Original Article

Alcohol consumption and the risk of type 2 diabetes mellitus: effect modification by hypercholesterolemia: The Third Korea National Health and Nutrition Examination Survey (2005)

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OBJECTIVE: While the protective nature of moderate alcohol consumption against diabetes mellitus is well known, inconsistent findings continue to be reported. The possibility of different mixes of effect modifiers has been raised as a reason for those inconsistent findings. Our study aim was to examine potential effect modifiers that can change the effect of alcohol consumption on type 2 diabetes. METHODS: From data in the third Korea National Health and Nutrition Examination Survey, 3,982 individuals over the age of 30 years who had not been diagnosed with diabetes were selected for inclusion in the study population. Breslow and Day's test and the Wald test between hypercholesterolemia and alcohol consumption in a multiple logistic regression model were used to assess effect modification. RESULTS: Odds ratios for diabetes stratified by alcohol consumption strata and assessed using Breslow and Day's tests for homogeneity indicated that hypercholesterolemia was not a significant confounding factor (p=0.01). However, the Wald test for interaction terms, which is a conservative method of effect modification, was significant (p=0.03). CONCLUSIONS: The results indicate that moderate alcohol consumption is not necessarily protective for type 2 diabetes mellitus, if a person has hypercholesterolemia. People who have hypercholesterolemia should be aware of the risk associated with alcohol consumption, a risk that contrasts with the reported protective effect of moderate alcohol consumption on diabetes.

Key Words: diabetes, alcohol consumption, hypercholesterolemia, dyslipidemia, effect modification, interaction

INTRODUCTION

The global burden of diabetes mellitus has steadily increased, and its incidence is greater in developing countries than in developed ones.[1,2] Globally, the prevalence of diabetes among adults is estimated to be 6.4%; thus, affecting approximately 285 million people in 2010. Its incidence is expected to increase to 7.7% (approximately 439 million adults) by 2030.[2]

The occurrence of type 2 diabetes is closely related to diet and lifestyle.[3-7] A relationship between drinking and diabetes is a popular theme in the literature because alcohol consumption is widespread and potentially modifiable. Nonetheless, the relationship is insufficiently understood to allow an unequivocal conclusion about the relationship. In many original articles and reviews, researchers report that moderate alcohol consumption lowers the possibility of an individual developing type 2 diabetes,[8-16] however, other researchers report that alcohol consumption increases an individual's chance of developing diabetes, even in the case of moderate consumption.[17-19] These contradictory findings may mean that a third component (a confounding factor or an effect modifier) can affect the relationship between alcohol consumption and diabetes. Many researchers have controlled for confounders in their studies, but effect modifiers have not been thoroughly investigated. Effect modification of some factor for effect of alcohol consumption on diabetes do not mean the factor is the cause of diabetes, but this means the factor changes effect of alcohol consumption on diabetes.[20] Some researchers have suggested further investigation of

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population characteristics, such as obesity and drinking types and patterns to help explain the inconsistencies [21, 22]. In addition, obesity was suggested as an effect modifier for explaining the contradictory findings and its effects have been tested.[8,10,18,19,23] The purpose of this study was to search for other possible effect modifiers that can alter the effect of alcohol consumption on type 2 diabetes.

METHODS

Study population

We analyzed data from the third Korea National Health and Nutrition Examination Survey (KNHANES), a survey conducted in 2005 among the general population of South Korean civilians by the Korean Ministry of Health and Welfare. The survey selected a primary survey unit (PSU) using a stratified cluster, systemic sampling method. Clusters of households were selected from each PSU; each cluster included between 20 and 26 households. The recruitment rate for the potential participants in the health interview survey (600 PSUs with 34,145 individuals) was 99.1%. The recruitment rates for the health examination (200 PSUs with 10,816 individuals) and nutritional (200 PSUs with 11,240 individuals) surveys were 70.2% and 80.6%, respectively.

A total of 4,423 individuals over the age of 30 years provided information about alcohol consumption and diabetes through KNHANES questionnaires and blood chemistry data. Of those individuals, 154 were excluded because of incomplete information. A further 287 people who already knew that they had diabetes were excluded based on a revealed significant difference in alcohol consumption in the results of a t-test between the diabetes patient group and the newly diagnosed group in KNHANES, as they might have reduced their alcohol consumption after their diagnosis. Ultimately, data for 3,982 individuals who provided complete information and had not yet been diagnosed with diabetes were analyzed.

