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Do traditional fermented foods protect against infantile atopic dermatitis

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Abstract

Background: Environmental and dietary factors during pregnancy may affect development of infantile atopic dermatitis (AD). This study analyzed whether maternal consumption of selected Turkish fermented foods (FF) and other factors during pregnancy affect the development of AD during the first 2 years of life.

Methods: Eighty-four children with physician-diagnosed AD (aged between 2 and 24 months) and mothers, and 56 similarly aged, healthy children and mothers were studied. Physician-administered questionnaires retrospectively surveyed maternal consumption of FF during pregnancy. The intake frequency of 8 selected Turkish FF was classified as either (1) daily or (2) less than daily. Other possible demographic and environmental risk factors were also analyzed.

Results: Daily maternal consumption of yogurt, fermented olive, and cheese in the control group was significantly higher than the AD group ($P < 0.001$, $P = 0.017$, and $P = 0.011$, respectively). Exposure to environmental tobacco smoking (ETS) was more common in the AD group than the control group ($P = 0.025$). In multivariate logistic regression analysis, maternal ETS exposure during pregnancy was associated with increased risk of infantile AD, and daily consumption of yogurt was associated with a reduced risk (odds ratio [OR]: 2.60, 95% confidence interval [CI]: 1.11-6.1, and OR: 0.22, CI: 0.09-0.54, respectively). The diversity of consumed FF during pregnancy was found to have a protective effect against infantile AD (OR: 0.27, CI: 0.14-0.53).

Conclusions: Daily maternal intake of yogurt and diversity of consumed Turkish FF during pregnancy may reduce the risk of AD. Maternal tobacco smoke exposure is associated with increased risk of infantile AD.

KEYWORDS

atopic dermatitis, environmental tobacco smoking, fermented foods, probiotics, yogurt

1 | INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory pruritic skin disease that affects a large number of children and adults, especially in industrialized countries. The prevalence of AD in pediatric patients

ranges from 5% to 20%, with the highest prevalence typically found in Northern Europe.¹

Emerging evidence suggests that environmental exposures during pregnancy and the early postnatal period can modify gene expression and disease propensity. Diet is a major environmental

exposure, and dietary factors, including polyunsaturated fatty acids, probiotics, oligosaccharides, antioxidants, folate, and other vitamins, affect immune function.²

Fermentation is a process by which a microorganism transforms food into other products, usually through the production of lactic acid, ethanol, and other metabolic end products.^{3,4} This process is used to preserve and increase the quality of foods; these foods are known as fermented foods (FF). The health benefits associated with the fermentation process may be the result of direct interactions between the ingested live microorganisms and the host (probiotic effect), or indirectly, through products, such as some vitamins, including folate, riboflavin, B12, vitamin K2, vitamin D, high-fiber, antioxidant, anti-inflammatory compounds such as short-chain fatty acids (SCFA), and tryptophan (biogenic effect).⁵⁻⁷ The fermenting microorganism plays an important role in the functional property of the food.⁶ The International Scientific Association of Probiotics and Prebiotics recommends that the term "probiotic" should be used only for products that deliver live microorganisms with a suitable viable count of well-defined strains with a reasonable expectation of delivering benefits for the well-being of the host.⁸ Although not all FF qualify as probiotic, and not all probiotics take the form of FF, most FF contain bacteria that have probiotic effects.^{3,8}

It has been suggested that the maternal intake of probiotics during pregnancy may prevent infantile eczema.^{2,3,9,10} Several studies have investigated the relationship between maternal intake of FF and infantile eczema.¹¹⁻¹⁵

Traditional Turkish cuisine is generally very nutritious and commonly includes many FF, including yogurt, cheese, fermented olive, kefir (fermented milk product), pickle, bozza (produced from wheat, millet, maize, or rice), tarhana (produced from wheat flour, yogurt, salt, baker's yeast, and various cooked vegetables), and shalgam (fermented turnip and its juice). These foods are fermented by lactic acid bacteria and may contain many live bacteria.^{16,17}

In this study, we investigate the relationship between infantile AD and maternal consumption of these FF during pregnancy.

