The association between individual metabolic syndrome components, primary liver cancer and cirrhosis: A study in the Swedish AMORIS cohort

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Metabolic syndrome (MetS) is associated with non-alcoholic fatty liver disease, which may progress to cirrhosis, a significant risk factor of hepatocellular carcinoma (HCC), the commonest malignant primary liver cancer (PLC). We investigated the association between the individual components of MetS (lipids, apolipoproteins, raised glucose, diabetes and obesity), PLC and cirrhosis.

A total of 509,436 participants from the Swedish AMORIS cohort, recruited between January 1985 and December 1996 (end-date December 2011), aged ≥20 with baseline triglycerides (TG), total cholesterol (TC), glucose and liver enzymes were included. Those with baseline benign liver tumours, PLC or cirrhosis were excluded. Multivariate Cox regression, adjusted for age, gender, socio-economic status, liver disease (excluding cirrhosis) and MetS factors were used to estimate the association with PLC and cirrhosis.

There were 766 PLC and 2,775 cirrhosis cases over 13 years. Raised TG, low TC, raised glucose, diabetes and low HDL were associated with an increased risk of developing PLC and cirrhosis. ApoB/ApoA-I ratio were also associated with PLC, whilst low LDL, raised TG/HDL, low ApoA-I and low ApoB were associated with cirrhosis. Obesity was significantly associated with PLC but not cirrhosis. Raised TG, low TC, raised glucose and diabetes showed stronger associations with PLC in participants with cirrhosis but many participants developed PLC without cirrhosis.

Individual components of MetS (lipids, apolipoproteins, raised glucose, diabetes and obesity) were associated with an increased risk of developing PLC or cirrhosis. MetS components were more strongly associated with PLC with preceding cirrhosis history but many participants developed PLC without cirrhosis.

Introduction

Primary liver cancer (PLC) is the sixth most common cancer worldwide with hepatocellular carcinoma (HCC) accounting for 85% of cases.1,2 There are many known risk factors for the development of HCC,3 however, in 5–30% of cases there is no identifiable underlying cause.3 Non-alcoholic fatty liver disease (NAFLD) is an asymptomatic hepatic manifestation of metabolic syndrome which can progress to non-alcoholic steatohepatitis (NASH), cirrhosis and may account for most such “cryptogenic” HCC cases.4–7 Metabolic syndrome (MetS) criteria, as described by the World Health Organisation (WHO), National Cholesterol Education Program (NCEP) and International Diabetes Federation (IDF) definitions, constitute several physiological biochemical, clinical and metabolic factors that confer increased risk of atherosclerotic cardiovascular disease and cancer.8–10 Although apolipoproteins are not included in current metabolic syndrome definitions, they correlate with metabolic syndrome components and are predictive of metabolic syndrome.11,12 It is estimated that a quarter of the world population have metabolic syndrome, and the prevalence of the syndrome continues to rise rapidly.13,14

Although there is great variability in the time of progression from NAFLD to cirrhosis (via NASH), ~11% of patients progress over a 15-year period.7 Equally ~7% of cirrhotic
patients progress to HCC over a 6.5 year period.\textsuperscript{7} It is unclear if metabolic syndrome and HCC are associated directly, independent of NAFLD, NASH or cirrhosis\textsuperscript{6,7,15,16} but reported associations between metabolic syndrome and NAFLD, together with the proposed progression to cirrhosis, make this at least one probable pathway.\textsuperscript{15} Given the rising prevalence of metabolic syndrome\textsuperscript{10} and its association with NAFLD, it is likely that the prevalence of HCC will continue to rise.\textsuperscript{6} However, few studies have investigated the association between the individual components of metabolic syndrome and PLC or explored the role of cirrhosis as an intercessory step. We therefore aim to investigate the association between the individual components of metabolic syndrome (lipids, raised glucose, diabetes and obesity), apolipoproteins and the risk of developing PLC or cirrhosis. In addition, we aimed to assess the strength of association between metabolic syndrome components and PLC in participants who developed cirrhosis during the study period to establish if this is potentially a common pathway by which patients develop PLC. Assessment of individual MetS components, rather than the absolute definition of MetS which includes at least three factors, may help future therapies target the important MetS components that attribute the greatest risk for the development of cirrhosis or PLC.

**Methods**

**Study data and setting**

The Swedish Apolipoprotein MOrtality RISk (AMORIS) database has been described in detail elsewhere.\textsuperscript{7,17,18} Briefly, the AMORIS database consists of the Central Automated Laboratory (CALAB) database which contains age, fasting status and clinical laboratory data from 812,073 generally healthy males and females recruited between January 1985 to December 1996. These data are linked to several Swedish national registries including the National Cancer Register, the National Patient Register, the Cause of Death Register, consecutive Swedish Censuses (1970–90) and the National Register of Emigration by use of the Swedish ten-digit personal identity number to provide socio-economic status (SES), vital statistics, cancer diagnosis and emigration data. The study was approved by the ethics review board of the Karolinska Institutet and respects the principles of the Declaration of Helsinki.

**History of liver disease and cirrhosis.** History of liver disease was defined as presence of viral hepatitis (ICD7 - 092, ICD8/9 - 070, ICD10 - B18), alcoholic liver disease (ICD10 - K70.0–70.3,70.9), acute liver disease (ICD7 - 580, ICD8/9-570), liver abscess (ICD7 - 582, ICD8/9-572), chronic hepatitis (ICD10 - K73), chronic liver disease (including alcoholic and toxic necrosis) (ICD10 - K70.4,K71.1), other liver disease (ICD10 - K72.9), toxic liver disease (ICD10 - K71.3–71.5,71.7) and other chronic liver disease (ICD7 - 583, ICD 8/9-573, ICD10 - K76.2–76.4,K76.8–76.9). The relative proportions of grouped liver disease diagnoses (excluding cirrhosis) are shown in Figure 2. History of cirrhosis was defined as a diagnosis of cirrhosis (ICD 7–581, ICD 8/9–571, ICD10 - K74), chronic liver failure (ICD10 - K72.1), other significant stigmata of liver disease including portal hypertension and hepatorenal syndrome (ICD10 - K76.5–76.7), oesophageal & gastric varices (ICD7 – 462.10,462.20, ICD8 – 456.0, 456.0, ICD9 – 456 A-C, ICD10 - I85.0, I85.9, I86.4, I98.2) during the study follow-up period. Liver enzymes (ALT, AST, ALP and GGT) taken at baseline were included in the descriptive analysis as biomarkers of liver function during the baseline measurement of metabolic syndrome components.

