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# Niacin intake and incident adult-onset atopic dermatitis in women

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## Capsule summary

Supplemental nicotinamide, a derivative of niacin, has been reported to decrease transepidermal water loss. However, in this analysis including 67,643 women from the Nurses' Health Study 2, niacin intake was not protective for atopic dermatitis.

### Keywords

Atopic dermatitis; eczema; niacin; nicotinamide; multivitamin; B-vitamin; dietary supplements; diet

## To the Editor

Adult-onset atopic dermatitis (AD) is a recognized entity[1] but little is known about risk factors for its development. Results from a randomized controlled trial of coated oral nicotinamide tablets for the prevention of skin cancer found that nicotinamide modestly decreased trans-epidermal water loss (TEWL), a measure of epidermal barrier integrity, among participants.[2] Nicotinamide is a derivative of niacin (vitamin B3, nicotinic acid), a nutrient found in many foods and supplements, including B vitamin complex and multivitamins. Given that increases in TEWL are associated with AD,[3] we hypothesized that increased niacin intake would be protective from the development of AD in adulthood. We aimed to investigate this association in the Nurses' Health Study 2 (NHS2), a large prospective cohort study of US female nurses.

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Conflicts of interest: None relevant

Disclosures not relevant to this work: Dr. Drucker has received honoraria from Astellas Canada (speaker). Dr. Qureshi has received honoraria that have been donated to charity from Abbvie, Amgen, Centers for Disease Control, Janssen, Merck, Novartis, Pfizer (Consultant) and Amgen (investigator). Dr. Drucker and Dr. Qureshi are investigators for Sanofi/Regeneron (no financial compensation).

NHS2 was established in 1989 with 116,430 participants between the ages of 25 and 42. Follow-up questionnaires are sent biennially to participants, updating information on diseases, anthropometric factors and other risk factors. Height and race/ethnicity were assessed at cohort baseline. Smoking status, physical activity, postmenopausal hormone use and history of asthma, hypertension, hypercholesterolemia, type 2 diabetes and cardiovascular disease (myocardial infarction and stroke) are all assessed and updated during cohort follow-up.

AD was assessed by self-report in 2013 when participants were asked about a history of clinician-diagnosed “eczema (atopic dermatitis),” in addition to the year they were diagnosed in intervals (before 1995, 1995–2002, 2003–2008, 2009–2010, 2011+). In this analysis, we included only incidence cases with reported diagnosis after 1995. Cases of AD diagnosed before 1995, when participants were between the ages of 31 and 48, were excluded.

A validated food frequency questionnaire (FFQ) was used to collect dietary information in 1991 and every four years thereafter.[4, 5] Participants responded to questions regarding how often on average they consumed specific types of food and drink, including alcohol, during the previous year. Total niacin intake was calculated using intake from both dietary sources and supplements using cumulative average intake up to the start of each follow-up interval to represent long-term dietary intake and to reduce measurement errors.

We followed participants for incident AD starting from 1995. Participants who reported AD diagnosed prior to 1995, who did not return the 2013 questionnaire and those missing niacin intake information were excluded, leaving 67,643 participants in the analysis. Person-time of follow-up was calculated from the return month of the 1995 questionnaire to the date of the first report of atopic dermatitis or end of follow-up (June 2013), whichever came first.

Cox proportional hazard models were used to compute the hazard ratios (HR) and 95% confidence intervals (CI) of AD with total, dietary and supplemental niacin intakes in quintiles. A separate analysis was conducted with B vitamin complex and multivitamin intake as the exposures. Covariates used in multivariate analyses are listed in the table legends. The most recent information for time-varying variables prior to each follow-up interval was used to take into account potential changes over the follow-up. Trend tests were performed by assigning median values for niacin intake categories and treating the new variable as a continuous term in the models. We performed stratified analyses by history of asthma and by history of hypertension, hypercholesterolemia, type 2 diabetes and cardiovascular disease. As niacin can be generated from dietary tryptophan, we performed a sensitivity analysis incorporating the contribution of tryptophan intake into our dietary and total niacin intake variables, using a 60:1 tryptophan to niacin conversion factor.[6]

We used SAS software version 9.2 (SAS Institute Inc., Cary, North Carolina) for all statistical analyses. All statistical tests were two-tailed, and the significance level was set at $P<0.05$.

Characteristics of the cohort according to quintiles of total niacin intake are presented in Table 1. Participant characteristics were similar across quintiles of niacin intake, but physical activity appeared to increase with niacin intake.

