A Cross-Sectional Study of Alcohol Consumption Patterns and Biologic Markers of Glycemic Control Among 459 Women

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OBJECTIVE — Little research has explored associations of drinking patterns with glycemic control, especially among women. Our objective was to determine the relationship of patterns of alcohol consumption—including average daily consumption, weekly frequency of consumption, drinking with meals, and beverage type—with biologic markers of insulin resistance in young women.

RESEARCH DESIGN AND METHODS — This study was cross-sectional in design. The subjects consisted of a stratified random subpopulation of 459 U.S. normal-weight and overweight female nurses, 33–50 years of age, drawn from the Nurses' Health Study II and sampled for distinct drinking patterns. Women provided blood samples and detailed information on dietary and lifestyle factors between 1995 and 1999. The main outcome measures were fasting insulin, C-peptide, and HbA_{1c}.

RESULTS — Adjusting for age, smoking, physical activity, television watching, BMI, and several dietary factors, average alcohol intake was inversely associated with HbA_{1c} (units in percentage of HbA_{1c}): 0 g/day (reference = 5.36%), 0.1 to <5.0 g/day (−0.04%), 5.0 to <15.0 g/day (−0.09%), 15.0 to <25.0 g/day (−0.10%), and ≥25.0 g/day (−0.17%) (*P* value, test for trend <0.001). We found an inverse association of alcohol intake and insulin, but only for women with a BMI ≥25 kg/m^2. Specifically, insulin levels were lowest for episodic drinkers consuming ≥2 drinks per day on 0–3 days per week. Consumption with meals and type of alcoholic beverage did not further influence these results.

CONCLUSIONS — Moderate alcohol consumption of 1–2 drinks per day on a few to several days of the week may have a beneficial glycemic effect, particularly among overweight women.

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Abbreviations: NHS2, Nurses' Health Study II.

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

Moderate alcohol consumption has been inversely associated with type 2 diabetes in several studies (1–5), with potentially direct and indirect effects on insulin secretion and insulin resistance (6–10). In particular, drinking patterns characterized by frequent, moderate consumption may lower the risk of type 2 diabetes and related biologic markers of glycemic control and insulin resistance (1,9,10), and, conversely, heavy episodic consumption may have opposite effects (11,12). Meyer et al. (13) found an inverse association between frequency of alcohol consumption and fasting C-peptide levels and a suggestion of an inverse association with fasting insulin concentrations in a cross-sectional study of middle-aged and older men in the Health Professionals' Follow-up Study. Davies et al. (9) found that moderate alcohol consumption reduced fasting insulin concentration and improved insulin sensitivity in a randomized controlled trial of 63 postmenopausal women. In this study, we explored similar relationships in a cross-sectional study of 459 premenopausal women, ages 33–50 years, in the Nurses' Health Study II (NHS2).

RESEARCH DESIGN AND METHODS

Subjects

NHS2 is a large prospective cohort study of 116,671 U.S. female nurses, 25–42 years of age at baseline in 1989. At baseline and during biennial follow-up periods, participants provided detailed lifestyle and medical history information through a mailed questionnaire. All women in the study were also asked to provide a venous blood sample; 29,613 study participants did so between 1996 and 1998.

For this analysis, we used blood samples provided by women who were premenopausal, were not taking exogenous hormones, were neither pregnant nor

breast-feeding in 1995 or 1997, and had responded to the questionnaire in the blood kit. Blood samples were collected during the luteal phase of the menstrual cycle. To study associations in a healthy population, women with preexisting cardiovascular disease (nongestational diabetes, coronary artery bypass graft, angioplasty, myocardial infarction, angina, stroke, or transient ischemic attack) (n = 397), cancer (excluding nonmelanoma skin cancer) (n = 88), cholesystectomy (n = 656), ulcers (n = 457), and other serious illness (n = 63) were excluded. After further excluding hemolyzed or lipemic blood samples (n = 351), duplicate blood donations (n = 216), nonfasting samples, or missing fasting data (n = 4,470), a stratified random sample of the remaining 7,390 women was drawn and blood insulin analyses were performed.

When drawing the sample, certain drinking patterns were oversampled to ensure sufficient variation. Sample participants were characterized as abstainers (n = 75), light drinkers (<0.5 drinks/day) who generally do not drink with meals (<25% with meals) (n = 25), light drinkers whose alcohol consumption occurs with meals approximately half of the time (25–75% with meals) (n = 25), light drinkers who generally drink with meals (>75% with meals) (n = 24), moderate drinkers (<1 drink/day 5–7 days/week) (n = 140), episodic drinkers (>2 drinks/day 1–3 days/week) (n = 73), and heavier drinkers (>1 drink/day) including sampling among heavy drinkers by percent with meals (n = 103 or three groups of 34 or 35 as described above). Of the 475 women sampled, we excluded those with missing outcome data (n = 6) or covariate data (n = 5) and insulin concentrations ≥40 μU/ml (n = 3). A total of 459 nurses were included in the dataset.

Data collection

Alcohol consumption, including light beer, regular beer, white wine, red wine, and liquor, as well as frequency of consumption were assessed in 1995 as part of a semiquantitative food frequency questionnaire. Percent of alcohol consumed with meals was assessed in 1997.

