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Alcohol intake and dyslipidemia in male patients with hypertension and diabetes enrolled in a China multicenter registry

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Abstract

Alcohol consumption is a proven risk factor of dyslipidemia. In the present analysis, we investigated the association of alcohol intake with dyslipidemia, an emerging epidemic in China, in male patients with hypertension and diabetes mellitus. Our study participants were from a nationwide registry (n = 1181). A questionnaire was administered to collect information on alcohol intake. Dyslipidemia was defined as an elevated concentration of serum triglycerides (≥2.3 mmol/L), total (≥6.2 mmol/L) or low-density lipoprotein (LDL) cholesterol (≥4.1 mmol/L), or a reduced high-density lipoprotein (HDL) cholesterol (< 1.0 mmol/L). Serum concentrations of triglycerides (1.60 mmol/L) and total (4.93 mmol/L) and LDL cholesterol (2.95 mmol/L) were highest with current usual drinking, with a significant *P* value for trend from never (n = 679) to ever (n = 107) and to rare (n = 187) and usual drinkers (n = 208, $P \leq .002$). Serum HDL cholesterol (1.13 mmol/L) was lowest in ever drinkers, with a nonsignificant *P* value for trend ($P = .22$). The prevalence was highest in usual drinkers for hypertriglyceridemia (27.4%) and total (12.5%) and LDL hypercholesterolemia (8.7%), and in ever drinkers for low HDL cholesterol (34.6%). The *P* value for trend was significant for hypertriglyceridemia and total hypercholesterolemia ($P \leq .01$), but not for LDL hypercholesterolemia or low HDL cholesterol ($P \geq .26$). The between-province ecological analysis showed that the proportion of usual drinking was significantly associated with the prevalence of any dyslipidemia across 10 China provinces ($r = .42$, $P < .0001$). In conclusion, alcohol drinkers showed a worse lipid profile in patients with hypertension and diabetes mellitus. Usual drinking ecologically explained the between-province variation in the prevalence of dyslipidemia.

KEYWORDS
alcohol intake, diabetes, dyslipidemia, hypertension, lipid profile, province

1 | INTRODUCTION

Alcohol drinking is a commonly seen habit in almost all populations. However, not only is the alcohol different between countries and populations, but also the drinking pattern. In China, alcohol drinking is largely a habit in men, except in several minority groups, in which women also drink alcohol habitually. According to a China national survey, the proportion of current regular alcohol intake was 33% in men and 2% in women. The proportion also differed significantly between China provinces from 7% to 51% in men.[1] There are two main original alcoholic beverages from China, that is, white spirits liquor and rice wine with a 40% to 60% and 10% to 20% of alcohol volume,[2] respectively. Beers are often drunk in summer. Imported and domestic white and red wines are increasingly consumed in high- and mid-income communities. Some people habitually drink alcohol with meal. Many others drink alcohol in various gatherings of family, friends, or business partners. On both conditions, the consumption of alcohol can be in a large amount, and therefore may have acute harms. However, the long-term chronic health consequence of alcohol intake can be beyond alcohol per se, because both calorie and sodium intake are high with alcohol drinking.

A major health concern associated with alcohol intake is dyslipidemia. Alcohol is known to increase high-density lipoprotein (HDL) cholesterol and decrease low-density lipoprotein (LDL) cholesterol,[3–7] which is assumed to be a favorable effect of moderate alcohol intake on cardiovascular disease. However, previous studies produced inconsistent results on the association between alcohol intake and LDL cholesterol. Several population-based studies showed that alcohol drinking was associated with a higher level of LDL cholesterol.[8–10] In addition, alcohol consumption is associated with elevated serum triglycerides.[11–16] It has been reported that at population level, 100 g higher ethanol intake per week was associated with .041 mmol/L higher serum triglycerides.[11] These alterations in lipids associated with alcohol intake may contribute to metabolic disorders, especially in patients with hypertension or diabetes mellitus. In the present study, we investigated the association of alcohol consumption with the prevalence of dyslipidemia in patients with hypertension and diabetes mellitus.

