Association of Caffeine Intake and Caffeinated Coffee Consumption With Risk of Incident Rosacea in Women

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IMPORTANCE Caffeine is known to decrease vasodilation and have immunosuppressant effects, which may potentially decrease the risk of rosacea. However, the heat from coffee may be a trigger for rosacea flares. The relationship between the risk of rosacea and caffeine intake, including coffee consumption, is poorly understood.

OBJECTIVE To determine the association between the risk of incident rosacea and caffeine intake, including coffee consumption.

DESIGN, SETTING, AND PARTICIPANTS This cohort study included 82,737 women in the Nurses’ Health Study II (NHS II), a prospective cohort established in 1989, with follow-up conducted biennially between 1991 and 2005. All analysis took place between June 2017 and June 2018.

EXPOSURES Data on coffee, tea, soda, and chocolate consumption were collected every 4 years during follow-up.

MAIN OUTCOMES AND MEASURES Information on history of clinician-diagnosed rosacea and year of diagnosis was collected in 2005.

RESULTS A total of 82,737 women responded to the question regarding a diagnosis of rosacea in 2005 in NHS II and were included in the final analysis (mean [SD] age at study entry, 50.5 [4.6] years). During 112,005 person-years of follow-up, we identified 4,945 incident cases of rosacea. After adjustment for other risk factors, we found an inverse association between increased caffeine intake and risk of rosacea (hazard ratio for the highest quintile of caffeine intake vs the lowest, 0.76; 95% CI, 0.69-0.84; P < .001 for trend). A significant inverse association with risk of rosacea was also observed for caffeinated coffee consumption (HR, 0.77 for those who consumed ≥ 4 servings/d vs those who consumed <1/mo; 95% CI, 0.69-0.87; P < .001 for trend), but not for decaffeinated coffee (HR, 0.80; 95% CI, 0.56-1.14; P = .39 for trend). Further analyses found that increased caffeine intake from foods other than coffee (tea, soda, and chocolate) was not significantly associated with decreased risk of rosacea.

CONCLUSIONS AND RELEVANCE Increased caffeine intake from coffee was inversely associated with the risk of incident rosacea. Our findings do not support limiting caffeine intake as a means to prevent rosacea. Further studies are required to explain the mechanisms of action of these associations, to replicate our findings in other populations, and to explore the relationship of caffeine with different rosacea subtypes.
Rosacea is a common chronic inflammatory skin disease.1,2 Many triggers for rosacea have been postulated, including caffeine, hot beverages, sunlight, spicy foods, strenuous exercise, and hormonal factors.3-8

The reported direction and magnitude of the association between the risk of rosacea and caffeine and coffee intake in prior epidemiologic studies have been inconsistent.8-11 Previous studies did not differentiate between caffeinated and decaffeinated coffee and other beverages, and the distinction between amounts of caffeine and coffee consumed was made in only 1 study.8 We conducted the first large cohort study to our knowledge to evaluate the association between caffeine intake, coffee consumption, and risk of incident rosacea in a large cohort of women from the Nurses’ Health Study II (NHS II).

Methods

Study Population

Details of NHS II have been described previously.12,13 The study was approved by the institutional review board of Brigham and Women’s Hospital and Harvard School of Public Health, Boston, Massachusetts. Participants’ completion and return of the questionnaires were considered informed consent.

In the cohort, participants were asked about their intake of food and beverages every 4 years. Participants could report the number of servings by selecting from 9 frequency responses (never, 1-3/mo, 1/wk, 2-4/wk, 5-6/week, 1/d, 2-3/d, 4-5/d, and 6/d) for caffeinated coffee, decaffeinated coffee, tea, soft drinks, and chocolate. The total caffeine intake was calculated by summing the caffeine content for a determined amount of each item and multiplying that by its frequency of intake, and the distinction between amounts of caffeine and coffee consumed was made in only 1 study.8 We conducted these analyses, caffeine intake was categorized as quintiles, with cutoffs derived from caffeine intake in 1991 in NHS II. Coffee consumption was categorized a priori into 5 serving groups (<1/mo, 1/mo to 4/wk, 5-7/wk, 2-3/d, or ≥4/d). Caffeine intake from coffee and caffeine intake from other food sources were assessed as continuous variables. Trend tests were carried out using continuous measures by assigning the median to each category. The adjusted Cox proportional hazard analyses were fitted to a restricted cubic spline model to obtain the HR of rosacea as a function of caffeine intake with adjustment for covariates.