Participants were asked how often on average they consumed one glass, bottle, or can of beer (or light beer); 4 oz of red (or white) wine; or one drink or shot of liquor in the past year. Intake of each beverage type was reported as one of nine categories ranging from never or less than monthly to six or more per day. Consumption of each beverage type was multiplied by the ethanol content (one can, bottle, or glass of beer = 12.8 g; one can, bottle, or glass of light beer = 11.3 g; one glass of white or red wine = 11.0 g; one glass of liquor = 14.0 g) (14) to provide grams of alcohol per day for that beverage. Beverage-specific intake was then summed to give total average grams of alcohol per day.

Participants were also asked, "In a typical week during the past year, on how many days did you consume an alcoholic beverage of any type?" Responses varied from 0 to 7 days per week. On the 1997 questionnaire, participants also recorded the percentage of beer, wine, and liquor consumed with meals, with choices of <25%, 25–50%, 50–75%, and >75%.

We assessed data on covariates (age, physical activity, BMI, and smoking) from the 1997 follow-up questionnaire, which was closest in time to the blood draws. Missing covariate values were replaced with values from the most recent available questionnaire (<2% for any covariate). Included in the blood kit was an additional questionnaire that queried the date and time of the blood draw as well as the time since the last meal.

Biologic markers of glycemic control included fasting insulin, C-peptide (an indicator of insulin secretion), and HbA_{1c}. Data collection of blood samples began in 1996 and continued through 1999. Blood samples were collected in three 10-ml sodium heparin blood tubes and returned to the laboratory, via overnight courier, on ice packs stored in Styrofoam containers. Over 95% of the samples arrived within 24 h of being drawn. Samples were centrifuged, aliquoted, and stored in the vapor phase of nitrogen freezers (−130°C or colder) until analyses were performed. The 3.4% that were moderately hemolyzed, lipemic, or not cool upon arrival were not included in our sample for this analysis.

Using packed red cells, HbA_{1c} was measured by a method based on turbidimetric immunoinhibition. Day-to-day variability reported from the lab was 1.9 and 3.0% at HbA_{1c} values of 5.5 and 9.1 g/dl, respectively. Plasma insulin and C-peptide were measured by radioimmunoassay using a commercial kit that limits cross-reactivity from proinsulin to <0.2% for insulin and <4% for C-peptide. The assay had inter- and intra-assay reproducibility of <10% over a wide range of C-peptide concentrations and a coefficient of variation from 2.9 to 6.0% at insulin concentrations varying from 8 to 54 units/ml.

Statistical analysis

We characterized the amount of total alcohol consumption using five categories: 0, 0.1 to <5.0, 5.0 to <15.0, 15.0 to <25, and ≥25 g/day, corresponding to 0, 0.5, 1, 2, and >2 drinks per day. Type of alcohol (beer, wine, or liquor) was also analyzed. Because of limited consumption of any particular type of alcohol, categories used were 0, 0.1 to <10, and ≥10 g/day for beer and wine, and 0, 0.1 to <5, and ≥5 g/day for liquor. Frequency of consumption was categorized as 0, 1–3, 4–5, or 6–7 days/week.

Using linear regression, we regressed potential confounding variables against categories of alcohol intake, adjusted for age (continuous), and estimated the P value for trend (Table 1). For remaining analyses, the robust variance was used to allow for valid inference, even when the regression residuals were not normally distributed (15).

We explored associations by type of alcohol, adjusting simultaneously for each. To differentiate the effects of regular versus episodic drinking, we concurrently evaluated the effects of frequency and quantity of consumption. We also created an additional variable—"grams per drinking day" (average amount divided by the average reported number of days per week)—to assess the association of amount of alcohol consumed independent of intake frequency. Finally, we evaluated drinking patterns based on both amount and frequency. Women were categorized as nondrinkers, moderate occasional drinkers (<25.0 g/day on 0–3 days per week), episodic drinkers (≥25.0 g/day on 0–3 days per week), moderate daily drinkers (<25.0 g/day on 4–7 days per week), and heavy daily drinkers (≥25.0 g/day on 4–7 days per week). We used the F value from the tests of fixed effects to evaluate overall differences between groups.

Because alcohol consumed with food may be absorbed more slowly and may have different glycemic effects than when consumed at other times, we also explored associations by percent alcohol

Table 1—*Selected diet and lifestyle characteristics across categories of average alcohol consumption in grams per day among 459 subjects*

