Factors Influencing Atopic Dermatitis Incidence in Offspring

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ABSTRACT

Atopic dermatitis (AD) is a chronic, recurrent skin condition resulting from both genetic and environmental factors. In recent decades, the prevalence of AD has increased considerably in some countries. However, given that the role of genetics is unlikely to have changed over this short period, the increased prevalence is more likely to be explained by changes in environmental and maternal factors. The aim of this review is to comprehensively summarize the various factors impacting AD incidence in offspring and provide guidance for primary prevention. Recent research has demonstrated that environmental and climate factors, maternal history of allergies, gestational diabetes, and stress play essential roles in increasing the risk of AD in infants. Some factors have protective effects against the incidence of AD, including probiotic supplementation, fish intake, and moisturizers. This review also considers fundamental research into AD prevalence and factors that in the past were mistakenly thought to affect that prevalence, such as caesarean section and antigen avoidance. The potential influence of these factors on infant AD incidence remains inconclusive and needs further study. Furthermore, infants with a family history of atopic disease may benefit from early weaning or reduced breastfeeding duration.

Keywords: Atopic dermatitis; Factors; Offspring; Prevalence; Primary prevention

INTRODUCTION

Atopic dermatitis (AD), also known as atopic eczema, is a chronic relapsing inflammatory skin condition that inflicts a substantial physical and psychological burden on patients and their families.1-3 AD usually starts in infancy, and up to 33% of cases persist into adulthood, thus prolonging the duration of suffering.4 Approximately 60% of patients with AD subsequently experience allergic rhinitis or asthma later in life.5 Currently, there is no cure for AD and its prevalence has increased considerably in several countries.6 Although genetic change is the most widely investigated factor, other causes such as environmental and maternal factors may, in fact, play a more important role in the increasing prevalence of AD. Previous reviews regarding the primary prevention of AD are far from sufficient and need to be updated. The aim of this review was to summarize the risk and protective factors in the prevalence of AD and provide summary guidelines for primary prevention.
Environmental and Climate Factors

Environmental factors play a vital role in AD progression and exacerbation. Several studies have revealed positive associations between eczema and the emission of airborne pollutants from vehicles and decorating materials, such as benzene, particles with a 50% cut-off aerodynamic diameter of 10 μm (PM$_{10}$), CO, and nitrogen oxides. A German birth cohort study (N=2,536) reported that redecorating activities before birth and in the first year of life were associated with a higher risk of eczema in offspring. Such findings demonstrate that the environment is an important risk factor for the development of infant AD.

A recent study analyzed the prevalence of pediatric allergic diseases in the Ogasawara Islands, located 1000 km south of mainland Japan. The prevalence of pediatric AD was lower in the Ogasawara Islands than in previous reports from mainland Japan, and the authors suggested that possible reasons included lower air pollution, a higher prevalence of young children playing in the sea, and exposure to strong ultraviolet rays. One important factor was the relatively warm and humid climate in the Ogasawara Islands, which the authors described as dramatically different from that in mainland Japan. This conclusion was consistent with other studies. Silverberg et al. used a merged analysis based on the National Survey of Children’s Health and climate variables in the United States. The results indicated that the prevalence of eczema was significantly lower in areas with higher UV indices, humidity levels, and mean temperatures, and less indoor heating and precipitation.

In 2012, Hanski et al. conducted a survey of atopic sensitization using a random sample of adolescents from eastern Finland. The surroundings of atopic patients’ homes showed lower environmental biodiversity than those of healthy individuals. One study in the United States reported that immigrants had a lower prevalence of AD than native-born residents. Similar research results were reported in other countries.

Collectively, these studies suggest that environmental biodiversity and a favorable climate could be protective factors for AD prevalence. Pregnant mothers and infants, especially those with a family history of AD, should be counseled to avoid air pollutants and consider creating an appropriate living environment to reduce AD incidence.

