Original Contribution

Evaluation of Moderate Alcohol Use With QT Interval and Heart Rate Using Mendelian Randomization Analysis Among Older Southern Chinese Men in the Guangzhou Biobank Cohort Study

Shiu Lun Au Yeung, Chaoqiang Jiang, Meijing Long, Kar Keung Cheng, Bin Liu, Weisen Zhang, Tai Hing Lam*, Gabriel Matthew Leung, and C. Mary Schooling

* Correspondence to Prof. Tai Hing Lam, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 5/F, William Mong Building, 21 Sassoon Road, Hong Kong SAR, People’s Republic of China (e-mail: hrmrlth@hku.hk).

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Western observational studies show that moderate alcohol use is associated with lower cardiovascular disease (CVD) risk, but these associations may be confounded by the healthier attributes of moderate users in these settings. Mendelian randomization analysis may help to ascertain the causal effect of moderate alcohol use on specific factors related to CVD and thereby clarify the role of alcohol. We used Mendelian randomization analysis with the aldehyde dehydrogenase 2 gene (ALDH2) as an instrumental variable to examine the association of alcohol units (10 g of ethanol) per day with heart rate–corrected QT interval and heart rate assessed from electrocardiogram among 4,588 older southern Chinese men in the Guangzhou Biobank Cohort Study (2003–2008). The $F$ statistic was 77 for ALDH2 on alcohol use, suggesting little weak-instrument bias. Instrumental variable analysis showed that alcohol units were not associated with the corrected QT interval, with $\beta = 1.04$ (95% confidence interval: $-0.61, 2.70$) milliseconds, but they were associated with increased heart rate, with $\beta = 0.98$ (95% confidence interval: 0.04, 1.92) beat per minute. This study suggests that moderate alcohol use in men is not beneficial for heart function via QT interval or heart rate but could be detrimental. Future studies using specific cardiovascular outcomes may elucidate how alcohol affects different aspects of the cardiovascular system and, hence, the overall effects of alcohol on CVD can be estimated.

alcohol; Chinese; electrocardiogram; Mendelian randomization

Abbreviations: ALDH2, aldehyde dehydrogenase 2 gene; CVD, cardiovascular disease; GBCS, Guangzhou Biobank Cohort Study; HDL, high-density lipoprotein; RCT, randomized controlled trial.

Observational studies, mainly concerning Western populations, consistently show that moderate alcohol use is associated with a lower risk of cardiovascular disease (CVD) (1). However, moderate users in the West tend to be systematically different from other and nonalcohol users, with moderate users having more favorable health-related attributes, including healthier lifestyles and higher socioeconomic position, that may generate residual confounding (2). In contrast, in studies from other settings, such as China, where the social patterning of alcohol use is different from that in the West, moderate alcohol use is less clearly associated with lower risk of CVD (3, 4). Discrepancies between settings may indicate confounding rather than a biological effect of alcohol or differences in the pattern of CVD. Alcohol may protect against ischemic CVD by raising high-density lipoprotein (HDL) cholesterol (5), although randomized controlled trials (RCTs) to study alcohol and HDL cholesterol have consistently shown no effect on CVD (6–8). In addition, RCTs suggest that alcohol could have negative effects on CVD by raising blood pressure (9), which may be particularly relevant in a Chinese setting where hemorrhagic stroke is more common than in Western settings (10, 11). To date, RCTs to investigate the long-term effects of moderate alcohol use on CVD have not been conducted because of ethical and logistic concerns.

