

Alcohol Intake and Incidence of Type 2 Diabetes in Men

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OBJECTIVE — To evaluate the relation between alcohol intake and incidence of type 2 diabetes.

RESEARCH DESIGN AND METHODS — This prospective study included 8,663 men with fasting plasma glucose measurements from at least two medical examinations. Alcohol intake was classified into five groups: nondrinkers and four quartiles (Qs) of drinkers according to the amount of alcohol intake. Type 2 diabetes was diagnosed by 1997 American Diabetes Association criteria.

RESULTS — There were 149 incident cases of type 2 diabetes during 52,588 person-years of follow-up. There was a U-shaped association between alcohol intake and diabetes, with the lowest incidence of diabetes at Q2 (61.9–122.7 g/week). As compared with Q2, men in Q3 and Q4 had a 2.2- (95% CI 1.2–3.9, $P = 0.01$) and 2.4-fold (1.4–4.4, $P < 0.01$) risk of developing diabetes, while nondrinkers and men in Q1 had 1.8- (1.0–3.3, $P < 0.05$) and 1.4-fold (0.7–2.6, $P = 0.34$) higher risk of diabetes, respectively. These associations persisted after adjustment for age, fasting plasma glucose, smoking, BMI, blood pressure, serum triglyceride concentration, cardiorespiratory fitness, HDL cholesterol, waist circumference, and parental diabetes.

CONCLUSIONS — We observed an elevated risk of developing type 2 diabetes in nondrinkers and men with high alcohol intakes, when compared with men who reported moderate alcohol intake. Men with a high alcohol intake may be able to reduce their risk of developing type 2 diabetes if they drink less.

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Type 2 diabetes is a common disease in industrialized countries. It is a major cause of cardiovascular disease and all-cause mortality (1), and the prevalence has risen continually over the few past decades (2,3). In 1998, the treatment of diabetes consumed 25% of all spending under the Medicare program in the U.S. (4). Prevention of diabetes is an important public health issue (5).

Although a positive association between drinking alcohol and type 2 diabetes has been reported in two small studies in which all men were screened for plasma glucose (6,7), an inverse association be-

tween alcohol intake and type 2 diabetes appeared in two relatively large studies with self-reported diabetes as the outcome measure (8,9). Two different reasons may explain these opposing results. On the one hand, studies using self-reported diabetes as the outcome may be misleading because type 2 diabetes is undiagnosed in ~33% of prevalent cases (10) and ~80% of incident cases (11,12). If patients with specific characteristics are more likely to be examined for glucose level than patients without such characteristics, it may create a bias regarding the association between self-reported diabetes and such characteristics (13). On

the other hand, positive findings between alcohol intake and diabetes in men might be due to chance in studies with diabetes diagnosed by plasma glucose criteria, because of the small number of incident cases (20 and 31, respectively) in these two reports (6,7).

To address these issues, we examined the association between alcohol intake and incidence of type 2 diabetes in a large cohort of men with alcohol intake and fasting plasma glucose measurements at baseline and at the end of follow-up.

RESEARCH DESIGN AND METHODS

Study subjects

Subjects for this study were 8,633 men 30–79 years of age at baseline (mean 43.5 years) who completed at least two medical evaluations at the Cooper Clinic in Dallas, Texas, between 1970 and 1995. Details of the study design and population characteristics of the cohort are available in earlier reports (12,14,15). Briefly, this is a population-based prospective study. Of the patients, >97% are white and most have white-collar or professional occupations. We excluded men with an abnormal resting or exercise electrocardiogram or a history of diabetes, heart attack, stroke, or cancer at baseline because cardiovascular disease and several other conditions could influence alcohol intake. We also excluded those with <1 year of follow-up.

