Coffee, Caffeine, and Risk of Depression Among Women

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Background: Caffeine is the world's most widely used central nervous system stimulant, with approximately 80% consumed in the form of coffee. However, studies that analyze prospectively the relationship between coffee or caffeine consumption and depression risk are scarce.

Methods: A total of 50 739 US women (mean age, 63 years) free of depressive symptoms at baseline (in 1996) were prospectively followed up through June 1, 2006. Consumption of caffeine was measured from validated questionnaires completed from May 1, 1980, through April 1, 2004, and computed as cumulative mean consumption with a 2-year latency period applied. Clinical depression was defined as self-reported physician-diagnosed depression and antidepressant use. Relative risks of clinical depression were estimated using Cox proportional hazards regression models.

Results: During 10 years of follow-up (1996-2006), 2607 incident cases of depression were identified. Compared with women consuming 1 or less cup of caffeinated coffee per week, the multivariate relative risk of depression was 0.85 (95% confidence interval, 0.75-0.95) for those consuming 2 to 3 cups per day and 0.80 (0.64-0.99; *P* for trend <.001) for those consuming 4 cups per day or more. Multivariate relative risk of depression was 0.80 (95% confidence interval, 0.68-0.95; *P* for trend=.02) for women in the highest (≥550 mg/d) vs lowest (<100 mg/d) of the 5 caffeine consumption categories. Decaffeinated coffee was not associated with depression risk.

Conclusions: In this large longitudinal study, we found that depression risk decreases with increasing caffeinated coffee consumption. Further investigations are needed to confirm this finding and to determine whether usual caffeinated coffee consumption can contribute to depression prevention.

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CAFFEINE (1,3,7-TRIMETHylxanthine) is the world's most frequently ingested psychoactive substance,[1] with approximately 80% consumed in the form of coffee.[2] However, its effect on depression is poorly understood and is understudied. To our knowledge, only 1 prospective study[3] among men has examined the association between coffee consumption and depression risk, reporting a significant inverse association between coffee drinking and depression but no association with tea or other caffeinated beverages. In 3 cohort studies, 2 from the United States and 1 from Finland,[4-6] strong inverse associations have been reported between coffee consumption and suicide, which is strongly associated with depression, and a J-shaped relationship was noted for coffee and suicide risk in a Finnish cohort.[6]

Depression is a chronic and recurrent illness that affects twice as many women as men,[7] and approximately 20% of US women will be affected during their lifetime.[8] Identification of risk factors for depression among women and the development of new preventive strategies are, therefore, a public health priority. Thus,

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we accessed data from the Nurses' Health Study, a large cohort of women, to examine prospectively whether caffeine consumption or intake of certain caffeinated beverages is associated with the risk of depression.

METHODS

STUDY POPULATION

The Nurses' Health Study is a prospective cohort of 121 700 US female registered nurses aged 30 to 55 years at enrollment in 1976. Ev-

ery 2 years, participants provide updated information via mailed questionnaires regarding lifestyle, medical history, and newly diagnosed medical illnesses. Women were first asked to report their use of antidepressants in 1996 and their history of physician-diagnosed depression in 2000. A total of 97 103 women had completed a 1996, 1998, or 2000 questionnaire. To examine prospectively the relationship of caffeine consumption to depression, we excluded from the analyses those women who could have had depression before 1996. This group included 35 892 women with an incomplete depression history (ie, those who did not report their depressive status in 1996, 1998, or 2000 or did not return or answer the Mental Health Index [MHI] questionnaire[9-11] [a 5-item subscale of the 36-Item Short-Form Health Survey] in 1992 or 1996), as well as women who reported taking antidepressants in 1996 (n=2052) or had a physician-diagnosed episode of depression in 1996 or earlier (n=3445), those with an unknown start date (n=131), or those who reported severe depressive symptoms (score, ≤52) on the 1992 (n=2381) or 1996 (n=2271) MHI questionnaire. A total of 50 931 women were considered depression free in 1996 and comprised the baseline population for the current analyses. After excluding those who had missing values for exposure variables (n=192), the final 1996 baseline population comprised 50 739 women. The study protocol was approved by the institutional review boards of Brigham and Women's Hospital and the Harvard School of Public Health.

ASSESSMENT OF EXPOSURE

In 1980, 1984, 1986, 1990, 1994, 1998, and 2002, caffeine consumption and other dietary variables among participants were assessed using a semiquantitative food frequency questionnaire.[12] Among items on these questionnaires were coffee (caffeinated and decaffeinated), tea (nonherbal), caffeinated soft drinks (sugared or low-calorie colas), caffeine-free soft drinks (sugared or low-calorie caffeine-free colas or other carbonated beverages), and chocolate. All the food frequency questionnaires addressed the usual consumption during the previous 12 months of a specified amount (eg, 1 cup for coffee and tea, 1 glass or can for soft drinks, and 1 bar or packet for chocolate) and allowed 9 possible response categories, ranging from never to 6 or more per day. Consumptions of nutrients and caffeine were calculated, as described elsewhere,[12] primarily using concurrent US Department of Agriculture food composition data. In these calculations, we assumed that the content of caffeine was 137 mg per cup of coffee, 47 mg per cup of tea, 46 mg per can or bottle of soft drink, and 7 mg per serving of chocolate. The food frequency questionnaires have been evaluated in detail with regard to reproducibility and validity.[12-14] The validation studies revealed high correlations between self-reported coffee consumption according to the food frequency questionnaires and the 2 or 4 weeks of diet records (r=0.78).[13] High correlations also were observed for other caffeinated beverages (tea: r=0.93; soft drinks: r=0.84).

