

Caffeinated Coffee, Decaffeinated Coffee, and Caffeine in Relation to Plasma C-Peptide Levels, a Marker of Insulin Secretion, in U.S. Women

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OBJECTIVE — Coffee consumption is associated with reduced risk of type 2 diabetes, but the mechanism is not clearly understood. Elevated C-peptide, as a marker of insulin secretion, has been linked to insulin-resistant type 2 diabetes. In this study, we examined consumption of caffeinated and decaffeinated coffee and total caffeine in relation to concentrations of plasma C-peptide.

RESEARCH DESIGN AND METHODS — Plasma C-peptide concentrations were measured in a cross-sectional setting among 2,112 healthy women from the Nurses' Health Study I who provided blood samples in 1989–1990. Consumption of caffeinated and decaffeinated coffee and total caffeine was assessed using a semiquantitative food-frequency questionnaire in 1990.

RESULTS — Intakes of caffeinated and decaffeinated coffee and caffeine in 1990 were each inversely associated with C-peptide concentration in age-adjusted, BMI-adjusted, and multivariable-adjusted analyses. In multivariable analysis, concentrations of C-peptide were 16% less in women who drank >4 cups/day of caffeinated or decaffeinated coffee compared with nondrinkers ($P < 0.005$ for each). Women in the highest quintile compared with the lowest quintile of caffeine intake had 10% lower C-peptide levels ($P = 0.02$). We did not find any association between tea and C-peptide. The inverse association between caffeinated coffee and C-peptide was considerably stronger in obese (27% reduction) and overweight women (20% reduction) than in normal weight women (11% reduction) ($P = 0.005$).

CONCLUSIONS — Our findings suggest a potential reduction of insulin secretion by coffee in women. This reduction may be related to other components in coffee rather than caffeine.

Diabetes Care 28:1390–1396, 2005

Coffee intake has been associated with a reduction in the risk of type 2 diabetes (1–4). Because of its widespread consumption, understanding the relationship between coffee intake and insulin secretion may have implications in the prevention and treatment of diabetes.

In contrast, short-term studies have consistently shown that acute administration of caffeine induces insulin resistance and impairs glucose tolerance (3,5,6). Long-term effects of caffeine and other components of coffee, which may be more relevant on insulin secretion, have been

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Received for publication 19 December 2004 and accepted in revised form 18 February 2005.

Abbreviations: SFFQ, semiquantitative food-frequency questionnaire.

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

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less well studied. In a recent cross-sectional study of 936 elderly men without diabetes, coffee was associated with increased insulin sensitivity but not with decreased secretion (7). However, this study did not distinguish between caffeinated and decaffeinated coffee, did not study women, and measured only the early insulin response under glucose stimulation.

C-peptide is cleaved from proinsulin and released into the bloodstream in equivalent amounts with insulin (8). Increased C-peptide has been associated with insulin resistance and diabetes (9), cardiovascular disease (10), and colon cancer (11). According to the National Coffee Association, 54% of adults in the U.S. drank coffee in 2000, with average per capita daily consumption of 1.9 cups for men and 1.4 cups for women (12). We found that C-peptide was positively associated with glycemic load and fructose intake (13). We thus assessed caffeinated coffee, decaffeinated coffee, and total caffeine intake in relation to plasma C-peptide levels cross-sectionally among 2,112 women from the Nurses' Health Study I.

RESEARCH DESIGN AND METHODS

The Nurses' Health Study I, established in 1976, consists of 121,700 female registered nurses 30–55 years of age who completed a mailed questionnaire and provided medical history and lifestyle information at baseline and on subsequent biennial questionnaires. Diet has been assessed approximately every 4 years using a previously validated (14,15) semiquantitative food-frequency questionnaire (SFFQ). Between 1989 and 1990, blood samples were collected as described previously from 32,826 cohort members who were then 43–69 years of age (13,16). A total of 2,112 women were included in this analysis; all were control participants in four nested case-control studies of breast can-

cer, colon cancer, hypertension, and diabetes. None had previously diagnosed cancer, cardiovascular diseases, or diabetes at time of blood draw. We included only those women who had both a measurement of C-peptide and provided a dietary questionnaire in 1990. The institutional review board of the Brigham and Women's Hospital in Boston approved the study.