Hygiene Hypothesis

Epidemiological data on AD suggest an overall higher prevalence in wealthier, developed regions than in poorer, developing countries. Therefore, exposure to “dirt” may protect residents of developing nations against AD. This is known as the “hygiene hypothesis”, which posits that exposure to specific microorganisms in early childhood benefits the development of the immune system and provides protection against allergic diseases. Although the hygiene hypothesis remains controversial, an abundance of studies has borne out its central point. A birth cohort study evaluated the association between AD incidence and prenatal farm-related exposure (N=1,063). The results demonstrated that greater exposure to farm animals or household pets during pregnancy can reduce the AD risk by more than half in children up to 2 years old. Similarly, children who live on farms or are exposed to pets during pregnancy, infancy, and/or childhood appear to be protected against AD development in early life. However, for pregnant women, who are often particularly sensitive to the environment, exposure to farm animals and pets during pregnancy may induce allergy and inflammation. This effect may influence AD incidence.

Maternal Diet, Polyunsaturated Fatty Acids, and Probiotics

Maternal dietary antigens can pass through the placenta, and antigen avoidance is commonly recommended for AD patients in clinical management. However, some researchers have argued that the maternal diet during pregnancy does not influence the atopic outcomes in offspring. A total of 763 mother–child pairs participated in a Japanese survey study in which they completed a diet history questionnaire about their diet during pregnancy. They were divided into three patterns according to their diet, “Healthy”, “Western”, and “Japanese”, and no statistical difference was observed among them with respect to the incidence of childhood eczema. Similarly, Kramer et al. extracted data from published reports and assessed the effects of antigen avoidance prescribed to atopic mothers on the prevention of atopic disease. No protective association was observed between early childhood AD and dietary antigen avoidance. In addition, it is widely acknowledged that alcohol intake and cigarette smoking during pregnancy adversely affect maternal and/or fetal nutrition.
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Regardless of the results of specific studies, avoidance of alcohol and smoking is strongly recommended.

A number of randomized trials have shown that perinatal probiotic supplementation can prevent early childhood AD, and the protective effects may be mediated through the regulation of gut microbiota and expression levels of immune cells.  

Simpson et al. reported that maternal probiotic supplementation was positively related to a significant reduction in the occurrence of AD at 2 years old, and there was a strong trend toward a reduced incidence at 6 years. Wickens et al. investigated the effect of *Lactobacillus rhamnosus* (HN001) and *Bifidobacterium animalis* subsp. *lactis* (HN019) on the prevention of eczema. They found that HN001 supplementation showed a protective effect against the incidence of eczema at 6 years in mothers from 35 weeks gestation until 6 months and in infants from birth until 2 years. No significant effect of HN019 supplementation was observed at any time point. Furthermore, there is substantial clinical evidence that maternal probiotic supplementation has marked protective effects against AD incidence until school age, and its long-term effects still need further evaluation. The efficacy of probiotics to prevent AD depends on multiple factors, such as specific probiotic strains, onset time, dosage, and duration. Doctors should provide a complete diet scheme if probiotics are recommended for AD patients. Further research and a multifaceted treatment schedule are necessary for probiotic usage in AD treatment.

Polyunsaturated fatty acids (PUFAs) are essential for fetal growth. A Spanish cohort study evaluated maternal FA composition to identify the effect on AD risk in offspring at 14 months old. The n-3 PUFAs level in cord blood showed a negative correlation with eczema development. Most clinical evidence indicates that maternal n-3 PUFAs intake exerts protective effects against AD during infancy and early childhood, although a few studies reached the opposite conclusion. Fish and fish oils are rich in long-chain n-3 PUFAs. Two studies found that fish intake during pregnancy could reduce the risk of early childhood AD and sensitivity to house dust mites, but no protective effect was observed for fish intake during breastfeeding. 

Miles et al. provided evidence that oily fish intake or fish oil supplementation in pregnancy may be associated with reduced allergic sensitization or a reduction in allergic manifestations. Gunaratne et al. published a review assessing the effect on infants’ atopic outcomes of long-chain n-3 PUFA supplementation during pregnancy, lactation, and birth. The results showed that supplementation reduced the incidence of IgE-mediated eczema in children at 12 to 36 months of age, but not at any other time point. Overall, n-3 PUFAs may exert protective effects in early childhood.