Variable definition

Diabetes in KNHANES is defined as when a person's fasting plasma glucose (FPG) level, which is possible indicator in mass health examination among the American Diabetes Association's diagnostic criteria, is above 126 mg/dL. Hypercholesterolemia in KNHANES is defined as when a person has a total cholesterol level above 240 mg/dL or takes cholesterol-lowering medication. Individuals were divided into three categories (non-drinker, less than 30 g/day, or 30 g/day or more) based on their amount of alcohol consumption, which was calculated from KNHANES questionnaires on the kinds and quantity of alcohol consumed during the one month previous to the survey. Calculation for daily amount of alcohol consumption was based on the standard concentration of ethanol in each type of alcohol in Korea.[24] Normal weight and overweight conditions were defined using BMI: <23.0, and ≥23.0, respectively.[18,19] The study population was categorized into three subgroups based on education level: <10 years, 10–12 years, and >12 years. Individuals were divided into five categories according to their average monthly household income during the previous year: <1,000,000, 1,000,000-1,999,999, 2,000,000-2,999,999, 3,000,000-3,999,999, and ≥4,000,000 Korean won. The study population was also categorized into three subgroups based on smoking behavior: current, past, and never. Past smokers were those who reported that they had smoked at least 100 cigarettes during their lifetime, but did not currently smoke. Marital status was collapsed into three categories: married, non-married, and single after marriage. Individuals were also divided into two categories based on physical activity level according to their responses on a KNHANES questionnaire that asked them to indicate whether they exercised regularly in their free time. Subjective health status assessed on a five-point Likert-type instrument was dichotomized: very good or good vs. moderate or bad or very bad.

Statistical analyses

Descriptive statistics with chi-square test results are summarized according to each alcohol consumption category. The confounding effect on alcohol consumption on type 2 diabetes was assessed using Breslow and Day's (BD) test for homogeneity, by stratifying by independent variables and comparing odds ratios (ORs). Effect modifiers were analyzed by using the Wald test and likelihood ratio (LR) tests by multiple logistic regressions including the interaction terms between independent variables and alcohol consumption on diabetes. Statistical significance was set at $p<0.05$, unless otherwise indicated. We used SAS 9.3 and MLwin 2.18 for all statistical testing.

RESULTS

Of the sample, 1,669 (42%) were male. A total of 315 (8%) participants had hypercholesterolemia, and 118 individuals had diabetes. For baseline alcohol intake, 1,668 (42%) were non-drinkers, 1,965 (49%) individuals drank less than 30g/day, and 349 (9%) individuals drank 30g/day or more. Male and middle-aged individuals reported greater alcohol consumption (see Table 1).

The relationship between alcohol consumption and diabetes was tested using stratified multiple logistic regressions by alcohol consumption strata. The adjusted ORs for the risk of diabetes were 1.02 (95% confidence interval (CI), 0.66-1.57) and 1.68 (95% CI, 0.90-3.15) with daily alcohol consumption of <30 g and ≥30 g, respectively. There was no significant correlation between alcohol consumption and prevalence of type 2 diabetes after controlling for socio-economic factors, lifestyle, and subjective and objective health status in the survey questionnaire.

Table 2 shows the stratified ORs and the results of the BD tests for homogeneity, which were used to determine the significance of the difference between ORs in each stratum. The results of the BD tests for three objective health variables that are related to type 2 diabetes and that may be direct effect modifiers are shown. There was a significant difference in the ORs between the hypercholesterolemia strata (p=0.01) but no significant differences in ORs were detected between the hypertension and BMI strata. Other socio-economic factors, lifestyle, and subjective health status were also not significant. The results show that hypercholesterolemia is not a confounding factor on the effect of alcohol consumption on type 2 diabetes.