Dietary assessment

An SFFQ in 1984, 1986, and 1990 assessed average consumption of caffeinated and decaffeinated coffee and tea over the previous year (frequency responses: never, one to three per month, one per week, two to four per week, five to six per week, one per day, two to three per day, four to five per day, and \geq six per day). Using sources on food composition including the U.S. Department of Agriculture, we estimated caffeine content as 137 mg/cup for coffee, 47 mg/cup for tea, and 46 mg/bottle or can for cola beverages. We assessed the total caffeine intake by summing the caffeine content for a specific amount of each item (one cup for coffee or tea, one 12-ounce bottle or can for carbonated beverages, and 1 oz for chocolate) multiplied by a weight proportional to the frequency of its use. Our validation study found a high correlation for intake of coffee and other caffeinated beverages from food-frequency questionnaires and four 1-week diet records (coffee, $r = 0.78$; tea, $r = 0.93$; and caffeinated sodas, $r = 0.85$) (17).

Measurement of nondietary factors

Height, current weight, and smoking history were reported at baseline and weight and smoking status were updated biennially. The correlation coefficient between self-reported weight and weight as measured by trained personnel was 0.96 (18). The reproducibility and validity of the physical activity questionnaire has been described elsewhere (19).

Assay of C-peptide

C-peptide was measured with enzyme-linked immunosorbent assay and radioimmunoassay as described previously (13). Samples were standardized on quality controls. We obtained a coefficient of variation of $<12\%$.

Statistical analysis

We used linear regression models with a robust variance estimate, which allows for valid inference without the assumption of normal distribution in the dependent variable (20). We conducted all statistical analyses with SAS software (Version 8; SAS Institute, Cary, NC). In multivariable models, we adjusted for age, BMI, physical activity, smoking, hours since last meal, laboratory batch, menopausal status, and dietary variables, including total energy, calcium intake, cereal fiber intake, glycemic load, and alcohol consumption. Because alcohol consumption (21) and calcium are inversely associated with C-peptide levels, and cereal fiber and glycemic load are significant predictors of C-peptide (13), we included these variables in our final model. Magnesium and *trans* fatty acids were not statistically significant and did not change the results substantially when controlled for these, so we did not include them in the final model.

We adjusted all micronutrients and glycemic load for total energy intake with the residual method (22,23). The residual method controls for confounding by total energy intake. We regressed the nutrient intake on total energy; the residuals from regression represent the differences between each individual and are not confounded by total energy intake. Because the residual has negative and positive values, a constant (usually a predicted mean intake) was added to convey an actual nutrient intake. Because consumption of caffeinated coffee and decaffeinated coffee was negatively correlated ($r = -0.21$, $P < 0.05$), we included both in the multivariable model.

In our primary analyses, we used the 1990 SFFQ, which assesses intake over the previous year, and the covariates in 1990 in relation to C-peptide level in 1989–1990. Secondary analyses used average intake in 1984, 1986, and 1990 to examine whether intake over a longer period increased predictive accuracy for C-peptide. We averaged the values of continuous covariates and regrouped categorical covariates over this period. Overall results did not change when we excluded the 10% of women who fasted <8 h before blood drawing. We conducted subgroup analysis stratified by BMI, smoking status, physical activity, and alcohol intake. In the model with main effects and the interaction term, we

used the Wald test P value for the interaction term to determine statistical significance for interaction.

RESULTS— Women who consumed more caffeinated coffee were more likely to smoke and to drink alcohol (Table 1). Caffeinated coffee consumption was positively associated with intake of total energy, fat, magnesium, alcohol, and caffeine and inversely associated with BMI, intake of *trans* fatty acids, carbohydrate, cereal fiber, total calcium, and glycemic load (Table 1). The overall pattern for the associations between decaffeinated coffee and covariates were somewhat different from those for caffeinated coffee. However, alcohol intake was inversely associated with consumption of decaffeinated coffee. Women who drank decaffeinated coffee were more likely to have lower intakes of energy and alcohol and caffeine but a higher intake of calcium. Intakes of total fat, *trans* fatty acids, and carbohydrates were not related to consumption of decaffeinated coffee.

In the cross-sectional analysis, after adjustment for age, BMI, fasting hours, and laboratory batch, consumption of both caffeinated coffee and decaffeinated coffee was statistically significantly associated with lower levels of plasma C-peptide (Table 2). The association did not change after further adjustment for other covariates. In the multivariable model, the magnitude of the decrease of C-peptide was similar for decaffeinated coffee or caffeinated coffee. In addition, we observed an inverse association between total caffeine intake and C-peptide in age-adjusted, BMI-adjusted, and multivariable-adjusted analyses (Table 3).

