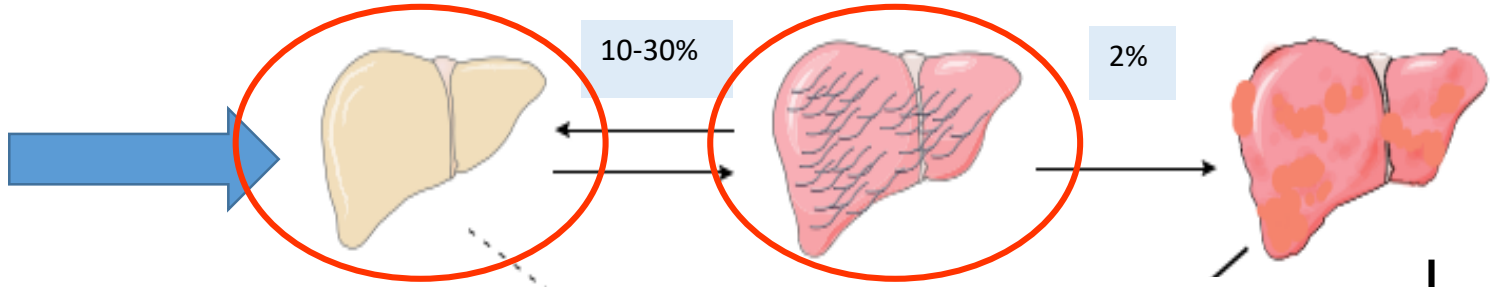
www.clinicaltrials.gov registration number NCT01680640

Content

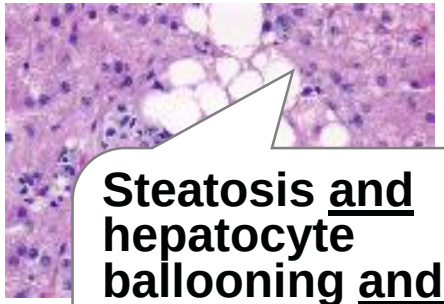
- Type 2 diabetes and NAFLD: a vicious cycle of metabolic and cardiovascular disease
- Evidence that diabetes (T2DM) is a crucially important risk factor for liver disease progression (fibrosis in NAFLD)
  - Biopsy and serial biopsy studies (fibrosis, fibrosis progression and disease/death outcomes)
  - Population registry and database-coded NAFLD outcome studies
  - NAFLD biomarker and outcome studies
- In patients with T2DM and NAFLD: is NAFLD a risk factor for CVD
- What is the logical treatment of NAFLD for patients with T2DM?

Spectrum of liver disease in NAFLD

Risk factors
e.g. obesity
diet, genetic
predisposition



NASH



Steatosis and hepatocyte ballooning and inflammation (with or without fibrosis)

Hepatocellular carcinoma

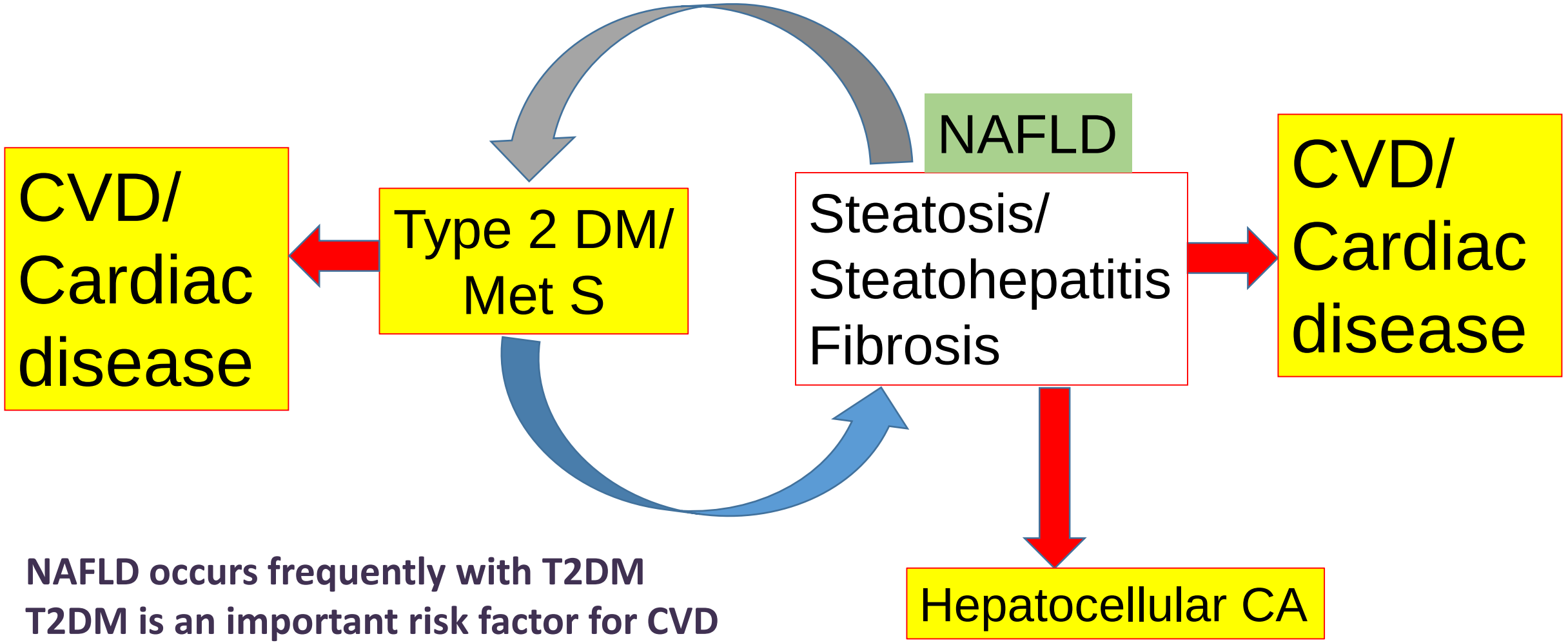
Death/embolization /liver transplantation

Death/liver transplantation

Modified from
Fan et al., J Hep 2017

NAFLD is defined by the presence of liver fat (i.e. TAG >5.5%)
Am J Physiol Endocrinol Metab. 2005 Feb;288(2):E462-8. Hepatology. 2004;40(6):1387–95.