CASE ASCERTAINMENT

Incident depression was defined as reporting a new diagnosis of clinical depression and beginning regular antidepressant use (in the past 2 years). In 2000, participants were asked to report the year of their first diagnosis of clinical depression (1996 or before, 1997, 1998, 1999, or 2000). Thereafter, this information was updated biennially through December 31, 2006. The question regarding regular antidepressant medication use was first asked in 1996 and then biennially updated through 2006. Hence, answers to the 1996 questionnaire cycle were considered to be the baseline.

COVARIATES ASSESSMENT

Demographic, lifestyle behavior, and comorbidity information were collected using the standardized questionnaires mailed to the nurses. In the baseline questionnaire (in 1996), we requested information about age, weight, smoking status, menopausal status, use of postmenopausal hormone therapy, and previously diagnosed medical conditions, including diabetes mellitus, cancer, myocardial infarction or angina, and high blood pressure. This information has been updated in the biennial follow-up questionnaires. Information regarding marital status, retirement, and social or community group involvement (eg, "How many hours each week do you participate in any church, volunteer, or other community group?") was determined at baseline and updated in 2000 and 2004. Participants were asked to report the hours spent per week on moderate (eg, brisk walking) and vigorous (eg, strenuous sports and jogging) exercise, then the total hours of metabolic equivalent tasks per week were estimated on the basis of the metabolic equivalent task score assigned to each activity.[15] Dietary variables were assessed using a validated semiquantitative food frequency questionnaire.[12] Mental health was assessed using the 36-Item Short-Form Health Survey in the 1996 questionnaire. The MHI score was categorized as 86 through 100, 76 through 85, and 53 through 75.

STATISTICAL ANALYSIS

To reduce random measurement error, instead of using a single measurement, analyses were conducted using the cumulative mean caffeine consumption from all the available questionnaires before the beginning of each 2-year follow-up period.[16] Because our last food frequency questionnaire used before baseline was in 1994, our analyses imply a latency of exposure of a minimum of 2 years. For example, the cumulative mean caffeine consumption information from 1980 through 1994 was used to predict clinical depression episodes in 1996 through 1998, consumptions from 1980 through 1994 for the 1998 through 2000 follow-up period, intakes from 1980 through 1998 for the 2000 through 2002 follow-up period, and so forth. Similar analyses were conducted for categories of coffee consumption and other sources of caffeine. Person-years of follow-up were calculated from the date of return of the 1996 questionnaire to the return date of the questionnaire with first occurrence of depression, date of death, and end of follow-up (June 1, 2006) or the return date of the participants' last questionnaire, whichever was earlier. Cox proportional hazards models, stratified by age in months and questionnaire cycle, were used to estimate the relative risks and their 95% confidence intervals (CIs) of developing clinical depression. All relevant covariates that remained significant at $P<.20$ in the multivariate model and made an important difference in the exposure effect estimate (ie, more than a 10% change in relative risks) were kept in the final multivariate model.[17] Initially, the relative risks were adjusted for known and putative risk factors of depression, including current postmenopausal hormonal use (binary); body mass index (calculated as weight in kilograms divided by height in meters squared; <25.0, 25.0-29.9, ≥30.0); marital status (married or partnered; widowed; separated, divorced, or single); social or community group involvement (binary); smoking (never smoked, past smoker, current smoker); total energy intake (continuous); physical activity (quintiles); retirement (binary); self-reported history of diagnosis of diabetes (binary), cancer (binary), myocardial infarction or angina (binary), and high blood pressure (binary); and the MHI score (86-100, 76-85, 53-75) in 1996, as in a previous study.[18] In the sensitivity analysis of the multivariate model, a minimum

Table 1. Age-Standardized Characteristics of the Cohort[a]