In multivariable models, C-peptide decreased with every additional cup of caffeinated coffee (0.057 ng/ml; $P < 0.0001$) and with every additional cup of decaffeinated coffee (0.063 ng/ml; $P = 0.0003$). For every 100-mg increase of caffeine intake, C-peptide decreased 0.03 ng/ml ($P = 0.02$). We found a statistically significant inverse association between decaffeinated coffee and C-peptide levels among women who drank no caffeinated coffee; the estimates were somewhat stronger than when we included those women. Tea consumption was not significantly associated with C-peptide, with or without adjustment for caffeinated or decaffeinated coffee (Table 2). The coefficient estimates for C-peptide levels of

Table 1—Baseline characteristics according to caffeinated coffee and decaffeinated coffee consumption among women in the Nurses' Health Study I

	Caffeinated coffee consumption in 1990 (cups/day)					Decaffeinated coffee consumption in 1990 (cups/day)				
	0	<1	1	2–3	≥4	0	<1	1	2–3	≥4
Participants (n)	640	290	357	629	196	925	484	284	350	69
Age (not standardized)	58	57	58	57	57	57	57	58	58	58
C-peptide (ng/ml)	2.03	2.02	2.02	1.96	1.71	2.08	1.93	1.86	1.91	1.68
BMI (kg/m ²)	25.9	25.8	25.4	25.6	24.9	25.8	25.5	25.5	25.4	25.2
Current smokers (%)	7.7	8.4	8.7	12.7	25.8	13.3	8.6	6.8	9.6	27.0
Pre-menopausal women (%)	17.1	19.5	16.1	17.9	18.1	17.0	18.8	18.0	15.4	24.2
Physical activity (METs/week)	16.3	18.2	16.8	15.6	16.9	16.3	16.9	16.8	16.1	17.1
Alcohol (g/day)	4.0	5.2	5.2	7.1	6.6	5.8	5.2	5.4	5.5	5.0
Daily dietary intake										
Total energy (kcal)	1,709	1,751	1,775	1,782	1,902	1,755	1,780	1,754	1,779	1,725
From fat (%)	30.5	30.9	30.9	31.6	33.4	31.5	31.1	30.4	31.5	31.4
From trans fatty acid (%)	2.4	1.5	1.5	1.5	1.6	1.5	1.5	1.4	1.5	1.5
From carbohydrate	51.2	50.1	50.4	49.0	48.0	49.9	50.2	50.6	49.4	49.3
Cereal fiber (g/day)	5.6	5.6	5.5	5.2	5.0	5.3	5.5	5.5	5.6	5.3
Magnesium (mg/day)	305	312	312	308	329	302	308	313	323	350
Calcium (mg/day)	1,110	1,086	1,034	1,014	1,013	1,014	1,065	1,056	1,106	1,218
Caffeine (mg/day)	58.3	88.1	179.4	372.4	648.4	288.0	238.0	167.0	143.0	148.0
Glycemic load	108	105	106	103	99	105	105	106	102	100

Cereal fiber, magnesium, calcium, caffeine, and glycemic load intake were energy-adjusted using the residual method. MET, metabolic equivalent.

total coffee (sum of caffeinated and decaffeinated coffee) were similar to those of caffeinated or decaffeinated coffee. When we included total coffee and caffeine in the multivariable model, the coefficient estimates for total coffee but not for caffeine remained statistically significant.

We analyzed average consumption in 1984, 1986, and 1990 and found that the overall associations of caffeinated and decaffeinated coffee and caffeine with C-peptide were similar to those in 1990 and were statistically significant. When we added coffee in 1990 and in 1984–86 simultaneously, the caffeinated and decaffeinated coffee and caffeine intake in 1990 but not intake in 1984–86 remained significantly related with C-peptide. This finding indicated that plasma levels of C-peptide were more closely related to current or relatively recent coffee intake.

Stratified analyses of the 1990 showed that the inverse association between caffeinated or decaffeinated coffee and C-peptide did not differ significantly according to smoking status, physical activity, or alcohol consumption. The inverse association between caffeinated coffee and C-peptide levels was strongest in obese women, weaker in overweight women, and weakest in the normal weight group ($P = 0.005$) (Fig. 1). A sim-

ilar but weaker trend was found for decaffeinated coffee ($P = 0.2$). For total coffee intake, the trend was similar to that for caffeinated coffee but slightly stronger ($P = 0.0007$).