2 | METHODS

2.1 | Study participants

Our study participants were recruited from a prospectively designed cross-sectional, multicenter (n = 40) registry in China, carried out in the departments of cardiovascular and endocrine medicine of hospitals from June 2011 to March 2012. The study protocol of the registry had been described in detail previously.[17,18] Briefly, we registered consecutive patients with previously diagnosed hypertension from the departments of cardiovascular medicine and patients with previously diagnosed diabetes mellitus from the departments of endocrine medicine. The study was in line with the Declaration of Helsinki and was ethically approved by the Ruijin Hospital Ethics Committee of Shanghai Jiao Tong University School of Medicine (ID: 2011–58). All patients gave written informed consent.

The registry included a total of 2510 patients. From the present analysis, we excluded 1329 women because of low proportion of alcohol intake (2.1%, n = 28), leaving 1181 men in the present study.

2.2 | Questionnaire and classification of alcohol intake

A standardized questionnaire was administered by physicians at the first of two clinic visits 2–5 days apart to collect information on medical history, alcohol intake and other lifestyle factors, and use of medications. Participants were classified into four groups according to alcohol consumption: never (had never drunk in the past), ever (almost never drank alcohol in the past year, but had drunk weekly 1 year before), rare (had drunk alcohol occasionally, ie, monthly and less than weekly in the past year), and usual drinkers (had drunk alcohol at least weekly during the past year). The latter two were combined as current drinkers.

2.3 | Serum lipids measurement and definition of dyslipidemia

Venous blood samples were drawn after overnight fasting for measurements of serum lipids, glycosylated hemoglobin A1 (HbA1c), and plasma glucose.

Dyslipidemia was defined as a serum triglycerides concentration of 2.3 mmol/L or higher, a serum total cholesterol concentration of 6.2 mmol/L or higher, a serum LDL cholesterol concentration of 4.1 mmol/L or higher, or serum HDL cholesterol concentration lower than 1.0 mmol/L.[19] Borderline dyslipidemia was defined as a serum triglycerides level between 1.7 and 2.2 mmol/L, a serum total cholesterol level between 5.2 and 6.1 mmol/L, a serum LDL cholesterol level between 3.4 and 4.0 mmol/L.

2.4 | Other clinical measurements

Blood pressure was measured using a validated Omron HEM-7201 automatic oscillometric blood pressure monitor (Omron Healthcare, Kyoto, Japan) at the first and second clinic visits. On each of the two occasions, three blood pressure readings were obtained in the seated position after the patients had rested for at least 5 min. These six readings on two clinic visits were averaged for statistical analysis.

Anthropometric measurements included body weight, body height, and waist and hip circumferences. Body mass index was calculated as the body weight in kilograms divided by the body height in meters squared. Overweight and obesity was defined as a body mass index of 25 kg/m^2 or greater. Abdominal obesity was defined as a waist circumference ≥90 cm.

