Risk of gout among Taiwanese adults with ALDH-2 rs671 polymorphism according to BMI and alcohol intake

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Abstract

Background: Gout stems from both modifiable and genetic sources. We evaluated the risk of gout among Taiwanese adults with aldehyde dehydrogenase-2 (ALDH2) rs671 single nucleotide polymorphism (SNP) according to body mass index (BMI) and alcohol drinking.

Methods: We obtained information of 9253 individuals having no personal history of cancer from the Taiwan Biobank (2008–2016) and estimated the association between gout and independent variables (e.g., rs671, BMI, and alcohol drinking) using multiple logistic regression.

Results: Alcohol drinking and abnormal BMI were associated with a higher risk of gout whereas the rs671 GA+AA genotype was associated with a lower risk. The odds ratios (ORs) and 95% confidence intervals (CIs) were 1.297 and 1.098–1.532 for alcohol drinking, 1.550 and 1.368–1.755 for abnormal BMI, and 0.887 and 0.800–0.984 for GA+AA. The interaction between BMI and alcohol on gout was significant for GG (p-value = 0.0102) and GA+AA (p-value = 0.0175). When we stratified genotypes by BMI, alcohol drinking was significantly associated with gout only among individuals with a normal BMI (OR; 95% CI = 1.533; 1.036–2.269 for GG and 2.109; 1.202–3.699 for GA+AA). Concerning the combination of BMI and alcohol drinking among participants stratified by genotypes (reference, GG genotype, normal BMI, and no alcohol drinking), the risk of gout was significantly higher in the following categories: GG, normal BMI, and alcohol drinking (OR, 95% CI = 1.929, 1.385–2.688); GG, abnormal BMI, and no alcohol drinking (OR, 95% CI = 1.721, 1.442–2.052); GG, abnormal BMI, and alcohol drinking (OR, 95% CI = 1.941, 1.501–2.511); GA+AA, normal BMI, and alcohol drinking (OR, 95% CI = 1.971, 1.167–3.327); GA+AA, abnormal BMI, and no alcohol drinking (OR, 95% CI = 1.498, 1.256–1.586); and GA+AA, abnormal BMI, and alcohol drinking (OR, 95% CI = 1.545, 1.088–2.194).

Conclusions: Alcohol and abnormal BMI were associated with a higher risk of gout whereas the rs671 GA+AA genotype was associated with a lower risk. Noteworthy, BMI and alcohol had a significant interaction on gout risk. Stratified analyses revealed that alcohol drinking especially among normal-weight individuals might elevate the risk of gout irrespective of the genotype.

Keywords: Alcohol drinking, BMI, ALDH2, rs671, Gout, Taiwan biobank

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Background
Gout is a metabolic disease that results from monosodium urate crystal deposits that are generally associated with high levels of urate serum [1, 2]. It is common worldwide and its incidence and prevalence are purportedly increasing [3]. Taiwan is among the top-tiered countries with a high prevalence of gout in the world [3, 4]. Data from Nutrition and Health Survey in Taiwan (NAHSIT) from 1993–1996 to 2005–2008 showed an increase in the prevalence of gout from 4.74 to 8.21% in men and 2.19 to 2.33% in women [5]. Moreover, a nationwide study revealed a prevalence of 6.24% and an incidence of 2.74 per 1000 person-years in 2010 [4].

Previous epidemiological studies identified numerous gout-related modifiable and non-modifiable factors, including but not limited to alcohol intake, BMI, cigarette smoking, sex, age, uric acid, and single nucleotide polymorphism [1, 2, 6–9]. BMI, a modifiable risk factor for gout [2, 3, 7, 8, 10, 11], is also related to well-established major risk factors for gout like hyperuricemia and alcohol consumption [3, 9, 12–15]. Alcohol is a proven key modifiable factor that has been specifically linked to higher incidence and prevalence of gout [2, 7, 8, 10, 11, 13, 16]. It is also a driving factor for hyperuricemia [17], a well-known precursor for gout [1, 2]. Alcohol could influence the risk of gout through its effect on uric acid [18–20]. ALDH2 rs671 attained genome-wide significance as a genetic locus for alcohol drinking [21].