CONCLUSIONS— Both caffeinated and decaffeinated coffee were inversely associated with C-peptide levels, particularly in obese and overweight women. Because our questionnaire assessed average intake over the past year, we could not precisely determine how quickly a change in coffee consumption altered insulin resistance and secretion to achieve equilibrium. Because the cross-sectional 1990 analysis captured the association and use of the 1984–86 questionnaires did not provide additional predictive ability, it is likely that this effect would be achieved within one or several years, or possibly much less, rather than over many years. Although acute administration of caffeine induces insulin resistance (3,5,6), complete tolerance can develop after several days, as assessed by blood pressure, plasma renin activity, and plasma catecholamines (24,25). Our findings provide support for the potential benefit of chronic coffee and caffeine consumption on insulin secretion and possibly diabetes (2).

The decreased insulin secretion (90%

of women were fasting) in our study is consistent with the increased insulin sensitivity observed by Arnlov et al. (7). In contrast, Arnlov et al. (7) did not observe a decrease in insulin secretion as assessed by early insulin response under glucose stimulation (7). However, C-peptide has a longer half-life than insulin and thus may better represent insulin secretion than insulin levels do (26). Also, our participants were women 42–69 years old; the subjects of Arnlov et al. were men 69.5–84 years old.

The independent association between decaffeinated coffee and C-peptide indicates active ingredients other than caffeine. Previous studies have suggested that plasma glucose concentrations are reduced by chlorogenic acid (also a strong antioxidant) (27), which may combine with other antioxidants in coffee to decrease oxidative stress. Antioxidants may improve insulin sensitivity (28,29) in type 2 diabetes and decrease insulin levels in rats (30). Tea also has many different types of antioxidants; however, total concentrations are much higher in coffee (11.1 mmol) than in tea (1.4 mmol) (31). Furthermore, the effect of caffeine may also depend on other components of coffee. We did not observe an association between C-peptide and tea, which pro-

Table 2—Plasma C-peptide levels by the amount of coffee and tea consumption

Consumption in 1990	Age and BMI adjusted			Multivariable adjusted		
	Mean \pm SE (ng/ml)	Change (%)	P value	Mean \pm SE (ng/ml)	Change (%)	P value
Caffeinated coffee						
Never	2.09 \pm 0.05	Reference		2.02 \pm 0.06	Reference	
<1 cup/day	2.06 \pm 0.07	-2	0.6	2.02 \pm 0.07	-3	0.9
1 cup/day	2.10 \pm 0.06	0.3	0.9	2.05 \pm 0.07	1	0.7
2-3 cups/day	2.03 \pm 0.05	-3	0.3	1.93 \pm 0.06	-4	0.2
\geq 4 cups/day	1.85 \pm 0.06	-12	0.001	1.69 \pm 0.08	-16	<0.0001
P for trend		0.003			0.002	
Decaffeinated coffee						
Never	2.13 \pm 0.04	Reference		2.09 \pm 0.05	Reference	
<1 cup/day	2.04 \pm 0.05	-4	0.2	2.04 \pm 0.06	-2	0.4
1 cup/day	1.94 \pm 0.06	-8	0.02	1.90 \pm 0.07	-9	0.01
2-3 cups/day	1.98 \pm 0.05	-7	0.04	1.94 \pm 0.06	-7	0.04
\geq 4 cups/day	1.80 \pm 0.08	-15	0.003	1.75 \pm 0.08	-16	0.0003
P for trend		0.0008			0.007	
Tea						
Never	2.00 \pm 0.04	Reference		1.97 \pm 0.05	Reference	
<1 cup/day	2.05 \pm 0.05	3	0.3	2.07 \pm 0.05	5	0.07
1 cup/day	2.10 \pm 0.07	5	0.2	2.08 \pm 0.08	6	0.2
2-3 cups/day	2.04 \pm 0.07	2	0.5	2.04 \pm 0.07	3	0.4
\geq 4 cups/day	2.24 \pm 0.17	12	0.2	2.20 \pm 0.17	12	0.2
P for trend		0.2			0.3	

The multivariable model was adjusted for dietary factors, including total energy intake (quintiles), alcohol intake (0, 0.1-4.9, 5-14.9, 15-29.9, \geq 30 g/day), calcium intake (continuous), cereal fiber intake (continuous), glycemic load (continuous), and other factors, including age (five categories), smoking (never, past, current), BMI (continuous), physical activity (quintiles), fasting hours, laboratory batch, and menopausal status. When we examined caffeinated coffee or decaffeinated coffee in relation to C-peptide in the multivariable model, caffeinated and decaffeinated coffee were adjusted simultaneously.

vides 47 mg of caffeine per cup. Salazar-Martinez et al. (2) found no association between tea and development of diabetes. We found that total caffeine was not a significant predictor of C-peptide when total coffee (caffeinated and decaffeinated) and caffeine were included in the same model, further suggesting a role of components other than coffee.