We calculated the significance of the effect modifica-

Table 1. Baseline characteristics of the study subjects

	Strata	Total (%)	Non-drinker (%)	<30 g/day (%)	≥30 g/day (%)	*p*-value
Gender	Male	1,669 (42)	411 (25)	933 (47)	325 (93)	<0.01
	Female	2,313 (58)	1,257 (75)	1,032 (53)	24 (7)	
Age (y)	30-39	1,115 (28)	361 (22)	654 (33)	100 (29)	<0.01
	40-49	1,144 (29)	405 (24)	627 (32)	112 (32)	
	50-59	741 (19)	330 (20)	339 (17)	72 (21)	
	60-69	615 (15)	336 (20)	234 (12)	45 (13)	
	≥70	367 (9)	236 (14)	111 (6)	20 (6)	
Education (y)	≤9	1,571 (39)	812 (49)	651 (33)	108 (31)	<0.01
	10-12	1,415 (36)	511 (31)	761 (39)	143 (41)	
	≥13	996 (25)	345 (21)	553 (28)	98 (28)	
Marital Status	Unmarried	174 (4)	63 (4)	88 (4)	23 (7)	<0.01
	married	3,230 (81)	1,278 (77)	1,656 (84)	296 (85)	
	single after marriage	578 (15)	327 (20)	221 (11)	30 (9)	
Average Household Income (×10^3 Won/mo)	<1,000	800 (20)	443 (27)	296 (15)	61 (17)	<0.01
	1,000-1,999	987 (25)	407 (24)	488 (25)	92 (26)	
	2,000-2,999	903 (23)	325 (19)	506 (26)	72 (21)	
	3,000-3,999	650 (16)	233 (14)	363 (18)	54 (15)	
	≥4,000	642 (16)	260 (16)	312 (16)	70 (20)	
Smoking	Never	2,372 (60)	1,277 (77)	1,060 (54)	35 (10)	<0.01
	Past	714 (18)	203 (12)	396 (20)	115 (33)	
	Current	896 (23)	188 (11)	509 (26)	199 (57)	
Regular Exercise	None	2,085 (52)	919 (55)	996 (51)	170 (49)	0.01
	Regular	1,897 (48)	749 (45)	969 (49)	179 (51)	
Subjective Health Status	≥Good	1,461 (37)	542 (32)	761 (39)	158 (45)	<0.01
	≤Moderate	2,521 (63)	1,126 (68)	1,204 (61)	191 (55)	
Hypertension	None	2,926 (73)	1,203 (72)	1,494 (76)	229 (66)	<0.01
	Yes	1,056 (27)	465 (28)	471 (24)	120 (34)	
Hypercholesterolemia	None	3,667 (92)	1,513 (91)	1,832 (93)	322 (92)	0.02
	Yes	315 (8)	155 (9)	133 (7)	27 (8)	
BMI	≤23.0	1,605 (40)	697 (42)	793 (40)	115 (35)	0.06
	>23.0	2,377 (60)	971 (58)	1192 (60)	214 (65)	
Diabetes	None	3,864 (97)	1,624 (97)	1,911 (97)	329 (94)	<0.01
	Diabetes	118 (3)	44 (3)	54 (3)	20 (6)	

Table 2. Stratum-specific odds ratios and *p*-values of Breslow and Day's test for homogeneity for diabetes

	Strata (%)	Non-drinker (Reference)	<30 g/day (OR)	BD test (*p* -value)	≥30 g/day (OR)	BD test (*p* -value)
Hypertension	None (71)	1	0.77	0.07	2.20	0.96
	Yes (29)	1	1.67		2.14	
Hypercholesterolemia	None (92)	1	0.84	0.01*	1.98	0.20
	Yes (8)	1	3.53		5.22	
BMI	≤23.0 (40)	1	1.11	0.85	3.10	0.57
	>23.0 (60)	1	1.00		2.10	

* Significantly different ($p< 0.05$) compared with the reference group (non-drinker).

tion of hypercholesterolemia by the Wald test using multiple logistic regression models that included interaction terms between hypercholesterolemia and alcohol consumption. The effect modification of hypercholesterolemia with moderate alcohol consumption (<30 g/day) significantly increased the likelihood of diabetes in the Wald test (p=0.03) (Table 3). The LR test also showed the presence of significant interaction terms (p<0.01). Figure 1 illustrates that the mean probability of diabetes is affected by hypercholesterolemia and by alcohol consumption. The probability difference of diabetes between non-hypercholesterolemia and hypercholesterolemia individuals increased significantly with moderate alcohol consumption over that shown by non-drinkers, indicating that the effects of moderate alcohol consumption and hypercholesterolemia are synergetic on the risk of type 2 diabetes.

