Daily Alcohol Consumption and the Risk of Type 2 Diabetes in Japanese Men

The Osaka Health Survey

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OBJECTIVE — To investigate the relationship between daily alcohol consumption and the risk of type 2 diabetes in a large Japanese cohort.

RESEARCH DESIGN AND METHODS — We enrolled 6,362 Japanese men aged 35–61 years who did not have diabetes, impaired fasting glucose, hypertension, or liver cirrhosis at study entry. Type 2 diabetes was defined as a fasting plasma glucose (FPG) level ≥126 mg/dl or was diagnosed by a physician. Data on alcohol consumption were obtained from questionnaires. We confirmed 456 cases of type 2 diabetes during the 62,016 person-years of follow-up.

RESULTS — The relationship between daily alcohol consumption and the risk of type 2 diabetes among lean men and among men with a higher BMI was paradoxical. Among lean men (BMI ≤22.0 kg/m²), heavy drinking was associated with an increased risk of type 2 diabetes. Men who consumed ≥50.1 ml/day of alcohol had a relative risk (RR) of 2.48 (95% CI 1.31–4.71) compared with nondrinkers after adjusting for age, BMI, regular physical exercise, parental history of diabetes, smoking habits, and FPG level. However, among men with a BMI ≥22.1 kg/m², moderate drinking (29.1–50.0 ml/day) was associated with a decreased risk of type 2 diabetes. Daily moderate drinkers had a multiple adjusted RR of 0.58 (0.39–0.87) compared with nondrinkers.

CONCLUSIONS — Among men with a BMI ≥22.1 kg/m², moderate alcohol consumption was associated with a reduced risk of type 2 diabetes, but among lean men (BMI ≤22.0 kg/m²), heavy alcohol consumption was associated with an increased risk of type 2 diabetes.

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Type 2 diabetes, which affects about 7 million Japanese individuals, is a complex disorder characterized by insulin resistance and impaired insulin secretion. Although the strongest predictors of type 2 diabetes are obesity and a family history of diabetes (1–3), lifestyle factors may also be important in the etiology of the disease.

Some cross-sectional studies have reported that habitual moderate consumption of alcohol may lower levels of insulin resistance and fasting insulin (4–6). Longitudinal epidemiological findings that related alcohol consumption to the risk of type 2 diabetes are equivocal (7–10); one prospective study has reported a positive association (7), but others have reported an inverse association (8–10). Until now, most large prospective studies of type 2 diabetes have underestimated the incidence of diabetes, particularly because the oral glucose tolerance test (OGTT) can be difficult to perform and because the cost and demands on participants' time can be excessive. Thus, the American Diabetes Association (ADA) has recommended that, for epidemiological studies, estimates of diabetes incidence should be based on a fasting plasma glucose (FPG) level of ≥126 mg/dl (7.0 mmol/l) (11).

In this study, the diagnosis of type 2 diabetes was based on the new ADA criterion (FPG level ≥126 mg/dl [7.0 mmol/l]) (11). We prospectively examined the relationship between daily alcohol consumption and the risk of type 2 diabetes during a 4- to 16-year observation period.

RESEARCH DESIGN AND METHODS

Osaka Health Survey

The Osaka Health Survey is an ongoing cohort study of risk factors for chronic diseases, including hypertension and diabetes, among male employees of a large gas company in Osaka, Japan. Japanese law requires that all employers conduct annual health screenings for all employees. In addition to these annual screenings, all employees in this gas company aged ≥35 years undergo more detailed medical checkups, including questionnaires on lifestyle characteristics and an exercise examination every 2 years. The Osaka Health Survey began in 1981 and includes subjects who have undergone detailed biennial checkups.