Variable	Caffeinated Coffee Consumption[b]				
	≤1 Cup/wk	2-6 Cups/wk	1 Cup/d	2-3 Cups/d	≥4 Cups/d
No. of women	12 215	6617	17 234	12 290	2383
Age, mean (SD), y	62.7 (7.3)	63.8 (7.0)	63.3 (7.0)	62.8 (6.7)	62.1 (6.6)
BMI, mean (SD)	26.4 (5.2)	26.4 (5.0)	26.2 (4.9)	26.0 (4.7)	25.8 (4.7)
Physical activity, mean (SD), MET/wk	18.7 (21.1)	19.6 (25.5)	19.3 (22.5)	18.9 (22.0)	17.5 (22.0)
Daily intake in 1994, mean (SD)					
Total energy, kcal	1695 (503)	1720 (503)	1729 (499)	1770 (512)	1791 (533)
Alcohol, % energy, kcal	2.9 (4.0)	3.1 (4.1)	3.6 (4.3)	3.9 (4.4)	3.6 (4.4)
Caffeine, mg[c]	73 (75)	127 (110)	232 (165)	386 (180)	649 (220)
Decaffeinated coffee, No. of cups	0.5 (0.9)	0.8 (1.1)	0.7 (1.1)	0.5 (1.1)	0.3 (1.0)
Tea, No. of cups	0.9 (1.3)	0.7 (1.0)	0.6 (0.9)	0.5 (0.8)	0.3 (0.8)
Chocolate, No. of bars or packets	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)
Caffeinated sugared soft drink, No. of glasses or cans	0.1 (0.3)	0.1 (0.2)	0.1 (0.2)	0.1 (0.3)	0.1 (0.3)
Caffeinated low-calorie soft drink, No. of glasses or cans	0.2 (0.6)	0.2 (0.5)	0.2 (0.5)	0.3 (0.6)	0.2 (0.6)
MHI score, %[d]					
≥86	45.2	44.2	43.9	42.7	44.8
76-85	35.1	37.4	36.6	37.2	35.3
53-75	19.5	18.2	19.3	19.9	19.4
White, %	97.3	97.3	98.2	98.8	99.0
Involved in church, volunteer, or community group ≥1 h/wk, %	67.8	66.2	61.5	59.4	54.3
Retired, %	49.1	49.8	48.8	49.2	50.0
Marital status, %					
Married or partnered	81.5	81.2	79.4	78.3	73.2
Widowed	12.4	12.6	13.4	14.1	17.4
Separated, divorced, or single	6.1	6.2	7.3	7.6	9.4
Current menopausal hormones, %	41.4	42.3	41.3	40.0	34.6
Reported diagnosis, %					
Myocardial infarction or angina	4.0	4.0	3.8	3.0	2.9
High blood pressure	31.0	32.7	30.1	26.5	22.5
Diabetes mellitus	5.3	4.8	3.9	3.7	2.5
Cancer	6.7	6.6	6.7	6.0	6.8
Smoking status, %					
Never smoker	60.1	51.9	44.0	35.5	25.0
Past smoker	34.9	42.8	47.5	49.0	40.3
Current smoker	5.0	5.3	8.5	15.5	34.7
BMI, %					
<25.0	46.4	46.3	47.1	47.3	47.9
25.0-29.9	32.4	33.8	33.9	34.8	34.8
≥30.0	20.9	19.7	18.8	17.7	17.1

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MET, metabolic equivalent of task; MHI, Mental Health Index (a 5-item subscale of the 36-Item Short-Form Health Survey).
[a] All characteristics are for 1996, except if otherwise indicated. Caffeinated coffee consumption was computed as the cumulative mean from 1980 through 2002.
[b] One cup equals 150 mL.
[c] Calculated from coffee and noncoffee sources (tea, soft drinks, and chocolate) and adjusted for total energy intake with residual model.
[d] Scores were measured in 1996; a higher score denotes better mental health.

latency of 8 years was applied (ie, cumulative mean consumption from 1980-1986 was used for the 1996-1998 follow-up period, consumption from 1980-1990 for the 1998-2000 follow-up period, and so forth). It is well known that the half-life of caffeine is reduced by 30% to 50% in smokers and doubled in women taking oral contraceptives or other exogenous forms of estrogen.[19] Therefore, we tested the interactions between these factors and caffeine or coffee consumption for depression risk. Because a significant percentage of depressed patients might never receive treatment and some proportion of those who do may receive treatment other than antidepressants, we repeated our main analyses using a broader definition of depression that required a physician diagnosis or the use of antidepressants (eTable; http://www.archinternmed.com). All analyses were performed with SAS software, version 9.1 (SAS Institute, Inc, Cary, North Carolina). All P values reported are 2-sided.

RESULTS

Participant characteristics according to categories of caffeinated coffee consumed are presented in **Table 1**. Compared with women with least frequent consumption of coffee, regular coffee drinkers were more likely to be current smokers and to consume more alcohol; were less likely to be involved in church, volunteer, or community groups; and reported a lower prevalence of obesity, high blood pressure, and diabetes mellitus. In this cohort, 6669 women (13.1%) reported that they never drink caffeinated coffee. In 1994, the most recent measure of diet before baseline, mean caffeine consumption was 236 mg/d for the entire cohort and ranged from 73 mg/d in women drinking ≤1 cups of

Table 2. Relative Risks (95% CIs) of Clinical Depression According to Caffeinated Coffee Consumption[a]

	Caffeinated Coffee Consumption					
Variable	≤1 Cup/wk	2-6 Cups/wk	1 Cup/d	2-3 Cups/d	≥4 Cups/d	P for Trend
No. of cases	670	373	905	564	95	. . .
Person-years	113 305	63 322	163 256	105 619	17 960	. . .
Age-adjusted model[b]	1 [Reference]	1.02 (0.90-1.16)	0.96 (0.87-1.06)	0.90 (0.80-1.01)	0.88 (0.71-1.09)	.03
Multivariate model[c]	1 [Reference]	1.00 (0.88-1.14)	0.92 (0.83-1.02)	0.85 (0.75-0.95)	0.80 (0.64-0.99)	<.001
Sensitivity model[d]	1 [Reference]	0.96 (0.84-1.01)	0.98 (0.88-1.09)	0.88 (0.78-0.98)	0.82 (0.68-0.98)	.005

Abbreviations: CI, confidence interval; ellipses, not applicable.

