Supplemental Online Content

Kim HS, Xiao X, Byun J, et al. Synergistic associations of PNPLA3 I148M variant, alcohol intake, and obesity with risk of cirrhosis, hepatocellular carcinoma, and mortality. *JAMA Netw Open*. 2022;5(10):e2234221. doi:10.1001/jamanetworkopen.2022.34221

eTable 1. ICD 10 and OPCS 4 Codes to Define Cirrhosis and HCC

eTable 2. ICD 10 of Liver-Related and Cardiovascular Deaths

eTable 3. Factors Associated With Secondary Outcomes

eTable 4. Overall and Cardiovascular Mortality by PNPLA3 Variant, Obesity and Alcohol Intake

eTable 5. Joint Associations of PNPLA3 Variant, Alcohol Intake, and Obesity Stratified by Sex

eTable 6. Joint Associations in People At Risk for Steatosis

eTable 7. Joint Associations With a Different Definition of Alcohol Intake

eTable 8. Joint Associations With a Different Classification of BMI

This supplemental material has been provided by the authors to give readers additional information about their work.
**eTable 1. ICD 10 and OPCS 4 Codes to Define Cirrhosis and HCC**

| Code type | Code   | Description                                                      |
|-----------|--------|------------------------------------------------------------------|
| ICD 10    | C22.0  | Hepatocellular carcinoma                                        |
|           | K70.2  | Alcoholic fibrosis and sclerosis of liver                       |
|           | K70.3  | Alcoholic cirrhosis of liver                                     |
|           | K72.1  | Chronic hepatic failure                                         |
|           | K74.0  | Hepatic fibrosis                                                |
|           | K74.1  | Hepatic sclerosis                                               |
|           | K74.6  | Other and unspecified cirrhosis of liver                        |
|           | K76.6  | Portal hypertension                                             |
|           | K76.7  | Hepatorenal syndrome                                            |
|           | I85.0  | Oesophageal varices with bleeding                                |
|           | I85.9  | Oesophageal varices without bleeding                            |
|           | I86.4  | Gastric varices                                                 |
|           | I98.2  | Oesophageal varices in diseases classified elsewhere            |
|           | I98.3  | Oesophageal varices with bleeding in diseases classified elsewhere |
|           | R18.0* | Ascites                                                          |
| OPCS4     | J06.1  | Transjugular intrahepatic insertion of stent into portal vein   |
|           | J06.2  | Transjugular intrahepatic insertion of stent graft into portal vein |
|           | G10.4  | Local ligation of varices of oesophagus                         |
|           | G10.8  | Other specified open operations on varices of oesophagus        |
|           | G10.9  | Unspecified open operations on varices of oesophagus            |
|           | G14.4  | Fibreoptic endoscopic injection sclerotherapy to varices of oesophagus |
|           | G17.4  | Endoscopic injection sclerotherapy to varices of oesophagus using rigid oesophagoscope |
|           | G43.7  | Fibreoptic endoscopic rubber band ligation of upper gastrointestinal tract varices |
|           | T46.1* | Paracentesis abdominis for ascites                              |
|           | T46.2* | Drainage of ascites                                             |

ICD-10 refers to International Classification of Disease version 10. OPCS4 refers to Operation/Procedure codes version 4. Those with R18.0 and T46.1 & T46.2 codes were considered to have cirrhosis if accompanied by at least one corroborating ICD code for chronic liver disease (K70-K77) to remove ascites from non-hepatic causes.
## eTable 2. ICD 10 of Liver-Related and Cardiovascular Deaths

| Cause of death | ICD 10 Code | Description                                      |
|----------------|-------------|--------------------------------------------------|
| Liver-related  |             |                                                  |
|                | C22.0       | Hepatocellular carcinoma                         |
|                | K70.X       | Alcoholic liver disease                          |
|                | K71.X       | Toxic liver disease                              |
|                | K72.X       | Hepatic failure, not elsewhere classified        |
|                | K73.X       | Chronic hepatitis, not elsewhere classified      |
|                | K74.X       | Fibrosis and cirrhosis of liver                  |
|                | K75.X       | Other inflammatory liver diseases                |
|                | K76.X       | Other diseases of liver                          |
|                | I85.0       | Oesophageal varices with bleeding                 |
|                | I85.9       | Oesophageal varices without bleeding              |
|                | I86.4       | Gastric varices                                  |
|                | I98.2       | Oesophageal varices in diseases classified elsewhere |
|                | I98.3       | Oesophageal varices with bleeding in diseases classified elsewhere |
| Cardiovascular |             |                                                  |
|                | I10-I15     | Hypertensive diseases                            |
|                | I20-I25     | Ischemic heart diseases                          |
|                | I26-I28     | Pulmonary heart disease and diseases of pulmonary circulation |
|                | I30-I52     | Other forms of heart diseases                    |
|                | I60-I69     | Cerebrovascular diseases                         |
|                | I70-I79     | Diseases of arteries, arterioles and capillaries  |
**eTable 3. Factors Associated With Secondary Outcomes**