Mendelian randomization analysis is increasingly used to assess empirically derived hypotheses, particularly where an
RCT is not feasible. Mendelian randomization analysis takes advantage of naturally occurring, genetically determined differences in exposure (12). As genetic differences are randomly allocated at conception, Mendelian randomization analysis is less susceptible to the confounding that often biases observational studies, but it requires stringent assumptions (12). To date, 3 Mendelian randomization analyses have examined the effect of alcohol use on CVD or its risk factors. One very large study showed that a specific genetic variant in the alcohol dehydrogenase gene associated with alcohol use was also associated with a higher risk of CVD events. However, the association of the alcohol dehydrogenase gene variant with CVD was evident for alcohol drinkers and for nondrinkers, perhaps because of misclassification of current or former users as nondrinkers, which might inflate the estimates (13), or because of an effect independent of alcohol, thus casting doubt on the estimate because of the violation of the key “exclusion-restriction” assumption for Mendelian randomization analysis (14, 15). The exclusion-restriction assumption states that the instrument (i.e., the genetic variant) should only be associated with the outcome (CVD) via the exposure (in this case alcohol use), but not otherwise. The 2 smaller studies both showed, as expected, that alcohol increased HDL cholesterol and blood pressure, but they did not provide conclusive information about associations with CVD events (16, 17), so the role of moderate alcohol use in CVD, as well as the means by which alcohol affects CVD, remains a subject of intense debate highly relevant to public health policy.

In contrast to an RCT, which usually tests whether an intervention works, Mendelian randomization may help to elucidate specific mechanistic pathways if the variables on the mechanistic pathway and their genetic variants are available. Understanding how alcohol affects CVD is not only important from a policy perspective but may also provide insight into overlooked harmful and protective risk factors for CVD. Moreover, in an increasingly globalized world where patterns and rates of CVD vary substantially among settings, understanding the mechanisms by which alcohol affects CVD will facilitate generalization across settings with different patterns of risk factors and diseases. Many unexplored pathways exist by which alcohol may affect the risk of CVD. For example, alcohol use may influence the electrical cycle in the heart or heart rate. Alcoholics have longer QT intervals (18), the period between the start of the Q wave to the end of the T wave, in the heart’s electrical cycle. Habitual alcohol use is also positively associated with heart rate (19). Both longer QT intervals and higher heart rate are associated with higher CVD mortality, providing another potential mechanism by which alcohol use may affect CVD events (20, 21).

Chinese men provide a particularly suitable setting for a Mendelian randomization analysis concerning the effect of moderate alcohol use. Among Chinese men, alcohol use is low to moderate and influenced by the aldehyde dehydrogenase 2 gene (ALDH2) polymorphism (22, 23). People with inactive ALDH2 alleles tend to drink less alcohol because slower acetaldehyde metabolism generates flushing and makes them feel unwell (24). In addition, we have shown that ALDH2 is a credible instrument for Mendelian randomization analysis in southern Chinese men (25). In this study, we investigated the association of alcohol use with QT interval and heart rate, measured from an electrocardiogram, among southern Chinese men using Mendelian randomization analysis.

METHODS

Ethics statement

The Guangzhou Medical Ethics Committee of the Chinese Medical Association approved the study, and all participants gave written, informed consent before participation.

Participants

The Guangzhou Biobank Cohort Study (GBCS) is a collaboration among the Guangzhou No. 12 Hospital, the University of Hong Kong, and the University of Birmingham (26). The participants were recruited from “The Guangzhou Health and Happiness Association for Respectable Elders,” a community social and welfare association unofficially aligned with the municipal government where membership is open to anyone aged 50 years or more for a monthly nominal fee of 4 Chinese yuan (~50 US cents). Recruitment for phase 1 took place from September 2003 to November 2004, for phase 2 from April 2005 to May 2006, and for phase 3 from September 2006 to January 2008. Follow-up of the participants started in 2008. Approximately 7% of permanent Guangzhou residents aged 50 years or more are members of “The Guangzhou Health and Happiness Association for Respectable Elders,” of whom 33% enrolled in all 3 phases were included if they were capable of consenting, ambulatory, and not receiving treatment modalities that, if omitted, might result in immediate life-threatening risk, such as chemotherapy or radiotherapy for cancer or dialysis for renal failure. Participants in GBCS are ethnic Chinese largely from southern China. Participants underwent a detailed interview and physical examination at baseline recruitment, including medical history and report of physician-diagnosed conditions. The methods of measurement have been reported previously (26). Alcohol use was recorded in terms of frequency, type of beverage, and usual amount per occasion. With participants in the supine position after resting for 5 minutes, a standard electrocardiogram was performed by using a 3-channel, 12-lead electrocardiograph (Marquette MAC-500; General Electric, Milwaukee, Wisconsin) in phase 1 and at the start of phase 2 and a synchronous 12-lead electrocardiograph (Marquette Cam-14 acquisition module; General Electric) in the rest of phase 2 and in phase 3 (27). The electrocardiogram tracings obtained by the Marquette MAC-500 electrocardiograph were evenly distributed to 2 qualified physicians and measured independently, blinded to other information (28). The QT interval was examined from the earliest QRS onset to the end of the T wave. Any uncertainties were resolved through discussion and consensus. In the rest of phase 2 and phase 3, the QT interval and heart rate were measured automatically by the electrocardiograph.