[a] Coffee consumption was computed as the cumulative mean from 1980 through 2002 (see the Methods section of the text). Clinical depression is defined as physician-diagnosed depression and antidepressant medication use (1996-2006).

[b] Adjusted for age (continuous) and interval.

[c] Further adjusted for total energy intake (continuous); current menopausal hormones (binary); smoking status (never, past, or current smoker); body mass index (<25, 25-29.9, or ≥30) (calculated as weight in kilograms divided by height in meters squared); physical activities (quintiles); marital status (married or partnered; widowed; or separated, divorced, or single); not involved in church, volunteer, or community group (binary); retired (binary); reported diagnosis of diabetes mellitus (binary), cancer (binary), high blood pressure (binary), or myocardial infarction or angina (binary); and Mental Health Index score (86-100, 76-85, or 53-75) in 1996.

[d] The same as the multivariate model but using a minimum latency of exposure of 8 years (see the Methods section of the text).

Table 3. Relative Risks (95% CIs) of Clinical Depression According to Decaffeinated Coffee Consumption[a]

	Decaffeinated Coffee Consumption					
Variable	<1 Cup/wk	1-4 Cups/wk	5-6 Cups/wk	1 Cup/d	≥2 Cups/d	P for Trend
No. of cases	1413	355	154	560	125	. . .
Person-years	258 704	59 296	23 743	95 469	26 249	. . .
Age-adjusted model[b]	1 [Reference]	1.12 (1.00-1.26)	1.25 (1.05-1.47)	1.10 (1.00-1.21)	0.87 (0.72-1.04)	.77
Multivariate model[c]	1 [Reference]	1.12 (1.00-1.26)	1.24 (1.05-1.46)	1.09 (0.98-1.20)	0.84 (0.70-1.01)	.89
Sensitivity model[d]	1 [Reference]	1.09 (0.95-1.25)	1.00 (0.83-1.21)	1.15 (1.04-1.28)	0.85 (0.73-0.99)	.75
Excluding coffee drinkers[e]						
No. of cases	521	141	56	262	63	. . .
Person-years	89 993	23 150	9553	41 443	12 487	. . .
Multivariate model[c]	1 [Reference]	1.05 (0.87-1.27)	1.04 (0.79-1.38)	1.07 (0.92-1.24)	0.80 (0.61-1.05)	.45

Abbreviations: CI, confidence interval; ellipses, not applicable.

[a] Coffee consumption was computed as the cumulative mean from 1980 through 2002 (see the Methods section of the text). Clinical depression is defined as physician-diagnosed depression and antidepressant medication use (1996-2006).

[b] Adjusted for age (continuous) and interval.

[c] Further adjusted for total energy intake (continuous); current menopausal hormones (binary); smoking status (never, past, or current smoker); body mass index (<25.0, 25.0-29.9, or ≥30.0) (calculated as weight in kilograms divided by height in meters squared); physical activities (quintiles); marital status (married or partnered; widowed; or separated, divorced, or single); not involved in church, volunteer, or community group (binary); retired (binary); reported diagnosis of diabetes mellitus (binary), cancer (binary), high blood pressure (binary), or myocardial infarction or angina (binary); and Mental Health Index score (86-100, 76-85, or 53-75) in 1996.

[d] The same as the multivariate model but using a minimum latency of exposure of 8 years (as shown in the Methods section of the text).

[e] Women drinking 1 or more cups of caffeinated coffee per day were excluded (1043 cases remaining).

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coffee per week to 649 mg/d in women drinking 4 cups or more per day. Caffeinated coffee contributed to 81.7% of total daily consumption of caffeine, but tea contributed to 12.7% and caffeinated soft drinks to 5.7%. Caffeinated coffee consumption was negatively correlated with decaffeinated coffee ($r=-0.13$) and tea ($r=-0.19$) consumption.

Among the 50 739 women who were free of clinical depression or severe depressive symptoms at baseline, we documented 2607 incident cases of clinical depression during the 10-year (463 462 person-years) follow-up (1996-2006). An inverse, age-adjusted, dose-response relationship was observed between caffeinated coffee and depression risk (P for trend=.03) (**Table 2**). This inverse gradient became slightly stronger after adjusting for all covariates, mainly reflecting negative confounding by smoking status. Similar results were

noted when we ran our multivariate models with a minimum latency of 8 years of exposure (Table 2, sensitivity model). We also observed similar risk estimates, somewhat stronger for caffeinated coffee, when we used the broader definition of depression that required a physician diagnosis or the use of antidepressants (eTable). Further adjustment for alcohol intake did not materially affect the results.