ALDH2 is a vital enzyme in the metabolism of alcohol [22, 23]. The ALDH2 variant, rs671 is a missense SNP that impedes the enzymatic activity of the ALDH2, probably impacting metabolism that results in uric acid synthesis [24]. ALDH2 polymorphisms contribute not only to the metabolism of ethanol and acetaldehyde [25] but also impact predisposition to alcohol-related morbid conditions like hyperuricemia and gout among Asians [18, 19, 26–28]. The link between ALDH2 polymorphisms and serum urate was found to be mediated by alcohol intake among Han Chinese men [19]. ALDH2 rs671 is proven gout-related SNP [22, 29, 30].

Insights into interconnections between modifiable and genetic factors could aid in both the prevention and management of diseases. So far, a meta-analysis revealed that alcohol intake could modulate the link between BMI and ALDH2 rs671 among Koreans and Chinese [31]. Moreover, findings from GWAS suggest that BMI-associated alleles of rs671 are also linked to alcohol drinking behavior [25] and alcohol clearance [23]. The role of both BMI and alcohol drinking in the risk of gout according to ALDH2 rs671 genotypes has not been sufficiently investigated. As such, it is currently inconclusive whether the risk of gout varies based on the combination of these variables. In this study, we evaluated ALDH-2 rs671 polymorphism and the risk of gout according to two modifiable factors (BMI and alcohol intake) among Taiwanese adults.

Materials and methods
Data source and sample size
We used data from the Taiwan Biobank dataset (2008–2016). The Taiwan Biobank was established to build a data resource consisting of lifestyle and genetic data of a large cohort of Taiwanese adults aged 30 to 70 years. Data collection at Taiwan Biobank recruitment centers is done through questionnaires, biochemical, and physical examinations by well-trained personnel. Each participant signed a consent form prior to the collection of data. Initially, 9553 individuals filled the Taiwan Biobank questionnaires (containing data on alcohol drinking, sex, age, cigarette smoking, coffee/tea intake, exercise, and diet) and underwent both physical (e.g., weight, height, waist-hip ratio, and body fat) and biochemical tests (including genotyping, blood urea nitrogen, creatinine, HDL, LDL, and TG). However, 300 of them were ineligible for the study due to missing information. Hence, 9253 individuals were included in the final analyses. The Institutional Review Board of Cheng Ching General Hospital approved this study (HP200010).

Description of variables
Gout cases were those who self-reported a clinical diagnosis of gout or those who were confirmed by biochemical tests to have serum urate levels ≥ 7 mg/dL (men) or ≥ 6 mg/dL (women). Alcohol drinking was defined as an intake of 150 cc of any alcoholic drink per week continuously for at least 6 months and at the time of data collection. No drinking was defined as drinking less than 150 cc of alcohol per week continuously for at least 6 months. Body mass index, calculated as weight (kg) divided by height squared (m²) was categorized into normal 18.5 ≤ BMI < 24 kg/m² and abnormal 0 ≤ BMI < 18.5 and BMI ≥24 kg/m². Waist-hip ratio (WHR), calculated as the ratio of waist to hip circumference was grouped into normal (< 0.9 for men and < 0.85 for women) and abnormal (≥ 0.9 for men and ≥ 0.85 for women). Body fat was classified as normal (< 25% for men and < 30% for women) or abnormal (≥ 25% and ≥ 30% for men and women, respectively). Tea consumption referred to drinking tea at least once per day. Exercise, cigarette smoking, coffee intake, and vegetarian diet were defined as previously elaborated [32–34]. Blood urea nitrogen levels above 20 mg/dL and creatinine levels (≥ 1.4 mg/dL in men and ≥ 1.2 mg/dL in women) were considered abnormal.
Statistical analyses
The SNP (rs671) passed the quality control criteria (Hardy-Weinberg Equilibrium test \( p\text{-value} > 0.001 \), minor allele frequency \( \geq 0.05 \), and call rate \( \geq 95\% \). Chi-square test was used to estimate differences between categorical variables and the results were presented as \( n \) (%). The Student’s \( t\)-test was used to estimate differences between continuous variables and the results were presented as mean \( \pm \) standard deviation (S.D). The interaction between BMI and alcohol drinking and the odds ratios for the association between the dependent (gout) and independent variables (rs671, BMI, alcohol drinking, etc.) were estimated using the multiple logistic regression analysis. In the regression models, we adjusted for covariates, including, sex, age, WHR, body fat, cigarette smoking, coffee intake, tea consumption, exercise, diet, blood urea nitrogen, creatinine, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG). We used the dominant model for the SNP data because the enzyme activity in those with the rs671 GG genotype is higher compared to the AG and AA [24]. Moreover, a previous GWAS on gout and rs671 suggested that the dominant model is the model most likely to have higher statistical significance [22]. Data were managed and analyzed using PLINK v1.90 and SAS 9.4 software and the statistical threshold was set at \( p\text{-value} < 0.05 \) or Bonferroni correction value.