DNA extraction and single-nucleotide polymorphism analysis

Biological samples for DNA extraction used in the present study were obtained in GBCS phase 3 at recruitment and in
phases 1 and 2 at follow-up. DNA was extracted at Guangzhou No. 12 Hospital from either fresh blood using a standard phenol-chloroform extraction procedure and stored at −80°C or blood oruffy coat stored previously at −80°C using a standard magnetic bead extraction procedure, and the results of our Mendelian randomization studies on cognition and traditional CVD risk factors have been reported elsewhere (29). Genotyping was performed by using the MassARRAY system (Sequenom, San Diego, California) and the iPLEX assay at a commercial company (Beijing CapitalBio Corporation, Beijing, People’s Republic of China).

Instrument

The ALDH2 single-nucleotide polymorphism rs671 was used as the genetic instrument.

Alcohol use

The main exposure was continuous alcohol units (10 g of ethanol per day) based on total alcohol consumption obtained from the frequency, quantity, and type recorded at recruitment, as reported previously (29). Specifically, we asked the participants how often they drank alcohol (once or twice per year, once every couple of months, <1 day/week, 1–2 days/week, 3–4 days/week, 5–6 days/week, daily, or almost every day), the type of alcohol usually consumed, and how much of each type of alcohol (beer, Western table wine, spirits, Chinese rice wine, or Chinese rice wine (high strength)) was usually consumed per occasion, from which we calculated units per day. Infeasible amounts (>30 alcohol units per day) were excluded (29). Former alcohol users were included as nondrinkers because former alcohol users may have abstained from alcohol because of poor health unrelated to former alcohol use; excluding them could create a bias. Many former users (58%) reported previously infrequent alcohol use, that is, once or twice a year.

Outcomes

The outcomes were heart rate (HR)–corrected QT interval, uncorrected QT interval, and HR. The QT correction was made by using the Framingham formula (corrected QT interval = uncorrected QT + 154 × (1 − HR)) (30).

Statistical analysis

We tested for Hardy-Weinberg equilibrium at the single-nucleotide polymorphism locus on a contingency table of observed-versus-predicted frequencies with an exact test. We used analysis of variance to assess the associations of ALDH2 genotypes with alcohol consumption. We used χ² tests to assess whether ALDH2 genotypes were associated with potential confounders, including socioeconomic position and lifestyle. To test the assumption that ALDH2 is associated with only the outcomes via alcohol use (exclusion-restriction assumption), we used multivariable linear regression to assess the adjusted association of ALDH2 with QT interval and heart rate in men who never used alcohol. We adjusted for age, socioeconomic position, and lifestyle to control for potential collider bias upon restriction on alcohol use status (31).

