Association of alcohol drinking with incident type 2 diabetes and pre-diabetes: The Guangzhou Biobank Cohort Study

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Abstract

Aims: We examined associations of baseline alcohol drinking with incident type 2 diabetes (T2D) or impaired fasting glucose (IFG), and explore whether the associations were modified by genetic polymorphisms of aldehyde dehydrogenase-2 (ALDH2) and alcohol dehydrogenase-1B (ADH1B).

Materials and methods: All participants were aged 50+ (mean = 60.45; standard deviation = 6.88) years. Information of alcohol consumption was collected at baseline from 2003 to 2008. Incident T2D was defined as fasting glucose ≥7.0 mmol/L or post-load glucose ≥11.1 mmol/L at follow-up examination (2008–2012), self-reported T2D and/or initiation of hypoglycaemia medication or insulin during follow-up. Impaired fasting glucose was defined as fasting glucose ≥5.6 mmol/L and <7 mmol/L.

Results: Of 15,716 participants without diabetes and 11,232 participants without diabetes and IFG at baseline, 1624 (10.33%) developed incident T2D and 1004 (8.94%) developed incident IFG during an average 4 years of follow-up. After multivariable adjustments, compared with never drinking, occasional or moderate alcohol drinking was not associated with risk of incident hyperglycaemia (T2D + IFG) (odds ratio (OR) = 1.10, 95% confidence interval (CI) 0.95–1.27, and 0.90 (0.69–1.18), respectively), whereas heavy alcohol drinking was associated with a higher risk of incident hyperglycaemia (T2D + IFG) (OR = 1.82, 95% CI 1.24–2.68).

No interactions of sex, overweight/obesity and genetic polymorphisms of ADH1B/ALDH2 genes with alcohol drinking on incident T2D and/or IFG were found (P for interaction from 0.12 to 0.85).

Conclusions: Our results support a detrimental effect of heavy alcohol use on IFG and T2D. No protective effect was found for those carrying lower risk alleles for ADH1B/ALDH2 genes.

Abbreviations: ADH1B, Alcohol dehydrogenase-1; ALDH2, Aldehyde dehydrogenase-2; ATP, Adenosine triphosphate; BMI, Body mass index; CI, Confidence interval; DNA, Deoxyribonucleic acid; FPG, Fasting plasma glucose; GBCS, Guangzhou Biobank Cohort Study; GHHARE, Guangzhou Health and Happiness Association for the Respectable Elders; GLUT-4, Glucose transporter 4; IFG, Impaired fasting glucose; OGTT, Oral glucose tolerance test; OR, Odds ratio; PI3K, Phosphatidylinositol 3-kinase; ROS, Reactive oxygen species; SNP, Single-nucleotide polymorphism; T2D, Type 2 diabetes.

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1 | INTRODUCTION

China has the highest number of people with diabetes mellitus in the world, with a prevalence of 10.9% in adults aged 20–79 years. The prevalence of diabetes and pre-diabetes in adults was 12.8% and 35.2%, respectively, in a cross-sectional study of a nationally representative sample in 2015–2017. Alcohol consumption has been associated with the risk of type 2 diabetes (T2D) mellitus in a J-shaped pattern among Asian men. For example, moderate alcohol drinking was associated with a lower risk, whereas heavy alcohol drinking tended to be associated with a higher risk of T2D, despite inconclusive results from three meta-analyses of prospective cohort studies. Two participants showed a positive association between heavy alcohol use and incident T2D but another showed no association for heavy alcohol consumption. Great heterogeneity of results and high variability in definitions of alcohol categories and T2D might lead to the discrepancies between these three meta-analyses. Notably, only one-fourth of the previous studies reported never and former drinkers separately. The risk of T2D attributable to heavy alcohol drinking would be underestimated in studies using a reference group combining never drinkers and less healthy former drinkers. In addition, about 40% of the previous studies defined incident T2D based on self-report, which might further underestimate the risk of T2D from heavy drinking. Asian populations have been considered to have higher genetic susceptibility to T2D and lower alcohol metabolism and clearance. Several genes related to alcohol and diabetes discovered through genome-wide association studies in white populations have been confirmed in Asians as well, despite significant interethnic differences in risk allele frequency. It has been shown that one of the alcohol metabolism-related genes, alcohol dehydrogenase 1C, can modify the effect of alcohol consumption on glycaemic metabolism through its function on ethanol oxidation. However, whether the results can be extended to other major polymorphisms related to alcohol metabolism (i.e., the polymorphisms of aldehyde dehydrogenase-2 (ALDH2) and alcohol dehydrogenase-1B (ADH1B)) is largely unknown.

To date, we found no study that addressed the association between alcohol use and incident diabetes accounting for effect modification by genetic susceptibility. Therefore, we examined the association of baseline alcohol drinking with incident T2D or impaired fasting glucose (IFG) in Guangzhou Biobank Cohort Study (GBCS), a large population-based cohort study of older Chinese in Guangzhou.

2 | METHODS

2.1 | Study population

Detailed information of GBCS has been reported elsewhere. Briefly, GBCS is a 3-way collaboration among Guangzhou 12th People’s Hospital and the Universities of Hong Kong, China and Birmingham, UK. Participants were recruited from an unofficial social and welfare organization that was affiliated with the local government: the “Guangzhou Health and Happiness Association for the Respectable Elders (GHHARE)”, whose membership was open to people aged >50 for a nominal monthly fee of 4 Renminbi (RMB) (US $1 = 7 RMB). The GHHARE had a city-wide network with more than 150 branches throughout Guangzhou, which included 7% of Guangzhou residents in this age group. It had more than 100,000 members of older Guangzhou permanent residents. The study was approved by the Guangzhou Medical Ethics Committee of the Chinese Medical Association in Guangzhou, China. All participants gave written, informed consent before participation.

Baseline examination was performed from September 2003 to January 2008, including face-to-face interview using a computer-assisted questionnaire including demographic characteristics, lifestyle and dietary factors, and disease history, and clinical and laboratory examinations including anthropometry, and fasting plasma glucose (FPG) and lipids. Physical activity was assessed using a validated Chinese version of the International Physical Activity Questionnaire. The first follow-up wave was from March 2008 to December 2012, and we conducted the interview and clinical and laboratory examinations as the baseline.

