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Inflammatory dietary pattern and incident psoriasis, psoriatic arthritis, and atopic dermatitis in women: a cohort study

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Abstract

Background: Diet is a modulator of inflammation and may impact inflammatory skin diseases.

Objective: To assess the relationship between pro-inflammatory dietary patterns and incident psoriasis, psoriatic arthritis (PsA), and atopic dermatitis (AD).

Methods: We conducted cohort studies among women in the Nurses' Health Study II. The empirical dietary inflammatory pattern (EDIP) score was calculated at baseline and every four years. Incident psoriasis, PsA, and AD were assessed by validated self-report. We used multivariable-adjusted Cox proportional hazards models to calculate hazard ratios (HRs) and 95%

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Conflicts of interest: In the last three years, Dr. Drucker served as an investigator and has received research funding from Sanofi and Regeneron and has been a consultant for Sanofi, RTI Health Solutions, Eczema Society of Canada and Canadian Agency for Drugs and Technology in Health. He has received honoraria from Prime Inc, Spire Learning, CME Outfitters and Eczema Society of Canada. His institution receives education grants from Sanofi. Dr. Qureshi has served as a consultant (honoraria donated to charity) for Eli Lilly, Amgen, Centers for Disease Control, Janssen, Merck, Novartis and Pfizer, has been an investigator (non-compensation) for Sanofi and has a patent pending for Nix-Tix tick remover.

confidence intervals (CIs) for the association between EDIP quintiles and risk of psoriasis, PsA and AD.

Results: We had 85,185 participants in the psoriasis analysis and 63,443 in the AD analysis. There were 1,432 cases of psoriasis, 262 cases of PsA and 403 cases of AD. Pro-inflammatory dietary patterns were not associated with risk of the outcomes in multivariable models (all P -trend > 0.05). HRs comparing the highest to the lowest EDIP quintile were 0.99 (95% CI 0.83 – 1.18) for psoriasis, 1.22 (0.81 – 1.83) for PsA and 0.96 (0.69 – 1.34) for AD.

Limitations: Recall and self-report.

Conclusions: Our findings do not support dietary inflammatory potential as a risk factor for psoriasis, PsA or AD.

Keywords

psoriasis; psoriatic arthritis; atopic dermatitis; inflammatory diet; NHS-II; CRP; IL-6; TNF- α ; EDIP

Introduction

Psoriasis and atopic dermatitis are chronic immune-mediated, inflammatory skin conditions affecting 3%^{1, 2} and 5 – 7%^{3, 4} of the US adult population, respectively. Psoriatic arthritis, a seronegative spondyloarthropathy, is present in up to 30% of patients with psoriasis.⁵ While intrinsic immunological processes play a role in the pathogenesis of these conditions,^{6–8} there are well-recognized factors such as obesity,^{9–11} smoking,^{12–15} and stress^{16, 17} that may modulate the risk, severity, and prognosis of these inflammatory conditions.

Diet is a modifiable factor implicated in chronic systemic inflammation^{18–20} and in the development and progression of several chronic diseases.^{21–24} Recent meta-analyses highlight the anti-inflammatory benefit of the Mediterranean diet with reductions of circulating C-reactive protein (CRP), interleukin-6 (IL-6), and adiponectin concentrations²⁵ in addition to decreased risk of diabetes²⁶ and cancer mortality,^{27, 28} both of which have known pro-inflammatory pathologies.^{29–33} The Empirical Dietary Inflammatory Pattern (EDIP) is a recently developed and validated measure;³⁴ dietary patterns with high EDIP scores are associated with higher levels of tumor necrosis factor alpha (TNF- α), TNF- α R1, TNF- α R2, CRP, IL-6, and adiponectin.^{34–36} Psoriasis and psoriatic arthritis are Th1- and Th17-mediated diseases with increased serum levels of IL-6, CRP, and TNF- α ³⁷ – biomarkers of systemic inflammation that are also elevated in other chronic inflammatory diseases such as diabetes,³⁸ cardiovascular disease,^{39, 40} and inflammatory bowel disease.⁴¹ In contrast to psoriasis and psoriatic arthritis, atopic dermatitis is primarily a Th2-mediated skin disease with lesser involvement of Th1/Th17 inflammatory cytokines.⁴²

Although many patients wonder whether an anti-inflammatory diet can decrease their risk of inflammatory skin disease, patients and clinicians have limited evidence on which to base ensuing discussions. The objective of our study was to assess whether pro-inflammatory dietary patterns increase the risk of incident psoriasis, psoriatic arthritis, and atopic dermatitis in a large cohort of US women. We hypothesized that consumption of a pro-

inflammatory diet, as measured by higher EDIP scores, would increase the risk of developing psoriasis and psoriatic arthritis. Given the divergent inflammatory mechanisms underlying psoriatic disease and atopic dermatitis, we expected the relationship between EDIP score and atopic dermatitis to be null.

