Habitual Caffeine Intake and the Risk of Hypertension in Women

Wolfgang C. Winkelmayer, MD, ScD
Meir J. Stampfer, MD, DrPH
Walter C. Willett, MD, DrPH
Gary C. Curhan, MD, ScD

Approximately 50 million people in the United States have hypertension, and the prevalence is increasing. Hypertension is a major risk factor for coronary heart disease, stroke, and congestive heart failure. Therefore, even small reductions in the prevalence of hypertension could have a potentially large public health and financial impact.

Much clinical lore about the possible association between caffeine intake and the risk of hypertension is available. Short-term studies have demonstrated that caffeine intake acutely increases blood pressure, but over time, attenuation of this effect does occur. Experimental studies have shown that caffeine can raise plasma levels of several stress hormones, such as epinephrine, norepinephrine, and cortisol, all of which can lead to an increase in blood pressure. However, these experiments have been limited to relatively short periods of observation, typically less than 1 week; information on a more sustained neuroendocrine response to regular exposure to caffeine is not available.

A long-term effect of caffeine intake on the risk of developing hypertension would be of substantial public health importance given the widespread consumption of beverages containing caffeine, but currently, studies of this association are scarce. A recent longitudinal study in 1017 men found a positive association between coffee consumption and blood pressure and incident hypertension in unadjusted analyses. Although the association with blood pressure level was significant in multivariate analyses, a nonsignificant 40% increase in the risk of incident diagnosis of hypertension (95% confidence interval [CI], 6% to 109%) for 3 to 4 cups per day and a 43% increase (95% CI, 6% to 118%) for 5 or more cups per day vs no coffee consumption was found. No published studies to date of the association between caffeine intake and the risk of hypertension in women are available.

To prospectively elucidate whether caffeine intake or consumption of certain caffeine-containing beverages is associated with the risk of incident hyper-
tension in women, we examined these questions in 2 large cohort studies of women, the Nurses’ Health Studies (NHSs) I and II.

METHODS

Study Populations

The NHS I cohort was assembled in 1976 when 121,700 female registered nurses, aged 30 to 55 years, completed and returned a mailed questionnaire.9 Follow-up questionnaires have been mailed every 2 years to update information on health-related behaviors and medical events. The NHS II began in 1989, when 116,671 female registered nurses, aged 25 to 42 years, completed and returned a mailed questionnaire. Questionnaires have been mailed every 2 years to update exposure information and diagnosis of new diseases. The follow-up for both cohorts exceeds 90%. In this analysis, all participants who had not been diagnosed with hypertension before the return of the 1990 NHS I or 1991 NHS II questionnaires were included. This study was approved by the institutional review board at Brigham and Women’s Hospital, Boston, Mass. Receipt of each questionnaire implies participant’s consent.

Dietary Assessment

Food frequency questionnaires were used to measure dietary intake and were completed in 1990, 1994, and 1998 for NHS I and 1991, 1995, and 1999 for NHS II. Participants were asked about their usual intake of foods and beverages during the past year. The response options for specified serving sizes were the following: never or less than once per month; 1 to 3 times per month; 1 per week; 2 to 4 per week; 5 to 6 per week; 1 per day; 2 to 3 per day; 4 to 5 per day; and 6 or more per day. The relevant beverages included on the questionnaire were the following: low-calorie cola (eg, Diet Coke or Diet Pepsi with caffeine), regular cola (eg, Coke, Pepsi, or other cola beverages with sugar), tea with caffeine, tea without caffeine, coffee with caffeine, and decaffeinated coffee. Total caffeine intake was calculated primarily using US Department of Agriculture food composition sources. In these calculations, it was 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 cola beverage, and 7 mg per serving of chocolate candy.10 This method of measuring coffee intake was shown to be valid in both the NHS I cohort and a similar cohort study of male health professionals.11-13

Assessment of Other Variables

Data on height and family history of hypertension were collected at baseline in both cohorts. Information on weight was updated every 4 years. Using each participant’s updated weight, body mass index was calculated by dividing the weight in kilograms by height in meters squared. Also, an updated variable for weight difference between baseline and the time of respective follow-up questionnaire was generated. Information on oral contraceptive use in the NHS II cohort also was updated every 4 years. The same semiquantitative food frequency questionnaires were used to determine intake of alcohol, sodium, potassium, magnesium, calcium, and phosphorus.14 Physical activity was assessed in NHS I (1988, 1992, and 1996) and NHS II (1989, 1993, and 1997) cohorts; energy expenditure was expressed in metabolic equivalent tasks.15 In addition, the frequency of analgesic drug use (aspirin, nonsteroidal anti-inflammatory drugs, and acetaminophen) was ascertained.16,17