We did not find an inverse association between niacin intake and risk of AD. In contrast, increased niacin intake was associated with increased risk of AD ($P_{trend}$ = 0.0009) in the multivariate-adjusted model (Table 2). This positive association was significant for supplemental niacin intake ($P_{trend}$ = 0.01) but not for dietary niacin intake ($P_{trend}$ = 0.83). Significant positive associations were also seen with B complex and multivitamin supplement intake (Supplementary Table 1). In the stratified analysis by history of asthma, increased risk for AD was only seen with total and supplementary niacin intake among participants without asthma (Supplementary Table 2). In the stratified analysis by history of cardiovascular risk factors and disease and in the sensitivity analysis incorporating tryptophan intake, there was no material difference in the results (data not shown).

Contrary to our hypothesis, total niacin intake was not protective for adult-onset AD in this study, and it appeared to increase the risk in a dose-dependent fashion as indicated by the significant trend tests. In previous studies intake of nicotinamide, a derivative of niacin, decreased TEWL[2] and maternal serum nicotinamide levels in late pregnancy were protective form the development of AD at 12 months in their offspring.[7] The positive association of niacin intake with AD risk in our study appeared to be driven by supplemental niacin intake in the form of B complex vitamins and multivitamins, rather than dietary niacin intake. While our findings are interesting, it is not clear why this relationship exists and what specific components of these supplements are causing the association; we cannot directly attribute this risk to niacin alone. Our stratified analysis by cardiovascular risk factors and disease suggest that the associations seen were not due to confounding by increased supplement intake in participants with those comorbidities; nevertheless, despite controlling for a number of important covariates, we cannot rule-out residual confounding by unmeasured factors. For example, NHS2 does not collect data on carcinoid syndrome, a rare condition that can lead to skin eruptions and derangements in niacin metabolism.

Our study is strengthened by the well-established cohort with high-quality data on participant characteristics and dietary factors. While NHS2 is a prospective study, elements of our analysis are retrospective, including participants' recall of their date of AD diagnosis. Self-reported history of AD in adults has good specificity and positive predictive value but sensitivity is low.[8] Some cases of reported adult-onset AD may represent cases of unremembered childhood AD followed by a prolonged remission and eventual relapse in adulthood. Other cases may represent other forms of dermatitis, including the possibility, though rare, that participants experience a systemic allergic contact dermatitis to components of supplement pills or capsules. We plan to conduct studies to better characterize the atopic dermatitis phenotype among NHS2 participants in the future. The study's inclusion of women only, predominantly white population and high median age (40 years) limit its generalizability. Caution must be taken when extrapolating our findings to other populations, including men, other races/ethnicities and other age groups. It is also important to note that while nicotinamide is a derivative of niacin, our study uses measures

of niacin intake specifically, rather than nicotinamide which was supplemented in the previously referenced randomized controlled trial.[2]

In conclusion, niacin intake was not protective for the development of AD in adulthood in this study of US women. Our findings of increased risk of AD with supplementary B complex and multivitamin intake should be replicated in other populations and warrant further study before any specific clinical recommendations can be made. Additionally, studies examining the clinical course of established AD in relation to B vitamin intake would be beneficial. The results of this study do not support a role for supplementary niacin intake as a means to prevent AD in adults.

Sincerely,

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Table 1**

Characteristics of participants by total baseline (1995) niacin intake in quintiles

| | Quintiles of total niacin intake | | | | |
|---|---|---|---|---|---|
| | **Q1** | **Q2** | **Q3** | **Q4** | **Q5** |
| Number of participants | 13,404 | 13,790 | 13,360 | 13,561 | 13,528 |
| Age, years * | 40.3 (4.6) | 40.5 (4.5) | 40.3 (4.6) | 39.9 (4.8) | 40.8 (4.7) |
| Total niacin intake (mg/d) ^ | 19.3 (2.4) | 24.2 (1.1) | 28.9 (1.9) | 38.5 (3.4) | 73.6 (36.5) |
| Dietary niacin intake (mg/d) ^ | 19.6 (2.5) | 23.9 (2.0) | 26.3(4.1) | 24.9 (5.4) | 26.4 (7.2) |
| Supplemental niacin intake (mg/d) | 0.2 (0.8) | 0.4 (1.3) | 2.6 (4.4) | 13.7 (6.6) | 44.0 (33.7) |
| Body mass index (kg/m$^2$) | 25.5 (5.9) | 25.8 (5.8) | 26.0 (5.8) | 25.4 (5.5) | 25.3 (5.6) |
| Physical activity level (metabolic-equivalents hrs/wk) | 18.6 (25.3) | 18.8 (23.9) | 20.2 (24.3) | 22.3 (28.3) | 23.8 (30.6) |
| Alcohol consumption (g/d) | 3.4 (7.1) | 3.6 (6.4) | 3.7 (6.7) | 3.5 (6.3) | 3.4 (6.6) |
| Current smoking, % | 11.1 | 10.5 | 9.7 | 8.1 | 8.7 |
| Past smoking, % | 21.5 | 23.4 | 25.4 | 23.9 | 25.5 |
| Postmenopausal, % | 6.6 | 6.7 | 6.7 | 7.2 | 8.0 |
| Hormone use among postmenopausal, % | 82.8 | 85.1 | 85.0 | 88.6 | 87.2 |
| Total energy intake (kcal/d) | 1660 (528) | 1824 (535) | 1937 (557) | 1941 (543) | 1701 (537) |
| White race, % | 95.7 | 96.5 | 96.6 | 96.6 | 96.0 |
| History of cardiovascular disease, % | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| History of type 2 diabetes, % | 0.3 | 0.5 | 0.6 | 0.5 | 0.6 |
| History of hypertension, % | 8.5 | 8.8 | 9.3 | 8.9 | 9.7 |
| History of hypercholesterolemia, % | 19.9 | 19.9 | 21.1 | 20.6 | 22.7 |
| History of asthma, % | 8.7 | 9.2 | 9.0 | 8.9 | 10.8 |