Materials & Methods

Study population

The Nurses' Health Study II (NHS-II) is a large prospective cohort study started in 1989 with 116,430 US female nurses aged 25 – 42 years. Data on risk factors and diseases are collected by questionnaire biennially.

Assessment of diet and calculation of EDIP scores

In NHS-II, food frequency questionnaires are administered every four years starting from 1991. The development of the EDIP score in a sample of 5230 women in the Nurses' Health Study has been described elsewhere.³⁴ In brief, the EDIP is an empirical score of the overall inflammatory potential of diets using food groups that were most predictive of 3 plasma markers of inflammation: IL-6, CRP, and TNF- α R2. The EDIP score is the weighted sum of 18 food groups maximally anti-inflammatory (lower scores) to maximally proinflammatory (higher scores). The EDIP score has been validated³⁴ and has a higher ability to predict concentrations of CRP, TNF- α , and adiponectin than nutrient-based dietary inflammatory indices.³⁵

The following food groups comprising the EDIP score are positively related to inflammatory marker concentrations (i.e. "pro-inflammatory"): processed meat, red meat, organ meat, white fish, vegetables other than green leafy vegetables and dark yellow vegetables, refined grains, high-energy beverages (cola and other carbonated beverages with sugar, fruit drinks), low-energy beverages (low-energy cola and other low-energy carbonated beverages), and tomatoes. The following food groups are inversely related to inflammatory marker concentrations (i.e. "anti-inflammatory"): beer, wine, tea, coffee, dark yellow vegetables, green leafy vegetables, snacks (i.e. popcorn, crackers), fruit juice, and pizza.³⁴ Some of these groupings are counter-intuitive and apparently contradictory, but this can be explained by the differential nutritional content of related foods. For example, fresh tomatoes have a low content of bioavailable lycopene (a major anti-inflammatory nutrient)⁴³ compared to 2–5 times higher concentrations in cooked tomato paste.⁴⁴ Furthermore, pizza typically contains large amounts of high fat dairy which have anti-inflammatory and low insulinemic properties.⁴⁵ This explains why pizza is grouped as anti-inflammatory while tomatoes are not. As the goal of the EDIP score is to account for the overall effect of dietary patterns, only food groups that explain maximal variation in the three noted inflammatory biomarkers are retained for analysis.

Diagnosis of psoriasis and psoriatic arthritis

Participants were asked whether they were ever diagnosed with psoriasis by a clinician periodically during cohort follow-up. Participants were asked the year of diagnosis in intervals when assessed in 2005 (before 1991, 1991 – 1994, 1995 – 1998, 1999 – 2002, and

2003+), 2009 (before 1995, 1995 – 1999, 2000 – 2004, 2005 – 2006, and 2007+), and 2013 (before 1995, 1995 – 2002, 2003 – 2008, 2009 – 2010, and 2011+). Psoriasis reports were confirmed using the Psoriasis Screening Tool (PST) questionnaire to confirm cases of psoriasis with 94% specificity.⁴⁷ Participants completing the PST were also asked the specific year in which their psoriasis was diagnosed. Participants with psoriasis were asked whether they had been diagnosed with psoriatic arthritis, with reports validated using the Psoriatic Arthritis Screening and Evaluation (PASE) questionnaire with 73–80% specificity.⁴⁸ Only validated cases of psoriasis and psoriatic arthritis are counted as incident cases in our analyses.