DISCUSSION

The main finding of the study is that moderate alcohol consumption (<30 g/day) increases the risk of type 2 diabetes mellitus when combined with hypercholesterolemia,

Table 3. Coefficients of multiple logistic regression including interaction terms

	Beta	CI (2.5%)	CI (97.5%)	*p*-value
Hypercholesterolemia	0.03	-0.95	1.01	0.95
Alcohol consumption (<30 g/day)	-0.20	-0.69	0.28	0.40
Hypercholesterolemia·alcohol consumption (<30 g/day)	1.27	0.09	2.45	0.03
Alcohol consumption (≥30 g/day)	0.37	-0.31	1.05	0.27
Hypercholesterolemia·alcohol consumption (≥30 g/day)	1.00	-0.57	2.58	0.20

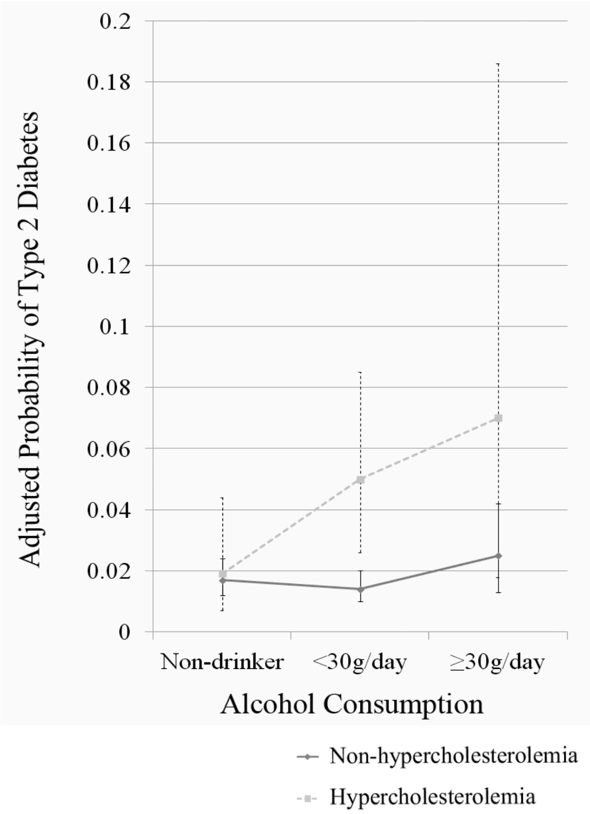

Figure 1. Effect modification by hypercholesterolemia

even though hypercholesterolemia and alcohol consumption individually have little effect on the risk of type 2 diabetes mellitus. This finding suggests hypercholesterolemia or some condition related with hypercholesterolemia change the effect of alcohol on diabetes.

Previous researchers found a U-shaped correlation between alcohol consumption and type 2 diabetes in Western countries,[2,8-10,12,13,25] and it is well known that moderate alcohol consumption has a protective effect on many metabolic diseases, such as diabetes. Previous effect modification studies have shown a significant difference when the researchers created subgroups according to BMI. In this study, hypercholesterolemia had a significant effect modification on alcohol and type 2 diabetes, whereas BMI had no effect modification. We retested BMI-based effect modification using the alternate BMI criteria used in previous effect modification studies to obtain an exact comparison, but the result did not changed. This BMI-related difference might be related to the omission of variables, like hypercholesterolemia or other related conditions that have association with diabetes, in the analyses of those previous studies.[8,18,19,23] Brown *et al*.[26] found a strong association between BMI and hypercholesterolemia. In addition, high BMI and hypercholesterolemia are associated with insulin resistance.[27, 8] These correlations can make BMI act as a confounder on the effect modification of hypercholesterolemia on the relationship between alcohol consumption and type 2 diabetes (Figure 2). In addition, our findings suggest that the effect modification by BMI discussed in previous studies[8, 18,19,23] may actually be related to cholesterol levels. Moreover, if our finding of an effect modification of hypercholesterolemia is correct, then the protective effect of moderate alcohol consumption on type 2 diabetes found in previous studies might have been because their samples were from a normo-cholesterol population.

