Supplemental material

Wester A, *et al. Gut* 2024;0:1–9. doi: 10.1136/gutjnl-2023-330962

Table of contents

Supplemental methods

Data sources

The Decoding the Epidemiology of LIVER disease in Sweden (DELIVER) cohort includes data from several Swedish national healthcare registers on all patients with any chronic liver disease in Sweden between 1964 and 2020 [1]. Data from the registers can be cross-linked using the unique personal identification number that is assigned to all Swedish residents [2]. The Swedish National Patient Register holds data on all International Classification of Diseases (ICD) codes from inpatient care since 1964 and specialized outpatient care since 2001 [3]. The positive predictive value in this register has been estimated to be 85-95% in general, 96% for non-alcoholic fatty liver disease with comorbid type 2 diabetes, and >90% for most diagnoses related to cirrhosis [3-5]. In addition, the Total Population Register contains information on country and date of birth, migration, and death dates; the LISA database records data on education; and the Swedish Cause of Death Register holds data on main and contributing causes of death and has a completeness of virtually 100% [6-8]. Moreover, the Swedish Cancer Register was founded in 1958 and covers more than 96% of all incident cancers in Sweden [9]. Lastly, the Swedish National Prescribed Drug Register was introduced in July 2005 and automatically records data on all filled prescriptions at any pharmacy in Sweden [10]. In this register, drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system and the defined daily dose is used as measuring unit as recommended by the World Health Organization [11]. The defined daily dose represents the average maintenance dose per day for a drug used in adults for its main indication, enabling comparability between different preparation forms or substances within the same drug class (e.g., GLP1 agonists). The number of days that a filled

Wester A, *et al. Gut* 2024;0:1–9. doi: 10.1136/gutjnl-2023-330962

prescription is intended for can be calculated by dividing the product of the drug's strength, the package size, and the number of dispensed packages, by the defined daily dose of that drug.

Liver disease etiology

If patients had ICD coding for more than one liver disease etiology, they were classified according to the following hierarchy based on the perceived risk of developing major adverse liver outcomes (MALO): alcohol-related liver disease (ALD) with or without viral hepatitis; viral hepatitis without ALD; other liver disease; metabolic dysfunction-associated steatotic liver disease (MASLD). Patients with compensated cryptogenic cirrhosis (i.e., coding for cirrhosis but not for any specific etiology) were classified as MASLD, since cryptogenic cirrhosis may often represent MASLD, especially in patients with type 2 diabetes [12, 13]. Patients who were classified as having MASLD were re-classified as having ALD if coding for alcohol use disorder was present before or at baseline.

Wester A, *et al. Gut* 2024;0:1–9. doi: 10.1136/gutjnl-2023-330962

Supplemental Table 1. ICD codes for chronic liver diseases and compensated cirrhosis.

	ICD-10
Alcohol-related liver disease	K70
Chronic viral hepatitis	B17.0, B18
MASLD	K75.8, K76.0
Other liver disease	Autoimmune liver disease: K75.4, K74.3, K74.5, K83.0A Alpha-1 antitrypsin deficiency: E88.0A, E88.0B Hemochromatosis: E83.1 Budd-Chiari syndrome: I82.0, K76.5 Wilson's disease: E83.0B
Compensated cirrhosis	K74.6, K70.3, K74.5, B18.2G, B18.2E, B18.1G, B18.1E, B18.0G, B18.0E, B18.8G, B18.8E, I85.9, I98.2 *Without any code for decompensation (I85.0, I98.3, R18.9, K76.6, K76.7)*

Abbreviations: ICD, International Classification of Diseases; MASLD, metabolic dysfunction-associated steatotic liver disease

Wester A, *et al. Gut* 2024;0:1–9. doi: 10.1136/gutjnl-2023-330962

Supplemental Table 2. ICD and ATC codes for type 2 diabetes, comorbidities, and medications.