2 | METHODS

2.1 | Study Subjects

This study was conducted at the Pediatric Allergy Department of Trakya University Medical School (Edirne, Turkey) between February 2017 and February 2018. A total of 84 children with AD, aged 2-24 months, and their mothers were included in the study (Group 1). Atopic dermatitis was diagnosed by a pediatric allergist according to the criteria defined by Hanifin and Rajka, including detailed clinical history and physical examination.¹⁸ Mothers of 56 healthy children, aged between 2 and 24 months, who applied to the general practitioners for routine physical examination or vaccination, were included in the study as a control group (Group 2). Written informed consent was obtained from all mothers. The Ethics Review

Key Message

Although few studies investigate the effects of FF, there are a number of studies which investigate the relationship between maternal intake of probiotics and infantile eczema. Fermented foods may have several potential advantages over probiotic supplements or foods. In this study we investigate the relationship between infantile AD and maternal consumption of these FF during pregnancy.

Committee at the Trakya University Medical Faculty approved the study.

2.2 | Questionnaire

Pediatric allergists from the study team completed questionnaires via face-to-face interviews with mothers from both groups. The questionnaire solicited information on infant's age and sex; maternal age; maternal educational level; household income; history of asthma, AD, and allergic rhinitis in parents; mode of delivery; antibiotic treatment; maternal active and passive smoking; and pet ownership during pregnancy.

The questionnaire retrospectively surveyed maternal consumption of traditional Turkish FF during pregnancy. The intake frequencies of yogurt, cheese, fermented olive, kefir, pickle, bozza, and tarhana were classified into two groups: (1) daily and (2) less than daily.

2.3 | Statistical Analyses

Statistical analyses were performed using the SPSS software version 23 and MedCalc software version 16. The chi-square, Fisher's exact, Student's *t*, and Mann-Whitney *U* tests were used for the comparison of the backgrounds of the mothers and their babies and the intake frequencies of the eight FF of mothers during pregnancy. The possible factors identified with univariate analyses were further analyzed with multivariate logistic regression analysis to determine independent predictors of patient outcome. *P*-values <0.05, 2-sided, were considered statistically significant.

3 | RESULTS

The study group included 84 AD patients and mothers (Group 1) and 56 healthy controls and mothers (Group 2). Eighty-two (56.6%) of the children were female, and 58 (43.4%) were male. The median patients' age was 3 months (minimum-maximum: 1-18 months) on symptom onset and 7 months (minimum-maximum: 2-24 months) on admission to our department and diagnosed as current AD by a pediatric allergist.¹⁸ There were no significant differences in demographic factors between the two groups (Table 1).

TABLE 1 Demographic variables of children and mothers

	Infant with atopic dermatitis (n = 84)	Infant without atopic dermatitis (n = 56)	P value
Infants' sex			
Female (%)	49 (58.3)	33 (58.9)	0.944
Male (%)	35 (41.7)	23 (41.1)	
Infants' age (months), median (minimum-maximum)	7 (2-24)	6 (2-24)	0.106
Maternal age (years) mean (standard deviation)	29 (±3.7)	29.4 (±4.4)	0.569
Maternal educational level (%)			
No school	2 (2.4)	2 (3.6)	0.149
Primary school	10 (11.9)	2 (3.6)	
High school	24 (28.6)	11 (19.6)	
University	48 (57.1)	41 (73.2)	
Monthly household income, Turkish lira			
≤1.500 (%)	9 (10.7)	4 (7.1)	0.294
1.501-4.500 (%)	48 (57.1)	26 (46.4)	
4.501-10.000 (%)	24 (28.6)	21 (37.5)	
>10.000 (%)	3 (3.6)	5 (8.9)	

Our study analyzed variables which may be associated with the development of infantile AD. There was no statistically significant difference between the two groups in terms of allergic disease (asthma, allergic rhinitis, or AD) history in parents, mode of delivery, maternal use of antibiotics during pregnancy, or having pets at home. While there was no significant difference in the mothers' active smoking between the two groups, passive smoking was significantly higher in Group 1 than Group 2 ($P = 0.027$) (Table 2).

