Complicanze epatiche ed extra-epatiche della MASLD

Prof. Alessandro Mantovani, MD, PhD

Metabolic Diseases Research Unit, IRCCS Sacro Cuore – Don Calabria Hospital

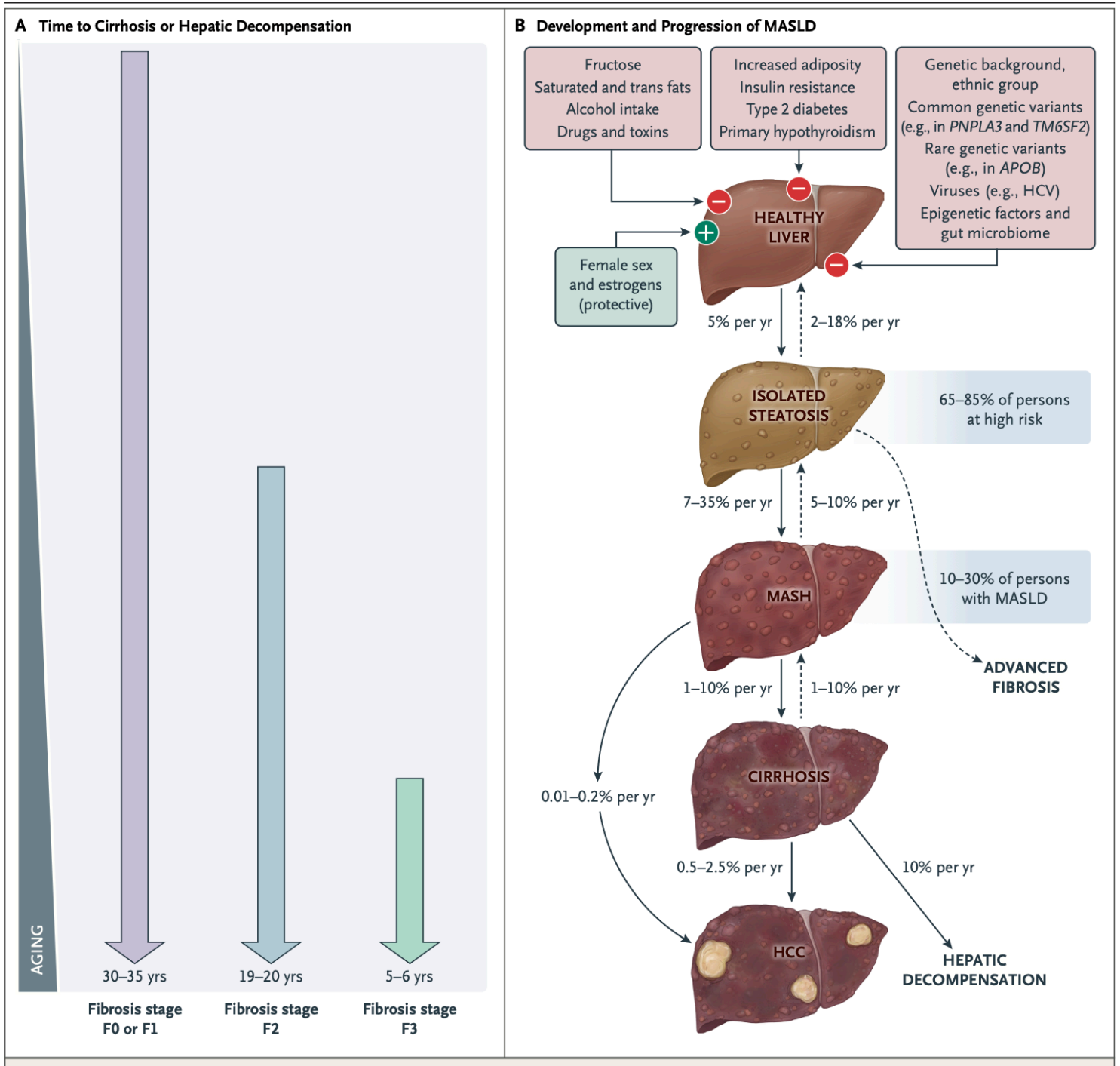
Department of Medicine, University of Verona, Italy

Il Prof. Alessandro Mantovani dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

COMPLICANZE EPATICHE

Natural History of Steatotic Liver Disease and MASLD



- **Dynamic process** where a minority of patients progress from MASLD to MASH, which involves inflammation and liver cell damage.
- **Fibrosis, the main predictor of severe outcomes**, develops in MASH and can lead to cirrhosis, liver decompensation, and hepatocellular carcinoma (HCC).
- Progression is **not always linear**: it can be bidirectional

Targher et al. N Engl J Med 2025;393:683-98.

Progression of non-alcoholic fatty liver disease and long-term outcomes: A nationwide paired liver biopsy cohort study

N = 718 adults with non-cirrhotic NAFLD and paired liver biopsies.
Between 11.7-12.5 median years of follow-up after 2nd biopsy.

Table 2. Distribution of NAFLD histology[1] at the first and second liver biopsies.

	Second biopsy, n (%)[1]				
	Normal	Simple steatosis	NASH without fibrosis	Non-cirrhotic fibrosis	Cirrhosis
First biopsy, n	—	—	—	—	—
Simple steatosis, n = 497	103 (20.7)	223 (44.9)	62 (12.5)	91 (18.3)	18 (3.6)
NASH without fibrosis, n = 90	4 (4.4)	17 (18.9)	37 (41.1)	25 (27.8)	7 (7.8)
Non-cirrhotic fibrosis, n = 131	11 (8.4)	29 (22.1)	18 (13.7)	58 (44.3)	15 (11.5)

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.
[1]NAFLD was defined from liver histology using a validated algorithm, as outlined in the Methods and Supplementary methods. Proportions shown represent the % of individuals in each NAFLD histological category at the second biopsy, divided by the total number of individuals in the original histological category at the time of the first liver biopsy.

Simon TG, et al. J Hepatol. 2023 Dec;79(6):1366-1373.

Progression of non-alcoholic fatty liver disease and long-term outcomes: A nationwide paired liver biopsy cohort study

N = 718 adults with non-cirrhotic NAFLD and paired liver biopsies.
Between 11.7-12.5 median years of follow-up after 2nd biopsy.

Table 2. Distribution of NAFLD histology[1] at the first and second liver biopsies.

	Second biopsy, n (%)[1]				
	Normal	Simple steatosis	NASH without fibrosis	Non-cirrhotic fibrosis	Cirrhosis
First biopsy, n	—	—	—	—	—
Simple steatosis, n = 497	103 (20.7)	223 (44.9)	62 (12.5)	91 (18.3)	18 (3.6)
NASH without fibrosis, n = 90	4 (4.4)	17 (18.9)	37 (41.1)	25 (27.8)	7 (7.8)
Non-cirrhotic fibrosis, n = 131	11 (8.4)	29 (22.1)	18 (13.7)	58 (44.3)	15 (11.5)

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.
[1]NAFLD was defined from liver histology using a validated algorithm, as outlined in the Methods and Supplementary methods. Proportions shown represent the % of individuals in each NAFLD histological category at the second biopsy, divided by the total number of individuals in the original histological category at the time of the first liver biopsy.

Simon TG, et al. J Hepatol. 2023 Dec;79(6):1366-1373.

Progression of non-alcoholic fatty liver disease and long-term outcomes: A nationwide paired liver biopsy cohort study

N = 718 adults with non-cirrhotic NAFLD and paired liver biopsies.
Between 11.7-12.5 median years of follow-up after 2nd biopsy.

Table 2. Distribution of NAFLD histology[1] at the first and second liver biopsies.

	Second biopsy, n (%)[1]				
	Normal	Simple steatosis	NASH without fibrosis	Non-cirrhotic fibrosis	Cirrhosis
First biopsy, n	—	—	—	—	—
Simple steatosis, n = 497	103 (20.7)	223 (44.9)	62 (12.5)	91 (18.3)	18 (3.6)
NASH without fibrosis, n = 90	4 (4.4)	17 (18.9)	37 (41.1)	25 (27.8)	7 (7.8)
Non-cirrhotic fibrosis, n = 131	11 (8.4)	29 (22.1)	18 (13.7)	58 (44.3)	15 (11.5)

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.
[1]NAFLD was defined from liver histology using a validated algorithm, as outlined in the Methods and Supplementary methods. Proportions shown represent the % of individuals in each NAFLD histological category at the second biopsy, divided by the total number of individuals in the original histological category at the time of the first liver biopsy.

Simon TG, et al. J Hepatol. 2023 Dec;79(6):1366-1373.

Progression of non-alcoholic fatty liver disease and long-term outcomes: A nationwide paired liver biopsy cohort study

Table 3. Characteristics of patients with NAFLD at the second biopsy date.

Characteristic	All NAFLD N = 718	Normal n = 118	Simple steatosis n = 269	NASH without fibrosis n = 117	Non-cirrhotic fibrosis n = 174	Cirrhosis n = 40
Female	302 [42.1]	59 [50.0]	100 [37.2]	53 [45.3]	71 [40.8]	19 [47.5]
Age, years, mean [SD]	55.0 [13.9]	57.2 [14.4]	53.6 [13.8]	55.5 [13.8]	53.7 [14.2]	61.3 [9.6]
Time between biopsies, years, median, [min, max]	3.4 [0.5, 34.7]	3.4 [0.5, 23.9]	3.4 [0.5, 33.2]	2.4 [0.5, 21.1]	4.3 [0.5, 25.8]	3.9 [0.5, 34.7]
Year of follow-up biopsy	—		—	—	—	—
1969–1989	102 [14.2]	21 [17.8]	41 [15.2]	26 [22.2]	9 [5.2]	5 [12.5]
1990–2000	243 [33.8]	41 [34.8]	86 [32.0]	44 [37.6]	57 [32.8]	15 37.5]
2001–2010	266 [37.1]	35 [29.7]	114 [42.4]	36 [30.8]	70 [40.2]	11 27.5]
2011–2017	107 [14.9]	21 [17.8]	28 [10.4]	11 [9.4]	38 [21.8]	9 [22.5]
Nordic country of birth	666 [92.8]	109 [92.4]	251 [93.3]	105 [89.7]	162 [93.1]	39 [97.5]
Highest education level[1]	(Among n = 616)	(Among n = 97)	(Among n = 228)	(Among n = 91)	(Among n = 165)	(Among n = 35)
≤9 years	196 [31.8]	28 [28.9]	78 [34.2]	27 [29.7]	45 [27.3]	18 51.4]
10–12 years	249 [40.4]	37 [38.1]	94 [41.2]	42 [46.2]	65 [39.4]	11 [31.4]
≥13 years	146 [23.7]	20 [20.6]	54 [23.7]	19 [20.9]	29.7]	4 [11.4]
Unknown	25 [4.1]	12 [12.4]	2 [0.9]	3 [3.3]	6 [3.6]	2 [5.7]
Cardiovascular disease	191 [26.6]	39 [33.1]	63 [23.4]	29 [24.8]	48 [27.6]	12 [30.0]
Dyslipidemia	87 [12.1]	10 [8.5]	26 [9.7]	12 [10.3]	32 [18.4]	7 [17.5]
Diabetes	136 [18.9]	17 [14.4]	44 [16.4]	17 [14.5]	46 [26.4]	12 [30.0]
Hypertension	171 [23.8]	28 [23.7]	49 [18.2]	21 [18.0]	59 [33.9]	14 [35.0]
Obesity	32 [4.5]	9 [7.6]	8 [3.0]	4 [3.4]	7 [4.0]	4 [10.0]
Any metabolic syndrome feature[2]	329 [45.8]	59 [50.0]	109 [40.5]	47 [40.2]	91 [52.3]	23 [57.5]
Available medication use data[3]	(Among n = 205)	(Among n = 40)	(Among n = 53)	(Among n = 24)	(Among n = 74)	(Among n = 14)
Aspirin	40 [19.5]	10 [25.0]	10 [18.9]	4 [16.7]	12 [16.2]	4 [28.6]
Statin	64 [31.2]	10 [25.0]	19 [35.9]	7 [29.2]	22 [29.7]	6 [42.9]
Antidiabetic medication	57 [27.8]	6 [15.0]	13 [24.5]	7 [29.2]	24 [32.4]	7 [50.0]

Simon TG, et al. J Hepatol. 2023 Dec;79(6):1366-1373.