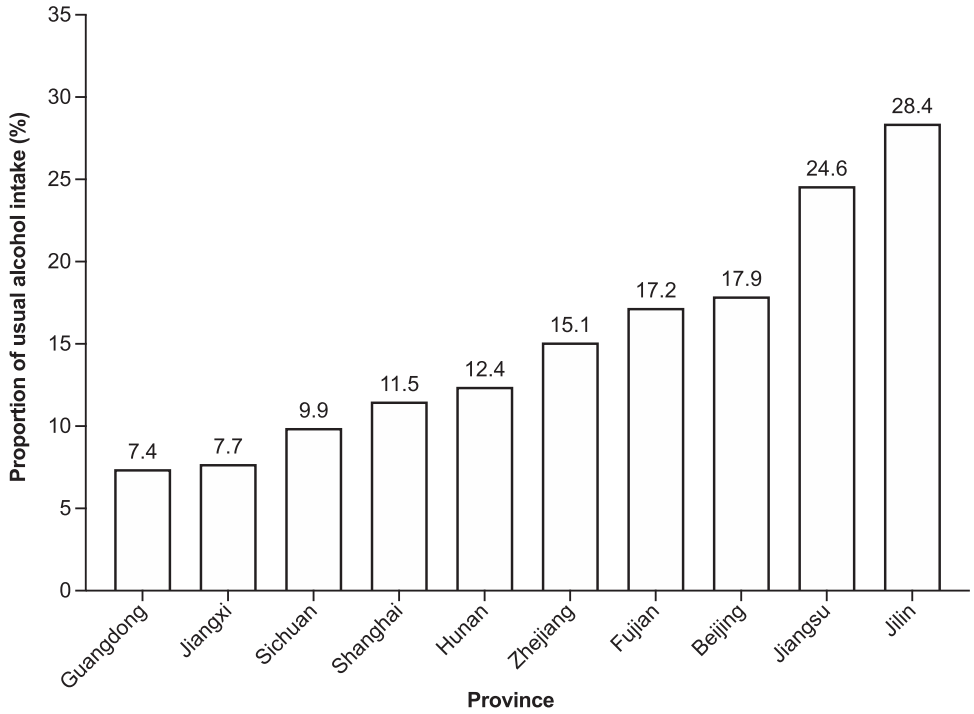

FIGURE 1 Proportion of usual alcohol intake by province, given per province above the bar

2.5 | Statistical analysis

Statistical analyses were performed using SAS software (version 9.4, SAS Institute, Cary, North Carolina, USA). Means were compared by the analysis of variance (ANOVA) with the Student-Newman-Keuls test for a posteriori between-group contrast at a significance level set at 5%. Proportions were compared by the Chi-square test. Continuous measurements with a skewed distribution were expressed as median with interquartile range and were analyzed using the non-parametric Kruskal-Wallis test. Logistic regression analyses were performed to calculate odds ratios (OR) and the corresponding 95% confidence interval (CI) for dyslipidemia, with never drinkers as the reference group and with age, body mass index, current smoking, and antihypertensive and antidiabetic treatment as confounding factors. We performed ecological analysis to investigate the contribution of usual alcohol intake to the prevalence of dyslipidemia across provinces in weighted linear regression models. $P < .05$ was considered statistically significant for two-sided tests.

3 | RESULTS

3.1 | Characteristics of the study participants

The 1181 male participants were enrolled from ten provinces. The proportion of usual drinkers varied substantially between provinces from 7.4% in Guangdong in southern China to 28.4% in Jilin in northern China (Figure 1). Overall, the prevalence of ever, rare, and usual alcohol drinking was 9.1%, 15.8%, and 17.6%, respectively.

The study participants differed across the alcohol consumption categories in most of the characteristics, such as the mean values of age (53.8 ± 10.6 to 58.4 ± 12.7 years), waist circumference (90.9 ± 8.9 to 93.6 ± 15.1 cm), HbA1c (6.6% ± 1.6% to 6.9% ± 1.7%), and diastolic blood pressure (77.4 ± 10.6 to 83.2 ± 12.0 mmHg), and the proportions for abdominal obesity (53.5% to 64.7%), current smoking (22.8% to 71.2%), use of antihypertensive (52.4% to 70.1%) and antidiabetic drugs (49.7% to 59.8%), and use of statins (15.4% to 30.8%) and all lipid-lowering agents (18.7% to 35.5%, $P \leq .04$). Ever drinkers had the highest use of statins and other lipid-lowering agents ($P \leq .009$ vs others). Nonetheless, they had similar body mass index (25.5 ± 3.2 kg/m^2), overweight and obesity (53.1%), systolic blood pressure (135.9 ± 16.7 mmHg), pulse rate (73.3 ± 12.6 beats/min), and plasma fasting glucose (6.29 [5.40–7.96] mmol/L, $P \geq .17$, Table 1).