We implemented Mendelian randomization as instrumental variable analysis with genetic instruments using 2-stage least-squares regression. Two-stage least-squares regression analysis first predicts the exposure from the instrumental variable, from which we reported the F statistic for ALDH2 on alcohol use, and the second stage estimates the association of predicted exposure with the outcome. An F statistic of <10 indicates weak-instrument bias. We used instrumental variable analysis (2-stage least-square analysis) with ALDH2 genotype categories as an instrumental variable for alcohol units, because there was a nonlinear association with alcohol consumption. We did not adjust for confounders in the instrumental variable analysis because ALDH2 genotypes randomly allocated at conception cannot be confounded by age or subsequent socioeconomic position and lifestyle. For comparison, we also present the adjusted associations of alcohol units with corrected QT interval, uncorrected QT interval, and heart rate under multivariable linear regression models in an observational design adjusted for potential confounders, that is, age, education, physical activity, smoking status, and tea consumption; tea consumption may be related to alcohol consumption and CVD (32).

Sensitivity analyses

In sensitivity analysis, we excluded men with a major intraventricular conduction defect, as indicated by QRS ≥120 milliseconds from the corrected QT interval, because the repolarization abnormalities in these men could be secondary to the conduction defects. We also excluded former alcohol users in a sensitivity analysis. To account for any potential U-shaped relation of alcohol use with QT interval or heart rate, we excluded heavy alcohol users (weekly drinking of >210 g of ethanol per week).

All statistical analyses were conducted by using Stata, version 13.1, software (StataCorp LP, College Station, Texas).

RESULTS

Of the 5,030 men with viable DNA, 4,588 had complete information on ALDH2 genotypes, alcohol use, and QT interval or heart rate. The QT interval had a mean of 387 (standard deviation, 28) milliseconds. Heart rate had a mean of 71 (standard deviation, 11) beats per minute. Table 1 shows that men with 2 active ALDH2 alleles on average consumed more than 10 times as much alcohol per day (0.9 unit) as men with 2 inactive alleles (0.07 unit). ALDH2 satisfied the assumptions for being a credible instrument for alcohol use, including an association with alcohol use (F statistic = 77) (Table 1), little association with potential confounders (Table 1), and no association with the corrected QT interval, uncorrected QT interval, or heart rate in never users (Table 2). ALDH2 genotypes had a distribution consistent with Hardy-Weinberg equilibrium (P = 0.75).

In the instrumental variable analysis, an increase of 1 unit of alcohol was not associated with QT interval but was associated with an increase in heart rate in the entire sample (Table 3). Similar results were seen in the multivariable linear
Table 1. Alcohol Consumption and Sociodemographic Characteristics by \( \text{ALDH2} \) Genotype Among 4,588 Men\(^a\) From The Guangzhou Biobank Cohort Study, 2003–2008

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>( \text{ALDH2} ) Genotype (From rs671)</th>
<th>( P ) Value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol units, 10 g of ethanol per day(^c)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two Inactive Alleles (AA), %</td>
<td>0.07 (0.70)</td>
<td></td>
</tr>
<tr>
<td>One Inactive Allele (GA), %</td>
<td>0.24 (1.16)</td>
<td></td>
</tr>
<tr>
<td>No Inactive Alleles (GG), %</td>
<td>0.92 (2.52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age group, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–54</td>
<td>11.2</td>
<td>10.1</td>
</tr>
<tr>
<td>55–59</td>
<td>20.3</td>
<td>21.2</td>
</tr>
<tr>
<td>60–64</td>
<td>25.1</td>
<td>23.7</td>
</tr>
<tr>
<td>65–69</td>
<td>20.1</td>
<td>23.3</td>
</tr>
<tr>
<td>70–74</td>
<td>17</td>
<td>15.8</td>
</tr>
<tr>
<td>75–79</td>
<td>5.8</td>
<td>4.5</td>
</tr>
<tr>
<td>≥80</td>
<td>0.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td>0.68</td>
</tr>
<tr>
<td>Less than primary</td>
<td>2.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Primary</td>
<td>25.4</td>
<td>27.2</td>
</tr>
<tr>
<td>Junior middle</td>
<td>30</td>
<td>30.4</td>
</tr>
<tr>
<td>Senior middle</td>
<td>26.4</td>
<td>25.3</td>
</tr>
<tr>
<td>Junior college</td>
<td>9.4</td>
<td>8.5</td>
</tr>
<tr>
<td>College</td>
<td>6.1</td>
<td>6.3</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td>0.69</td>
</tr>
<tr>
<td>Never</td>
<td>41.4</td>
<td>40.4</td>
</tr>
<tr>
<td>Former</td>
<td>29.7</td>
<td>27.3</td>
</tr>
<tr>
<td>Current</td>
<td>28.9</td>
<td>32.2</td>
</tr>
<tr>
<td>Physical activity (IPAQ)</td>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td>Inactive</td>
<td>8.6</td>
<td>7.6</td>
</tr>
<tr>
<td>Minimally active</td>
<td>35.8</td>
<td>38.6</td>
</tr>
<tr>
<td>HEPA active</td>
<td>55.6</td>
<td>53.8</td>
</tr>
<tr>
<td>Tea use</td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Never(^d)</td>
<td>23.6</td>
<td>26.8</td>
</tr>
<tr>
<td>Current</td>
<td>76.4</td>
<td>73.2</td>
</tr>
</tbody>
</table>