The baseline evaluation was performed after participants gave their informed written consent for the initial medical examination and follow-up. Examinations followed an overnight fast of at least 12 h and included personal and family health histories, a questionnaire on demographic characteristics and health habits, a physical examination, anthropometry, electrocardiogram, blood chemistry analyses, blood pressure measurements, and a maximal exercise test on a motor-driven treadmill. Technicians who followed a standard manual of operations administered all procedures. The study has been reviewed and approved annually by the Cooper Institute Institutional Review Board.

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Abbreviations: OGTT, oral glucose tolerance test; Q, quartile.

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

Table 1—Baseline characteristics of 8,633 men according to alcohol consumption level

| Characteristics | Nondrinkers | Alcohol intake (g/week) | | | |
|----------------------------|-------------|-------------------------|-----------------|------------------|---------------|
| | | Q1 (1–61.8) | Q2 (61.9–122.7) | Q3 (122.8–276.6) | Q4 (>276.6) |
| Subjects (n) | 1,847 | 1,696 | 1,698 | 1,690 | 1,702 |
| Alcohol (g/week) | 0 | 33.7 ± 16.0 | 91.9 ± 16.4 | 185.9 ± 43.2 | 584.6 ± 425.8 |
| Age (years) | 45 ± 9 | 43 ± 8 | 43 ± 8 | 43 ± 8 | 44 ± 8 |
| Treadmill time (min) | 18 ± 5 | 19 ± 5 | 19 ± 5 | 19 ± 5 | 18 ± 5 |
| Glucose level (mmol/l) | 5.4 ± 0.5 | 5.4 ± 0.5 | 5.4 ± 0.5 | 5.5 ± 0.5 | 5.6 ± 0.5 |
| BMI (kg/m ²) | 26 ± 4 | 26 ± 3 | 26 ± 3 | 26 ± 3 | 27 ± 3 |
| Waist circumference (cm) | 91 ± 19 | 90 ± 16 | 90 ± 16 | 90 ± 17.4 | 91.0 ± 19.4 |
| Total cholesterol (mmol/l) | 5.4 ± 1.0 | 5.4 ± 1.4 | 5.4 ± 0.9 | 5.5 ± 1.0 | 5.7 ± 1.0 |
| HDL cholesterol (mmol/l) | 1.1 ± 0.3 | 1.1 ± 0.3 | 1.2 ± 0.3 | 1.3 ± 0.3 | 1.3 ± 0.3 |
| Triglyceride (mmol/l) | 1.5 ± 1.1 | 1.4 ± 1.0 | 1.4 ± 1.1 | 1.5 ± 1.1 | 1.6 ± 1.1 |
| Blood pressure (mmHg) | | | | | |
| Diastolic | 80 ± 10 | 79 ± 9 | 80 ± 9 | 81 ± 17 | 91 ± 19 |
| Systolic | 119 ± 13 | 119 ± 13 | 120 ± 13 | 121 ± 13 | 122 ± 13 |
| Current smoking (%) | 8.3 | 14 | 18 | 19 | 28 |
| Parental diabetes (%) | 28 | 26 | 29 | 25 | 23 |

Data are n, means ± SD, or %. For waist circumference, n = 5,759. For HDL cholesterol, n = 6,535. All tests for homogeneity of variance across drinking groups were significant except for waist circumference.

We defined type 2 diabetes according to fasting plasma glucose criteria of the American Diabetes Association (16): fasting plasma glucose ≥ 126 mg/dl (7.0 mmol/l). Subjects who did not meet this criterion but who gave a history of diabetes and reported current therapy with insulin also were considered to have diabetes. Patients with diabetes at baseline by any of these criteria were excluded from the present study. We also used these same criteria to determine diabetes incidence at the follow-up examination. No oral glucose tolerance test (OGTT) was available in the study.

The question to obtain information on current alcohol intake was: "How many 12-ounce drinks of beer, 3-ounce drinks of wine (5-ounce drinks of wine in the more recent data), and/or 1.5-ounce drinks of hard liquor do you consume per week?" The alcohol content was estimated as 1.1 g for 1 ounce of beer, 2.7 g for 1 ounce of wine, and 15.1 g for 1 ounce of liquor. Some investigators report a good association between data on alcohol intake from general questionnaires and from dietary records (9). In our data, self-reported alcohol intake at the first examination was significantly associated with intake at the last examination ($r = 0.56$, $P < 0.0001$) even after an average 6-year interval.