Progression of non-alcoholic fatty liver disease and long-term outcomes: A nationwide paired liver biopsy cohort study

Table 3. Characteristics of patients with NAFLD at the second biopsy date.

Characteristic	All NAFLD N = 718	Normal n = 118	Simple steatosis n = 269	NASH without fibrosis n = 117	Non-cirrhotic fibrosis n = 174	Cirrhosis n = 40
Female	302 [42.1]	59 [50.0]	100 [37.2]	53 [45.3]	71 [40.8]	19 [47.5]
Age, years, mean [SD]	55.0 [13.9]	57.2 [14.4]	53.6 [13.8]	55.5 [13.8]	53.7 [14.2]	61.3 [9.6]
Time between biopsies, years, median, [min, max]	3.4 [0.5, 34.7]	3.4 [0.5, 23.9]	3.4 [0.5, 33.2]	2.4 [0.5, 21.1]	4.3 [0.5, 25.8]	3.9 [0.5, 34.7]
Year of follow-up biopsy	—		—	—	—	—
1969–1989	102 [14.2]	21 [17.8]	41 [15.2]	26 [22.2]	9 [5.2]	5 [12.5]
1990–2000	243 [33.8]	41 [34.8]	86 [32.0]	44 [37.6]	57 [32.8]	15 37.5]
2001–2010	266 [37.1]	35 [29.7]	114 [42.4]	36 [30.8]	70 [40.2]	11 27.5]
2011–2017	107 [14.9]	21 [17.8]	28 [10.4]	11 [9.4]	38 [21.8]	9 [22.5]
Nordic country of birth	666 [92.8]	109 [92.4]	251 [93.3]	105 [89.7]	162 [93.1]	39 [97.5]
Highest education level[1]	(Among n = 616)	(Among n = 97)	(Among n = 228)	(Among n = 91)	(Among n = 165)	(Among n = 35)
≤9 years	196 [31.8]	28 [28.9]	78 [34.2]	27 [29.7]	45 [27.3]	18 51.4]
10–12 years	249 [40.4]	37 [38.1]	94 [41.2]	42 [46.2]	65 [39.4]	11 [31.4]
≥13 years	146 [23.7]	20 [20.6]	54 [23.7]	19 [20.9]	29.7]	4 [11.4]
Unknown	25 [4.1]	12 [12.4]	2 [0.9]	3 [3.3]	6 [3.6]	2 [5.7]
Cardiovascular disease	191 [26.6]	39 [33.1]	63 [23.4]	29 [24.8]	48 [27.6]	12 [30.0]
Dyslipidemia	87 [12.1]	10 [8.5]	26 [9.7]	12 [10.3]	32 [18.4]	7 [17.5]
Diabetes	136 [18.9]	17 [14.4]	44 [16.4]	17 [14.5]	46 [26.4]	12 [30.0]
Hypertension	171 [23.8]	28 [23.7]	49 [18.2]	21 [18.0]	59 [33.9]	14 [35.0]
Obesity	32 [4.5]	9 [7.6]	8 [3.0]	4 [3.4]	7 [4.0]	4 [10.0]
Any metabolic syndrome feature[2]	329 [45.8]	59 [50.0]	109 [40.5]	47 [40.2]	91 [52.3]	23 [57.5]
Available medication use data[3]	(Among n = 205)	(Among n = 40)	(Among n = 53)	(Among n = 24)	(Among n = 74)	(Among n = 14)
Aspirin	40 [19.5]	10 [25.0]	10 [18.9]	4 [16.7]	12 [16.2]	4 [28.6]
Statin	64 [31.2]	10 [25.0]	19 [35.9]	7 [29.2]	22 [29.7]	6 [42.9]
Antidiabetic medication	57 [27.8]	6 [15.0]	13 [24.5]	7 [29.2]	24 [32.4]	7 [50.0]

Simon TG, et al. J Hepatol. 2023 Dec;79(6):1366-1373.

Progression of non-alcoholic fatty liver disease and long-term outcomes: A nationwide paired liver biopsy cohort study

Table 3. Characteristics of patients with NAFLD at the second biopsy date.

Characteristic	All NAFLD N = 718	Normal n = 118	Simple steatosis n = 269	NASH without fibrosis n = 117	Non-cirrhotic fibrosis n = 174	Cirrhosis n = 40
Female	302 [42.1]	59 [50.0]	100 [37.2]	53 [45.3]	71 [40.8]	19 [47.5]
Age, years, mean [SD]	55.0 [13.9]	57.2 [14.4]	53.6 [13.8]	55.5 [13.8]	53.7 [14.2]	61.3 [9.6]
Time between biopsies, years, median, [min, max]	3.4 [0.5, 34.7]	3.4 [0.5, 23.9]	3.4 [0.5, 33.2]	2.4 [0.5, 21.1]	4.3 [0.5, 25.8]	3.9 [0.5, 34.7]
Year of follow-up biopsy	—		—	—	—	—
1969–1989	102 [14.2]	21 [17.8]	41 [15.2]	26 [22.2]	9 [5.2]	5 [12.5]
1990–2000	243 [33.8]	41 [34.8]	86 [32.0]	44 [37.6]	57 [32.8]	15 37.5]
2001–2010	266 [37.1]	35 [29.7]	114 [42.4]	36 [30.8]	70 [40.2]	11 27.5]
2011–2017	107 [14.9]	21 [17.8]	28 [10.4]	11 [9.4]	38 [21.8]	9 [22.5]
Nordic country of birth	666 [92.8]	109 [92.4]	251 [93.3]	105 [89.7]	162 [93.1]	39 [97.5]
Highest education level[1]	(Among n = 616)	(Among n = 97)	(Among n = 228)	(Among n = 91)	(Among n = 165)	(Among n = 35)
≤9 years	196 [31.8]	28 [28.9]	78 [34.2]	27 [29.7]	45 [27.3]	18 51.4]
10–12 years	249 [40.4]	37 [38.1]	94 [41.2]	42 [46.2]	65 [39.4]	11 [31.4]
≥13 years	146 [23.7]	20 [20.6]	54 [23.7]	19 [20.9]	29.7]	4 [11.4]
Unknown	25 [4.1]	12 [12.4]	2 [0.9]	3 [3.3]	6 [3.6]	2 [5.7]
Cardiovascular disease	191 [26.6]	39 [33.1]	63 [23.4]	29 [24.8]	48 [27.6]	12 [30.0]
Dyslipidemia	87 [12.1]	10 [8.5]	26 [9.7]	12 [10.3]	32 [18.4]	7 [17.5]
Diabetes	136 [18.9]	17 [14.4]	44 [16.4]	17 [14.5]	46 [26.4]	12 [30.0]
Hypertension	171 [23.8]	28 [23.7]	49 [18.2]	21 [18.0]	59 [33.9]	14 [35.0]
Obesity	32 [4.5]	9 [7.6]	8 [3.0]	4 [3.4]	7 [4.0]	4 [10.0]
Any metabolic syndrome feature[2]	329 [45.8]	59 [50.0]	109 [40.5]	47 [40.2]	91 [52.3]	23 [57.5]
Available medication use data[3]	(Among n = 205)	(Among n = 40)	(Among n = 53)	(Among n = 24)	(Among n = 74)	(Among n = 14)
Aspirin	40 [19.5]	10 [25.0]	10 [18.9]	4 [16.7]	12 [16.2]	4 [28.6]
Statin	64 [31.2]	10 [25.0]	19 [35.9]	7 [29.2]	22 [29.7]	6 [42.9]
Antidiabetic medication	57 [27.8]	6 [15.0]	13 [24.5]	7 [29.2]	24 [32.4]	7 [50.0]

Simon TG, et al. J Hepatol. 2023 Dec;79(6):1366-1373.

Type 2 diabetes, hepatic decompensation, and hepatocellular carcinoma in patients with non-alcoholic fatty liver disease: an individual participant-level data meta-analysis