	Categories of alcohol (g/day)					
	Abstainers	0.1 to <5.0	5.0 to <15.0	15.0 to <25.0	≥25.0	*P*, test for trend
n	72	62	219	64	42	—
Median (g/day)	0	1.6	11.0	17.1	30.6	—
Age in 1997 (years)	42	42	43	42	42	0.77
BMI (kg/m^2)	25.1	24.7	23.5	24.7	24.2	0.32
Biological markers						
HDL (mg/dl)	60.8	62.7	70.3	67.5	77.2	<0.01
Insulin (μU/ml)	12.1	11.0	10.8	11.1	11.7	0.76
C-peptide (ng/ml)	2.02	1.92	1.84	2.04	1.88	0.66
HbA_{1c} (%)	5.30	5.27	5.23	5.23	5.15	<0.01
Family history of diabetes (%)	18.0	14.5	10.6	10.8	21.4	0.83
Exercise (MET/wk)	17.3	19.9	26.0	23.2	26.5	0.07
Current smokers (%)	2.6	4.8	5.7	13.7	16.5	<0.01
Watch TV ≥3 h per day (%)	2.5	9.7	5.3	0.5	16.5	0.07
Dietary variables*						
Calories/day (with alcohol)	1,744	1,840	1,825	2,006	1,972	<0.01
Calories/day (excluding alcohol)	1,744	1,826	1,748	1,881	1,724	0.94
Saturated fat (% kcal)	12.0	10.6	10.6	10.1	10.3	0.05
Transaturated fat (% kcal)	1.6	1.5	1.4	1.3	1.4	0.04
Animal protein (% kcal)	14.3	13.8	13.2	13.6	14.1	0.78
Vegetable protein (% kcal)	5.4	5.6	5.9	5.6	5.7	0.22
Glycemic load (units/day)	129	127	119	115	99	<0.01
Type of alcohol consumption						
Beer (g/day)	0	0.5	3.3	6.7	9.3	<0.01
Wine (g/day)	0	1.2	6.4	7.8	20.2	<0.01
Red wine (g/day)	0	0.3	2.5	3.2	6.3	<0.01
White wine (g/day)	0	0.8	3.8	4.7	13.8	<0.01
Liquor (g/day)	0	0.4	1.3	3.2	6.0	<0.01
Drinks per drinking day	0	1.0	2.3	3.1	4.0	<0.01
Days/week alcohol consumed	0	0.6	4.9	4.0	5.6	<0.01
Percent alcohol with meals (% of *n* in each alcohol category)						
<25% with meals (125)	†	8.3	39.9	44.8	35.9	0.07‡
25 to <50% with meals (62)	†	29.2	17.8	19.0	18.0	
50 to 75% with meals (47)	†	8.3	13.0	17.2	20.5	
>75% with meals (95)	†	54.2	29.3	19.0	25.6	
Days per week alcohol consumed (% of *N* in each alcohol category)						
Drink 0 days/week (143)	100	82.3	5.0	9.4	7.1	<0.01‡
Drink 1–3 days/week (89)	0	17.7	17.8	51.5	14.3	
Drink 4–7 days/week (227)	0	0	77.2	39.1	78.6	

All variables are age-standardized. $N = 459$ except where indicated. *All nutrients represented as percent of kilocalories minus kilocalories from alcohol. Glycemic load reflects the extent to which diet raises blood glucose levels. †No one from the category indicated was represented in the abstainers. ‡*P* value Mantel-Haenszel χ^2 test, not for trend. MET, metabolic equivalent.

consumed with meals, eliminating abstainers from the analysis.

Initial analyses were adjusted for continuous age and BMI. Continuous covariates were mean-centered. Multiple regression analyses were adjusted for age, BMI, and diet and lifestyle characteristics noted in Tables 2 and 3. All nutrients were adjusted for energy intake using the residual method (16). Further adjustment for polyunsaturated fat, fiber, magnesium, and potassium had no effect on results (data not shown).

Stratified and sensitivity analyses

To address differences of alcohol within populations (17–23), we conducted separate analyses for overweight (BMI ≥25 kg/m^2) and normal-weight (BMI <25 kg/m^2) women and among women consuming alcohol <50 vs. ≥50% of the time with meals, with nondrinkers as the reference group.

Because the drinking habits of "episodic drinkers" may not represent the drinking patterns of women from the NHS2 in general, we conducted an analysis excluding this group. Additionally, because nondrinkers might be a heterogeneous group comprising both never-

Table 2—*Absolute differences in biomarker levels associated with different levels of alcohol intake in grams per drinking day among 459 young and middle-aged women*

	Average grams of alcohol consumed per drinking day [range (*n*)]				
	0 (72) (reference†)	0.1 to <15.0 (144)	15.0 to <35.0 (133)	≥35.0 (110)	
		Absolute difference compared with reference (95% CI)			*P**
Age- and BMI-adjusted					
Insulin (μU/ml)	11.69	0.05 (−1.69 to 1.78)	−1.11 (−2.71 to 0.50)	−0.91 (−2.65 to 0.83)	0.12
C-peptide (ng/ml)	1.92	0.01 (−0.20 to 0.22)	0.02 (−0.18 to 0.22)	−0.08 (−0.29 to 0.14)	0.46
HbA_{1c} (%)	5.29	−0.04 (−0.09 to 0.01)	−0.10 (−0.14 to −0.05)	−0.06 (−0.11 to 0.00)	0.03
Multivariate-adjusted‡					
Insulin (μU/ml)	11.75	0.09 (−1.56 to 1.74)	−1.17 (−2.78 to 0.45)	−1.19 (−2.94 to 0.56)	0.05
C-peptide (ng/ml)	1.69	0.07 (−0.14 to 0.28)	0.08 (−0.13 to 0.29)	−0.04 (−0.26 to 0.18)	0.46
HbA_{1c} (%)	5.29	−0.05 (−0.10 to 0.00)	−0.11 (−0.17 to −0.05)	−0.06 (−0.12 to −0.01)	0.05
Multivariate-adjusted‡					
BMI <25 kg/m^2					
n	44	110	91	68	
Insulin (μU/ml)	7.93	2.20 (0.33 to 4.06)	0.88 (−1.16 to 2.93)	0.79 (−1.40 to 2.97)	0.88
C-peptide (ng/ml)	1.55	0.09 (−0.09 to 0.28)	0.02 (−0.18 to 0.23)	−0.06 (−0.34 to 0.21)	0.27
HbA_{1c} (%)	5.21	−0.03 (−0.10 to 0.04)	−0.07 (−0.14 to 0.00)	−0.04 (−0.11 to 0.02)	0.10
BMI ≥25 kg/m^2					
n	28	34	42	42	
Insulin (μU/ml)	17.68	−3.89§ (−6.88 to −0.89)	−4.32 (−7.80 to −0.83)	−5.12 (−8.06 to −2.17)	0.01
C-peptide (ng/ml)	1.88	0.04 (−0.46 to 0.54)	0.22 (−0.32 to 0.75)	−0.01 (−0.38 to 0.35)	0.94
HbA_{1c} (%)	5.45	−0.07 (−0.17 to 0.03)	−0.16 (−0.28 to −0.05)	−0.09 (−0.17 to −0.02)	0.07