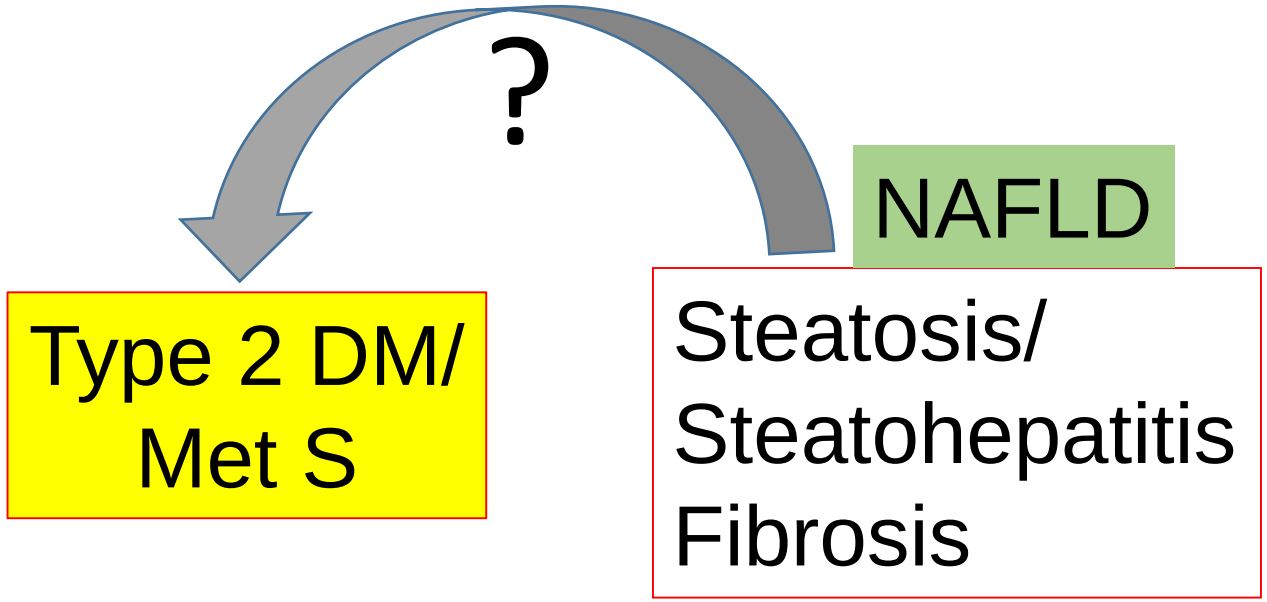
Type 2 diabetes and NAFLD: a vicious cycle of metabolic and cardiovascular disease



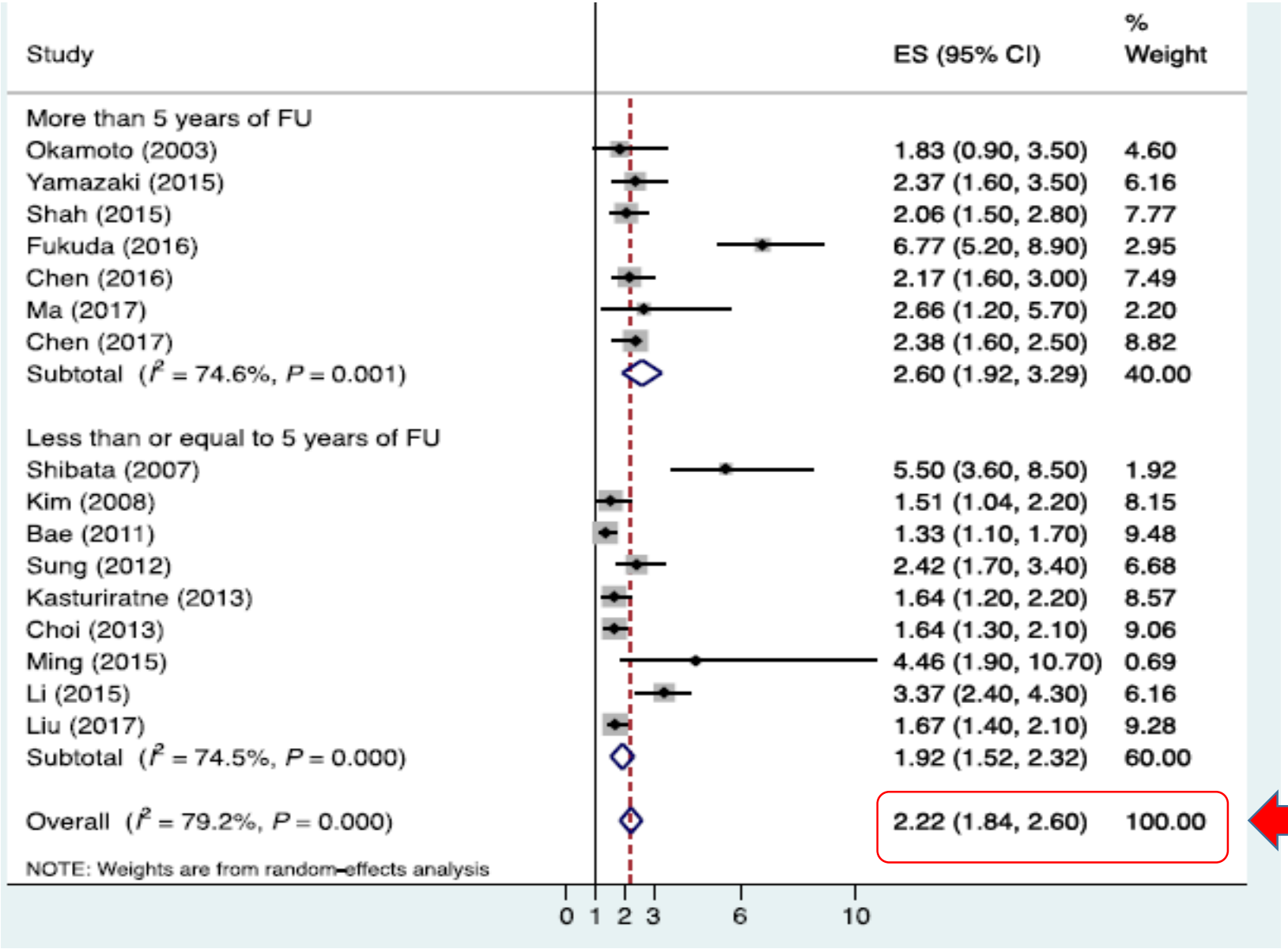
- NAFLD occurs frequently with T2DM
- T2DM is an important risk factor for CVD
- Does NAFLD increase risk of CVD in people with T2DM?

J Nutr Sci. 2017 May 8;6:e15.

Type 2 diabetes and NAFLD:
a vicious cycle of metabolic and cardiovascular disease



NAFLD increases risk of incident diabetes



Summary HR (95%CIs)

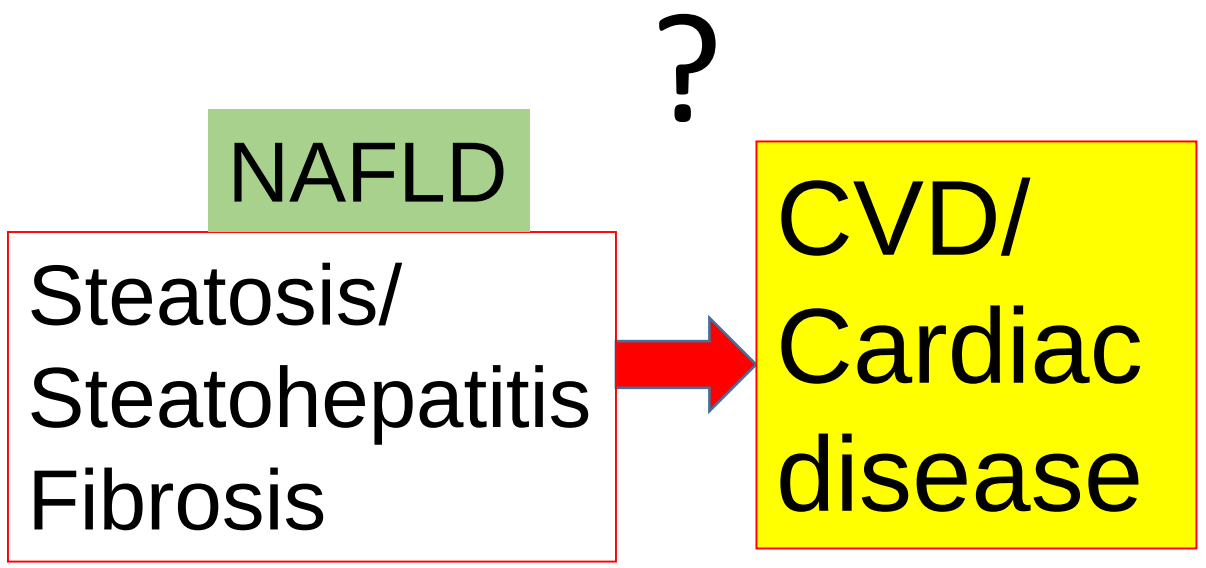
= 2.22 (1.84, 2.60)