Study population

We enrolled 8,410 men aged 35–61 years at entry between 1981 and 1991. We excluded 1,932 men because they had diabetes, impaired fasting glucose, hypertension (determined by a systolic blood pressure of ≥140 mmHg, a diastolic blood pressure of ≥90 mmHg, or both, or the use of antihypertensive medications), or liver cirrhosis at entry. We excluded 116 men

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Abbreviations: ADA, American Diabetes Association; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; RR, relative risk.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Conversion of ounces of various alcoholic beverages to the equivalent of milliliters of ethanol*

12 oz. regular beer = 16.0 ml ethanol
1 oz. whiskey = 12.7 ml ethanol
4 oz. wine = 14.2 ml ethanol
1 oz. shochu* = 7.4 ml ethanol

*Japanese distilled liquor made from rice, wheat, and sweet potatoes.

who did not undergo a medical checkup during the follow-up period. The study population thus consisted of 6,362 men.

Measurements

The biennial clinical examination consisted of a medical history, a physical examination, blood pressure measurements, anthropometric measurements, and questionnaires on lifestyle characteristics (e.g., physical activity, the number of cigarettes smoked and daily alcohol consumption). Trained nurses took all measurements. Participants were asked to fast for 12 h and to avoid smoking and heavy physical activity for at least 2 h before the examinations. After a 5-min rest in a quiet room, systolic and diastolic blood pressure levels were measured twice at an interval of a few minutes on the right arm with a standard mercury sphygmomanometer. Anthropometric measurements, which included height and body weight, were measured while the subject was wearing light clothing without shoes. The BMI was calculated as the weight in kilograms divided by the height in meters squared. Fasting blood samples were obtained to measure the serum level of HDL cholesterol and FPG.

The questionnaire on physical activity elicited information on leisure-time physical activity. Subjects were queried about the type and weekly frequency of leisure-time physical activity. Regularly physically active subjects were defined as those who engaged in any regular physical activity (e.g., jogging, bicycling, swimming, and tennis) long enough to work up a sweat at least once a week. The questions about regular physical activity have been validated (12–14).

Questions about alcohol intake concerned the type of alcoholic beverages consumed, the weekly frequency of alcohol consumption, and the usual amount of alcohol consumed daily. Alcohol intake was converted to total alcohol consumption (in milliliters of ethanol per day) by using standard Japanese tables (Table 1). The data on alcohol consumption were indirectly validated by a positive and significant correlation between alcohol consumption and the serum level of HDL cholesterol (Table 2) (15–17). Current and past smoking habits were classified according to the type and quantity of cigarettes smoked daily. Subjects were classified as current or past smokers or as nonsmokers.

Diagnosis of type 2 diabetes

All cases of type 2 diabetes were diagnosed by physicians (FPG level ≥140 mg/dl [7.8 mmol/l] or an OGTT with the 2-h postload plasma glucose level ≥200 mg/dl [11.1 mmol/l]) since study entry. We could not administer the OGTT to all subjects. Therefore, in addition to these criteria, we redefined type 2 diabetes by using the new ADA criterion (FPG level ≥126 mg/dl [7.0 mmol/l]) (11). Impaired fasting glucose was determined when subjects had no history of diagnosed type 2 diabetes and when the FPG level was ≥110 (6.1 mmol/l) and <126 mg/dl (7.0 mmol/l) (the new ADA criterion) (11). Because of the age range of the study population, all cases of diabetes were diagnosed after age 35 years and were thus classified as type 2 diabetes.

Statistical analysis

The association between daily alcohol consumption and selected continuous variables was analyzed with a multiple regression model. The association between daily alcohol consumption and selected categorical variables was analyzed with a logistical regression model. In both analyses, daily alcohol consumption was a continuous variable, and analyses were adjusted for age.