Abbreviations: \( \text{ALDH2} \), aldehyde dehydrogenase 2 gene; HEPA, health-enhancing physical activity (i.e., vigorous activity at least 3 days per week achieving at least 1,500 metabolic equivalent minutes per week or activity on 7 days of the week, achieving at least 3,000 metabolic equivalent minutes per week); IPAQ, International Physical Activity Questionnaire.

\(^a\) Men with 2 inactive alleles (\( n = 394 \)); 1 inactive allele (\( n = 1,917 \)); and no inactive alleles (\( n = 2,277 \)).

\(^b\) \( P \) value from analysis of variance for continuous variables and from a 2-sided \( \chi^2 \) test for categorical variables.

\(^c\) Presented as mean (standard deviation).

\(^d\) Never use includes never, occasional, and former users.

Table 2. Adjusted Association\(^a\) of \( \text{ALDH2} \) Genotype With Corrected QT Interval, Uncorrected QT Interval, and Heart Rate Among 2,326 Male Never Alcohol Users From The Guangzhou Biobank Cohort Study, 2003–2008

<table>
<thead>
<tr>
<th>Outcome</th>
<th>( \text{ALDH2} ) Genotype</th>
<th>( P_{\text{trend}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( AA (n = 305) )</td>
<td>( GA (n = 1,113) )</td>
</tr>
<tr>
<td></td>
<td>( \beta )</td>
<td>95% CI</td>
</tr>
<tr>
<td>Corrected QT interval, milliseconds</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>Uncorrected QT interval, milliseconds</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>Heart rate, beats per minute</td>
<td>1.0</td>
<td>Referent</td>
</tr>
</tbody>
</table>

Abbreviations: \( \text{ALDH2} \), aldehyde dehydrogenase 2 gene; CI, confidence interval.

\(^a\) Adjusted for age, education, physical activity, smoking, and tea consumption.
regression, but the estimates were smaller and the confidence intervals narrower.

In sensitivity analysis (Table 4), alcohol use was associated with a higher corrected QT interval after excluding men with QRS ≥ 120 milliseconds. However, in the sensitivity analyses excluding former alcohol users or heavy alcohol users or both former and heavy alcohol users, alcohol use remained unassociated with the QT interval in any form (uncorrected, corrected, or corrected excluding QRS ≥ 120 milliseconds) in the instrumental variable analysis and the observational analysis. In the sensitivity analysis, excluding former users or heavy users did not change the direction of the association of alcohol use with heart rate in the instrumental variable analysis, but all the confidence intervals included no effect. In the sensitivity analysis, excluding specifically heavy alcohol users from the observational analysis also attenuated the association of alcohol use with heart rate from positive to the null.