Results
Table 1 presents the demographic features of cases \( (n = 2352) \) and non-cases \( (n = 6901) \) of gout. Individuals with and without gout were significantly different based on ALDH2 rs671 genotypes \( (p\text{-value} = 0.0122) \), alcohol drinking \( (p\text{-value} < 0.0001) \), and BMI \( (p\text{-value} < 0.0001) \).
Table 2 shows the relationship of alcohol drinking, rs671 polymorphism, and BMI with gout. Alcohol drinking (reference, no drinking) and abnormal BMI (reference, normal BMI) were associated with a higher risk of gout while the GA+AA genotype (reference, GG) was associated with a lower risk. The ORs; 95% CIs; p-values were 1.297; 1.098–1.532; 0.0022 for alcohol drinking, 1.550; 1.368–1.755; <0.0001 for abnormal BMI, and 0.887; 0.0240 for the GA+AA genotype. The interaction between BMI and alcohol on gout was significant (p-value = 0.006). However, the interaction of rs671 with alcohol and BMI was not significant (Table 2).

Table 3 shows the association of alcohol drinking and BMI with gout stratified by rs671 genotypes (GG and GA+AA). Both BMI and alcohol drinking were associated with a higher risk of gout. For alcohol, the association was significant in only the GG category (OR = 1.289; 95% CI = 1.048–1.586; p-value = 0.162). However, for BMI, the association was significant in both the GG (OR = 1.584; 95% CI = 1.332–1.883; p-value < 0.0001) and GA+AA (OR = 1.518; 95% CI = 1.268–1.818; p-value < 0.0001) categories. The interaction between BMI and alcohol on gout was significant for both GG (p-value = 0.0102) and GA+AA (p-value = 0.0175).

Tables 4 and 5 illustrate the association between alcohol drinking and gout among participants with ALDH2 rs671 GG and GA+AA stratified by BMI. Alcohol drinking was significantly associated with gout only among individuals with a normal BMI. This results were observed for both GG: OR; 95% CI; p-value = 1.533; 1.036–2.269; 0.0325 (Table 4) and GA+AA: OR; 95% CI; p-value = 2.109; 1.202–3.699; 0.0092 (Table 5).

Table 6 shows the risk of gout in relation to the combination of BMI and alcohol drinking among participants stratified by ALDH2 rs671 genotypes. Compared to the reference category (no alcohol drinking and normal BMI), the risk of gout was significantly higher for both GG and GA+AA. For the GG category, the ORs (95% CI; p-value) were 1.851 (1.316–2.603; 0.0004) for normal BMI and alcohol drinking, 1.727 (1.433–2.080; < 0.0001) for abnormal BMI and no alcohol drinking, and 1.913 (1.451–2.523; < 0.0001) for abnormal BMI and alcohol drinking. For the GA+AA category, the OR (95% CI; p-value) were 2.212 (1.302–3.757; 0.0033) for normal BMI and alcohol drinking, 1.592 (1.323–1.916; < 0.0001) for abnormal BMI and no alcohol drinking, and 1.675 (1.166–2.407; 0.0053) for abnormal BMI and alcohol drinking.