In summary, differences in overall dietary patterns are unlikely to affect AD incidence because of the complexity of dietary factors and the numerous interferential factors. However, single-factor trials of fish intake or other factors of potential importance may be an effective and straightforward way to illustrate the protective effect of these specific supplements. Probiotic supplementation and fish consumption are safe and effective for pregnant mothers in terms of reducing the AD risk in offspring, but further studies are needed to determine the multiple-factor effects and AD-prevention mechanism.

**Dust Mite Avoidance**

Many airborne allergens that induce AD are derived from house dust mites. A systematic review and meta-analysis (N=3,040) evaluated the relationship between dust mite avoidance intervention and the risk of developing AD in high-risk infants. The study concluded that dust mite avoidance strategies starting at birth and/or during pregnancy did not affect AD incidence. The data on antigen avoidance were mutually complementary with, and supportive of, the hygiene hypothesis. Early dust mite avoidance in childhood does not protect against allergic diseases.

**Vitamin Supplementation**

In recent years, numerous studies have focused on the effect of vitamin D on the incidence and severity of AD. A Japanese study (N=1,354) showed that higher vitamin D intake during pregnancy increased the risk of infantile eczema. Likewise, Back et al reported that higher vitamin D supplementation before 1 year of age was correlated with increased risk of eczema at 6 years of age. In another study, higher maternal vitamin D levels were significantly associated with lower risk of eczema at 4 years of age. A population-based prospective cohort study showed that vitamin D levels in the second trimester and at birth had no significant effect on the risk of developing eczema in the first 4 years of life. Benson et al proposed that the relationship between vitamin D and
allergic skin diseases maybe bimodal and/or gender-mediated.\textsuperscript{37} This hypothesis certainly seems consistent with the currently available results.

Vitamin B9, also known as folic acid, is required in increased amounts by pregnant women. Supplementation with vitamins of the B family during pregnancy may impact the development of the prenatal immune system. Some researchers have concluded that B-group vitamins such as B9 and B12 affect the prevalence of allergic disorders. Magdelijns et al demonstrated that maternal folic acid supplementation during pregnancy did not increase the AD risk at 2 years of age.\textsuperscript{38} However, the findings on the relationship between folic acid status and AD are inconsistent. A relatively high maternal-serum folic acid level ($\geq$9.5 ng/mL) during the second trimester was associated with a decreased risk of AD at 24 months, but not at other time points.\textsuperscript{39} A birth cohort study (N=8,742) showed that high folic acid ($>$16.2 nmol/L or $>$7.15 ng/mL) and vitamin B12 levels ($>$178 pmol/L) during pregnancy were positively associated with increased AD prevalence in offspring.\textsuperscript{40} However, another study found no significant effect of maternal consumption of vitamin B2, B6, B9, and B12 during pregnancy on the risk of eczema in infants aged 16–24 months.\textsuperscript{41} The influences of these conditions on AD and, under certain circumstances, consumption of B-group vitamins may alter the AD incidence in offspring. These conflicting results might also be reconciled by the above-mentioned hypothesis of Benson et al.\textsuperscript{37}

In addition, Gromadzinska et al. reported that there were no statistically significant associations between vitamins A and E, and the risk of AD from birth up to 2 years of age.\textsuperscript{42}

The conflicting findings of these studies highlight the ambiguity of the relationship between vitamin supplementation and AD and the need for further research to provide clarity.

**Antibiotic Exposure**

In a cohort study conducted in Singapore involving 792 participants, researchers found that antibiotic treatment in the first 6 months of life was significantly correlated with increased risk of developing AD between 6 and 12 months.\textsuperscript{43} Likewise, Wickens et al. in New Zealand reported that antibiotic exposure in the first 15 months of infancy increased the risk of developing AD and rash from 15 months to 4 years.\textsuperscript{44} However, studies from some European countries have reported contradictory findings. Data from the Netherlands and Spain showed no significant effect of antibiotic exposure on AD risk during infancy or early childhood.\textsuperscript{45,46} The discrepancy between these results might be related to the different patterns of antibiotic consumption in those countries, consistent with the results of Van Boeckel et al., who analyzed the global antibiotic consumption from 2000 to 2010.\textsuperscript{47} They found that the rate of antibiotic consumption per person in New Zealand was much higher than in many European countries, and the consumption of antibiotics per person in Singapore also ranked in the top eight of Asian countries. Although the above studies do not conclusively prove whether higher antibiotic consumption and antibiotic exposure are related to the risk of developing AD, they indicate a research direction and emphasize that the possible relationship requires further direct investigation.

