

earlier age of onset and history of FPIES reaction to a vegetable or fruit.³

The most commonly implicated trigger foods for FPIES in the United States include milk, soy, rice, and oat.^{1,3–6} Although grains have been commonly implicated in FPIES, and high cross-reactivity exists among related grains, wheat FPIES has rarely been reported in the United States.^{1,7} In Europe, the prevalence of FPIES to wheat was 7.1% in a small cohort of 14 patients in France and 11% in a cohort of 54 patients in the United Kingdom.^{8,9}

Scarce data exist regarding the incidence of wheat FPIES in the United States after a period of tolerance. Mehr et al³ showed that grains (52%) were the most common FPIES trigger in a large-scale survey of Australian children (n = 230), and 39% of patients in that category developed FPIES after more than 2 tolerant exposures to the food.³ Of note, 8 patients (3%) of the cohort had an FPIES reaction to wheat.³ The authors did not comment on the association between multiple food FPIES and number of tolerated exposures. The patient in our case had recurrent FPIES reactions to multiple different foods, notably wheat, after a month period of sustained unresponsiveness with 2 to 3 age-appropriate servings/week. Of note, this frequency of wheat consumption was similar to previously published guidelines for the prevention of IgE-mediated peanut allergy.¹⁰

Our case demonstrates a unique presentation of FPIES because our patient presented with FPIES to several foods (wheat, sweet potato, peanut) after multiple tolerant exposures. Although it remains unclear if this presentation is unique to the aforementioned foods, it suggests that atypical clinical phenotypes of FPIES exist. Along with the findings from Mehr et al,³ our case presentation emphasizes the need to provide appropriate anticipatory guidance after negative oral food challenges, because select patients still may react to the suspect food, even after a period of tolerance. Parents should be counseled that although most patients with FPIES will maintain tolerance after a negative OFC, recognizing symptoms and implementing prompt rehydration should their child develop recurrent symptoms is important to halt morbidity. For the introduction of new high-risk foods, parents should institute a period of 4 days between each new food.¹

As illustrated in our case, 1 month of sustained tolerance to wheat from ingestion of 2 to 3 weekly servings did not prevent FPIES recurrence. Further studies are required to guide optimal food reintroduction frequency and assess the threshold protein level necessary to maintain tolerance against FPIES. The pathogenesis of FPIES is complex and has been shown to involve TH2 cells¹; possibly less frequent exposures to the offending food may delay T cell anergy. Whether FPIES patients that become intolerant to previously tolerated foods have better or worse prognosis for eventual resolution of FPIES is

unknown. Additional longitudinal studies are needed to identify risk factors, such as presence of atopy, concurrent IgE-mediated food allergy, that would predispose patients to recurrent FPIES reactions despite periods of tolerance.

Although OFCs are necessary to confirm a diagnosis of FPIES and assess for resolution of disease, our case and others raise the question of the utility of office OFCs for introducing high-risk foods in a patient with a known diagnosis of FPIES. In the interim, patients with FPIES should have close follow-up with an allergist for safe food introduction, with emphasis on a detailed emergency preparedness plan, given that varying clinical phenotypes of FPIES exist.

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Mold exposure affects the development of atopic dermatitis in infants with skin barrier dysfunction



Mold exposure is considered a risk factor for allergic diseases such as atopic dermatitis (AD), although with some debate.¹ The inconsistency of the results obtained in regard to this association may be attributable in part to differences in the dosage, time, and duration of the

exposure. Skin barrier dysfunction and immune dysregulation have recently been highlighted as key factors in the development of AD. The transepidermal water loss (TEWL) level reflects skin barrier integrity, the loss of which is 1 of the most important features of AD.² In our study, we elucidated the effects of fetal mold exposure on the later development of AD. In addition, we investigated the impact of skin barrier dysfunction, as reflected in the TEWL levels, on the development of AD in combination with mold exposure during the critical periods.

From the subcohort from the Cohort for Childhood Origin of Asthma and Allergic Diseases (COCOA) birth cohort study, 383