	ICD-10 or ATC code
Type 2 diabetes	ICD: E11 ATC codes for metformin: A10BA02, A10BD05, A10BD07, A10BD08, A10BD10, A10BD11, A10BD13, A10BD15, A10BD16, A10BD20, A10BD23
Contraindications to GLP1 agonists	
Pancreatitis	K85, K86.0/1
Inflammatory bowel disease	K50, K51
Severe chronic kidney disease	Diagnostic codes: N18.4/5/9, Z49, Z99.2 Procedure codes (dialysis): DR016, DR024
Obesity	ICD: E65, E66 ATC: A08
Cardiovascular disease	E78, G45.9, I10-I15, I20-I25, I50, I60-I69, I73.9, I74
Non-HCC cancer	C00-C97 except C22.0
Microvascular complications to diabetes	
Chronic kidney disease	N18, E11.2, N08.3, D63.8, Z94.0, T86.1, N25.8, or the coding for dialysis above
Retinopathy	E11.3, H35.0, H35.1, H35.2, H35.3, H35.4, H36.0, H36.8
Neuropathy	E11.4, G99.0, G63.2, G63.3, G63.8
Chronic obstructive pulmonary disease	J41-J44 + age≥40 years at the time of coding
Alcohol use disorder	F10, X65, Y15, Y90, Y91, R78.0
Mental health disorder	F20-F40
Antidiabetic medications except metformin or GLP1 agonists	Insulin: A10A SGLT2i: A10BK, A10BD15/16/19/20/21/23/24 DPP4i: A10BH, A10BD07/08/09/10/11/13 Other: A10BB, A10BC, A10BD06, A10BF, A10BG, A10BX
Direct-acting antivirals	J05AP

Abbreviations: ATC, Anatomical Therapeutic Chemical; DPP4i, Dipeptidyl peptidase-4 inhibitor; GLP1, glucagon-like peptide-1 receptor; HCC, hepatocellular carcinoma; ICD, International Classification of Diseases; SGLT2i, sodium-glucose cotransporter-2 inhibitor

Supplemental Table 3. ICD codes for major adverse liver outcomes.

	ICD-10
Decompensated cirrhosis	
Variceal bleeding	I85.0, I98.3
Ascites	R18.9
Portal hypertension	K76.6
Hepatorenal syndrome	K76.7
HCC	C22.0
Liver transplantation	Diagnostic code: Z94.4 Procedure codes: JJC00, JJC10, JJC20, JJC30, JJC40, DJ005, DJ006

Abbreviations: HCC, hepatocellular carcinoma; ICD, International Classification of Diseases

Wester A, *et al. Gut* 2024;0:1–9. doi: 10.1136/gutjnl-2023-330962

Supplemental Table 4. Positive predictive values of diagnostic codes related to cirrhosis in the Swedish National Patient Register [5].

	Positive predictive value
Cirrhosis	
K703	93%
K746	91%
K74.5, B18.2G, B18.2E, B18.1G, B18.1E, B18.0G, B18.0E, B18.8G, B18.8E	Not been validated
Esophageal varices with or without bleeding	
I85.0, I98.3, I85.9, I98.2	96%
Hepatocellular carcinoma in patients with chronic liver disease	
C22.0	91%
Ascites in patients with chronic liver disease	
R18.9	93%
Portal hypertension	
K76.6	Not been validated
Hepatorenal syndrome	
K76.7	Not been validated
Liver transplantation	
Z94.4, JJC00, JJC10, JJC20, JJC30, JJC40, DJ005, DJ006	Not been validated

Wester A, *et al. Gut* 2024;0:1–9. doi: 10.1136/gutjnl-2023-330962

Supplemental Table 5. Inverse-probability weights.

	Mean	Median	Minimum	Maximum
Stabilized inverse-probability of treatment weights	1.00	0.99	0.21	6.74
Stabilized inverse-probability of censoring weights	1.00	1.00	0.93	1.09
Product of the stabilized treatment and censoring weights	1.00	0.99	0.21	6.74

Supplemental Table 6. Sensitivity analysis of the risk of major adverse liver outcomes at 10 years, allowing 0.5 g of metformin per day at inclusion instead of 1 g, in 1,292 initiators and 22,599 non-initiators.

	Number of events, GLP1 agonist initiators	Number of events, non-initiators	Absolute risk (%), GLP1 agonist initiators (95% CI)	Absolute risk (%), non-initiators (95% CI)	Risk difference (%) (95% CI)	Risk ratio (95% CI)
Intention-to-treat						
	54	1,499	12.1 (7.5, 16.7)	12.9 (11.8, 14.0)	-0.8 (-5.4, 3.8)	0.94 (0.58, 1.30)
Per-protocol						
	28	1,499	8.1 (3.4, 12.8)	12.8 (11.7, 13.9)	-4.7 (-9.4, -0.0)	0.63 (0.27, 0.99)

Abbreviations: CI, confidence interval; GLP1, glucagon-like peptide-1 receptor

Wester A, *et al. Gut* 2024;0:1–9. doi: 10.1136/gutjnl-2023-330962

Supplemental Table 7. Sensitivity analysis of the risk of major adverse liver outcomes at 10 years, allowing a maximum of 30 days gap between two successive prescriptions.