Diabetes Care 2018; 41: 372-382

NAFLD and multimorbidity

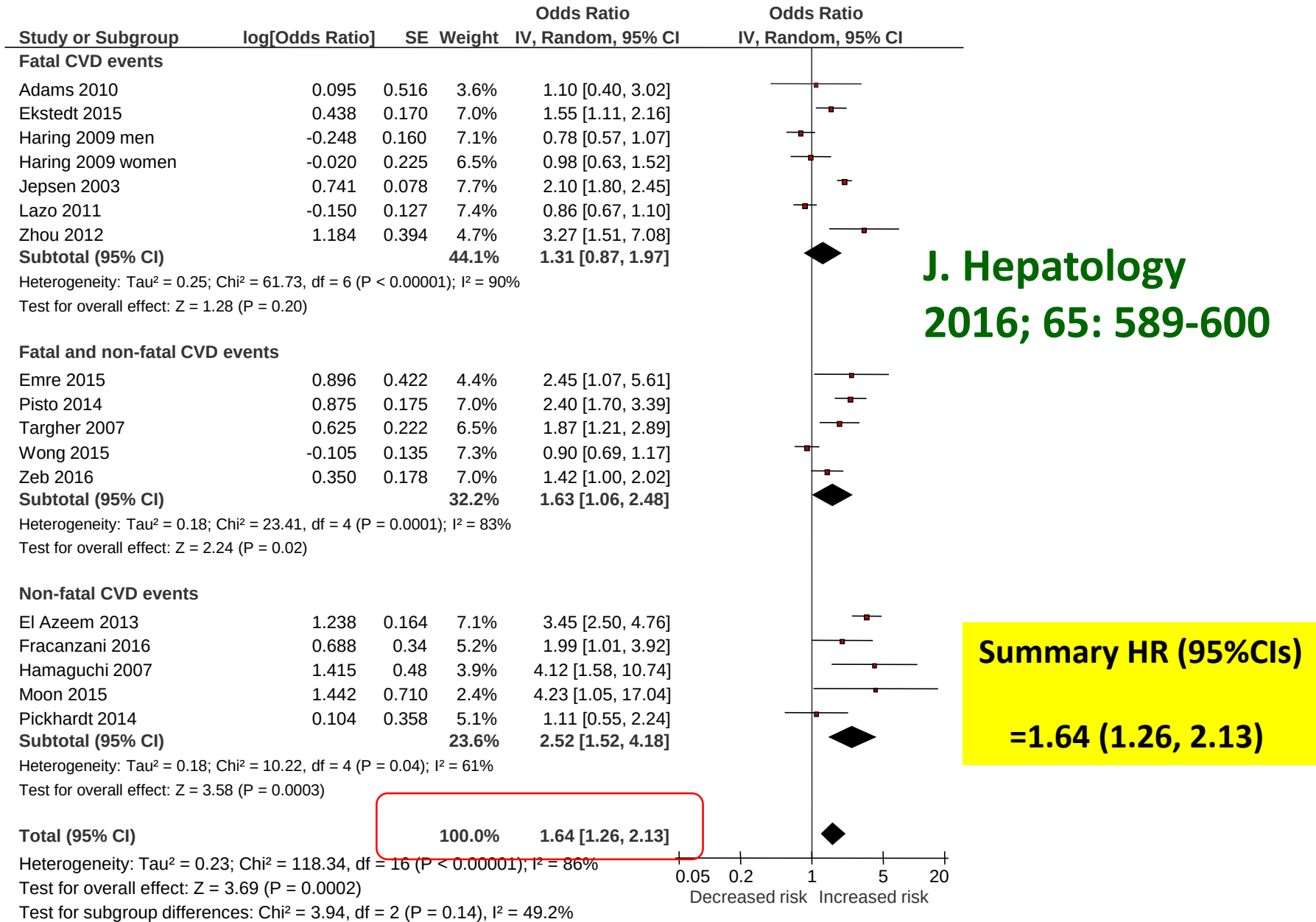
Type 2 diabetes, CVD and cardiac disease and cirrhosis

Type 2 diabetes and NAFLD:
a vicious cycle of metabolic and cardiovascular disease



NAFLD increases risk of incident CVD events (fatal, non-fatal or both)

Meta-analysis of the risk of incident CVD events associated with NAFLD.