The three most consumed FF in each group were cheese, fermented olive, and yogurt, respectively. The number of daily consumers of yogurt, fermented olive, and cheese was higher in Group 2 than in Group 1 ($P < 0.001$, $P = 0.017$, and $P = 0.011$, respectively). Other FF were less commonly consumed by mothers in both groups, and there were no statistically significant differences between the groups. A variable measuring diversity of fermented foods was created by counting the number of different FF consumed daily by mothers from the eight FF evaluated in our study. The median number of FF consumed daily by mothers (diversity of FF) in Group 2 was 3 (minimum-maximum: 1-4) per day, while it was 2 (minimum-maximum: 0-4) per day for the mothers in Group 1. The diversity of FF consumed daily in Group 2 was higher than Group 1 ($P < 0.001$) (Table 2).

Several variables were identified by univariate analyses and found to be statistically significant: mother's ETS exposure, and frequency of daily consumption of yogurt, fermented olive, and cheese. These factors were further analyzed with multivariate logistic regression analysis (backward stepwise method). In this model, the mother's passive smoking increased the risk of eczema by 2.6 times (odds ratio [OR]: 2.60, 95% confidence interval [CI]: 1.11-6.1). Daily consumption of yogurt was 4.6 times more protective against AD (OR: 0.22, CI: 0.09-0.54), while no evident associations were found

between daily consumption of fermented olive and cheese and infantile AD (Table 3). The diversity of FF variable could not be included in this model. Because the diversity of fermented foods' data reflected the sum of all FF such as yogurt, fermented olive, and cheese, there was a strong correlation. For this reason, passive smoking exposure and diversity of FF during pregnancy were compared with the multiple logistic regression analysis in a separate model (enter method). In this model, it was found that the consumption of a higher diversity of FF was independently inversely associated with the risk of infantile AD, indicating a protective effect (OR: 0.27, CI: 0.14-0.53) (Table 4). We were concerned that the presence of yogurt and its strong correlation might affect our measurement of the sum of diverse FF. We wanted to investigate the effect of diversity of FF excluding yogurt, but including the other FF consumed daily by the mothers. We created a new variable named "diversity of FF without yogurt" which was the sum of FF consumed daily by the mothers excluding yogurt. Passive smoking exposure and diversity of FF without yogurt during pregnancy were compared with the multiple logistic regression analysis in a separate model (enter method). In this model, it was found that the consumption of a higher diversity of FF without yogurt was inversely associated with the risk of infantile AD (OR: 0.38; CI: 0.17-0.84) (Table 4).

4 | DISCUSSION

To the best of our knowledge, this is the first study from Turkey to investigate the effects of maternal consumption of FF during pregnancy on infantile AD. In our study, the frequency of daily consumption of yogurt, fermented olive, and cheese during pregnancy was significantly higher in healthy children's mothers than