	Number of events, GLP1 agonist initiators	Number of events, non-initiators	Absolute risk (%), GLP1 agonist initiators (95% CI)	Absolute risk (%), non-initiators (95% CI)	Risk difference (%) (95% CI)	Risk ratio (95% CI)
Per-protocol						
	21	1,079	6.9 (1.7, 12.2)	14.4 (12.9, 16.0)	-7.5 (-12.9, -2.1)	0.48 (0.11, 0.85)

Abbreviations: CI, confidence interval; GLP1, glucagon-like peptide-1 receptor

Wester A, *et al. Gut* 2024;0:1–9. doi: 10.1136/gutjnl-2023-330962

Supplemental Table 8. Sensitivity analysis of the risk of major adverse liver outcomes at 10 years, where non-initiators are censored if starting a glucagon-like peptide-1 receptor (GLP1) agonist during follow-up, regardless of if they were indicated.

	Number of events, GLP1 agonist initiators	Number of events, non-initiators	Absolute risk (%), GLP1 agonist initiators (95% CI)	Absolute risk (%), non-initiators (95% CI)	Risk difference (%) (95% CI)	Risk ratio (95% CI)
Per-protocol						
	22	970	7.2 (2.5, 11.9)	13.1 (11.7, 14.5)	-5.9 (-10.7, -1.0)	0.55 (0.18, 0.92)

Abbreviations: CI, confidence interval; GLP1, glucagon-like peptide-1 receptor

Supplemental Table 9. Sensitivity analysis of the risk of major adverse liver outcomes at 10 years, where the inverse-probability weights were truncated at the 1st and 99th percentile.

	Number of events, GLP1 agonist initiators	Number of events, non-initiators	Absolute risk (%), GLP1 agonist initiators (95% CI)	Absolute risk (%), non-initiators (95% CI)	Risk difference (%) (95% CI)	Risk ratio (95% CI)
Intention-to-treat						
	42	1,079	12.2 (7.0, 17.4)	14.5 (13.0, 16.0)	-2.3 (-7.5, 2.9)	0.84 (0.48, 1.20)
Per-protocol						
	22	1,079	7.9 (2.4, 13.4)	14.4 (12.9, 15.9)	-6.5 (-12.2, -0.9)	0.55 (0.16, 0.93)

Abbreviations: CI, confidence interval; GLP1, glucagon-like peptide-1 receptor

Wester A, *et al. Gut* 2024;0:1–9. doi: 10.1136/gutjnl-2023-330962

Supplemental Table 10. Sensitivity analysis of the risk of major adverse liver outcomes at 10 years using standardization.

	Number of events, GLP1 agonist initiators	Number of events, non-initiators	Absolute risk (%), GLP1 agonist initiators (95% CI)	Absolute risk (%), non-initiators (95% CI)	Risk difference (%) (95% CI)	Risk ratio (95% CI)
Intention-to-treat						
	42	1,079	12.6 (7.7, 17.5)	14.4 (13.0, 15.9)	-1.8 (-6.8, 3.2)	0.87 (0.53, 1.22)
Per-protocol						
	22	1,079	8.3 (2.8, 13.8)	14.4 (13.0, 15.8)	-6.1 (-11.7, -0.4)	0.58 (0.19, 0.97)