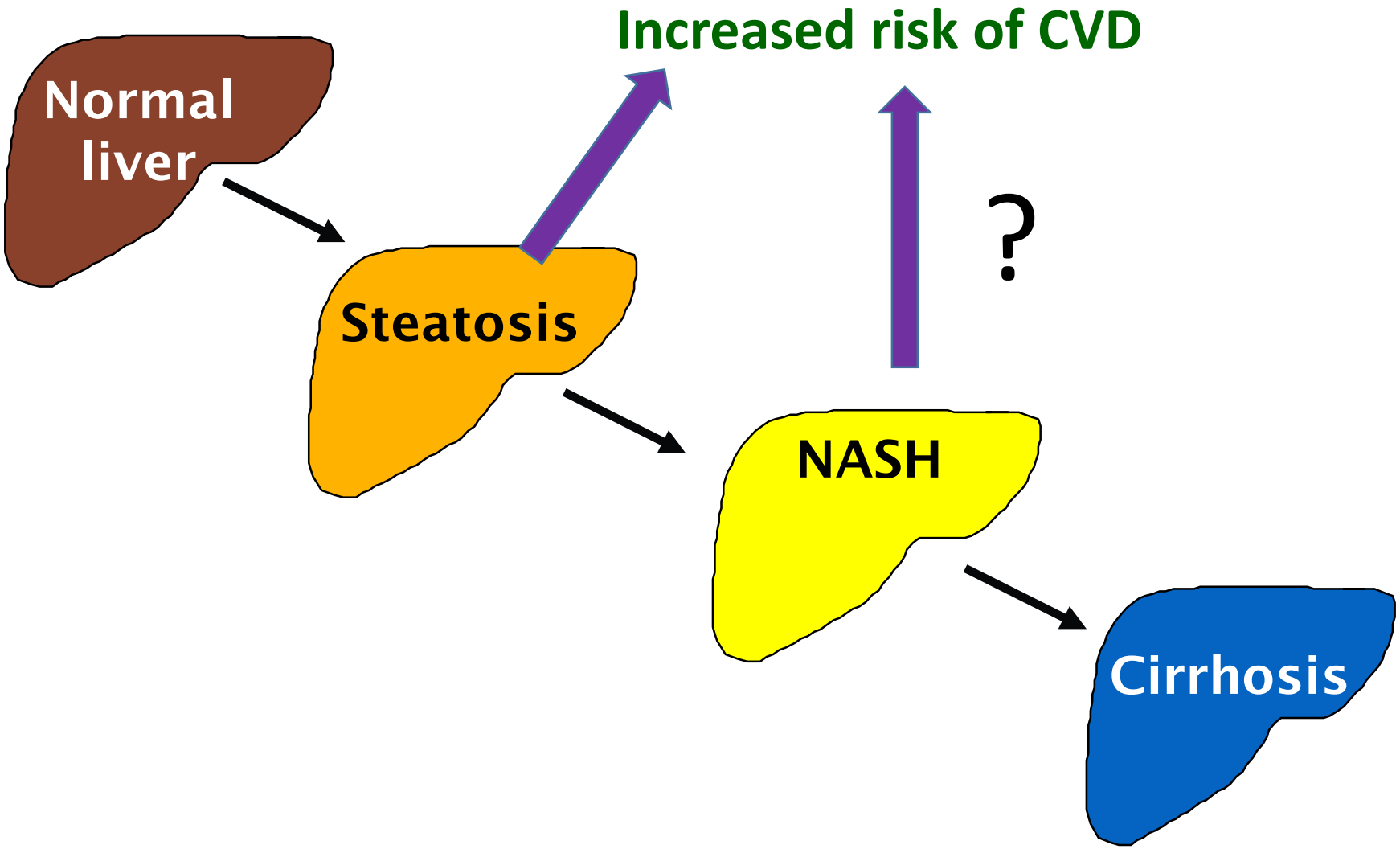


J. Hepatology 2016; 65: 589-600

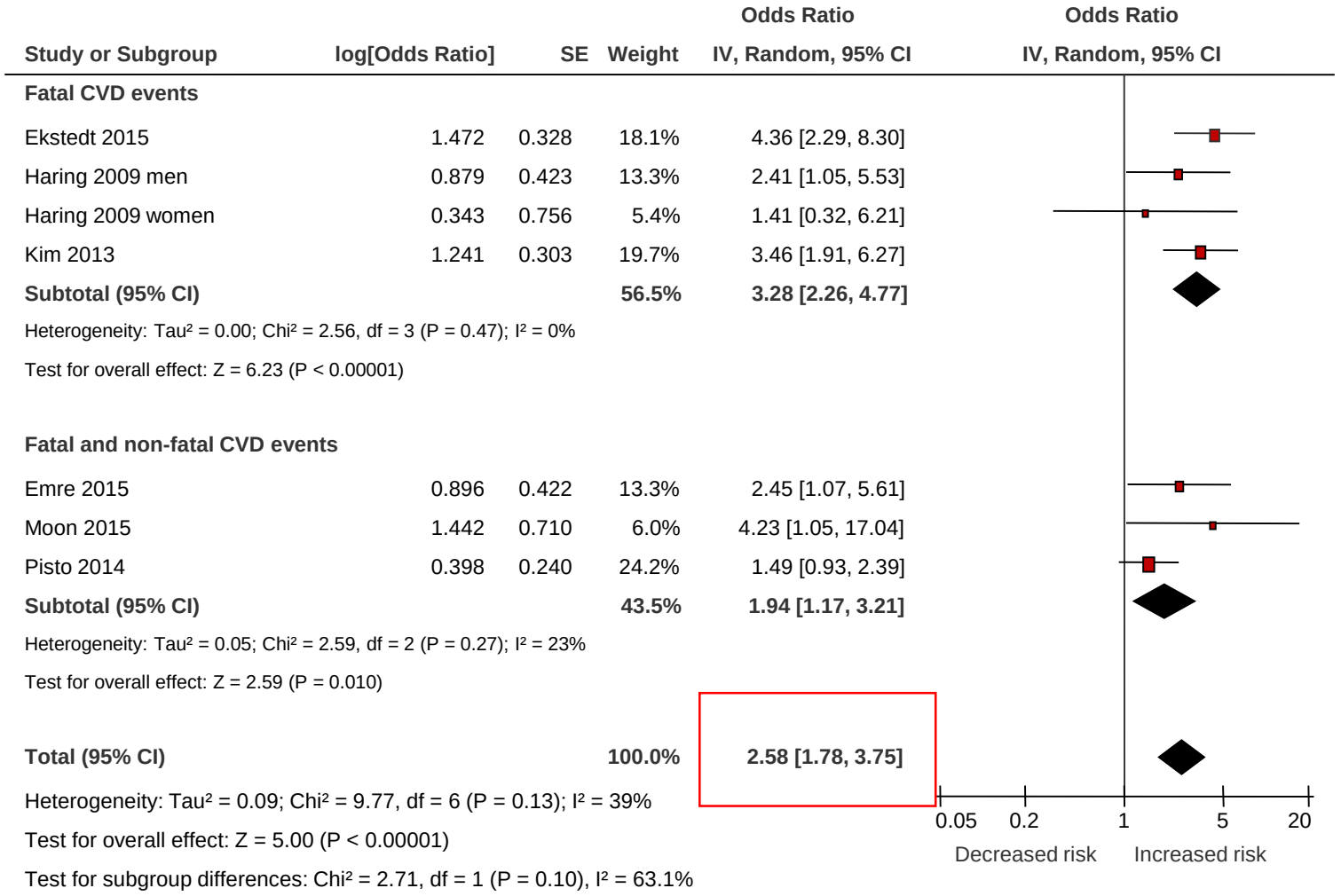
Summary HR (95%CIs)

=1.64 (1.26, 2.13)

Does progression of NAFLD further increase risk of CVD?



Random-effects meta-analysis of the risk of fatal and non-fatal CVD events associated with more severe NAFLD