We conducted stratified analyses by smoking status, alcohol intake, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), and physical activity, as well as interaction analyses between these factors and the main exposure because they have been associated with rosacea in prior studies.11,17-19

A 4-year lag analysis excluding rosacea cases documented within the first 4 years of each updated assessment of caffeine and coffee intake was performed to address potential reverse- causation bias. To address the concern of potential residual confounding, we conducted a sensitivity analysis additionally adjusting for oral contraceptive use, cumulative UV (UV) flux, personal history of major chronic diseases, antidepressant medication use, and phobic anxiety. Because rosacea epidemiology varies with respect to race,20 a secondary sensitivity analysis was performed excluding nonwhite participants.

All statistical analyses were conducted using SAS software, version 9.4. All statistical tests were 2-tailed with a significance level of P < .05.

Key Points

**Question** Is there an association between risk of incident rosacea and caffeine intake, including from coffee consumption?

**Findings** In this cohort of 82,737 participants in the Nurses’ Health Study II, we identified 4,945 incident cases of rosacea, and found a significant inverse association between risk of rosacea and increased caffeine intake, particularly that from coffee. This association was not found for caffeine intake from other food sources (tea, soda, and chocolate).

**Meaning** Our findings do not support limiting caffeine intake as a means to prevent rosacea and may have implications for the causes of and clinical approach to rosacea.
Results

Table 1 summarizes the participant characteristics in 1991 stratified by quintile of caffeine intake. The proportion of current and past smokers and users of oral contraceptives were increased with increasing caffeine intake. In addition, participants with higher caffeine intake tended to be older and have higher alcohol intake. Other characteristics were similar among the 5 groups of caffeine intake. The biggest source of caffeine was caffeinated coffee, which showed the greatest difference in intake across quintiles of overall caffeine intake among the investigated food and drink groups.

During the 1120051 person-years of follow-up, we identified 4945 incident cases of rosacea. As supported by the data...
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Original Investigation Research

Table 3. Age- and Multivariate-Adjusted Hazard Ratios for Rosacea by Coffee Intake in the Nurses’ Health Study II (1991–2005)

<table>
<thead>
<tr>
<th>Coffee Servings, No.</th>
<th>Cases, No.</th>
<th>Person-Years, No.</th>
<th>Crude Incidence Rate per 100 000 Person-Years</th>
<th>Age-Adjusted Incidence Rate per 100 000 Person-Years*</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeinated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1/mo</td>
<td>1549</td>
<td>358 137</td>
<td>433</td>
<td>495</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>1/mo to 4/wk</td>
<td>802</td>
<td>170 772</td>
<td>470</td>
<td>510</td>
<td>1.01 (0.93-1.10)</td>
</tr>
<tr>
<td>5-7/wk</td>
<td>544</td>
<td>135 956</td>
<td>400</td>
<td>440</td>
<td>0.91 (0.83-1.00)</td>
</tr>
<tr>
<td>2-3/d</td>
<td>1643</td>
<td>343 578</td>
<td>478</td>
<td>482</td>
<td>0.96 (0.90-1.03)</td>
</tr>
<tr>
<td>≥4/d</td>
<td>407</td>
<td>111 608</td>
<td>365</td>
<td>364</td>
<td>0.79 (0.71-0.88)</td>
</tr>
<tr>
<td>P value for trend</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Decaffeinated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1/mo</td>
<td>2486</td>
<td>622 552</td>
<td>399</td>
<td>448</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>1/mo to 4/wk</td>
<td>1578</td>
<td>315 378</td>
<td>500</td>
<td>515</td>
<td>1.15 (1.08-1.23)</td>
</tr>
<tr>
<td>5-7/wk</td>
<td>403</td>
<td>83 536</td>
<td>482</td>
<td>489</td>
<td>1.12 (1.01-1.24)</td>
</tr>
<tr>
<td>2-3/d</td>
<td>447</td>
<td>88 837</td>
<td>503</td>
<td>476</td>
<td>1.15 (1.04-1.27)</td>
</tr>
<tr>
<td>≥4/d</td>
<td>31</td>
<td>97 477</td>
<td>318</td>
<td>292</td>
<td>0.83 (0.58-1.19)</td>
</tr>
<tr>
<td>P value for trend</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; NA, not applicable.

* Adjusted for age (continuous variable), race (non-Hispanic white, African American, Asian, or other race), postmenopausal hormone use (premenopause, never, current, or past users), alcohol drinking (none, <4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, or ≥30.0 g/d), smoking status (never smokers, past smokers 1-4 cigarettes/d, past smokers 5-14/d, past smokers 15-24/d, past smokers ≥25/d, current smokers 1-4/d, current smokers 5-14/d, current smokers 15-24/d), body mass index (continuous variable), and physical activity (metabolic equivalent in quintiles, h/wk).