**Maternal Obesity and Pregnancy Complications**

Maternal obesity is a widespread problem for both mothers and children and a high-risk factor for developing gestational diabetes mellitus (GDM) and macrosomia. One cohort study reported that maternal obesity during pregnancy was not associated with increased risk of AD in offspring, but another birth cohort study found that neonatal adiposity increased the AD risk during the first year of life.\textsuperscript{38,49} Remarkably, a 7.90-times increased risk of developing AD was found in infants who were born to mothers with GDM.\textsuperscript{50} A Taiwanese birth cohort study found an association between AD risk and GDM, but not with other maternal pregnancy complications.\textsuperscript{51}

**Caesarean Section, Maternal Allergic History, and Feeding**

In 2010 and 2015, two published reviews concluded that there was no reasonable evidence to suggest that birth by cesarean section increased the AD risk in offspring.\textsuperscript{52,53} Likewise, Kahr et al. found that maternal age, cesarean section, and season of birth did not affect AD prevalence in a Danish population of 850 monozygotic and 2279 same-sex dizygotic twin pairs at 3–9 years of age.\textsuperscript{54}

Epidemiological data support that allergy risk is preferentially transmitted through mothers and that maternal allergic history and breastfeeding behavior...
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can be considered extremely relevant to AD prevalence. Bhatia et al. assessed the associations between the incidence of childhood atopic disease and the level of maternal asthma control and asthma severity during pregnancy. Maternal asthma during pregnancy was linked with an 11% increased risk of AD development in the first 10 years, but asthma control measures and severity during pregnancy were not associated with AD incidence. To the best of our knowledge, current evidence on the effects of AD control measures and AD severity during pregnancy on childhood eczema is insufficient, and more research is needed.

Currently, the protective effect of breastfeeding against AD occurrence remains debatable. On the balance of evidence, breastfeeding does not appear to afford consistent protection against long-term eczema, and may even be a risk factor for AD. A birth cohort study (N=38,757) in Japan indicated that breastfeeding was linked with an increased risk of developing AD up to 42 months, and moreover, exclusive breastfeeding of infants and longer breastfeeding duration were positively associated with an increased risk of childhood eczema compared with infants fed with formula alone. Another matched case-control study provided evidence that early weaning, i.e., breastfeeding only for the first 4–5 months, acted to reduce AD incidence in young children. However, the World Health Organization (WHO) and the European Academy of Allergy and Clinical Immunology recommends breastfeeding for at least 4–6 months for health benefits. There is no doubt that breastfeeding is optimal for infant nutrition.

Gut microbiota is a key factor in influencing the predisposition to allergic diseases, including AD. The mode of delivery and feeding strongly affect the microbiome species in neonates. Backhed et al. found that 72% of the early gut microbiota of vaginally born infants could be matched with the maternal stool, whereas the equivalent matching was only 41% in neonates born by cesarean section. At present there is no mechanistic evidence for the preventive effect of early weaning, nor have the protective effects of probiotic supplementation or gut microbiota been well elucidated. It is difficult, therefore, to fully clarify the complex relationships among these factors. However, we propose that among children whose mothers have atopy, vaginally born and breastfed infants may be more susceptible to genetic factors, especially through breastfeeding. Early weaning allows infants to establish a different gut microbiota from their mothers and proceed toward a more adult composition. For infants at high risk of AD, we suggest that although breastfeeding for 4–6 months is still advisable, early weaning or reducing the breastfeeding duration is worth considering. In practice, though, for ethical and scientific reasons, it is difficult to give consistent recommendations on early weaning for lactating mothers while the mechanism of the effect of breastfeeding is still unclear.