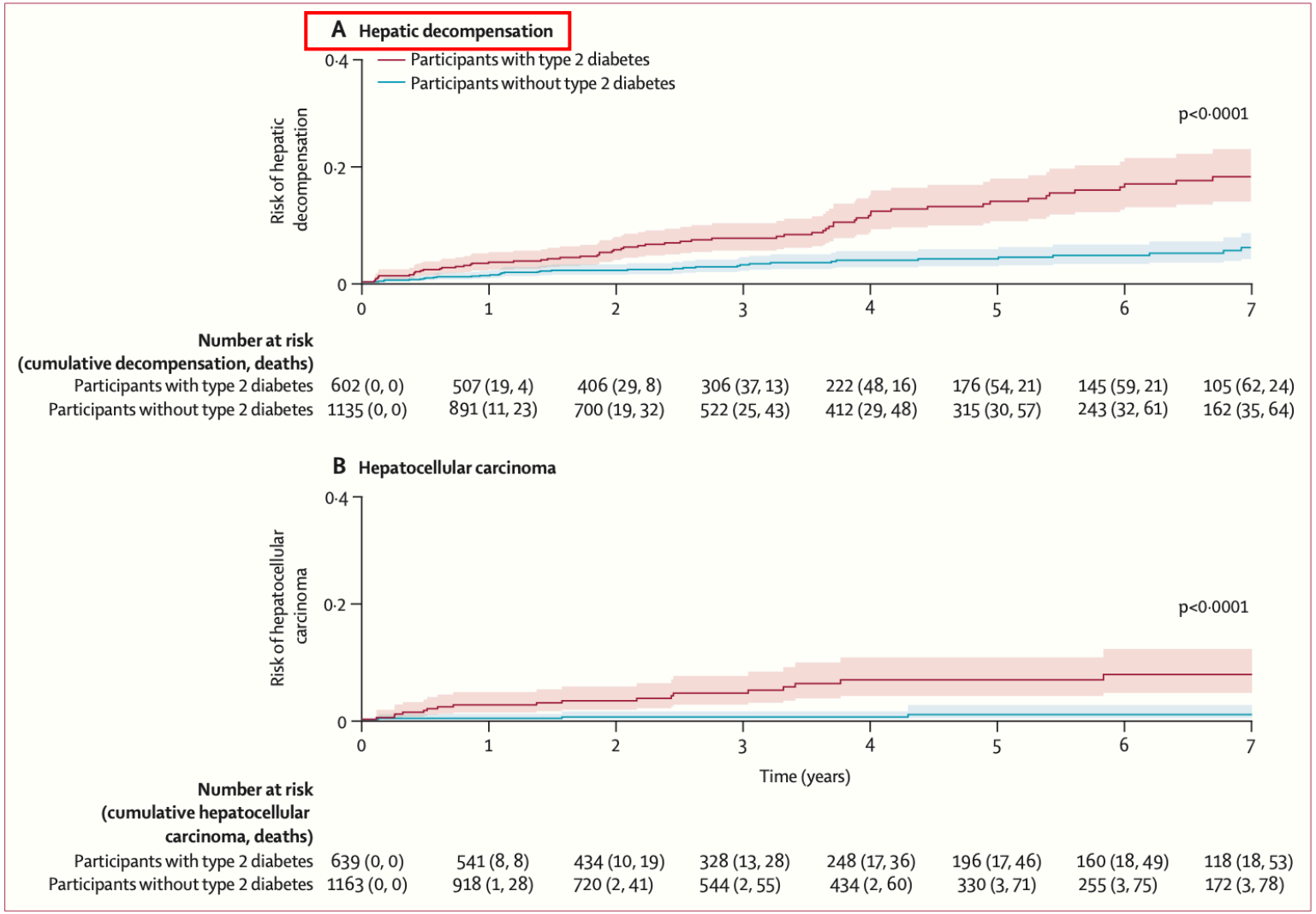


Figure 1: **Risk of hepatic decompensation (A) and hepatocellular carcinoma (B) in participants with non-alcoholic fatty liver disease, with death as a competing risk, stratified by type 2 diabetes status**

Hepatic decompensation was defined as ascites, hepatic encephalopathy, or variceal bleeding. Cumulative cases of decompensation, deaths, and hepatocellular carcinoma are shown until year 7 of follow-up. Graphs are truncated as the number of participants at risk was low after 7 years.

- Meta-analysis of individual participant-level data from six cohorts in the USA, Japan, and Turkey: 2016 participants (736 with type 2 diabetes; 1280 without type 2 diabetes)
- Included participants had magnetic resonance elastography between Feb 27, 2007, and June 4, 2021.

Huang DQ et al. Lancet Gastroenterol Hepatol 2023; 8: 829–36

Type 2 diabetes, hepatic decompensation, and hepatocellular carcinoma in patients with non-alcoholic fatty liver disease: an individual participant-level data meta-analysis

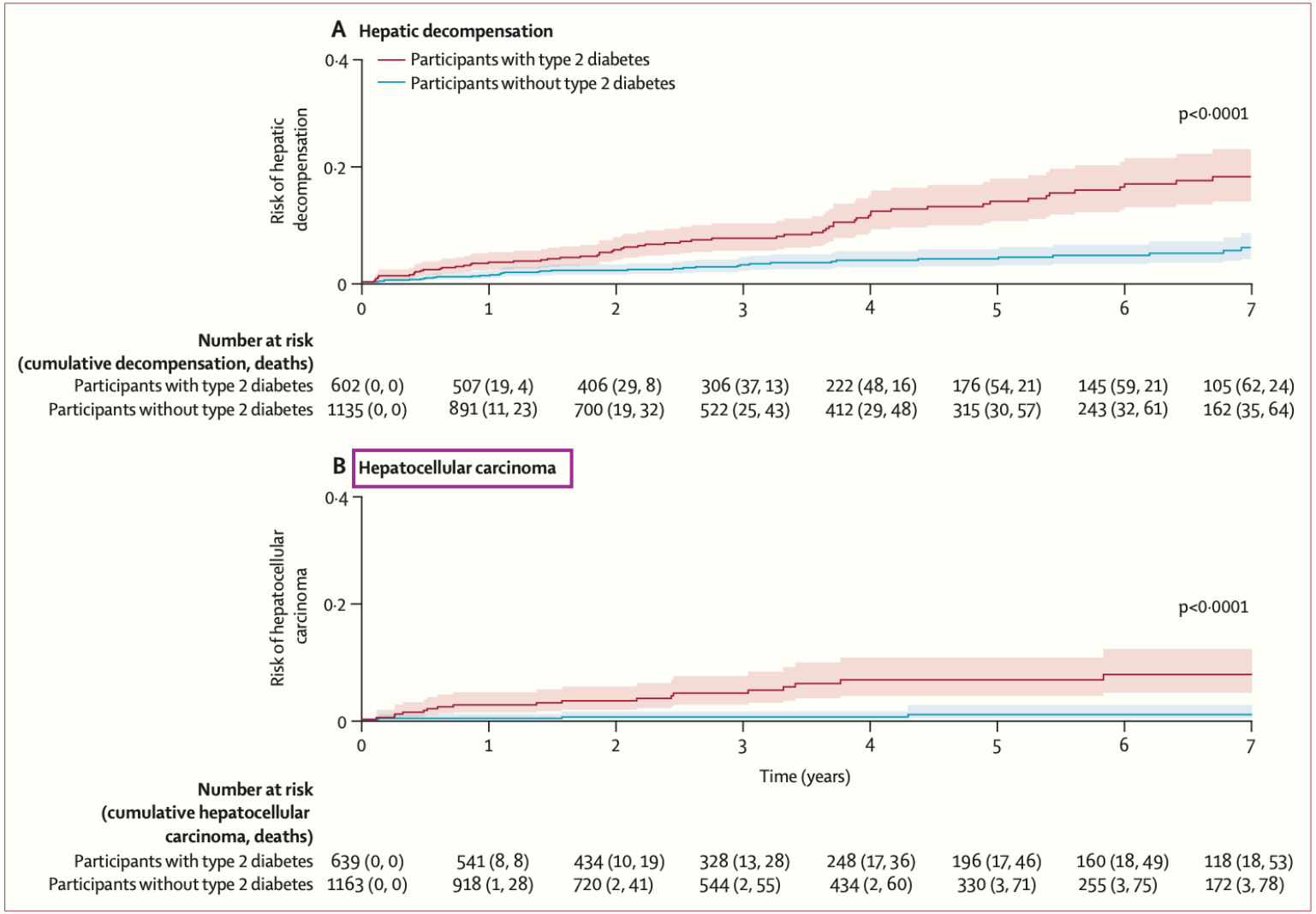


Figure 1: **Risk of hepatic decompensation (A) and hepatocellular carcinoma (B) in participants with non-alcoholic fatty liver disease, with death as a competing risk, stratified by type 2 diabetes status**

Hepatic decompensation was defined as ascites, hepatic encephalopathy, or variceal bleeding. Cumulative cases of decompensation, deaths, and hepatocellular carcinoma are shown until year 7 of follow-up. Graphs are truncated as the number of participants at risk was low after 7 years.

- Meta-analysis of individual participant-level data from six cohorts in the USA, Japan, and Turkey: 2016 participants (736 with type 2 diabetes; 1280 without type 2 diabetes)
- Included participants had magnetic resonance elastography between Feb 27, 2007, and June 4, 2021.

Huang DQ et al. Lancet Gastroenterol Hepatol 2023; 8: 829–36

KEY POINT - 1

- People with hepatic steatosis are at an increased risk of developing cirrhosis and hepatocellular carcinoma.
- About 10-20% of people with MASH can progress to decompensated cirrhosis and the severity of hepatic fibrosis is an important predictor of adverse liver-related outcomes.
- In this respect, fibrosis stages F3 (severe fibrosis) and F4 (cirrhosis) were associated with increased risks of liver-related complications and death
- Furthermore, in patients with hepatic fibrosis, the presence of diabetes strongly increases this risk.

COMPLICANZE EXTRA-EPATICHE

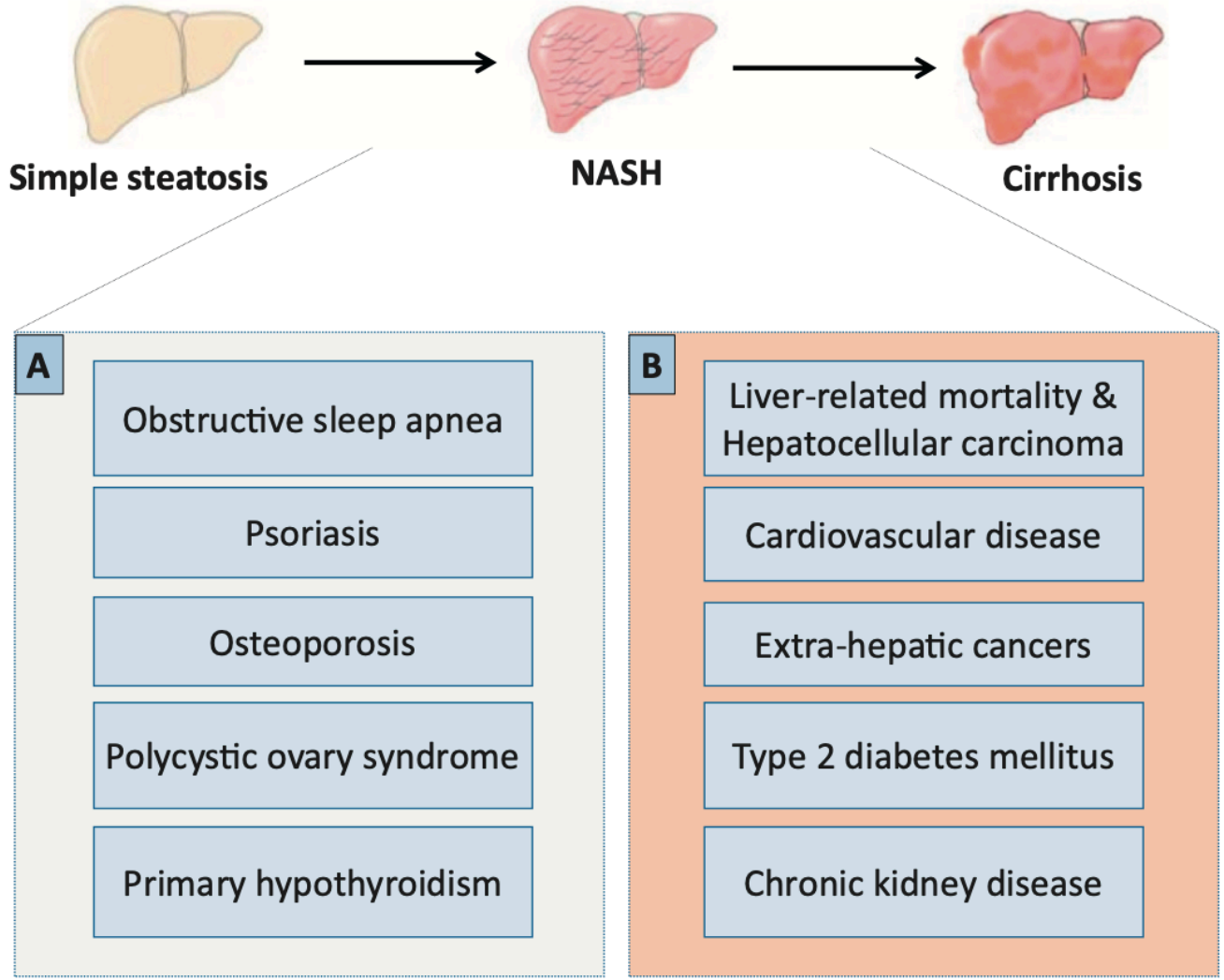


Fig. 1. Principal hepatic complications and extra-hepatic diseases associated with NAFLD (Panel A and Panel B). Only those shown in Panel B are discussed in the text.