Serum samples were analyzed by automated techniques in a laboratory that participates in the Centers for Disease Control and Prevention Lipid Standardiza-

tion Program. Serum total cholesterol and serum triglyceride concentrations were measured using a Technicon Autoanalyzer (Technicon, Tarrytown, NY). Serum HDL cholesterol concentration was measured using an RA 1000 analyzer (Technicon) after VLDL and LDL cholesterol were precipitated with sodium phosphotungstate in the presence of magnesium chloride. Blood pressure was measured by auscultatory methods with a mercury sphygmomanometer. Height and weight were measured on a standard physician's scale and stadiometer, and BMI was calculated as weight (in kilograms) divided by height (in meters) squared. Waist circumference was measured at the umbilicus level to the nearest 0.5 cm on a subset (n = 5,759) of the study group.

Data were analyzed using SAS statistical programs (17). We calculated incidence rates of diabetes by dividing the number of incident cases occurring during the study period by the number of person-years of observation over the same period. The study period was defined as the interval between the baseline and last follow-up examinations. Logistic regression models were used to estimate the association between incidence of diabetes and predictor variables (18). All P values provided are for two-sided tests. P values < 0.05 were considered statistically significant. Since this is a prospective study and only a small number of nondiabetic men became diabetic, the odds ratios should be similar to the rel-

ative risks. Therefore, population attributable risk was calculated as $p(RR - 1)/(p[RR - 1] + 1)$ where p = the proportion of persons having a given risk factor and $RR =$ relative risk \approx odds ratio (19).

RESULTS— The average alcohol intake at baseline was 175.3 g/week with the median 90.3 g/week. Men who drank alcohol were assigned to quartiles of intake based on grams per week. Although tests for differences in baseline characteristics across drinking groups were significant except for waist circumference, only systolic blood pressure, HDL cholesterol, and current cigarette smoking showed a linear trend related to alcohol intake (Table 1).

During an average 6 years (± 4.8 SD) of follow-up, 149 subjects developed type 2 diabetes. We first examined the alcohol-diabetes association by a continuous variable of alcohol dose with the outcome of type 2 diabetes. Each 100 g/week of alcohol intake (~ 8 drinks) was associated with a 10% higher incidence of type 2 diabetes (95% CI 2–24%, $P = 0.02$), even after adjustment for history of parental diabetes, age, BMI, fitness level, blood pressure, HDL cholesterol, serum triglyceride concentration, and smoking status. We next examined incidence of diabetes by categories of alcohol intake. The categories were nondrinkers and four quartiles of baseline alcohol intake (Q1: 1–61.8 g, [~ 0.1 –5 drinks], Q2: 61.9–122.7 g [5–10 drinks], Q3: 122.8–276.6 g [10–22 drinks],

Table 2—Incidence of type 2 diabetes by alcohol intake level

| Characteristics | Nondrinkers | Alcohol intake (g/week) | | | |
|------------------------------|---------------|-------------------------|-----------------|------------------|---------------|
| | | Q1 (1–61.8) | Q2 (61.9–122.7) | Q3 (122.8–276.6) | Q4 (>276.6) |
| Person-years of follow-up | 11,327 | 9,624 | 10,330 | 10,355 | 10,951 |
| Incidence of diabetes | 36 | 21 | 16 | 35 | 41 |
| Incidence/1,000 person-years | 3.2 | 2.2 | 1.5 | 3.4 | 3.7 |
| Odds ratio (95% CI) | 1.8 (1.0–3.3) | 1.4 (0.7–2.6) | 1.0 (—) | 2.2 (1.2–3.9) | 2.4 (1.4–4.4) |
| P value for the odds ratio | 0.046 | 0.34 | — | 0.011 | 0.003 |

Q2 is the reference group. Odds ratios are adjusted for age, parental diabetes, and years of follow-up.

and Q4: >276.6 g [≥ 22 drinks]). There were 174 former drinkers. Incidence rates of type 2 diabetes were similar between former drinkers and never-drinkers (3.0 vs. 3.2 per 1,000 person-years), and we therefore classified both as nondrinkers for our analyses.