**Participant selection**

**Study cohort.** We identified a cohort of 509,436 participants aged 20 years or older at entry into the cohort who all had baseline measurements of serum triglycerides (TG, mmol/L), total cholesterol (TC, mmol/L), glucose (mmol/L) and liver enzymes (ALT, AST, ALP and GGT, IU/L). There were a further two subgroups who had additional baseline measurements: subgroup A (n = 117,003) included participants with additional baseline measurements of serum high density lipoprotein (HDL, mmol/L), low density lipoprotein (LDL, mmol/L), apolipoprotein A-I (ApoA-I, g/L) and apolipoprotein B (ApoB, g/L); subgroup B (n = 65,151) included participants with an additional baseline measurement of BMI (kg/m$^2$). Participants were followed up from baseline measurement until diagnosis of PLC or cirrhosis, death, emigration or end of follow-up (December 31, 2011). Participants with benign liver tumours, PLC or cirrhosis at baseline were excluded. The construction of the study population is shown in Figure 1.
Exposure definition

**Lipid and apolipoprotein components.** TG and TC were measured using enzymatic methods, ApoA-I and ApoB were measured using immuniturbidimetric methods with levels standardised per WHO International Federation of Clinical Chemists Protocols. ApoA-I and ApoB are not included in current metabolic syndrome definitions but are included in this study as they correlate with metabolic syndrome components (HDL and LDL) and are predictive of metabolic syndrome and are therefore of clinical interest.

The concentrations of HDL and LDL were calculated using validated methods with non-HDL defined as the difference between total cholesterol and HDL cholesterol. All methods were fully automated with automatic calibration and performed at one accredited laboratory. Balance of cholesterol components was reflected in the TC/HDL, TG/HDL, LDL/HDL and ApoB/ApoA-I ratios.

Lipids, apolipoproteins and associated lipid ratios were analysed using both quartiles and dichotomized values based on clinical cardiovascular disease prevention cut-offs, NCEP guidelines and IDF metabolic syndrome definitions (cut-offs: TG - 1.70 mmol/L; TC - 6.50 mmol/L; HDL - 1.03 mmol/L male or 1.29 mmol/L female; LDL - 4.10 mmol/L; LDL/HDL - 3.50; TC/HDL - 5.00; Log(TG/HDL) - 0.50; ApoA-I - 1.05, ApoB - 1.50 and ApoB/ApoA-I - 1.00). 

**Raised glucose and diabetes.** Raised glucose status was defined as a plasma glucose ≥6.1 mmol/L for fasting samples or ≥7.8 mmol/L for non-fasting or unknown fasting status samples. Diabetic status was defined as a history of recorded diabetes diagnosis or a plasma glucose ≥7.0 mmol/L for fasting samples or ≥11.1 mmol/L for non-fasting or unknown fasting status samples. The chosen cut-offs are in line with the WHO diagnostic criteria recommendations for diabetes and intermediate hyperglycaemia. Glucose was measured enzymatically with a glucose oxidase/peroxidase method.

**Obesity.** Patients who had a BMI measurement at baseline (subgroup B) were categorised into BMI < 25 kg/m², 25–29.99 kg/m² and ≥ 30 kg/m². Obesity was defined as a BMI ≥ 30 kg/m².
Table 1. Descriptive statistics by liver cancer and cirrhosis status

| Factor                    | Study population N = 509,436 | Cirrhosis N = 2,775 | Liver cancer N = 766 | Liver cancer with cirrhosis N = 158 | Subgroup A N = 117,003 | Subgroup B N = 65,224 |
|---------------------------|-------------------------------|---------------------|----------------------|------------------------------------|------------------------|--------------------|
| Age (years)               |                               |                     |                      |                                    |                        |                    |
| Mean (SD)                 | 44 (14)                       | 48 (12)             | 54 (11)              | 50 (10)                            | 46 (14)                | 43 (14)            |
| Gender (%)                |                               |                     |                      |                                    |                        |                    |
| Female                    | 237,269 (46.6)                | 895 (32.3)          | 242 (31.6)           | 33 (20.9)                          | 49,020 (41.9)          | 27,924 (42.8)      |
| Male                      | 272,167 (53.4)                | 1,880 (67.7)        | 544 (68.4)           | 125 (79.1)                         | 67,983 (58.1)          | 37,300 (57.2)      |
| SES (%)                   |                               |                     |                      |                                    |                        |                    |
| Low                       | 221,536 (43.5)                | 1,376 (49.6)        | 366 (47.8)           | 80 (50.6)                          | 47,264 (40.4)          | 32,234 (49.4)      |
| High                      | 238,265 (46.8)                | 1,157 (41.7)        | 309 (40.3)           | 64 (40.5)                          | 58,140 (49.7)          | 29,438 (45.1)      |
| Unclassified or Missing   | 49,635 (9.7)                  | 242 (4.7)           | 91 (11.9)            | 14 (8.9)                           | 11,599 (9.9)           | 3,552 (5.4)        |
| BMI [kg/m^2] (%)^1        |                               |                     |                      |                                    |                        |                    |
| <25                       | See Subgroup B                | 125 (4.5)           | 28 (3.7)             | 2 (1.3)                            | 9,260 (7.9)            | 40,066 (61.4)      |
| 25 - 29.99                | See Subgroup B                | 99 (3.6)            | 31 (4.0)             | 4 (2.5)                            | 5,324 (4.6)            | 20,185 (30.9)      |
| ≥30                       | See Subgroup B                | 27 (1.3)            | 12 (1.6)             | 2 (1.3)                            | 1,373 (1.2)            | 4,973 (7.6)        |
| Not Measured              | 444,212 (87.2)                | 2,524 (90.6)        | 695 (90.7)           | 150 (94.9)                         | 101,046 (86.3)         | N/A                |
| Fasting status (%)        |                               |                     |                      |                                    |                        |                    |
| Fasting                   | 284,705 (55.9)                | 1,623 (58.5)        | 428 (55.9)           | 88 (55.7)                          | 68,983 (59.0)          | 38,201 (58.6)      |
| Non-fasting               | 166,142 (32.6)                | 768 (27.7)          | 235 (30.7)           | 44 (27.8)                          | 37,412 (32.0)          | 24,019 (36.8)      |
| Unknown                   | 58,589 (11.5)                 | 384 (13.8)          | 103 (13.4)           | 26 (16.5)                          | 10,608 (9.0)           | 3,004 (4.6)        |
| Glucose (mmol/L)          |                               |                     |                      |                                    |                        |                    |
| Mean (SD)                 | 4.97 (1.27)                   | 5.51 (2.06)         | 5.59 (1.99)          | 5.70 (2.00)                        | 5.00 (1.29)            | 4.92 (1.17)        |
Table 1. Descriptive statistics by liver cancer and cirrhosis status (Continued)

