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Alcohol Intake and Risk of Incident Psoriatic Arthritis in Women

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Abstract

Objective—Alcohol intake has been associated with an increased risk of psoriasis. However, the association between alcohol intake and risk of psoriatic arthritis (PsA) has been unclear. We evaluated the association between alcohol intake and risk of incident PsA in a large cohort of US women.

Methods—The present study included a total of 82,672 US women who provided repeated data on alcohol intake over the follow-up (1991–2005). Self-reported PsA was validated using psoriatic arthritis screening and evaluation (PASE) questionnaire. Cox proportional hazards models were used to estimate the age- and multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the PsA in association with alcohol intake.

Results—We documented 141 incident PsA cases during 14 years (1,137,763 person-years) of follow-up. Compared to non-drinkers, the multivariate hazard ratios for PsA were 0.70 [95% confidence interval (CI): 0.48–1.01] for 0.1–14.9 g/d, 1.43 (95% CI: 0.67–3.08) for 15.0–29.9 g/d, and 4.45 (95% CI: 2.07–9.59) for ≥30.0 g/d of cumulative average alcohol intake. Risk estimates were generally consistent when using updated alcohol intake and baseline alcohol intake in 1991 as the exposures, and when the analysis was restricted to those who developed psoriasis during the follow-up.

Conclusions—Excessive alcohol intake was associated with an increased risk of incident PsA in a cohort of US women.

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DISCOLURE STATEMENT

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Keywords

alcohol; cohort study; psoriatic arthritis

Psoriasis is a common inflammatory immune-mediated disease that affects about 2–3% of the general population[1,2]. Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis that can develop into a deforming erosive arthropathy and result in disability[3]. PsA occurs in 6–42% of psoriatic patients and affects an estimated 520,000 individuals in the United States[4,5]. Clarification on the disease pathogenesis is critical for prevention and management of psoriasis and PsA.

Psoriasis is characterized by T-cell mediated hyperproliferation of keratinocytes and inflammatory processes[1,2]. Alcohol (ethanol) may influence the immune system in different ways. Whereas acute alcohol exposure is inhibitory, chronic alcohol exposure leads to an increase in inflammatory cell responses[6,7]. It has been demonstrated *in vivo* that excessive ethanol consumption contributes to the increased levels of several important makers, including tumour necrosis factor (TNF)-α-converting enzyme (TACE) and transforming growth factor (TGF)-α receptor 1, which are involved in systemic immunodysregulation in psoriasis[8–10]. There is also substantial epidemiologic evidence suggesting that alcohol intake is associated with risk of psoriasis[11–17]. However, the causality between alcohol and psoriasis is not conclusive because psoriasis may also increase alcohol use due to social anxiety and depression[14,18]. As a result, prospective data are critical and valuable in assessing the timing relationship between alcohol and psoriasis and PsA. Our previous prospective analysis suggests an association between alcohol intake and risk of incident psoriasis in a large cohort of US women, the Nurses' Health Study II (NHS II)[15]. However, prospective data for the relationship between alcohol intake and risk of PsA have been unavailable to date. To examine whether alcohol intake may be associated with an increased risk of incident PsA, we performed an updated analysis using data from the same NHS II cohort.

PATIENTS AND METHODS

Study population

The NHS II was established in 1989 when 116,430 registered female nurses aged 25–42 years were enrolled using a mailed baseline questionnaire inquiring about their medical history and lifestyle factors. Cohort participants receive biennial questionnaires enquiring about disease outcomes and health related factors during the follow-up. A response rate exceeding 90% has been achieved in each follow-up cycle[19]. The institutional review board of Partners Health Care System approved this study. The completion and return of the self-administered questionnaire was considered as informed consent.

Assessment of alcohol intake

We collected information on alcohol use as part of food-frequency questionnaires completed in 1991, 1995, 1999, and 2003. Participants were asked how often, on average, they had consumed regular beer, light beer (12 oz.), red wine, white wine (4 oz.), or liquor (one

standard drink) during the previous year, with the use of nine frequency categories ranging from never to six or more times per day[15,20]. Total alcohol intake was calculated in grams by adding the intake from each alcoholic-beverage: regular beer, 12.8 g; light beer 11.3g, wine, 11.0 g; and liquor, 14.0 g[15]. The reproducibility and validity of the assessment of alcohol intake were evaluated among 173 Boston-area participants of NHS, a similar cohort of female nurses, who completed written one-week dietary records every three months for a year, during which time they weighed or measured all their food and drinks[21]. The correlation of alcohol intake on the questionnaire with alcohol intake on the dietary records was 0.9[21].