Table 2 shows the person-years of follow-up, number of incident cases of diabetes, incidence per 1,000 person-years, and the odds of developing type 2 diabetes according to levels of alcohol consumption. There was a U-shaped association between alcohol intake and diabetes, with the lowest incidence of diabetes at Q2. After adjustment for age, follow-up years, and a history of parental diabetes, compared with Q2, those in Q3 and Q4 had a 2.2- and 2.4-fold risk of developing type 2 diabetes, and nondrinkers had a 1.8-fold risk of developing diabetes. Diabetes rates for men in Q1 and Q2 were not significantly statistically different.

We next evaluated the possible effects of several other potentially confounding variables on the alcohol and diabetes relationship. Baseline cardiorespiratory fitness level, high blood pressure, HDL cholesterol, serum triglyceride concentration, current smoking status, fasting plasma glucose, and waist circumference were entered into the model one by one. However, these adjustments had little effect on the association between baseline alcohol intake and diabetes incidence. When rates were adjusted simultaneously for all potential confounding variables, the association between alcohol intake and diabetes showed little change: compared with Q2, those in Q3 and Q4 had a 2.2-fold (95% CI 1.2–3.9) and a 2.3-fold (95% CI 1.3–4.3) risk of developing type 2 diabetes, and nondrinkers had a 1.8-fold (1.0–3.3) risk of developing diabetes.

We calculated population attributable risks of alcohol intake for type 2 diabetes by multivariable-adjusted odds ratios. We

combined the light (Q1) and moderate (Q2) alcohol intake categories to form a reference group, and designated nondrinkers, Q3, and Q4 as high-risk groups. As compared with Q1 and Q2, nondrinkers had a 1.5-fold higher risk (95% CI 1.0–2.5) of developing diabetes, and a change from nondrinking to light-to-moderate drinking might have reduced incident diabetes in the population by 10% (95% CI 0–24%). Those in Q3 and Q4 had a 1.8-fold higher risk of developing diabetes (95% CI 1.2–2.8). Reducing alcohol intake in the high alcohol intake group to light-to-moderate alcohol intake might have reduced the incidence of diabetes by 24% (95% CI 7–41%) in this population.

We also used the World Health Organization criterion of fasting plasma glucose ≥ 140 mg/dl (7.8 mmol/l) to define the diabetes cases. There were 95 incident cases by this definition, and the U-shaped association between alcohol intake and diabetes also was present. As compared with Q1 and Q2, nondrinkers had a 2.3-fold higher risk (95% CI 1.3–4.0), and men in Q3 and Q4 had a 2.0-fold (1.2–3.3) higher risk of developing diabetes.

CONCLUSIONS — We found that a high alcohol intake was associated with an approximately twofold increase in risk of type 2 diabetes when compared with moderate intake. This observation differs from findings in studies with self-reported diabetes as the outcome (8,9), but was consistent with findings from two previous small prospective studies with plasma glucose measurement (6,7). Another 5-year prospective study found no linear association between alcohol and diabetes in a small group of 285 men with 15 incident cases. This study probably had insufficient statistical power to detect an association (20). Clearly, the large size and objective outcomes used in the present study are strengths in contrast to smaller studies or

those using self-reported diabetes. In the Paris Prospective Study, where plasma glucose also was measured, persons with diabetes had a higher risk of death by cirrhosis, which was highly associated with alcohol consumption (21).