TABLE 2 Characteristics of children and mothers

	Infant with atopic dermatitis (n = 84)	Infant without atopic dermatitis (n = 56)	P value
Maternal and/or parental history of allergic disease			
Yes (%)	25 (31.3)	13 (23.2)	0.305
No (%)	55 (68.8)	43 (76.8)	
Mode of delivery			
Cesarean section (%)	62 (73.8)	41 (73.2)	0.938
Vaginal delivery (%)	22 (26.2)	15 (26.8)	
Maternal history of antibiotic use during pregnancy			
Yes (%)	29 (34.5)	15 (27.3)	0.369
No (%)	55 (65.5)	40 (72.7)	
Smoking during pregnancy			
Yes (%)	10 (12.3)	6 (11.1)	0.828
No (%)	71 (87.7)	48 (88.9)	
Environmental tobacco smoking during pregnancy			
Yes (%)	33 (40.7)	12 (22.2)	0.025
No (%)	48 (59.3)	42 (77.8)	
Pet ownership during pregnancy			
Yes (%)	6 (7.3)	6 (11.3)	0.425
No (%)	76 (92.7)	47 (88.7)	
Yogurt			
Yes (%)	38 (45.2)	48 (85.7)	<0.001
No (%)	46 (54.8)	8 (14.3)	
Fermented olive			
Yes (%)	70 (83.3)	54 (96.4)	0.017
No (%)	14 (16.7)	2 (3.6)	
Cheese			
Yes (%)	75 (89.3)	56 (100)	0.011
No (%)	9 (10.7)	0 (0)	
Pickle			
Yes (%)	6 (7.1)	1 (1.8)	0.243
No (%)	78 (92.9)	55 (98.2)	
Bozza			
Yes (%)	1 (1.2)	0 (0)	1.0
No (%)	83 (98.8)	56 (100)	
Tarhana			
Yes (%)	2 (2.4)	3 (5.4)	0.395
No (%)	80 (97.6)	53 (94.6)	
Kefir			
Yes (%)	0 (0)	1 (1.8)	0.4
No (%)	84 (100)	55 (98.2)	
Shalgam			
Yes (%)	0 (0)	0 (0)	Cannot be calculated
No (%)	84 (100)	56 (100)	
Diversity of fermented foods during pregnancy, median (minimum-maximum)	2 (0-4)	3 (1-4)	<0.001

TABLE 3 Association between maternal intake frequencies of the three fermented foods, maternal passive smoking during pregnancy, and infantile atopic dermatitis

	Crude		Adjusted	
	P	OR (95% CI)	P	OR (95% CI)
Environmental tobacco smoking during pregnancy	0.025	2.41 (1.10-5.25)	0.027	2.60 (1.11-6.1)
Yogurt	<0.001	0.14 (0.06-0.33)	0.001	0.22 (0.09-0.54)
Fermented olive	0.017	0.19 (0.40-0.85)	0.096	0.25 (0.05-1.28)
Cheese	0.011	0.05 (0.01-0.94)	Cannot calculated	Cannot calculated

CI, confidence interval; OR, odds ratio.

TABLE 4 Association between maternal daily intake diversity of fermented foods with or without yogurt during pregnancy, maternal passive smoking during pregnancy, and infantile atopic dermatitis

	Crude		Adjusted ^a	
	P	OR (95% CI)	P	OR (95% CI)
Diversity of fermented foods during pregnancy ^b	<0.001	0.30 (0.16-0.56)	<0.001	0.27 (0.14-0.53)
Diversity of fermented foods without yogurt during pregnancy ^c	0.032	0.45 (0.21-0.94)	0.018	0.38 (0.17-0.84)

CI, confidence interval; OR, odds ratio.

^aAdjusted for maternal environmental tobacco smoking during pregnancy.

^bMultivariate logistic regression analysis for maternal environmental tobacco smoking and intake diversity of fermented foods during pregnancy.

^cMultivariate logistic regression analysis for maternal environmental tobacco smoking and intake diversity of fermented foods without yogurt during pregnancy.

AD patients' mothers. Other possible factors that might play a role in early presentation of AD include parental history of atopy, maternal education level, exposure to ETS, and maternal smoking during pregnancy. Maternal exposure to ETS during pregnancy was more frequently reported by mothers of children with AD. In the multiple logistic regression analysis to exclude confounding effects of ETS and individual FF consumed during pregnancy, yogurt intake during pregnancy was associated with a reduction in the risk of infantile AD.