In results from stratified analyses, coffee appeared to have a stronger influence in obese and overweight women than in normal weight women. Among obese

women, C-peptide levels in women who consumed $>$ 4 cups of caffeinated coffee per day for 1 year were 0.84 ng/ml lower than in those women who never drank caffeinated coffee. Our data also suggested that caffeinated coffee has a stronger heterogeneous effect across BMI strata than decaffeinated coffee. Experimental evidence suggests that caffeine may facilitate weight reduction and maintenance (32). Caffeine can increase basal energy expenditure (33) and stimulate fat oxidation and mobilization of glycogen in muscle (34).

Some limitations of our study need to be addressed. First, we did not test insulin sensitivity with the gold standard of the hyperinsulinemic clamp, which requires complicated procedures and could not be used in this epidemiologic study. If we also measured fasting glucose, we would be able to calculate insulin resistance using the homeostatic model assessment, an insulin sensitivity index validated against the gold standard (35). However, both fasting insulin and insulin resistance calculated from the homeostatic model as-

Table 3—Means and differences of plasma C-peptide levels by quintiles of caffeine intake

Quintile	Caffeine intake in 1990 Median intake (mg/day)	Age and BMI adjusted			Multivariable adjusted		
		Mean \pm SE (ng/ml)	Change (%)	P value	Mean \pm SE (ng/ml)	Change (%)	P value
Q1	9	2.14 \pm 0.06	Reference		2.13 \pm 0.07	Reference	
Q2	80	2.05 \pm 0.06	-4	0.3	2.04 \pm 0.06	-4	0.3
Q3	174	2.05 \pm 0.06	-4	0.3	2.04 \pm 0.06	-4	0.2
Q4	355	2.05 \pm 0.06	-4	0.3	2.07 \pm 0.07	-3	0.5
Q5	503	1.97 \pm 0.05	-8	0.02	1.91 \pm 0.06	-10	0.006
P for trend			0.05			0.02	

The multivariable model was adjusted for dietary factors including total energy intake (quintiles), alcohol intake (0, 0.1-4.9, 5-14.9, 15-29.9, \geq 30 g/day), calcium intake (continuous), cereal fiber intake (continuous), glycemic load (continuous), and other factors including age (five categories), smoking (never, past, current), BMI (continuous), physical activity (quintiles), fasting hours, laboratory batch, and menopausal status.