**Stress Factors and Moisturizers**

Women’s rate of employment and their psychological stress have increased rapidly in recent decades. Moreover, many employed women are of child-bearing age. Previous studies found that the prevalence of childhood AD was significantly increased in mothers who had been exposed to stressful life events during pregnancy. Furthermore, a Taiwanese birth cohort study reported that postpartum depression increased the risk of childhood AD.

Moisturizers play an important role in suppressing dry skin by improving its barrier functions, delaying AD relapse, and reducing the need for topical corticosteroid use. The use of moisturizers is also considered standard therapy for AD treatment. In Japan, 118 neonates with a high familial AD risk participated in an investigator-blinded, randomized, controlled study. Emollient was applied to the intervention group each day for 32 weeks. The results supported that daily application of moisturizer prevented AD development in infants. In the same year and the same journal, the preventive effects of daily emollient were also demonstrated by another research group. Improved psychological well-being and the use of moisturizers are both highly promising strategies to reduce children’s risk of developing AD; however, well designed clinical trials are still needed.

**Fundamental Research**

Only a few studies have investigated the influence of chemical exposure on AD incidence in offspring. Di-(2-ethylhexyl) phthalate (DEHP) is widely used in polyvinyl chloride products, including vinyl flooring, food containers, and infant toys. Maternal exposure to DEHP in NC/Nga mice during neonatal periods aggravates AD-like skin lesions related to mite allergens in male offspring, and the aggravating effect...
Table 1. Risk and protective factors for atopic dermatitis (AD) incidence in offspring