Diagnosis of atopic dermatitis

Atopic dermatitis was assessed by self-report in 2013. Patients were asked if they ever received a diagnosis of ‘eczema (atopic dermatitis)’ by a clinician and what year they were diagnosed, in intervals (before 1995, 1995 – 2002, 2003 – 2008, 2009 – 2010, and 2011 +). In 2017, women who had reported a diagnosis of atopic dermatitis were sent a supplemental questionnaire asking them to reaffirm their self-report and answer related questions.⁴⁹ Questions from that supplemental questionnaire are used in two separate algorithms to confirm a diagnosis of atopic dermatitis with 84% specificity.⁵⁰ Our primary atopic dermatitis case definition (definition 1) included women who reaffirmed their self-report on the supplemental questionnaire. In sensitivity analyses, we applied the two validated algorithms to enhance the specificity of the diagnosis (definitions 2 and 3).

Assessment of covariates

At cohort baseline (1989), participants were asked their height and race/ethnicity. Biennially, participants were asked about their weight, smoking status, physical activity and diagnoses of hypercholesterolemia, type 2 diabetes, cardiovascular disease, and asthma.

Statistical analysis

We excluded participants with unknown birth years. For the psoriasis/psoriatic arthritis analysis, participants were excluded if they: 1) had died before 1991, 2) had prevalent psoriasis at baseline in 1991, or 3) reported having psoriasis, but without confirmation during validation. For the atopic dermatitis analysis, participants were excluded if they: 1) had died before 1995, 2) had prevalent atopic dermatitis at baseline in 1995, or 3) reported atopic dermatitis on the main questionnaire but did not have their report confirmed during validation. Participants were also asked about a history of atopic dermatitis in 2009 without year of diagnosis; patients who reported having atopic dermatitis in 2009 but not in 2013 were excluded – 3589 for self-reported atopic dermatitis, and 352 from the validation study. In total, 85,185 patients were included in the psoriasis and psoriatic arthritis analysis, and 63,443 patients were included in the atopic dermatitis analysis.

We calculated person-years of follow-up from the return date of the baseline questionnaire for each analysis until the date of death, diagnosis of psoriasis, psoriatic arthritis or atopic dermatitis, respectively, or end of follow up (2013), whichever was earliest. The date of diagnosis of skin disease was considered the specific year of diagnosis, if available, or the middle value of the given range of diagnosis years.

EDIP scores were calculated as the cumulative average score from all reports up to the start of each two-year follow-up interval to best represent habitual long-term dietary intake and reduce within-person variation. Due to the high within-person correlations in EDIP scores between adjacent data cycles, we carried forward non-missing dietary intake data from the previous data cycle to replace any missing data in the next cycle. Covariate data were treated similarly.

We used Cox proportional hazards models to calculate age- and multivariable-adjusted hazard ratios (HR) with 95% confidence intervals (CI) for the association of EDIP quintiles with the risk of developing incident psoriasis, psoriatic arthritis and atopic dermatitis. We tested the proportional hazards assumption and found it was not violated for any of the outcomes (all $P > 0.05$). Covariates adjusted for in the main multivariable model (multivariable model 1) included age, race (Caucasian vs. non-Caucasian), BMI (kg/m^2), smoking (never smoker, past smoker, current smoker 1 – 14 cigarettes per day (CPD), 15 – 25 CPD, and 25+ CPD), alcohol intake (0 g/d, 0.1 – 4.9 g/d, 5.0 – 9.9 g/d, and 10+ g/d), calorie consumption (kcal/day in quintiles), and exercise (METs/week in quintiles). The second multivariable model (multivariable model 2) included all of the above covariates in addition to comorbid cardiovascular disease, hypertension, hypercholesterolemia, and type 2 diabetes. For atopic dermatitis, we also used a third multivariable model (multivariable model 3) additionally adjusting for a history of asthma. Further, for atopic dermatitis analyses, we conducted stratified analyses of multivariable models 1 and 2 by comorbid asthma. For each of the analyses, P for trend was calculated using the median EDIP score within each quintile.

All statistical analysis was performed with SAS, version 9.2 (SAS Institute, Inc., Cary, NC). A two-tailed $P < 0.05$ was considered statistically significant.

Results

We had 85,185 participants in the psoriatic disease analysis and 63,443 participants in the atopic dermatitis analysis. Baseline characteristics of participants in the psoriasis analysis according to EDIP quintile are presented in Table I. Participants with higher EDIP scores generally had higher BMI, lower physical activity and alcohol consumption and higher rates of hypercholesterolemia and hypertension. Similar patterns were seen in the baseline characteristics of participants included in the atopic dermatitis analysis with the addition that asthma was somewhat more common with higher EDIP scores.

