Non-invasive fibrosis scores as predictors for clinical events in obesity: a longitudinal study

Maximilian Jara[1], Quentin M. Anstee[2,3], Tina L. Berentzen[1], Louise M. Nitze[1], Mette S. Kjær[1], Kamal K. Mangla[1], Jens M. Tarp[1], **Joshua Neuman**,[4]* Kamlesh Khunti[5]

[1]Novo Nordisk A/S, Søborg, Denmark; [2]Translational & Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK; [3]Newcastle NIHR Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Trust, Newcastle upon Tyne, UK; [4]Novo Nordisk Inc., New Jersey, USA; [5]Diabetes Research Centre, University of Leicester, Leicester General Hospital, Leicester, UK

*Author added only for presentation purposes.

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Disclosures

- Dr Joshua Neuman is a full-time employee and shareholder of Novo Nordisk.

Introduction

Many patients with NASH have obesity.[1] NASH is associated with life-threatening liver-related complications,[2,3] CVD,[4] and increased liver-specific and all-cause mortality[5,6]

Biopsy-confirmed liver fibrosis is an important predictor of these severe outcomes; however, biopsies are not scalable for use outside of specialist practice[7]

Recent clinical guidelines in NASH[7,8] recommend using FIB-4 to screen patients with obesity to identify those at risk for clinically significant fibrosis

CVD, cardiovascular disease; FIB4, Fibrosis-4 Index; NASH, non-alcoholic steatohepatitis.

1. Younossi Z, et al. Hepatology 2016;64:73–84; 2. Ascha MS, et al. Hepatology 2010;51:1972–78; 3. Ratziu V, et al. J Hepatol 2010;53:372–84;
4. Ekstedt M, et al. Hepatology 2015;61:1547–54; 5. Younossi Z, et al. Hepatology 2011;53:1874–82; 6. Söderberg C, et al. Hepatology 2010;51:595–602;
7. Kanwal F, et al. Gastroenterology 2021;161:1657–69; 8. European Association for the Study of the Liver. J Hepatol 2021;75:659–68.

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Objective

This longitudinal cohort study investigated the prognostic potential of six non-invasive scores for NASH-related clinical outcomes in patients with obesity (BMI ≥30 kg/m^2) seen in routine general practice in the UK

Based on recent guideline recommendations to use FIB-4 to identify people at risk for clinically significant fibrosis,[1,2] this presentation focuses on FIB-4

BMI, body mass index; FIB4, Fibrosis-4 Index; NASH, non-alcoholic steatohepatitis.
1. Kanwal F, et al. Gastroenterology 2021;161:1657–69; 2. European Association for the Study of the Liver. J Hepatol 2021;75:659–89.

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Methods

Study design

- Longitudinal, non-interventional, observational cohort study
  - Country: UK
  - Study period: 2001–2020
- Patients were followed from inclusion date* until time of first clinical event, database migration, 10 years after inclusion or 1 January 2020 (whichever came first)
- FIB-4 at inclusion was categorized as low (<1.30), indeterminate (1.30–2.67) or high (>2.67) risk

Data sources

- Clinical Practice Research Datalink (CPRD) is a UK Government real-world research service
- Contains de-identified patient data from a network of general practitioners across the UK
- General practitioner medical records are linked to two other data sources in the current study: Hospital Episodes Statistics (HES) and Office for National Statistics (ONS) death registration data

Population

- Adults aged ≥18 years with obesity (BMI ≥30 kg/m^2)
- ≥1 FIB-4 score calculable from CPRD†
- No record of alcohol-related and/or other chronic liver disease registered in HES
- No prescriptions of drugs inducing liver disease registered in CPRD

**Date of first FIB4 measurement after 1 January 2001 and all eligibility criteria met for the first time; †FIB4 score was not taken directly from CPRD, but was calculated using data available from CPRD.*
CPRD, Clinical Practice Research Datalink; FIB-4, Fibrosis-4 Index; HES, Hospital Episode Statistics; ONS, Office for National Statistics.

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Methods

Endpoints

- Time to first liver event (liver-related hospitalisation or death)
- Time to first CV event (CV-related hospitalization or death)
- Time to death of any cause

Statistical analysis*

- Cumulative incidence functions were calculated with the Aalen-Johansen calculator
- Hazard ratios estimated using Cox proportional hazards models with calendar time as underlying timescale

**Although FIB-4 is the focus of this presentation, separate statistical analyses were performed for each non-invasive score.*
CV, cardiovascular; FIB-4, Fibrosis-4 Index.