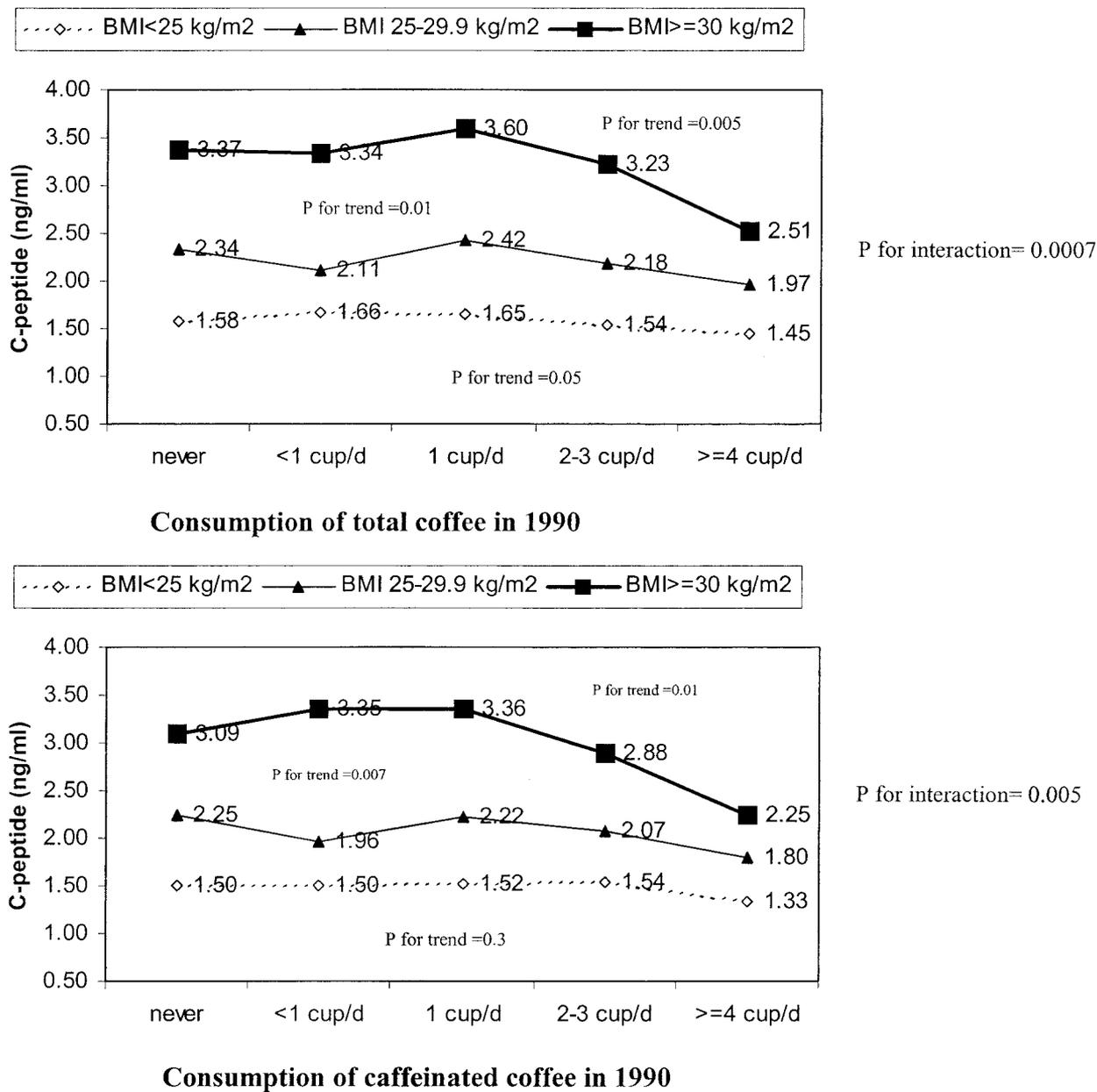


Figure 1—Consumption of total and caffeinated coffee in 1990. Total coffee included caffeinated and decaffeinated coffee. Model was adjusted for dietary factors, including total energy intake (quintiles), alcohol intake (0, 0.1–4.9, 5–14.9, 15–29.9, ≥30 g/day), calcium intake (continuous), and other demographic factors including age (five categories), smoking (never, past, current), BMI (continuous), physical activity (quintiles), fasting hours, laboratory batch, and menopausal status. For consumption of caffeinated coffee, model was adjusted for decaffeinated coffee (continuous).

assessment model were strong predictors of type 2 diabetes, although insulin resistance is a stronger predictor (36). Another limitation was that we assumed lower fasting insulin reflected greater insulin sensitivity but it could also reflect a failure of the pancreatic β -cell to produce insulin. However, this second possibility is unlikely for several reasons. First, β -cell dysfunction usually follows hyperinsulinemia and is a long, cumulative process. If the inverse association between coffee

and C-peptide were due to β -cell dysfunction, we would have expected a stronger effect of long-term average coffee consumption on insulin secretion than cross-sectional data. However, we observed the opposite. Second, we excluded subjects who had diabetes, and the proportion of undiagnosed diabetes in healthy subjects should be small. Finally, coffee consumption has been associated with decreased development of diabetes in our and several other cohorts (1–4),

providing internal and external validity to the conclusion that coffee consumption is unlikely to lead to a failure of the pancreatic β -cell dysfunction.

An observational study does not allow us to draw firm conclusions about cause and effect. However, it is unlikely that lower C-peptide levels caused women to increase coffee consumption. In addition, we controlled for many factors that influence insulin resistance and secretion. Although uncontrolled or re-

sidual confounding cannot be discounted, caffeinated and decaffeinated coffee had dissimilar patterns with covariates (Table 1), so it would be unusual for a confounding factor to influence these similarly.

In conclusion, we provide evidence that chronic consumption of caffeinated coffee and/or decaffeinated coffee reduces insulin secretion. Adequately powered clinical trials are needed to investigate the long-term effects on insulin secretion and sensitivity, glucose homeostasis, and hemodynamic variables. If our results are confirmed in other populations, caffeinated and decaffeinated coffee consumption might prove to be an effective strategy for reducing insulin resistance, especially in overweight women.

Acknowledgments—This study was supported by National Institutes of Health Grants CA49449, 5 P01 CA 87969, and 5 R01 DK58845 and American Heart Association Grant 0430202N.

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