*Test for trend. †0 g/drinking day is the reference group. Values presented are reference group means (i.e., intercepts from models). ‡Multivariate models adjusted for age (continuous, mean-centered), BMI (continuous, mean-centered), family history of diabetes (yes/no), physical activity (quintiles, metabolic equivalents/week), hours per week watching television (0–5 h, 6–10 h [ref], 11–20 h, 21–90 h), current smoking (%), daily caloric intake (kcal, continuous, mean-centered, excluding calories from alcohol), saturated fat, transaturated fat, animal protein, vegetable protein (quintiles, % kcal), and glycemic load (quintiles). §$P = 0.02$, interaction between alcohol and BMI.

drinkers and those who quit for health reasons, we conducted subanalyses, excluding nondrinkers. Finally, we conducted analyses excluding those with a family history of diabetes or those who were hypertensive.

We also examined the possibly nonlinear relationship between alcohol intake and fasting insulin, nonparametrically, with restricted cubic splines (24). Tests for nonlinearity used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms.

Finally, we checked for influential points using the method by Belsley et al. (25) and reevaluated models excluding any influential points.

RESULTS — Mean insulin, HbA_{1c}, and C-peptide were 11.2 μU/ml, 5.2%, and 1.9 ng/ml, respectively. Mean levels were slightly lower for normal-weight women than for overweight women. Adjusted for age only, insulin and C-peptide varied in a U-shaped pattern with average alcohol intake, and HbA_{1c} declined with each increasing category of intake (Table 1).

Women who averaged 0.1–4.9 g (~0.5 drinks) of alcohol per day usually drank <1 day per week. Women in the upper three categories consumed, on average, ~1, 1.5, and 3 drinks per day. Those consuming 1 drink per day consumed alcohol nearly every day of the week. Those consuming 1.5 drinks consumed alcohol on about half the days in a week, suggesting 2–3 drinks per drinking day. Women who consumed ≥25 g alcohol per day were heavy drinkers, consuming, on average, 3 drinks per day on nearly every day of the week (Table 1).

The alcoholic beverage of choice was wine, particularly white wine, comprising two-thirds of wine consumption. In general, despite oversampling extreme drinking patterns, women drank little liquor. Overall, mean consumption of liquor, beer, and wine was 1.66, 3.42, and 7.36 g/day (1:2:4 ratio), and median daily consumption was 0, 0.79, and 6.27 g/day, respectively.

Several dietary and lifestyle variables were assessed across categories of average alcohol consumption (Table 1). The percent of current smokers increased across categories of alcohol intake. Levels of physical activity were lowest and BMIs were highest among abstainers, but women in the highest category of alcohol consumption were more likely than other women to report watching ≥3 h of television per day. BMI, animal protein, insulin, and C-peptide levels exhibited a U-shaped relationship with categories of alcohol consumption and were lowest among those drinking ~1 drink per day on average or 2 drinks per drinking day.

When adjusted for multiple covariates, but not frequency of consumption, average alcohol intake was inversely associated with HbA_{1c} (units in percentage of HbA_{1c}): 0 g/day (reference = 5.36%), 0.1 to <5.0 g/day (−0.04%), 5.0 to <15.0 g/day (−0.09%), 15.0 to <25.0 g/day (−0.10%), and ≥25.0 g/day (−0.17%) (*P* value, test for trend <0.001). There was a suggestion of a U-shaped relationship in the main effects model with insulin. However, there was no apparent

relationship with C-peptide. Results were similar for analyses adjusted for age and BMI and those analyses adjusted for multiple covariates including frequency of consumption (data not shown). Insulin levels were lowest among women, averaging 0.1–4.9 g alcohol per day or 15.0–24.9 g (~2 drinks) per drinking day.

Frequency of consumption (days/week) was similarly associated with the outcome measures; this was due in part to the high correlation between frequency and amount of alcohol intake ($r = 0.52$). Compared with abstainers, women who consumed alcohol 1–3 days per week had significantly lower insulin levels (−1.58 μU/ml [95% CI −3.13 to −0.04]), and frequency of consumption was inversely associated with HbA_{1c} (*P* value, test for trend <0.001). Upon simultaneous adjustment, frequency of consumption did not appreciably alter the results for average consumption (data not shown), although standard errors were somewhat inflated because of collinearity between the variables.