Mantovani A, et al. Metabolism. 2020 Oct;111S:154170.

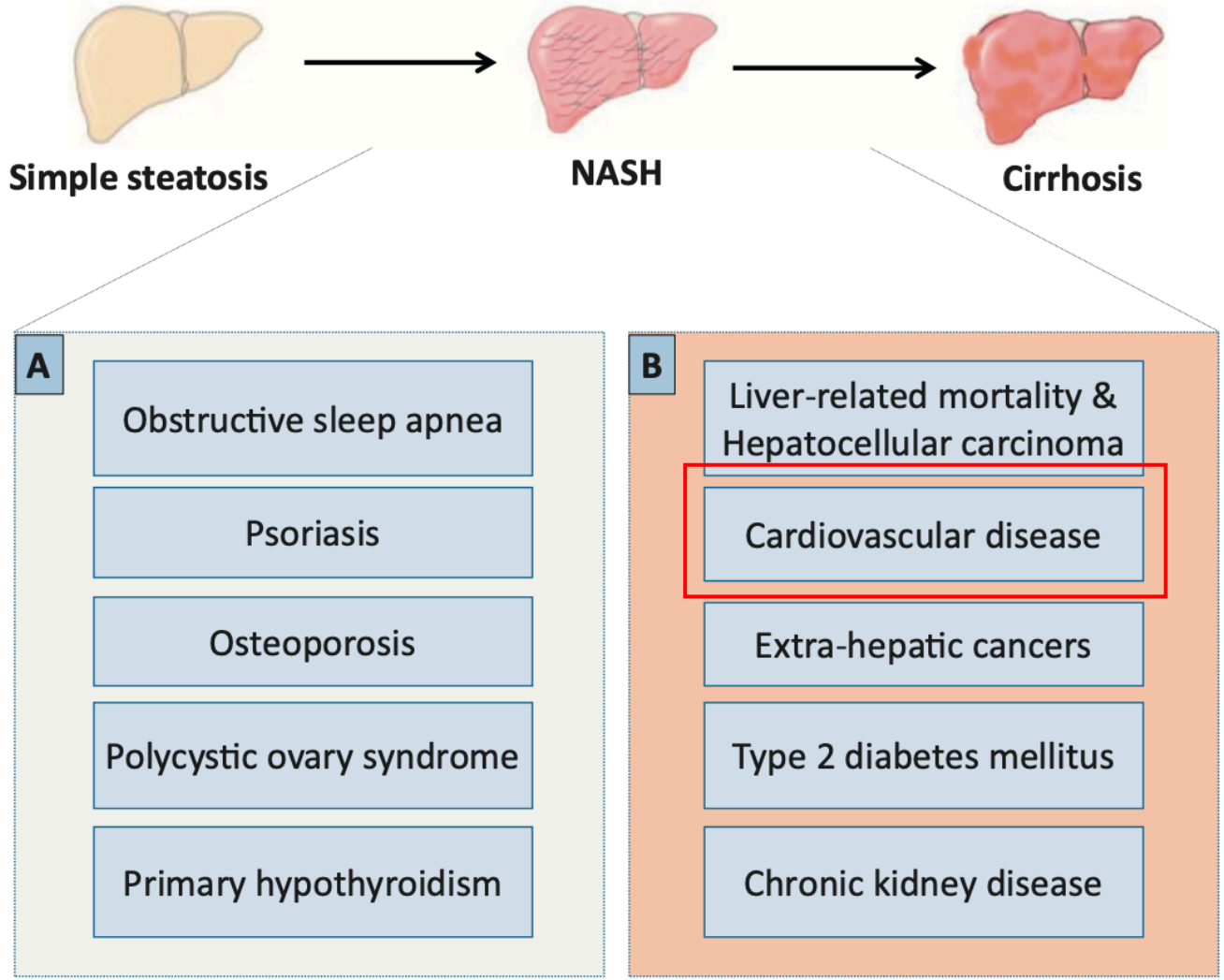
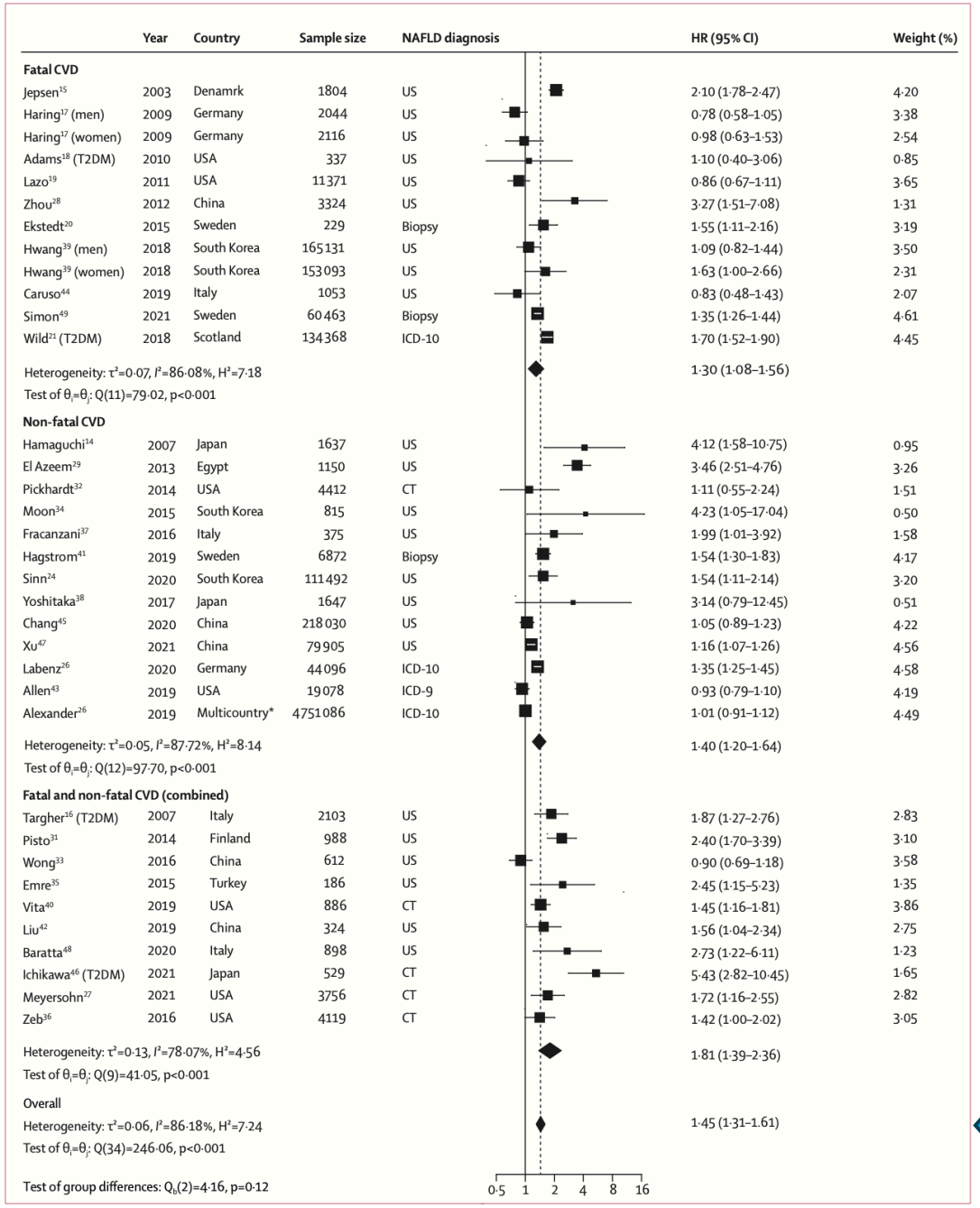


Fig. 1. Principal hepatic complications and extra-hepatic diseases associated with NAFLD (Panel A and Panel B). Only those shown in Panel B are discussed in the text.

Mantovani A, et al. Metabolism. 2020 Oct;111S:154170.

Non-alcoholic fatty liver disease and risk of fatal and non-fatal cardiovascular events: an updated systematic review and meta-analysis



	Year	Country	Sample size	NAFLD diagnosis	HR (95% CI)	Weight (%)
Fatal CVD						
Jepsen[15]	2003	Denamrk	1804	US	2·10 (1·78–2·47)	4·20
Haring[17] (men)	2009	Germany	2044	US	0·78 (0·58–1·05)	3·38
Haring[17] (women)	2009	Germany	2116	US	0·98 (0·63–1·53)	2·54
Adams[18] (T2DM)	2010	USA	337	US	1·10 (0·40–3·06)	0·85
Lazo[19]	2011	USA	11371	US	0·86 (0·67–1·11)	3·65
Zhou[28]	2012	China	3324	US	3·27 (1·51–7·08)	1·31
Ekstedt[20]	2015	Sweden	229	Biopsy	1·55 (1·11–2·16)	3·19
Hwang[39] (men)	2018	South Korea	165131	US	1·09 (0·82–1·44)	3·50
Hwang[39] (women)	2018	South Korea	153093	US	1·63 (1·00–2·66)	2·31
Caruso[44]	2019	Italy	1053	US	0·83 (0·48–1·43)	2·07
Simon[49]	2021	Sweden	60463	Biopsy	1·35 (1·26–1·44)	4·61
Wild[21] (T2DM)	2018	Scotland	134368	ICD-10	1·70 (1·52–1·90)	4·45
Heterogeneity: τ^2=0·07, I^2=86·08%, H^2=7·18					1·30 (1·08–1·56)	
Test of $\theta_i=\theta_j$: Q(11)=79·02, p<0·001						
Non-fatal CVD						
Hamaguchi[14]	2007	Japan	1637	US	4·12 (1·58–10·75)	0·95
El Azeem[29]	2013	Egypt	1150	US	3·46 (2·51–4·76)	3·26
Pickhardt[32]	2014	USA	4412	CT	1·11 (0·55–2·24)	1·51
Moon[34]	2015	South Korea	815	US	4·23 (1·05–17·04)	0·50
Fracanzani[37]	2016	Italy	375	US	1·99 (1·01–3·92)	1·58
Hagstrom[41]	2019	Sweden	6872	Biopsy	1·54 (1·30–1·83)	4·17
Sinn[24]	2020	South Korea	111492	US	1·54 (1·11–2·14)	3·20
Yoshitaka[38]	2017	Japan	1647	US	3·14 (0·79–12·45)	0·51
Chang[45]	2020	China	218030	US	1·05 (0·89–1·23)	4·22
Xu[47]	2021	China	79905	US	1·16 (1·07–1·26)	4·56
Labenz[26]	2020	Germany	44096	ICD-10	1·35 (1·25–1·45)	4·58
Allen[43]	2019	USA	19078	ICD-9	0·93 (0·79–1·10)	4·19
Alexander[26]	2019	Multicountry*	4751086	ICD-10	1·01 (0·91–1·12)	4·49
Heterogeneity: τ^2=0·05, I^2=87·72%, H^2=8·14					1·40 (1·20–1·64)	
Test of $\theta_i=\theta_j$: Q(12)=97·70, p<0·001						
Fatal and non-fatal CVD (combined)						
Targher[16] (T2DM)	2007	Italy	2103	US	1·87 (1·27–2·76)	2·83
Pisto[31]	2014	Finland	988	US	2·40 (1·70–3·39)	3·10
Wong[33]	2016	China	612	US	0·90 (0·69–1·18)	3·58
Emre[35]	2015	Turkey	186	US	2·45 (1·15–5·23)	1·35
Vita[40]	2019	USA	886	CT	1·45 (1·16–1·81)	3·86
Liu[42]	2019	China	324	US	1·56 (1·04–2·34)	2·75
Baratta[48]	2020	Italy	898	US	2·73 (1·22–6·11)	1·23
Ichikawa[46] (T2DM)	2021	Japan	529	CT	5·43 (2·82–10·45)	1·65
Meyersohn[27]	2021	USA	3756	CT	1·72 (1·16–2·55)	2·82
Zeb[36]	2016	USA	4119	CT	1·42 (1·00–2·02)	3·05
Heterogeneity: τ^2=0·13, I^2=78·07%, H^2=4·56					1·81 (1·39–2·36)	
Test of $\theta_i=\theta_j$: Q(9)=41·05, p<0·001						
Overall						
Heterogeneity: τ^2=0·06, I^2=86·18%, H^2=7·24					1·45 (1·31–1·61)	
Test of $\theta_i=\theta_j$: Q(34)=246·06, p<0·001						
Test of group differences: $Q_b(2)$=4·16, p=0·12						