To evaluate whether the association between caffeine and depression risk could be explained by components of coffee other than caffeine, we examined the association between decaffeinated coffee and depression (**Table 3**). After controlling for caffeinated coffee and other covariates, compared with women with the lowest consumption of decaffeinated coffee (≤1 cup per week), the risk of depression was increased for higher consumption, with the exception of the very highest con-

sumption category (≥2 cups per day). After further excluding women drinking 1 or more cups per day of caffeinated coffee to avoid contamination by caffeinated coffee consumption, no significant association was noted between decaffeinated coffee and depression. In addition, no associations were found between caffeinated tea (*P* for trend=.92), sugared soft drink (*P* for trend=.58), or chocolate (*P* for trend=.89) consumption and depression risk (data not shown).

An inverse dose-response relationship was observed between caffeine consumption and depression risk in our multivariate model (*P* for trend=.02, **Figure**). Compared with the group that consumed the least caffeine (<100 mg/d), the multivariate relative risk for depression in the group consuming the highest amount of caffeine (≥550 mg/d) was 0.80 (95% CI, 0.68-0.95). Because coffee contributes most to total caffeine consumption, we examined the association between caffeine from noncoffee sources and depression risk after excluding women who consumed 1 or more cups of caffeinated coffee daily (21 016 women and 1043 cases remaining). No significant association was found between caffeine from noncoffee sources and depression risk (*P* for trend=.18). Compared with the lowest amount of caffeine from noncoffee sources (<50 mg/d), the multivariate relative risk for depression was 0.99 (95% CI, 0.84-1.15) for consumption of 50 to 100 mg/d, 0.89 (0.71-1.11) for 100 to 150 mg/d, and 0.85 (0.63-1.14) for consumption of 150 mg/d or more (data not shown). For the 1089 women (49 cases) who consumed 150 mg/d of caffeine or more from these sources, the wide CI included the null value and the relative risk seen for caffeine from coffee.

A marginally significant interaction (*P*=.06) was noted between current smoking (yes/no) and caffeinated coffee consumption (cups per day) for depression risk. For each increase of caffeinated coffee of 2 cups per day, the multivariate relative risk for depression was 0.78 (95% CI, 0.66-0.93) for current smokers (263 cases) and 0.95 (0.89-1.01) for never and past smokers (2344 cases). However, interaction between current menopausal hormone use (yes/no) and caffeinated coffee consumption (cups per day) was not significant (*P*=.42) for depression risk.

COMMENT

In this large prospective cohort of older women free of clinical depression or severe depressive symptoms at baseline, risk of depression decreased in a dose-dependent manner with increasing consumption of caffeinated coffee. Consumption of decaffeinated coffee was not associated with reduced risk of depression. Most previous studies[20-28] that investigated the relationship between caffeine or coffee consumption and depression were cross-sectional and thus unable to determine whether coffee consumption affects depression or vice versa. The only previous prospective study[3] was conducted in Finland in a population-based cohort of 2232 men; 49 cases of depression were identified after a 17.5-year follow-up through the national hospi-
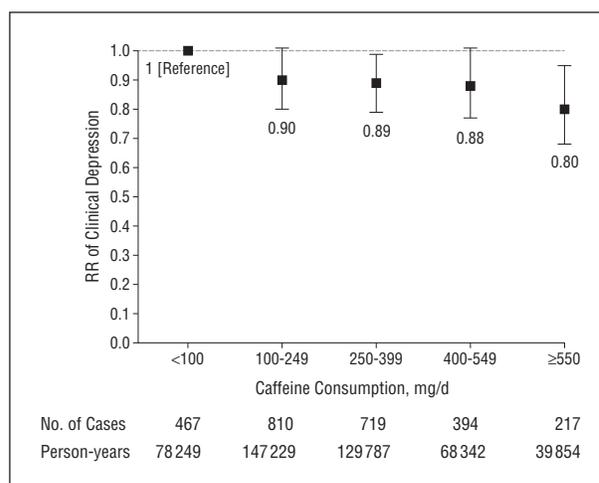
Figure. Multivariate-adjusted relative risks (RR) of clinical depression according to caffeine consumption (*P* for trend=.02). Error bars indicate 95% confidence intervals. Caffeine was calculated from coffee and noncoffee sources (tea, soft drinks, and chocolate) and adjusted for total energy intake with a residual model. Adjusted for age (continuous); interval; total energy intake (continuous); current menopausal hormones (binary); smoking status (never, past, or current smoker); body mass index (<25.0, 25.0-29.9, or ≥30.0) (calculated as weight in kilograms divided by height in meters squared); physical activities (quintiles); marital status (married or partnered; widowed; or separated, divorced, or single); not involved in a church, volunteer, or community group (binary); retired (binary); reported diagnosis of diabetes mellitus (binary); cancer (binary); high blood pressure (binary); or myocardial infarction or angina (binary); and Mental Health Index score (86-100, 76-85, 53-75) in 1996.