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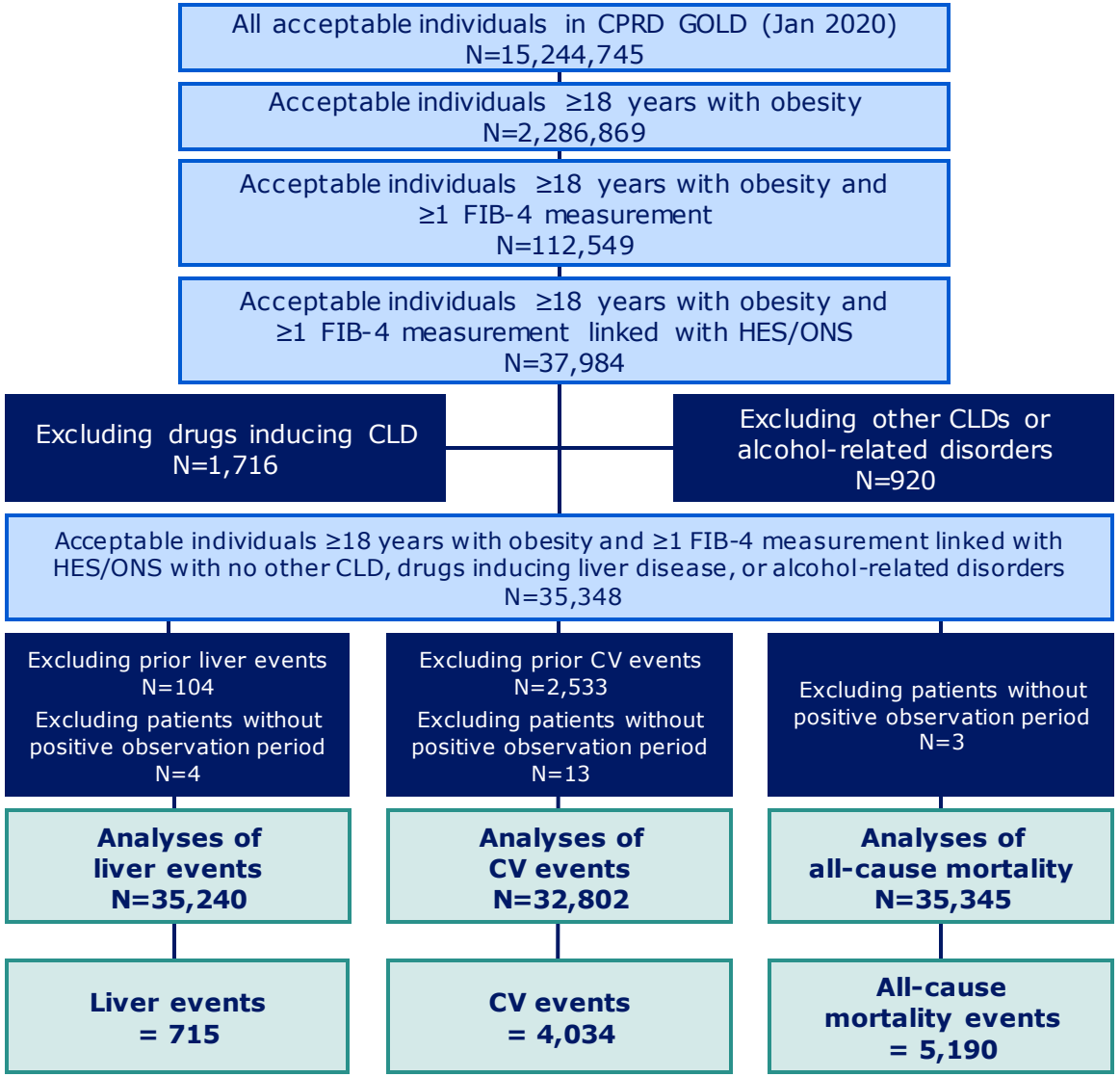
Patient population

- Of the 2,286,869 adults with obesity in the CPRD, 112,549 (4.9%) had available measures for FIB-4 calculation and a total of 35,348 patients were included in the study
- Median follow-up was 3,652 days (10 years)



CLD, chronic liver disease; CPRD, Clinical Practice Research Datalink; CV, cardiovascular; FIB4, Fibrosis-4 Index; HES, Hospital Episode Statistics; ONS, Office of National Statistics.