0·5 1 2 4 8 16

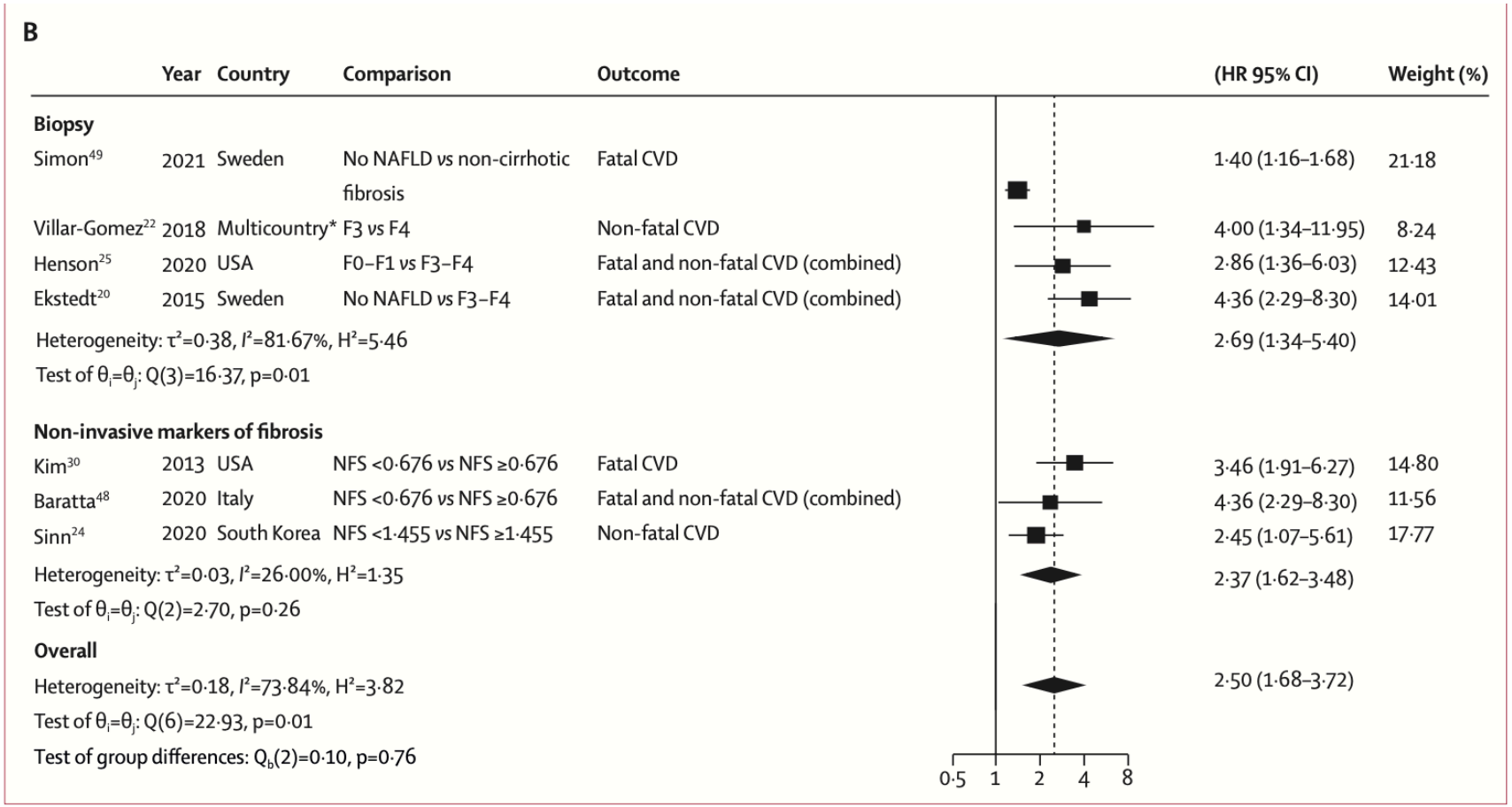
Figure 2: **Forest plot and pooled estimates of the effect of NAFLD on the risk of fatal and non-fatal CVD, stratified by outcome**
CVD=cardiovascular disease. HR=hazard ratio. ICD=International Classification of Diseases. NAFLD=non-alcoholic fatty liver disease. T2DM=type 2 diabetes. US=ultrasound. *Data from Italy, Netherlands, Spain, and the UK.

- 36 longitudinal studies with aggregate data on 5,802,226 middle-aged individuals (mean age 53 years [SD 7]) and 99,668 incident cases of fatal and non-fatal CVD events over a median follow-up of 6.5 years (IQR 5·0–10·2).
- NAFLD was diagnosed by imaging, International Classification of Diseases codes, or liver biopsy.
- The primary outcomes were CVD death, non-fatal CVD events, or both.

HR 1.45 (1.31-1.61)

Mantovani A et al. Lancet Gastroenterol Hepatol. 2021;6:903-913.

Non-alcoholic fatty liver disease and risk of fatal and non-fatal cardiovascular events: an updated systematic review and meta-analysis



HR 2.50 (1.68-3.72)

Mantovani A et al. Lancet Gastroenterol Hepatol. 2021;6:903-913.

Relationship between NAFLD and coronary artery disease: A Mendelian randomization study

MR analyses using summary-level data to assess the association between genetically predicted NAFLD (i.e., chronically elevated serum alanine aminotransferase levels [cALT], imaging-based and biopsy-confirmed NAFLD) and risk of CAD.

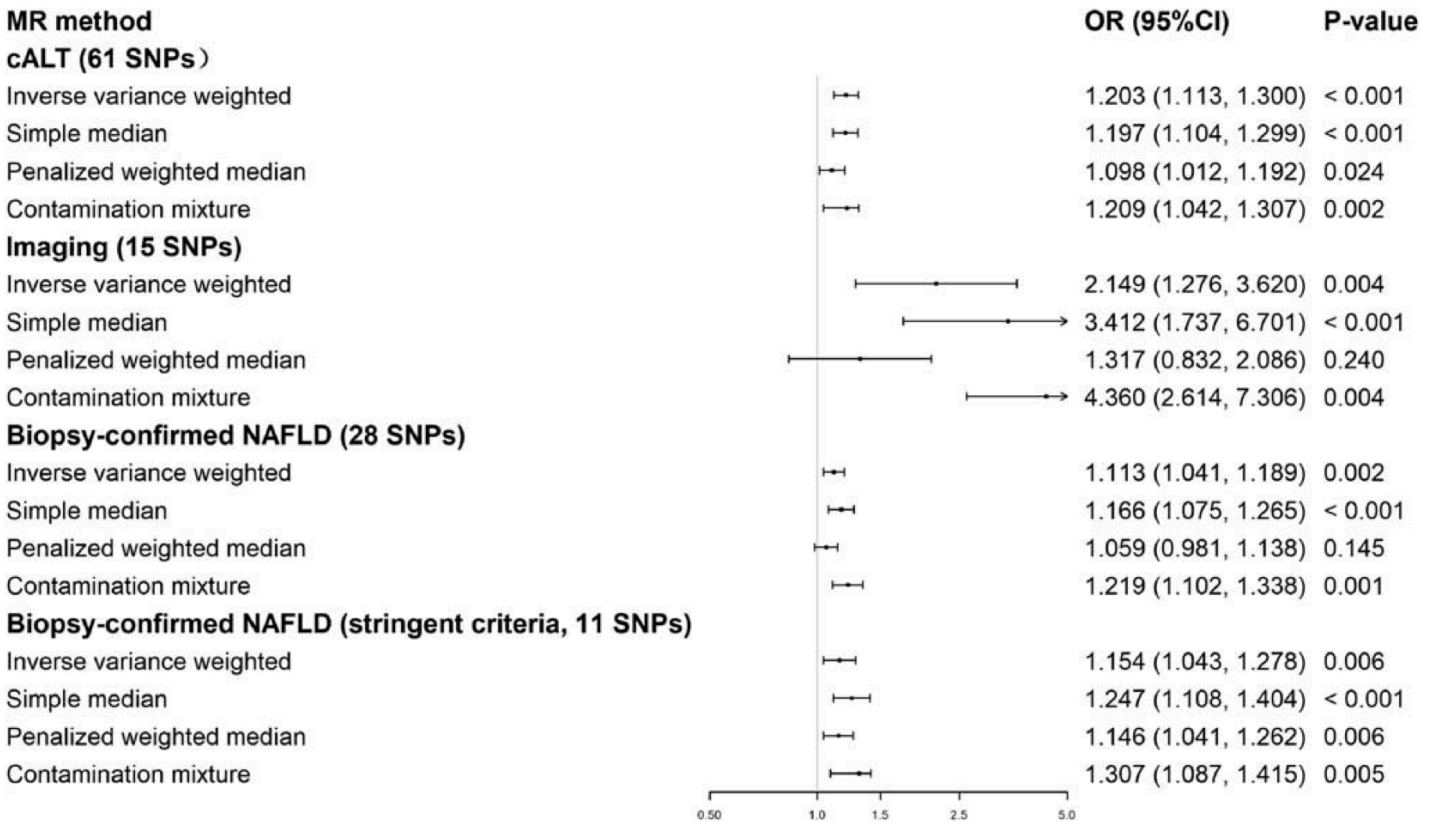


FIGURE 3 Association of genetically predicted cALT, imaging-based and biopsy-confirmed NAFLD (using either general or stringent criteria, see methods section) (after exclusion of genes associated with impaired VLDL secretion) with risk of CAD, analyzed with four different MR methods. Effect estimates are presented as increase in odds of CAD per SD increase in imaging, or per unit increase in (log)odds of cALT-based or biopsy-confirmed NAFLD

