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Gluten intake and risk of psoriasis, psoriatic arthritis and atopic dermatitis among US women

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Abstract

Background: Associations between gluten intake and psoriasis, psoriatic arthritis and atopic dermatitis are poorly understood.

Objective: To determine whether increased gluten intake is associated with incident psoriasis, psoriatic arthritis, and atopic dermatitis.

Methods: Cohort studies among women in Nurses' Health Study II. Gluten content of participants' diet was calculated every four years (1991-2015 for psoriatic disease, 1995-2013 for atopic dermatitis) using food frequency questionnaires. Disease outcomes were assessed by self-report and subsequently validated. We used multivariable-adjusted Cox proportional hazards models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between gluten intake (quintiles) and psoriasis, psoriatic arthritis and atopic dermatitis.

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Conflicts of interest: In the last three years, Dr. Drucker has 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, Eczema Society of Canada and the Canadian Dermatology Association. His institution has received educational grants from Sanofi and Abbvie. Dr. Qureshi reports personal fees from AbbVie, Amgen, CDC, Janssen, Pfizer, Novartis as a Consultant, personal fees from Regeneron and Sanofi as an Investigator. All honoraria are donated to charity. The other authors do not report any recent or relevant disclosures.

An earlier iteration of the results related to psoriatic disease only was presented as an abstract at the Society for Investigative Dermatology meeting, 2016

Results: We included 85,185 participants in the psoriasis analysis, 85,324 in the psoriatic arthritis analysis and 63,443 in the atopic dermatitis analysis. Increased gluten intake was not associated with any of the outcomes (all $P_{trend}>0.05$). Comparing highest and lowest gluten intake quintiles, the multivariable HR (95% CI) were 1.15 (0.98-1.36) for psoriasis, 1.12 (0.78-1.62) for psoriatic arthritis and 0.91 (0.66-1.25) for atopic dermatitis.

Limitations: No assessment of strictly gluten-free diet.

Conclusions: Our findings do not support the amount of dietary gluten intake as a risk factor for psoriasis, psoriatic arthritis or atopic dermatitis in adult women.

Capsule summary

• Associations between gluten intake and inflammatory skin diseases are poorly understood. We found no association between gluten intake and new-onset psoriatic disease or atopic dermatitis.

• Our study does not support gluten intake as an actionable modifiable risk factor for psoriasis, psoriatic arthritis or atopic dermatitis in adult women.

Keywords

psoriasis; psoriatic arthritis; atopic dermatitis; diet; gluten

Introduction

Dietary intake of gluten is pathogenic in celiac disease and its cutaneous manifestation, dermatitis herpetiformis. Patients often ask about the potential for dietary factors, and gluten intake in particular, to modify risk of other inflammatory skin diseases including psoriasis and atopic dermatitis. A few small, uncontrolled studies have demonstrated improvement in psoriasis severity with a gluten-free diet.[1, 2] Some atopic dermatitis patients report improvement in their skin disease when eliminating gluten, but this has not been studied prospectively.[3] In epidemiologic studies, celiac disease is reported to be more common among patients with both psoriasis and atopic dermatitis.[4-6] To our knowledge, no studies to date have investigated gluten intake as a risk factor for the development of psoriatic disease or atopic dermatitis.

The objective of this study was to determine whether dietary gluten intake in adulthood increased the risk of developing psoriasis, psoriatic arthritis and atopic dermatitis. We hypothesized that increased gluten intake would be associated with an increased risk of psoriatic disease but not of atopic dermatitis.

Methods

We conducted cohort studies in the Nurses' Health Study 2 (NHS2), a cohort of US female nurses. NHS2 began in 1989 with 116,430 women aged 25-42 completing a baseline questionnaire with subsequent follow-up questionnaires biennially. We excluded participants whose birth year was unknown. NHS2 is approved by the Brigham and Women's Hospital Institutional Review Board.

Assessment of gluten intake

In NHS2, food frequency questionnaires are administered every four years starting in 1991. The validity of these food frequency questionnaires has been demonstrated previously.[7] Respondents were asked to estimate average intake of specific food servings (e.g. 1 slice of bread) during the last year with options including: never or less than once per month, 1-3 per month, 1 per week, 2-4 per week, 5-6 per week, 1 per day, 2-3 per day, 4-5 per day, 6+ per day. Common gluten-containing food products were included such as bread, pasta, and beer. An estimate of gluten content of each food item was calculated, based on the protein content of the food in question. Because gluten comprises 70-75% of the total protein content of wheat, the total protein content of each gluten-containing food item was multiplied by a factor of 0.75.[8] Combining estimates from all gluten-containing food items yielded an approximation of daily gluten consumption in grams/day.

Assessment of psoriatic disease and atopic dermatitis

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 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 which has 94% specificity.[9] 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.[10] Only psoriasis and psoriatic arthritis cases confirmed with these validated questionnaires are included as cases in our analysis.