<table>
<thead>
<tr>
<th>Influence</th>
<th>Participants</th>
<th>Design</th>
<th>Outcomes</th>
<th>OR/RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air pollution</td>
<td>6,683 children (9-11 yrs)</td>
<td>Prospective cohort study</td>
<td>AD was significantly positively associated with benzene, particles with a 50% cut-off aerodynamic diameter of 10 μm (PM_{10}), NO\textsubscript{x}, nitrogen oxides(NO\textsubscript{x}), and CO.</td>
<td>Benzene: 1.11 (1.00–1.28); PM\textsubscript{10}: 1.13 (1.01–1.24); NO\textsubscript{x}: 1.23 (1.04–1.42); NO\textsubscript{x}: 1.06 (1.00–1.18); CO: 1.08 (1.00–1.21).</td>
</tr>
<tr>
<td>Redecorating activities</td>
<td>2,536 children (6-7 yrs)</td>
<td>Epidemiologic cross-sectional study</td>
<td>Redecorating activities increased the risk of AD.</td>
<td>1.95 (1.43–2.67)</td>
</tr>
<tr>
<td>Climatic factors</td>
<td>91,642 children (0-17 yrs)</td>
<td>2007 National Survey of Children’s Health (Cross-sectional questionnaire)</td>
<td>Areas with higher UV index, relative humidity, mean temperatures, less indoor heating, and precipitation had significantly lower AD prevalence.</td>
<td>UV index: 0.73 (0.64–0.84); Relative humidity: 0.82 (0.71–0.96); Mean temperatures: 0.80 (0.70–0.92); less indoor heating: 1.11 (0.97–1.27); Precipitation: 1.29 (1.07–1.54); Immigration: 0.43 (0.30–0.61).</td>
</tr>
<tr>
<td>Hygiene hypothesis</td>
<td>1063 children (data available on AD at least once between 1 and 2 years of age and on farming status)</td>
<td>A prospective birth cohort study</td>
<td>Maternal contact with farm animals and cats during pregnancy had a significantly protective effect on AD in the first 2 years of life.</td>
<td>Dogs: 0.72 (0.61–0.85)</td>
</tr>
<tr>
<td></td>
<td>Twenty-six publications from 21 birth cohort studies</td>
<td>Meta-analysis of birth cohort studies</td>
<td>This meta-analysis reported a favorable effect of exposure to dogs and pets on the risk of AD in infants or children.</td>
<td>Pets: 0.75 (0.67–0.85)</td>
</tr>
<tr>
<td></td>
<td>763 mother-child pairs</td>
<td>Prospective cohort study</td>
<td>The three dietary patterns (Healthy pattern, Western pattern and Japanese pattern) during pregnancy were not related to the risk of eczema in the offspring.</td>
<td>Healthy pattern: 0.70 (0.41–1.20); Western pattern: 1.09 (0.64–1.85); Japanese pattern: 1.11 (0.64–1.94).</td>
</tr>
<tr>
<td>Dietary patterns</td>
<td>415 pregnant women</td>
<td>Randomized controlled trial (RCT)</td>
<td>There was a trend toward a lower cumulative incidence of AD in the probiotic group compared to the placebo group.</td>
<td>0.48 (0.25–0.92)</td>
</tr>
<tr>
<td></td>
<td>474 children (probiotic supplementation from 35 weeks gestation until 2 years old)</td>
<td></td>
<td>This study showed that the protective effect of Lactobacillus rhamnosus HN001 against AD, when given for the first 2 years of life only, extended to at least 6 years of age.</td>
<td>0.56 (0.39–0.80)</td>
</tr>
<tr>
<td>Polyunsaturated fatty acids (PUFAs)/Fish take</td>
<td>3366 women and their 3175 children</td>
<td>Cochrane Systematic Review - Intervention</td>
<td>There was a clear reduction in medically diagnosed IgE-mediated eczema with long-chain n-3 PUFA for children 12 to 36 months of age.</td>
<td>0.61 (0.39–0.95)</td>
</tr>
<tr>
<td></td>
<td>469 women (18–35 yrs) during pregnancy</td>
<td>Prospective cohort study</td>
<td>Maternal fish intake of more than 205 g/week decreased the risk of eczema by 43%.</td>
<td>0.57 (0.35–0.93)</td>
</tr>
<tr>
<td>Dust mite avoidance</td>
<td>7 RCTs (total n = 3040)</td>
<td>A systematic review and meta-analysis</td>
<td>Dust mite avoidance provided no benefit in the prevention of AD.</td>
<td>1.08 (0.78–1.49)</td>
</tr>
<tr>
<td>Vitamin</td>
<td>1,354 mother-child pairs</td>
<td>Prospective prebirth cohort study</td>
<td>Higher maternal intake of vitamin D during pregnancy may increase the risk of infantile eczema.</td>
<td>1.63 (1.07–2.51)</td>
</tr>
<tr>
<td></td>
<td>3,019 mother-child pairs</td>
<td>A population-based prospective cohort study</td>
<td>Levels of 25-hydroxyvitamin D in mid-gestation and at birth were not associated with the risk of eczema among children until the age of 4 years.</td>
<td>1.09 (0.82–1.43); 1.04 (0.87–1.25); 0.94 (0.81–1.10).</td>
</tr>
</tbody>
</table>
|                          | 8,742 mothers and 3,175 children | Population-based birth cohort study | High folate and vitamin B-12 levels during pregnancy. | B9(folic acid): 1.18 (1.05–1.33);
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<table>
<thead>
<tr>
<th>Factors/Groups</th>
<th>Children Studied</th>
<th>Study Type</th>
<th>Description</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Their children</td>
<td>763 mother-child pairs</td>
<td>Prospective cohort study</td>
<td>Pregnancy were associated with an increased prevalence of AD in the offspring.</td>
<td>B12: 1.30 (1.06–1.60)</td>
</tr>
<tr>
<td>Antibiotic</td>
<td>792 children (6–7 and 12–15 yrs)</td>
<td>Birth cohort study</td>
<td>GUSTO (Growing Up in Singapore Towards healthy Outcomes) study</td>
<td>Active or Passive Smokers A0.29(0.01–12.72);E:1.55 (0.82–2.36) Non-Smokers. A0.21(0.01–4.35);E: 1.03 (0.79–1.33).</td>
</tr>
<tr>
<td>Gestational diabetes mellitus (GDM)</td>
<td>680 children (1-6 yrs)</td>
<td>Birth cohort study</td>
<td>Cesarean section did not affect AD prevalence.</td>
<td>Vaginal delivery:1.00; Cesarean section: 0.87 (0.75–1.01).</td>
</tr>
<tr>
<td>Maternal allergic history</td>
<td>26,265 children (0-10 yrs)</td>
<td>Cohort study</td>
<td>Maternal asthma during pregnancy was associated with an increased AD risk.</td>
<td>1.11(1.02-1.21)</td>
</tr>
<tr>
<td>Feeding</td>
<td>38,757 children (6–42 months)</td>
<td>Population-based birth cohort study</td>
<td>Exclusively breastfed infants were 1.26 times more likely to have AD than infants fed formula alone.</td>
<td>1.26(1.12–1.41)</td>
</tr>
<tr>
<td>Stress factors</td>
<td>24,200 mother-newborn pairs</td>
<td>Multistage, stratified systematic sampling</td>
<td>(a) Working in professional or technical occupations increased the risk of childhood AD in addition to work stress during pregnancy. (b) Postpartum depression increased the risk of subsequent physician-diagnosed AD in children.</td>
<td>(a) 1.64(1.44–1.87); (b) 1.42(1.21-1.66).</td>
</tr>
<tr>
<td>Moisturizers</td>
<td>124 neonates at high risk for AD</td>
<td>Multicenter, multinational, 2-arm parallel-group, assessor-blind, randomized controlled pilot trial</td>
<td>A statistically significant protective effect was found with the use of daily emollient on the cumulative incidence of AD with a relative risk reduction of 50%.</td>
<td>0.50(0.28-0.9)</td>
</tr>
<tr>
<td>Di-(2-ethylhexyl) phthalate (DEHP)</td>
<td>NC/Nga mice</td>
<td>Fundamental research</td>
<td>Maternal exposure to DEHP in NC/Nga mice during neonatal periods aggravated atopic dermatitis-like skin lesions related to mite allergen in male offspring.</td>
<td>/</td>
</tr>
<tr>
<td>Fructo-oligosaccharide (FOS)</td>
<td>NC/Nga mice</td>
<td>Fundamental research</td>
<td>Maternal consumption of FOS reduced the severity of atopic dermatitis-like skin lesions in the offspring of NC/Nga mice.</td>
<td>/</td>
</tr>
</tbody>
</table>