2.2 | Exposure

Alcohol drinking was classified as never, occasional, moderate and heavy, based on the frequency of alcohol drinking and the usual amount per occasion as described in our previous papers. The usual frequency and quantity of alcohol drinking were assessed. Never drinkers were those who did not drink any alcoholic beverage throughout their life. Occasional drinkers were those who drank less than once per week, or drank only on special occasions, such as wedding parties or festivals, in the past 12 months. Moderate drinkers were people who drank at least once per week with less than or equal to 140 g of ethanol for women and 210 g of ethanol for men. Heavy drinkers were those who weekly drank more than 140 g of ethanol in women and 210 g of ethanol in men. Participants who had abstained from alcohol for at least 1 year were treated as former drinkers.
2.3 | Genotyping

Details of deoxyribonucleic acid (DNA) extraction and genotyping have been published previously.\textsuperscript{17,20} Briefly, DNA was either extracted at baseline from fresh blood using a standard phenol-chloroform extraction procedure or was extracted from blood or buffy coat previously stored at minus 80°C using a standard magnetic bead extraction procedure. Single-nucleotide polymorphism analysis was performed using a Sequenom Mass-Array platform. Individuals with an active genotype (i.e., ADH2 AA/AG or ALDH2 GG) metabolise both ethanol and acetaldehyde quickly and have high acetic acid exposure on alcohol use.\textsuperscript{21}

2.4 | Outcomes

Incident T2D was defined as fasting glucose $\geq 7.0$ mmol/L or post-load glucose $\geq 11.1$ mmol/L in 2-h oral glucose tolerance test at the follow-up examination during 2008–2012.\textsuperscript{22} Self-reported new physician diagnosis of diabetes, and/or initiation of hypoglycaemic medications during the follow-up period. Impaired fasting glucose was defined as fasting glucose $\geq 5.6$ mmol/L and $< 7$ mmol/L,\textsuperscript{22,23} and normoglycaemia was defined as fasting glucose $< 5.6$ mmol/L and post-load glucose $< 7.8$ mmol/L.

2.5 | Potential confounders

Confounders were chosen based on previous studies,\textsuperscript{19,24,25} and possible confounding on the associations of interest, including age, education, occupation, personal annual income, smoking, physical activity, body mass index (BMI), waist/hip ratio, hypertension, health status and family history of diabetes. All potential confounders were adjusted in the full adjustment model. Education was categorised as primary or below, middle school and college or above. Occupation was categorised as manual (agricultural work, factory work, or sales and services), non-manual (administrative/managerial, professional/technical, or military/police) or others (housewife/husband or retired). Personal annual income was categorised as $< 10,000$, 10,000–15,000, $> 15,000$ RMB/year, and unknown. Smoking status was categorised as never, former, and current smokers. Physical activity was categorised as inactive, minimally active, and active. Health status was dichotomised as good or poor, with poor health status being defined as 1) regular use of medication for chronic diseases, such as hypercholesterolaemia or vascular diseases, 2) any hospital admission during the past 6 months, 3) self-reported cardiovascular disease history, or 4) self-reported cancer history.\textsuperscript{26} Hypertension was defined by self-reported hypertension, take of hypotensive medication, a systolic blood pressure of $> 140$ mmHg, and/or diastolic blood pressure $> 90$ mmHg. As the food frequency questionnaire (FFQ) was modified after September 2006 and information on daily energy intake was not available after that time, we conducted sensitivity analyses on 11,709 (65%) participants with adjustment for daily energy intake and diet quality (consumption of rice, meat, egg, vegetable, and fruit). Participants were asked their average frequency of consumption of different kinds of foods and beverages over the past 7 days based on a validated FFQ.\textsuperscript{27}

2.6 | Statistical analysis

For comparison of baseline categorical variables by alcohol drinking status, we used Fisher’s exact probability test for groups with small number of participants and chi-squared test for larger groups. For comparison of continuous variables, we used one-way analysis of variance. We used generalised linear models to assess the association of alcohol drinking with fasting glucose at baseline or follow-up, as well as differences in glucose level between baseline and follow-up, reporting regression coefficient (β) and 95% confidence interval (CI). We also used logistic regression to calculate odds ratio (OR) and 95% CI for the development of T2D and IFG. Potential confounder adjusted included age, education, occupation, personal annual income, smoking, physical activity, BMI, waist/hip ratio, health status, and family history of diabetes mellitus. Besides, we also assessed interactions between alcohol drinking and genetic variants (ALDH2 (AA + AG vs. GG) and ADH1B (AA vs. AG + GG genotypes), sex, overweight/obesity (BMI $\geq 25$ kg/m$^2$) or health status because previous studies suggested that the associations of alcohol with T2D might vary by these risk factors.\textsuperscript{7,8} Interactions were tested by fitting models with and without the interaction term, with statistical significance determined by the likelihood ratio test of the difference between the two models on the relevant $\chi^2$ distribution. Sensitivity analyses with adjustment for daily total energy intake were conducted. Data analysis was performed using Stata/SE 15.0 (Stata Corp LP, College Station, TX, USA). All tests were two-sided with $P < 0.05$ as statistically significant.

3 | RESULTS

As of 31 December 2012, of 18,104 (13,178 women and 4926 men) who returned for repeated examination, 269 were excluded because of incomplete information on fasting glucose or alcohol drinking, leaving 17,835 participants (4849 men and 12,986 women) with all variables of interest. Of these 17,835, 2119 (11.88%) with diabetes and 4484 (25.14%) with IFG at baseline were excluded from the analysis on incident T2D and IFG, respectively, leaving 15,716 participants without diabetes and 11,232 participants without diabetes and IFG at baseline. During an average of 4-year of follow-up, of 15,716 participants without baseline diabetes, 1624 (10.33%) participants developed incident T2D; while of 11,232 participants without diabetes and IFG at baseline, 1004 (8.94%) participants developed incident IFG and 1638 (14.6%) developed T2D + IFG.

Table 1 shows that, in both men and women, compared to occasional drinkers, heavy alcohol drinkers had lower socioeconomic position (lower education, manual occupation and lower personal...
| Alcohol drinking status | Never | Occasional (<1/week) | Moderate (women <140 g/week; men <210 g/week) | Heavy (women ≥140 g/week; men ≥210 g/week) | Ex-drinkers | p value |
|-------------------------|-------|----------------------|---------------------------------------------|---------------------------------------------|-------------|--------|
| Men                     |       |                      |                                             |                                             |             |        |
| Number (%)              | 2260 (52.96) | 1045 (24.49) | 494 (11.58) | 233 (5.46) | 235 (5.51) |        |
| Age, years              | 63.41 (6.52) | 61.73 (6.65) | 63.55 (6.62) | 62.79 (6.37) | 63.25 (6.68) | <0.001 |
| Education, N (%)        |       |                      |                                             |                                             |             |        |
| Primary or below        | 581 (25.73) | 229 (21.91) | 164 (33.20) | 96 (41.20) | 80 (34.04) | <0.001 |
| Middle school           | 1283 (56.82) | 620 (59.33) | 265 (53.64) | 112 (48.07) | 123 (52.34) |        |
| College or above        | 394 (17.45) | 196 (18.76) | 65 (13.16) | 25 (10.73) | 32 (13.62) |        |
| Occupation, N (%)       |       |                      |                                             |                                             |             |        |
| Manual                  | 1064 (47.31) | 483 (46.71) | 247 (50.20) | 135 (58.19) | 116 (49.36) | 0.001  |
| Non-manual              | 872 (38.77) | 392 (37.91) | 175 (35.57) | 67 (28.88) | 68 (28.94) |        |
| Others                  | 313 (13.92) | 159 (15.38) | 70 (14.23) | 30 (12.93) | 51 (21.70) |        |
| Personal annual income, RMB/year, N (%) |       |                      |                                             |                                             |             |        |
| <10,000                 | 485 (21.48) | 234 (22.39) | 109 (22.11) | 70 (30.04) | 61 (25.96) | 0.001  |
| 10,000–15,000           | 905 (40.08) | 358 (34.26) | 203 (41.18) | 79 (33.91) | 100 (42.55) |        |
| >15,000                 | 732 (32.42) | 398 (38.09) | 153 (31.03) | 73 (31.33) | 59 (25.11) |        |
| Unknown                 | 136 (6.02) | 55 (5.26) | 28 (5.68) | 11 (4.72) | 15 (6.38) |        |
| Smoking status, N (%)   |       |                      |                                             |                                             |             |        |
| Never                   | 1118 (49.53) | 423 (40.48) | 143 (28.95) | 23 (9.87) | 60 (25.53) | <0.001 |
| Former                  | 567 (25.12) | 266 (25.45) | 152 (30.77) | 67 (28.76) | 93 (39.57) |        |
| Current                 | 572 (25.34) | 356 (34.07) | 199 (40.28) | 143 (61.37) | 82 (34.89) |        |
| Physical activity, N (%)|       |                      |                                             |                                             |             |        |
| Inactive                | 240 (10.62) | 45 (4.31) | 44 (8.91) | 23 (9.87) | 12 (5.11) | <0.001 |
| Minimally active        | 990 (43.81) | 393 (37.61) | 215 (43.52) | 96 (41.20) | 114 (48.51) |        |
| Active                  | 1030 (45.58) | 607 (58.09) | 235 (47.57) | 114 (48.93) | 109 (46.38) |        |
| BMI, kg/m²              | 23.34 (3.13) | 23.55 (3.01) | 23.45 (3.16) | 23.46 (3.07) | 23.69 (3.18) | 0.28   |
| Waist/hip ratio         | 0.89 (0.06) | 0.89 (0.06) | 0.90 (0.06) | 0.91 (0.06) | 0.91 (0.06) | <0.001 |
TABLE 1 (Continued)