|                        | aHR for overall mortality [95% CI] N=25,698 | P-value | aHR for cardiovascular mortality [95% CI] N=8,983 | P-value |
|------------------------|--------------------------------------------|---------|-----------------------------------------------|---------|
| Age                    | 1.11 [1.10-1.11]                             | <0.001  | 1.12 [1.12-1.12]                              | <0.001  |
| Sex                    |                                            |         |                                               |         |
| Female                 | REF                                        | REF     | REF                                           | REF     |
| Male                   | 1.56 [1.51-1.60]                             | <0.001  | 2.11 [2.01-2.22]                              | <0.001  |
| Race                   |                                            |         |                                               |         |
| White                  | 1.34 [1.26-1.43]                             | <0.001  | 1.06 [0.96-1.17]                              | 0.23    |
| Others                 | REF                                        | REF     | REF                                           | REF     |
| Smoking                |                                            |         |                                               |         |
| Never                  | REF                                        | REF     | REF                                           | REF     |
| Former                 | 1.31 [1.27-1.35]                             | 0.01    | 1.36 [1.29-1.43]                              | <0.001  |
| Current                | 2.72 [2.62-2.82]                             | <0.001  | 2.89 [2.72-3.08]                              | <0.001  |
| Alcohol intake         |                                            |         |                                               |         |
| Non-excessive          | REF                                        | REF     | REF                                           | REF     |
| Excessive              | 1.15 [1.11-1.19]                             | <0.001  | 1.08 [1.01-1.15]                              | 0.01    |
| Townsend Index         | 1.06 [1.05-1.06]                             | <0.001  | 1.07 [1.07-1.08]                              | <0.001  |
| Hypertension           | 1.18 [1.14-1.21]                             | <0.001  | 1.55 [1.47-1.64]                              | <0.001  |
| Dyslipidemia           | 1.11 [1.08-1.14]                             | <0.001  | 1.39 [1.32-1.46]                              | <0.001  |
| Diabetes               | 1.75 [1.68-1.81]                             | <0.001  | 2.30 [2.18-2.43]                              | <0.001  |
| Obesity                | 1.18 [1.15-1.22]                             | <0.001  | 1.35 [1.29-1.42]                              | <0.001  |
| PNPLA3 variant status  |                                            |         |                                               |         |
| Non-carrier (CC)       | REF                                        | REF     | REF                                           | REF     |
| Heterozygous carrier (GC) | 1.01 [0.98-1.04]             | 0.54    | 1.02 [0.97-1.06]                              | 0.52    |
| Homozygous carrier (GG) | 1.05 [0.99-1.11]             | 0.12    | 1.07 [0.97-1.19]                              | 0.16    |

Abbreviation: aHR- adjusted hazard ratio, 95% CI: 95% confidence interval

© 2022 Kim HS et al. *JAMA Network Open.*
**eTable 4. Overall and Cardiovascular Mortality by PNPLA3 Variant, Obesity and Alcohol Intake**

