**SUPPLEMENTARY MATERIAL**

**Supplementary Table 1.** Number of cases with cirrhosis-related symptoms or events.

Reported occurrence at any time; note that patients may have experienced more than one of

these.

|  |  |  |
| --- | --- | --- |
|  | N | % |
| Total Cases | 1293 | 100 |
|  |  |  |
| Ascites | 980 | 75.8 |
| Oesophageal varices | 410 | 31.7 |
| Encephalopathy | 663 | 51.3 |
| Hepatocellular carcinoma | 147 | 11.4 |
| Liver transplant | 145 | 11.2 |

**Supplementary Table 2**. Case and control numbers by sex and country of recruitment.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Australia | | France | | Germany | | Switzerland | | UK | | USA | |
|  | CASE | CONTROL | CASE | CONTROL | CASE | CONTROL | CASE | CONTROL | CASE | CONTROL | CASE | CONTROL |
| Female | 30 | 60 | 107 | 25 | 30 | 41 | 5 | 13 | 88 | 38 | 55 | 22 |
| Male | 117 | 155 | 332 | 112 | 51 | 128 | 26 | 28 | 234 | 78 | 218 | 54 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| Total | 147 | 215 | 439 | 137 | 81 | 169 | 31 | 41 | 322 | 116 | 273 | 76 |

**Supplementary Table 3.** Alcohol consumption in cases and controls from the UK Biobank. Cases = alcohol-related cirrhosis, controls = reported alcohol intake 80 g/day or more for men, 50 g/day or more for women, similar or greater alcohol intake 10 years previously, with no reported alcohol-related liver disease. Means ± SEM. For the log-transformed alcohol measure, grams of alcohol per day, the means converted back to grams or kilograms (geometric means) are shown in italics.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Males | | Females | |
|  | Age (at assessment) | Log Alcohol grams/day | Age (at assessment) | Log Alcohol grams/day |
| Controls: alcohol intake 80M/50F g/day or more | 56.5 ± 0.11 | 2.012 ± 0.0014  *103 grams* | 54.8 ± 0.20 | 1.816 ± 0.0026  *66 grams* |
| Cases: alcoholic cirrhosis | 58.1 ± 0.37 | 1.122 ± 0.048  *13 grams* | 58.1 ± 0.88 | 0.860 ± 0.089  *7 grams* |
| p-values | 1.66 x 10-4 | < 10-200 | 3.98 x 10-4 | < 10-200 |

**Supplementary Table 4**. Comparison of associations with Case-Control status by country of patient recruitment.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Odds Ratios for binary variables** | | | | | | | | | | | | | | | |
|  | **Cannabis** | | | **Diabetes** | | | **Coffee** | | | **Tea** | | | **Ever Smoker** | | |
|  | OR | 95% CI | p | OR | 95% CI | p | OR | 95% CI | p | OR | 95% CI | p | OR | 95% CI | p |
| Australia | 0.235 | 0.134 - 0.414 | 1.53E-07 | 5.726 | 2.864 - 11.451 | 1.82E-07 | 0.361 | 0.234 - 0.556 | 4.00E-06 | 1.011 | 0.653 - 1.564 | 1.000 | 0.405 | 0.251 - 0.656 | 2.33E-04 |
| France | 0.094 | 0.052 - 0.171 | 2.52E-16 | 4.963 | 2.242 - 10.987 | 4.00E-06 | 0.723 | 0.469 - 1.115 | 0.167 | 1.670 | 0.628 - 4.436 | 0.388 | 0.193 | 0.082 - 0.453 | 7.00E-06 |
| Germany | 0.339 | 0.096 - 1.193 | 0.087 | 4.400 | 1.925 - 10.058 | 4.24E-04 | 0.458 | 0.264 - 0.795 | 0.0065 | 0.760 | 0.384 - 1.507 | 0.501 | 0.849 | 0.445 - 1.622 | 0.619 |
| Switzerland | 0.864 | 0.222 - 3.371 | 1.000 | 2.040 | 0.520 - 8.000 | 0.494 | 0.264 | 0.073 - 0.961 | 0.061 | 2.436 | 0.535 - 11.091 | 0.278 | 1.636 | 0.444 - 6.026 | 0.536 |
| UK | 0.252 | 0.137 - 0.461 | 1.00E-05 | 2.423 | 1.195 - 4.913 | 0.012 | 0.622 | 0.405 - 0.956 | 0.037 | 0.913 | 0.595 - 1.402 | 0.742 | 0.438 | 0.259 - 0.741 | 0.0019 |
| USA | 0.458 | 0.263 - 0.798 | 0.0088 | 2.966 | 1.136 - 7.745 | 0.018 | 0.711 | 0.426 - 1.189 | 0.198 | 0.856 | 0.433 - 1.696 | 0.720 | 0.739 | 0.425 - 1.287 | 0.339 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Heterogeneity p |  |  | 0.0017 |  |  | 0.471 |  |  | 0.147 |  |  | 0.635 |  |  | 0.015 |
| Common OR | 0.251 | 0.191 - 0.330 |  | 3.795 | 2.697 - 5.340 |  | 0.547 | 0.446 - 0.671 |  | 0.980 | 0.767 - 1.251 |  | 0.493 | 0.385 - 0.631 |  |
| Overall p-value |  |  | 3.37E-23 |  |  | 1.94E-14 |  |  | 7.71E-09 |  |  | 0.871 |  |  | 1.98E-08 |