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.[11] Questions from that supplemental questionnaire are used in two separate algorithms to confirm a diagnosis of atopic dermatitis with ≥ 84% specificity.[12] Our primary atopic dermatitis case definition included women who reaffirmed their self-report on the supplemental questionnaire. In sensitivity analyses, we applied the two validated algorithms for enhanced specificity.

Statistical analysis

For the psoriatic disease analysis, baseline was 1991. We included NHS2 participants who were alive and did not have prevalent psoriasis at baseline. We excluded participants who reported having psoriasis but did not have their diagnosis validated using the PST.

For the atopic dermatitis analysis, baseline was 1995. Participants were included if they were alive and did not have prevalent atopic dermatitis at baseline. Participants were excluded if they reported atopic dermatitis on the main questionnaire but did not reiterate their report 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.

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 (2015 for psoriatic disease, 2013 for atopic dermatitis), whichever was earliest. For each of psoriasis, psoriatic arthritis and atopic dermatitis, only incident cases (i.e., those whose reported onset occurred after our study baseline) were included; prevalent cases were excluded from the analysis. 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.

Gluten intake was calculated as the cumulative average intake 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. 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 gluten intake (quintiles) with the risk of developing incident psoriasis, psoriatic arthritis and atopic dermatitis. For each of the analyses, P for trend was calculated using the median gluten intake within each quintile. 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) and 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. For psoriasis and psoriatic arthritis, we conducted analyses stratified by BMI (<30 vs ≥ 30 kg/m^2). For atopic dermatitis analyses, we conducted stratified analyses of multivariable model 2 by comorbid asthma and assessed for interaction between asthma and gluten intake.

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

In total, 85,185 participants were included in the psoriasis analysis, 85,324 in the psoriatic arthritis analysis and 63,443 in the atopic dermatitis analysis. Baseline characteristics of the

cohort were fairly balanced across quintiles of gluten intake, although participants with lower gluten intake were more likely to smoke (Table 1). We identified 1,432 cases of incident psoriasis, 262 cases of incident psoriatic arthritis and 403 cases of incident atopic dermatitis.

Increased gluten intake was not associated with the risk of incident psoriasis, psoriatic arthritis or atopic dermatitis (all p for trend >0.05, Table 2). Comparing the highest with the lowest quintiles of gluten intake, the HR (95% CI) were 1.15 (0.98-1.36) for psoriasis, 1.12 (0.78-1.62) for psoriatic arthritis and 0.91 (0.66-1.25) for atopic dermatitis in the main multivariable analyses. These results were not substantially different from the age-adjusted or other multivariable models. Null findings were also seen when more strict definitions of atopic dermatitis were applied (data not shown).

In the stratified analyses, the risk for psoriasis (P for interaction = 0.34) and psoriatic arthritis (P for interaction = 0.29) associated with gluten intake was not differential according to BMI. There appeared to be a lower risk of atopic dermatitis associated with increased gluten intake for participants with asthma (Quintile 5 vs Quintile 1, HR 0.50 (0.25-1.02), p for trend = 0.09) compared to those without asthma (Quintile 5 vs Quintile 1, HR 1.14 (0.79, 1.64), p for trend 74). However, there was no significant interaction between asthma and gluten intake (P for interaction = 0.10).

Discussion

In this observational study, we found no association between the amount of gluten consumed and risk for incident psoriasis, psoriatic arthritis and atopic dermatitis. Participants with asthma, who are at higher risk for atopic dermatitis, had a lower risk for atopic dermatitis associated with gluten intake compared to participants without asthma. These findings do not support dietary restriction of gluten intake as a means of preventing these inflammatory skin and musculoskeletal conditions.

Our study examined the impact of gluten intake on incident disease, rather than on modulating disease severity in patients already diagnosed. As such, our findings are not directly applicable to management of patients who already have psoriatic disease or atopic dermatitis. Indirectly, our findings are consistent with current guidance on the role of diet in these conditions. Dietary recommendations from the National Psoriasis Foundation based on a systematic review recommend against gluten-free diets except in patients with clinical or serologic evidence of gluten sensitivity.[13] Screening for serologic evidence of gluten sensitivity is not recommended in this population. Guidelines for the management of atopic dermatitis do not recommend elimination of specific foods in the absence of clinically relevant food allergies.[14] While those guidelines do not specifically mention gluten, the general statements on avoiding elimination diets can be applied to restricting gluten intake as well.

Our study was limited in its inability to specifically assess diets with no gluten intake (“gluten-free”) and we did not assess the impact of gluten intake on disease severity. Further, we did not have serologic data on markers of gluten sensitivity; however, it is not currently

recommended that patients with psoriasis or atopic dermatitis be screened for any food sensitivities.[13, 15] Our population consisted of US adult women only; generalizing our results to other populations should be approached with caution. Specifically, the age of onset of psoriatic disease and atopic dermatitis is often substantially younger than in our analysis. For example, the impact of gluten intake on typical childhood-onset atopic dermatitis may be different than that observed in our study.

In this study with a long duration of follow-up, we found no evidence that levels of dietary gluten intake influence the development of psoriasis, psoriatic arthritis or atopic dermatitis in adult women. This is in keeping with current dietary recommendations for psoriasis and atopic dermatitis which do not recommend eliminating gluten.