| Factor                        | Study population N = 509,436 | Cirrhosis N = 2,775 | Liver cancer N = 766 | Liver cancer with cirrhosis N = 158 | Subgroup A N = 117,003 | Subgroup B N = 65,224 |
|-------------------------------|------------------------------|---------------------|---------------------|--------------------------------------|------------------------|------------------------|
| Raised glucose level (%)     |                              |                     |                     |                                      |                        |                        |
| No                            | 488,154 (95.8)               | 2,452 (88.4)        | 659 (86.0)          | 132 (83.5)                           | 111,638 (95.4)         | 62,805 (96.3)          |
| Yes                           | 21,282 (4.2)                 | 323 (11.6)          | 107 (14.0)          | 26 (16.5)                            | 5,365 (4.6)            | 2,419 (3.7)            |
| Diabetic status (%)           |                              |                     |                     |                                      |                        |                        |
| No                            | 498,154 (97.8)               | 2,586 (93.2)        | 702 (91.6)          | 143 (90.5)                           | 114,103 (97.5)         | 64,103 (98.3)          |
| Yes                           | 11,218 (2.2)                 | 189 (6.8)           | 64 (8.4)            | 15 (9.5)                             | 5,365 (4.6)            | 1,121 (1.7)            |
| Triglycerides (mmol/L)        |                              |                     |                     |                                      |                        |                        |
| Mean (SD)                     | 1.31 (0.99)                  | 1.75 (1.66)         | 1.55 (1.01)         | 1.51 (0.89)                          | 1.35 (1.03)            | 1.35 (1.03)            |
| Total cholesterol (mmol/L)    |                              |                     |                     |                                      |                        |                        |
| Mean (SD)                     | 5.56 (1.16)                  | 5.67 (1.35)         | 5.58 (1.23)         | 5.37 (1.28)                          | 5.70 (1.19)            | 5.55 (1.14)            |
| HDL cholesterol (mmol/L)²     |                              |                     |                     |                                      |                        |                        |
| Mean (SD)                     | See Subgroup A               | 1.47 (0.58)         | 1.41 (0.45)         | 1.37 (0.48)                          | 1.53 (0.45)            | 1.50 (0.45)            |
| LDL cholesterol (mmol/L)²     |                              |                     |                     |                                      |                        |                        |
| Mean (SD)                     | See Subgroup A               | 3.50 (1.19)         | 3.71 (1.15)         | 3.44 (1.16)                          | 3.56 (1.08)            | 3.53 (1.07)            |
| LDL/HDL ratio²                |                              |                     |                     |                                      |                        |                        |
| Mean (SD)                     | See Subgroup A               | 10.56 (177.81)      | 3.02 (1.97)         | 3.09 (2.76)                          | 3.00 (18.03)           | 3.24 (23.52)           |
| Total cholesterol/HDL ratio²  |                              |                     |                     |                                      |                        |                        |
| Mean (SD)                     | See Subgroup A               | 16.49 (259.34)      | 4.78 (3.17)         | 4.96 (4.17)                          | 4.76 (28.65)           | 5.13 (39.11)           |
| Triglycerides/HDL ratio²      |                              |                     |                     |                                      |                        |                        |
| Mean (SD)                     | See Subgroup A               | 11.05 (195.28)      | 1.61 (3.12)         | 1.86 (3.61)                          | 1.69 (24.69)           | 2.00 (34.90)           |
| Apolipoprotein A-I (g/L)²     |                              |                     |                     |                                      |                        |                        |
| Mean (SD)                     | See Subgroup A               | 1.42 (0.34)         | 1.37 (0.23)         | 1.34 (0.26)                          | 1.42 (0.24)            | 1.40 (0.23)            |
| Apolipoprotein B (g/L)²       |                              |                     |                     |                                      |                        |                        |
| Mean (SD)                     | See Subgroup A               | 1.23 (0.37)         | 1.27 (0.35)         | 1.15 (0.35)                          | 1.23 (0.42)            | 1.22 (0.71)            |
| ApoB/ApoA-I ratio²            |                              |                     |                     |                                      |                        |                        |
| Mean (SD)                     | See Subgroup A               | 0.91 (0.36)         | 0.97 (0.30)         | 0.94 (0.36)                          | 0.89 (0.34)            | 0.89 (0.49)            |
| ALT (IU/L)                    |                              |                     |                     |                                      |                        |                        |
| Mean (SD)                     | 0.44 (0.55)                  | 1.25 (1.97)         | 1.18 (1.64)         | 1.87 (1.99)                          | 0.45 (0.42)            | 0.43 (0.46)            |
| AST (IU/L)                    |                              |                     |                     |                                      |                        |                        |
| Mean (SD)                     | 0.38 (0.34)                  | 0.95 (1.26)         | 0.84 (1.16)         | 1.25 (1.32)                          | 0.37 (0.23)            | 0.37 (0.27)            |
| ALP (IU/L)                    |                              |                     |                     |                                      |                        |                        |
| Mean (SD)                     | 2.66 (1.03)                  | 3.65 (3.04)         | 3.55 (3.11)         | 3.72 (1.90)                          | 2.69 (1.02)            | 2.62 (0.89)            |
| GGT (IU/L)                    |                              |                     |                     |                                      |                        |                        |
| Mean (SD)                     | 0.45 (0.72)                  | 2.16 (3.65)         | 1.52 (2.25)         | 2.26 (2.75)                          | 0.47 (0.73)            | 0.42 (0.59)            |
| History of liver disease      |                              |                     |                     |                                      |                        |                        |
| No                            | 501,958 (98.5)               | 1,382 (49.8)        | 558 (72.8)          | 65 (41.1)                            | 115,446 (98.7)         | 64,462 (98.8)          |
| Yes                           | 7,478 (1.5)                  | 1,393 (50.2)        | 208 (27.2)          | 93 (58.9)                            | 1,557 (1.3)            | 762 (1.2)              |
| Deceased (%)                  |                              |                     |                     |                                      |                        |                        |
| No                            | 413,522 (81.2)               | 954 (43.7)          | 138 (18.0)          | 41 (25.9)                            | 95,055 (81.2)          | 55,861 (85.6)          |
| Yes                           | 95,914 (18.8)                | 1,821 (65.6)        | 628 (82.0)          | 117 (74.1)                           | 21,948 (18.8)          | 95,914 (14.4)          |
| Follow-up time (years)        |                              |                     |                     |                                      |                        |                        |
| Mean (SD)                     | 20.03 (5.69)                 | 12.97 (7.33)        | 13.62 (7.13)        | 15.04 (6.60)                         | 19.46 (5.58)           | 20.42 (4.86)           |

¹Measured in subgroup B.
²Measured in subgroup A.
Statistical methods and outcomes
Continuous variables were analysed as means and standard deviations (SD) and dichotomous variables were analysed as counts and percentages. Parametric tests for statistical differences were determined using ANOVA or Chi-squared ($\chi^2$) test as appropriate.