tal discharge register. In this cohort, the multivariate-adjusted relative risks of depression were 0.28 (95% CI, 0.08-0.96) for light coffee drinkers (<375 mL/d), 0.45 (0.16-1.29) for moderate coffee drinkers (375-813 mL/d), and 0.23 (0.06-0.83) for heavy coffee drinkers (>813 mL/d) compared with nondrinkers. Although no associations were observed for quartiles of caffeine consumption, an inverse association could have been obfuscated by the high caffeine consumption of the lowest quartile (up to 425 mg/d) and by the small sample size. In 2 US cohort studies,[4,5] a lower risk of suicide has been reported with higher coffee consumption. However, a J-shaped association was noted for coffee and suicide risk in a cohort study from Finland. The risk of suicide decreased progressively until coffee consumption reached 6 to 7 cups per day but increased with consumption of 8 to 9 cups per day and 10 or more cups per day.[6] It is possible that persons with more severe forms of depression used very high doses of coffee as a form of self-medication that was, nevertheless, insufficient to elevate their mood. We observed an inverse dose-response relationship between caffeine or caffeinated coffee consumption and depression risk, but we were unable to address the effects of very high consumption because only 0.52% of our participants drank 6 or more cups per day of caffeinated coffee. Also, we did not see a relationship between caffeine from noncoffee sources and depression risk, perhaps due to insufficient power, particularly after those who consume 1 or more cups of caffeinated coffee daily were excluded.

In North America and in many European countries, coffee and tea are the primary dietary sources of caffeine

for adults.[2] According to the US Department of Agriculture survey data (1994-1996 and 1998), 90% of the US adult population consumed caffeine, and mean consumption ranged from 166 to 336 mg/d.[2] Coffee accounts for approximately 81% of the total daily caffeine consumed by adults older than 36 years.[2] The elimination half-life of caffeine can be influenced by many factors, including sex, use of oral contraceptives or other exogenous forms of estrogen (approximately twice as long among users), and smoking (reduced by 30%-50%).[19] At doses lower than 10 mg/kg of caffeine, the half-life ranges from 2.5 to 4.5 hours.[19] The significant interaction that we noted between caffeinated coffee and current smoking was unexpected and may be due to chance. Alternatively, caffeine may antagonize the adverse effects of smoking on depression through still-unknown mechanisms or may interact with genetic factors that predispose patients to smoking and depression.[29]

Long-term caffeine consumption has several biological effects that should be taken into account when considering the plausibility of its potential to reduce depression risk. At low to moderate doses, caffeine has well-known psychostimulant effects, such as improved psychomotor performance, increased vigilance, elevated arousal (ie, lesser somnolence and greater activation), and increased sensations of well-being and energy.[30,31] The known effects of caffeine are dose dependent but typically biphasic (ie, low doses are perceived as pleasant and stimulating, but the reverse effect is observed with higher doses).[32] Most individuals seem to adapt their caffeine consumption to their own level of tolerance so that their habitual consumption level is within the range between reinforcing and aversive effects.[32] Caffeine affects brain function mainly by its antagonist action on the adenosine A2A receptor and, therefore, plays a role in the modulation of dopaminergic transmission.[30,33] The antagonist effect of caffeine on adenosine also might imply nondopaminergic mechanisms, such as modulation of the release of acetylcholine and serotonin.[30]

The major strengths of this study include its large sample size, prospective design, and repeated measures of caffeine, caffeinated beverages, and other covariates, which relied on the use of validated food frequency questionnaires administered 7 times during a period of 22 years. This study also has limitations; thus, the results should be interpreted with caution. First and foremost, because of its observational design, this study cannot prove that caffeine or caffeinated coffee reduces the risk of depression but only suggests the possibility of such a protective effect. Reverse causation is another concern in most epidemiologic studies. To minimize this bias, we excluded at baseline 10 280 women with severe depressive symptoms and we computed the cumulative mean of caffeinated and noncaffeinated beverages with at least a 2-year latency; yet, we cannot exclude the possibility that mild depressive symptoms were the common reason for low caffeine consumption and incident depression. Furthermore, we confirmed the robustness of our results in sensitivity analyses using at least an 8-year lag of exposure.

In individuals with a particular genetic background[34] or who are otherwise sensitive, caffeine might induce sleep disturbances and insomnia[35] or anxiogenic effects.[20,36,37] It is possible that sleep-sensitive or anxious women are aware of the stimulatory effects of caffeine and lower their consumption accordingly. Thus, a similar behavior among depressed women or women predisposed to depression in our cohort might explain our results because most late-life depression occurs among women who have already had previous episodes[38]; lacking a lifetime history of depression, we cannot exclude this possibility. Biased relative risk estimates also may result from error in assessing caffeine consumption. Dietary validation studies, however, have indicated that the frequency of coffee consumption reported on a food frequency questionnaire is highly reproducible ($r=0.78$) and agrees well with assessments using diet records.[13] Although between-person variation in cup size and strength of the coffee brew probably has contributed to some random misclassification with regard to the exposure, this would be more likely to weaken rather than to strengthen observed associations between coffee consumption and depression risk. Finally, some outcome misclassification bias is inevitable because of a combination of errors in reporting depression and antidepressant use, low recognition of depression by physicians,[39] undertreatment of depression,[40] and use of antidepressant medication for indications other than depression.[41-43] We tried to maximize the specificity of case definition, accepting as incident cases of depression only those cases that occurred in women who reported a diagnosis of clinical depression and the use of antidepressants. This definition excludes women with untreated depression, as well as women who used antidepressants for a short period and were not regular users at the time of completing a biennial questionnaire. However, to the extent that the probability of correctly classifying women with an incident case of depression is independent of their dietary habits (ie, nondifferential misclassification of outcome), the low sensitivity of this strict case definition should not bias relative risk estimates.[44] During 10 years of follow-up, we noted an incident rate of clinical depression of 5.6 per 1000 person-years. This incidence is not directly comparable to that observed in unselected populations because to minimize reverse causation, we excluded women with severe depressive symptoms at baseline, thus eliminating a group at higher risk of depression.