The incidence of type 2 diabetes between 1981 and 1997 was computed according to the level of daily alcohol consumption at entry. For each subject, person-years of follow-up were counted from the date of entry (1981–1991) to the date of diagnosis of diabetes or 1 April 1997, whichever came first. The follow-up rate was 94% of total potential person-years of follow-up. Participants were classified as nondrinkers or were classified into quartiles of daily alcohol consumption. The rates of type 2 diabetes were obtained by dividing the number of cases by person-years in each category of daily alcohol consumption. Relative risk (RR) was calculated as the rate of occurrence of type 2 diabetes in a specific

Table 2—*Age-adjusted baseline characteristics according to daily alcohol consumption at study entry*

	Daily alcohol consumption					
Characteristics	Nondrinkers (0 ml)	Quartile 1 (0.1–19.0 ml)	Quartile 2 (19.1–29.0 ml)	Quartile 3 (29.1–50.0 ml)	Quartile 4 (≥50.1 ml)	*P* for trend
Subjects (*n*)	1,134	1,321	1,506	1,117	1,284	
Age (years)	42.6	42.0	41.8	41.2	39.3	<0.001
BMI (kg/m^2)	22.3	22.3	22.6	22.7	23.0	<0.001*
Smoking habits (%)						
Lifelong nonsmokers	25.5	27.0	22.5	15.9	13.5	<0.001†
Former smokers	16.4	19.0	19.1	18.4	14.5	0.07†
Smokers	58.1	54.0	58.4	65.7	72.0	<0.001†
Cigarettes per day (*n*)	14.6	12.1	13.4	15.9	19.6	<0.001*
Regular physical activity at least once a week (%)	27.4	32.3	33.4	30.9	32.3	0.07†
FPG (mmol/l)	4.97	4.97	5.03	5.03	5.02	<0.001*
HDL cholesterol (mmol/l)	1.16	1.22	1.30	1.35	1.37	<0.001*

Data are means or %. All variables except for age were adjusted for the age distribution of all the study subjects. *Multiple regression model adjusted for age; †logistical regression model adjusted for age.

category of daily alcohol consumption divided by the incidence rate in nondrinkers. Cox proportional hazards regression analyses were used to evaluate the simultaneous effects of daily alcohol consumption, BMI, age, leisure-time physical activity (regular physical activity at least once a week), parental history of diabetes (yes or no), smoking habit (<20 cigarettes/day, ≥20 cigarettes/day, past smokers, or nonsmokers), and FPG level. The linear trends in risks were evaluated by entering indicators for each categorical level of exposure and using the median value for each category. In multiple adjusted analysis, FPG level was included in the analysis of alcohol consumption and the risk of type 2 diabetes. This was because, even after stratified analyses by alcohol consumption (nondrinkers and drinkers), FPG level was significantly associated with an increased risk of type 2 diabetes in both groups, and we concluded that FPG level may not be in the causal pathway between daily alcohol consumption and type 2 diabetes (data not shown). Because age and FPG level were linearly related to the risk of type 2 diabetes (data not shown), these predictors were entered into the model as continuous variables.

We calculated the 95% CIs for each RR. *P* values are two-tailed. Statistical analyses were performed with the SPSS 7.5J software package (SPSS, Chicago).

RESULTS — During the 62,016 person-years follow-up (range 4–16 years), 456 men developed type 2 diabetes. BMI, FPG level, serum level of HDL cholesterol, and the proportion of current smokers increased significantly with increases in daily alcohol consumption (Table 2). There was no significant relationship between daily alcohol consumption and the frequency of engaging in regular physical activity.

Men who consumed ≥50.1 ml/day of alcohol had an age-adjusted RR of type 2 diabetes of 1.40 (95% CI 1.04–1.88) compared with nondrinkers. The relationship between heavy alcohol consumption and type 2 diabetes was weaker after the data were adjusted for age, BMI, smoking habit (<20 cigarettes/day, ≥20 cigarettes/day, past smokers, or nonsmokers), leisure-time physical activity (regular physical activity at least once a week), parental history of diabetes (yes or no), and FPG level (see Model 1 in Table 3). On the other hand, after multiple adjustment, including FPG level, moderate alcohol consumption was associated with a significantly lower risk of type 2 diabetes. Men who consumed 29.1–50.0 ml/day of alcohol had an RR of developing type 2 diabetes of 0.67 (0.47–0.94) compared with nondrinkers (see Model 1 in Table 3).