Multivariate Cox proportional hazards regression models with biomarkers of interest as exposures and adjusted for age, gender, socio-economic status, history of liver disease (excluding cirrhosis) were used to estimate the association with the study outcomes of: 1) diagnosis of PLC (ICD-10: 155.0), 2) diagnosis of cirrhosis and 3) diagnosis of PLC in participants who had developed cirrhosis during the study period. Those with HDL, LDL, ApoA-I and ApoB measurements (subgroup A) underwent multivariate Cox proportional hazards analyses with adjustment for the aforementioned variables with exception of cholesterol for the HDL/LDL components and additionally triglycerides for TG/HDL components. Participants with a BMI measurement (subgroup B) were also included in multivariate Cox proportional hazards analyses with additional adjustment for BMI (continuous) as well as aforementioned variables. Trend tests were conducted by assigning quartiles as an ordinal scale. All statistical analyses were carried out on SPSS, version 23.0, IBM, USA.

Results
There were 766 PLC and 2,775 cirrhosis diagnoses with a mean follow-up period of 13.6 (SD: 7.1) and 13.0 (SD: 7.3) years respectively. Of these, 158 patients developed cirrhosis then PLC within the study period with a slightly higher percentage of males in this group (79%) compared to the cirrhosis or PLC only (68%) groups. Baseline characteristics of the study population are shown in Table 1.

Lipids and apolipoproteins
Raised triglycerides. The hazard ratios (HRs) for the associations between TG, TC, raised glucose, diabetes and the risk of PLC and cirrhosis, are shown in Table 2. Raised TG levels were associated with an increased risk of developing PLC (TG ≥ 1.70 mmol/L vs < 1.70 mmol/L, HR: 1.38 (95% CI: 1.17–1.63)), cirrhosis and PLC with a history of cirrhosis. The risk of developing PLC was higher amongst those with a prior history of cirrhosis.

Total cholesterol, HDL and LDL. Increasing TC levels were inversely associated with PLC, cirrhosis and PLC with cirrhosis history. The estimates for an inverse association between TC and PLC were greater if participants had a history of cirrhosis. To check for reverse causation, we excluded participants with < 5 years’ follow-up from baseline. After this exclusion, TC levels remained negatively associated with a risk of PLC (TC ≥ 6.50 mmol/L vs < 6.50 mmol/L, HR: 0.74 (95% CI: 0.62–0.90)).

Subgroup analysis results for participants with additional measurements of HDL, LDL, and apolipoproteins B and A-I are shown in Table 3. Clinically low HDL was associated with a 16% and 28% increased risk of developing PLC and cirrhosis respectively with a trend effect seen with PLC risk. The risk did not reach statistical significance for developing PLC in participants with a history of cirrhosis.

Raised LDL quartiles were not associated with PLC or PLC with cirrhosis history but there was an inverse correlation with cirrhosis in the trend analysis. Raised LDL/HDL and TC/HDL ratios clinical cut-offs or quartiles were not associated with PLC, cirrhosis or PLC with cirrhosis history. However, clinically raised TG/HDL ratio and quartiles were associated with a moderately increased risk of cirrhosis, but not PLC or PLC with cirrhosis history.

ApoA-I and ApoB. Low ApoA was not associated with PLC or PLC with cirrhosis history but it was associated with an increased risk of cirrhosis but trend effects were not significant. Low ApoB quartiles were also associated with cirrhosis, however, raised ApoB was associated with an increased risk of developing PLC (HR: 2.17 (95% CI: 1.32–3.58)) with no significant trend effects noted. A raised ApoB/ApoA-I ratio was associated with an increased risk of PLC (HR: 1.54 (95% CI: 1.03–2.31)) with a statistically significant trend.

Raised glucose and diabetes
Raised glucose were associated with an increased risk of developing PLC [HR: 2.14 (95% CI: 1.73–2.65)] and cirrhosis [HR: 1.69 (95% CI: 1.49–1.91)]. Similarly, diabetes was associated with an increased risk of developing PLC [HR: 2.35 (95% CI: 1.80–3.06)] and cirrhosis [HR: 1.74 (95% CI: 1.49–2.02)]. The associations between raised glucose and diabetes with PLC were greater amongst participants who had a history of cirrhosis.

BMI
Subgroup analysis results for those with additional measurements of BMI are shown in Table 4. Obesity was significantly associated with PLC but not cirrhosis after adjusting for other individual metabolic syndrome components. After adjustment for BMI, increasing TG quartiles remained associated with an increased risk of cirrhosis. The association between raised glucose, diabetes and PLC or cirrhosis also remained significant following BMI adjustment.

Discussion
In this detailed prospective long-term cohort study, individual metabolic syndrome components (raised TG, low TC, low LDL, raised ApoB/ApoA-I ratio, raised glucose and diabetes) were associated with an increased risk of PLC. Raised TG, low TC, low LDL, raised TG/HDL, low ApoA-I and low ApoB, raised glucose and diabetes were also associated with an increased risk of cirrhosis. Obesity was significantly associated with an increased risk of PLC and positive associations between raised glucose and diabetes with PLC and cirrhosis remained after adjustment for BMI. Metabolic syndrome components showed
Table 2. Association between lipids, raised glucose and diabetes with primary liver cancer and cirrhosis.