**DISCUSSION**

To our knowledge, the present study is the first study to examine the association of alcohol use with QT interval and heart rate using Mendelian randomization analysis. It also takes advantage of an understudied population where alcohol use is mainly low to moderate. Consistent with previous studies, our study found that alcohol use was not clearly associated with a shorter QT interval but was associated with a higher heart rate (19, 33). This study contributes to accumulated knowledge by showing that low-to-moderate alcohol use is not associated with a shorter QT interval in a design better suited to establishing causality and, hence, any potential

<table>
<thead>
<tr>
<th>Selection and Outcome</th>
<th>No. of Men</th>
<th>F Statistic</th>
<th>Mendelian Randomization by Instrumental Variable Analysis</th>
<th>Observational Multivariable Linear Regression Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>β</td>
<td>95% CI</td>
</tr>
<tr>
<td>Corrected QT interval (milliseconds), QRS &lt;120 milliseconds</td>
<td>4,401</td>
<td>78.3</td>
<td>1.67</td>
<td>0.06, 3.28</td>
</tr>
<tr>
<td>Corrected QT interval, milliseconds</td>
<td>4,303</td>
<td>67.6</td>
<td>3.14</td>
<td>−4.10, 10.4</td>
</tr>
<tr>
<td>Uncorrected QT interval, milliseconds</td>
<td>4,303</td>
<td>67.6</td>
<td>−2.35</td>
<td>−12.4, 7.71</td>
</tr>
<tr>
<td>Corrected QT interval, milliseconds; QRS &lt;120 milliseconds</td>
<td>4,125</td>
<td>64.7</td>
<td>5.19</td>
<td>−1.90, 12.3</td>
</tr>
<tr>
<td>Heart rate, beats per minute</td>
<td>4,303</td>
<td>67.6</td>
<td>3.27</td>
<td>−0.84, 7.39</td>
</tr>
</tbody>
</table>

**Table 4.** Associations of Alcohol With Corrected QT Interval, Uncorrected QT Interval, and Heart Rate Using a Mendelian Randomization Design and an Observational Multivariable Linear Regression Analysis, Excluding QRS ≥ 120 Milliseconds, Heavy Alcohol Users, or Former Alcohol Users, Among Men From the Guangzhou Biobank Cohort Study, 2003–2008

Abbreviations: CI, confidence interval; QRS, QRS complex.

*a Based on 10 g of ethanol per day.

*b Adjusted for age, education, physical activity, smoking, and tea consumption.
beneficial effects of alcohol are unlikely to be mediated by effects on the electrical cycle in the heart. On the other hand, this study cannot rule out the possibility that alcohol lengthens the corrected QT interval and suggests that alcohol's increase of the heart rate could be a potential pathway by which alcohol has effects on CVD that are not beneficial.

Low-to-moderate alcohol use is consistently associated with lower risk of CVD in observational studies (1), with the mechanisms thought to include increasing HDL cholesterol, increasing adiponectin, and decreasing fibrinogen. However, the causal role of these mechanisms in protecting against CVD remains to be established. A meta-analysis of several HDL cholesterol–modifying drugs showed no effect on CVD against a background of statin treatment (8), whereas genetic markers associated with adiponectin (not fibrinogen) are associated with CVD (34, 35). Conversely, alcohol increases blood pressure, but blood pressure does not necessarily increase heart rate (16). A biologically plausible explanation strengthens a theory but does not confirm or refute. For example, the observed U-shaped relation between alcohol use and CVD could indicate confounding by healthier attributes of moderate users than nonusers and other alcohol users, which cannot be completely adjusted for in statistical analyses (2).

Our study is consistent with this argument, given that the association of alcohol use with QT interval and heart rate did not suggest benefit, but possibly harm, for CVD. We have previously examined the association of the same exposure with CVD and its risk factors (16) and cognitive function (29). Thus, we cannot rule out the possibility of false positives, due to multiple comparisons, concerning alcohol use and heart rate, albeit the association is biologically plausible. Hence, these associations should be verified in future studies.

Other than confounding, methodological issues may also bias observational estimates in favor of moderate alcohol use. The recent European Prospective Investigation into Cancer and Nutrition (EPIC) study suggested that the association of alcohol use with health may be an artifact of selection bias and competing risks (36).