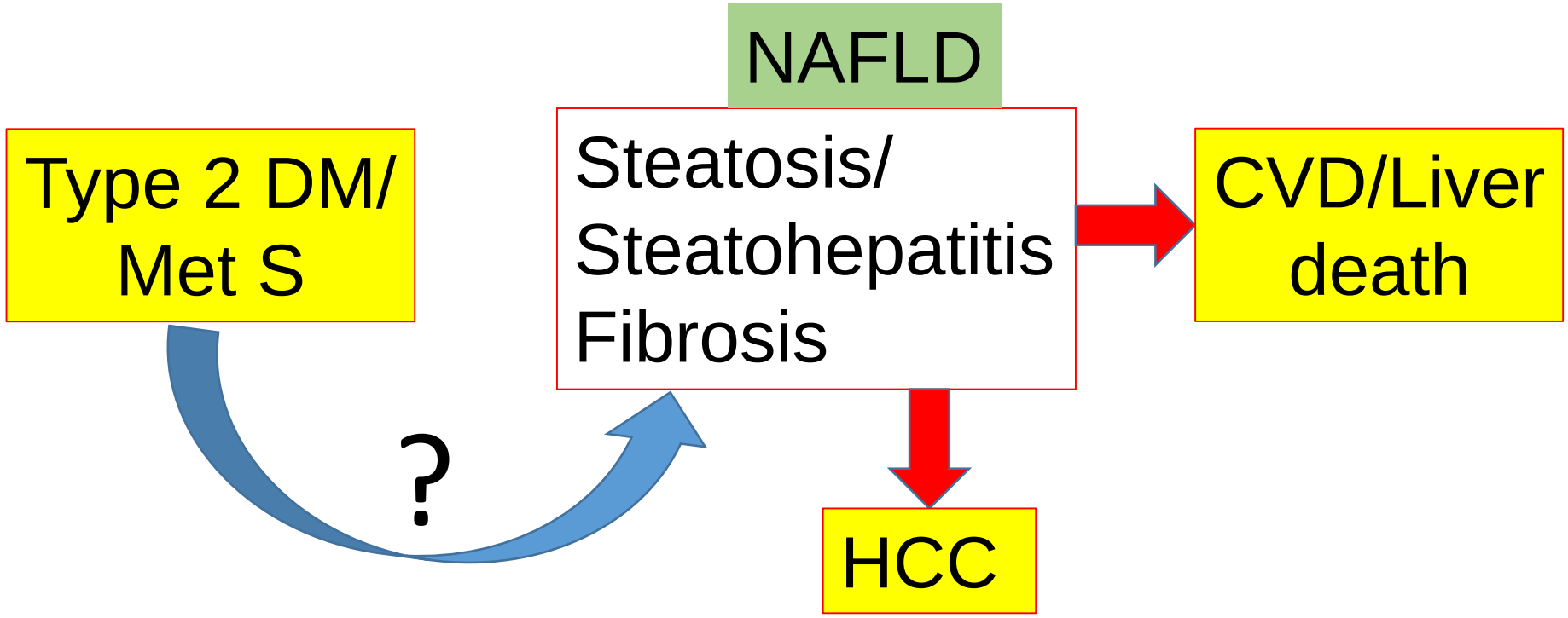
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Fatal CVD events				
Ekstedt 2015	1.472	0.328	18.1%	4.36 [2.29, 8.30]
Haring 2009 men	0.879	0.423	13.3%	2.41 [1.05, 5.53]
Haring 2009 women	0.343	0.756	5.4%	1.41 [0.32, 6.21]
Kim 2013	1.241	0.303	19.7%	3.46 [1.91, 6.27]
Subtotal (95% CI)			**56.5%**	**3.28 [2.26, 4.77]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.56$, df = 3 (P = 0.47); $I^2 = 0\%$				
Test for overall effect: Z = 6.23 (P < 0.00001)				
Fatal and non-fatal CVD events				
Emre 2015	0.896	0.422	13.3%	2.45 [1.07, 5.61]
Moon 2015	1.442	0.710	6.0%	4.23 [1.05, 17.04]
Pisto 2014	0.398	0.240	24.2%	1.49 [0.93, 2.39]
Subtotal (95% CI)			**43.5%**	**1.94 [1.17, 3.21]**
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 2.59$, df = 2 (P = 0.27); $I^2 = 23\%$				
Test for overall effect: Z = 2.59 (P = 0.010)				
Total (95% CI)			**100.0%**	**2.58 [1.78, 3.75]**
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 9.77$, df = 6 (P = 0.13); $I^2 = 39\%$				
Test for overall effect: Z = 5.00 (P < 0.00001)				
Test for subgroup differences: $Chi^2 = 2.71$, df = 1 (P = 0.10), $I^2 = 63.1\%$				

J. Hepatology 2016; 65: 589-600

Summary HR (95%CIs) = 2.58 (1.78, 3.75)

More severe NAFLD defined either by presence of fatty liver on imaging *plus* either elevated serum gamma-glutamyltransferase concentrations or high NAFLD fibrosis score or high FDG uptake on positron emission tomography, or by increasing fibrosis stage on liver biopsy).

Type 2 diabetes and NAFLD:
a vicious cycle of metabolic and cardiovascular disease



Evidence of NAFLD progression from steatosis to NASH plus fibrosis using paired biopsies

Characteristic	NAFL N = 27	NASH n = 83	*p* value
Age (years)	41 ± 11	50 ± 12	<0.001*
Gender (% male)	67%	65%	0.91#
BMI (kg/m^2)	32.9 ± 5.2	34.1 ± 4.9	0.33*
T2DM	21%	56%	0.004#

108 patients had serial biopsies
Median interval 6.6 years (range 1.3 -22.6 years)
45 fibrosis progression
43 no change
20 fibrosis regression

McPherson et al.
J. Hepatol. 2015; 62: 1148-1155

Evidence of NAFLD progression from steatosis to NASH plus fibrosis using paired biopsies

Identification of factors at follow up indicating presence of fibrosis progression

Multivariable regression

- **T2DM (OR 6.25 (95%CIs 1.88,20.0) p=0.003**

- Among patients with NAFL – 80% with fibrosis progression had T2DM at follow-up, compared to 25% with no progression

McPherson et al.
J. Hepatol. 2015; 62: 1148-1155

Risk factors for progression to liver fibrosis (multivariable regression)

(adusted for age, smoking BMI, albumin, eGFR, dyslipidaemia, T2DM, steatosis)

	HR	95% CI	*P* value
Age (years)			
< 50 (*n* = 574)	1	1.462–3.076	< 0.001
≥ 50 (*n* = 988)	2.121		
Smoking			
No (*n* = 935)	1	0.700–1.320	0.807
Yes (*n* = 505)	0.961		
BMI (kg/m^2)			
< 30 (*n* = 1384)	1	0.502–1.410	0.512
> 30 (*n* = 178)	0.841		
Albumin (g/dL)			
≥ 4.2 (*n* = 1342)	1	1.285–2.528	< 0.001
< 4.2 (*n* = 220)	1.802		
eGFR (mL/min/1.73 m^2)			
≥ 60 (*n* = 1475)	1	0.661–1.987	0.628
< 60 (*n* = 86)	1.146		
Dyslipidemia			
No (*n* = 544)	1	0.641–1.166	0.341
Yes (*n* = 1015)	0.865		
T2DM			
No (*n* = 1077)	1		
Yes (*n* = 485)	1.879	1.401–2.520	< 0.001
Fatty liver			
Mild (*n* = 835)	1	0.662–1.202	0.451
Severe (*n* = 727)	0.892		

Japan: 2006-2016
1562 adults (36-64 years) with NAFLD
& FIB-4 <1.3
186 patients progressed to advanced fibrosis
>2.67

Median follow up 7.5 years.

10 year cumulative incidence of progression to advanced fibrosis =12.9% (no diabetes)
And 24.0% in T2DM

US or FLI

Journal of Gastroenterology and Hepatology 2019: 34: 2011-2018

Components of metabolic syndrome are independent predictors of mortality in patients with NAFLD : a population-based study

Variable/cohort	Overall mortality	Cardiovascular mortality	Liver-related mortality	Diabetes mortality
Age	1.10* (1.08 to 1.12)	1.13* (1.11 to 1.16)	1.10* (1.08 to 1.12)	1.18* (1.10 to 1.28)
Male gender	1.27 (0.77 to 2.08)	0.63 (0.27 to 1.44)	9.53* (1.36 to 66.55)	0.49 (0.15 to 1.59)
White	0.79 (0.50 to 1.23)	0.72 (0.37 to 1.41)	0.24 (0.05 to 1.10)	0.47 (0.10 to 2.17)
Smoking	1.40 (0.79 to 2.47)	2.35 (0.78 to 7.09)	0.14 (0.02 to 0.92)	3.66 (0.75 to 18.01)
Type 2 diabetes	2.31* (1.17 to 4.56)	2.76* (1.26 to 6.05)	1.05* (1.00 to 1.65)	99.11* (7.54 to 1302.76)
Insulin resistance	1.48 (0.91 to 2.39)	1.37 (0.67 to 2.82)	53.55* (9.22 to 344.29)	177.30* (9.72 to 3234.02)
Hypercholesterolaemia	1.03 (0.49 to 2.17)	0.60 (0.22 to 1.63)	0.37 (0.06 to 2.15)	39.52* (13.30 to 235.47)
Hypertension	1.17 (0.71 to 1.93)	0.65 (0.32 to 1.32)	0.07 (0.01 to 0.30)	0.63 (0.04 to 11.05)
Obesity	0.65 (0.34 to 1.23)	1.17 (0.54 to 2.54)	11.19* (2.43 to 51.56)	0.08 (0.02 to 0.40)
Metabolic syndrome	2.36* (1.21 to 4.59)	2.28 (0.75 to 6.93)	12.08* (1.10 to 132.22)	7.09* (1.24 to 40.53)

*p Value for the adjusted HR (aHR) is ≤0.05.