Table 7 displays the risk of gout in relation to the combination of BMI and alcohol drinking among participants stratified by ALDH2 rs671 genotypes. Compared to the reference category (GG genotype, normal BMI, and no alcohol drinking), the risk of gout was significantly higher for all but one category (GA+AA, normal BMI, and no alcohol drinking). The OR (95% CI; p-value) was 1.929 (1.385–2.688; 0.0001) for GG, normal BMI, and alcohol drinking; 1.721 (1.442–2.052; < 0.0001) for GG, abnormal BMI, and no alcohol drinking; 1.941 (1.501–2.511; < 0.0001) for GG, abnormal BMI, and alcohol drinking; 0.937 (0.779–1.126; 0.4862) for GA+AA,
normal BMI, and no alcohol drinking: 1.971 (1.167–3.327; 0.0111) for GA+AA, normal BMI, and alcohol drinking: 1.498 (1.1256–1.786; < 0.0001) for GA+AA, abnormal BMI, and no alcohol drinking; and 1.545 (1.088–2.194; 0.0150) for GA+AA, abnormal BMI, and alcohol drinking. Some covariates that were consistently associated with gout (Tables 2, 3, 4, 5, 6, and 7) included sex (high risk in men compared to women), HDL-C (lower risk), LDL-C (higher risk), and TG (higher risk).

**Discussion**

In the present study, the rs671 GA+AA genotype was associated with a lower risk of gout, while alcohol and abnormal BMI were associated with a higher risk. Of note, BMI and alcohol had a significant interaction on gout risk among individuals with GG and GA+AA. However, there was no significant interaction of rs671 with either BMI or alcohol drinking. Stratified analyses revealed that alcohol drinking especially among normal-weight
individuals could confer susceptibility to gout, irrespective of genotype. These findings confirm the major role of alcohol consumption in the risk of gout. However, we cannot state the precise underlying biological mechanisms. Similar to our results, significant interactions between BMI and alcohol on hyperuricemia have been documented [17, 35]. Based on their findings, Shiraishi and Une advised obese people to reduce the amount of alcohol they consume [35]. Many past studies reported significant associations between gout and rs671 [22, 29, 30, 36]. This variant was described as a real gout-SNP [22, 29, 30]. The A allele of the rs671 has been linked to reduced susceptibility to gout [22]. ALDH2 rs671 also demonstrated the strongest GWA significance for alcohol drinking [21]. It was found to be related to alcohol drinking habits and alcohol flushing responses in Asians [25, 37]. Rapid metabolism of acetaldehyde and ethanol associated with a homozygous ALDH2 rs671 genotype was linked to higher levels of UA in Japanese alcoholic men [26]. The relationship between gout and rs671 could in part be accounted for by alcohol drinking [22].