| Factor                                      | N (%)       | Study population | N (%)       | Cirrhosis | 1Adjusted HR (95%CI) | N (%)       | Liver cancer | 1Adjusted HR (95%CI) | N (%)       | Liver cancer with cirrhosis | 1Adjusted HR (95%CI) |
|---------------------------------------------|-------------|------------------|-------------|-----------|----------------------|-------------|--------------|----------------------|-------------|-----------------------------|----------------------|
|                              | N = 509,436 | N = 2,775        | N = 509,436 | N = 2,775 |                      | N = 509,436 | N = 509,436 |                      | N = 509,436 | N = 509,436                  |                      |
| Raised triglycerides (mmol/L)²             |             |                  |             |           |                      |             |              |                      |             |                             |                      |
| <1.70                                      | 407,723 (80.0) | 1,903 (68.6) | 1.00 (Ref) | 536 (70.0) | 1.00 (Ref)           | 115 (72.8) | 1.00 (Ref) |                      |             |                             |                      |
| ≥1.70                                      | 101,713 (20.0) | 872 (31.4)  | 1.31 (1.20–1.43) | 230 (30.0) | 1.38 (1.17–1.63) | 43 (27.2) | 1.09 (0.75–1.58) |                      |             |                             |                      |
| Triglyceride quartiles (mmol/L)²           |             |                  |             |           |                      |             |              |                      |             |                             |                      |
| <0.70                                      | 89,740 (17.6) | 275 (9.9)   | 1.00 (Ref) | 80 (10.4)  | 1.00 (Ref)           | 12 (7.6)   | 1.00 (Ref) |                      |             |                             |                      |
| 0.70 - 0.99                                 | 130,685 (25.7) | 498 (17.9)  | 1.09 (0.94–1.26) | 129 (16.8) | 0.90 (0.68–1.19) | 26 (16.5) | 1.24 (0.64–2.51) |                      |             |                             |                      |
| 1.00 - 1.59                                 | 158,200 (31.1) | 910 (32.8)  | 1.48 (1.29–1.70) | 272 (35.5) | 1.42 (1.10–1.83) | 63 (39.9) | 2.34 (1.25–4.39) |                      |             |                             |                      |
| ≥1.60                                      | 130,811 (25.7) | 1,092 (39.4) | 1.75 (1.52–2.02) | 285 (37.2) | 1.63 (1.25–2.13) | 57 (36.1) | 2.14 (1.11–4.11) |                      |             |                             |                      |
| p-value for trend                           |             |                  |             |           |                      |             |              |                      |             |                             | <0.001               |
| Raised total cholesterol (mmol/L)³         |             |                  |             |           |                      |             |              |                      |             |                             | <0.001               |
| <6.50                                      | 404,484 (79.4) | 2,097 (75.5) | 1.00 (Ref) | 581 (75.8) | 1.00 (Ref)           | 127 (80.4) | 1.00 (Ref) |                      |             |                             | 0.005                |
| ≥6.50                                      | 104,952 (20.6) | 678 (24.5)  | 0.95 (0.86–1.04) | 185 (24.2) | 0.77 (0.65–0.92) | 31 (19.6) | 0.71 (0.48–1.08) |                      |             |                             |                      |
| Total cholesterol quartiles (mmol/L)³      |             |                  |             |           |                      |             |              |                      |             |                             |                      |
| <4.70                                      | 114,608 (22.5) | 625 (22.5)   | 1.00 (Ref) | 167 (21.8) | 1.00 (Ref)           | 50 (31.6) | 1.00 (Ref) |                      |             |                             |                      |
| 4.70 - 5.49                                | 137,391 (27.0) | 630 (22.7)  | 0.74 (0.69–0.83) | 197 (25.7) | 0.68 (0.55–0.84) | 33 (20.9) | 0.45 (0.29–0.70) |                      |             |                             |                      |
| 5.50 - 6.29                                | 128,517 (25.2) | 687 (24.8)  | 0.73 (0.65–0.82) | 190 (24.8) | 0.52 (0.42–0.64) | 40 (25.3) | 0.44 (0.29–0.68) |                      |             |                             |                      |
| ≥6.30                                      | 128,920 (25.3) | 833 (30.0)  | 0.77 (0.70–0.86) | 212 (27.7) | 0.46 (0.37–0.57) | 35 (22.2) | 0.34 (0.21–0.55) |                      |             |                             | <0.001               |
| p-value for trend                           |             |                  |             |           |                      |             |              |                      |             |                             | <0.001               |
| Raised glucose level⁴                       |             |                  |             |           |                      |             |              |                      |             |                             | <0.001               |
| No                                         | 488,154 (95.8) | 2,452 (88.4) | 1.00 (Ref) | 659 (86.0) | 1.00 (Ref)           | 132 (83.5) | 1.00 (Ref) |                      |             |                             |                      |
| Yes                                        | 21,282 (4.2)  | 323 (11.6)   | 1.69 (1.49–1.91) | 107 (14.0) | 2.14 (1.73–2.65) | 26 (16.5) | 2.55 (1.64–4.00) |                      |             |                             |                      |
| Diabetic status⁴                            |             |                  |             |           |                      |             |              |                      |             |                             |                      |
| No                                         | 498,218 (97.8) | 2,586 (93.2) | 1.00 (Ref) | 702 (91.6) | 1.00 (Ref)           | 143 (90.5) | 1.00 (Ref) |                      |             |                             |                      |
| Yes                                        | 11,218 (2.2)  | 189 (6.8)    | 1.74 (1.49–2.02) | 64 (8.4)   | 2.35 (1.80–3.06) | 15 (9.5)  | 2.62 (1.50–4.57) |                      |             |                             |                      |
| History of liver disease                   |             |                  |             |           |                      |             |              |                      |             |                             |                      |
| No                                         | 501,958 (98.5) | 1,382 (49.8) | 1.00 (Ref) | 558 (72.8) | 1.00 (Ref)           | 65 (41.1) | 1.00 (Ref) |                      |             |                             |                      |
| Yes                                        | 7,478 (1.5)   | 1,393 (50.2) | 68.03 (63.05–73.36) | 208 (27.2) | 24.69 (20.99–29.03) | 93 (58.9) | 92.36 (66.86–127.59)|                      |             |                             |                      |