Excluding former users did not substantially change the estimate, suggesting that little bias was introduced by classifying former users as nondrinkers, although alcohol use was associated with a higher heart rate in the observational analysis. Excluding heavy users made the estimates larger, possibly because of the narrower range of mean alcohol units by \textit{ALDH2} genotype. Nevertheless, the direction of the estimate remained the same. Exclusion of men with QRS ≥120 milliseconds also did not change the direction of the estimates, suggesting that the absence of potential cardioprotection via the QT interval was not due to inclusion of men with wide QRS, which can also increase the QT interval but is related to impaired ventricular conduction (37). The positive association of alcohol use with the corrected QT interval was evident only after excluding men with QRS ≥120 milliseconds (Table 4), suggesting that alcohol use may act via prolonging the QT interval rather than by generating a major intraventricular conduction defect.

Although we used a Mendelian randomization analysis that is less susceptible to confounding, limitations exist. First, alcohol use was self-reported, but we previously observed the known effects of alcohol use, that is, higher HDL cholesterol and blood pressure (38). Although Mendelian randomization analysis can better capture the lifetime effect of alcohol use and the outcomes concerned (39), the use of only current alcohol use in our data may inflate the Mendelian randomization estimates (13). Second, we did not use CVD mortality because too few events have occurred for a meaningful Mendelian randomization analysis. Instead, this study focused on potential pathways by which alcohol may affect CVD, that is, via the QT interval or heart rate. However, our study cannot rule out the possibility that moderate alcohol use could still overall be protective for CVD via other pathways not examined in this study, although our previous, albeit underpowered, Mendelian randomization study found no association of alcohol use with self-reported CVD (16). Third, GBCS is not population representative, which would affect internal validity only if the recruitment of participants had generated selection bias, which is unlikely (40).

Although violation of the exclusion restriction assumption was not evident (Table 2), estimates in nondrinkers were not exactly null, possibly because of misclassification of alcohol use and/or residual collider bias. On the other hand, although genes are usually not related to the common confounders of the association of alcohol use with CVD, we cannot rule out the possibility that parental \textit{ALDH2} may be an unmeasured confounder if it also affected the QT interval and heart rate via a pro–drinking environment related to parental \textit{ALDH2}. However, alcohol use was low in China during the 1950s and 1960s and, hence, most people would have grown up in a nondrinking household, making confounding by parental \textit{ALDH2} unlikely (42).

This Mendelian randomization analysis suggests that low-to-moderate alcohol use does not have a beneficial effect on some potential mediators linking alcohol use with lower CVD, but that it might be harmful for the QT interval and heart rate. Previous studies in the West showing an inverse association of moderate alcohol use with CVD may be due to confounding by unmeasured healthier attributes of moderate users. However, the cardioprotective effect of alcohol could also be mediated via other pathways not examined here. Future Mendelian randomization analyses, with credible genetic instruments, examining the mechanism by which alcohol affects cardiovascular events are needed to elucidate the overall effect of alcohol use on cardiovascular health across the globe.
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Author affiliations: School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, People’s Republic of China (Shiu Lun Au Yeung, Meiijing Long, Tai Hing Lam, Gabriel Matthew Leung, C. Mary Schooling); Guangzhou No. 12 Hospital, Guangzhou, People’s Republic of China (Chaoqiang Jiang, Bin Liu, Weisen Zhang); Department of Public Health and Epidemiology, University of Birmingham, Birmingham, United Kingdom (Kar Keung Cheng); School of Public Health, City University of New York, New York, New York (C. Mary Schooling); and Hunter College, New York, New York (C. Mary Schooling).

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In addition to Kar Keung Cheng’s appointment at the University of Birmingham, he is affiliated with the Department of General Practice at the Peking University Health Science Centre. The latter receives support from Pfizer China to fund the training of family physicians (approximately US $100,000 a year for 2014–2016). The other authors report no conflicts.

REFERENCES