Ren Z et al. Hepatology. 2023;77:230-238

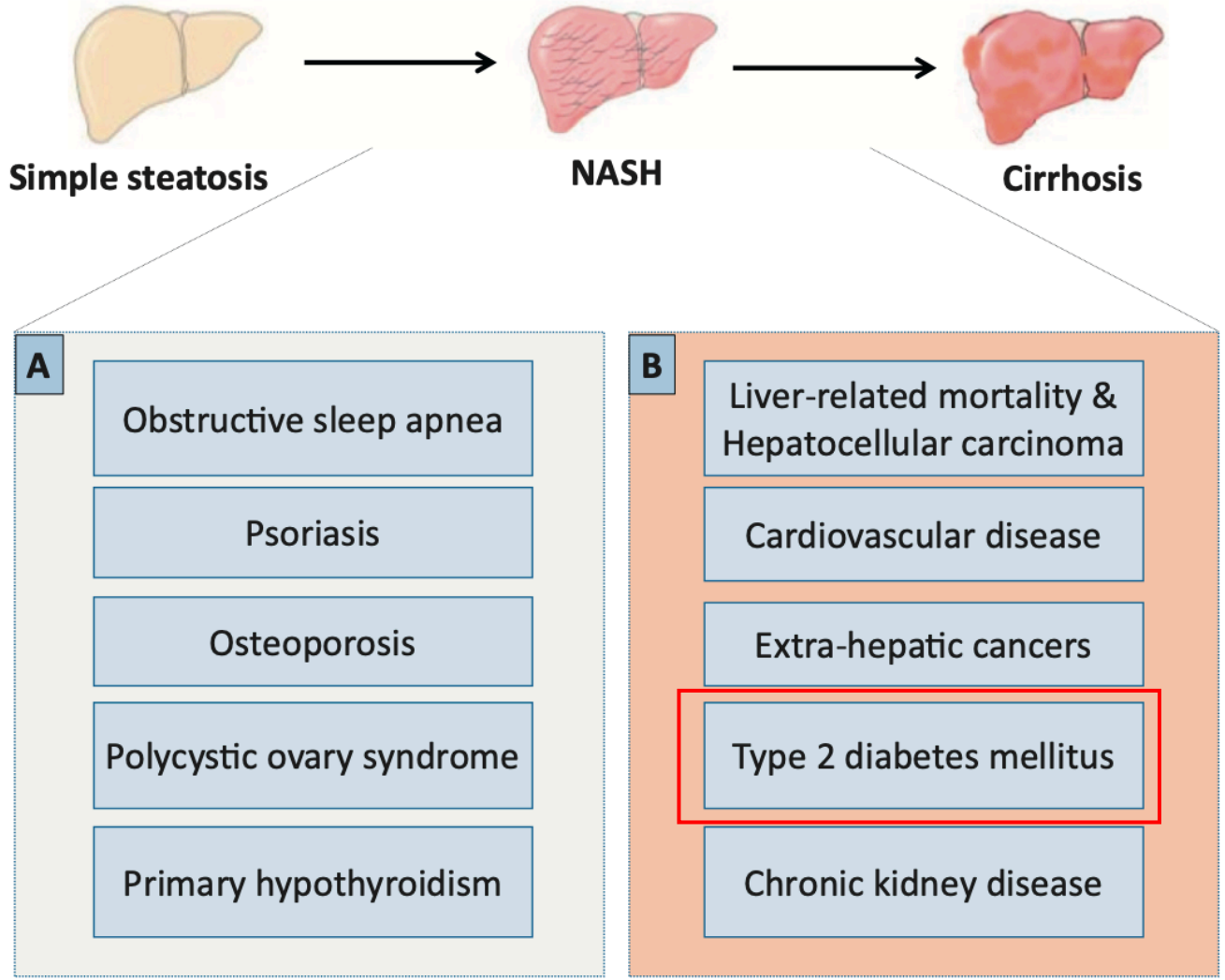
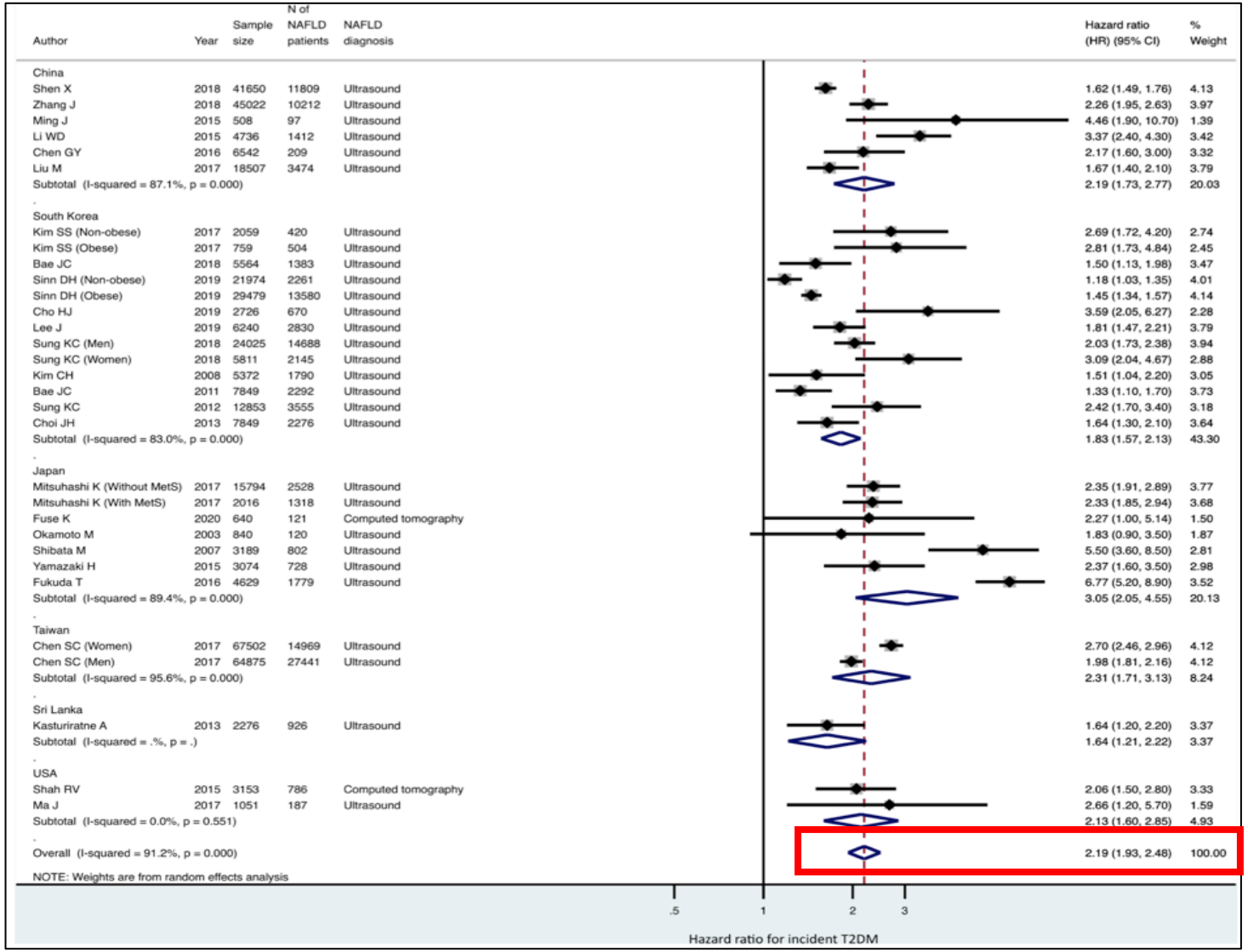


Fig. 1. Principal hepatic complications and extra-hepatic diseases associated with NAFLD (Panel A and Panel B). Only those shown in Panel B are discussed in the text.

Mantovani A, et al. Metabolism. 2020 Oct;111S:154170.

NAFLD and risk of incident diabetes mellitus

A **meta-analysis** of 33 observational studies with 501,022 individuals (30.8% with NAFLD) and 27,953 cases of incident diabetes over a median of 5 years.



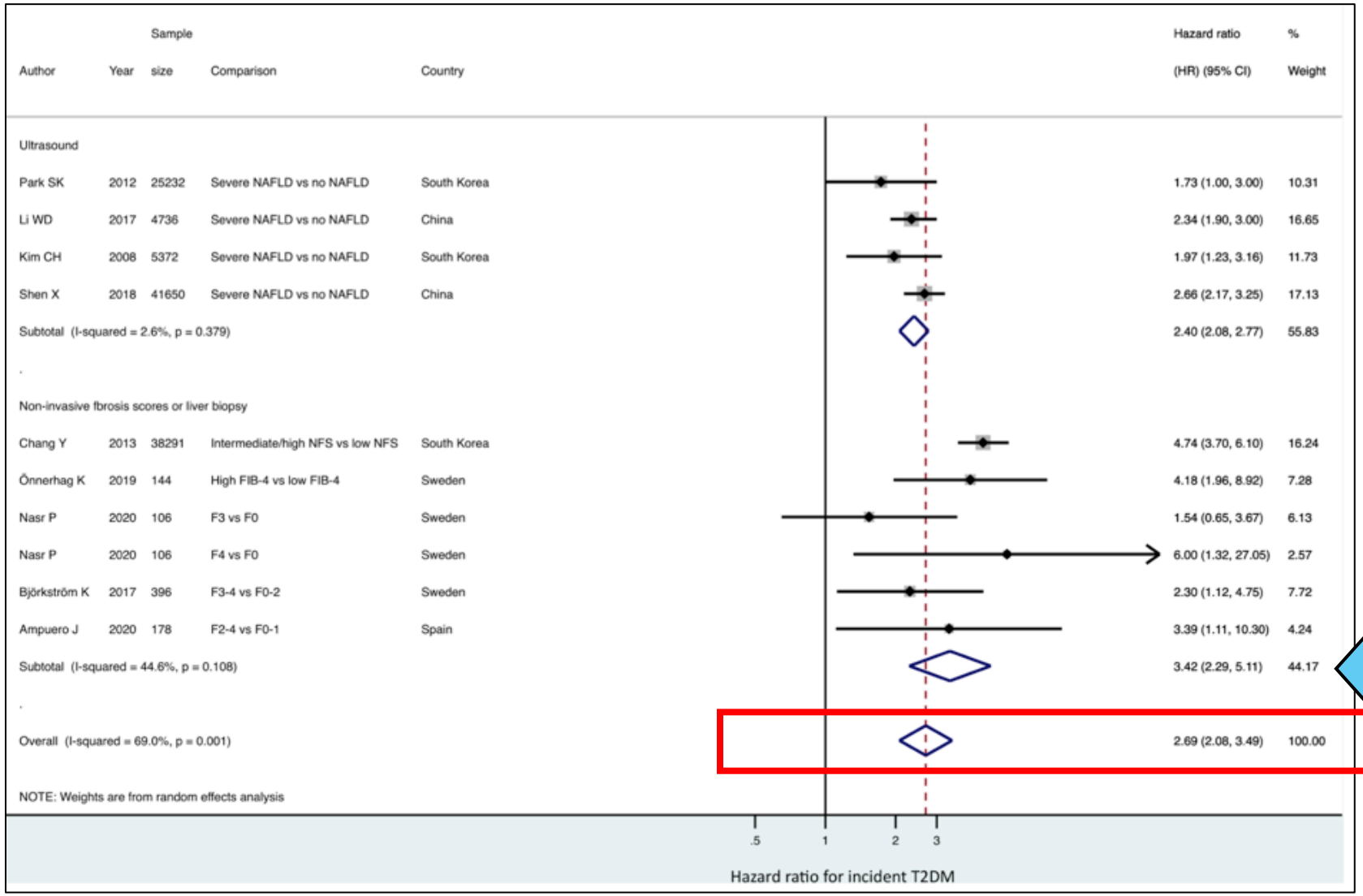
- Patients with **NAFLD** had a higher risk of incident diabetes than those without NAFLD (n=26 studies; random-effects **HR 2.19**, 95% CI 1.93 to 2.48; I^2=91.2%)

Random-effects HR 2.19 (95% CI 1.93-2.48)

Mantovani A *et al.* Gut. 2021 May;70(5):962-969.