There were 1,425 cases of psoriasis over 2,014,487 person-years and 262 cases of psoriatic arthritis over 2,030,235 person-years. There was no association between pro-inflammatory diet and incident psoriasis in the age- or multivariable-adjusted models (all P -trend > 0.05) (Table II). For psoriatic arthritis, a direct association was seen between high EDIP scores (quintile 5 vs quintile 1: 1.67 [95% CI 1.14 – 2.45], p -trend = 0.007) in the age-adjusted analysis, but this was no longer significant in multivariable model 1 (quintile 5 vs quintile 1: 1.22 [95% CI 0.81 – 1.83], p -trend = 0.54), or multivariable model 2 (quintile 5 vs quintile 1: 1.17 [95% CI 0.77 – 1.76], p -trend = 0.70). To assess reasons for attenuation of the association with psoriatic arthritis in the multivariable models, we conducted analyses with

EDIP as the exposure, psoriatic arthritis as the outcome and age plus each individual covariate individually in separate models. We found that BMI was largely responsible for the attenuation. To assess possible effect modification by BMI, we then conducted age- and multivariable-adjusted analyses stratified by BMI (<25 , 25 kg/m²), with further adjustment for BMI as a continuous variable within each stratum. There was no significant difference between the BMI strata (p for interaction = 0.94); results are shown in Table III.

There were 403 cases of atopic dermatitis over 1,130,810 person-years. EDIP scores were not associated with incident atopic dermatitis in the age- or multivariable-adjusted models (all P -trend > 0.05) (Table IV). Sensitivity analyses using more stringent atopic dermatitis definitions were similar to our primary analysis, and stratified analyses found no differential results according to history of asthma (data not shown).

Conclusions

In this large retrospective cohort study of US women, we did not find any association between a pro-inflammatory diet and increased risk of incident psoriasis, psoriatic arthritis or atopic dermatitis. In our age-adjusted model, pro-inflammatory dietary patterns were associated with psoriatic arthritis, but the HR was attenuated and no longer statistically significant once we adjusted for important confounders, particularly BMI. For atopic dermatitis, no significant relationship was found with pro-inflammatory diet. Though we found no convincing evidence for an association with EDIP score for any of the investigated diseases, the results followed an internal pattern consistent with our hypotheses that higher EDIP scores would have more of an association with psoriatic disease than with atopic dermatitis.

Previous studies have shown robust associations between psoriatic disease and inflammatory bowel disease, cardiovascular disease, and metabolic syndrome.^{51–56} Like psoriasis and psoriatic arthritis, these diseases share elevated serum inflammatory biomarkers such as CRP, TNF- α , and IL-6.^{38–41} Recently, the association between Mediterranean diet and psoriasis was assessed in the French NutriNet-Santé study.⁵⁷ Researchers found that low adherence to a Mediterranean diet, which has pro-inflammatory effects similar to those measured with the EDIP,^{25–28} was associated with increased odds of severe but not milder psoriasis. Those results are consistent with evidence showing that a diet with anti-inflammatory properties has beneficial health effects such as reduced systemic inflammation,⁵⁸ metabolic syndrome,^{59, 60} and cardiovascular events.⁶¹ The divergent results between that study and ours are likely related to important methodological differences, specifically that psoriasis was classified by severity in the NutriNet-Santé study whereas we examined the risk of incident psoriasis overall.⁵⁷ The inflammatory potential of diet may not be as crucial for psoriatic disease incidence compared to other lifestyle risks and genetic factors.^{62, 63} Currently, the strongest recommendation for dietary change in psoriatic disease is weight loss.⁶⁴

We did not find evidence of a relationship between pro-inflammatory diet and incident atopic dermatitis which, like psoriasis, has a strong genetic component.⁶⁵ Furthermore, unlike psoriasis and psoriatic arthritis, atopic dermatitis is not as strongly associated with

Th1- associated inflammation⁶⁶ though new evidence is emerging of associations between atopic dermatitis, obesity, and cardiovascular risk factors.^{11, 67} Additionally, one study found CRP levels to be elevated in patients with more severe atopic dermatitis.⁶⁸ Overall, though, we found no evidence that a diet with pro-inflammatory properties, in particular one associated with increased levels of IL-6, CRP, and TNF- α , increased atopic dermatitis risk. It is possible that a dietary index associated more with Th-2 inflammation would yield different results.