In evaluating the variable "drinks per drinking day," we found a similar pattern to that found in evaluating amount alone (Table 2). For example, women drinking 15–34.9 g/drinking day had significantly lower HbA_{1c} and modestly lower insulin (but not C-peptide) than abstainers.

In analyses of drinking patterns based on amount and frequency, heavy alcohol consumption on a couple of days per week was associated with the lowest insulin levels, and heavy daily consumption was associated with the lowest HbA_{1c} levels (Table 3).

Consuming alcohol more frequently with meals was not related to HbA_{1c} levels. There was a suggestion of lower insulin levels when alcohol was not consumed with meals. C-peptide levels showed a similar pattern. Compared with women who consumed >75% of alcohol with meals (reference = 1.51 ng/ml), C-peptide was −0.04 ng/ml (95% CI −0.29 to 0.21) for 50–75% of alcohol with meals, −0.19 ng/ml (−0.42 to 0.05) for 25 to <50%, and −0.16 ng/ml (−0.36 to 0.05) for <25% (*P* value, test for trend = 0.09).

Associations of individual beverages with outcomes were generally similar, adjusting simultaneously for other beverage types (data not shown), suggesting that beverage type does not modify the associ-

Table 3—*Absolute differences in biomarker levels associated with different patterns of alcohol intake among 459 young and middle-aged women stratified by BMI*

	Drinking type				
	Nondrinker (*n* = 72) (reference†)	Moderate occasional, <25 g/day on a couple of days/week (*n* = 45)	Episodic drinking, ≥25 g/day on a couple days/week (*n* = 115)	Moderate daily, <25 g/day nearly every day of week (*n* = 184)	Heavy daily, ≥25 g/day nearly every day of week (*n* = 38)	*P*
	Absolute difference compared with reference (95% CI)					
Total sample‡						
Insulin (μU/ml)	11.12	−0.28 (−2.38 to 1.82)	−1.38 (−3.11 to 0.35)	−0.32 (−1.96 to 1.33)	0.02 (−2.30 to 2.34)	0.35
C-peptide (ng/ml)	1.73	0.12 (−0.16 to 0.40)	−0.02 (−0.23 to 0.19)	0.05 (−0.15 to 0.26)	−0.02 (−0.32 to 0.28)	0.80
HbA_{1c} (%)	5.33	−0.04 (−0.10 to 0.02)	−0.07 (−0.13 to −0.02)	−0.09 (−0.14 to −0.03)	−0.16 (−0.25 to −0.07)	<0.01
BMI ≥25 kg/m^2						
n	28	16	42	47	13	
Insulin (μU/ml)	16.37	−4.16 (−7.66 to −0.65)	−5.24 (−8.64 to −1.84)	−4.61 (−7.88 to −1.35)	−2.15 (−5.96 to 1.67)	0.03
C-peptide (ng/ml)	2.01	0.32 (−0.29 to 0.92)	−0.14 (−0.65 to 0.36)	0.11 (−0.40 to 0.62)	0.05 (−0.58 to 0.68)	0.53
HbA_{1c} (%)	5.47	−0.07 (−0.17 to 0.04)	−0.10 (−0.21 to 0.01)	−0.15 (−0.26 to −0.04)	−0.18 (−0.34 to −0.01)	0.09
BMI <25 kg/m^2						
n	44	29	73	142	25	
Insulin (μU/ml)	6.96	1.67 (−0.99 to 4.33)	0.52 (−1.54 to 2.57)	2.00 (0.11 to 3.88)	1.79 (−1.15 to 4.73)	0.14
C-peptide (ng/ml)	1.57	0.06 (−0.17 to 0.30)	−0.02 (−0.21 to 0.18)	0.06 (−0.15 to 0.26)	0.03 (−0.32 to 0.38)	0.89
HbA_{1c} (%)	5.24	−0.01 (−0.09 to 0.07)	−0.06 (−0.13 to 0.01)	−0.06 (−0.12 to 0.01)	−0.13 (−0.23 to −0.03)	0.12

*For overall differences between groups. †0 g/drinking day is the reference group. Values presented are reference group means (i.e., intercepts from models). ‡Multivariate-adjusted models adjusted for age (continuous, mean-centered), BMI (continuous, mean-centered), family history of diabetes (yes/no), physical activity (quintiles, metabolic equivalents/week), hours per week watching television (0–5 h, 6–10 h [ref], 11–20 h, 21–90 h), current smoking (%), daily caloric intake (kcal, continuous, mean-centered, excluding calories from alcohol), saturated fat, transaturated fat, animal protein, vegetable protein (quintiles, % kcal), and glycemic load (quintiles).