Severe forms of NAFLD and risk of incident diabetes mellitus

A **meta-analysis** of 33 observational studies with 501,022 individuals (30.8% with NAFLD) and 27,953 cases of incident diabetes over a median of 5 years.



- Patients with more **'severe' NAFLD** were also more likely to develop incident diabetes (n=9 studies; random-effects **HR 2.69**, 95% CI 2.08 to 3.49; I^2=69%).

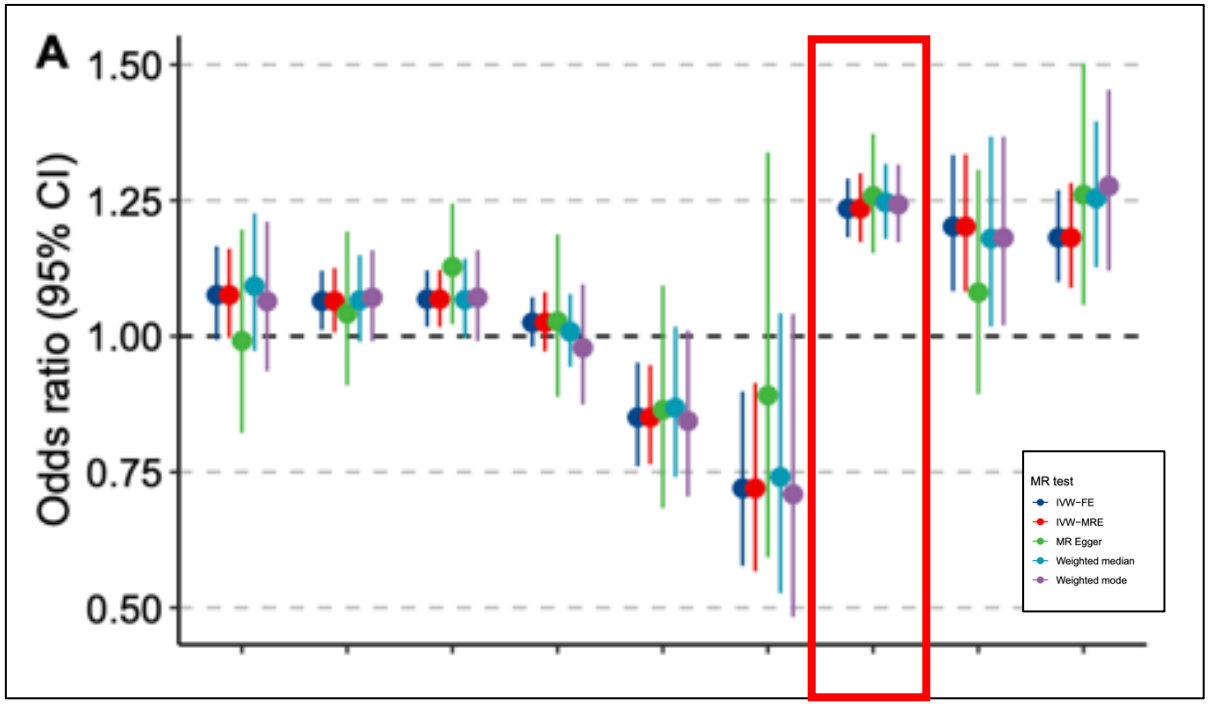
- This risk markedly increased across the severity of liver fibrosis (n=5 studies; random-effects HR 3.42, 95% CI 2.29 to 5.11; I^2=44.6%)

Mantovani A *et al.* Gut. 2021 May;70(5):962-969.

Association estimates of NAFLD with diabetes mellitus- MR

Mendelian randomization (MR) analysis: Genetic instrumental variables for NAFLD (54 SNPs were used as instrumental variables for NAFLD) and eligible extrahepatic diseases, **including T2DM**, were retrieved from the corresponding genome-wide association analyses.

A. Validation analysis based on genetic instrumental variables from the biopsy cohort



Diabetes mellitus

B. Validation analysis based on genetic instrumental variables from the imaging cohort

Diabetes mellitus

Liu Z *et al.* Metabolism. 2022 Oct;135:155270.

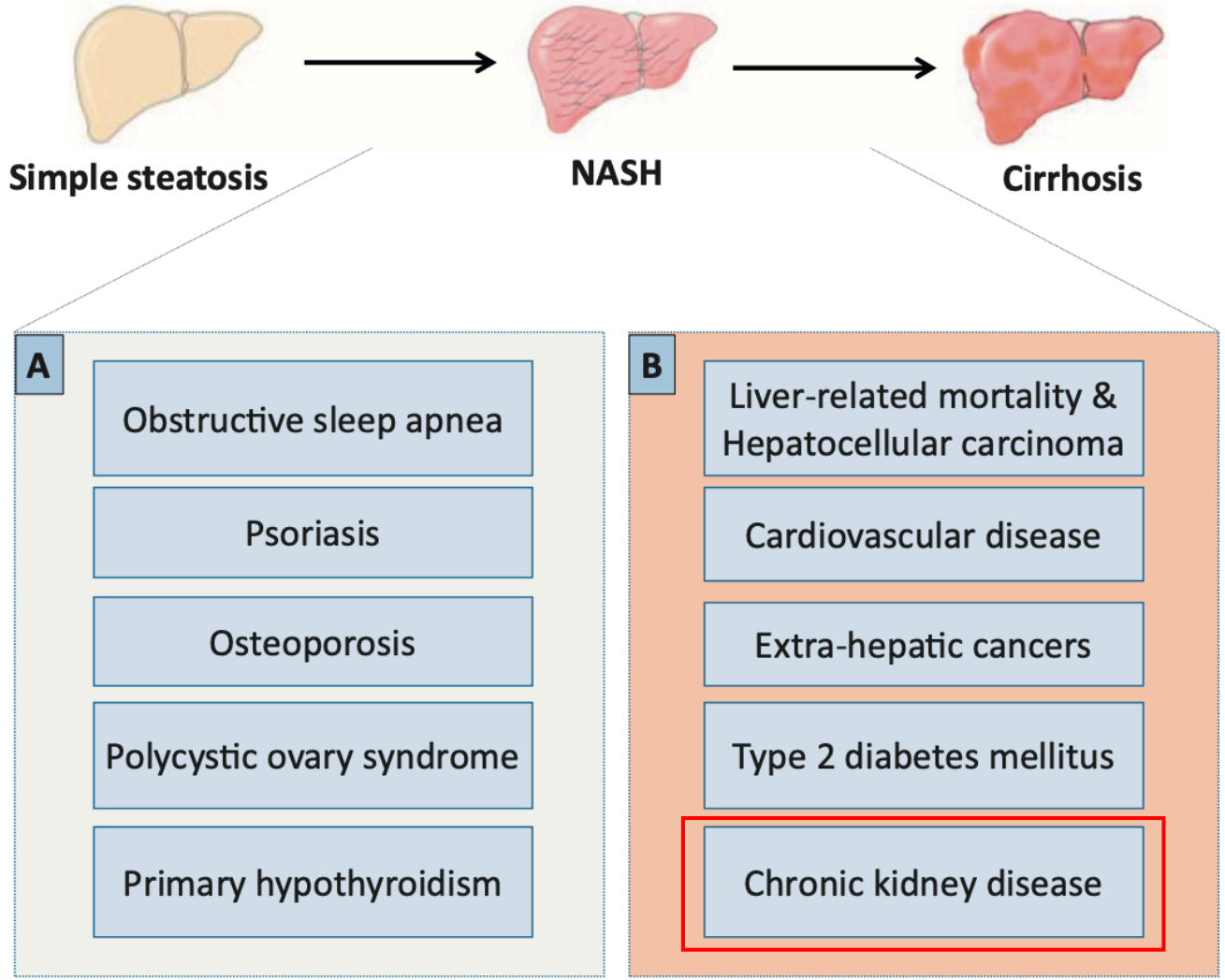
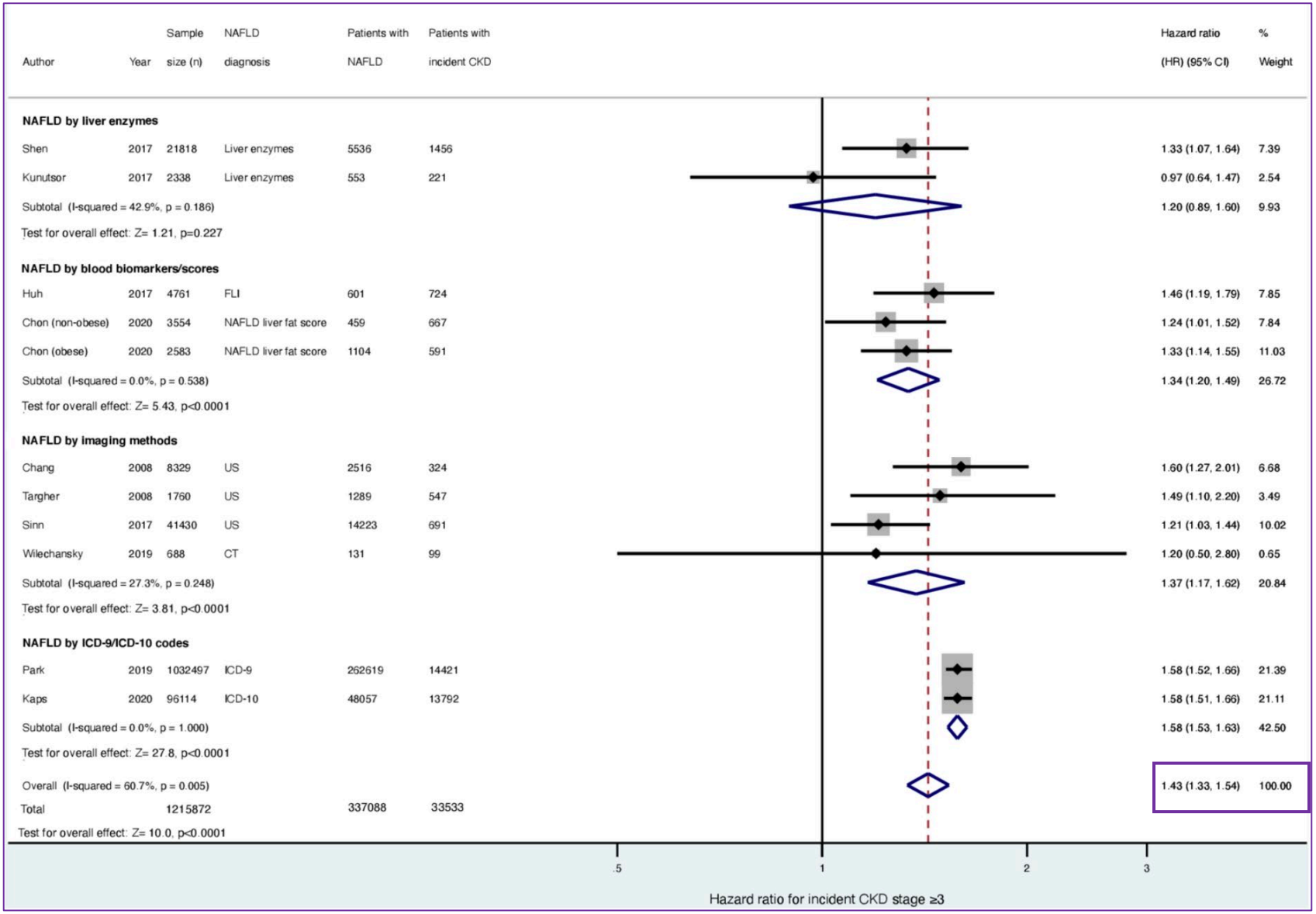