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Abbreviations and acronyms

BMI	body mass index
CI	confidence interval
CPD	cigarettes per day
HR	hazard ratio
METs	metabolic equivalents
MV	multivariable
NHS2	Nurses' Health Study 2
PASE	Psoriatic Arthritis Screening and Evaluation
PST	Psoriasis Screening Questionnaire

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Table 1

Baseline (1991) characteristics of Nurses' Health Study 2 participants according to quintiles of gluten intake

	1st Quintile (n=16,977)	2nd Quintile (n=17,154)	3rd Quintile (n=16,979)	4th Quintile (n=17,064)	5th Quintile (n=17,011)
Average daily gluten intake (g/day)	3.5 (0.8)	4.9 (0.3)	5.9 (0.3)	7 (0.4)	9.3 (1.5)
Age (years)*	36 (5)	36 (5)	36 (5)	36 (5)	36 (5)
Caucasian,%	91	96	97	97	98
Body mass index (kg/m2)	25 (6)	25 (5)	25 (5)	24 (5)	24 (5)
Physical activity level (METS/wk)	21 (28)	21 (27)	20 (26)	20 (25)	22 (28)
Alcohol intake (g/d)	3 (7)	3 (6)	3 (6)	3 (6)	3 (5)
Current smoking, %	16	13	11	10	8
Cardiovascular disease, %	<1	<1	<1	<1	<1
Type 2 diabetes, %	<1	<1	<1	<1	<1
Hypertension, %	8	6	6	6	5
Hypercholesterolemia, %	16	15	14	14	14
Asthma,%	7	7	7	7	7
Average daily calorie intake (kcal/day)	1772 (566)	1806 (554)	1826 (544)	1817 (532)	1729 (524)

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

*Value is not age adjusted

METS: metabolic-equivalents hrs

Table 2.

Risk of psoriasis, psoriatic arthritis and atopic dermatitis according to quintiles of gluten intake in Nurses' Health Study 2

	Person-years	# of cases	Age-adjusted HR (95% CI)	MV-adjusted HR-1 (95% CI)†	MV-adjusted HR-2 (95% CI)‡	MV-adjusted HR-3 (95% CI)*
Psoriasis						
Q1	401,723	289	1 [reference]	1 [reference]	1 [reference]	--
Q2	403,689	282	0.97 (0.82, 1.14)	0.96 (0.81, 1.13)	0.96 (0.81, 1.13)	--
Q3	403,163	301	1.04 (0.88, 1.22)	1.03 (0.87, 1.21)	1.03 (0.87, 1.21)	--
Q4	403,457	250	0.88 (0.74, 1.04)	0.89 (0.75, 1.06)	0.90 (0.75, 1.06)	--
Q5	402,473	310	1.09 (0.93, 1.28)	1.15 (0.98, 1.36)	1.16 (0.99, 1.37)	--
		P for trend	0.43	0.11	0.09	--
Psoriatic Arthritis						
Q1	404,950	62	1 [reference]	1 [reference]	1 [reference]	--
Q2	406,978	50	0.81 (0.55, 1.17)	0.82 (0.56, 1.19)	0.82 (0.56, 1.19)	--
Q3	406,043	48	0.77 (0.53, 1.13)	0.82 (0.56-1.20)	0.83 (0.56, 1.21)	--
Q4	406,618	45	0.75 (0.51, 1.11)	0.83 (0.56-1.22)	0.83 (0.57-1.23)	--
Q5	405,664	57	0.94 (0.66, 1.35)	1.12 (0.78-1.62)	1.14 (0.79, 1.65)	--
		P for trend	0.89	0.39	0.36	--
Atopic dermatitis						
Q1	226,110	83	1 [reference]	1 [reference]	1 [reference]	1 [reference]
Q2	226,423	86	1.03 (0.76, 1.39)	1.04 (0.77, 1.41)	1.04 (0.77 1.41)	1.05 (0.78, 1.42)
Q3	226,519	75	0.89 (0.65, 1.22)	0.91 (0.66, 1.24)	0.91 (0.66, 1.25)	0.92 (0.67, 1.25)
Q4	226,054	86	1.03 (0.76, 1.39)	1.06 (0.78, 1.44)	1.06 (0.78, 1.44)	1.07 (0.79, 1.45)
Q5	225,704	73	0.87 (0.64, 1.19)	0.91 (0.66, 1.25)	0.91 (0.66, 1.26)	0.92 (0.67, 1.27)
		P for trend	0.36	0.54	0.55	0.58

HR, Hazard ratio; *MV,* multivariable

† Adjusted for age, race, BMI, smoking, alcohol intake, calorie consumption, exercise (METs)

‡ Adjusted for age, race, BMI, smoking, alcohol intake, calorie consumption, exercise (METs), cardiovascular disease, hypertension, hypercholesterolemia, diabetes

* Adjusted for age, race, BMI, smoking, alcohol intake, calorie consumption, exercise (METs), cardiovascular disease, hypertension, hypercholesterolemia, diabetes, asthma