3.2 | Dyslipidemia in relation to alcohol intake

Serum concentrations of triglycerides (1.35 [.93–2.02] to 1.60 [1.08–2.38] mmol/L) and total (4.37 ± .94 to 4.93 ± 1.07 mmol/L) and LDL cholesterol (2.62 ± .83 to 2.95 ± .90 mmol/L) were highest with current usual drinking, with a statistically significant *P* value for trend from never to ever and to rare and usual drinkers ($P \leq .002$, Table 2). Serum HDL cholesterol (1.13 ± .27 to 1.25 ± .43 mmol/L) was lowest in ever drinkers. The *P* value for trend did not attain statistical significance (*P* for trend = .22).

In categorical analyses, the prevalence of dyslipidemia was accordingly highest in current usual drinkers for hypertriglyceridemia (18.7% to 27.4%) and total (3.7% to 12.5%) and LDL hypercholesterolemia (5.6% to 8.7%), and in ever drinkers for low HDL cholesterol (20.3% to

TABLE 1 Characteristics of patients according to alcohol intake

Characteristic	Non-drinkers (No. = 679)	Past drinkers (No. = 107)	Current drinkers		*P* (ANOVA)
			Rare (No. = 187)	Usual (No. = 208)	
Age, years	58.4 ± 12.7	58.4 ± 12.3	55.5 ± 11.6	53.8 ± 10.6	<.0001
Body mass index, kg/m^2					
Mean ± SD	25.4 ± 3.2	25.5 ± 3.3	25.7 ± 3.4	25.6 ± 3.3	.49
≥25, no. (%)	356 (52.4)	57 (53.3)	105 (56.2)	109 (52.4)	.83
Waist circumference, cm					
Mean ± SD	90.9 ± 8.9	91.8 ± 9.5	93.6 ± 15.1	92.7 ± 9.1	.005
≥90, no. (%)	363 (53.5)	64 (59.8)	121 (64.7)	126 (60.6)	.02
Current smoking, no. (%)	155 (22.8)	25 (23.4)	85 (45.5)	148 (71.2)	<.0001
Systolic blood pressure, mmHg	136.7 ± 16.7	133.2 ± 18.4	135.0 ± 15.6	135.5 ± 17.0	.17
Diastolic blood pressure, mmHg	81.0 ± 11.6	77.4 ± 10.6	83.1 ± 11.0	83.2 ± 12.0	<.0001
Pulse rate, beats/min	73.7 ± 12.4	72.7 ± 12.0	72.3 ± 12.4	73.5 ± 13.5	.53
Plasma fasting glucose, mmol/L	6.30 (5.42-8.00)	6.14 (5.32-7.27)	6.17 (5.20-7.71)	6.42 (5.50-8.22)	.21
Glycosylated hemoglobin A1c, %	6.9 ± 1.6	6.9 ± 1.6	6.6 ± 1.5	6.9 ± 1.7	.04
Antihypertensive treatment, no. (%)	446 (65.7)	75 (70.1)	126 (67.4)	109 (52.4)	.02
Antidiabetic treatment, no. (%)	383 (56.4)	64 (59.8)	93 (49.7)	104 (50.0)	.0001
Use of lipid-lowering agents, no. (%)	155 (22.8)	38 (35.5)	35 (18.7)	39 (18.8)	.004
Use of statins, no. (%)	134 (19.7)	33 (30.8)	33 (17.7)	32 (15.4)	.01
Use of other lipid-lowering agents, no. (%)	21 (3.1)	5 (4.7)	2 (1.1)	7 (3.4)	.31

Note: Values are arithmetic mean ± standard deviation, median (interquartile range) or percentage of participants (number), unless otherwise indicated.