There are several important strengths and limitations to our study. We had a large sample size, prospectively collected dietary and psoriatic disease data, and were able to adjust for important confounders. However, given that participants were US women, our results may not be generalizable to other populations. Further, we examined adult-onset atopic dermatitis, and so our results may not be applicable for more classic, childhood-onset disease. Questionnaire-based diagnoses, though validated, are subject to misclassification, as is the year of atopic dermatitis diagnosis. It is likely that dilution of the case pool with false-positive cases would bias our results towards the null. Most NHS-II participants with psoriasis and atopic dermatitis have mild disease;⁴⁹ longitudinal investigation of an inflammatory diet's impact on disease severity over time would be interesting, but is not possible within our dataset. Finally, as in any observational study, there may be residual confounding by unmeasured factors.

In conclusion, a pro-inflammatory diet did not substantially modify the risk for psoriasis, psoriatic arthritis or atopic dermatitis among women in this study. While a pro-inflammatory diet may be associated with other health risks,^{69, 70} we found no reason to counsel patients about a potential impact on psoriatic disease or atopic dermatitis.

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Abbreviations:

NHS-II	Nurses' Health Study II
EDIP	empirical dietary inflammatory pattern
CRP	C-reactive protein
IL-6	interleukin-6
TNF-α	tumor necrosis factor-alpha

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Capsule Summary

- Diet is an important modulator of systemic inflammation and may play a role in the development and progression of inflammatory skin diseases.
- Our findings do not support dietary modification to decrease inflammatory potential as a preventive measure in patients at risk for the psoriasis, psoriatic arthritis, or atopic dermatitis.

Characteristics of Nurses' Health Study II participants by baseline EDIP score in quintiles

Table 1.

Characteristic	Q1	Q2	Q3	Q4	Q5
<i>Psoriatic disease cohort (1991)</i>					
Number of participants	17,037	17,037	17,037	17,037	17,037
Age (years) * in 1991	37 ± 4	37 ± 5	36 ± 5	36 ± 5	35 ± 5
EDIP score	-477 ± 214	-174 ± 52	-18 ± 42	140 ± 53	465 ± 217
White race (%)	98	97	96	95	94
Body mass index (kg/m ²)	24 ± 4	24 ± 5	24 ± 5	25 ± 5	26 ± 6
Physical activity level (metabolic-equivalents h/wk.)	25 ± 32	22 ± 27	20 ± 26	19 ± 25	18 ± 25
Total energy intake (kcal/d)	1802 ± 54	1693 ± 508	1694 ± 509	1771 ± 528	1999 ± 581
Alcohol intake (g/d)	6 ± 9	3 ± 5	3 ± 5	2 ± 4	2 ± 5
Current smoking (%)	15	11	10	9	12
Comorbid cardiovascular disease (%)	<1	<1	<1	<1	<1
Comorbid type 2 diabetes (%)	<1	<1	<1	<1	<1
Comorbid hypertension (%)	5	5	6	7	9
Comorbid hypercholesterolemia (%)	13	13	14	15	18
<i>Atopic dermatitis cohort (1995)</i>					
Number of participants	12,688	12,689	12,689	12,689	12,688
Age (years) * in 1995	42 ± 4	41 ± 5	40 ± 5	40 ± 5	40 ± 5
EDIP score	-406 ± 174	-149 ± 45	-9 ± 38	135 ± 48	429 ± 193
White race (%)	98	97	96	95	94
Body mass index (kg/m ²)	24 ± 5	25 ± 5	25 ± 6	26 ± 6	28 ± 7
Physical activity level (metabolic-equivalents h/wk.)	25 ± 30	22 ± 29	21 ± 25	19 ± 24	18 ± 25
Total energy intake (kcal/d)	1780 ± 532	1721 ± 519	1741 ± 524	1811 ± 547	2006 ± 586
Alcohol intake (g/d)	7 ± 10	4 ± 6	3 ± 5	2 ± 5	2 ± 4
Current smoking (%)	13	10	8	8	10
Comorbid cardiovascular disease (%)	<1	<1	<1	<1	<1
Comorbid type 2 diabetes (%)	<1	<1	<1	1	1
Comorbid hypertension (%)	7	7	8	10	13

Characteristic	Quintiles of total EDIP score				
	Q1	Q2	Q3	Q4	Q5
Comorbid hypercholesterolemia (%)	17	18	20	23	26
Comorbid asthma (%)	8	8	9	9	10

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

* Value is not age-adjusted

Table II.