In conclusion, our results support a possible protective effect of caffeine, mainly from coffee consumption, on risk of depression. These findings are consistent with earlier observations that suicide risk is lower among persons with higher consumption of coffee. Further investigations are needed to confirm this finding and to determine whether usual caffeinated coffee consumption may contribute to prevention or treatment of depression.

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REFERENCES

1. Heckman MA, Weil J, Gonzalez de Mejia E. Caffeine (1, 3, 7-trimethylxanthine) in foods: a comprehensive review on consumption, functionality, safety, and regulatory matters. *J Food Sci.* 2010;75(3):R77-R87.
2. Frary CD, Johnson RK, Wang MQ. Food sources and intakes of caffeine in the diets of persons in the United States [published correction appears in *J Am Diet Assoc.* 2008;108(4):727]. *J Am Diet Assoc.* 2005;105(1):110-113.
3. Ruusunen A, Lehto SM, Tolmunen T, Mursu J, Kaplan GA, Voutilainen S. Coffee, tea and caffeine intake and the risk of severe depression in middle-aged Finnish men: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Public Health Nutr.* 2010;13(8):1215-1220.
4. Klatsky AL, Armstrong MA, Friedman GD. Coffee, tea, and mortality. *Ann Epidemiol.* 1993;3(4):375-381.
5. Kawachi I, Willett WC, Colditz GA, Stampfer MJ, Speizer FE. A prospective study of coffee drinking and suicide in women. *Arch Intern Med.* 1996;156(5):521-525.
6. Tanskanen A, Tuomilehto J, Viinamäki H, Vartiainen E, Lehtonen J, Puska P. Heavy coffee drinking and the risk of suicide. *Eur J Epidemiol.* 2000;16(9):789-791.
7. Kessler RC. Epidemiology of women and depression. *J Affect Disord.* 2003;74(1):5-13.
8. Kessler RC, Berglund P, Demler O, et al; National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA.* 2003;289(23):3095-3105.
9. Ware JE, Kosinski M, Keller SD. *SF-36 Physical and Mental Health Summary Scales: A User's Manual.* Vol 8. Boston, MA: Health Institute, New England Medical Center; 1994:23-28.
10. Yamazaki S, Fukuhara S, Green J. Usefulness of five-item and three-item Mental Health Inventories to screen for depressive symptoms in the general population of Japan. *Health Qual Life Outcomes.* 2005;3:48. doi:10.1186/1477-7525-3-48.
11. Berwick DM, Murphy JM, Goldman PA, Ware JE Jr, Barsky AJ, Weinstein MC. Performance of a five-item mental health screening test. *Med Care.* 1991;29(2):169-176.
12. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol.* 1985;122(1):51-65.
13. Salvini S, Hunter DJ, Sampson L, et al. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. *Int J Epidemiol.* 1989;18(4):858-867.
14. Willett WC. *Nutritional Epidemiology.* 2nd ed. New York, NY: Oxford University Press; 1998.
15. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of Physical Activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc.* 2000;32(9)(suppl):S498-S504.
16. Hu FB, Stampfer MJ, Rimm E, et al. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. *Am J Epidemiol.* 1999;149(6):531-540.
17. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. *Am J Epidemiol.* 1993;138(11):923-936.
18. Kroenke CH, Bennett GG, Fuchs C, et al. Depressive symptoms and prospective incidence of colorectal cancer in women. *Am J Epidemiol.* 2005;162(9):839-848.
19. Arnaud MJ. The pharmacology of caffeine. *Prog Drug Res.* 1987;31:273-313.
20. Greden JF, Fontaine P, Lubetsky M, Chamberlin K. Anxiety and depression associated with caffeinism among psychiatric inpatients. *Am J Psychiatry.* 1978;135(8):963-966.
21. Gilliland K, Andress D. Ad lib caffeine consumption, symptoms of caffeinism, and academic performance. *Am J Psychiatry.* 1981;138(4):512-514.
22. Leibenluft E, Fiero PL, Bartko JJ, Moul DE, Rosenthal NE. Depressive symptoms and the self-reported use of alcohol, caffeine, and carbohydrates in normal volunteers and four groups of psychiatric outpatients. *Am J Psychiatry.* 1993;150(2):294-301.
23. Quinlan PT, Lane J, Moore KL, Aspen J, Rycroft JA, O'Brien DC. The acute physiological and mood effects of tea and coffee: the role of caffeine level. *Pharmacol Biochem Behav.* 2000;66(1):19-28.
24. Haskell CF, Kennedy DO, Wesnes KA, Scholey AB. Cognitive and mood improvements of caffeine in habitual consumers and habitual non-consumers of caffeine. *Psychopharmacology (Berl).* 2005;179(4):813-825.
25. Hintikka J, Tolmunen T, Honkalampi K, et al. Daily tea drinking is associated with a low level of depressive symptoms in the Finnish general population. *Eur J Epidemiol.* 2005;20(4):359-363.
26. Kendler KS, Myers J, Gardner CO. Caffeine intake, toxicity and dependence and lifetime risk for psychiatric and substance use disorders: an epidemiologic and co-twin control analysis. *Psychol Med.* 2006;36(12):1717-1725.
27. Smith AP. Caffeine, cognitive failures and health in a non-working community sample. *Hum Psychopharmacol.* 2009;24(1):29-34.
28. Xu Q, Anderson D, Courtney M. A longitudinal study of the relationship between lifestyle and mental health among midlife and older women in Australia: findings from the Healthy Aging of Women Study. *Health Care Women Int.* 2010;31(12):1082-1096.
29. Kendler KS, Neale MC, MacLean CJ, Heath AC, Eaves LJ, Kessler RC. Smoking and major depression: a causal analysis. *Arch Gen Psychiatry.* 1993;50(1):36-43.
30. Ferré S. An update on the mechanisms of the psychostimulant effects of caffeine. *J Neurochem.* 2008;105(4):1067-1079.
31. Adan A, Prat G, Fabbri M, Sànchez-Turet M. Early effects of caffeinated and decaffeinated coffee on subjective state and gender differences. *Prog Neuropsychopharmacol Biol Psychiatry.* 2008;32(7):1698-1703.
32. Fredholm BB, Bättig K, Holmén J, Nehlig A, Zvartau EE. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacol Rev.* 1999;51(1):83-133.
33. Ferre S, Ciruela F, Borycz J, et al. Adenosine A1-A2$_A$ receptor heteromers: new targets for caffeine in the brain. *Front Biosci.* 2008;13:2391-2399.
34. Yang A, Palmer AA, de Wit H. Genetics of caffeine consumption and responses to caffeine. *Psychopharmacology (Berl).* 2010;211(3):245-257.
35. Bchir F, Dogui M, Ben Fradj R, Arnaud MJ, Saguem S. Differences in pharmacokinetic and electroencephalographic responses to caffeine in sleep-sensitive and non-sensitive subjects. *C R Biol.* 2006;329(7):512-519.
36. Boulenger J-P, Uhde TW, Wolff EA III, Post RM. Increased sensitivity to caffeine in patients with panic disorders: preliminary evidence. *Arch Gen Psychiatry.* 1984;41(11):1067-1071.
37. Lee MA, Cameron OG, Greden JF. Anxiety and caffeine consumption in people with anxiety disorders. *Psychiatry Res.* 1985;15(3):211-217.
38. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of *DSM-IV* disorders in the National Comorbidity Survey Replication [published correction appears in *Arch Gen Psychiatry.* 2005;62(7):768]. *Arch Gen Psychiatry.* 2005;62(6):593-602.
39. Löwe B, Spitzer RL, Gräfe K, et al. Comparative validity of three screening questionnaires for *DSM-IV* depressive disorders and physicians' diagnoses. *J Affect Disord.* 2004;78(2):131-140.
40. Demyttenaere K, Bruffaerts R, Posada-Villa J, et al; WHO World Mental Health