### Table 4

| Variables                          | GG genotype (n = 4660) |             | P-value | Abnormal (n = 2421) |             | P-value |
|------------------------------------|------------------------|-------------|---------|---------------------|-------------|---------|
|                                    | Normal (n = 2239) | OR (95% CI) |         | OR (95% CI)         |         |         |
| Alcohol drinking (ref: no)         | yes                    | 1.533       | 1.036-2.269 | 0.0325 | 1.205       | 0.945-1.538 | 0.1331 |
| Sex (ref: women)                   | men                    | 2.742       | 1.996-3.765 | <0.0001 | 2.116       | 1.671-2.681 | <0.0001 |
| Age group (ref: 30-40 years)       | 41-50                  | 0.711       | 0.492-1.028 | 0.0697 | 0.578       | 0.450-0.742 | <0.0001 |
|                                    | 51-60                  | 1.064       | 0.740-1.531 | 0.7370 | 0.638       | 0.495-0.823 | 0.0005 |
|                                    | 61-70                  | 0.906       | 0.591-1.391 | 0.6533 | 0.850       | 0.634-1.141 | 0.2792 |
| Waist-hip ratio (ref: normal)      | abnormal               | 1.647       | 1.246-2.177 | 0.0005 | 1.166       | 0.959-1.418 | 0.1236 |
| Body fat (ref: normal)             | abnormal               | 1.244       | 0.900-1.718 | 0.1861 | 1.595       | 1.282-1.985 | <0.0001 |
| Cigarette smoking status (ref: never) | former               | 1.098       | 0.720-1.675 | 0.6640 | 1.121       | 0.861-1.459 | 0.3961 |
|                                    | current                | 1.032       | 0.666-1.600 | 0.8881 | 0.839       | 0.629-1.120 | 0.2344 |
| Coffee consumption (ref: no)       | yes                    | 1.235       | 0.946-1.611 | 0.1207 | 1.112       | 0.922-1.341 | 0.2660 |
| Tea consumption (ref: no)          | yes                    | 1.237       | 0.946-1.618 | 0.1204 | 1.181       | 0.985-1.416 | 0.0721 |
| Exercise (ref: no)                 | yes                    | 1.303       | 0.995-1.706 | 0.0545 | 0.860       | 0.712-1.039 | 0.1180 |
| Diet status (ref: non-vegetarian)  | former vegetarian      | 0.770       | 0.386-1.539 | 0.4603 | 1.480       | 0.966-2.268 | 0.0716 |
|                                    | vegan                  | 0.689       | 0.383-1.238 | 0.2124 | 0.554       | 0.323-0.950 | 0.0318 |
| Blood urea nitrogen (ref: normal)  | abnormal               | 0.865       | 0.441-1.694 | 0.6721 | 1.544       | 1.028-2.319 | 0.0363 |
| Creatinine (ref: normal)           | abnormal               | 19.851      | 3.691-106.761 | 0.0005 | 3.885       | 1.542-9.790 | 0.0040 |
|                                    | HDL-C                  | 0.980       | 0.969-0.999 | 0.0006 | 0.981       | 0.973-0.990 | <0.0001 |
|                                    | LDL-C                  | 1.010       | 1.006-1.014 | <0.0001 | 1.005       | 1.002-1.008 | 0.0004 |
|                                    | Triglycerides          | 1.004       | 1.002-1.006 | <0.0001 | 1.002       | 1.001-1.003 | <0.0001 |

BMI body mass index, OR odds ratio, ref reference, ALDH2 aldehyde dehydrogenase 2, HDL-C high density lipoprotein cholesterol, LDL-C low density lipoprotein cholesterol
Previous studies on the risk of gout based on alcohol consumption showed conflicting findings. Most pioneer epidemiological research reported no association, probably because of a relatively small number of gout cases and failure to adjust for vital confounders [38–40]. Nonetheless, subsequent studies with higher gout cases showed significant associations [13, 16]. A potential explanatory mechanism implicated in the relationship between gout and alcohol is that it enhances uric acid production and the hepatic breakdown of adenosine triphosphate (ATP) [41]. Moreover, alcoholic drinks like beer are rich in purine, which is associated with high levels of uric acid [42].

Evidence from a study using the UK biobank data suggested that genetic polymorphisms have a strong effect on gout regardless of BMI [43]. ALDH2 rs671 attained a significant genome-wide association for BMI [31] and was reported as the only locus having a significant independent association with BMI [31]. Numerous prospective studies on Asians, Europeans, and Americans