In previous studies conducted by Sausenthaler et al,¹⁴ Miyake et al,¹⁵ and Ozowa et al,¹³ no significant associations were observed between maternal intake of yogurt during pregnancy and infantile AD. In these studies, the diagnosis of AD was not based on a thorough assessment and did not include a physical examination. Instead, these studies relied on self-administered questionnaires to diagnose AD. Ozowa et al¹³ classified the intake frequencies of FF by pregnant mothers as either daily or 2-3 times a week or less, which was similar to our assessment of maternal diet history during pregnancy. The methodology of these other studies differs from ours in several respects. Observation of maternal diet was limited to the last four weeks of pregnancy, whereas our survey asked mothers about their diet over the full range of their pregnancy.

On the other hand, in a recent pre-birth cohort study conducted in Japan, Miyake et al¹² reported that higher maternal intake of yogurt during pregnancy may reduce the risk of physician-diagnosed atopic eczema in children aged 23 to 29 months. Similarly, in a Norwegian cohort study, researchers found that consumption of probiotic milk and yogurt during pregnancy was associated with a

reduced risk of AD at 6 months.¹¹ These studies were also questionnaire-based. In our study, AD was diagnosed by a pediatric allergist according to the criteria defined by Hanifin and Rajka.¹⁸

To the best of our knowledge, ours is the first study to investigate the relationship between consumption of other non-yogurt FF such as olives, pickle, bozza, tarhana, and shalgam during pregnancy and children's AD. In our study, no significant relationship was observed between the maternal daily intake of individual non-yogurt FF during pregnancy and infantile AD. The relationship between the maternal daily consumption of cheese during pregnancy and infantile AD was evaluated in a Japanese¹² and a Singaporean cohort study¹⁹; however, as in our study, no statistically significant effect on AD was found.

Although we found no association between intake of individual non-yogurt FF during pregnancy and infantile AD, the diversity of FF, with or without yogurt, consumed during pregnancy was found to have a protective effect against AD. This effect of the diversity of FF on AD has not been previously investigated. There are two previous meta-analyses which reported that a mixture of different probiotic strains might be more effective in providing an ecological barrier than a single strain.^{10,20}

Yogurt is the most commonly investigated fermented food for its relationship with allergic disease.^{8-10,16,19-21} Many countries include yogurt as part of a healthy diet, and some countries include yogurt in their dietary guidelines.⁸

Probiotics are known to be very beneficial during pregnancy and provide a mechanism for microbial transfer from mother to fetus. Zucotti et al found that when taken in the third trimester of

pregnancy, probiotics reduce the risk of eczema in children until 24 months of age.¹⁰

However, fermented foods may have several potential advantages over probiotic supplements or foods. Levels of metabolites produced by intestinal microbiota, such as SCFA, have been shown to be increased in fecal and plasma samples after yogurt consumption.²² Moreover, it has been suggested that SCFA might have anti-inflammatory properties,²³ and thus, it has been proposed that factors that influence intestinal microbiota and the production of SCFA might have an effect on immune and inflammatory responses.²⁴

Additionally, tryptophan, an essential amino acid, is found in foods such as red meat, fish, eggs, yogurt, and many vegetables.⁷ Tryptophan is converted to kynurenine by the immune-regulatory enzyme indoleamine 2,3-dioxygenase, and indoleamine 2,3-dioxygenase activity is linked to suppression of T-cell responses, promotion of T regulatory (Treg) cells, and immune tolerance.^{7,25}

The gut microbiota has been proposed as a major driver for the normal age-related maturation of both Th1 and Treg pathways that appear important in suppressing early propensity for Th2 allergic responses.²⁶ Some effects of resident symbionts are mediated by bacterial metabolites such as SCFA, which play a critical role in mucosal integrity and local and systemic metabolic function and stimulate the regulatory immune responses.^{26,27} Contrary to the "sterile womb" paradigm, recent studies suggest that maternal microbial transfer to the offspring may begin during pregnancy, providing a pioneer microbiome. Microbial DNA can be detected during normal healthy pregnancy in amniotic fluid, placental and fetal membranes, umbilical cord blood, and meconium.^{10,26} It is likely that appropriate microbial stimulation, both pre- and post-natally, is required for optimal Th1 and Treg development and to avoid the pathophysiological process that leads to allergy.^{2,26}