Survey Consortium. Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization World Mental Health Surveys. *JAMA*. 2004;291(21):2581-2590.

41. Olfson M, Marcus SC. National patterns in antidepressant medication treatment. *Arch Gen Psychiatry*. 2009;66(8):848-856.

42. Brown J, O' Brien PMS, Marjoribanks J, Wyatt K. Selective serotonin reuptake inhibitors for premenstrual syndrome. *Cochrane Database Syst Rev*. 2009;(2):CD001396. doi:10.1002/14651858.CD001396.pub2.

43. Stearns V, Ullmer L, López JF, Smith Y, Isaacs C, Hayes D. Hot flushes. *Lancet*. 2002;360(9348):1851-1861.

44. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008:737.

Coffee Consumption and Depression Risk

Despite being widely consumed worldwide, relatively little is known about the long-term health effects of coffee and its main psychoactive component, caffeine. In this issue of the *Archives*, Lucas et al present the results of a large, prospective epidemiological study of coffee consumption and depression incidence, finding an inverse association. This study makes an important contribution because it is, to my knowledge, the first large-scale study of coffee consumption to evaluate a mental health outcome in women. Previous work has focused mainly on the effects of caffeine on cardiovascular disease (generally finding no overall effect on cardiovascular disease incidence or mortality), inflammation (generally showing modest decreases in markers of systemic inflammation), and particular types of malignant neoplasms, including breast cancer and esophageal cancer (generally showing no or modest protective effects). Taken together, these results reassure coffee drinkers that there seem to exist no glaringly deleterious health consequences to coffee consumption. As health care professionals, however, it seems premature to recommend coffee consumption until studies with methodologies better able to determine causality are conducted.

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The beautiful fall of Erie, Pennsylvania.

Courtesy of: Deepak Pahuja, MBBS, MD, Internal Medicine, St Vincent Health Center, Erie, Pennsylvania.