NHANES III 1988-1994. Mortality census 31st December 2006
NAFLD = 991
13,004 controls
Median follow up 13.3 years. Mortality rate 16.3%

Stepanova M. et al
GUT 2010; 59: 1410-1415

Diabetes is associated with increased risk of HCC in patients with cirrhosis from NAFLD

- Adult liver transplant registrants with NASH between 2004 and 2017 were identified using the United Network for Organ Sharing (UNOS)/Organ Procurement and the Transplantation registry for external validation.

- Among 354 Mayo Clinic patients with NASH cirrhosis, 253 (71%) had diabetes and 145 (41%) were male. Mean age at cirrhosis evaluation was 62. During a median follow-up of 47 months, 30 patients developed HCC.

- Diabetes was associated with an increased risk of developing HCC in multivariable analysis (HR = 4.2; 95% CI = 1.2-14.2; P = 0.02).

- Other metabolic risk factors, including body mass index, hyperlipidemia, and hypertension, were not associated with HCC risk

Yang JD et al. Hepatology 2019 Jul 15 doi: 10.1002/hep.30858 Epub ahead of pri

‘The strongest independent predictor of a diagnosis of HCC or cirrhosis was a baseline diagnosis of diabetes’

Proportional Hazards model (Cox regression) adjusted for age, smoking and pooled across databases

	NAFLD/NASH HR (95% CI)	Matched control HR (95% CI)
Smoking status (current/not current)	1.19 (0.94; 1.51)	1.50 (1.41; 1.60)
Age (years)	1.04 (1.03; 1.05)	1.04 (1.03; 1.04)
History of diabetes (yes/no)	2.30 (1.90; 2.78)	2.92 (2.76; 3.08)
History of hypertension (yes/no)	0.92 (0.76; 1.12)	1.07 (1.01; 1.13)
BMI (kg/m^2)	1.01 (1.00; 1.03)	1.04 (1.03; 1.04)

18,782,281 adults 136,703 identified via the European Medical Information Framework (EMIF) network coded NAFLD/NASH (each matched with up to 100 ‘controls’.
UK, NL, Italy, Spain.
Median follow up 3.3 years (IQR 1.8, 5.3)

N.B. may be misclassification of ‘controls’ and some may have NAFLD

Alexander et al BMC Medicine 2019; 17:95

Fibrosis is the strongest predictor of disease-specific mortality in NAFLD: 33 years of follow up

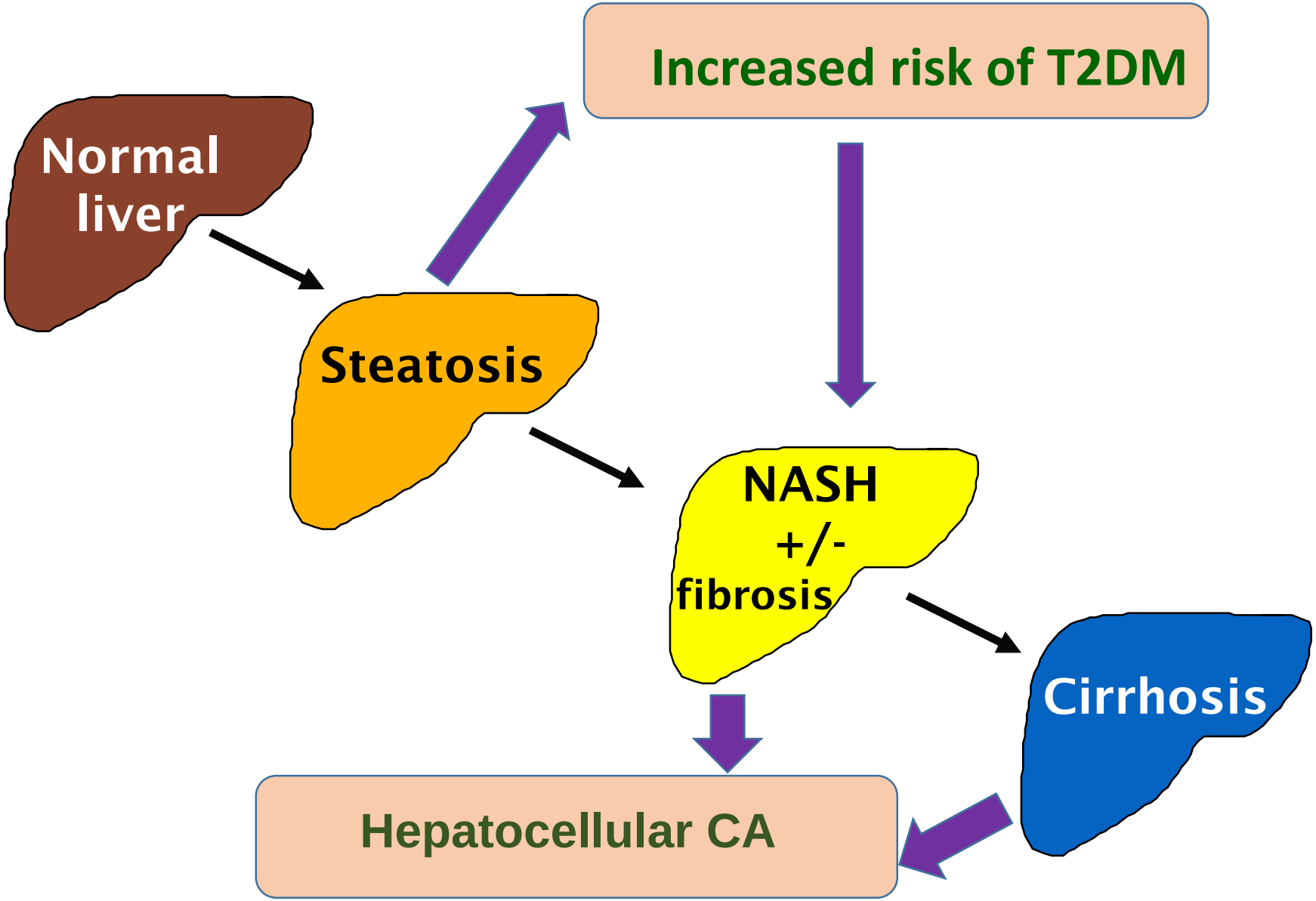
Proportional hazard model (Cox regression) HRs (95%CIs) for causes of death by histological subgroup