| Alcohol drinking status | Never | Occasional (<1/week) | Moderate (women <140 g/week; men <210 g/week) | Heavy (women ≥140 g/week; men ≥210 g/week) | Ex-drinkers | p value |
|-------------------------|-------|----------------------|-----------------------------------------------|---------------------------------------------|-------------|--------|
| Hypertension, yes, N (%)| 946 (41.99) | 409 (39.25) | 212 (43.18) | 110 (48.03) | 117 (50.21) | 0.01 |
| Family history of diabetes, yes, N (%) | 208 (9.20) | 122 (11.67) | 43 (8.70) | 18 (7.73) | 27 (11.49) | 0.11 |
| Health status, N (%) | | | | | | |
| Good | 1942 (85.93) | 916 (87.66) | 428 (86.64) | 209 (89.70) | 185 (78.72) | 0.004 |
| Poor | 318 (14.07) | 129 (12.34) | 66 (13.36) | 24 (10.30) | 50 (21.28) | |
| Women | | | | | | |
| Number (%) | 8915 (77.87) | 1910 (16.68) | 302 (2.64) | 16 (0.14) | 306 (2.67) | |
| Age, years | 59.78 (6.69) | 58.04 (6.69) | 60.87 (7.10) | 61.88 (6.97) | 59.11 (7.20) | <0.001 |
| Education, N (%) | | | | | | |
| Primary or below | 3946 (44.27) | 630 (32.98) | 119 (39.40) | 10 (62.50) | 120 (39.22) | <0.001 |
| Middle school | 4431 (49.71) | 1139 (59.63) | 165 (54.64) | 6 (37.50) | 167 (54.58) | |
| College or above | 536 (6.01) | 141 (7.38) | 18 (5.96) | 0 (0.00) | 19 (6.21) | |
| Occupation, N (%) | | | | | | |
| Manual | 5797 (65.31) | 1178 (62.49) | 196 (65.77) | 12 (75.00) | 201 (65.90) | 0.37 |
| Non-manual | 1709 (19.25) | 381 (20.21) | 58 (19.46) | 2 (12.50) | 51 (16.72) | |
| Others | 1370 (15.43) | 326 (17.29) | 44 (14.77) | 2 (12.50) | 53 (17.38) | |
| Personal annual income, RMB/year, N (%) | | | | | | |
| <10,000 | 3385 (37.97) | 483 (25.30) | 102 (33.77) | 8 (50.00) | 88 (28.76) | <0.001 |
| 10,000–15,000 | 4018 (45.08) | 1019 (53.38) | 143 (47.35) | 6 (37.50) | 164 (53.59) | |
| >15,000 | 1102 (12.36) | 347 (18.18) | 50 (16.56) | 1 (6.25) | 45 (14.71) | |
| Unknown | 409 (4.59) | 60 (3.14) | 7 (2.32) | 1 (6.25) | 9 (2.94) | |
| Smoking status, N (%) | | | | | | |
| Never | 8707 (97.67) | 1854 (97.22) | 282 (93.38) | 10 (62.50) | 289 (94.44) | <0.001 |
| Former | 97 (1.09) | 31 (1.63) | 8 (2.65) | 3 (18.75) | 7 (2.29) | |
(Continues)
| Alcohol drinking status | Never | Occasional (<1/week) | Moderate (women <140 g/week; men <210 g/week) | Heavy (women ≥140 g/week; men ≥210 g/week) | Ex-drinkers | p value |
|-------------------------|-------|----------------------|---------------------------------------------|---------------------------------------------|-------------|---------|
| Current                 | 111 (1.25) | 22 (1.15) | 12 (3.97) | 3 (18.75) | 10 (3.27) |         |
| Physical activity, N (%) |       |                     |                                             |                                             |             |         |
| Inactive                | 891 (9.99) | 36 (188) | 12 (3.97) | 1 (6.25) | 7 (2.29) | <0.001 |
| Minimally active        | 3681 (41.29) | 470 (24.61) | 93 (30.79) | 6 (37.50) | 97 (31.70) |         |
| Active                  | 4343 (48.72) | 1404 (73.51) | 197 (65.23) | 9 (56.25) | 202 (66.01) |         |
| BMI, kg/m²              | 23.65 (3.29) | 23.85 (3.09) | 23.99 (3.13) | 24.34 (3.17) | 24.22 (3.37) | 0.002 |
| Waist/hip ratio         | 0.85 (0.06) | 0.84 (0.06) | 0.85 (0.06) | 0.87 (0.06) | 0.85 (0.07) | 0.02 |
| Hypertension, yes, N (%)| 3.394 (38.23) | 543 (28.50) | 85 (28.43) | 9 (56.25) | 126 (41.58) | <0.001 |
| Family history of diabetes, yes, N (%) | 1008 (11.31) | 295 (15.45) | 26 (8.61) | 1 (6.25) | 30 (9.80) | <0.001 |
| Health status, N (%)    |       |                     |                                             |                                             |             |         |
| Good                    | 7716 (86.55) | 1699 (88.95) | 258 (85.43) | 16 (100.00) | 272 (88.89) | 0.02 |
| Poor                    | 1199 (13.45) | 211 (11.05) | 44 (14.57) | 0 (0.00) | 34 (11.11) |         |

Note: Data are means (standard deviation) unless otherwise indicated; p values were for differences among categories of alcohol drinking status. US $1 = 7 RMB. Abbreviations: BMI, body mass index N, number.
annual income), higher prevalence of unhealthy lifestyle (physical inactivity and smoking), hypertension and levels of waist/hip ratio, but better health status (P from 0.004 to 0.02). In men, no association between BMI and alcohol drinking status was observed (p = 0.28); whilst in women, heavy alcohol drinkers had the highest levels of BMI (p = 0.002).