TABLE 2 Lipid profile according to alcohol intake

Serum lipids	Non-drinkers (No. = 679)	Past drinkers (No. = 107)	Current drinkers		*P* (for trend)
			Rare (No. = 187)	Usual (No. = 208)	
Serum triglycerides, mmol/L					
Median (interquartile range)	1.35 (.93-2.02)	1.41 (.98-1.85)	1.53 (.96-2.49)	1.60 (1.08-2.38)*,†	.002
Serum cholesterol, mmol/L					
Total, Mean ± SD	4.63 ± 1.05	4.37 ± .94	4.75 ± 1.20	4.93 ± 1.07*,†	<.0001
LDL, Mean ± SD	2.77 ± .89	2.62 ± .83	2.84 ± .93	2.95 ± 0.90†	.002
Serum HDL cholesterol, mmol/L					
Mean ± SD	1.23 ± .32	1.13 ± .27*	1.16 ± .31	1.25 ± .43†	.22

Note: Values are arithmetic mean ± standard deviation, median (interquartile range) or percentage of participants (number), unless otherwise indicated.
*$P \leq .05$ vs non-drinkers; †$P \leq 0.05$ vs past drinkers.
Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.

34.6%). The *P* value for trend reached statistical significance for hypertriglyceridemia, total hypercholesterolemia, and any dyslipidemia ($P \leq .01$), but not for LDL hypercholesterolemia, low HDL cholesterol or the use of lipid-lowering agents ($P \geq .15$).

After adjustment for age, body mass index, current smoking, and antihypertensive and antidiabetic treatment, the adjusted ORs for any lipid abnormality were statistically significant for current rare drinkers (1.43, 95% CI 1.02–2.02, $P = .02$) and for the combined ever with current rare and usual drinkers (1.30, 95% CI 1.003–1.68, $P = .047$), in spite of nonsignificant *P* values for trend ($P \geq .11$, Table 3).

3.3 | Between-province ecological analysis

The distributions of alcohol consumption and dyslipidemia in ten provinces in China are shown in the Supplementary Figures S1 and S2. The between-province ecological analysis showed that the proportion of usual drinkers was significantly associated with the prevalence of any dyslipidemia across provinces, with a correlation coefficient of .42 ($P < .0001$) and 18% of the variance in the prevalence of any dyslipidemia explained by the proportion of usual drinkers (Figure 2).

TABLE 3 Dyslipidemia according to alcohol intake

Dyslipidemia	Non-drinkers (No. = 679)	Past drinkers (No. = 107)	Current drinkers		*P* (for trend)
			Rare (No. = 187)	Usual (No. = 208)	
Serum triglycerides ≥2.3 mmol/L					
Prevalence, % (no.)	19.2 (130)	18.7 (20)	25.7 (48)	27.4 (57)	.004
Odds ratio (95% CI)[a]	1	.91 (.53-1.56)	1.24 (.83-1.84)	1.24 (.83-1.86)	.21
Serum total cholesterol ≥6.2 mmol/L					
Prevalence, % (no.)	7.2 (49)	3.7 (4)	10.7 (20)	12.5 (26)	.01
Odds ratio (95% CI)	1	.49 (.17-1.39)	1.40 (.80-2.45)	1.50 (.86-2.62)	.11
Serum LDL-cholesterol ≥4.1 mmol/L					
Prevalence, % (no.)	8.4 (57)	5.6 (6)	7.5 (14)	8.7 (18)	.94
Odds ratio (95% CI)	1	.67 (.28-1.61)	.84 (.45-1.57)	.97 (.52-1.78)	.75
Serum HDL-cholesterol < 1.0 mmol/L					
Prevalence, % (no.)	20.3 (138)	34.6 (37)	28.9 (54)	20.7 (43)	.26
Odds ratio (95% CI)	1	1.95 (1.23-3.06)	1.49 (1.01-2.19)	.93 (.61-1.42)	.56
Any dyslipidemia					
Any above lipid abnormality					
Prevalence, % (no.)	37.7 (256)	44.9 (48)	49.2 (92)	45.7 (95)	.005
Odds ratio (95% CI)	1	1.27 (.83-1.95)	1.43 (1.02-2.02)	1.18 (.83-1.68)	.12
Use of lipid-lowering agents					
Prevalence, % (no.)	22.8 (155)	35.5 (38)	18.7 (35)	18.8 (39)	.15
Odds ratio (95% CI)	1	1.77 (1.12-2.80)	.81 (.53-1.25)	.94 (.60-1.46)	.33

Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]Odds ratios (95% CI) were computed for each category of alcohol drinking versus never drinking after adjustment for age, body mass index, current smoking, and antihypertensive and antidiabetic treatment.

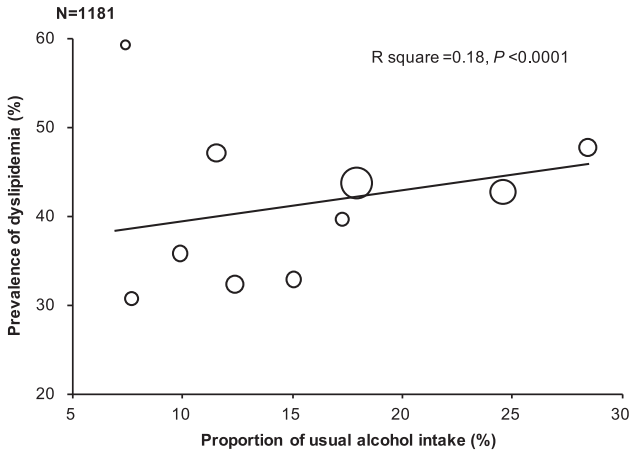

FIGURE 2 Between-province ecological analysis on the prevalence of dyslipidemia in relation to usual alcohol intake in a weighted linear regression model (sample size per province). The *r* square and *P* values are given

3.4 | Analyses on the combined dyslipidemia and borderline dyslipidemia

Further analyses on dyslipidemia and borderline dyslipidemia were confirmatory (Table 4). With a much higher prevalence, the *P* values for trend reached statistical significance in all unadjusted analyses ($P \leq .05$) and in adjusted analyses on any dyslipidemia and borderline dyslipidemia ($P = .003$).

3.5 | Subgroup analyses in hypertension, diabetes mellitus, or both

Further subgroup analyses showed that the prevalence of any dyslipidemia was higher with various categories of alcohol drinking, similarly in patients with hypertension and diabetes mellitus alone or both. The *P* value for trend, however, reached statistical significance only in patients with diabetes mellitus alone ($P = .02$), but not in patients with hypertension either alone or in combination with diabetes mellitus ($P \geq .14$, Figure 3). Similar results were observed in analyses on dyslipidemia and borderline dyslipidemia (data not shown).

4 | DISCUSSION

The key finding of our study was that current alcohol intake, especially usual drinking, was associated with an unfavorable lipid profile and a higher prevalence of dyslipidemia. This observation may have ecological implications for the between-province comparisons in China.

TABLE 4 Dyslipidemia and borderline dyslipidemia according to alcohol intake

Dyslipidemia and borderline dyslipidemia	Non-drinkers (No. = 679)	Past drinkers (No. = 107)	Current drinkers		P (for trend)
			Rare (No. = 187)	Usual (No. = 208)	
Serum triglycerides ≥1.7 mmol/L					
Prevalence, % (no.)	34.3 (233)	31.8 (34)	43.9 (82)	46.2 (96)	.0005
Odds ratio (95% CI)[a]	1	.80 (.51-1.27)	1.28 (.90-1.81)	1.31 (.92-1.88)	.08
Serum total cholesterol ≥5.2 mmol/L					
Prevalence, % (no.)	27.1 (184)	18.7 (20)	31.0 (58)	38.9 (81)	.002
Odds ratio (95% CI)	1	.60 (.36-1.02)	1.11 (.77-1.60)	1.36 (.95-1.95)	.11
Serum LDL-cholesterol ≥3.4 mmol/L					
Prevalence, % (no.)	22.7 (154)	17.8 (19)	23.5 (44)	30.3 (63)	.05
Odds ratio (95% CI)	1	.74 (.43-1.27)	.97 (.65-1.44)	1.28 (.87-1.89)	.33
Any dyslipidemia and borderline dyslipidemia					
Prevalence, % (no.)	55.8 (379)	63.6 (68)	69.5 (130)	69.2 (144)	<.0001
Odds ratio (95% CI)	1	1.34 (.87-2.07)	1.67 (1.17-2.40)	1.53 (1.06-2.22)	.003