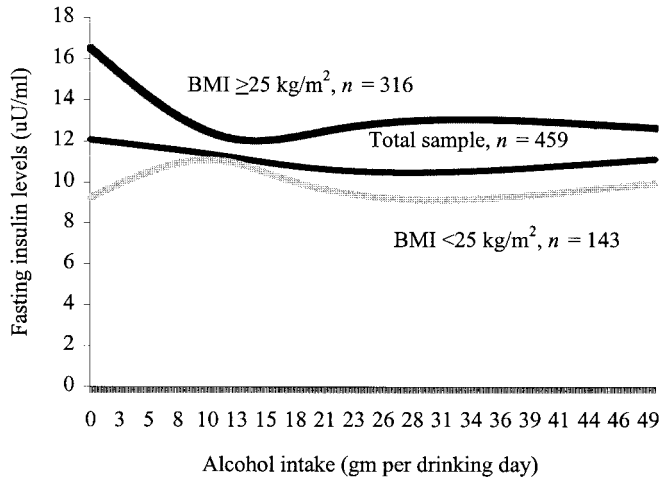

Figure 1—*Fasting insulin levels by alcohol intake in grams consumed per drinking day by category of BMI. Model is adjusted for age, BMI, family history of diabetes, physical activity, hours per week watching television, current smoking, daily caloric intake, saturated fat, transaturated fat, animal protein, vegetable protein, and glycemic load. Significance of test for nonlinear association between alcohol intake and fasting insulin among individuals with BMIs ≥25 kg/m² was* P = *0.04.*

ation between alcohol and markers of glycemic control.

We further examined the associations between alcohol consumption and glycemic control among the 313 normal-weight women (BMI <25 kg/m^2) and the 146 overweight women (BMI ≥25 kg/m^2). Although the amount of alcohol was inversely associated with HbA_{1c} in both normal-weight and overweight women, the association with insulin was statistically significant only among women with BMI ≥25 kg/m^2 (Table 2; *P* value, test for interaction = 0.02). Amount of alcohol was not related to C-peptide in either stratum (Table 2). Compared with overweight women who abstained (insulin = 17.68 μU/ml), overweight women who drank <15 g/drinking day had insulin levels that were 3.89 μU/ml (95% CI, −6.88 to −0.89) lower, those who drank 15–34.9 g/drinking day had insulin levels that were 4.32 μU/ml (−7.80 to −0.83) lower, and those who drank ≥35.0 g/drinking day had insulin levels that were 5.12 μU/ml (−8.06 to −2.17) lower (*P* value, test for trend = 0.01). Despite this apparent linear trend, an analysis using spline curves provided evidence of a nonlinear component. The significance of the test for nonlinear association between alcohol intake and fasting insulin among those with BMI ≥25 kg/m^2 was *P* = 0.04 (Fig. 1).

In other sensitivity analyses, results were unchanged (data not shown). There were no evident influential points. Moreover, removing those observations with the largest differences in βs (standardized difference for each individual coefficient estimate resulting from the omission of the i-th observation) had no appreciable effect on results.

CONCLUSIONS — In this population of young and middle-aged women, we found a modest inverse association between moderate alcohol consumption and several markers of glycemic control. We noted the strongest inverse association for HbA_{1c}, a marker of long-term glycemic control, but also found that moderate drinking was associated with lower levels of fasting insulin, particularly among overweight women. Finally, analyses of beverage choice or consumption with meals did not substantially modify our results.

Previous evidence among women generally supports an inverse association between moderate alcohol consumption and markers of glycemic control (6–8,26) in both cross-sectional (27) and longitudinal (6) studies, with the greatest glycemic benefits appearing at 0.5–2.0 drinks per day. Definitive mechanisms for a possible causal effect are unknown, but proposed mechanisms include suppression of growth factors and increases in insulin binding factors (28,29), alterations in hepatic glucose metabolism with decreased hepatic gluconeogenesis (4,5,30), alterations in the action of counterregulatory hormones (4), increases in HDL levels (31), decreases in C-reactive protein (32,33), and increases in circulating leptin (34), which may decrease appetite for sweets and other carbohydrates (35) with subsequent or independent effects on body weight (36).

In this population of women, we found that both amount and frequency predicted decreases in HbA_{1c} and insulin. Specifically, ≥2 drinks per day on a daily basis were related to the lowest levels of HbA_{1c}, whereas episodic drinking predicted the lowest levels of insulin. This contrasts with the findings of Meyer et al. (13) in men, where only frequency of consumption was important. Differences in results between sexes may be due to chance or to less variability in drinking patterns among the women in this study. Women from the NHS2 drank on average 0.5 drinks vs. 1 drink per day among men in the Health Professionals' Follow-up Study. Hormonal differences or slower first-pass metabolism of alcohol among women (37) could also explain discrepancies in results between sexes. Further research into patterns of consumption among postmenopausal women may help to further disentangle these alternative hypotheses.

In our analyses, the inverse association between alcohol consumption and insulin was evident only among overweight (BMI ≥25 kg/m^2) and not among normal-weight women. Among overweight women, those who consumed 1–2 drinks on a few to several days per week had the lowest insulin levels but not necessarily the lowest C-peptide levels. This finding suggests that moderate alcohol intake may improve insulin sensitivity, potentially through enhanced binding, rather than through effects on gluconeogenesis or insulin production. The effects of alcohol may be more evident in people with a broader variation in biologic factors normally limited by homeostatic controls.

Differences in glycemic response to alcohol by body weight have some support in the literature (22,38,39). Studies of alcohol and risk of diabetes (2,40,41) or alcohol and coronary heart disease risk among women with type 2 diabetes (42) also show stronger inverse associations among heavier participants.