¹Adjusted for age (continuous), gender, SES, triglycerides (continuous), cholesterol (continuous), raised glucose, diabetic status and history of liver disease.
²Not adjusted for triglycerides.
³Not adjusted for total cholesterol.
⁴Not adjusted for diabetic status.
⁵Not adjusted for raised glucose.
| Factor                          | Study population  | Cirrhosis  | Liver Cancer | Liver cancer with cirrhosis | p-value for trend |
|--------------------------------|-------------------|------------|--------------|-----------------------------|------------------|
| **Low HDL (mmol/L)^2**         |                   |            |              |                             |                  |
| ≥1.03 (Male) ≥1.29 (Female)    | 98,960 (84.6)     | 447 (76.0) | 1.00 (Ref)   | 129 (76.3)                  | 0.635            |
| <1.03 (Male) <1.29 (Female)    | 180,043 (15.4)    | 141 (24.0) | 1.28 (1.04–1.59) | 40 (23.7) | 1.16 (1.06–2.44) | 0.001 |
| **HDL quartiles (mmol/L)^2**   |                   |            |              |                             |                  |
| ≥1.80                          | 30,283 (25.9)     | 139 (23.6) | 1.00 (Ref)   | 30 (17.8)                  | 0.006            |
| 1.79 - 1.52                    | 29,815 (23.8)     | 125 (21.3) | 0.91 (0.71–1.17) | 35 (20.7) | 1.43 (0.87–2.37) | 0.907 |
| 1.51 - 1.25                    | 27,815 (23.8)     | 125 (21.3) | 0.91 (0.71–1.17) | 35 (20.7) | 1.43 (0.87–2.37) | 0.907 |
| <1.25                          | 29,090 (24.9)     | 202 (34.4) | 1.06 (0.83–1.35) | 67 (39.6) | 2.40 (1.47–3.92) | 0.585 |
| **Raised LDL (mmol/L)^2**      |                   |            |              |                             |                  |
| <4.10                          | 83,197 (71.2)     | 415 (70.7) | 1.00 (Ref)   | 104 (61.5)                  | 0.006            |
| ≥4.10                          | 33,625 (28.8)     | 172 (29.3) | 0.89 (0.74–1.07) | 65 (38.5) | 1.08 (0.79–1.48) | 0.083 |
| **LDL quartiles (mmol/L)^2**   |                   |            |              |                             |                  |
| <2.80                          | 29,143 (24.9)     | 158 (26.9) | 1.00 (Ref)   | 39 (23.1)                  | 0.006            |
| 2.80 - 3.47                    | 28,771 (24.6)     | 146 (24.9) | 0.92 (0.73–1.15) | 24 (14.2) | 0.47 (0.28–0.78) | 0.058 |
| 3.48 - 4.21                    | 29,262 (25.0)     | 137 (23.3) | 0.79 (0.62–0.99) | 47 (27.8) | 0.76 (0.49–1.18) | 0.963 |
| ≥4.22                          | 29,646 (25.4)     | 146 (24.9) | 0.74 (0.58–0.93) | 59 (34.9) | 0.79 (0.52–1.21) | 0.963 |
| p-value for trend              |                   |            |              |                             |                  |
| **Raised LDL/HDL ratio^2**     |                   |            |              |                             |                  |
| <3.50                          | 95,595 (81.8)     | 455 (77.5) | 1.00 (Ref)   | 133 (78.7)                  | 0.143            |
| ≥3.50                          | 21,227 (18.2)     | 132 (22.5) | 0.93 (0.75–1.15) | 36 (21.3) | 0.85 (0.57–1.28) | 0.091 |
| **LDL/HDL ratio quartiles (mmol/L)^2** |   |            |              |                             |                  |
| <1.68                          | 28,655 (24.5)     | 133 (22.7) | 1.00 (Ref)   | 25 (14.8)                  | 0.143            |
| 1.68 - 2.27                    | 28,972 (24.8)     | 136 (23.2) | 0.96 (0.74–1.20) | 34 (20.1) | 1.06 (0.63–1.78) | 0.091 |
| 2.28 - 3.10                    | 29,335 (25.1)     | 142 (24.2) | 0.85 (0.68–1.10) | 48 (28.4) | 1.26 (0.77–2.07) | 0.963 |
| ≥3.11                          | 29,861 (25.6)     | 176 (30.0) | 0.83 (0.66–1.08) | 62 (36.7) | 1.47 (0.88–2.44) | 0.963 |
| p-value for trend              |                   |            |              |                             |                  |
| **Raised total cholesterol/HDL ratio^2** |   |            |              |                             |                  |
| <5.00                          | 93,368 (79.8)     | 436 (74.1) | 1.00 (Ref)   | 116 (68.6)                  | 0.143            |
| ≥5.00                          | 23,635 (20.2)     | 152 (25.9) | 0.90 (0.73–1.12) | 53 (31.4) | 1.45 (0.98–2.14) | 0.091 |

Table 3. Association between lipids and apolipoproteins with primary liver cancer and cirrhosis

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Table 3. Association between lipids and apolipoproteins with primary liver cancer and cirrhosis (Continued)

| Factor | Study population N = 117,003 | Cirrhosis N = 588 | Liver Cancer N = 169 | Liver cancer with cirrhosis N = 32 | Total cholesterol/HDL ratio quartiles (mmol/L)²³ | Raised Log (triglycerides/HDL)²³ | Triglycerides/HDL ratio quartiles (mmol/L)²³ | Low Apo A-I (g/L) | Apo A-I quartiles (g/L) | Raised Apo B (g/L) | Apo B quartiles (g/L) |
|--------|-------------------------------|-------------------|---------------------|-----------------------|---------------------------------|--------------------------------|----------------------------------------|-----------------|----------------------|-----------------|----------------------|
| <2.91  | 28,448 (24.3)                | 121 (20.6)        | 22 (13.0)           | 5 (15.6)              | 1.00 (Ref)                      | 0.247                          | 0.045                                  | 0.001           | 0.739                | 0.051           | 0.739                |
| 2.92 - 3.61 | 29,343 (25.1)              | 127 (21.6)        | 34 (20.1)           | 6 (18.8)              | 0.89 (0.69–1.15)                | 0.89 (0.69–1.15)                | 0.89 (0.69–1.15)                     | 1.00 (Ref)      | 1.00 (Ref)           | 1.00 (Ref)      | 1.00 (Ref)           |
| 3.62 - 4.64 | 29,412 (25.1)              | 154 (26.2)        | 52 (30.8)           | 10 (31.2)             | 0.93 (0.72–1.19)                | 1.53 (0.91–2.57)                | 1.31 (0.42–4.04)                     | 1.00 (Ref)      | 1.00 (Ref)           | 1.00 (Ref)      | 1.00 (Ref)           |
| ≥4.65  | 29,800 (25.5)                | 186 (31.6)        | 61 (36.1)           | 11 (34.4)             | 0.83 (0.64–1.09)                | 1.65 (0.95–2.89)                | 1.40 (0.41–4.79)                     | 1.00 (Ref)      | 1.00 (Ref)           | 1.00 (Ref)      | 1.00 (Ref)           |
| p-value for trend | 0.001                        | 0.070              | 0.407               |                       |                                |                                |                                |                      |                      |        |
| Raised Log (triglycerides/HDL)²³ |                              |                   |                     |                       |                                |                                |                                |                      |                      |        |
| <0.50  | 110,451 (94.4)               | 527 (89.6)        | 158 (93.5)          | 30 (93.7)             | 1.34 (1.02–1.75)                | 1.16 (0.98–1.34)                | 1.49 (1.15–1.92)                     | 1.00 (Ref)      | 1.00 (Ref)           | 1.00 (Ref)      | 1.00 (Ref)           |
| ≥0.50  | 6,552 (5.6)                  | 61 (10.4)         | 11 (6.5)            | 2 (6.3)               | 0.77 (0.41–1.43)                | 0.94 (0.55–1.58)                | 1.40 (0.42–4.44)                     | 1.00 (Ref)      | 1.00 (Ref)           | 1.00 (Ref)      | 1.00 (Ref)           |
| p-value for trend |                              |                   |                     |                       |                                |                                |                                |                      |                      |        |
stronger associations with PLC in participants with a history of cirrhosis, but the majority of participants developed PLC without a history of cirrhosis.