|                                      | aHR for Overall mortality | aHR for Cardiovascular mortality |
|--------------------------------------|---------------------------|---------------------------------|
| Normal drinkers, non-obese with PNPLA3 non carriers | REF | REF |
| Normal drinkers, non-obese with PNPLA3 variant heterozygous | 1.00 [95% CI: 0.97-1.04] | 1.03 [95% CI: 0.97-1.10] |
| Normal drinkers, non-obese with PNPLA3 variant **homozygous** | 1.01 [95% CI: 0.93-1.09] | 1.04 [95% CI: 0.90-1.19] |
| Normal drinkers, **obese** with PNPLA3 variant non-carriers | 1.19 [95% CI: 1.14-1.24] | 1.38 [95% CI: 1.30-1.47] |
| Normal drinkers, **obese** with PNPLA3 variant heterozygous | 1.23 [95% CI: 1.17-1.29] | 1.42 [95% CI: 1.31-1.52] |
| Normal drinkers, **obese** with PNPLA3 variant homozygous | 1.30 [95% CI: 1.16-1.45] | 1.41 [95% CI: 1.17-1.69] |
| **Excessive** drinkers, non-obese with PNPLA3 variant non-carriers | 1.20 [95% CI: 1.14-1.27] | 1.14 [95% CI: 1.03-1.25] |
| **Excessive** drinkers, non-obese with PNPLA3 variant heterozygous | 1.18 [95% CI:1.09-1.27] | 1.12 [95% CI: 0.98-1.28] |
| **Excessive** drinkers, non-obese with PNPLA3 variant homozygous | 1.34 [95% CI: 1.12-1.61] | 1.39 [95% CI: 1.03-1.89] |
| **Excessive** drinkers, **obese** with PNPLA3 variant non-carriers | 1.26 [95% CI: 1.16-1.37] | 1.42 [95% CI: 1.25-1.62] |
| **Excessive** drinkers, **obese** with PNPLA3 variant heterozygous | 1.24 [95% CI: 1.12-1.39] | 1.25 [95% CI: 1.05-1.49] |
| **Excessive** drinkers, **obese** with PNPLA3 variant **homozygous** | 1.61 [95% CI: 1.26-2.06] | 2.17 [95% CI: 1.54-3.06] |

Abbreviation: aHR- adjusted hazard ratio, 95% CI: 95% confidence interval
Adjusted for age, sex, race, smoking, Townsend index, hypertension, diabetes, dyslipidemia
**eTable 5. Joint Associations of PNPLA3 Variant, Alcohol Intake, and Obesity Stratified by Sex**

| Risk factors | Male | Female |
|--------------|------|--------|
| | aHR for incident cirrhosis [95% CI] | aHR for incident cirrhosis [95% CI] |
| Non-excessive drinkers, non-obese with PNPLA3 non-carriers | REF | REF |
| Non-excessive drinkers, non-obese with PNPLA3 variant heterozygous | 1.26 [1.05-1.51] | 1.19 [0.96-1.46] |
| Non-excessive drinkers, non-obese with PNPLA3 variant **homozygous** | 1.90 [1.38-2.61] | 1.54 [1.04-2.30] |
| Non-excessive drinkers, **obese** with PNPLA3 variant non-carriers | 1.89 [1.59-2.27] | 1.54 [1.24-1.91] |
| Non-excessive drinkers, **obese** with PNPLA3 variant heterozygous | 2.93 [2.43-3.53] | 2.56 [2.05-3.19] |
| Non-excessive drinkers, **obese** with PNPLA3 variant homozygous | 4.98 [3.63-6.83] | 4.44 [3.05-6.46] |
| **Excessive** drinkers, non-obese with PNPLA3 variant non-carriers | 2.67 [2.18-3.27] | 1.70 [1.19-2.44] |
| **Excessive** drinkers, non-obese with PNPLA3 variant heterozygous | 3.65 [2.91-4.59] | 3.07 [2.14-4.42] |
| **Excessive** drinkers, non-obese with PNPLA3 variant homozygous | 5.64 [3.69-8.64] | 2.79 [1.04-7.50] |
| Group Description                                      | Odds Ratio | 95% CI          |
|--------------------------------------------------------|------------|-----------------|
| Excessive drinkers, obese with PNPLA3 variant non-carriers | 3.93       | [3.10-4.98]     |
|                                                        | 2.95       | [1.86-4.68]     |
| Excessive drinkers, obese with PNPLA3 variant heterozygous | 6.04       | [4.71-7.75]     |
|                                                        | 1.56       | [0.69-3.52]     |
| Excessive drinkers, obese with PNPLA3 variant homozygous | 18.4       | [13.0-26.1]     |
|                                                        | 18.3       | [9.04-37.2]     |
## eTable 6. Joint Associations in People At Risk for Steatosis