Table 2 shows that, after adjusting for age, education, occupation, physical activity, smoking, BMI, waist/hip ratio, health status, hypertension and family history of diabetes, in men, heavy alcohol drinking (the median alcohol consumption 378 g/week) was associated with higher levels of fasting glucose at follow-up (adjusted β (95% CI) = 0.19 (0.06–0.32)). In women, no significant association of alcohol drinking with fasting glucose or changes in fasting glucose was found. As alcohol drinking and sex showed no interaction on FPG or changes in FPG (p values for interaction ranged 0.16–0.71), men and women were pooled. After adjusting for similar confounders above and sex, heavy alcohol drinking was association with FPG at follow-up, and greater increase in FPG at follow-up (adjusted β (95% CI) = 0.20 (0.08–0.32), and 0.13 (0.02–0.24), respectively).

As we found no interactions of alcohol drinking with sex, normal/obesity and health status (p values for interaction from 0.36 to 0.85), no subgroup analysis was done by these factors except for sex, as alcohol use was much less common in Chinese women. Table 3 shows that, in men, compared to never drinkers, heavy and former alcohol drinking was associated with a higher risk of T2D (adjusted OR (95% CI) = 1.67 (1.11–2.50) and 1.54 (1.03–2.28), respectively), whereas the negative association was non-significant (adjusted OR (95% CI) = 0.77 (0.54–1.12)) for moderate alcohol drinking. In women, we found no association of moderate and heavy alcohol drinking with T2D. In all participants, heavy alcohol drinking was significantly associated with a higher risk (adjusted OR (95% CI) = 1.54 (1.05–2.25), and moderate alcohol drinking was associated with a lower risk of incident T2D (adjusted OR (95% CI) = 0.71 (0.53–0.94)). However, non-significant associations of moderate and heavy alcohol drinking with incident IFG in men and women separately were found. In all participants, heavy alcohol drinking was associated with a higher risk of IFG (adjusted OR (95% CI) = 1.81 (1.14–2.87)). Furthermore, of participants without IFG and T2D at baseline, compared to never drinkers, heavy alcohol drinking was associated with a higher risk of T2D + IFG in men (adjusted OR (95% CI) = 1.72 (1.14–2.61)) and total participants (adjusted OR (95% CI) = 1.82 (1.24–2.68)). No association between moderate alcohol drinking and incident T2D + IFG was found (Table 3). Similarly, heavy alcohol drinking was significantly associated with higher risks of T2D + IFG (ESM Table 1).

Table 4 shows no interaction between ALDH2 or ADH1B polymorphism and alcohol drinking on incident T2D in all participants and in men (P for interaction from 0.12 to 0.79). In men, the adjusted OR of incident T2D for heavy alcohol drinking was 1.68 (95% CI 0.99–2.87) in those with ALDH2 GG genotype and 1.68 (95% CI 0.54–5.21) in those with AA/AG genotype. In men, the association appeared to be slightly stronger in those with ADH1B AA genotype (adjusted OR (95% CI) = 2.30 (1.27–4.17)) than those with ADH1B GG/AG genotype (adjusted OR (95% CI) = 1.29 (0.65–2.55)), although the 95% CIs overlapped. In all participants, the adjusted ORs were slightly attenuated, and became non-significant, except for the ADH1B AA genotype (adjusted OR (95% CI) = 2.15 (1.21–3.82)). Similarly, no significant interaction between alcohol drinking and ALDH2/ADH1B genotypes was found regarding the association with incident T2D + IFG (ESM Table 2).

4 DISCUSSION

In this large population-based prospective cohort study of older Chinese, we found that moderate alcohol drinking was associated with a lower risk of incident T2D, whereas heavy alcohol drinking was significantly associated with higher risks of incident T2D and IFG. The association did not vary by sex or genetic polymorphism related to alcohol metabolism, although the non-significant interactions could be due to the relatively small number of alcohol users in our study.

We found that moderate alcohol drinking was not associated with a lower risk of incident T2D + IFG, but showed suggestively protective effect on T2D, which are generally consistent with most previous prospective cohort studies. However, these apparently protective associations do not necessarily mean that moderate alcohol drinking per se is protective against T2D. For example, poor health might affect alcohol use (reverse causation), and systematic differences might exist between individuals with different drinking patterns that were not fully adjusted (residual confounding). Moreover, Mendelian randomisation study shows that the association between alcohol intake and T2D risk was likely causal and in a linear relationship. The lower risks of T2D and IFG in ours and previous studies may have reflected biases of reverse causation or confounding.

It is alarming that heavy alcohol drinkers (≥140 g/week in women and ≥210 g/week in men) had a 82% higher risk of incident T2D + IFG than never drinkers, which is consistent with two meta-analyses showing positive association between heavy alcohol use and incident T2D. Regarding the high prevalence of diabetes and a continuing increase in alcohol use, our findings add to the evidence on the harmful effects of heavy alcohol drinking, and further indicate no protection from low-risk alleles (i.e., ALDH2 G allele or ADH1B A allele), suggesting that more strict governmental alcohol control policies are urgently needed to tackle the rapid increase in alcohol consumption and diabetes epidemic.