Current epidemiological studies suggest important associations between metabolic syndrome and HCC and intra-ductal cholangiocarcinoma (ICC). However, underlying biological mechanisms that mediate the interactions between metabolic syndrome, NAFLD, NASH, cirrhosis and HCC (which comprises the majority of PLC cases) have not been fully elucidated. The development of HCC is slow and multifactorial resulting in the promotion of pro-oncogenic pathways and inhibition of tumour suppression pathways. Significant contributors to tumour development are chronic low-grade inflammation induced by excess visceral adipose tissue, insulin resistance with resultant high free fatty acid (FFA) flux, hyperglycemia and hyperinsulinaemia driving liver parenchymal damage through hepatic lipid accumulation and oxidative stress. Raised insulin and insulin-like growth factor (IGF) also promote the development of HCC by activating pro-oncogenic pathways. Many of the proposed mechanisms are independent of fibrosis which might explain the prevalence non-cirrhotic HCC associated with metabolic syndrome and our findings showing that many participants developed PLC independent of a diagnosis of cirrhosis. Metabolic syndrome components also seem to act synergistically with each other to amplify HCC risk.

Lipids and apolipoproteins

Raised triglycerides. Our study findings showing an increased risk of developing PLC with raised TG are concordant with those of the SEER study. However, other studies have reported no association between raised TG and PLC. Differences in outcomes are likely due to the differing ethnic study populations, smaller PLC sample sizes as well as differences in adjusted confounders, particularly other liver diseases. Significant associations between lipids and various stages of liver disease (NAFLD to HCC) have been reported, with the severity of liver disease correlating with lipid levels although not always in a linear fashion. Therefore, the interpretation of associations between lipid levels and liver disease is complex and can be influenced by the degree of underlying liver pathology.

Total cholesterol, HDL and LDL. The inverse association between TC and PLC matches the Me-Can study who reported a similar inverse risk association even with a sensitivity analysis to assess for reverse causation. Our study findings uniquely show that lower TC is also associated with a higher risk of cirrhosis and the association with PLC is greater in those with a history of cirrhosis. It is possible that this reverse association may as a result of increased statin use in patients with raised cholesterol either by influencing cholesterol levels or reducing PLC risk. TC, HDL and LDL have also been reported to decrease with increasing liver disease
severity and this is likely an effect of reduced synthetic liver function.25,28–32. Therefore, those patients with asymptomatic liver disease at baseline with reduced synthetic liver function hence lower TC levels were more likely to later to develop cirrhosis and PLC resulting in the observed inverse association. But, there is evidence that the lowering of lipid levels with worsening liver disease is non-linear.27

### ApoA-I and ApoB.
ApoA-I and ApoB levels have been found to be low in patients with liver failure and cirrhosis27,32,33 but few studies have reported on the association between ApoA-I and ApoB with PLC. The liver is involved in the synthesis of ApoA-I and ApoB polypeptides present in HDL and LDL fractions.24 It would be expected that ApoA-I and ApoB would show similar associations with PLC and cirrhosis.

### Table 4. Association between lipids, raised glucose and diabetes with primary liver cancer and cirrhosis after adjustment for BMI

| Factor                                | Study population N = 65,224 | Cirrhosis N = 260 | \(^{1}\)Adjusted HR (95%CI) | Liver cancer N = 71 | \(^{1}\)Adjusted HR (95%CI) |
|----------------------------------------|----------------------------|-------------------|----------------------------|---------------------|---------------------------|
| **BMI (kg/m\(^2\))**                   |                            |                   |                            |                      |                           |
| <25                                    | 40,066 (61.4)              | 124 (47.7)        | 1.00 (Ref)                 | 28 (39.4)           | 1.00 (Ref)                |
| 25 - 29.99                             | 20,185 (31.0)              | 99 (38.1)         | 1.14 (0.87–1.51)           | 31 (43.7)           | 1.54 (0.90–2.63)          |
| ≥30                                    | 4,973 (7.6)                | 37 (14.2)         | 1.38 (0.93–2.04)           | 12 (16.9)           | 2.05 (1.00–4.22)          |
| **Raised triglycerides (mmol/L)**      |                            |                   |                            |                      |                           |
| <1.70                                  | 51,340 (78.7)              | 173 (66.5)        | 1.00 (Ref)                 | 48 (67.6)           | 1.00 (Ref)                |
| ≥1.70                                  | 13,884 (21.3)              | 87 (33.5)         | 1.30 (0.99–1.72)           | 23 (32.4)           | 1.28 (0.75–2.18)          |
| **Triglyceride quartiles (mmol/L)**    |                            |                   |                            |                      |                           |
| <0.70                                  | 11,120 (17.0)              | 20 (7.7)          | 1.00 (Ref)                 | 6 (8.5)             | 1.00 (Ref)                |
| 0.70 - 0.99                            | 16,060 (24.6)              | 44 (16.9)         | 1.33 (0.78–2.26)           | 14 (19.7)           | 1.35 (0.52–3.53)          |
| 1.00 - 1.59                            | 20,279 (31.1)              | 86 (33.1)         | 2.01 (1.22–3.31)           | 21 (29.6)           | 1.45 (0.57–3.68)          |
| ≥1.60                                  | 17,765 (27.2)              | 110 (42.3)        | 2.28 (1.37–3.77)           | 30 (42.3)           | 1.93 (0.76–4.90)          |
| p-value for trend                      |                            |                   | 0.001                      | 0.129               |                           |
| **Raised total cholesterol (mmol/L)**  |                            |                   |                            |                      |                           |
| <6.50                                  | 52,339 (80.2)              | 195 (75.0)        | 1.00 (Ref)                 | 57 (80.3)           | 1.00 (Ref)                |
| ≥6.50                                  | 12,885 (19.8)              | 65 (25.0)         | 1.05 (0.78–1.42)           | 14 (19.7)           | 0.68 (0.37–1.24)          |
| **Total cholesterol quartiles (mmol/L)**|                            |                   |                            |                      |                           |
| <4.70                                  | 14,490 (22.2)              | 44 (16.9)         | 1.00 (Ref)                 | 12 (16.9)           | 1.00 (Ref)                |
| 4.70 - 5.49                            | 17,963 (27.6)              | 64 (24.6)         | 1.02 (0.69–1.50)           | 18 (25.4)           | 0.89 (0.43–1.86)          |
| 5.50 - 6.29                            | 16,860 (25.8)              | 73 (28.1)         | 1.07 (0.72–1.57)           | 23 (32.4)           | 0.95 (0.46–1.95)          |
| ≥6.30                                  | 15,911 (24.4)              | 79 (30.4)         | 1.10 (0.74–1.63)           | 18 (25.4)           | 0.66 (0.30–1.45)          |
| p-value for trend                      |                            |                   | 0.601                      | 0.887               |                           |
| **Raised glucose level**               |                            |                   |                            |                      |                           |
| No                                     | 62,805 (96.3)              | 231 (88.8)        | 1.00 (Ref)                 | 59 (83.1)           | 1.00 (Ref)                |
| Yes                                    | 2,419 (3.7)                | 29 (11.2)         | 1.81 (1.19–2.73)           | 12 (16.9)           | 3.52 (1.83–6.79)          |
| **Diabetic status**                    |                            |                   |                            |                      |                           |
| No                                     | 64,103 (98.3)              | 244 (93.8)        | 1.00 (Ref)                 | 64 (90.1)           | 1.00 (Ref)                |
| Yes                                    | 1,121 (1.7)                | 16 (6.2)          | 2.00 (1.19–3.38)           | 7 (9.9)             | 4.21 (1.86–9.54)          |
| **History of liver disease**           |                            |                   |                            |                      |                           |
| No                                     | 64,462 (98.8)              | 142 (54.6)        | 1.00 (Ref)                 | 55 (77.5)           | 1.00 (Ref)                |
| Yes                                    | 762 (1.2)                  | 118 (45.4)        | 72.97 (56.94–93.51)        | 16 (22.5)           | 23.55 (13.35–41.54)       |