Cause of death	Entire cohort (n = 229)	*P*	NAS 0-4, F0-2 (n = 76)	*P*	NAS 5-8, F0-2 (n = 57)	*P*	NAS 0-8, F3-4 (n = 16)	*P*
Overall mortality	1.29 (1.04-1.59)	0.020	1.13 (0.79-1.60)	0.511	1.41 (0.97-2.06)	0.072	3.28 (2.27-4.76)	<0.001
Cardiovascular disease	1.55 (1.11-2.15)	0.01	1.19 (0.65-2.20)	0.557	1.38 (0.72-2.65)	0.335	4.36 (2.29-8.29)	<0.001
Hepatocellular carcinoma	6.55 (2.14-20.0)	0.001	No outcome	-	15.7 (4.1-59.9)	<0.001	16.9 (1.95-146)	0.01
Cirrhosis	3.2 (1.05-9.81)	0.041	4.86 (1.08-22.0)	0.04	No outcome	-	10.8 (1.38-83.9)	0.023

1980- 1993 recruitment, increased ALT or AST (Alk Phos Normal). 93 deaths (41 CVD; 5 HCC; 4 cirrhosis)
229 biopsy-proven patients with NAFLD; 149 NASH
Mean age 48.8 years (67% men); follow-up 26.4 years (range 6-33 years)
59 obese
31 T2DM
118 Hypertriglyceridaemia

Ekstedt et al Hepatology 2015; 61: 1547-54

NAFLD and increased risk of extra-hepatic complications



Does the presence of NAFLD further increase risk of CVD?

In patients with established type 2 diabetes

Cardiovascular disease, cancer and mortality among people with type 2 diabetes with NAFLD (or ALD) requiring hospital admission

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

CVD events HR (95%CIs)

= 1.70 (1.52, 1.90)

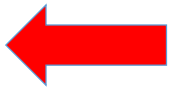
National cohort = 134,368 people with T2DM - mean follow up of 4.3 years
No liver disease = 21,873 CVD events
NAFLD =320 CVD events
ALD = 378 CVD events

Diabetes Care 2018; 41: 1-7

Does the presence of fibrosis/cirrhosis with NAFLD further increase risk of CVD and CVD mortality?

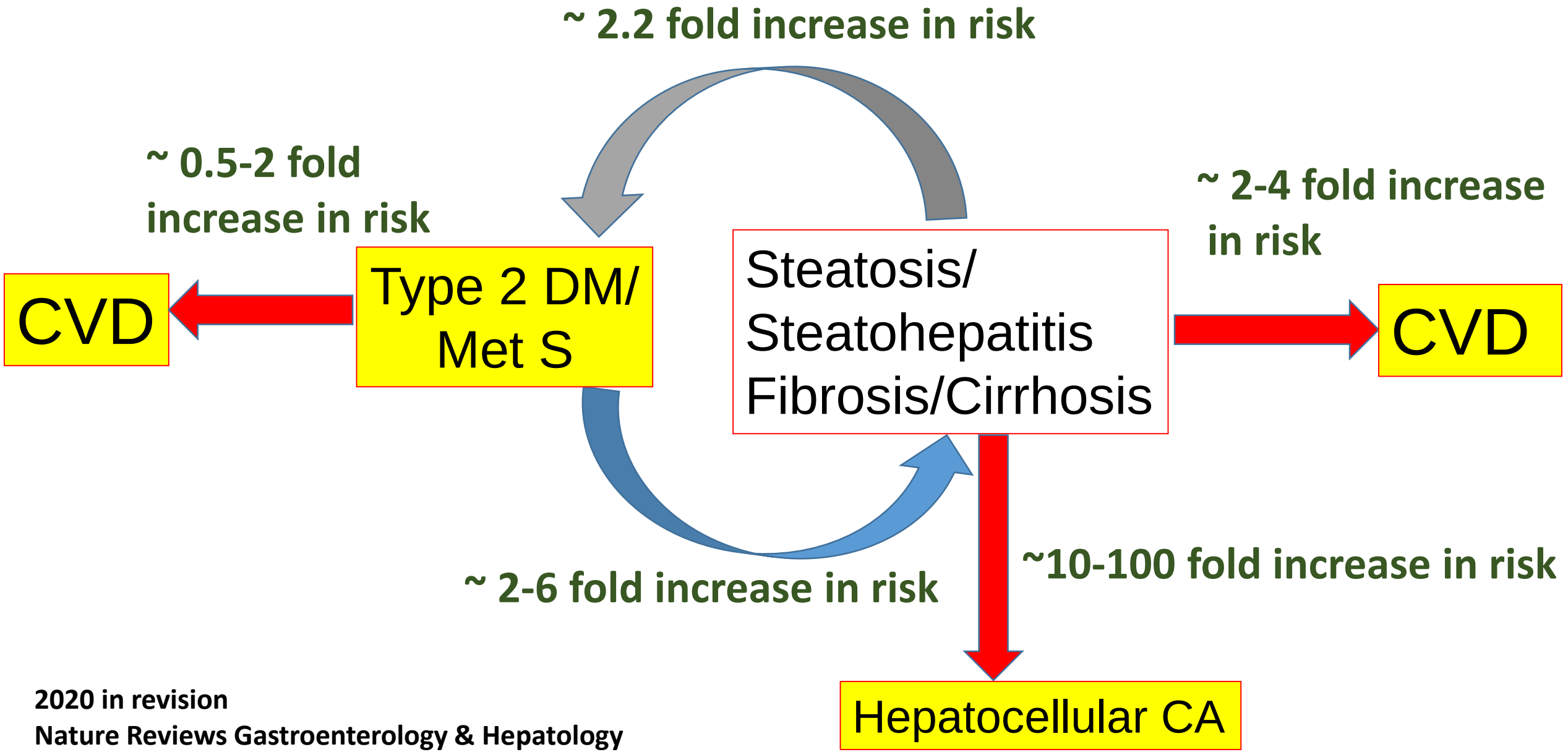
Diabetes UK
Annual scientific meeting
2019

	Hazard ratios (95% CI)		
Outcome	**Whole NAFLD group [a] (n = 1998)**	**Fatty liver / NASH sub-group [a,b] (n = 1283)**	**Cirrhosis / fibrosis/ Sclerosis/ PH sub-group [a,c] (n = 715)**
Incident or recurrent CVD event after diagnosis of diabetes	1.62 (1.47, 1.77)	1.66 (1.47, 1.87)	1.57 (1.36, 1.80)
All-cause mortality	2.11 (1.92, 2.32)	1.29 (1.10, 1.51)	3.20 (2.84, 3.60)
CVD mortality	1.39 (1.10, 1.74)	1.10 (0.78, 1.54)	1.78 (1.31, 2.42)
HCC mortality	41.89 (27.1, 64.8)	2.42 (0.33, 17.5)	90.81 (58.0, 142.1)
Cancer mortality (excluding HCC)	1.15 (0.92, 1.42)	0.81 (0.58, 1.13)	1.60 (1.21, 2.10)
Other causes of death	3.16 (2.77, 3.59)	1.89 (1.52, 2.35)	4.82 (4.11, 5.64)