Ascertainment of PsA cases

In 2005, cohort participants were asked if they had been diagnosed with psoriasis by a physician and the date of diagnosis (before 1991, 1991–1994, 1995–1998, 1999–2002 or 2003–2005). We confirmed self-reported psoriasis by Psoriasis Screening Tool (PST) questionnaire, which has 99% sensitivity and 94% specificity[22]. The confirmation rate reached 92% for psoriasis during the follow-up. Diagnosis of psoriasis with concomitant PsA was ascertained using psoriatic arthritis screening and evaluation (PASE) questionnaire, which includes a symptom scale with seven items and a function scale with eight items[23]. PASE has good test–retest reliability[24]. Furthermore, PASE can distinguish between the symptoms of PsA and osteoarthritis[23]. A total score of 47 or greater has been shown to identify PsA with high accuracy[23,24]. Our validation study also showed a high agreement between the score cutoff of 47 and the rheumatologist's diagnosis on PsA[25]. We sent out two waves of PST and PASE questionnaires to participants with self-reported psoriasis during 2008–2011 and confirmed a total of 1,600 psoriasis cases, among which 348 were diagnosed with concomitant PsA.

Assessment of covariates

Information on weight, smoking, menopausal status, postmenopausal hormone use, multivitamin use, and personal histories of chronic diseases (cardiovascular disease, type 2 diabetes, hypertension, and hypercholesterolemia) was collected biennially since 1989. Height was reported in 1989. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared for each two-year follow-up period. Physical activity was assessed in 1991, 1997, 2001, and 2005 based on the methodology documented elsewhere[26]. Information on acetaminophen and non-steroidal anti-inflammatory drugs use was first asked in 1989 and then collected biennially since 1993. Information on folate intake was available in 1991, 1995, 1999, and 2003.

Statistical analysis

Analysis was restricted to women who responded to the 2005 psoriasis questions and had completed a baseline diet questionnaire in 1991. We further excluded participants who had baseline psoriasis/PsA in 1991 (n=1,186), self-reported psoriasis but denied diagnosis in the PST and PASE questionnaires (n=430), and confirmed to have psoriasis/PsA but with missing diagnosis date (n=27) from the data analysis. A total of 82,672 women (with 573 confirmed cases of incident psoriasis) were included in the present analysis, and they contributed person-years of follow-up from the return date of the baseline questionnaire to a

confirmed diagnosis of psoriasis or PsA, or the end of follow-up (June 2005), whichever came first. For details of the derivation of the final study population, see Supplemental Figure 1. We used Cox proportional hazards models to estimate the age- and multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the PsA in association with alcohol intake. We categorized alcohol intake into the following categories: none, 0.1–14.9 grams per day (g/d, moderate), 15.0–29.9 g/d (high), and ≥30 g/d (excessive). To examine the consistency of the association, we used three forms of alcohol intake as the exposures: cumulative average intake, simple updated alcohol intake, and baseline intake in 1991[27]. Cumulative average intake was calculated as the mean of all previously reported intakes (e.g., average intake in 1995 was calculated as the mean of reported intakes in 1991 and 1995, and average intake in 1999 was calculated as the mean of reported intakes in 1991, 1995 and 1999), and may serve as a more accurate estimate of long-term intake. For updated alcohol intake, we used intake in 1991 for the follow-up between 1991 and 1995, and intake in 1995 for the follow-up between 1995 and 1999, and so forth. In addition, using baseline intake in 1991 as the exposure for the entire follow-up could also help address the potential reverse causality between alcohol intake and incidence of PsA. Multivariate analyses were conducted with adjustment for potential confounders. We used the most updated information for all adjusted variables prior to each follow-up interval to take into account potential changes over time. Missing data during any follow-up period were coded as a missing indicator category for categorical variables (e.g., smoking status) and with carried-forward values for continuous variables. To examine the influence of chronic diseases, multivariate HRs were estimated before and after adjusting for histories of chronic diseases. Secondary analyses were performed only among participants who were diagnosed with psoriasis during the follow-up. We also examined the associations of incident PsA with intake of individual alcoholic beverages. All statistical analyses were performed using Statistical Analysis System software (SAS, version 9.2; SAS Institute Inc, Cary, NC). All statistical tests were 2-tailed, and the significance level was set at $P<0.05$.