Most of the previous studies in the West or Asia showed no association of heavy alcohol drinking with incident T2D, except one retrospective Korean cohort study showing that heavy drinking (ethanol intake ≥30 g/day) was associated with a higher risk of T2D or IFG obese men, and one prospective Chinese cohort study showing that heavy drinking (ethanol intake >60 g/day) was associated with a higher risk of T2D in men, and another prospective Japanese cohort study showing similarly positive association with incident T2D in lean, but not in overweight/obese men. It is unclear why BMI may modify
| Alcohol drinking status | Moderate (women < 140 g/week; men < 210 g/week) | Heavy (women ≥ 140 g/week; men ≥ 210 g/week) | Ex-drinkers |
|-------------------------|-----------------------------------------------|-----------------------------------------------|------------|
|                         | Never                                        | Occasional (<1/week)                          |            |
| **Baseline FPG**        |                                               |                                               |            |
| Alcohol drinking status |                                               |                                               |            |
| Never                   | 2260                                         | 1045                                          | 494        | 233        | 235          |
| Crude FPG (mmol/L)      | 5.36                                         | 5.30                                          | 5.33       | 5.41       | 5.34         |
| Crude β (95% CI)        | 0.00                                         | −0.05 (−0.10, −0.01)‡                         | −0.03 (−0.09, 0.03) | 0.05 (−0.03, 0.14) | −0.02 (−0.10, 0.06) |
| Adjusted β (95% CI)      | 0.00                                         | −0.05 (−0.09, −0.00)‡                         | −0.03 (−0.09, 0.03) | 0.06 (−0.02, 0.14) | −0.03 (−0.11, 0.05) |
| **Follow-up FPG**       |                                               |                                               |            |
| Crude FPG (mmol/L)      | 5.29                                         | 5.26                                          | 5.28       | 5.55       | 5.30         |
| Crude β (95% CI)        | 0.00                                         | −0.03 (−0.10, 0.04)                           | −0.00 (−0.10, 0.09) | 0.26 (0.13, 0.39) | 0.01 (−0.12, 0.14) |
| Adjusted β (95% CI)      | 0.00                                         | −0.04 (−0.11, 0.04)                           | −0.02 (−0.12, 0.07) | 0.19 (0.06, 0.32) | −0.04 (−0.17, 0.09) |
| **FPG changes during follow-up** |                                               |                                               |            |
| Crude β (95% CI)        | 0.00                                         | 0.03 (−0.04, 0.09)                            | 0.02 (−0.06, 0.11) | 0.21 (0.08, 0.33) | 0.03 (−0.09, 0.15) |
| Adjusted β (95% CI)      | 0.00                                         | 0.01 (−0.06, 0.08)                            | 0.01 (−0.08, 0.10) | 0.13 (−0.00, 0.25) | −0.01 (−0.14, 0.11) |
| **Women**               |                                               |                                               |            |
| Number                  | 8915                                         | 1910                                          | 302        | 16         | 306          |
| Baseline FPG            |                                               |                                               |            |
| Alcohol drinking status |                                               |                                               |            |
| Never                   |                                               |                                               |            |
| Crude FPG (mmol/L)      | 5.29                                         | 5.31                                          | 5.36       | 5.28       | 5.37         |
| Crude β (95% CI)        | 0.00                                         | 0.01 (−0.02, 0.04)                            | 0.06 (−0.00, 0.13) | −0.02 (−0.31, 0.27) | 0.07 (0.01, 0.14)‡ |
| Adjusted β (95% CI)      | 0.00                                         | −0.00 (−0.03, 0.03)                           | 0.03 (−0.04, 0.09) | −0.09 (−0.36, 0.19) | 0.05 (−0.02, 0.11) |
| **Follow-up FPG**       |                                               |                                               |            |
| Crude FPG (mmol/L)      | 5.26                                         | 5.28                                          | 5.23       | 5.31       | 5.31         |
| Crude β (95% CI)        | 0.00                                         | 0.02 (−0.02, 0.07)                            | −0.03 (−0.14, 0.08) | 0.05 (−0.40, 0.51) | 0.05 (−0.05, 0.16) |
| Adjusted β (95% CI)      | 0.00                                         | 0.03 (−0.01, 0.08)                            | −0.03 (−0.14, 0.07) | 0.00 (−0.44, 0.44) | 0.04 (−0.07, 0.14) |
| **FPG changes during follow-up** |                                               |                                               |            |
| Crude β (95% CI)        | 0.00                                         | 0.01 (−0.04, 0.05)                            | −0.09 (−0.19, 0.01) | 0.07 (−0.35, 0.49) | −0.02 (−0.12, 0.08) |
| Adjusted β (95% CI)      | 0.00                                         | 0.03 (−0.01, 0.07)                            | −0.06 (−0.16, 0.04) | 0.09 (−0.33, 0.51) | −0.01 (−0.11, 0.09) |
| **Total**               |                                               |                                               |            |
| Number                  | 11,175                                       | 2,955                                         | 796        | 249        | 541          |
| Baseline FPG            |                                               |                                               |            |
| Alcohol drinking status |                                               |                                               |            |
| Never                   |                                               |                                               |            |
| Crude FPG (mmol/L)      | 5.31                                         | 5.31                                          | 5.34       | 5.40       | 5.35         |
| Crude β (95% CI)        | 0.00                                         | 0.00 (−0.02, 0.02)                            | 0.03 (−0.01, 0.08) | 0.09 (0.02, 0.17)‡ | 0.05 (−0.00, 0.10) |
| Adjusted β (95% CI)      | 0.00                                         | −0.01 (−0.04, 0.01)                           | −0.00 (−0.04, 0.04) | 0.07 (−0.01, 0.14) | 0.02 (−0.03, 0.07) |
| **Follow-up FPG**       |                                               |                                               |            |
| Crude FPG (mmol/L)      | 5.26                                         | 5.27                                          | 5.26       | 5.53       | 5.31         |
| Crude β (95% CI)        | 0.00                                         | 0.01 (−0.03, 0.05)                            | −0.00 (−0.07, 0.06) | 0.27 (0.15, 0.38) | 0.04 (−0.04, 0.12) |
| Adjusted β (95% CI)      | 0.00                                         | 0.01 (−0.03, 0.05)                            | −0.02 (−0.09, 0.05) | 0.20 (0.08, 0.32)‡ | 0.01 (−0.07, 0.09) |
the association between alcohol consumption and incident T2D. A possible explanation for this effect modification by overweight/obesity is that adiposity-induced insulin resistance is suppressed through moderate alcohol drinking.\textsuperscript{37} Prior studies examining effect modification by overweight/obesity showed inconsistent findings.\textsuperscript{34,36} Our study found no evidence that the association of alcohol drinking with incident T2D and/or IFG differed by overweight/obesity status. The effect modification by adiposity warrants further clarification, although scientifically we expect causal factors to be consistent.

We also found that heavy alcohol drinking was associated with higher risks of incident IFG. However, the association of alcohol use and incident IFG was inconclusive in previous studies.\textsuperscript{28,34,38} A prospective cohort study showed that moderate alcohol drinking (ethanol intake 23–46 g/day) was associated with lower risks of incident IFG and T2D on healthy Japanese men.\textsuperscript{28} Another prospective study showed that moderate alcohol drinking (20–36 g/day) was associated with a lower risk of incident T2D but not risk of incident hyperglycaemia (including both T2D and IFG).\textsuperscript{38} Furthermore, a study of obese men showed that both moderate (15–29 g/day) and high alcohol drinking (≥30 g/day) were associated with higher risks of incidence IFG and T2D.\textsuperscript{34} However, all studies above did not report the association between heavy alcohol drinking and incident IFG alone.\textsuperscript{28,34,38} Given the limited and inconsistent evidence available on the association of heavy alcohol drinking with incident T2D and IFG, our results add to the literature highlighting the potential detrimental effect of heavy alcohol use on hyperglycaemia.

We found no evidence for the sex difference in the association of moderate or heavy alcohol drinking with incident T2D, although a small non-significant sex-specific difference in moderate alcohol drinking was found. The sex differences in previous studies could be explained by the sex-specific categorisation of moderate and heavy alcohol drinking as well as varying T2D risk factors between men and women. A meta-analysis of clinical trials showed that moderate alcohol drinking was associated with reduced fasting insulin concentrations and improved insulin sensitivity in women but not men.\textsuperscript{39} As the results of this meta-analysis were based on five small interventional studies, the non-significant results could be due to the small size, heterogeneous designs and populations.\textsuperscript{40,41}

Heavy alcohol drinking may have a direct toxic effect on the pancreas, irrespective of sex.\textsuperscript{32} Some rodent studies showed that excessive ethanol intake caused damage to islets and beta-cells by interfering insulin signalling, reducing beta-cell mass and subsequently leading to a decrease in insulin secretion and an increase in fasting glucose.\textsuperscript{43,44} Ethanol may also cause beta-cell apoptosis through mitochondrial dysfunction, manifested by an increased reactive oxygen species and decreased adenosine triphosphate production.\textsuperscript{45} Furthermore, ethanol could also inhibit the insulin-induced phosphatidylinositol 3-kinase activity and glucose transporter 4 expression in skeletal muscle and lead to insulin resistance.\textsuperscript{43} Our results supported that heavy alcohol drinking was associated with higher risks of incident diabetes. However, in our study, as only a small number of female participants were heavy alcohol drinkers (only 0.14% women were in the ≥140 g/week group), we had limited ability to examine associations in women.