Although we partly controlled for reverse causality by excluding individuals who knew that they had diabetes before taking the survey, we could not rule out reverse causalities related to other independent variables because our research was based on a cross-sectional survey. This also means our results can only show an association, but not a causal relationship.

Moreover KNHANES is mass health examination and survey for general population, specific data for hypercholesterolemia, such as chylomicrons, very-low-density lipoprotein, or their remnants, cannot be collected through KNHANES. However KNHANES collected data related to almost all major health problems on a large scale through stratified randomization selection of sample in the Korean general population. Thus this data can be meaningful in investigating the relationship between

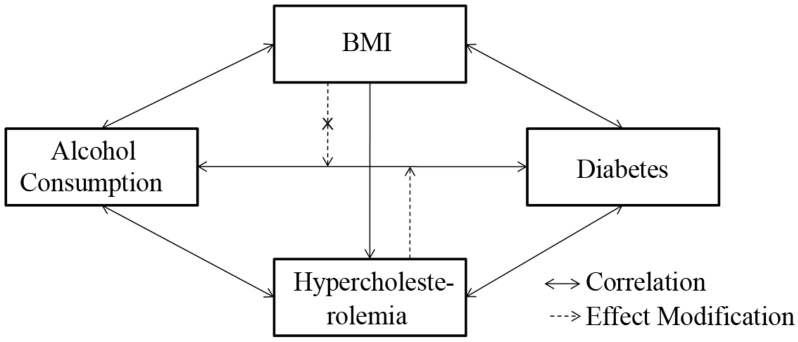

Figure 2. Effect modification of alcohol consumption on type 2 diabetes

health problems.

Further research on effect modification related to the relationship between alcohol consumption and diabetes is needed to clarify the effect of alcohol on type 2 diabetes.

Our findings suggest that hypercholesterolemia or hypercholesterolemia related condition can act as an effect modifier and can increase the risk of type 2 diabetes in moderate drinkers through some unknown interaction between cholesterol and alcohol. Even though moderate alcohol consumption is known to be a protective factor against diabetes, people who have hypercholesterolemia should be aware of the relationship between alcohol consumption level and the risk of diabetes. Moreover, further studies into effect modification by substances related to hypercholesterolemia and diabetes, such as chylomicrons, very-low-density lipoprotein, or their remnants, are needed to clarify the interaction mechanism.

AUTHOR DISCLOSURES

There was no source of funding and conflict of interests for this research.

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Original Article

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酒精攝取與第 2 型糖尿病罹患風險：高膽固醇血症之效應修飾：第三次韓國國民健康與營養調查(2005)

目的：已知適量飲酒對於糖尿病具有保護作用，但仍有報告指出不一致的結果，造成此差異的原因可能來自於效應修飾因子之間互相影響。本研究目的為檢視酒精攝取對第 2 型糖尿病影響之潛在效應修飾因子。方法：本研究資料來自第三次韓國國民健康與營養調查，納入之研究對象共有 3982 位，條件為 30 歲以上未被診斷為糖尿病者。在多元邏輯斯迴歸模式下，以 Breslow -Day 檢定和 Wald 檢定來分析高膽固醇血症與飲酒之間的效應修飾作用。結果：利用 Breslow-Day 檢定來檢測同質性，在不同飲酒狀況之糖尿病勝算比(OR)指出，高膽固醇血症並不是一項顯著干擾因子(p=0.01)。然而，由較保守之效應修飾分析方法-Wald 檢定的結果顯示，兩者之間具有顯著之交互作用(p=0.03)。結論：由結果指出，對於有高膽固醇血症者，適量飲酒對第 2 型糖尿病風險不一定具有保護作用。因此高膽固醇血症患者應對飲酒相關風險有所警覺，此風險與適量飲酒對糖尿病之保護作用卻是相對立的。

關鍵字：糖尿病、酒精攝取、高膽固醇血症、血脂異常、效應修飾、交互作用