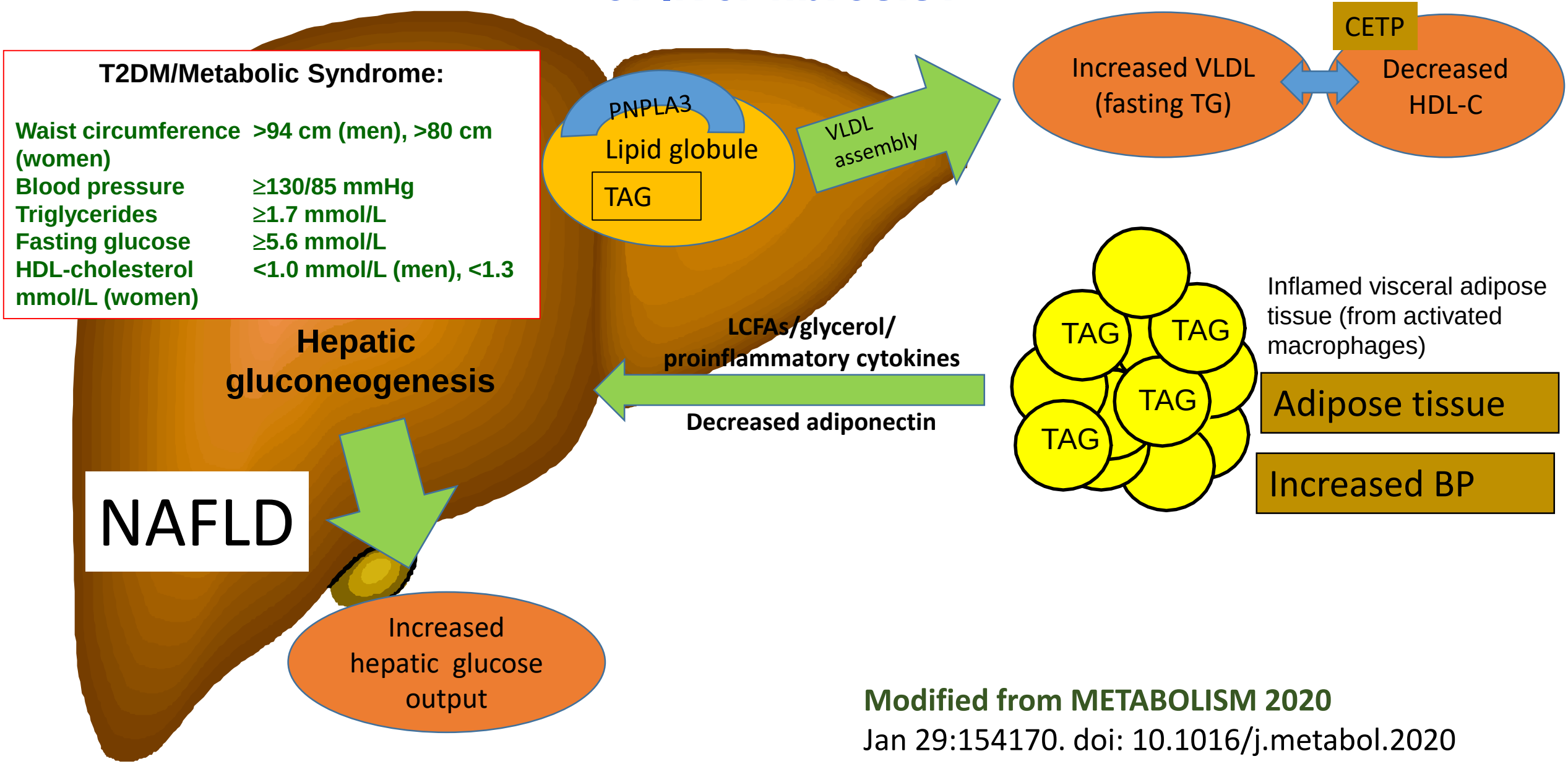
134,368 people with type 2 diabetes and ≥1 hospital admission record and no record of other chronic liver diseases aged 40-89 years from 2004-2013.

The presence of NAFLD and type 2 diabetes creates a vicious spiral of disease



2020 in revision
Nature Reviews Gastroenterology & Hepatology

What simple risk factors should highlight the possibility of liver fat or liver fibrosis?



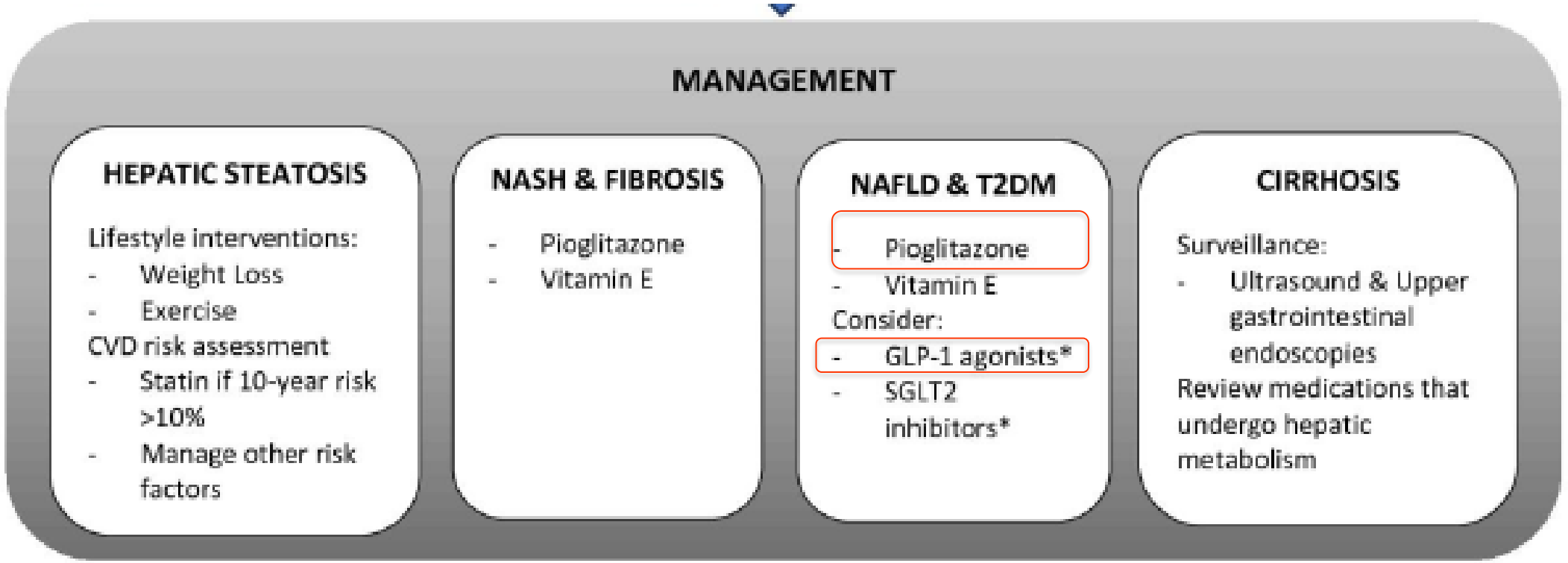
Modified from METABOLISM 2020

Jan 29:154170. doi: 10.1016/j.metabol.2020

What treatment for T2DM, NAFLD and CVD risk?

Postgrad Med J. 2019 May 13. pii: postgradmedj-2018-136316

MANAGEMENT OF NAFLD ACCORDING TO NAFLD SEVERITY AND DIABETES STATUS



Postgrad Med J. 2019 May 13. pii: postgradmedj-2018-136316

Summary

- NAFLD increases risk of diabetes
- In patients with established T2DM
  - T2DM increases risk of progression of liver fibrosis and HCC in NAFLD
  - Liver fibrosis increases risk of CVD events and mortality and HCC
- In T2DM, features of the metabolic syndrome should highlight the possibility of liver fat and/or liver fibrosis
- Treatment with pioglitazone should be considered for patients with T2DM & NAFLD.

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