As ADH1B and ALDH2 are major enzymes involved in alcohol metabolism,\textsuperscript{46,47} genetic variants in these genes may also be effect modifiers of the association between alcohol consumption and incident diabetes. The ALDH2 A allele is common in Asians but rare in Caucasians.\textsuperscript{46,48} Previous studies showed that up to 40% of East Asian populations were carrying the heterozygous ALDH2 A genotype, which has only about one-third the enzymatic activity to convert acetaldehyde into acetic acid as compared to those with the ALDH2 G genotype.\textsuperscript{49} After drinking alcohol, those carrying the less active ADH G variant develop high acetaldehyde concentration in blood, they become more prone to alcoholic complications such as headache, facial flushing or nausea and are less likely to drink or drink heavily. Previous studies showed that the ALDH2 genetic polymorphisms modified the effects of alcohol drinking on some diseases such as cardiovascular disease and liver cirrhosis.\textsuperscript{50-52} We found only one cross-sectional study showing that alcohol drinking (vs. non-drinking) was significantly associated with higher odds of

| Alcohol drinking status | Never | Occasional (<1/week) | Moderate (women <140 g/week; men <210 g/week) | Heavy (women ≥140 g/week; men ≥210 g/week) | Ex-drinkers |
|-------------------------|-------|----------------------|-----------------------------------------------|-----------------------------------------------|------------|
| FPG changes during follow-up |       |                      |                                               |                                               |            |
| Crude β (95% CI)       | 0.00  | 0.01 (−0.03, 0.04)   | −0.03 (−0.10, 0.03)                           | 0.17 (0.06, 0.28)$^a$                          | −0.01 (−0.08, 0.07) |
| Adjusted β (95% CI)$^b$| 0.00  | 0.02 (−0.01, 0.06)   | −0.02 (−0.08, 0.05)                           | 0.13 (0.02, 0.24)$^a$                          | −0.01 (−0.09, 0.06) |

$^a$adjusted for age education, occupation, personal annual income, smoking, physical activity, BMI, waist/hip ratio, health status, hypertension and family history of diabetes mellitus.

$^b$Additionally adjusted for sex.

$^p$-value for sex-interaction was 0.16 for baseline FPG, 0.48 for follow up FPG and 0.71 for changes in FPG.

$^p < 0.05.$

$^p < 0.01.$

$^p < 0.001.$
### Table 3: Odds ratios (ORs) for incident type 2 diabetes (T2D), impaired fasting glucose (IFG) and incident T2D + IFG by baseline alcohol consumption

| Alcohol consumption         | Never | Occasional (<1/week) | Moderate (women < 140 g/week; men < 210 g/week) | Heavy (women ≥ 140 g/week; men ≥ 210 g/week) | Ex-drinkers |
|-----------------------------|-------|-----------------------|--------------------------------------------------|-----------------------------------------------|-------------|
| **Incident T2D**            |       |                       |                                                  |                                               |             |
| **Men**                     |       |                       |                                                  |                                               |             |
| Total number                | 2239  | 1037                  | 492                                              | 232                                           | 234         |
| Number of incident cases (%)| 215 (9.60) | 108 (10.41) | 40 (8.13)                                              | 38 (16.38)                                             | 37 (15.81) |
| Crude OR                    | Reference (1.00) | 1.09 (0.86, 1.40) | 0.83 (0.59, 1.19) | 1.84 (1.27, 2.68)e | 1.77 (1.21, 2.58)e |
| Adjusted OR<sup>a</sup>     | Reference (1.00) | 1.12 (0.87, 1.44) | 0.77 (0.54, 1.12) | 1.67 (1.11, 2.50)d | 1.54 (1.03, 2.28)d |
| **Women**                   |       |                       |                                                  |                                               |             |
| Total number                | 8842  | 1904                  | 301                                              | 16                                            | 304         |
| Number of incident cases (%)| 949 (10.73) | 174 (9.14) | 22 (7.31)                                              | 2 (12.50)                                             | 39 (12.83) |
| Crude OR                    | Reference (1.00) | 0.84 (0.71, 0.99)d | 0.66 (0.42, 1.02) | 1.19 (0.27, 5.24) | 1.22 (0.87, 1.72) |
| Adjusted OR<sup>a</sup>     | Reference (1.00) | 0.93 (0.78, 1.12) | 0.66 (0.42, 1.05) | 1.04 (0.22, 4.81) | 1.18 (0.82, 1.68) |
| **Total**                   |       |                       |                                                  |                                               |             |
| Total number                | 11,081 | 2941                  | 793                                              | 248                                           | 538         |
| Number of incident cases (%)| 1164 (10.50) | 282 (9.59) | 62 (7.82)                                              | 40 (16.13)                                             | 76 (14.13) |
| Crude OR                    | Reference (1.00) | 0.90 (0.79, 1.04) | 0.72 (0.55, 0.94)d | 1.64 (1.16, 2.31)e | 1.40 (1.09, 1.80)e |
| Adjusted OR<sup>a</sup>     | Reference (1.00) | 0.98 (0.85, 1.14) | 0.71 (0.53, 0.94)d | 1.54 (1.05, 2.25)d | 1.30 (1.00, 1.69) |
| **Incident IFG**            |       |                       |                                                  |                                               |             |
| **Men**                     |       |                       |                                                  |                                               |             |
| Total number                | 1450  | 720                   | 319                                              | 139                                           | 145         |
| Number of incident cases (%)| 144 (9.93) | 78 (10.83) | 34 (10.66)                                              | 24 (17.27)                                             | 17 (11.72) |
| Crude OR                    | Reference (1.00) | 1.10 (0.82, 1.47) | 1.08 (0.73, 1.61) | 1.89 (1.18, 3.04)e | 1.20 (0.71, 2.05) |
| Adjusted OR<sup>a</sup>     | Reference (1.00) | 1.04 (0.77, 1.41) | 1.05 (0.70, 1.58) | 1.61 (0.98, 2.65) | 1.05 (0.61, 1.83) |
| **Women**                   |       |                       |                                                  |                                               |             |
| Total number                | 6052  | 1321                  | 209                                              | 11                                            | 203         |
| Number of incident cases (%)| 524 (8.66) | 135 (10.22) | 19 (9.09)                                              | 2 (18.18)                                             | 27 (13.30) |
| Crude OR                    | Reference (1.00) | 1.20 (0.98, 1.47) | 1.05 (0.65, 1.70) | 2.34 (0.51, 10.88) | 1.62 (1.07, 2.45)d |
| Adjusted OR<sup>a</sup>     | Reference (1.00) | 1.25 (1.01, 1.54)d | 1.09 (0.67, 1.77) | 2.17 (0.46, 10.25) | 1.56 (1.02, 2.39)d |
| Alcohol consumption | Never | Occasional (<1/week) | Moderate (women < 140 g/week; men < 210 g/week) | Heavy (women ≥ 140 g/week; men ≥ 210 g/week) | Ex-drinkers |
|---------------------|-------|----------------------|-----------------------------------------------|-----------------------------------------------|------------|
| Total<sup>b</sup>   |       |                      |                                               |                                               |            |
| Total number        | 7502  | 2041                 | 528                                           | 150                                           | 348        |
| Number of incident cases (%) | 668 (8.90) | 213 (10.44) | 53 (10.04) | 26 (17.33) | 44 (12.64) |
| Crude OR            | Reference (1.00) | 1.19 (1.01, 1.40)<sup>d</sup> | 1.14 (0.85, 1.53) | 2.15 (1.40, 3.30)<sup>e</sup> | 1.48 (1.07, 2.05)<sup>d</sup> |
| Adjusted OR<sup>a</sup> | Reference (1.00) | 1.19 (1.00, 1.41) | 1.09 (0.80, 1.49) | 1.81 (1.14, 2.87)<sup>d</sup> | 1.35 (0.96, 1.89) |