| Variables                                | GA+AA genotype (n = 4593) | Abnormal (n = 2377) |
|------------------------------------------|---------------------------|---------------------|
|                                          | Normal (n = 2216)         |                      |
|                                          | OR  | 95% CI | p-value | OR  | 95% CI | p-value |
| Alcohol drinking (ref, no)               |     |        |         |     |        |         |
| Yes                                      | 2.109 | 1.202–3.699 | 0.0092 | 1.108 | 0.789–1.557 | 0.5525 |
| Sex (ref, women)                         |     |        |         |     |        |         |
| Men                                      | 2.561 | 1.854–3.539 | <0.0001 | 2.190 | 1.724–2.780 | <0.0001 |
| Age group (ref, 30–40 years)             |     |        |         |     |        |         |
| 41–50                                    | 1.119 | 0.766–1.635 | 0.5601 | 0.664 | 0.514–0.857 | 0.0017 |
| 51–60                                    | 1.329 | 0.905–1.951 | 0.1469 | 0.743 | 0.572–0.965 | 0.0260 |
| 61–70                                    | 1.536 | 0.991–2.382 | 0.0552 | 0.589 | 0.433–0.803 | 0.0008 |
| Waist-hip ratio (ref, normal)            |     |        |         |     |        |         |
| Abnormal                                 | 1.410 | 1.063–1.869 | 0.0171 | 1.441 | 1.176–1.766 | 0.0004 |
| Body fat (ref, normal)                   |     |        |         |     |        |         |
| Abnormal                                 | 1.331 | 0.955–1.856 | 0.0913 | 1.392 | 1.113–1.742 | 0.0038 |
| Cigarette smoking status (ref, never)    |     |        |         |     |        |         |
| Former                                   | 0.527 | 0.326–0.851 | 0.0088 | 0.950 | 0.725–1.243 | 0.7065 |
| Current                                  | 0.890 | 0.580–1.365 | 0.5936 | 0.591 | 0.438–0.798 | 0.0006 |
| Coffee consumption (ref, no)             |     |        |         |     |        |         |
| Yes                                      | 0.955 | 0.720–1.268 | 0.7516 | 0.996 | 0.820–1.211 | 0.9712 |
| Tea consumption (ref, no)                |     |        |         |     |        |         |
| Yes                                      | 1.562 | 1.193–2.046 | 0.0012 | 1.150 | 0.953–1.387 | 0.1454 |
| Exercise (ref, no)                       |     |        |         |     |        |         |
| Yes                                      | 1.155 | 0.873–1.527 | 0.3127 | 1.024 | 0.841–1.248 | 0.8108 |
| Diet status (ref, non-vegetarian)        |     |        |         |     |        |         |
| Former vegetarian                        | 0.443 | 0.200–0.979 | 0.0442 | 1.090 | 0.721–1.650 | 0.6821 |
| Vegan                                    | 0.492 | 0.247–0.980 | 0.0437 | 0.765 | 0.466–1.254 | 0.2876 |
| Blood urea nitrogen (ref, normal)        |     |        |         |     |        |         |
| Abnormal                                 | 2.231 | 1.313–3.791 | 0.0030 | 1.217 | 0.792–1.871 | 0.3696 |
| Creatinine (ref, normal)                 |     |        |         |     |        |         |
| Abnormal                                 | 1.715 | 0.407–7.234 | 0.4626 | 10.705 | 2.082–55.046 | 0.0045 |
| HDL-C                                    | 0.979 | 0.967–0.991 | 0.0007 | 0.979 | 0.969–0.989 | <0.0001 |
| LDL-C                                    | 1.006 | 1.002–1.010 | 0.0053 | 1.006 | 1.003–1.009 | 0.0002 |
| Triglycerides                            | 1.004 | 1.002–1.005 | <0.0001 | 1.003 | 1.002–1.004 | <0.0001 |

BMI body mass index, OR odds ratio, CI confidence interval, ref reference, ALDH2 aldehyde dehydrogenase 2, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol
suggested that BMI is positively related to the odds of gout and this relationship is possibly mediated by several factors [8, 9, 39, 43–52]. However, there were also reports of no significant relationship between BMI and gout [40]. The role of BMI in gout pathogenesis could be elucidated based on how leptin responds to inflammation related to monosodium urate crystals [53, 54]. BMI could also cause gout through its effect on serum urate [52, 55], potentially through insulinemia which affects renal reabsorption and uric acid clearance [56–59].

Previous studies also had similar findings on the risk of gout pertaining to sex, cigarette smoking, lipoproteins, and other variables [6, 7, 60, 61].

The current study is limited in that the gout population in this study may not be representative of gout patients in the general population. This is because about

