

# 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<sub>1c</sub>.

**RESULTS** — Adjusting for age, smoking, physical activity, television watching, BMI, and several dietary factors, average alcohol intake was inversely associated with HbA<sub>1c</sub> (units in percentage of HbA<sub>1c</sub>): 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<sup>2</sup>. 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.

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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) ( $n = 88$ ), cholecystectomy ( $n = 656$ ), 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 ( $25\text{--}75\%$  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  $\geq 40$   $\mu\text{U/ml}$  ( $n = 3$ ). 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  $<25\%$ ,  $25\text{--}50\%$ ,  $50\text{--}75\%$ , 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<sub>1c</sub>. 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 ( $-130^\circ\text{C}$  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<sub>1c</sub> 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<sub>1c</sub> 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  $\geq 25$  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  $\geq 10$  g/day for beer and wine, and 0, 0.1 to  $<5$ , and  $\geq 5$  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 ( $\geq 25.0$  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 ( $\geq 25.0$  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)					P, test for trend
	Abstainers	0.1 to <5.0	5.0 to <15.0	15.0 to <25.0	≥25.0	
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 <sup>2</sup> )	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 <sub>1c</sub> (%)	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  $\chi^2$  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<sup>2</sup>) and normal-weight (BMI <25 kg/m<sup>2</sup>) women and among women consum-

ing 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)]				P*
	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)				
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 <sub>1c</sub> (%)	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 <sub>1c</sub> (%)	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 <sup>2</sup>					
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 <sub>1c</sub> (%)	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 <sup>2</sup>					
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 <sub>1c</sub> (%)	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<sub>1c</sub>, 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<sub>1c</sub> 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<sub>1c</sub> (units in percentage of HbA<sub>1c</sub>): 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 ( $-1.58 \mu\text{U/ml}$  [95% CI  $-3.13$  to  $-0.04$ ]), and frequency of consumption was inversely associated with HbA<sub>1c</sub> ( $P$  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<sub>1c</sub> 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<sub>1c</sub> levels (Table 3).

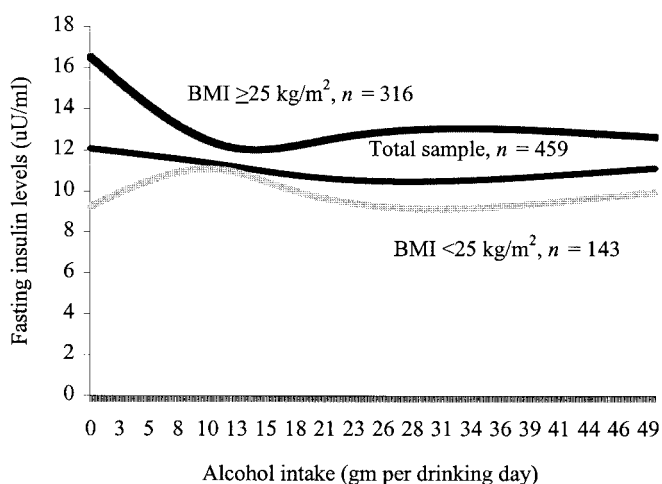
Consuming alcohol more frequently with meals was not related to HbA<sub>1c</sub> levels. There was a suggestion of lower insulin levels when alcohol was not consumed with meals. C-peptide levels showed a similar pattern. Compared with women who consumed  $>75\%$  of alcohol with meals (reference =  $1.51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

Total sample <sup>‡</sup>	Drinking type				P	
	Nondrinker (n = 72) (reference <sup>†</sup> )	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)
Insulin ( $\mu\text{U/ml}$ )	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 <sub>1c</sub> (%)	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 <sup>2</sup>						
n	28	16	42	47	13	
Insulin ( $\mu\text{U/ml}$ )	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 <sub>1c</sub> (%)	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 <sup>2</sup>						
n	44	29	73	142	25	
Insulin ( $\mu\text{U/ml}$ )	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 <sub>1c</sub> (%)	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. <sup>†</sup>0 g/drinking day is the reference group. Values presented are reference group means (i.e., intercepts from models). <sup>‡</sup>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  $\geq 25$   $\text{kg/m}^2$  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 ( $\text{BMI} < 25 \text{ kg/m}^2$ ) and the 146 overweight women ( $\text{BMI} \geq 25 \text{ kg/m}^2$ ). Although the amount of alcohol was inversely associated with  $\text{HbA}_{1c}$  in both normal-weight and overweight women, the association with insulin was statistically significant only among women with  $\text{BMI} \geq 25 \text{ kg/m}^2$  (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 =  $17.68 \mu\text{U/ml}$ ), overweight women who drank  $< 15$  g/drinking day had insulin levels that were  $3.89 \mu\text{U/ml}$  (95% CI,  $-6.88$  to  $-0.89$ ) lower, those who drank  $15$ – $34.9$  g/drinking day had insulin levels that were  $4.32 \mu\text{U/ml}$  ( $-7.80$  to  $-0.83$ ) lower, and those who drank  $\geq 35.0$  g/drinking day had insulin levels that were  $5.12 \mu\text{U/ml}$  ( $-8.06$  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  $\text{BMI} \geq 25 \text{ kg/m}^2$  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  $\beta$ s (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  $\text{HbA}_{1c}$ , 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  $\text{HbA}_{1c}$  and insulin. Specifically,  $\geq 2$  drinks per day on a daily basis were related to the lowest levels of  $\text{HbA}_{1c}$ , 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 ( $\text{BMI} \geq 25 \text{ kg/m}^2$ ) 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<sub>1c</sub> concentrations in all women. Followed mainly in diabetic subjects, HbA<sub>1c</sub> 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<sub>1c</sub> in this sample lends support to the notion of a general beneficial glyce-mic 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<sub>1c</sub> 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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