Incident T2D + IFG

Men

|              | Total number |       |       |       |       |
|--------------|--------------|-------|-------|-------|-------|
| Number of incident cases (%) | 222 (14.53) | 116 (15.30) | 50 (14.93) | 39 (25.32) | 37 (22.42) |
| Crude OR     | Reference (1.00) | 1.06 (0.83, 1.36) | 1.03 (0.74, 1.44) | 2.00 (1.35, 2.95)<sup>e</sup> | 1.70 (1.15, 2.52)<sup>e</sup> |
| Adjusted OR<sup>a</sup> | Reference (1.00) | 1.03 (0.80, 1.33) | 0.99 (0.70, 1.40) | 1.72 (1.14, 2.61)<sup>d</sup> | 1.47 (0.97, 2.21) |

Women

|              | Total number |       |       |       |       |
|--------------|--------------|-------|-------|-------|-------|
| Number of incident cases (%) | 909 (14.12) | 202 (14.55) | 23 (10.80) | 3 (25.00) | 37 (17.37) |
| Crude OR     | Reference (1.00) | 1.04 (0.88, 1.22) | 0.74 (0.47, 1.14) | 2.03 (0.55, 7.50) | 1.28 (0.89, 1.83) |
| Adjusted OR<sup>a</sup> | Reference (1.00) | 1.13 (0.95, 1.35) | 0.77 (0.49, 1.21) | 2.04 (0.54, 7.74) | 1.28 (0.88, 1.85) |

Total<sup>b</sup>

|              | Total number |       |       |       |       |
|--------------|--------------|-------|-------|-------|-------|
| Number of incident cases (%) | 1131 (14.20) | 318 (14.82) | 73 (13.32) | 42 (25.30) | 74 (19.58) |
| Crude OR     | Reference (1.00) | 1.05 (0.92, 1.20) | 0.93 (0.72, 1.20) | 2.05 (1.43, 2.92)<sup>f</sup> | 1.47 (1.13, 1.91)<sup>e</sup> |
| Adjusted OR<sup>a</sup> | Reference (1.00) | 1.10 (0.95, 1.27) | 0.90 (0.69, 1.18) | 1.82 (1.24, 2.68)<sup>e</sup> | 1.36 (1.03, 1.78)<sup>d</sup> |

<sup>a</sup>Adjusted for age, education, occupation, personal annual income, smoking, physical activity, body mass index, waist/hip ratio, health status, hypertension and family history of diabetes mellitus.

<sup>b</sup>Additionally adjusted for sex.

<sup>c</sup>P-value for sex-interaction from 0.55 to 0.85 for incident T2D, IFG and T2D+IFG.

<sup>d</sup>P < 0.05.

<sup>e</sup>P < 0.01.