RESULTS

During 1,137,763 person-years of follow-up from 1991 to 2005, we documented a total of 141 incident PsA cases with complete data on alcohol intake. Table 1 shows the baseline characteristics of the study participants. Compared to non-drinkers, participants who consumed ≥30.0 g/d tended to be older and had higher prevalence of smoking and medication use (except postmenopausal hormone use) and lower intake of folate.

Compared to non-drinkers, the fully-adjusted HRs for PsA were 0.70 (95% CI: 0.48–1.01) for women who consumed 0.1–14.9 g/d, 1.43 (95% CI: 0.67–3.08) for 15.0–29.9 g/d, and 4.45 (95% CI: 2.07–9.59) for ≥30.0 g/d of cumulative average alcohol intake (Table 2). Risk estimates were similar before and after adjusting for histories of chronic diseases, and were also consistent when using updated alcohol intake and baseline alcohol intake in 1991 as the exposures. Interestingly, moderate drinkers (0.1–14.9 g/d) appeared to have a lower risk of PsA when compared to non-drinkers. The fully-adjusted HR for PsA was 0.69 (95% CI: 0.49–0.99) for women who consumed 0.1–14.9 g/d as compared to non-drinkers when using baseline alcohol intake as the exposure. We performed alternative analyses using moderate drinkers (0.1–14.9 g/d) as the reference, and found that the fully-adjusted HRs for PsA were

1.43 (95% CI: 0.99–2.06) for non-drinkers, 2.04 (95% CI: 0.98–4.27) for 15.0–29.9 g/d, and 6.35 (95% CI: 3.01–13.4) for ≥30.0 g/d of cumulative average alcohol intake (Supplemental Table 1). When we used baseline alcohol intake as the exposure, the fully-adjusted HR was 1.44 (95% CI: 1.01–2.06) for non-drinkers as compared to moderate drinkers.

Among participants who developed psoriasis during the follow-up (n=573), the association between alcohol intake and risk of PsA showed a similar pattern over the intake categories. Compared to non-drinkers, the fully-adjusted HRs for PsA were 0.75 (95% CI: 0.50–1.12) for 0.1–14.9 g/d, 1.09 (95% CI: 0.48–2.47) for 15.0–29.9 g/d, and 2.09 (95% CI: 0.90–4.84) for ≥30.0 g/d of cumulative average intake (Table 3). This fully-adjusted HR for ≥30.0 g/d was elevated to 2.79 (95% CI: 1.24–6.26) when using moderate drinkers as the reference.

Analyses for individual alcoholic beverages similarly suggest indicative higher HRs of PsA for heavier consumers (≥5 drink/wk) when compared to non-drinkers, and there was a significant association between regular beer consumption and risk of PsA in the multivariate-adjusted model (fully-adjusted HR: 2.84, 95% CI: 1.03–7.78).

DISCUSSION

In this prospective cohort study, we found that excessive alcohol intake (≥30.0 g/d) was associated with an increased risk of incident PsA in women. In contrast, moderate drinkers who consumed alcohol 0.1–14.9 g/d appeared to have the lowest risk of PsA as compared to non-drinkers. These results were generally consistent when using updated alcohol intake and baseline alcohol intake as the exposures, and when the analysis was restricted to those who developed psoriasis during the follow-up. Our findings suggest that excessive alcohol intake may be associated with a significantly increased risk of PsA (fully-adjusted HR for cumulative average intake of ≥30.0 g/d vs. non-drinkers: 4.45, 95% Cl: 2.07–9.59), which is consistent with our previous report on the association between alcohol intake and risk of psoriasis (fully-adjusted HR for cumulative average intake of ≥30.0 g/d vs. non-drinkers: 2.53, 95% CI: 1.45–4.40)[15].