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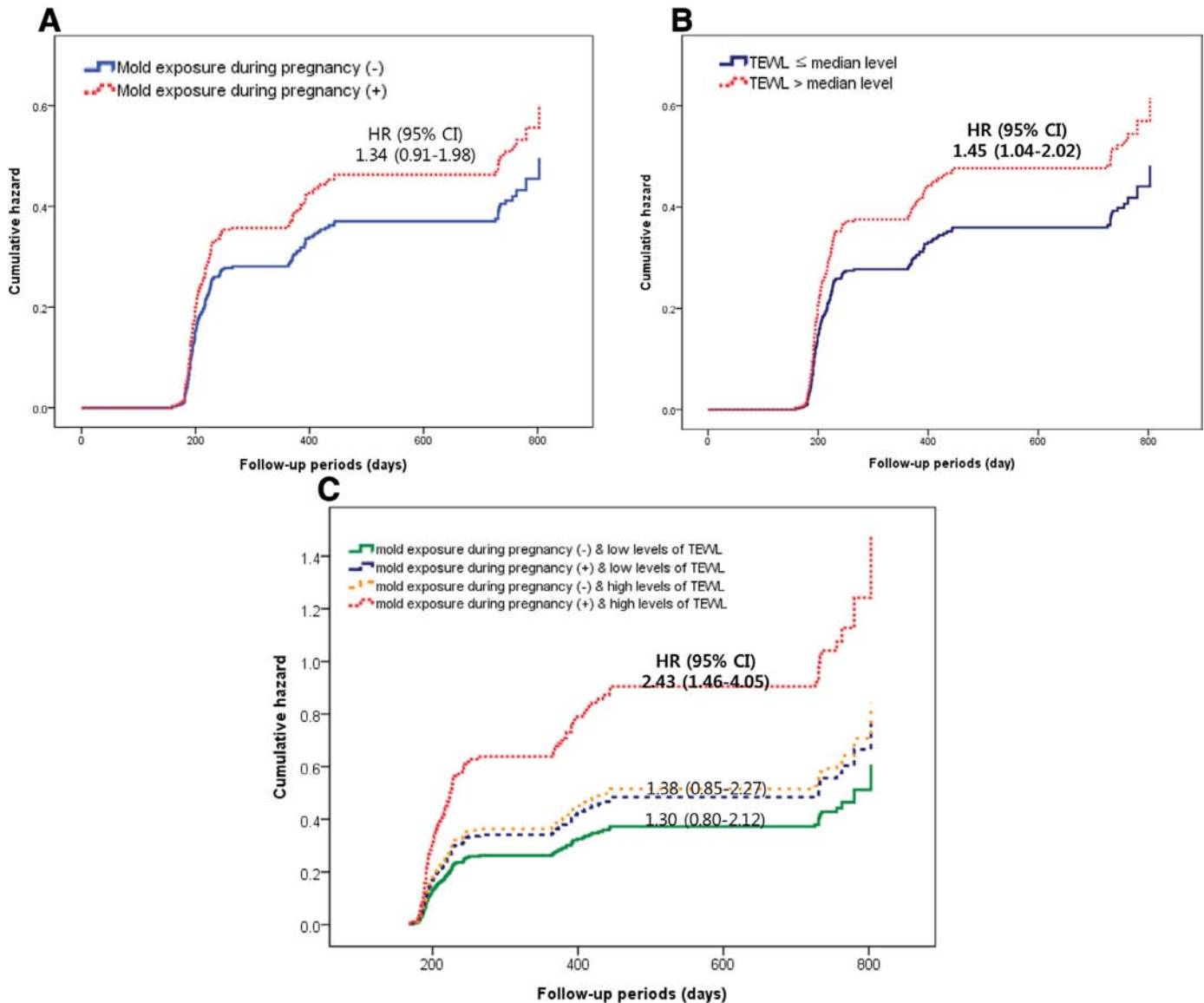


Figure 1. Cumulative hazard ratios for a physician's diagnosis of atopic dermatitis in infants according to mold exposure during pregnancy (A), level of transepidermal water loss (TEWL) (B), and a combination of these 2 variables (C). Each value was adjusted for maternal age, educational level, delivery mode, family history of allergic diseases, child's sex, and postnatal mold exposure.

infants were enrolled in the study. AD was assessed by pediatric allergists at 6 months, 1 year, and 2 years of age based on the criteria of Hanifin and Rajka.³ The presence of visible mold or dampness was assessed at 36 weeks of gestation, at 6 months, and at 1 year of age, using the question: "Do you have visible damp stains and molds at home?"⁴ The TEWL was measured in the infants at 1 year of age on the lower volar site of the forearm with the widely used open-chamber system (Tewameter TM 300; Courage+Khazaka Electronic, Cologne, Germany) in temperatures of 20°C to 25°C and humidity of 30% to 45%.⁵ The measurement was repeated 3 times, and the average value was recorded. The Cox proportional hazards model was used for statistical analysis of the development of AD. Adjustments were made for maternal age at birth, maternal body mass index, maternal educational level, sex, and parental history of allergic diseases. We adjusted for postnatal mold exposure to identify the effect of prenatal mold exposure on the development of AD and vice versa. The TEWL levels were dichotomized based on median values. All statistical analyses were performed using SPSS version 22 (SPSS Inc, Chicago, Illinois).