Table 4. Hazard Ratios for Rosacea Associated With Caffeine Intake Per 100 mg/d Increment From Coffee and Other Foods in the Nurses’ Health Study II (1991–2005)

<table>
<thead>
<tr>
<th>Caffeine Source</th>
<th>Age-Adjusted HR (95% CI)</th>
<th>P Value for Trend</th>
<th>Multivariate-Adjusted* HR (95% CI)</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coffee</td>
<td>0.97 (0.96-0.99)</td>
<td>&lt;.001</td>
<td>0.96 (0.95-0.98)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Other foods including tea, soda, and chocolate</td>
<td>0.99 (0.94-1.05)</td>
<td>.82</td>
<td>1.02 (0.96-1.08)</td>
<td>.58</td>
</tr>
</tbody>
</table>

Abbreviation: HR, hazard ratio.

* Adjusted for age (continuous variable), race (non-Hispanic white, African American, Asian, or other race), postmenopausal hormone use (premenopause, never, current, or past users), alcohol drinking (none, <4.9 g/d, 5.0-9.9, 10.0-14.9, 15.0-29.9, or ≥30.0 g/d), smoking status (never smokers, past smokers 1-4 cigarettes/d, past smokers 5-14/d, past smokers 15-24/d, past smokers ≥25/d, current smokers 1-4/d, current smokers 5-14/d, current smokers 15-24/d), body mass index (continuous variable), and physical activity (metabolic equivalent in quintiles, h/wk).

reported in Table 2. We found a significant inverse association between increased caffeine intake and risk of rosacea. From the lowest to highest quintile of caffeine intake, the cohort age-adjusted incidence rates (AAIRs) of rosacea were 504, 502, 501, 478, and 372 per 100 000 person-years, respectively. Compared with the lowest quintile, the absolute risks of rosacea were decreased by 2, 3, 26, and 132 per 100 000 person-years, respectively, for the second to fifth quintile. The multivariate-adjusted HRs (95% CIs) for rosacea from the lowest to highest quintiles of caffeine intake were 1 [reference], 0.91 (0.84-1.00), 0.92 (0.84-1.00), 0.85 (0.77-0.93), and 0.76 (0.69-0.84) (P < .001 for trend). The approximately line downward-sloping restricted cubic spline curve (eFigure 1 in the Supplement) demonstrates the inverse association between caffeine intake and the risk of rosacea.

As supported by the data reported in Table 3, a significant inverse association was also observed between caffeinated coffee consumption and risk of incident rosacea (P < .001 for trend). Compared with individuals who consumed less than 1 serving of caffeinated coffee per month (AAIR, 495/100 000 person-years), participants who consumed 4 servings per day or more had the lowest risk of rosacea (AAIR, 364/100 000 person-years; HR = 0.77; 95% CI, 0.69-0.87). Decaffeinated coffee consumption was not associated with a decreased risk of rosacea (P = .39 for trend).

The data reported in Table 4 supports the association of caffeine intake with incident rosacea based on the caffeine source. Caffeine intake from coffee was inversely associated with risk of incident rosacea (P < .001 for trend), whereas caffeine intake from other sources (tea, soda, and chocolate) showed no association with risk of rosacea (P = .58 for trend).

We further examined the risk of rosacea associated with servings of caffeinated tea, caffeinated soda, and chocolate, and these data are reported in eTable 1 in the Supplement. We did not find a significant association between caffein-
ated tea or soda and risk of rosacea (P = .30 for trend and P = .08 for trend, respectively). Results suggested chocolate as a potential risk factor for rosacea (P = .04 for trend) (eTable 1 in the Supplement).

Analyses stratified by smoking, alcohol intake, physical activity, and BMI showed generally similar associations between caffeine intake and risk of rosacea as detailed with supporting data in eTables 2 through 5 in the Supplement. We did not find effect modification by smoking status (P = .37 for interaction), alcohol intake (P = .13 for interaction), physical activity (P = .33 for interaction), or BMI (P = .61 for interaction) on the association between caffeine intake and risk of rosacea.

The 4-year lag analysis and sensitivity analyses did not change the results materially (data not shown).

**Discussion**

In the present study, we found that caffeine intake from coffee but not from other foods (tea, soda, and chocolate) was associated with a decreased risk of incident rosacea in a dose-dependent manner. Although the relative risk of rosacea associated with caffeine intake and caffeinated coffee consumption was moderate, the absolute risk of rosacea was decreased remarkably by 132 per 100 000 person-years for the highest versus lowest quintile of caffeine intake and 131 per 100 000 person-years for caffeinated coffee consumption of 4 servings per day or more vs less than 1 serving per month.