It is well known that activated T lymphocytes and keratinocyte hyperproliferation are key features of psoriasis, whereas chronic alcohol exposure have been shown to be linked with an increase in inflammatory cell responses[6,7]. In an *in vitro* model using psoriatic keratinocytes and a T-cell-lymphoma cell line, ethanol (0.05%) activated T lymphocytes and keratinocyte hyperproliferation, as evidenced by increased levels of proinflammatory cytokines transforming TGF-α, interleukin-6 (IL-6), and interferon-α[28]. Another study showed that ethanol (0.0005–0.5%) markedly induces mitogen-derived lymphocyte proliferation in psoriatic patients[29]. Results from *in vitro* experiments further demonstrated that ethanol and acetone upregulate messenger RNA levels of genes coding for proliferating keratinocytes (e.g., α5 integrin, cyclin D1 and keratinocyte growth factor receptor) and lead to proliferation of nontumorigenic human (HaCaT) keratinocytes[30]. The transdermal alcohol concentration, and another alcohol metabolite, acetaldehyde, are thought to be important and direct triggers for psoriasis[31].

Together with our previous analysis which demonstrated that alcohol intake was associated with an increased risk of incident psoriasis in women[15], our data suggest that excessive alcohol intake is associated with increased risks of both incident psoriasis and PsA in women. Interestingly, moderate drinkers appeared to have a lower risk of PsA when compared to non-drinkers, though the risk estimates were not statistically significant in multivariate models. Similarly, our previous analysis also suggests indicative lower risk estimates of psoriasis for some medium intake categories when compared to non-drinkers, and the increased risk of psoriasis was generally specific to participants in the highest intake category[15]. It is well known that moderate alcohol intake can be protective of human health. For example, alcohol is linked to an extensively documented J-shaped dose effect curve, with regular moderate consumption reducing cardiovascular and overall mortality[32–34], whereas excessive or binge drinking has the opposite effect[34,35]. In addition, a nested case-control study also found a U-shaped association between alcohol intake and plasma IL-6 levels, a maker of inflammation, in patients with preclinical rheumatoid arthritis in the NHS[36]. Therefore, dose information is critical when assessing the relationship between alcohol intake and risk of inflammatory diseases such as PsA. Two previous case-control studies have assessed the association of alcohol with PsA among psoriasis patients[37,38]. However, both studies simply classified the psoriasis patients into drinkers and non-drinkers without dose information, and found no association between alcohol intake and PsA. It is possible that the positive relationship between higher alcohol intake and PsA may have been underestimated by not differentiating low or moderate versus excessive drinkers.

In addition, a recent case-control study with 127 PsA patients and 5,868 controls reported an inverse association between alcohol intake and risk of PsA as well as between alcohol and other forms of arthritis[39]. However, given the case-control nature of the study, the timing relationship between alcohol intake and PsA diagnosis was unclear, and the authors acknowledged that the inverse association between alcohol and arthritis may be secondary to disease development, with arthritis patients being less inclined to consume alcohol due to their decreased general well-being[39]. In contrast, our study collected alcohol intake data before the onset of disease, and the significant association between excessive alcohol intake and risk of PsA was unchanged even using baseline alcohol intake in 1991 (a time point long before the onset of most PsA cases) as the exposure. Furthermore, our secondary analyses found that the association between alcohol and PsA showed a similar trend among participants who were diagnosed with psoriasis during the follow-up, and the risk estimate for excessive alcohol intake (≥30.0 g/d) was significant when using moderate drinkers as the reference. This finding suggests that the positive association between excessive alcohol intake and risk of PsA is likely to be independent of psoriasis, which has been associated with alcohol intake in a number of previous studies[6,11–18].

Our study has several strengths. First, we were able to evaluate the effect of long-term alcohol intake using detailed, updated information on alcohol intake over 14 years. Second, because alcohol intake data were obtained prior to diagnosis of PsA, our study avoided the potential recall bias of case-control studies which collected exposure data after the diagnosis of PsA. Any errors in recall of exposure would be likely to attenuate rather than exaggerate the true associations. Third, our participants were all registered, well-educated nurses, and the accuracy of self-reported alcohol intake is likely to be high and to reflect actual

consumption. Previous studies have demonstrated good applicability of such alcohol data in identifying associated health risk[20,40,41]. Finally, based on detailed cohort follow-up information, we were able to control for a number of potential confounders which may have affected the association of interest.