Outcome Definition

The baseline and biennial follow-up questionnaires inquired about physician-diagnosed hypertension and the year of diagnosis. Self-reported diagnosis of hypertension was found to be reliable in the NHS I cohort.18 In a subset of women who reported hypertension, review of medical records confirmed a documented systolic and diastolic blood pressure, respectively, higher than 140 mm Hg and 90 mm Hg in 100% and higher than 160 mm Hg and 95 mm Hg in 77% of participants. Additionally, self-reported hypertension was predictive of subsequent cardiovascular events.18 A study participant was considered to have a history of hypertension if she reported a diagnosis of high blood pressure on any questionnaire up to and including the 1990 questionnaire in NHS I and the 1991 questionnaire in NHS II, and therefore was excluded from the study. Among the remaining women in each cohort, incident cases were included as those who first reported hypertension on any of the subsequent biennial questionnaires and whose date of diagnosis was after the return of the 1990 NHS I or the 1991 NHS II questionnaire. This method recently has been used in a study of folate intake and the risk of hypertension in women.19

Statistical Methods

The time of observation was between return of the 1990 NHS I and 1991 NHS II and the 2002 NHS I and 2003 NHS II questionnaires. Participants who did not return the baseline questionnaires for this study were allowed to contribute person-time for later time intervals, provided that they had not been diagnosed with hypertension prior to return of the respective questionnaire. Participants were censored after being diagnosed with hypertension or at the time of death. Each cohort was analyzed separately. Age-adjusted Cox proportional hazards regression models were used to estimate relative risks and 95% CIs. In addition, multivariate models were constructed that adjusted for other known risk factors of the study outcome: age (continuous), body mass index (continuous), alcohol use (6 categories), physical activity (quantiles of metabolic equivalent tasks), smoking status (current, past, or never), family history of hypertension (yes/no), and current oral contraceptive use (yes/no; only in NHS II). In addition, analyses were adjusted for sodium, magnesium, calcium, potassium, and phosphorus intake (quantiles) did not confound the estimates from these multivariate models. All variables were updated to reflect the most recent value provided by the participants on the biennial questionnaires. Participants with missing data were assigned to a missing category for that specific time pe-
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RESULTS

In NHS I, 53,175 women had not been diagnosed with hypertension at baseline in 1990. Another 7916 participants who did not respond to the 1990 questionnaire but who did respond to a later questionnaire disclosing that they previously had not been diagnosed with hypertension allowed them to contribute person-time from that point in time. Over the 12 years (539,388 person-years of follow-up), 19,541 incident cases of physician-diagnosed hypertension were reported.

In NHS II, 94,503 participants who were free of hypertension (87,369 in 1991 and an additional 7134 at a later point in time) were included in the analyses of younger women. During 909,199 person-years of observation, 13,536 participants responded that they were diagnosed with hypertension by a physician. Another 7916 participants who did not respond to the 1990 questionnaire but who did respond to a later questionnaire disclosing that they previously had not been diagnosed with hypertension were reported.

Participant characteristics by quintile of caffeine intake are presented in Table 1. In both cohorts, mean caffeine consumption ranged from less than 20 mg/d in the lowest quintile to approximately 600 mg/d in the highest quintile. Caffeine intake was correlated positively with alcohol consumption and smoking status. The findings in the NHS II

Table 1. Baseline Characteristics of Cohort by Quintile of Caffeine Intake in Nurses’ Health Study I (N = 53,175) and Nurses’ Health Study II (N = 87,369)*

<table>
<thead>
<tr>
<th>Quintile of Caffeine Intake</th>
<th>Nurses’ Health Study I (1990)</th>
<th>Nurses’ Health Study II (1991)</th>
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</thead>
<tbody>
<tr>
<td>Quadrant, mg/d</td>
<td>No. of women</td>
<td>Caffeine intake, mg/d</td>
</tr>
<tr>
<td></td>
<td>0-45</td>
<td>45-144</td>
</tr>
<tr>
<td>1</td>
<td>9864</td>
<td>10,070</td>
</tr>
<tr>
<td>2</td>
<td>14.8 (12.9)</td>
<td>97.0 (31.4)</td>
</tr>
<tr>
<td>3</td>
<td>55.4 (7.2)</td>
<td>55.4 (7.3)</td>
</tr>
<tr>
<td>4</td>
<td>24.8 (4.4)</td>
<td>25.0 (4.4)</td>
</tr>
<tr>
<td>5</td>
<td>8.9</td>
<td>10.5</td>
</tr>
<tr>
<td>Diastolic</td>
<td>74.9 (7.9)</td>
<td>75.5 (7.8)</td>
</tr>
<tr>
<td></td>
<td>4.6</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>2.13 (0.36)</td>
<td>2.12 (0.36)</td>
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<tr>
<td></td>
<td>112.0 (9.0)</td>
<td>112.6 (9.2)</td>
</tr>
<tr>
<td></td>
<td>73.8 (5.6)</td>
<td>74.1 (5.7)</td>
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<tr>
<td></td>
<td>73.8 (5.6)</td>
<td>74.1 (5.7)</td>
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*Data are presented as mean (SD) unless specified otherwise.