Risk of psoriasis and psoriatic arthritis according to quintiles of EDIP score in Nurses' Health Study II

EDIP	Person-years	# of cases	Age-adjusted HR (95% CI)	MV-adjusted HRI (95% CI) [†]	MV-adjusted HR2 (95% CI) [‡]
<i>Psoriasis</i>					
Q1	402,913	298	1 [reference]	1 [reference]	1 [reference]
Q2	403,114	276	0.94 [0.80 – 1.11]	0.96 [0.81 – 1.13]	0.96 [0.81 – 1.13]
Q3	402,684	269	0.93 [0.78 – 1.09]	0.95 [0.80 – 1.12]	0.94 [0.79 – 1.12]
Q4	402,999	283	0.98 [0.83 – 1.15]	0.98 [0.82 – 1.16]	0.97 [0.81 – 1.15]
Q5	402,776	306	1.07 [0.91 – 1.26]	0.99 [0.83 – 1.18]	0.97 [0.82 – 1.16]
		<i>P</i> for trend	0.31	0.85	0.67
<i>Psoriatic Arthritis</i>					
Q1	406,087	44	1 [reference]	1 [reference]	1 [reference]
Q2	406,250	51	1.20 [0.80 – 1.80]	1.23 [0.82 – 1.84]	1.22 [0.81 – 1.83]
Q3	405,855	47	1.13 [0.75 – 1.71]	1.11 [0.73 – 1.69]	1.09 [0.71 – 1.66]
Q4	406,133	53	1.30 [0.87 – 1.94]	1.16 [0.76 – 1.76]	1.13 [0.74 – 1.71]
Q5	405,909	67	1.67 [1.14 – 2.45]	1.22 [0.81 – 1.83]	1.17 [0.77 – 1.76]
		<i>P</i> for trend	0.007	0.54	0.70

HR, Hazard ratio; MV, multivariable

[†] Adjusted for age, race (Caucasian vs. non-Caucasian), BMI (kg/m²), smoking (never smoker, past smoker, current smoker 1 – 14 cigarettes per day (CPD), 15 – 25 CPD, and 25+ CPD), alcohol intake (0 g/d, 0.1 – 4.9 g/d, 5.0 – 9.9 g/d, and 10+ g/d), calorie consumption (kcal/day in quintiles), and exercise (METs/week in quintiles).

[‡] Adjusted for age, race (Caucasian vs. non-Caucasian), BMI (kg/m²), smoking (never smoker, past smoker, current smoker 1 – 14 cigarettes per day (CPD), 15 – 25 CPD, and 25+ CPD), alcohol intake (0 g/d, 0.1 – 4.9 g/d, 5.0 – 9.9 g/d, and 10+ g/d), calorie consumption (kcal/day in quintiles), and exercise (METs/week in quintiles), cardiovascular disease, hypertension, hypercholesterolemia, and type 2 diabetes.

Table III.

Psoriatic arthritis risk in quintiles of baseline EDIP score stratified by BMI in Nurses' Health Study II

EDIP	Person-years	# of cases	Age-adjusted HR (95% CI)	MV-adjusted HRI (95% CI) [†]	MV-adjusted HR2 (95% CI) [‡]
<i>BMI < 25 kg/m²</i>					
Q1	235,207	12	1 [reference]	1 [reference]	1 [reference]
Q2	222,998	18	1.67 [0.80 – 3.46]	1.82 [0.87 – 3.82]	1.81 [0.86 – 3.80]
Q3	208,175	16	1.61 [0.76 – 3.42]	1.82 [0.84 – 3.93]	1.79 [0.83 – 3.87]
Q4	185,686	13	1.51 [0.68 – 3.32]	1.74 [0.77 – 3.94]	1.70 [0.75 – 3.86]
Q5	150,558	8	1.18 [0.48 – 2.91]	1.37 [0.54 – 3.52]	1.32 [0.51 – 3.39]
		<i>P</i> for trend	0.74	0.55	0.61
<i>BMI > 25 kg/m²</i>					
Q1	169,242	32	1 [reference]	1 [reference]	1 [reference]
Q2	181,568	33	0.99 [0.61 – 1.61]	1.04 [0.64 – 1.70]	1.04 [0.63 – 1.69]
Q3	196,100	31	0.87 [0.53 – 1.43]	0.90 [0.55 – 1.50]	0.89 [0.54 – 1.47]
Q4	218,890	39	0.99 [0.62 – 1.58]	0.97 [0.59 – 1.57]	0.94 [0.58 – 1.53]
Q5	253,541	58	1.28 [0.83 – 1.98]	1.07 [0.67 – 1.70]	1.02 [0.64 – 1.63]
		<i>P</i> for trend	0.18	0.84	0.97