Abbreviations: CI, confidence interval; LDL, low-density lipoprotein.
[a]Odds ratios (95% CI) were computed for each category of alcohol drinking versus never drinking after adjustment for age, body mass index, current smoking, and antihypertensive and antidiabetic treatment.

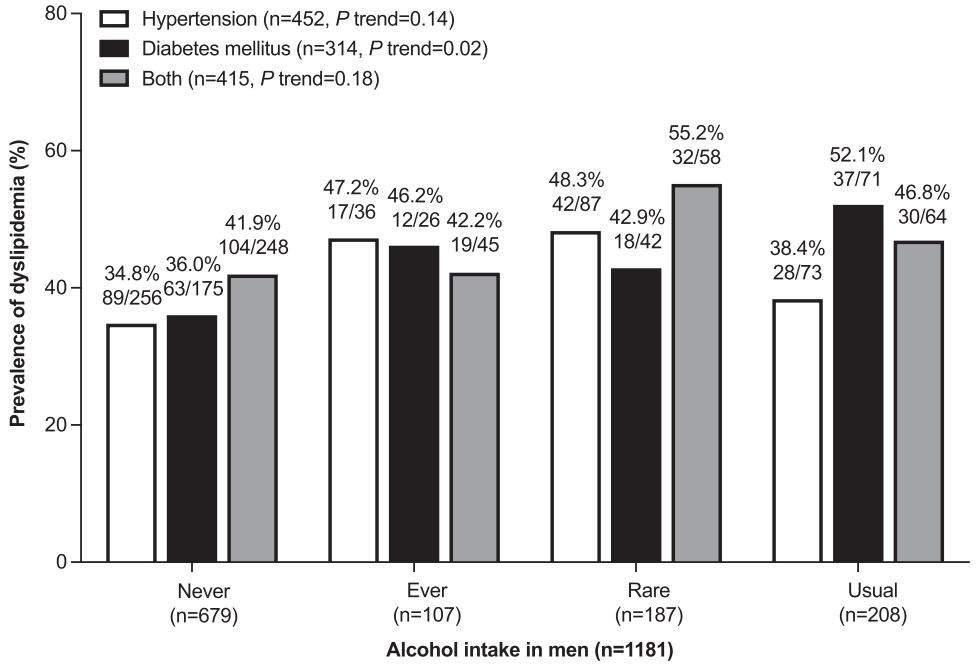

FIGURE 3 Prevalence of dyslipidemia in patients with hypertension, diabetes mellitus, or both according to the status of alcohol intake (never, ever, rare, and usual drinkers). The number of participants is given at the bottom. The prevalence of dyslipidemia is given on the top of the bars with the number of patients. The *P* values for trend are given

A unique feature of our present analysis is the multicenter recruitment of participants with hypertension and diabetes mellitus. Nonetheless, our observations on the worse lipid profile and higher prevalence of dyslipidemia associated with usual alcohol drinking is in keeping with the results of several previous studies in China and other Asian countries with similar alcohol drinking pattern.[6,12,14] In a community-based study in Chinese men and women (n = 71 379), serum total and LDL cholesterol were significantly ($P < .0001$) higher in any drinkers than never drinkers.[6] In another Chinese study with an even larger number of participants (n = 163 641), the prevalence of hypercholesterolemia and hypertriglyceridemia was higher in current excessive alcohol drinkers than non-drinkers.[12] As commonly believed, the association between alcohol intake and dyslipidemia seemed to be stronger for hypertriglyceridemia than for hypercholesterolemia. Indeed, in a Korean study in 1893 older (≥60 years) men, both the serum concentration of triglycerides and the prevalence of

hypertriglyceridemia were significantly ($P < .001$) higher in drinkers consuming ≥30 g/day than non-drinkers.[14]