The gut microbiome may also contribute to the development, persistence, and severity of AD via neuroendocrine pathways.²⁷ Additionally, dysbiosis of the gut and skin commensal microbiome has been linked to alterations of immune homeostasis and promotes the development of AD.²⁷

S. aureus species of the skin microbiome play key roles in the development and establishment of AD, but the proportional differences among other skin microbes are implicated in AD development. Therefore, extensive research is required to identify the interactions between the skin microbiomes or between the gut and skin microbiomes and how the mechanisms involved influence the development of AD dysbiosis. Moreover, additional investigations are needed to confirm that AD dysbiosis through the skin microbiome affects the skin response and systemic immune response in AD. It is also unclear whether *S. aureus* species or other microbes may have some function in the gut.²⁷

The results of studies investigating the development of AD in children with active or passive smoking during pregnancy are contradictory. Passive smoking during pregnancy was associated with a reduced risk of eczema in our study. Wang et al²⁸ observed that

maternal ETS exposure in pregnancy was significantly higher in mothers of AD children than mothers of healthy children. In contrast with our study, Taylor-Robinson et al²⁹ reported that gestational smoking had protective effect against AD. Researchers in two additional studies found that active smoking or ETS during pregnancy was not associated with AD in offspring.^{30,31} There are more than 4000 chemicals in tobacco, and one or more of them may affect fetal immune regulation.²⁸ Smoking also affects the intestinal microbiome which may contribute to the development of AD.³²

Interestingly, our study showed no significant association between active smoking and eczema, although passive smoking was more frequent in mothers of children with AD than in mothers of healthy children. Most women quit smoking after they become pregnant. In our study, pregnant women were exposed to smoke mainly from ETS and only a few from active smoking. Furthermore, nicotine vapor may persist over the succeeding few days after the last cigarette was smoked in a room because of emission from contaminated room surfaces, people's clothing, or house dust.²⁸

In our study, we exclusively investigated the pregnancy period and collected no information about postnatal mothers' and household members' smoking behavior. We speculate that household smokers who caused ETS exposure in pregnant women may continue to smoke at home after birth. It has been suggested that the skin-barrier function can be damaged by toxic substances produced by smoking, such as nicotine and carbon monoxide, which disturb the blood flow and oxygenation of the skin.³³ These disturbances of the skin and associated subcutaneous structures allow allergens to permeate into the skin, which results in AD.^{28,33}

Our study has some potential limitations which leave room for further research. Our study only investigated intake frequencies of FF and not the effects of intake volume. However, previous studies investigated only intake frequencies and also found protective effects against AD, as in our study.¹³ Bertelsen et al¹¹ reported in their study that while yogurt protects against AD, there is no dose-responsive relationship between the volume of yogurt/probiotic milk consumed and AD. Another limitation is that the study population was not very large and was selected from an urban area in Turkey, so our findings may not be generalizable or applicable to other populations.

In conclusion, our findings indicate that maternal consumption of FF during pregnancy may reduce the incidence of AD in infants, which is also corroborated by existing literature. Daily consumption of FF, which have been used safely for thousands of years, may be recommendable for pregnant women, especially those who are at high risk of having an allergic child. Tobacco smoking is another preventable factor of AD which should be avoided by not only the mother, but also other household members during and after pregnancy.

CONFLICT OF INTEREST

The authors have no conflict of interest.

AUTHOR CONTRIBUTIONS

VC and MY designed the study and wrote the manuscript. VC, BB, and PGO contributed to data collection. NS performed the statistical analysis. All authors read, corrected, and approved the final manuscript.

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