<sup>f</sup>P < 0.001.
| Alcohol consumption | Never | Occasional (<1/week) | Moderate (women <140 g/week; men <210 g/week) | Heavy (women ≥140 g/week; men ≥210 g/week) | Ex-drinkers |
|---------------------|-------|-----------------------|-----------------------------------------------|-------------------------------------------|-------------|
| **ALDH2 (rs671) GG genotype** |       |                       |                                               |                                           |             |
| **Men**             |       |                       |                                               |                                           |             |
| Total number        | 701   | 443                   | 277                                           | 172                                       | 120         |
| Number of incident cases (%) | 64 (9.13) | 42 (9.48) | 25 (9.03)                                    | 28 (16.28)                                 | 15 (12.50)  |
| Crude OR            | Reference (1.00) | 1.04 (0.69, 1.57) | 0.99 (0.61, 1.60) | 1.94 (1.20, 3.13)* | 1.42 (0.78, 2.59) |
| Adjusted OR         | Reference (1.00) | 1.04 (0.68, 1.60) | 0.91 (0.55, 1.52) | 1.68 (0.99, 2.87) | 1.20 (0.64, 2.26) |
| **Total**           | 1,591 | 816                   | 333                                           | 178                                       | 187         |
| Number of incident cases (%) | 161 (10.12) | 69 (8.46) | 28 (8.41)                                    | 28 (15.73)                                 | 22 (11.76)  |
| Crude OR            | Reference (1.00) | 0.82 (0.61, 1.10) | 0.82 (0.54, 1.24) | 1.66 (1.07, 2.56) | 1.18 (0.74, 1.90) |
| Adjusted OR         | Reference (1.00) | 0.86 (0.63, 1.19) | 0.77 (0.49, 1.21) | 1.45 (0.88, 2.38) | 1.01 (0.61, 1.66) |
| **ALDH2 (rs671) AA/AG genotype** |       |                       |                                               |                                           |             |
| **Men**             |       |                       |                                               |                                           |             |
| Total number        | 1,108 | 422                   | 116                                           | 29                                        | 80          |
| Number of incident cases (%) | 97 (8.75) | 47 (11.14) | 7 (6.03)                                     | 4 (13.79)                                 | 13 (16.25)  |
| Crude OR            | Reference (1.00) | 1.31 (0.90, 1.89) | 0.67 (0.30, 1.48) | 1.67 (0.57, 4.89) | 2.02 (1.08, 3.80) |
| Adjusted OR         | Reference (1.00) | 1.27 (0.86, 1.88) | 0.64 (0.29, 1.44) | 1.68 (0.54, 5.21) | 1.64 (0.84, 3.19) |
| **Total**           | 2,057 | 721                   | 141                                           | 30                                        | 114         |
| Number of incident cases (%) | 192 (9.33) | 74 (10.26) | 7 (4.96)                                     | 4 (13.33)                                 | 17 (14.91)  |
| Crude OR            | Reference (1.00) | 1.11 (0.84, 1.47) | 0.51 (0.23, 1.10) | 1.49 (0.52, 4.33) | 1.70 (1.00, 2.91) |
| Adjusted OR         | Reference (1.00) | 1.18 (0.87, 1.59) | 0.51 (0.23, 1.13) | 1.50 (0.49, 4.63) | 1.51 (0.86, 2.66) |
| Alcohol consumption | Never | Occasional (<1/week) | Moderate (women <140 g/week; /men <210 g/week) | Heavy (women ≥140 g/week; men ≥210 g/week) | Ex-drinkers |
|---------------------|-------|----------------------|-----------------------------------------------|---------------------------------------------|-------------|
| **ADH1B (rs1229984) GG/AG genotype** |       |                      |                                               |                                             |             |
| **Men**             |       |                      |                                               |                                             |             |
| Total number        | 825   | 400                  | 193                                           | 102                                         | 91          |
| Number of incident cases (%) | 77 (9.33) | 43 (10.75) | 16 (8.29)                                      | 13 (12.75)                                  | 19 (20.88)  |
| Crude OR            | Reference (1.00) | 1.17 (0.79, 1.73) | 0.88 (0.50, 1.54)                              | 1.42 (0.76, 2.66)                           | 2.56 (1.47, 4.48)* |
| Adjusted OR         | Reference (1.00) | 1.14 (0.75, 1.73) | 0.83 (0.46, 1.50)                              | 1.29 (0.65, 2.55)                           | 2.00 (1.09, 3.64)d |
| **Total**           | 1668  | 709                  | 237                                           | 106                                         | 139         |
| Number of incident cases (%) | 172 (10.31) | 68 (9.59) | 17 (7.17)                                      | 13 (12.26)                                  | 23 (16.55)  |
| Crude OR            | Reference (1.00) | 0.92 (0.69, 1.24) | 0.67 (0.40, 1.13)                              | 1.22 (0.67, 2.22)                           | 1.72 (1.07, 2.77)d |
| Adjusted OR         | Reference (1.00) | 0.94 (0.69, 1.29) | 0.63 (0.36, 1.08)                              | 1.07 (0.56, 2.07)                           | 1.34 (0.81, 2.23) |
| **ADH1B (rs1229984) AA genotype** |       |                      |                                               |                                             |             |
| **Men**             |       |                      |                                               |                                             |             |
| Total number        | 984   | 465                  | 200                                           | 99                                          | 109         |
| Number of incident cases (%) | 84 (8.54) | 46 (9.89) | 16 (8.00)                                      | 19 (19.19)                                  | 9 (8.26)    |
| Crude OR            | Reference (1.00) | 1.18 (0.81, 1.72) | 0.93 (0.53, 1.63)                              | 2.54 (1.47, 4.40)*                          | 0.96 (0.47, 1.98) |
| Adjusted OR         | Reference (1.00) | 1.26 (0.84, 1.88) | 0.92 (0.52, 1.64)                              | 2.30 (1.27, 4.17)*                          | 0.85 (0.41, 1.79) |
| **Total**           | 1980  | 828                  | 237                                           | 102                                         | 162         |
| Number of incident cases (%) | 181 (9.14) | 75 (9.06) | 18 (7.59)                                      | 19 (18.63)                                  | 16 (9.88)   |
| Crude OR            | Reference (1.00) | 0.99 (0.75, 1.31) | 0.82 (0.49, 1.35)                              | 2.28 (1.35, 3.83)*                          | 1.09 (0.64, 1.87) |
| Adjusted OR         | Reference (1.00) | 1.09 (0.81, 1.47) | 0.86 (0.50, 1.45)                              | 2.15 (1.21, 3.82)*                          | 1.04 (0.59, 1.82) |

*aAdjusted for age, education, occupation, personal annual income, smoking, physical activity, BMI, waist/hip ratio, health status, hypertension and family history of diabetes mellitus.

*bAdditionally adjusted for sex.

*p-values for alcohol-interaction from 0.12 to 0.79 in men.

*p < 0.05.

*p < 0.01.
T2D in those with ADH1B AA genotype, but not in those with ADH1B GG genotype. However, no results on interaction tests were reported in this study. Our study consistently showed that those with ADH1B AA genotype appeared to have higher risk of incident T2D than those carrying ADH1B AG/GG genotypes despite a non-significant interaction.

The strengths of this study included a large sample size with an adequate follow-up period, repeated objective assessment of T2D, and comprehensive measurement of alcohol drinking. In addition, we also tested for interactions between genetic polymorphisms and alcohol drinking. However, there were several limitations in our study. Firstly, drinking pattern may affect the association of alcohol and diabetes. Because of the limited range of alcohol consumption in our sample, we could not examine the effect of binge drinking on the risk of T2D or IFG. Secondly, GBCS participants represented a relatively healthy group of older people in Guangzhou, given the recruitment from the GHHARE. However, representativeness only affects the generalisability of results, and we have no evidence to support or refute the influence of participation on the results although it is biologically quite unlikely.

Thirdly, alcohol drinking was assessed based on self-report and might be affected by social desirability bias, leading to a underreporting of alcohol drinking, especially in excessive drinkers and women. Additionally, as glycated haemoglobin $\text{A}_1\text{C}$ ($\text{HbA}_1\text{C}$) was not measured, the incident of T2D or IFG could be underestimated. Thus, the strength of the association of heavy alcohol on incident T2D or IFG could be underestimated. Fourthly, as the sample size was moderate, especially for subgroup analysis by genotypes or sex, interpretation of the results needs caution. Fifthly, as this is an observational study, residual confounding (i.e., due to the lack of data on body composition or adipose tissue distribution) could not be ruled out. Finally, Chinese people may differ from westerners genetically in terms of insulin sensitivity and beta-cell function. Further, large prospective studies in other ethnic populations or in Chinese populations with younger age are warranted.

In conclusion, we found that heavy alcohol drinking was associated with higher risk of incident T2D and IFG. No protective effect was found for those carrying lower risk alleles for ADH1B and ALDH2 genes.

AUTHOR CONTRIBUTIONS
Lin Xu, Tai Hing Lam, Chao Qiang Jiang, Wei Sen Zhang, Ya Li Jin, G. Neil Thomas and Kar Keung Cheng have substantial contributions to conception and design, acquisition of funding, data and interpretation of data; Lin Xu, Mei Jiao Li and Jing Ren analysed the data, Mei Jiao Li and Jing Ren drafted the article, Lin Xu, Tai Hing Lam, G. Neil Thomas and Kar Keung Cheng revised it critically for important intellectual content and all authors contributed to final approval of the paper.

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CONFLICT OF INTEREST
The authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

ETHICS STATEMENT
The study was approved by the Guangzhou Medical Ethics Committee of the Chinese Medical Association in Guangzhou, China. All participants gave written, informed consent before participation.

DATA AVAILABILITY STATEMENT
Due to ethical restrictions protecting patient privacy, data are available on request from the GBCS Data Access Committee. Please contact us at gbcsdata@hku.hk for fielding data accession requests.

PEER REVIEW
The peer review history for this article is available at https://publons.com/publon/10.1002/dmrr.3548.

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**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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