Significant associations between alcohol intake and hypertriglyceridemia were also observed in several studies with participants of European ancestry.[15,16] In a Swiss study (n = 5769), heavy and very heavy drinkers had a significantly higher serum triglycerides concentration than non-drinkers.[15] In a Polish national health survey in 2003–2005 (6912 men, 20–74 years), moderate and heavy drinkers had a 25% and 46%, respectively, higher prevalence of hypertriglyceridemia than light drinkers.[16] In both of the European studies, heavy drinkers had a higher HDL cholesterol than light- or non-drinkers, probably because of wine drinking.[15,16]

In contrast to the results of the above-mentioned[15,16] and several other European studies, our study showed lower, not higher, serum HDL cholesterol in ever or rare drinkers than non-drinkers. The underlying mechanism is not known. A possible explanation may be that the Chinese mainly drink alcoholic beverages other than red wine. There is some evidence that red wine, not any other alcoholic beverage, increases serum HDL cholesterol.[20] In our present study, we cannot test this hypothesis, because we did not collect information on the type of alcoholic beverages.

We observed a highest use of statins and other lipid-lowering agents and a highest prevalence of low HDL cholesterol in ever drinkers. This finding is in keeping with the results of several previous studies,[21,22] and may have implications in clinical research on the risk associated with alcohol intake, in policy making on alcohol restriction, and in cardiovascular prevention. These ever drinkers might have stopped alcohol drinking because of cardiovascular or non-cardiovascular illnesses. In longitudinal studies on the risk of alcohol intake, ever drinking might have to be taken into account. Otherwise, the risk can be substantially underestimated. Accordingly, various strict regulations might have to be implemented for reducing alcohol consumption in general and reducing production of high ethanol volume alcohol beverages in particular.

Although the sample size of our study was not sufficiently large for a per-province analysis, usual alcohol drinking showed a significant association with the between-province variation in the prevalence of dyslipidemia. This finding, if confirmed in even larger studies, may have important public health implications. The evidence would build the ground for more intensive regulations on the production, sales, and consumption of alcohol in several provinces with a high prevalence of alcohol intake. Lifestyle factors, such as alcohol drinking, are largely but not entirely personal. Governmental regulations and policy can and should play a part in lifestyle modification, including alcohol restriction and moderation.

Our study should be interpreted within the context of its limitations. First, our study had a cross-sectional design and does not allow any causal inference. Second, because of the low proportion of alcohol intake in women, our analysis had to restrict to men. The results of our study should be cautiously extrapolated to female drinkers. Third, we did not collect information on the exact volume or type of alcoholic beverages. The possibility that characteristics other than alcohol intake frequency also play a part cannot be entirely excluded.

In conclusion, alcohol drinking, especially usual drinking, was associated with a worse lipid profile and higher prevalence of dyslipidemia in patients with hypertension and diabetes mellitus. This association might have ecological implications for the prevention of dyslipidemia, because usual drinking seemed to explain a quite significant proportion of the between-province variation in the prevalence of dyslipidemia.

AUTHOR CONTRIBUTIONS

J.G.W. and L.N.J. contributed to the conception and design of the work. X.F.Y. performed data analysis and prepared the first draft of the manuscript together with J.G.W. All authors critically revised the manuscript and gave the final approval.

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CONFLICT OF INTEREST

Dr Wang reports receiving lecture and consulting fees from Merck, Novartis, Omron, Servier, and Takeda. The other authors declared no conflicts of interest.

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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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