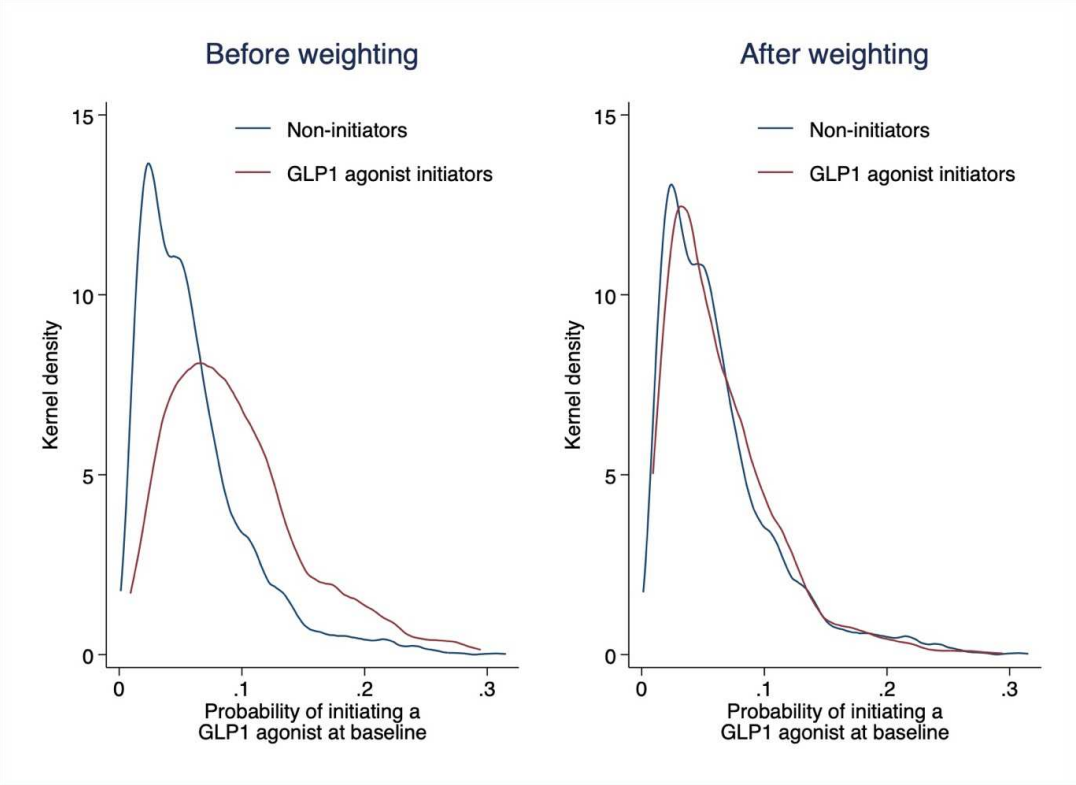
Abbreviations: CI, confidence interval; GLP1, glucagon-like peptide-1 receptor

Supplemental Table 11. Point estimates for risk of major adverse liver outcomes at 10 years according to intention-to-treat and per-protocol analyses, including all identified non-initiators.

	Number of events, GLP1 agonist initiators	Number of events, non-initiators	Absolute risk (%), GLP1 agonist initiators	Absolute risk (%), non-initiators	Risk difference (%)	Risk ratio
Intention-to-treat						
	42	21,624	13.7	13.6	0.1	1.01
Per-protocol						
	22	21,624	7.2	13.6	-6.4	0.53

Abbreviations: CI, confidence interval; GLP1, glucagon-like peptide-1 receptor

Wester A, *et al. Gut* 2024;0:1–9. doi: 10.1136/gutjnl-2023-330962



Supplemental Figure 1. Distribution of the probability of initiating a glucagon-like peptide-1 receptor (GLP1) agonist at baseline before and after inverse probability of treatment weighting.

References

[1] Hagstrom H, Shang Y, Wester A, Widman L. Cohort profile: decoding the epidemiology of liver disease in Sweden (DELIVER). Scand J Gastroenterol 2022;57:978-983.
[2] Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol 2009;24:659-667.
[3] Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;11:450.
[4] Astrom H, Wester A, Hagstrom H. Administrative coding for non-alcoholic fatty liver disease is accurate in Swedish patients. Scand J Gastroenterol 2023:1-6.
[5] Bengtsson B, Askling J, Ludvigsson JF, Hagstrom H. Validity of administrative codes associated with cirrhosis in Sweden. Scand J Gastroenterol 2020;55:1205-1210.
[6] Brooke HL, Talback M, Hornblad J, Johansson LA, Ludvigsson JF, Druid H, et al. The Swedish cause of death register. Eur J Epidemiol 2017;32:765-773.
[7] Ludvigsson JF, Almqvist C, Bonamy AK, Ljung R, Michaelsson K, Neovius M, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol 2016;31:125-136.
[8] Ludvigsson JF, Svedberg P, Olen O, Bruze G, Neovius M. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. Eur J Epidemiol 2019;34:423-437.
[9] Barlow L, Westergren K, Holmberg L, Talback M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol 2009;48:27-33.
[10] Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf 2007;16:726-735.
[11] WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC classification and DDD assignment, 2023. Oslo, 2022.
[12] Caldwell SH, Oelsner DH, Iezzoni JC, Hespenheide EE, Battle EH, Driscoll CJ. Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease. Hepatology 1999;29:664-669.
[13] Younossi Z, Stepanova M, Sanyal AJ, Harrison SA, Ratziu V, Abdelmalek MF, et al. The conundrum of cryptogenic cirrhosis: Adverse outcomes without treatment options. J Hepatol 2018;69:1365-1370.