| Category                                                                 | aHR for cirrhosis | aHR for HCC    | aHR for liver-related death |
|--------------------------------------------------------------------------|-------------------|----------------|-----------------------------|
| Non-excessive drinkers, non-obese with PNPLA3 non-carriers              | REF               | REF            | REF                         |
| Non-excessive drinkers, non-obese with PNPLA3 variant heterozygous      | 1.43 [95% CI: 1.16-1.77] | 1.54 [95% CI: 0.89-2.66] | 1.29 [95% CI: 0.91-1.83]   |
| Non-excessive drinkers, non-obese with PNPLA3 variant homozgyous        | 2.13 [95% CI: 1.47-3.10] | 1.84 [95% CI: 0.64-5.24] | 2.02 [95% CI: 1.10-3.71]   |
| Non-excessive drinkers, obese with PNPLA3 variant non-carriers          | 1.16 [95% CI: 0.97-1.39] | 1.17 [95% CI: 0.72-1.90] | 1.05 [95% CI: 0.79-1.42]   |
| Non-excessive drinkers, obese with PNPLA3 variant heterozygous          | 1.87 [95% CI: 1.55-2.25] | 2.12 [95% CI: 1.31-3.44] | 1.72 [95% CI: 1.27-2.33]   |
| Non-excessive drinkers, obese with PNPLA3 variant homozygous            | 3.19 [95% CI: 2.42-4.20] | 8.09 [95% CI: 4.63-14.1] | 4.09 [95% CI: 2.72-6.15]   |
| Excessive drinkers, non-obese with PNPLA3 variant non-carriers          | 2.54 [95% CI: 2.00-3.22] | 1.51 [95% CI: 0.71-3.21] | 3.03 [95% CI: 2.14-4.29]   |
| Excessive drinkers, non-obese with PNPLA3 variant heterozygous          | 3.51 [95% CI: 2.70-4.56] | 4.38 [95% CI: 2.30-8.35] | 4.89 [95% CI: 3.39-7.04]   |
| Excessive drinkers, non-obese with PNPLA3 variant homozygous            | 4.96 [95% CI: 3.02-8.16] | 4.06 [95% CI: 0.97-17.1] | 4.93 [95% CI: 2.27-10.7]   |
| Excessive drinkers, obese with PNPLA3 variant non-carriers              | 2.44 [95% CI: 1.92-3.10] | 2.09 [95% CI: 1.06-4.12] | 2.86 [95% CI: 2.00-4.11]   |
| **Excessive drinkers, obese with PNPLA3 variant heterozygous** | 3.37 [95% CI: 2.60-4.37] | 3.41 [95% CI: 1.72-6.73] | 3.86 [95% CI: 2.61-5.69] |
| **Excessive drinkers, obese with PNPLA3 variant homozygous** | 11.9 [95% CI: 8.50-16.7] | 24.6 [95% CI: 12.7-47.8] | 13.1 [95% CI: 7.90-21.7] |
### eTable 7. Joint Associations With a Different Definition of Alcohol Intake

| Status                        | aHR for cirrhosis | aHR for HCC | aHR for liver-related death |
|-------------------------------|-------------------|-------------|-----------------------------|
| **Safe drinkers, non-obese with PNPLA3 non-homozygous carriers** | REF               | REF         | REF                         |
| **Safe drinkers, obese with PNPLA3 non-homozygous** | 1.98 [95% CI: 1.76-2.22] | 1.58 [95% CI: 1.14-2.17] | 2.25 [95% CI: 1.83-2.77] |
| **Safe drinkers, non-obese with PNPLA3 variant homozygous** | 1.54 [95% CI: 1.16-2.03] | 1.60 [95% CI: 0.78-3.28] | 0.98 [95% CI: 0.52-1.85] |
| Safe drinkers, obese with PNPLA3 variant homozygous | 4.90 [95% CI: 3.82-6.29] | 8.60 [95% CI: 5.22-14.2] | 7.55 [95% CI: 5.15-11.1] |
| **Hazardous drinkers, non-obese with PNPLA3 non-homozygous carriers** | 1.18 [95% CI: 1.02-1.35] | 0.88 [95% CI: 0.59-1.32] | 1.54 [95% CI: 1.23-1.94] |
| **Hazardous drinkers, obese with PNPLA3 non-homozygous** | 2.18 [95% CI: 1.85-2.56] | 1.94 [95% CI: 1.27-2.97] | 2.76 [95% CI: 2.12-3.60] |
| **Hazardous drinkers, non-obese with PNPLA3 variant homozygous** | 1.66 [95% CI: 1.06-2.59] | 1.13 [95% CI: 0.28-4.60] | 2.10 [95% CI: 1.03-4.26] |
| **Hazardous drinkers, obese with PNPLA3 variant homozygous** | 5.40 [95% CI: 3.62-8.07] | 14.0 [95% CI: 7.45-26.4] | 7.26 [95% CI: 3.94-13.4] |
| **Harmful drinkers, non-obese with PNPLA3 non-homozygous carriers** | 3.93 [95% CI: 3.34-4.62] | 2.64 [95% CI: 1.60-4.37] | 5.84 [95% CI: 4.58-7.46] |
| **Harmful drinkers, obese with PNPLA3 non-homozygous** | 5.09 [95% CI: 4.18-6.20] | 4.15 [95% CI: 2.41-7.13] | 7.11 [95% CI: 5.27-9.60] |
| **Harmful drinkers, non-obese with PNPLA3 variant homozygous** | 9.40 [95% CI: 6.25-14.2] | 8.10 [95% CI: 2.56-25.7] | 13.0 [95% CI: 7.25-23.4] |
| **Harmful drinkers, obese with PNPLA3 variant homozygous** | 22.2 [95% CI: 15.1-32.7] | 32.9 [95% CI: 15.1-71.7] | 34.5 [95% CI: 20.3-58.6] |
**eTable 8. Joint Associations With a Different Classification of BMI**