We also found that nondrinkers had a higher incidence of type 2 diabetes than men consuming a moderate amount of alcohol. Perhaps because of the small sample size, the two previous studies with plasma glucose measurements did not report this association (6,7). Actually, the association between alcohol intake and diabetes appears U-shaped, but did not achieve statistical significance when nondrinkers were compared with moderate drinkers in one of the previous studies (7). Another study used the continuous variable of alcohol intake only (6).

It is possible that men abstaining from alcohol were ill or recovering alcoholics (8), and this could affect our results. We cannot evaluate this hypothesis fully with our data; however, the risk of type 2 diabetes was similar between ex-drinkers and never-drinkers in our study.

The finding that high alcohol intake is associated with high risk of type 2 diabetes and mild-to-moderate alcohol intake is associated with lower risk is biologically plausible. It has been reported previously that large amounts of alcohol decrease insulin-mediated glucose uptake and that alcoholics have decreased glucose tolerance (22). This finding may be due to the toxic effect of alcohol acting directly on pancreatic islet cells, or to inhibition of insulin secretion and increase in insulin resistance (22–24). Ethanol, 2,3-butanediol and 1,2-propanediol, the metabolites of ethanol, are potent inhibitors of basal and insulin-stimulated adipocyte metabolism in vitro (25). This effect may be relevant to the pathogenesis of a high incidence of type 2 diabetes in heavy drinkers. On the other hand, light-to-moderate alcohol intake may be associ-

ated with enhanced insulin sensitivity (26). Moderate alcohol intake may improve the glucose response to ingested carbohydrate. An inverse U-shaped relation between alcohol intake and insulin sensitivity was observed in the Insulin Resistance and Atherosclerosis Study (27).

A limitation of our study is that we do not have data from an OGTT. However, it is well known that nearly all persons with fasting plasma glucose >140 mg/dl (7.8 mmol/l) have 2-h glucose concentrations >200 mg/dl (11.1 mmol/l) (1,16,28). When we used fasting plasma >140 mg/dl as the cutpoint for diabetes, the association between alcohol intake and diabetes was similar to the analyses where we used the American Diabetes Association cutpoint of ≥ 126 mg/dl (7.0 mmol/l). Therefore, our results are not attributable to identifying patients with 126–139 mg/dl as diabetic.

As with previous studies on alcohol and diabetes (6–9), we estimated alcohol intake from a questionnaire of self-reported drinking habits. Although this approach may lead to misclassification because of inaccurate recall or reluctance to report the true amount of alcohol consumed, we are unaware of any validated methods of assessing alcohol intake in population-based studies that do not rely on self-report. It would be virtually impossible to obtain objective data on alcohol intake in a free-living population. Although alcohol intake was self-reported, it was indirectly validated in our cohort by a significant positive correlation with HDL cholesterol, diastolic blood pressure, and systolic blood pressure. We also found moderate reproducibility of self-reported alcohol intake in our men, even over an average 6-year interval between examinations. In addition, average doses of alcohol intake in subjects in the present study were similar to the general population (29). Data on alcohol intake in this study were collected before the development of type 2 diabetes, precluding the possibility of recall bias (30). Our study population is well educated and comes to the Cooper Clinic for medical examinations and health advice. Results from this population for conventional risk factors of cardiovascular disease and diabetes are consistent with those from other populations (12,31–36). Our study participants are all men, >97% are white, and most have professional occupations. The homogeneity of socioeconomic status in our cohort

may be considered an advantage because this limits potential confounding on this variable. But whether our results also apply to women, other socioeconomic groups, or members of minority groups remains to be determined. Additional observational human studies and animal data are needed to confirm these findings.

In conclusion, our data suggest that a proportion of type 2 diabetes might be attributable to alcohol consumption habits. Of our subjects, 40% were in the Q3 and Q4 alcohol intake (≥ 10 drinks/week) groups, and these men had a 1.8-fold higher risk for developing diabetes. We calculated that 24% of the incident cases of diabetes in this population might be attributable to high alcohol intake. Those men might have been able to reduce their risk of developing type 2 diabetes if they drank less.

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