To examine whether the BMI modified the association between daily alcohol consumption and the risk of type 2 diabetes, we stratified subjects according to BMI (see Model 2 in Table 3). Among lean men (BMI ≤22.0 kg/m^2), daily heavy alcohol consumption was strongly and positively associated with the risk of type 2 diabetes; men who consumed ≥50.1 ml/day of alcohol had an RR of developing type 2 diabetes of 2.48 (1.31–4.71) compared with nondrinkers after adjusting for several known or suspected predictors of type 2 diabetes. In contrast, among men with a BMI of ≥22.1 kg/m^2, moderate alcohol consumption was associated with a significantly lower risk of type 2 diabetes; men who consumed 29.1–50.0 ml/day of alcohol had a multiple adjusted RR of developing type 2 diabetes of 0.58 (0.39–0.87) compared with nondrinkers.

Because people may alter their drinking habits over time, additional analyses were performed on the basis of using both the data at study entry (1981–1990) and at the third examination performed 4 years after each participant was enrolled (1985–1994). We also performed analyses that excluded participants who developed type 2 diabetes between study entry (1981–1990) and the third examination 4 years later (1985–1994) (see Model 3 in Table 3). In the third examination (1985–1994), 50.2% of participants reported the same level of alcohol consumption, 16.3% reported a reduced level of consumption, and 33.5% reported an increased level of consumption. After adjusting for several known or suspected predictors of type 2 diabetes, among lean men (BMI ≤22.0 kg/m^2), men who consumed ≥50.1 ml/day of alcohol at both time points had an RR of developing type 2 diabetes of 2.01 (1.01–4.01) compared with men who were nondrinkers or consumed 0.1–29.0 ml/day of alcohol at both time points. In contrast, among men with a BMI ≥22.1 kg/m^2, those who consumed 29.1–50.0 ml/day of alcohol at both time points had a multiple adjusted RR of type 2 diabetes of 0.43 (0.21–0.89) compared with nondrinkers or men who consumed 0.1–29.0 ml/day of alcohol at both time points.

CONCLUSIONS — These prospective data indicate that, among lean men (BMI ≤22.0 kg/m^2), habitual heavy alcohol consumption (≥50.1 ml/day) was positively related to the development of type 2 diabetes, but among men with a higher BMI (≥22.1 kg/m^2), habitual moderate alcohol consumption (29.1–50.0 ml/day) was associated with a decreased risk of type 2 diabetes. These associations persisted despite adjustments for age, BMI, smoking habit, leisure-time physical activity, parental history of type 2 diabetes, and FPG level.

All subjects underwent medical screening by a physician at least once annually, and cases of type 2 diabetes were diagnosed by the physicians (FPG level of ≥140 mg/dl or an OGTT with a 2-h postload plasma glucose level of ≥200 mg/dl). Because an OGTT could not be performed in every subject, we redefined type 2 diabetes according to the ADA criterion of an FPG level ≥126 mg/dl or an OGTT with a 2-h postload plasma glucose level of ≥200 mg/dl (11). We considered the possibility that there may be bias due to misclassification if the proportion of cases of type 2 diabetes determined by an OGTT differed across levels of alcohol consumption, but that proportion of cases did not differ across levels of alcohol consumption (data not shown). All subjects in the study were registered employees of the same company and thus may not always be representative of the general Japanese population, but these relationships are thought to apply to most white-collar urban workers in Japan. However, the relative homogeneity of the cohort may actually enhance the study's internal validity. Because of the relatively uniform educational background and socioeconomic status of the men in this cohort, these variables are not likely to represent confounding factors.

Shaper et al. (18) argued that the reference group of persons who identify themselves as alcohol abstainers is typically contaminated by subjects who have reduced their alcohol consumption because of preexisting disease or who are recovering alcoholics. Alcoholics and patients with liver cirrhosis have a higher risk of diabetes (19–21). We considered the possibility that these men may have stopped drinking because of illness. Including these men in the reference group of alcohol abstainers could artificially create an inverse association between alcohol consumption and type 2 diabetes, but we excluded men with these conditions from our analysis. There were no alcoholics in this cohort. Therefore, these biases are not likely to have affected the relationships observed in the study.