|                                      | aHR for cirrhosis | aHR for HCC | aHR for liver-related death |
|--------------------------------------|-------------------|-------------|-----------------------------|
| Non-excessive drinkers, normal weight with PNPLA3 non-homozygous carriers | REF               | REF         | REF                         |
| Non-excessive drinkers, normal weight with PNPLA3 **homozygous carriers** | 1.63 [95% CI: 1.08-2.45] | 2.72 [95% CI: 1.07-6.97] | 0.99 [95% CI: 0.40-2.44] |
| Non-excessive drinkers, **overweight** with PNPLA3 non-homozygous carriers | 1.18 [95% CI: 1.02-1.36] | 1.30 [95% CI: 0.86-1.95] | 0.99 [95% CI: 0.77-1.28] |
| Non-excessive drinkers, **overweight** with PNPLA3 **homozygous carriers** | 1.90 [95% CI: 1.39-2.60] | 1.26 [95% CI: 0.44-3.55] | 1.28 [95% CI: 0.68-2.39] |
| Non-excessive drinkers, **obese** with PNPLA3 non-homozygous carriers | 2.19 [95% CI: 1.89-2.53] | 2.05 [95% CI: 1.34-3.11] | 2.07 [95% CI: 1.61-2.67] |
| Non-excessive drinkers, **obese** weight with PNPLA3 **homozygous carriers** | 4.96 [95% CI: 3.84-6.40] | 11.1 [95% CI: 6.49-19.1] | 6.59 [95% CI: 4.46-9.75] |
| **Excessive** drinkers, normal weight with PNPLA3 non-homozygous carriers | 3.06 [95% CI: 2.45-3.81] | 0.94 [95% CI: 0.33-2.66] | 4.56 [95% CI: 3.32-6.26] |
| **Excessive** drinkers, normal weight with PNPLA3 **homozygous carriers** | 7.63 [95% CI: 4.46-13.1] | 9.77 [95% CI: 2.34-40.8] | 12.0 [95% CI: 6.05-23.9] |
| **Excessive** drinkers, **overweight** with PNPLA3 non-homozygous carriers | 2.68 [95% CI: 2.23-3.22] | 2.73 [95% CI: 1.63-4.59] | 3.07 [95% CI: 2.29-4.13] |

© 2022 Kim HS et al. *JAMA Network Open.*
| Excessive drinkers, overweight with PNPLA3 homozygous carriers | 3.58 [95% CI: 2.05-6.25] | 4.13 [95% CI: 0.98-17.3] | 3.42 [95% CI: 1.39-8.43] |
| --- | --- | --- | --- |
| Excessive drinkers, obese with PNPLA3 non-homozygous carriers | 4.18 [95% CI: 3.46-5.04] | 3.98 [95% CI: 2.34-6.76] | 5.17 [95% CI: 3.85-6.95] |
| Excessive drinkers, obese weight with PNPLA3 homozygous carriers | 18.1 [95% CI: 13.1-25.0] | 35.0 [95% CI: 18.1-67.7] | 20.6 [95% CI: 12.7-33.4] |