Our study has several limitations. First, survivorship and response bias could be concerns due to retrospective nature of the study. Psoriasis questions were asked in 2005 and we could not obtain information from those who died during the follow-up. However, this is a cohort of relatively young women (mean age=34 years at baseline) and we have achieved a follow-up rate higher than 90% through each of the biennial follow-up cycles. Therefore, the potential selection bias is likely to be immaterial. In addition, we compared the baseline characteristics of participants who responded and not responded to the 2005 main questionnaire, and found that their major characteristics (i.e., age, alcohol intake level, BMI) were similar. In particular, average alcohol intake levels were 3.1 g/d in responders and 2.9 g/d in nonresponders. Therefore, it is less likely that the response bias would distort the observed association materially. Second, we ascertained PsA cases using the PASE questionnaire among women with psoriasis. PASE picks up individuals with active disease who are more likely to have inflamed joints and increased systemic inflammation, and thus it probably underestimates the number of real cases. However, our pilot studies suggested that PASE questionnaire was a reliable tool for PsA screening[23,24,42]. As a result, we expect a high validity of PsA ascertainment among the cohort of health professionals. There is another concern about the potential misclassification of PsA with other musculoskeletal conditions (e.g., osteoarthritis), whereas PASE can distinguish symptoms of PsA and osteoarthritis[23,42]. Third, the numbers of incident PsA cases are limited in the two highest alcohol intake categories, which could potentially cause distortion of the estimated HR and thus the results may not be directly applicable to other populations. Further prospective studies with larger numbers of incident PsA cases are needed to confirm our findings. Fourth, our cohort consisted entirely of women, most of whom were white, and thus the generalizability of the results to males and other ethnicities is limited.

In conclusion, our study suggests that alcohol intake above a certain threshold (≥30.0 g/d) is associated with an increased risk of incident PsA. Our findings were consistent in analyses using different alcohol intake variables. These findings are also in line with the biological evidence that high levels of alcohol intake contribute to systemic inflammation and may trigger psoriatic eruption, and thus may have potential important implications for the prevention of PsA. Interestingly, moderate alcohol drinkers appeared to have a lower risk of PsA when compared to non-drinkers. Our findings imply that psoriasis patients with excessive alcohol intake may gain potential health benefits by lowering their alcohol intake levels. Nevertheless, further research is needed to confirm whether the risk of PsA may vary according to alcohol dose and help draw more informative recommendations for the prevention and management of PsA in clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Age-adjusted baseline characteristics of the study population according to alcohol intake[a]

	None (n=34,788)	0.1–14.9 g/d (n=44,264)	15.0–29.9 g/d (n=2,206)	≥30.0 g/d (n=869)
Age, years, mean (SD)	36.3(4.6)	36.1(4.7)	37.0(4.6)	37.7(4.3)
White race, %	94.1	97.2	97.7	97.8
Body mass index, kg/m^2, mean (SD)	25.3(5.8)	23.9 (4.7)	23.2(3.8)	23.6(4.2)
Physical activity, metabolic-equivalents hrs/wk, mean (SD)	18.3(24.9)	22.3(27.5)	24.7(28.7)	22.8(28.4)
Current smoking, %	8.4	12.8	22.5	36.4
Current acetaminophen use, %	21.8	20.5	20.5	23.0
Current nonsteroidal anti-inflammatory drugs use, %	17.7	19.8	23.6	22.5
Postmenopausal status, %	4.1	3.2	3.0	3.1
Current postmenopausal hormone use,[b] %	75.9	77.4	76.7	73.2
Current multivitamin use, %	44.8	43.5	44.0	45.2
Folate intake, µg/d	494(318)	472(273)	428(219)	413(215)
History of chronic diseases				
Cardiovascular disease, %	0.03	0.03	0	0
Type 2 diabetes, %	0.3	0.1	0.04	0.1
Hypertension, %	7.2	5.3	6.7	8.0
Hypercholesterolemia, %	15.6	13.7	12.3	14.6

[a] All variables other than age are standardized to the age distribution of the study population. SD, standard deviation.

[b] Percent of use among postmenopausal women only.