Table 3—*Relative risk of type 2 diabetes according to daily alcohol consumption*

Daily alcohol consumption (ml/day)			Total person-years	Cases	Rate per 10,000 person-years	Age-adjusted RR (95% CI)	Multiple adjusted RR (95% CI)*
Model 1†							
Nondrinkers			10,638	76	71.4	1.00	1.00
Quartile 1 (0.1–19.0)			13,438	95	70.6	0.98 (0.73–1.33)	0.99 (0.73–1.36)
Quartile 2 (19.1–29.0)			15,364	120	78.1	1.08 (0.81–1.44)	1.00 (0.74–1.34)
Quartile 3 (29.1–50.0)			10,788	60	55.6	0.80 (0.57–1.12)	0.67 (0.47–0.94)
Quartile 4 (≥50.1)			11,788	105	89.1	1.40 (1.04–1.88)	1.10 (0.81–1.51)
P for trend						0.10	0.87
Model 2†							
BMI ≤22.0 kg/m²							
Nondrinkers			4,996	16	32.0	1.00	1.00
0.1–19.0			6,374	25	39.2	1.22 (0.65–2.28)	1.20 (0.62–2.34)
19.1–29.0			6,194	29	46.8	1.44 (0.78–2.65)	1.39 (0.74–2.62)
29.1–50.0			4,254	16	37.6	1.19 (0.60–2.38)	1.07 (0.52–2.21)
≥50.1			4,122	29	70.4	2.37 (1.28–4.37)	2.48 (1.31–4.71)
P for trend						0.009	0.004
BMI ≥22.1 kg/m²							
Nondrinkers			5,642	60	106.3	1.00	1.00
0.1–19.0			7,064	70	99.1	0.92 (0.65–1.30)	0.94 (0.66–1.34)
19.1–29.0			9,170	91	99.2	0.93 (0.67–1.28)	0.91 (0.65–1.27)
29.1–50.0			6,534	44	67.3	0.65 (0.44–0.96)	0.58 (0.39–0.87)
≥50.1			7,666	76	99.1	1.06 (0.75–1.49)	0.88 (0.62–1.26)
P for trend						0.75	0.23
Model 3‡							
BMI ≤22.1 kg/m²							
Study entry		Third examination					
Nondrinkers, 0.1–19.0, 19.1–29.0	→	Nondrinkers, 0.1–19.0, 19.1–29.0	11,878	29	24.4	1.00	1.00
29.1–50.0	→	29.1–50.0	1,484	7	47.2	1.98 (0.87–4.53)	1.61 (0.68–3.76)
≥50.1	→	≥50.1	2,846	14	49.2	2.11 (1.09–4.04)	2.01 (1.01–4.01)
P for trend						0. 01	0.03
BMI ≥22.1 kg/m²							
Study entry		Third examination					
Nondrinkers, 0.1–19.0, 19.1–29.0	→	Nondrinkers, 0.1–19.0, 19.1–29.0	13,598	116	85.3	1.00	1.00
29.1–50.0	→	29.1–50.0	2,056	8	38.9	0.46 (0.22–0.95)	0.43 (0.21–0.89)
≥50.1	→	≥50.1	4,744	33	70.0	1.01 (0.68–1.51)	0.94 (0.62–1.41)
P for trend						0.69	0.64

*Adjusted for age, BMI, smoking habits (<20 cigarettes daily, ≥20 cigarettes daily, past smokers, nonsmokers), leisure-time physical activity (regular physical activity at least once a week), parental history of diabetes (yes or no), and FPG level. †Based on data of daily alcohol consumption from the study entry and including cases of type 2 diabetes from 1981 to 1997. ‡Based on data of daily alcohol consumption from the study entry (1981–1990) and the third examination done 4 years after each subject was enrolled (1985–1994), excluding cases of type 2 diabetes during the first 4-year follow-up period.