Previous case-control studies and review articles have asserted differing effects of caffeine intake or coffee consumption on the risk of rosacea.8-31 One case-control study from Estonia20 and a literature review from France21 found no significant difference in risk of rosacea between groups consuming different amounts of caffeine. A case-control study from Poland reported increased risk of rosacea among coffee drinkers.21 In addition, a clinical narrative review and randomized clinical study analyzed caffeine as a potential trigger for rosacea flares.3,8 In the randomized clinical trial,8 participants with rosacea consumed caffeinated coffee and water at different temperatures. Caffeinated coffee was shown to have no effect on flushing in patients with rosacea, whereas heat led to flushing reactions.8

A variety of specific agents and mechanisms may be responsible for caffeine’s influence on rosacea. One possibility is its effect on vascular contractility. Specifically, vasodilation from neurovascular dysfunction has been documented in the pathogenesis of rosacea, particularly papulopustular rosacea.21,22 and caffeine is known to lead to vasoconstriction23,24 through its effect on the renin-angiotensin-aldosterone system.25 Increased caffeine intake may decrease vasodilation and consequently lead to diminution of rosacea symptoms. Second, caffeine has been documented to contain antioxidant agents and to have immunosuppressant effects,26-30 which may result in decreased inflammation in rosacea. Third, hormonal factors have been implicated in the development of rosacea,5,7 and caffeine can modulate hormone levels, including levels of adrenaline, noradrenaline, and cortisol.25

Heat has been shown to be a trigger factor in patients with rosacea.8 That decaffeinated coffee showed no association suggests that ingredients other than caffeine may have countered the effects of heat. One potential ingredient is polyphenol present in coffee. Polyphenols have antioxidant, anti-inflammatory, and vascular effects,31 and they have been shown benefit in rosacea treatment, especially for facial erythema, papules, and pustules.31 Further studies are needed to elucidate determinants for risk of rosacea in decaffeinated coffee.

We hypothesize that the lack of association with rosacea found for caffeinated food and drinks other than coffee is due to the low absolute intake of caffeine from sources other than coffee. For the different quintiles of total caffeine intake, the tea, soda, and chocolate consumption amounts did not show an increasing trend, illustrating the dominance of coffee as a source of caffeine. An alternative explanation is that coffee may contain other compounds that lower the risk of rosacea. However, since no association was found with decaffeinated coffee consumption, caffeine is the putative component of coffee responsible for the inverse association between coffee and risk of rosacea.

The positive association found between chocolate consumption and risk of rosacea has a few possible explanations. First, the amount of caffeine per serving of chocolate varies widely.32,33 Second, chocolate itself may be a risk factor for rosacea.34 Because the caffeine content in chocolate is low, other compounds may be responsible for the observed association.

**Limitations**

We acknowledge some limitations. First, data on lifetime diagnosis of rosacea and diagnosis year were self-reported in 2005 by participants, leaving our study prone to recall bias. However, misclassification of rosacea would be expected to be nondifferential with respect to caffeine and coffee intake. Our lag analysis limits the impact of misclassification of year of diagnosis. The validation study based on medical record review and the clinic-based validation study provide some support for the validity of the rosacea self-reports (unpublished data, W.-Q.L., June 1, 2018). However, we were only able to review the medical records for a small subset of cases to verify the accuracy of self-reported rosacea in the cohort. Efforts are warranted to better assess the accuracy of self-reported rosacea in the cohort.

Second, caffeine intake, consumption of coffee and other beverages, was assessed in 4-year intervals. Third, etiologic heterogeneity may underlie different types of rosacea, but we did not have data on rosacea subtypes. Fourth, although we had detailed data on many covariates, we cannot rule out the possibility of residual confounding from unmeasured confounders (such as family history, stress, heat, and hot beverages) or imperfectly measured confounders (as were adjusted for in our analyses). Compounds other than caffeine in the food and drinks investigated may influence risk of rosacea. Fifth, all participants were well-educated women, and most were white, which limits the generalizability of our findings.
Conclusions

In summary, we provide evidence that caffeine intake and caffeinated coffee consumption are associated with a decreased risk of incident rosacea. Our study may have implications for the causes and clinical approach to rosacea. Our findings do not support limiting caffeine intake as a preventive strategy for rosacea. Further studies are required to explain the underlying mechanisms of observed associations and to explore the relationship of caffeine with rosacea subtypes.

REFERENCES