Values are means(SD) or percentages and are standardized to the age distribution of the study population.

* Value is not age adjusted

^ Value is energy-adjusted

**Table 2**

Risk of atopic dermatitis associated with total, dietary and supplemental niacin intake among participants in the Nurses' Health Study 2 (1995–2013)

| | Median niacin intake (mg/d) | Person years | Atopic dermatitis cases | Age-adjusted HR (95% CI) | MV-adjusted HR (95% CI)* |
|---|---|---|---|---|---|
| **Total niacin intake** | | | | | |
| 1st quintile | 19.9 | 237,367 | 355 | 1.00 (ref) | 1.00 (ref) |
| 2nd quintile | 24.2 | 239,793 | 379 | 1.05 (0.91–1.21) | 1.04 (0.90–1.20) |
| 3rd quintile | 28.7 | 238,675 | 382 | 1.06 (0.91–1.22) | 1.05 (0.90–1.21) |
| 4th quintile | 38.4 | 239,438 | 427 | 1.17 (0.91–1.22) | 1.16 (1.01–1.34) |
| 5th quintile | 59.9 | 239,245 | 458 | 1.26 (1.09–1.44) | 1.23 (1.07–1.42) |
| | | | P for trend | 0.0003 | 0.0009 |
| **Dietary niacin intake** | | | | | |
| 1st quintile | 18.5 | 241,182 | 407 | 1.00 (ref) | 1.00 (ref) |
| 2nd quintile | 21.7 | 238,242 | 390 | 0.97 (0.84–1.11) | 0.95 (0.83–1.09) ^ |
| 3rd quintile | 23.8 | 236,777 | 388 | 0.97 (0.84–1.11) | 0.95 (0.83–1.09) ^ |
| 4th quintile | 26.0 | 238,573 | 413 | 1.02 (0.89–1.17) | 1.00 (0.87–1.14) ^ |
| 5th quintile | 30.0 | 239,744 | 403 | 0.99 (0.86–1.13) | 0.96 (0.84–1.11) ^ |
| | | | P for trend | 0.90 | 0.82 |
| **Supplemental niacin intake** | | | | | |
| None | 0 | 343,456 | 506 | 1.00 (ref) | 1.00 (ref) |
| 0.1–2.0 mg/d | 1.6 | 57,287 | 82 | 0.90 (0.71–1.15) | 0.92 (0.72–1.17)$ |
| 2.1–10 mg/d | 2.8 | 247,204 | 411 | 0.99 (0.87–1.14) | 1.00 (0.87–1.15)$ |
| 10.1–18 mg/d | 11.4 | 204,165 | 359 | 1.01 (0.87–1.16) | 1.02 (0.88–1.17)$ |
| >18 mg/d | 20.0 | 342406 | 643 | 1.16 (1.03–1.31) | 1.15 (1.02–1.30)$ |
| | | | P for trend | 0.007 | 0.01 |

*adjusted for BMI (in 10 categories), smoking status (never, past, current (1–14, 15–25, 25+ cigarettes per day)), physical activity (quintiles), alcohol intake (0, 0.1–4.9, 5–9.9, 10+ g/day), race (white, other), history of hypertension, hypercholesterolemia, type 2 diabetes, cardiovascular disease (myocardial infarction or stroke) and asthma, postmenopausal hormone use, and total calorie intake (quartiles)

^additionally adjusted for supplementary niacin intake (in categories)

$additionally adjusted for dietary niacin intake (in quintiles)