HR, Hazard ratio; MV, multivariable

[†] Adjusted for age, race (Caucasian vs. non-Caucasian), BMI (kg/m²), smoking (never smoker, past smoker, current smoker 1 – 14 cigarettes per day (CPD), 15 – 25 CPD, and 25+ CPD), alcohol intake (0 g/d, 0.1 – 4.9 g/d, 5.0 – 9.9 g/d, and 10+ g/d), calorie consumption (kcal/day in quintiles), and exercise (METs/week in quintiles).

[‡] Adjusted for age, race (Caucasian vs. non-Caucasian), BMI (kg/m²), smoking (never smoker, past smoker, current smoker 1 – 14 cigarettes per day (CPD), 15 – 25 CPD, and 25+ CPD), alcohol intake (0 g/d, 0.1 – 4.9 g/d, 5.0 – 9.9 g/d, and 10+ g/d), calorie consumption (kcal/day in quintiles), and exercise (METs/week in quintiles), cardiovascular disease, hypertension, hypercholesterolemia, and type 2 diabetes.

Risk of atopic dermatitis according to quintiles of EDIP score in Nurses' Health Study II

Table IV.

EDIP	Person-years	# of cases	Age-adjusted HR (95% CI)	MV-adjusted HRI (95% CI) [†]	MV-adjusted HR2 (95% CI) [‡]	MV-adjusted HR3 (95% CI) [*]
Q1	226,264	84	1 [reference]	1 [reference]	1 [reference]	1 [reference]
Q2	226,318	78	0.93 [0.68 – 1.27]	0.95 [0.69 – 1.30]	0.95 [0.69 – 1.29]	0.95 [0.69 – 1.30]
Q3	225,998	76	0.90 [0.66 – 1.22]	0.93 [0.67 – 1.28]	0.93 [0.68 – 1.28]	0.93 [0.67 – 1.28]
Q4	226,209	85	1.01 [0.75 – 1.37]	1.04 [0.76 – 1.43]	1.05 [0.76 – 1.44]	1.04 [0.76 – 1.43]
Q5	226,021	80	0.95 [0.69 – 1.29]	0.96 [0.69 – 1.34]	0.96 [0.69 – 1.35]	0.96 [0.68 – 1.34]
		<i>P</i> for trend	0.94	0.98	0.95	0.99

HR, Hazard ratio; MV, multivariable

[†] Adjusted for age, race (Caucasian vs. non-Caucasian), BMI (kg/m²), smoking (never smoker, past smoker, current smoker 1 – 14 cigarettes per day (CPD), 15 – 25 CPD, and 25+ CPD), alcohol intake (0 g/d, 0.1 – 4.9 g/d, 5.0 – 9.9 g/d, and 10+ g/d), calorie consumption (kcal/day in quintiles), and exercise (METs/week in quintiles).

^{*} Adjusted for age, race (Caucasian vs. non-Caucasian), BMI (kg/m²), smoking (never smoker, past smoker, current smoker 1 – 14 cigarettes per day (CPD), 15 – 25 CPD, and 25+ CPD), alcohol intake (0 g/d, 0.1 – 4.9 g/d, 5.0 – 9.9 g/d, and 10+ g/d), calorie consumption (kcal/day in quintiles), and exercise (METs/week in quintiles), cardiovascular disease, hypertension, hypercholesterolemia, and type 2 diabetes.

^{*} Adjusted for age, race (Caucasian vs. non-Caucasian), BMI (kg/m²), smoking (never smoker, past smoker, current smoker 1 – 14 cigarettes per day (CPD), 15 – 25 CPD, and 25+ CPD), alcohol intake (0 g/d, 0.1 – 4.9 g/d, 5.0 – 9.9 g/d, and 10+ g/d), calorie consumption (kcal/day in quintiles), and exercise (METs/week in quintiles), cardiovascular disease, hypertension, hypercholesterolemia, type 2 diabetes and asthma