†Body mass index was calculated by dividing the weight in kilograms by height in meters squared.

Over the 12 years (539,388 person-years of observation), 13,536 participants responded that they were diagnosed with hypertension by a physician. Another 7916 participants who did not respond to the 1990 questionnaire but who did respond to a later questionnaire disclosing that they previously had not been diagnosed with hypertension were reported.

Participant characteristics by quintile of caffeine intake are presented in Table 1. In both cohorts, mean caffeine consumption ranged from less than 20 mg/d in the lowest quintile to approximately 600 mg/d in the highest quintile. Caffeine intake was correlated positively with alcohol consumption and smoking status. The findings in the NHS II cohort were marginally significant for an inverse association between caffeine intake and the risk of hypertension (Table 3; P for trend = .02). The findings in the NHS II cohort were practically identical (P for trend = .03). The results for intake of decaffeinated coffee also were similar to those in the highest quintile were not at an increased risk of hypertension (Table 2). Multivariate adjustment did not materially change these findings (Table 2).

To further examine this inverse U-shaped association, the frequency of use of different caffeine-containing beverages in relation to the risk of incident hypertension was evaluated. In multivariate models including beverage type, rather than actual caffeine intake, no association between frequency of intake of decaffeinated coffee and incident hypertension was observed in either cohort. Compared with those in the lowest quintile of caffeine consumption, the risk of hypertension was increased by 14% (95% CI, 9%-19% for NHS I) and 15% (95% CI, 9%-21% for NHS II) for those in the third quintile, whereas those


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the data for caffeinated coffee intake (data not shown); the trend suggested an inverse association of risk of hypertension in the NHS I cohort (P for trend = .08) but not in the NHS II cohort (P for trend = .79). An association between caffeinated tea intake and incident hypertension in the NHS I cohort (Table 4; P for trend = .08) was not found. However, in the cohort of younger women in NHS II, a moderate increase in risk of hy-

### Table 2. Age-Adjusted and Multivariate Relative Risks for Incident Hypertension According to Quintile of Caffeine Intake

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<tbody>
<tr>
<td>No. of cases</td>
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<td>Person-years</td>
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<td>Age-adjusted relative risk (95% CI)</td>
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<td>Multivariate relative risk (95% CI)*</td>
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### Table 3. Age-Adjusted and Multivariate Relative Risks for Incident Hypertension According to Frequency of Coffee Intake

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<td>No. of cases</td>
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<tr>
<td>Person-years</td>
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<tr>
<td>Age-adjusted relative risk (95% CI)</td>
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<td>Multivariate relative risk (95% CI)*</td>
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### Table 4. Age-Adjusted and Multivariate Relative Risks for Incident Hypertension According to Frequency of Caffeinated Tea Intake

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<tbody>
<tr>
<td>No. of cases</td>
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<td>Person-years</td>
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<td>Age-adjusted relative risk (95% CI)</td>
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<td>Multivariate relative risk (95% CI)*</td>
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Abbreviation: CI, confidence interval.
*Adjusted for age, body mass index, intake of alcohol, family history of hypertension, oral contraceptive use (in Nurses’ Health Study II only), physical activity, and smoking status, as well as the other classes of beverage.
pertension (P for trend = .01; Table 4) was detected.

Finally, an examination of the possible associations between caffeinated cola beverages and the risk of hypertension showed that sugared caffeinated cola (NHS I, P for trend = .03; NHS II, P for trend < .001) (Table 5) and diet caffeinated cola (NHS I, P for trend = .02; NHS II, P for trend < .001) (Table 6) were positively associated with hypertension in both cohorts.