Although the inverse association for insulin was evident only among over-

weight women, alcohol was strongly inversely related to HbA_{1c} concentrations in all women. Followed mainly in diabetic subjects, HbA_{1c} is a measure of chronic blood glucose control (glycosylation signifies binding of blood hemoglobin with circulating glucose) and has a limited variation among healthy subjects (4.6–6.1% in this study; interquartile range 5.1–5.4). Nevertheless, the consistent inverse relationship of amount of alcohol with HbA_{1c} in this sample lends support to the notion of a general beneficial glycemic effect of regular alcohol intake.

The blood samples were collected over a 2- to 4-year period, making it difficult to adjust adequately for alcohol and covariate data at the exact time of venipuncture. Nevertheless, unadjusted results were very similar to fully adjusted results; therefore, bias from residual confounding by these covariates was unlikely. Our results are based on a cross-sectional analysis, and thus our ability to assess causality is limited. However, it is unlikely that insulin, C-peptide, and HbA_{1c} levels would influence alcohol consumption, as people with preexisting clinical disease were excluded. Oversampling of extreme drinking patterns enabled sufficient variation in most independent variables to detect associations. Further, we used a validated alcohol and dietary assessment tool, which allowed us to evaluate patterns of consumption versus quantity of intake only.

In summary, moderate consumption of 1–2 drinks on a few to several days of the week may have beneficial effects on insulin sensitivity, particularly among overweight women.

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References

1. Conigrave KM, Hu BF, Camargo CA Jr, Stampfer MJ, Willett WC, Rimm EB: A prospective study of drinking patterns in relation to risk of type 2 diabetes among men. *Diabetes* 50:2390–2395, 2001
2. Tsumura K, Hayashi T, Suematsu C, Endo G, Fujii S, Okada K: Daily alcohol consumption and the risk of type 2 diabetes in Japanese men: the Osaka Health Survey. *Diabetes Care* 22:1432–1437, 1999
3. Rimm EB, Chan J, Stampfer MJ, Colditz GA, Willett WC: Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. *BMJ* 310:555–559, 1995
4. Avogaro A, Tiengo A: Alcohol, glucose metabolism and diabetes. *Diabetes Metab Rev* 9:129–146, 1993
5. Avogaro A, Valerio A, Miola M, Crepaldi C, Pavan P, Tiengo A, del Prato S: Ethanol impairs insulin-mediated glucose uptake by an indirect mechanism. *J Clin Endocrinol Metab* 81:2285–2290, 1996
6. Kiechl S, Willeit J, Poewe W, Egger G, Oberhollenzer F, Muggeo M, Bonora E: Insulin sensitivity and regular alcohol consumption: large, prospective, cross sectional population study (Bruneck study). *BMJ* 313:1040–1044, 1996
7. Facchini F, Chen YD, Reaven GM: Light-to-moderate alcohol intake is associated with enhanced insulin sensitivity. *Diabetes Care* 17:115–119, 1994
8. Mayer EJ, Newman B, Quesenberry CP Jr, Friedman GD, Selby JV: Alcohol consumption and insulin concentrations: role of insulin in associations of alcohol intake with high-density lipoprotein cholesterol and triglycerides. *Circulation* 88:2190–2197, 1993
9. Davies MJ, Baer DJ, Judd JT, Brown ED, Campbell WS, Taylor PR: Effects of moderate alcohol intake on fasting insulin and glucose concentrations and insulin sensitivity in postmenopausal women: a randomized controlled trial. *JAMA* 287: 2559–2562, 2002
10. Harding AH, Sargeant LA, Khaw KT, Welch A, Oakes S, Luben RN, Bingham S, Day NE, Wareham NJ: Cross-sectional association between total level and type of alcohol consumption and glycosylated haemoglobin level: the EPIC-Norfolk Study. *Eur J Clin Nutr* 56:882–890, 2002
11. Kao WH, Puddey IB, Boland LL, Watson RL, Brancati FL: Alcohol consumption and the risk of type 2 diabetes mellitus: atherosclerosis risk in communities study. *Am J Epidemiol* 154:748–757, 2001
12. Wei M, Gibbons LW, Mitchell TL, Kampert JB, Blair SN: Alcohol intake and incidence of type 2 diabetes in men. *Diabetes Care* 23:18–22, 2000
13. Meyer KA, Conigrave KM, Chu N-F, Spiegelman D, Stampfer MJ, Rimm EB: Associations between alcohol consumption patterns and HbA1c, c-peptide, and insulin concentrations in men. *JACN*. In press
14. United States Department of Agriculture: *Nutrient Database for Standard Reference, Release 12*. Beltsville, MD, United States Department of Agriculture, 1999
15. White H: Maximum likelihood estimation of misspecified models. *Econometrica* 50: 1–25, 1982
16. Willett W, Howe G, Kushi L: Adjustment for total energy intake in epidemiologic studies. *Am J Clin Nutr* 65:1220S–1228S, 1997
17. Jones AW, Jonsson KA, Kechagias S: Effect of high-fat, high-protein, and high-carbohydrate meals on the pharmacokinetics of a small dose of ethanol. *Br J Clin Pharmacol* 44:521–526, 1997
18. Jones AW, Jonsson KA: Food-induced lowering of blood-ethanol profiles and increased rate of elimination immediately after a meal. *J Forensic Sci* 39:1084–1093, 1994
19. Friedenberg R, Metz R, Mako M, Surmaczynska B: Differential plasma insulin response to glucose and glucagon stimulation following ethanol priming. *Diabetes* 20:397–403, 1971
20. McMonagle J, Felig P: Effects of ethanol ingestion on glucose tolerance and insulin secretion in normal and diabetic subjects. *Metabolism* 24:625–632, 1975
21. Koivisto VA, Tulokas S, Toivonen M, Haapa E, Pelkonen R: Alcohol with a meal has no adverse effects on postprandial glucose homeostasis in diabetic patients. *Diabetes Care* 16:1612–1614, 1993
22. Christiansen C, Thomsen C, Rasmussen O, Glerup H, Berthelsen J, Hansen C, Orskov H, Hermansen K: Acute effects of graded alcohol intake on glucose, insulin and free fatty acid levels in non-insulin-dependent diabetic subjects. *Eur J Clin Nutr* 47:648–652, 1993
23. Knip M, Ekman AC, Ekman M, Leppaluoto J, Vakkuri O: Ethanol induces a paradoxical simultaneous increase in circulating concentrations of insulin-like growth factor binding protein-1 and insulin. *Metabolism* 44:1356–1359, 1995
24. Durrleman S, Simon R: Flexible regression models with cubic splines. *Stat Med* 8:551–561, 1989
25. Belsley D, Kuh E, Welsch R: *Regression Diagnostics*. New York, Wiley, 1980
26. Razay G, Heaton KW: Moderate alcohol consumption has been shown previously to improve insulin sensitivity in men. *BMJ* 314:443–444, 1997
27. Razay G, Heaton KW, Bolton CH, Hughes AO: Alcohol consumption and its relation to cardiovascular risk factors in British women. *BMJ* 304:80–83, 1992
28. Rojdmark S, Rydvald Y, Aquilonius A, Brismar K: Insulin-like growth factor (IGF)-1 and IGF-binding protein-1 concentrations in serum of normal subjects after alcohol ingestion: evidence for decreased IGF-1 bioavailability. *Clin Endocrinol (Oxf)* 52:313–318, 2000
29. de la Monte SM, Ganju N, Tanaka S, Banerjee K, Karl PJ, Brown NV, Wands JR: Differential effects of ethanol on insulin-signaling through the insulin receptor substrate-1. *Alcohol Clin Exp Res* 23:770–777, 1999
30. Siler SQ, Neese RA, Christiansen MP, Hellerstein MK: The inhibition of glu-