The characteristics of the study population are presented in eTable 1. After adjustment for postnatal mold exposure, prenatal mold exposure showed an association with a higher hazard ratio (HR) for AD (HR, 1.34; 95% confidence interval [95% CI], 0.91-1.98) (Fig 1A). Higher TEWL levels were also found to be associated with a higher HR for AD (HR, 1.45; 95% CI, 1.04-2.02) (Fig 1B). In infants with prenatal exposure to mold, the HR for AD was increased when they had a higher TEWL level (HR, 2.43; 95% CI, 1.46-4.05) compared with the subjects with a lower TEWL level and no history of fetal mold exposure (Fig 1C). However, no significantly increased risk of AD was found in infants with higher levels of TEWL, if they were not exposed to mold during pregnancy compared with those with lower levels of TEWL and no history of fetal mold exposure.

We have determined from our analyses that mold exposure during pregnancy is only weakly associated with the development of AD in early life. Skin barrier dysfunction, as reflected by the TEWL level, is markedly higher in infants with AD. We found that the risk of AD is higher in infants with a combination of prenatal mold exposure and a high TEWL. Our findings suggest a role of skin barrier impairment as a higher risk factor for the

development of AD when combined with certain environmental factors, particularly in susceptible infants.

Mold can cause health effects through the production of free radicals and inflammation-associated cytokine production.⁶ In addition, fungal exposure can play a role in the development of allergic diseases through both immunoglobulin E (IgE)- and non-IgE-mediated mechanisms.⁷ In a humid atmosphere, diverse factors, including house dust mites (HDM), may be confounding factors for habitation by mold. However, we found no significant differences between the exposed levels to HDM at home during the fetal period according to mold exposure. Moreover, the sensitization rate against *Alternaria alternata* was 0.5% (6/1,096), and that for *Aspergillus fumigatus* was 0.4% (4/1,098), as determined by skin prick tests in the entire COCOA birth cohort study at 3 years of age. No significant differences were found in the sensitization rate for molds, including *Alternaria alternata* and *Aspergillus fumigatus*, between infants exposed or not exposed to mold during gestation. Our observations thus suggest that mold exposure during pregnancy might affect the development of AD postnatally in infants via certain chemicals in the mold or through unknown mechanisms, rather than through HDM exposure or sensitization to molds. Mold exposure during gestation also can cause epigenetic changes, such as messenger RNA modulation,⁸ and thereby may affect the health of the resulting offspring.

Our study had some limitations of note. First, TEWL was measured only once and independently of AD severity. Our study population was relatively small because of the recent introduction of TEWL measurements in only 1 center involved in the COCOA birth cohort study. Dichotomization of the TEWL levels has limited value for the assessment of the effect of near-median values. Another limitation of our analysis was that mold exposure was evaluated using a questionnaire. Notably, however, numerous previous studies have used the same questionnaire to evaluate the association between mold exposure and the development of allergic diseases.^{9,10} The strength of our current analysis is that we conducted a prospective birth cohort study, thereby avoiding recall bias for mold exposure and the diagnosis of AD.

In conclusion, our current findings suggest that mold exposure during critical periods can affect the development of AD in combination with skin barrier dysfunction. Hence, the avoidance of mold exposure during critical periods and enhancement of skin barrier function may prevent the development of AD in early life, particularly in susceptible infants.

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Supplementary Data

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eTable 1

Characteristics of the study population

Characteristics, n (%) or mean $\pm$ SD	Non-AD (n = 228)	AD (n = 155)	P value
Maternal age	34.0 $\pm$ 3.6	33.2 $\pm$ 3.6	.046
Maternal body mass index	21.0 $\pm$ 2.5	20.7 $\pm$ 2.5	.370
Maternal education level			.133
$\leq$ 12 years	16 (7.0)	8 (5.2)	
12–16 years	177 (77.6)	111 (71.6)	
>16 years	35 (15.4)	36 (23.2)	
Male	113 (49.6)	93 (60.0)	.044
Gestational age, weeks	38.9 $\pm$ 1.1	38.9 $\pm$ 1.3	.954
Birth weight, g	3,150.9 $\pm$ 440.8	3,158.0 $\pm$ 436.0	.881
Parental history of allergic diseases	113 (49.6)	86 (55.5)	.255
TEWL, g/m ² /h	13.8 $\pm$ 8.5	16.4 $\pm$ 13.1	.035

AD, atopic dermatitis; SD, standard deviation; TEWL, transepidermal water loss.