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is accompanied by increased eotaxin expression. Fujitani et al. showed that maternal consumption of fructo-oligosaccharide reduced the severity of AD-like skin lesions in the offspring of NC/Nga mice, and the diminution of skin lesions may be mediated through regulation by gut microbiota, and lower expression levels of IgG1 and TNF-α.

CONCLUSION

Although genetic factors clearly play a role in the risk of AD, many other factors also affect its prevalence. Table 1 summarizes the risk and protective factors for AD in offspring.

First, it is indisputable that air borne pollutants and environmental chemicals are risk factors. Changes to the living environment and moving to an area with a different climate can reduce the risk of AD. The restricted use of antibiotics is suggested for infants with a family history of allergy, particularly in countries with a higher consumption of antibiotics. Second, maternal avoidance of dietary antigens and dust mites, and the use of vitamin supplements (except folic acid) are unnecessary during pregnancy and lactation. However, pregnant women must be made aware of the risk of GDM. Maternal allergic history and stress factors have a strong correlation with the development and exacerbation of AD. We suggest that pregnant women follow a consistent program of antibiotic control and seek a relaxed and stress-free state of mind. Finally, we note that data on the effects of probiotic supplementation, fish intake, and breastfeeding are inconsistent, and differences in intake and duration may affect AD development. In our opinion, probiotic supplementation and fish intake are relatively safe for pregnant women and infants, and appropriate supplementation should thus be encouraged. However, the current state of research does not permit us to provide a complete dietary scheme that would obviate the need for all supplementation. We propose that vaginally born and breastfed infants may be more susceptible to genetic factors from mothers with atopy. Therefore, reducing breastfeeding duration is suggested for infants with a family history of atopic disease. The gut microbiota composition has a strong correlation with the development and prevention of atopic disease. Furthermore, moisturizers are recommended for pregnant and breastfeeding mothers.

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