coneogenesis following alcohol in humans. *Am J Physiol* 275:E897–E907, 1998
31. van de Wiel A: Alcohol and insulin sensitivity. *Neth J Med* 52:91–94, 1998
32. Albert MA, Glynn RJ, Ridker PM: Alcohol consumption and plasma concentration of C-reactive protein. *Circulation* 107:443–447, 2003
33. Wu T, Dorn JP, Donahue RP, Sempos CT, Trevisan M: Associations of serum C-reactive protein with fasting insulin, glucose, and glycosylated hemoglobin: the Third National Health and Nutrition Examination Survey, 1988–1994. *Am J Epidemiol* 155:65–71, 2002
34. Mantzoros CS, Liolios AD, Tritos NA, Kaklamani VG, Doulgerakis DE, Griveas I, Moses AC, Flier JS: Circulating insulin concentrations, smoking, and alcohol intake are important independent predictors of leptin in young healthy men. *Obes Res* 6:179–186, 1998
35. Colditz GA, Giovannucci E, Rimm EB, Stampfer MJ, Rosner B, Speizer FE, Gordis E, Willett WC: Alcohol intake in relation to diet and obesity in women and men. *Am J Clin Nutr* 54:49–55, 1991
36. McCarty MF: The insulin-sensitizing activity of moderate alcohol consumption may promote leanness in women. *Med Hypotheses* 54:794–797, 2000
37. Lieber CS: Microsomal ethanol-oxidizing system (MEOS): the first 30 years (1968–1998): a review. *Alcohol Clin Exp Res* 23: 991–1007, 1999
38. Flanagan DE, Moore VM, Godsland IF, Cockington RA, Robinson JS, Phillips DI: Alcohol consumption and insulin resistance in young adults. *Eur J Clin Invest* 30:297–301, 2000
39. Nikkila EA, Taskinen MR: Ethanol-induced alterations of glucose tolerance, postglucose hypoglycemia, and insulin secretion in normal, obese, and diabetic subjects. *Diabetes* 24:933–943, 1975
40. Stampfer MJ, Colditz GA, Willett WC, Manson JE, Arky RA, Hennekens CH, Speizer FE: A prospective study of moderate alcohol drinking and risk of diabetes in women. *Am J Epidemiol* 128:549–558, 1988
41. Ajani UA, Hennekens CH, Spelsberg A, Manson JE: Alcohol consumption and risk of type 2 diabetes mellitus among US male physicians. *Arch Intern Med* 160: 1025–1030, 2000
42. Solomon CG, Hu FB, Stampfer MJ, Colditz GA, Speizer FE, Rimm EB, Willett WC, Manson JE: Moderate alcohol consumption and risk of coronary heart disease among women with type 2 diabetes mellitus. *Circulation* 102:494–499, 2000