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Baseline characteristics

Baseline parameters	FIB-4 low (N=24,971)	FIB-4 indeterminate (N=9,178)	FIB-4 high (N=1,199)
Patient characteristics			
Female, %	60	48	40
Age, years	50.2 (25.8, 73.1)	68.6 (48.9, 84.9)	71.3 (48.4, 88.5)
BMI, kg/m^2	33.4 (30.1, 45.2)	32.5 (30.0, 42.1)	32.4 (30.0, 42.6)
Type 2 diabetes, %	25	37	41
Clinical/laboratory parameters			
AST, U/L	23 (15, 43)	26 (17, 64)	41 (20, 212)
ALT, U/L	27 (13, 73)	26 (12, 84)	33 (11, 188)
HbA_{1c}*, %	7.1 (5.4, 10.9)	6.9 (5.5, 10.2)	6.8 (5.5, 10.0)
Creatinine, mg/dL	0.9 (0.6, 1.3)	1.0 (0.7, 1.6)	1.0 (0.7, 1.9)
HDL*, mg/dL	46 (31, 73)	48 (31, 77)	46 (27, 81)
LDL*, mg/dL	120 (62, 190)	104 (50, 182)	97 (43, 174)
Triglycerides*, mg/dL	142 (66, 354)	142 (71, 328)	133 (62, 328)

All values are median (5^{th} percentile, 95^{th} percentile), unless otherwise stated.
**Missing for more than 20% of the population.*
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, Fibrosis-4 Index; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

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Baseline characteristics

Baseline parameters	FIB-4 low (N=24,971)	FIB-4 indeterminate (N=9,178)	FIB-4 high (N=1,199)
Comorbidities			
Hospitalization for:			
Hypertension, %	43	68	68
Dyslipidemia, %	21	34	30
Chronic kidney disease, %	7	19	22
Medication use			
Anti-hypertensive agent, %	22	45	50
Metformin, %	12	15	17
Statin, %	23	46	44

FIB-4, Fibrosis-4 Index.

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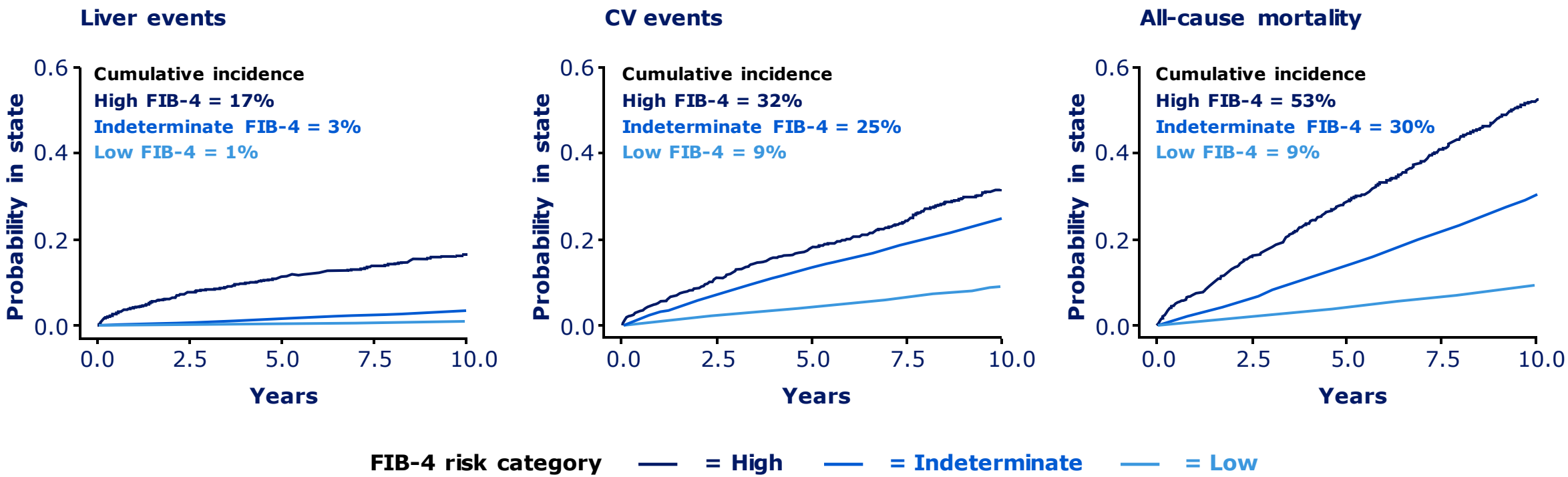
Cumulative incidence (over 10 years) for liver events, CV events, and mortality according to FIB-4