Table 2

Hazard ratios of psoriatic arthritis according to alcohol intake among all participants

	Cases	Person-Years	Age-adjusted HR (95% CI)	Multivariate-adjusted HR[a] (95% CI)	Multivariate-adjusted HR[b] (95% CI)
Cumulative average alcohol intake					
None	55	386,298	1.00	1.00	1.00
0.1–14.9 g/d	70	702,511	0.64 (0.45–0.91)	0.70 (0.48–1.01)	0.70 (0.48–1.01)
15.0–29.9 g/d	8	38,478	1.19 (0.56–2.50)	1.39 (0.65–2.99)	1.43 (0.67–3.08)
≥30.0 g/d	8	10,476	4.42 (2.10–9.31)	4.27 (1.99–9.19)	4.45 (2.07–9.59)
Updated alcohol intake					
None	65	465,786	1.00	1.00	1.00
0.1–14.9 g/d	61	612,878	0.70 (0.49–0.99)	0.83 (0.58–1.18)	0.83 (0.58–1.20)
15.0–29.9 g/d	4	41,122	0.53 (0.19–1.45)	0.71 (0.25–1.97)	0.73 (0.26–2.03)
≥30.0 g/d	11	16,978	3.45 (1.81–6.58)	3.80 (1.95–7.37)	3.96 (2.03–7.70)
Baseline alcohol intake in 1991					
None	73	482,080	1.00	1.00	1.00
0.1–14.9 g/d	57	613,193	0.62 (0.44–0.88)	0.69 (0.48–0.98)	0.69 (0.49–0.99)
15.0–29.9 g/d	5	30,506	1.03 (0.42–2.56)	1.21 (0.48–3.03)	1.23 (0.49–3.09)
≥30.0 g/d	6	11,985	3.01 (1.31–6.93)	2.79 (1.21–3.11)	2.87 (1.22–6.71)

[a] Hazard ratios were further adjusted for body mass index (<25.0, 25–29.9, 30–34.9, and ≥35 kg/m^2), physical activity (<3, 3–8.9, 9–17.9, 18–26.9, and ≥27 metabolic equivalent hours/week), smoking status (never, past, current smoking with 1–14, 15–24, or ≥25 cigarettes/d), acetaminophen use (yes or no), nonsteroidal anti-inflammatory drugs use (yes or no), menopausal status and postmenopausal hormone use (premenopausal, postmenopausal use or no use), multivitamin use (yes or no), and folate intake (in quintiles).

[b] Hazard ratios were adjusted for the covariates listed above plus personal histories of cardiovascular disease (yes or no), type 2 diabetes (yes or no), hypertension (yes or no), and hypercholesterolemia (yes or no).

Table 3

Hazard ratios of psoriatic arthritis according to cumulative average alcohol intake among participants with confirmed psoriasis

	Cases	Person-Years	Age-adjusted HR (95% CI)	Multivariate-adjusted HR[a] (95% CI)	Multivariate-adjusted HR[b] (95% CI)
Non-drinkers as the reference					
None	55	2,524	1.00	1.00	1.00
0.1–14.9 g/d	70	4,734	0.68 (0.47–0.99)	0.75 (0.50–1.12)	0.75 (0.50–1.12)
15.0–29.9 g/d	8	370	0.92 (0.42–2.00)	1.13 (0.50–2.55)	1.09 (0.48–2.47)
≥30.0 g/d	8	191	1.89 (0.88–4.09)	2.12 (0.92–4.88)	2.09 (0.90–4.84)
Moderate drinkers as the reference					
None	55	2,524	1.47 (1.01–2.12)	1.33 (0.90–1.98)	1.33 (0.89–1.99)
0.1–14.9 g/d	70	4,734	1.00	1.00	1.00
15.0–29.9 g/d	8	370	1.35 (0.63–2.87)	1.51 (0.70–3.27)	1.45 (0.67–3.16)
≥30.0 g/d	8	191	2.77 (1.30–5.92)	2.82 (1.26–6.31)	2.79 (1.24–6.26)

[a] Hazard ratios were further adjusted for body mass index (<25.0, 25–29.9, 30–34.9, and ≥35 kg/m^2), physical activity (<3, 3–8.9, 9–17.9, 18–26.9, and ≥27 metabolic equivalent hours/week), smoking status (never, past, current smoking with 1–14, 15–24, or ≥25 cigarettes/d), acetaminophen use (yes or no), nonsteroidal anti-inflammatory drugs use (yes or no), menopausal status and postmenopausal hormone use (premenopausal, postmenopausal use or no use), multivitamin use (yes or no), and folate intake (in quintiles).

[b] Hazard ratios were adjusted for the covariates listed above plus personal histories of cardiovascular disease (yes or no), type 2 diabetes (yes or no), hypertension (yes or no), and hypercholesterolemia (yes or no).