| Table 6 | Risk of gout in relation to the combination of BMI and alcohol drinking among participants stratified by ALDH2 rs671 genotypes |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Variables       | GG (n = 4660)   | GA+AA (n = 4593) | p-value   | GG (n = 4660)   | GA+AA (n = 4593) | p-value   |
| BMI and alcohol drinking (ref, normal BMI and no alcohol drinking) | Normal BMI and alcohol drinking | 1.851 | 1.131–2.603 | 0.0004 | 2.212 | 1.302–3.757 | 0.0033 |
|                 | Abnormal BMI and no alcohol drinking | 1.727 | 1.433–2.080 | < 0.0001 | 1.592 | 1.323–1.916 | < 0.0001 |
|                 | Abnormal BMI and alcohol drinking | 1.913 | 1.451–2.523 | < 0.0001 | 1.675 | 1.166–2.407 | 0.0053 |
| Sex (ref, women) | Men              | 2.312 | 1.915–2.790 | < 0.0001 | 2.377 | 1.965–2.876 | < 0.0001 |
| Age group (ref, 30–40 years) | 41–50 | 0.633 | 0.516–0.777 | < 0.0001 | 0.798 | 0.648–0.983 | 0.0343 |
|                 | 51–60            | 0.798 | 0.649–0.981 | 0.0320 | 0.904 | 0.731–1.118 | 0.3501 |
|                 | 61–70            | 0.914 | 0.720–1.161 | 0.4632 | 0.820 | 0.639–1.052 | 0.1189 |
| Waist-hip ratio (ref, normal) | Abnormal | 1.304 | 1.111–1.529 | 0.0011 | 1.426 | 1.211–1.679 | < 0.0001 |
| Body fat (ref, normal) | Abnormal | 1.479 | 1.237–1.767 | < 0.0001 | 1.415 | 1.178–1.699 | 0.0002 |
| Cigarette smoking status (ref, never) | Former | 1.078 | 0.863–1.347 | 0.5082 | 0.810 | 0.643–1.021 | 0.0745 |
|                 | Current          | 0.903 | 0.710–1.149 | 0.4079 | 0.692 | 0.541–0.884 | 0.0033 |
| Coffee consumption (ref, no) | Yes | 1.131 | 0.971–1.317 | 0.1130 | 0.984 | 0.839–1.155 | 0.8477 |
| Tea consumption (ref, no) | Yes | 1.192 | 1.026–1.384 | 0.0215 | 1.266 | 1.086–1.476 | 0.0026 |
| Exercise (ref, no) | Yes | 1.001 | 0.858–1.168 | 0.9904 | 1.084 | 0.924–1.272 | 0.3235 |
| Diet status (ref, non-vegetarian) | Former vegetarian | 1.155 | 0.815–1.636 | 0.4186 | 0.869 | 0.612–1.234 | 0.4333 |
|                 | Vegan            | 0.641 | 0.433–0.950 | 0.0267 | 0.663 | 0.447–0.985 | 0.0417 |
| Blood urea nitrogen (ref, normal) | Abnormal | 1.279 | 0.909–1.801 | 0.1576 | 1.561 | 1.114–2.187 | 0.0097 |
| Creatinine (ref, normal) | Abnormal | 6.192 | 2.726–14.067 | < 0.0001 | 4.449 | 1.639–12.076 | 0.0034 |
|                 | HDL-C            | 0.980 | 0.973–0.987 | < 0.0001 | 0.979 | 0.972–0.987 | < 0.0001 |
|                 | LDL-C            | 1.027 | 1.005–1.009 | < 0.0001 | 1.006 | 1.003–1.008 | < 0.0001 |
|                 | Triglycerides    | 1.003 | 1.002–1.004 | < 0.0001 | 1.003 | 1.002–1.004 | < 0.0001 |

BMI: body mass index, OR: odds ratio, CI: confidence interval, ref: reference, ALDH2: Aldehyde dehydrogenase 2, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol
33% of gout cases were women. This percentage appears high given that the prevalence of gout in Taiwanese men is about 4 times higher than that in women. Moreover, we defined cases as those who self-reported a clinical diagnosis of gout or those with uric acid levels ≥ 7 mg/dL (men) or ≥ 6 mg/dL (women). However, there was no information regarding patients on effective ULT and so the results are possibly not generalizable. In addition, the cohort is 25% gout cases and is thus closer to a case-control cohort than a general population sample.

