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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See Editor’s Note at end of article

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-
every 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 had not had a depression diagnosis 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). Among these women, we defined a depression event as a change in antidepressant medication use from no medication in 1996 to any medication in 1998 or 1999. The sensitivity analysis of the multivariate model, a minimum relevant covariate 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. 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. 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. Diet variables were assessed using a validated semiquantitative food frequency questionnaire. 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.

**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.

**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. 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. 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. In the sensitivity analysis of the multivariate model, a minimum
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. 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 cup of coffee per week to 649 mg/d in women drinking 4 cups per day.
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 2,607 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 exposure of 8 years (see the Methods section of the text).

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 decaffeinated 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 consumption, with the exception of the very highest consumption.

<table>
<thead>
<tr>
<th>Variable</th>
<th>&lt;1 Cup/wk</th>
<th>1-4 Cups/wk</th>
<th>5-6 Cups/wk</th>
<th>1 Cup/d</th>
<th>≥2 Cups/d</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>1413</td>
<td>355</td>
<td>154</td>
<td>560</td>
<td>125</td>
<td>. . .</td>
</tr>
<tr>
<td>Person-years</td>
<td>258,704</td>
<td>59,296</td>
<td>23,743</td>
<td>95,469</td>
<td>26,249</td>
<td>. . .</td>
</tr>
<tr>
<td>Age-adjusted model</td>
<td>1 [Reference]</td>
<td>1.12 (1.00-1.26)</td>
<td>1.25 (1.05-1.47)</td>
<td>1.10 (1.00-1.21)</td>
<td>0.87 (0.72-1.04)</td>
<td>.77</td>
</tr>
<tr>
<td>Multivariate model</td>
<td>1 [Reference]</td>
<td>1.12 (1.00-1.26)</td>
<td>1.24 (1.05-1.46)</td>
<td>1.09 (0.98-1.20)</td>
<td>0.84 (0.70-1.01)</td>
<td>.89</td>
</tr>
<tr>
<td>Sensitivity model</td>
<td>1 [Reference]</td>
<td>1.09 (0.95-1.25)</td>
<td>1.00 (0.83-1.21)</td>
<td>1.15 (1.04-1.28)</td>
<td>0.85 (0.73-0.99)</td>
<td>.75</td>
</tr>
<tr>
<td>Excluding coffee drinkers</td>
<td>No. of cases</td>
<td>521</td>
<td>141</td>
<td>56</td>
<td>262</td>
<td>63</td>
</tr>
<tr>
<td>Person-years</td>
<td>89,993</td>
<td>23,150</td>
<td>9553</td>
<td>41,443</td>
<td>12,487</td>
<td>. . .</td>
</tr>
<tr>
<td>Multivariate model</td>
<td>1 [Reference]</td>
<td>1.05 (0.87-1.27)</td>
<td>1.04 (0.79-1.38)</td>
<td>1.07 (0.92-1.24)</td>
<td>0.80 (0.61-1.05)</td>
<td>.45</td>
</tr>
</tbody>
</table>
 consume whether coffee consumption affects depression between caffeine or coffee consumption and risk of depression. In addition, no associations were found between caffeine intake and depression. 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 coffee. Consumption of decaffeinated coffee was not associated with reduced risk of depression. Most previous studies 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 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 hospital 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 association could have been observed 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, 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. 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 decaffeinated 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 decaffeinated 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 decaffeinated coffee daily were excluded.

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

**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 (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.
for adults. 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. Coffee accounts for approximately 81% of the total daily caffeine consumed by adults older than 36 years. The elimination half-life and smoking (reduced by 30%-50%). At doses lower of estrogen (approximately twice as long among users), and smoking (reduced by 30%-50%). 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.

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. 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). 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. 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. The antagonist effect of caffeine on adenosine also might imply nondopaminergic mechanisms, such as modulation of the release of acetylcholine and serotonin.

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 caffeine, caffeinated 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 or who are otherwise sensitive, caffeine might induce sleep disturbances and insomnia or anxiogenic effects. 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, 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. 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, undertreatment of depression, and use of antidepressant medication for indications other than depression. 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. 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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Author Contributions: Drs Lucas, Mirzai, Okereke, Willett, O’Reilly, Koenen, and Ascherio had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Lucas, Okereke, Willett, Koenen, and Ascherio. Acquisition of data: Lucas, Willett, and Ascherio. Analysis and interpretation of data: Lucas, Mirzai, Pan, Okereke, Willett, O’Reilly, and Ascherio. Drafting of the manuscript: Lucas and O’Reilly. Critical revision of the manuscript for important intellectual content: Lucas, Mirzai, Pan, Okereke, Willett, Koenen, and Ascherio. Statistical analysis: Lucas, Pan, Willett, and Ascherio. Obtained funding: Willett and Ascherio. Administrative, technical, and material support: Mirzai, Okereke, and O’Reilly. Study supervision: Okereke and Ascherio.

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REFERENCES


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.

Seth A. Berkowitz, MD

Images From Our Readers

The beautiful fall of Erie, Pennsylvania.

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