Additional analyses adjusting for intake of sodium, magnesium, potassium, phosphorus, and calcium or analgesic drug use did not change the results materially for the caffeine intake or specific beverage intake analyses. When testing the robustness of the results, such as by limiting the analysis to those women who reported having had a routine physical examination during the time interval or by using baseline body mass index and updated change in weight rather than updated body mass index, the results were virtually unchanged (data not shown).

**COMMENT**

In this prospective study of the association between caffeine intake and the risk of physician-diagnosed hypertension in 2 large cohorts of women, we found a modest inverse U-shaped association between caffeine intake and hypertension in both cohorts. The magnitude of the highest multivariate relative risk was 1.13 in NHS I and 1.12 in NHS II.

To better understand this nonlinear relation between caffeine intake and the risk of hypertension, we evaluated the individual associations of several caffeine-containing beverages. Neither caffeine nor decaffeinated coffee demonstrated a positive association with incident hypertension in either cohort. The results for consumption of caffeinated tea were inconclusive: although no association was observed in the NHS I cohort, a positive trend was shown in the NHS II cohort. By contrast, we found a highly significant association between cola intake (sugared or low-calorie cola) and incident hypertension that was consistent across the cohorts.

To our knowledge, this study is the first to prospectively evaluate the putative effect of caffeine consumption on the long-term risk of hypertension in women. The speculation that coffee may cause hypertension was supported by several small experiments over short periods of observation (<80 days). If the short-term effects of caffeine on blood pressure persist, then habitual coffee drinking might contribute to an excess risk of hypertension. Such an effect would be of great public health importance given the widespread use of coffee and other caffeinated beverages. In this study with more than 1.4 million person-years of follow-up, the relevant exposures and outcomes have been found valid and accurate. and coffee intake was updated to reflect changes in individual behavior. We found strong evidence to refute
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Speculation that coffee consumption is associated with an increased risk of hypertension in women.

The associations found between caffeinated tea consumption and the risk of hypertension differed between the 2 cohorts. In the NHS I cohort, no association was found; however, in the NHS II cohort, a significant positive trend was observed. A recent study conducted among 711 men and 796 women in Taiwan found a strong inverse association between both frequency and duration of tea intake and hypertension. Since the types of tea (green or oolong) consumed in that study are likely different from those consumed in our study of US women, the comparability of the findings from these 2 studies appears uncertain.

In both NHS cohorts we found a positive association between frequency of caffeinated soft drink consumption and the risk of hypertension. The findings were consistent between the cohorts and were present across types of soda beverages: both sugared cola and diet cola beverages were associated with an increased risk of hypertension (Table 5 and Table 6). Hence, we speculate that it is not caffeine but perhaps some other compound contained in soda-type soft drinks that may be responsible for the increased risk in hypertension. If these associations are causal, they may have considerable impact on public health. Recent studies have found an effect of the intake of cola beverages on insulin resistance in a rat model; in humans, the intake of cola beverages was associated with an increased risk of diabetes in the NHS II cohort. These studies have attributed these associations to the glycomic load of corn syrup, which is used as sweetener in these beverages, and the caramel coloring, which is rich in advanced glycation end products. Further studies on the possible mechanisms underlying these associations are clearly needed.

We acknowledge the limitations of this study. We cannot rule out that individuals susceptible to adverse effects of caffeinated coffee intake on their blood pressure in the past may have reduced their consumption of beverages containing caffeine. Patients were asked about the frequency of their food intake, but no information was available on the daily timing of such ingestion. We did not directly measure the participants' blood pressure and the diagnosis of hypertension was self-reported. Nonetheless, self-reported blood pressure has been validated and demonstrated to be a strong predictor of actual values. Furthermore, we do not know whether these findings are generalizable beyond populations of predominantly white women. We also cannot exclude the possibility that the associations found are residually confounded. Last, no statement can be made on the effect of coffee intake on the control of blood pressure among individuals already diagnosed with hypertension.

In conclusion, consumption of coffee in women does not appear to increase the risk of developing hypertension. Whether caffeinated soft drinks are causally related to the risk of hypertension and its underlying mechanism will require further study.

Author Contributions: Dr Winkelmayer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Winkelmayer, Willett, Curhan. Acquisition of data: Stamper, Willett, Curhan. Analysis and interpretation of data: Winkelmayer, Stamper, Willett, Curhan. Drafting of the manuscript: Winkelmayer. Critical revision of the manuscript for important intellectual content: Winkelmayer, Stamper, Willett, Curhan. Administrative, technical, or material support: Stamper, Willett, Curhan. Study supervision: Curhan.

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References