Table 7 Risk of gout in relation to the combination of BMI, alcohol drinking, and ALDH2 rs671 polymorphism

| Variables                                                                 | OR     | 95% CI         | p-value |
|---------------------------------------------------------------------------|--------|----------------|---------|
| ALDH2 rs671 genotypes, BMI, and alcohol drinking (ref, GG, normal BMI, no alcohol drinking) |        |                |         |
| GG, normal BMI, and alcohol drinking                                      | 1.929  | 1.385–2.688    | 0.0001  |
| GG, abnormal BMI, and no alcohol drinking                                 | 1.721  | 1.442–2.052    | <0.0001 |
| GG, abnormal BMI, and alcohol drinking                                    | 1.941  | 1.501–2.511    | <0.0001 |
| GA+AA, normal BMI, and no alcohol drinking                               | 0.937  | 0.779–1.126    | 0.4862  |
| GA+AA, normal BMI, and alcohol drinking                                   | 1.971  | 1.167–3.327    | 0.0111  |
| GA+AA, abnormal BMI, and no alcohol drinking                              | 1.498  | 1.256–1.786    | <0.0001 |
| GA+AA, abnormal BMI, and alcohol drinking                                 | 1.545  | 1.088–2.194    | 0.0150  |
| Sex (ref, women)                                                          |        |                |         |
| Men                                                                       | 2.355  | 2.061–2.692    | <0.0001 |
| Age group (ref, 30–40 years)                                              |        |                |         |
| 41–50                                                                     | 0.709  | 0.613–0.820    | <0.0001 |
| 51–60                                                                     | 0.849  | 0.732–0.984    | 0.0297  |
| 61–70                                                                     | 0.869  | 0.731–1.032    | 0.1083  |
| Waist-hip ratio (ref, normal)                                            |        |                |         |
| Abnormal                                                                  | 1.362  | 1.216–1.527    | <0.0001 |
| Body fat (ref, normal)                                                    |        |                |         |
| Abnormal                                                                  | 1.450  | 1.276–1.647    | <0.0001 |
| Cigarette smoking status (ref, never)                                     |        |                |         |
| Former                                                                    | 0.937  | 0.799–1.100    | 0.4268  |
| Current                                                                   | 0.782  | 0.659–0.928    | 0.0049  |
| Coffee consumption (ref, no)                                              |        |                |         |
| Yes                                                                       | 1.058  | 0.948–1.180    | 0.3177  |
| Tea consumption (ref, no)                                                 |        |                |         |
| Yes                                                                       | 1.223  | 1.099–1.360    | 0.0002  |
| Exercise (ref, no)                                                        |        |                |         |
| Yes                                                                       | 1.039  | 0.930–1.160    | 0.5007  |
| Diet status (ref, non-vegetarian)                                         |        |                |         |
| Former vegetarian                                                         | 1.006  | 0.787–1.286    | 0.9623  |
| Vegan                                                                     | 0.656  | 0.497–0.867    | 0.0030  |
| Blood urea nitrogen (ref, normal)                                         |        |                |         |
| Abnormal                                                                  | 1.426  | 1.123–1.812    | 0.0036  |
| Creatinine (ref, normal)                                                  |        |                |         |
| Abnormal                                                                  | 5.324  | 2.845–9.962    | <0.0001 |
| HDL-C                                                                     | 0.980  | 0.975–0.985    | <0.0001 |
| LDL-C                                                                     | 1.006  | 1.005–1.008    | <0.0001 |
| Triglycerides                                                             | 1.003  | 1.002–1.004    | <0.0001 |

BMI, body mass index; OR, odds ratio; CI, confidence interval; ref, reference; ALDH2, Aldehyde dehydrogenase 2; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
Another limitation of our study is that we could not clearly explain the precise biological mechanisms underlying the reported relationships.

**Conclusion**

Alcohol and abnormal BMI were associated with a higher risk of gout, while the rs671 GA+AA genotype was associated with a lower risk. Of note, BMI and alcohol had a significant interaction on gout risk among individuals with GG and GA+AA. Stratified analyses revealed that alcohol drinking, especially among normal-weight individuals confers a great risk of gout irrespective of genotype. These findings confirm the major role of alcohol consumption on gout and so both normal weight and abnormal weight individuals are advised to reduce the amount of alcohol they consume. Reducing the amount of alcohol intake could play a great role in public health as it might mitigate the risk of gout.

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