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Odds Ratios from logistic regression for continuous variables** | | | | | | | | | | | | |
|  | **Wine percent** | | | **Drink with meals (ordinal\*)** | | | **BMI** | | | **Pre-morbid BMI** | | |
|  | OR | CI95 | p | OR | CI95 | p | OR | CI95 | p | OR | CI95 | p |
| Australia | 0.995 | 0.989 - 1.001 | 0.083 | 2.153 | 1.106 - 4.191 | 0.024 | 1.067 | 1.023 - 1.111 | 0.0022 | 1.100 | 1.054 - 1.149 | 1.48E-05 |
| France | 1.002 | 0.996 - 1.007 | 0.555 | 2.025 | 1.084 - 3.784 | 0.027 | 1.083 | 1.038 - 1.129 | 2.00E-04 | 1.079 | 1.031 - 1.129 | 9.79E-04 |
| Germany | 1.013 | 1.006 - 1.020 | 0.001 | 4.814 | 1.404 - 16.507 | 0.012 | 1.063 | 1.005 - 1.124 | 0.034 | 1.031 | 0.968 - 1.097 | 0.342 |
| Switzerland | 1.001 | 0.988 - 1.014 | 0.869 | 1.769 | 0.258 - 12.105 | 0.561 | 1.175 | 1.049 - 1.315 | 0.0051 | 1.153 | 1.015 - 1.310 | 0.028 |
| UK | 1.005 | 0.998 - 1.011 | 0.167 | 0.986 | 0.435 - 2.234 | 0.972 | 1.101 | 1.051 - 1.153 | 5.10E-05 | 1.074 | 1.027 - 1.125 | 0.0020 |
| USA | 0.999 | 0.986 - 1.012 | 0.863 | 0.767 | 0.310 - 1.895 | 0.565 | 1.000 | 0.957 - 1.045 | 0.998 | 1.032 | 0.985 - 1.080 | 0.189 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| All | 0.995 | 0.993 - 0.998 | 1.74E-04 | 1.576 | 1.153 - 2.153 | 0.0043 | 1.071 | 1.052 - 1.091 | 1.44E-13 | 1.078 | 1.057 - 1.099 | 2.72E-14 |

\*The ‘Drink with meals’ variable was recoded as ‘Mostly drink with meals’ = 1, ‘Mostly drink between meals’ = 0, ‘Both’ = 0.5.

**Supplementary Figure 1.** Estimated lifetime alcohol intake in Cases and Controls, by country of recruitment.