Because a relationship between pancreatitis and the risk of diabetes has been reported (22,23), we considered the possibility that, among lean men, pancreatitis due to heavy alcohol consumption may cause diabetes (23). In our study, among 29 lean men who consumed ≥50.1 ml/day of alcohol and developed diabetes, there were no subjects with pancreatitis either at study entry or during the observation period. Therefore, there was no possibility that pancreatitis caused diabetes in any of these men.

Previous epidemiological findings concerning the association between alcohol consumption and the risk of type 2 diabetes are inconclusive (7–10). One prospective study reported a positive association (7), but others have reported inverse associations (8–10). In a study of 41,810 health professionals followed for 6 years, men who drank 30.0–49.9 g/day of alcohol had a 39% reduced risk of developing type 2 diabetes (9). Alcohol drinking was also inversely associated with the risk of type 2 diabetes in a cohort of 7,735 middle-aged British men and in the Nurses' Health Study (8,10). In some cross-sectional studies, low to moderate alcohol consumption among healthy people is associated with increased insulin sensitivity and a decreased level of fasting plasma insulin (4–6). The mean BMI in these studies was ≥25.0 kg/m². In our study, we also found an inverse association between habitual moderate alcohol consumption (29.1–50.0 ml/day) and the risk of type 2 diabetes in men with a BMI of ≥22.1 kg/m².

In this study, we did not determine why daily heavy alcohol consumption among lean men increases the risk of type 2 diabetes. Holbrook et al. (7) reported that, in a cohort of 524 adults aged 30–79 years, alcohol consumption was a significant and independent predictor of type 2 diabetes in

men but not in women (RR 1.5/137.8 g alcohol for intake during the past week and 1.5/24.5 g alcohol for intake during the past 24 h). In that study, a limited number of incidence cases may have been responsible for the positive association, and the relationship between alcohol consumption and the risk of type 2 diabetes was not limited to lean people. Type 2 diabetes is a complex disorder characterized by insulin resistance and impaired insulin secretion. Because obesity mostly modifies insulin resistance, nonobese individuals usually do not have insulin resistance, except for those with hypertension or some genetic etiology (24,25). In our study, we excluded men with hypertension at study entry. Thus, daily heavy alcohol consumption among lean men may have a toxic effect on the pancreatic islet cells rather than on insulin resistance.

Matsumoto et al. (26) reported that impaired early-phase insulin secretion is the initial abnormality in the development of impaired glucose tolerance in Japanese people rather than insulin resistance. Kadowaki et al. (27) reported that insulin deficiency is a strong predictor of the development of type 2 diabetes. Moreover, Sereny and Endrenyi (28) reported that a significant decrease in insulin secretion was found in the early phase of the intravenous glucose tolerance test in chronic alcoholics. Shah et al. (29) reported inhibition of glucose-stimulated insulin secretion after oral ethanol gavage before an intravenous glucose tolerance test in rats, and Singh and Patel (30) also reported the same results. Therefore, among lean Japanese individuals without diabetes who are heavy alcohol drinkers, heavy alcohol consumption may lead to an impairment of early-phase insulin secretion. The effect of heavy alcohol consumption in relation to insulin secretion among Japanese lean subjects without diabetes must be investigated.

In conclusion, our results provide evidence that, among men with a higher BMI ($\geq$22.1 kg/m^2), moderate alcohol consumption (29.1–50.0 ml/day) is associated with a decreased risk of type 2 diabetes, but among lean men (BMI $\leq$22.0 kg/m^2), heavy alcohol consumption ($\geq$50.1 ml/day) is associated with an increased risk of type 2 diabetes. Further investigation of the interrelationships among alcohol consumption, obesity, insulin resistance, and diabetes is needed to clarify these mechanisms.

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