1Adjusted for age (continuous), gender, SES, BMI (continuous), triglycerides (continuous), cholesterol (continuous), raised glucose, diabetic status and history of liver disease.
2Not adjusted for BMI.
3Not adjusted for triglycerides.
4Not adjusted for total cholesterol.
5Not adjusted for diabetic status.
6Not adjusted for raised glucose.
reflective of the associations found with HDL and LDL which our findings reflect. This was the case for ApoA-I and ApoB in regards to cirrhosis but a reversed trend was found between ApoB and PLC with raised levels seemingly associated with increased PLC risk. The ApoA-I and ApoB results should be interpreted with caution due to the discordancy of the dichotomised and quartile results as the difference may be secondary to a type 1 error. However, the characterisation of metabolic syndrome by raised ApoB/ApoA-I levels\(^{11}\) indicates that reported associations between a raised ApoB/ApoA-I ratio with PLC found in this study is of clinical interest.

**Raised glucose and diabetes**

Diabetes mellitus was an independent risk factor for developing PLC in this study and has been reported to be an independent risk factor for HCC with risk estimates ranging from two to three times greater.\(^{2,14,22}\) Studies also report a four times prevalence of diabetics in patients with cryptogenic cirrhosis,\(^{15}\) reflecting our own results with cirrhosis risk. This study uniquely demonstrates that prediabetic hyperglycaemia is associated with PLC and cirrhosis signaling the importance of insulin resistance in conferring PLC risk. Moreover, both, diabetes and raised glucose were associated with PLC and cirrhosis independent of obesity suggesting their roles as important drivers of PLC and cirrhosis risk.

**BMI**

Obesity has been implicated in the genesis of metabolic syndrome and in the contribution to NAFLD, NASH and cirrhosis.\(^{35}\) Obesity has also been associated with PLC and specifically HCC.\(^{2,14,22}\) These studies agree with our findings which show a similar risk association between obesity and PLC. The lack of association between obesity and cirrhosis in this study is likely due to the relatively limited sample size. Importantly however, our study findings demonstrate that after BMI adjustment, diabetes, raised glucose and raised TG remain significantly associated with cirrhosis or PLC suggesting they may be key effectors that confer disease risk. This study includes a large prospective cohort with a long follow-up period which allows for the delayed development of cirrhosis or PLC to become evident. We performed a comprehensive analysis of metabolic syndrome components and included both internationally recognised clinical definitions and quartiles to define trend effects. Our study analysed in detail important apolipoprotein associations with PLC and cirrhosis which is of clinical relevance given their reported associations with metabolic syndrome. Incident cases of PLC were identified through the Swedish National Cancer Register with mandatory reporting of diagnosed cases of cancer since 1958. This study also begins to indicate the role of cirrhosis as a transitional step in the development of PLC by demonstrating the strength of association with individual metabolic syndrome components in patients who developed cirrhosis then PLC. Finally, our study adjusted for important confounders in the development of cirrhosis and PLC, allowing for an assessment of the independent risk contribution of individual metabolic syndrome components. However, as an observational study, and given the complex interplay between metabolic syndrome components and liver function, it is difficult to ascertain causality and avoid residual confounding. Measurement of metabolic syndrome components was taken at baseline with a long interval before the diagnosis of PLC or cirrhosis. Therefore, reported associations may not directly relate to the development of liver disease if there were interval changes in the measured metabolic syndrome components. Due to the asymptomatic nature of NAFLD, NASH and early cirrhosis, the measured levels of metabolic syndrome components made at baseline may be representative of changes caused by early asymptomatic liver disease, presence of which can influenced PLC or cirrhosis risk. Although the study incorporated both dichotomised and quartile values for metabolic syndrome components to correlate any statistically significant findings, results of low significance should be interpreted with caution as there is a risk of type 1 errors due to the multiple comparisons made. Data on the treatment for dyslipidaemia (e.g. statins) and diabetes (e.g. metformin) which may have an influence cholesterol or glucose levels and the risk of developing PLC or cirrhosis were not adjusted for in this study. Data on alcohol consumption was not available for this study, however, we adjusted for the presence of alcoholic liver disease. Only PLC diagnosis was available in this study and not HCC or ICC sub-types. However, as HCC forms the majority of PLC cases (85%), the study findings are largely applicable to HCC.

**Conclusions**

This study uniquely demonstrates important associations between the individual metabolic syndrome components with PLC and cirrhosis. Most notably, we found raised TG, low TC, raised glucose, diabetes and obesity were associated with an increased risk of developing PLC or cirrhosis. Development of PLC in many participants was independent of cirrhosis but in those participants with a history of cirrhosis, the development of PLC was more strongly associated with metabolic syndrome components. The associations between individual metabolic syndrome components and cirrhosis further suggest that metabolic syndrome is an important underlying cause of cryptogenic cirrhosis. Future studies should explore the etiology underlying patients who develop PLC independent of cirrhosis. Future studies should also evaluate if strategies to control the burden of the individual metabolic syndrome components results in a reduction in the risk of developing PLC or cirrhosis.
Ethical Approval
The study was approved by the ethics review board of the Karolinska Institutet.

Contributors
PN, CB, HG, MVH: Conception, design, data collection, data analysis, interpretation of results, manuscript writing (PN) and editing, approval of final version. LH, HM, NH, GW, IJ, PR: Data collection, data analysis, interpretation of results, manuscript editing, approval of final version.

Acknowledgements
The authors thank all participants, the Gunnar and Ingmar Jungner Foundation, FORTE Sweden and Cancerfonden for their contributions that have made this study possible.

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