Percentage risks are for 10 years' follow-up. Event risks plotted as Aalen-Johansen cumulative incidence functions, with all-cause mortality included as a competing risk factor in plots of liver and CV events.
CV, cardiovascular; FIB-4, Fibrosis-4 Index.

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Hazard ratios for liver events, CV events, and mortality according to FIB-4 in patients with obesity

	Patients (n)	Events (n)		Crude HR (95% CI)	Adjusted (age and sex) HR (95% CI)
Liver events			**Liver events**		
FIB-4 low	24,932	255		1	1
FIB-4 indeterminate	9,144	279		3.32 (2.80, 3.93)	2.86 (2.35, 3.48)
FIB-4 high	1,164	181		21.29 (17.58, 25.77)	18.77 (15.05, 23.40)
CV events			**CV events**		
FIB-4 low	23,770	1,921		1	1
FIB-4 indeterminate	8,025	1,822		3.21 (3.01, 3.42)	1.07 (1.00, 1.15)
FIB-4 high	1,007	291		4.90 (4.33, 5.34)	1.37 (1.20, 1.57)
All-cause mortality			**All-cause mortality**		
FIB-4 low	24,968	2,100		1	1
FIB-4 indeterminate	9,178	2,517		3.62 (3.42, 3.84)	1.03 (0.96, 1.10)
FIB-4 high	1,199	573		7.73 (7.05, 8.48)	1.71 (1.55, 1.89)

Cox proportional hazards models, either unadjusted crude values or adjusted for age and sex, with calendar time as the timescale. FIB-4 was categorized as low (<1.30), indeterminate (1.30–2.67), or high (>2.67). CI, confidence interval; CV, cardiovascular; FIB-4, Fibrosis-4 Index; HR, hazard ratio.

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Liver events, CV events, and mortality according to FIB-4 in patients with obesity and available FIB-4 and Framingham CV risk scores*

	Patients (n)	Events (n)	Crude HR (95% CI)	Adjusted (age and sex) HR (95% CI)
Liver events			**Liver events**	
FIB-4 low	10,715	112	1	1
FIB-4 indeterminate	3,730	122	3.28 (2.54, 4.24)	3.37 (2.54, 4.48)
FIB-4 high	398	81	24.91 (18.71, 33.17)	25.46 (18.58, 34.88)
CV events			**CV events**	
FIB-4 low	10,015	908	1	1
FIB-4 indeterminate	3,285	582	2.09 (1.88, 2.32)	1.14 (1.02, 1.28)
FIB-4 high	365	67	2.46 (1.92, 3.15)	1.26 (0.98, 1.62)
All-cause mortality			**All-cause mortality**	
FIB-4 low	10,732	846	1	1
FIB-4 indeterminate	3,748	656	2.32 (2.09, 2.57)	1.15 (1.03, 1.28)
FIB-4 high	413	136	5.13 (4.28, 6.15)	2.38 (1.97, 2.87)

**Adjustment for Framingham CV risk score was at the time of FIB4 measurement.*
CI, confidence interval; CV, cardiovascular; FIB-4, Fibrosis-4 Index; HR, hazard ratio.

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Conclusions

Hazard ratios for clinical events were greater with high versus low baseline FIB-4. This was also the case after additional adjustment for baseline Framingham CV risk score

These findings support recent guidelines on the use of non-invasive tests in patients at risk of liver fibrosis[1,2] and integration of FIB-4 into the evaluation of patients with obesity in clinical practice

This study provides valuable insights into the prognostic potential of FIB-4 in a broad population of patients with obesity

CV, cardiovascular; FIB-4, Fibrosis-4 Index; HR, hazard ratio.
1. Kanwal F, et al. Gastroenterology 2021;161:1657–69; 2. European Association for the Study of the Liver. J Hepatol 2021;75:659–89.