Fig. 1. Principal hepatic complications and extra-hepatic diseases associated with NAFLD (Panel A and Panel B). Only those shown in Panel B are discussed in the text.

Mantovani A, et al. Metabolism. 2020 Oct;111S:154170.

Non-alcoholic fatty liver disease and risk of incident chronic kidney disease: an updated meta-analysis



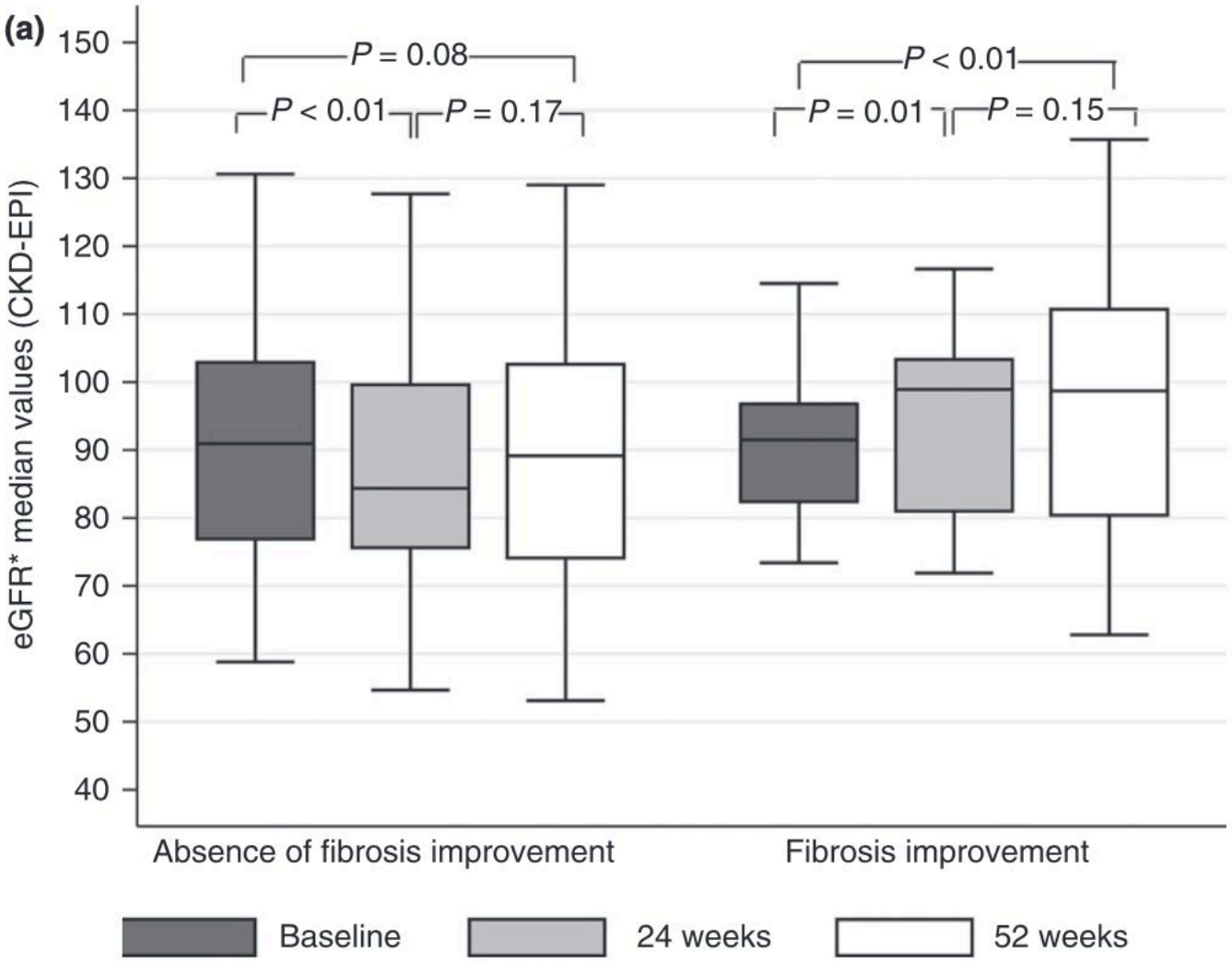
13 studies with 1,222,032 individuals (28.1% with NAFLD) and 33,840 cases of incident CKD stage ≥3 over a median follow-up of 9.7 years

HR 1.43 (1.33-1.54); I^2=60.7%

Mantovani A et al. Gut 2022;71:156–162.

Dynamic changes in eGFR during the follow-up based on histological outcome

Post hoc analysis: 261 patients with biopsy-proven NASH treated with lifestyle modifications during 52 weeks.



Note 1: One-point of fibrosis improvement was defined as a decrease of at least 1 point in the fibrosis score.

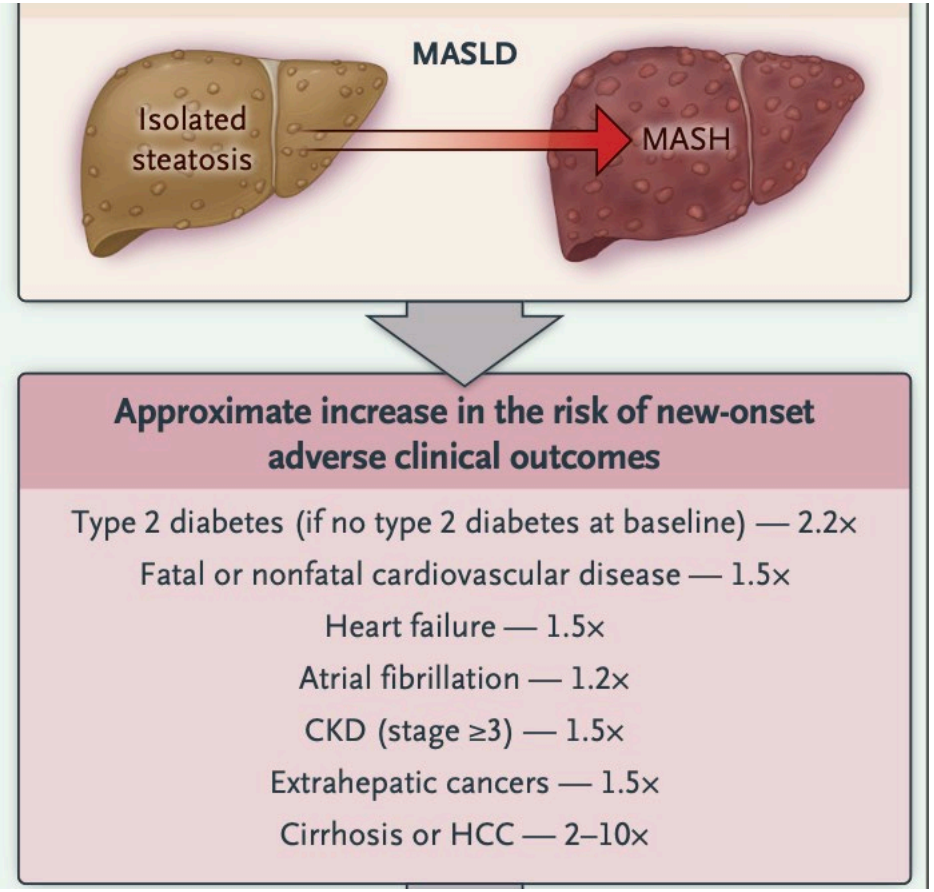
Note 2: lifestyle modifications = low-fat diet that was750 kcal/day less than their daily energy need + physical activities, particularly walking, toat least 200 min/week,

Vilar-Gomez E et al. Aliment Pharmacol Ther. 2017;45(2):332-344.

KEY POINT - 2

- MASLD increases the risk of fatal and nonfatal cardiovascular disease events by a factor of 1.5 independent of traditional risk factors; notably, this risk increases further with more severe liver disease, especially in persons with higher stages of fibrosis.

- Recent meta-analyses showed that MASLD is also associated with an increased risk of type 2 diabetes and CKD.



Targher et al. N Engl J Med 2025;393:683-98.

Recommendations

- Clinicians should assess associated comorbidities (*e.g.* type 2 diabetes, dyslipidaemia, hypertension, kidney disease, sleep apnoea, polycystic ovary syndrome) and cardiovascular risk in adults with MASLD (**LoE 2, strong recommendation, strong consensus**).

- At initial diagnosis of MASLD and at regular follow-up intervals, laboratory tests and physical examinations for related comorbidities are recommended (Table 7) (**LoE 2, strong recommendation, strong consensus**).

Journal of Hepatology 2024; 81: 492–542

CONCLUSIONS

- MASLD is a multisystem disease that has become a public-health problem worldwide.
- MASLD is associated with an increased risk of hepatic complications, such as decompensated cirrhosis, and hepatocellular carcinoma.
- The presence of diabetes strongly increases such risk.
- MASLD is also associated with an increased risk of extra-hepatic complications, such as CVD, CKD and type 2 diabetes.
- Addressing the growing clinical burden of MASLD requires the assembly of a multidisciplinary working group and framework to develop and embrace new collaborative ways of working to deliver holistic, person-centered care and treatment of patients with MASLD.