“Let Them Eat Peanuts: Early Exposure to Peanuts as an Effective Primary and Secondary Allergy Prevention Method”

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A life with severe food allergies is a difficult obstacle to overcome. While scrutinizing food labels and discussing details of kitchen conditions with school officials or restaurant owners is certainly inconvenient, severe food allergies can be life-threatening. Peanut allergies are among the most common and most dangerous of all food allergies. For those with this allergy, isolation from social situations and burdensome measures are frequent occurrences as even minor contact with the allergen can be deadly. Despite societal progress towards more clear food labels, and an increased awareness of food allergens in schools and other public places, food allergies appear to be on the rise in the U.S. Thus, the desire to prevent these allergies from occurring in the first place has captured medical attention for it holds the potential to save many lives. While initially counterintuitive, recent research shows that early exposure to the peanut allergen is an effective primary and secondary prevention method for peanut allergies.

The body's immune system has incredible potential to fight off foreign invaders. Unfortunately, the system is imperfect and sometimes the attack is mounted against an otherwise innocuous substance, such a food protein. In these "hypersensitivity reactions," the reaction involves the production of the specific antibody Immunoglobulin E (IgE), and the symptoms can range from skin rashes and irritation to severe airway blockages and anaphylactic shock which can be fatal. There are multiple ways to test for an allergy including a skin-prick test that scans for sensitivities, blood tests that identify allergen-specific IgE, and oral food challenge (OFC).

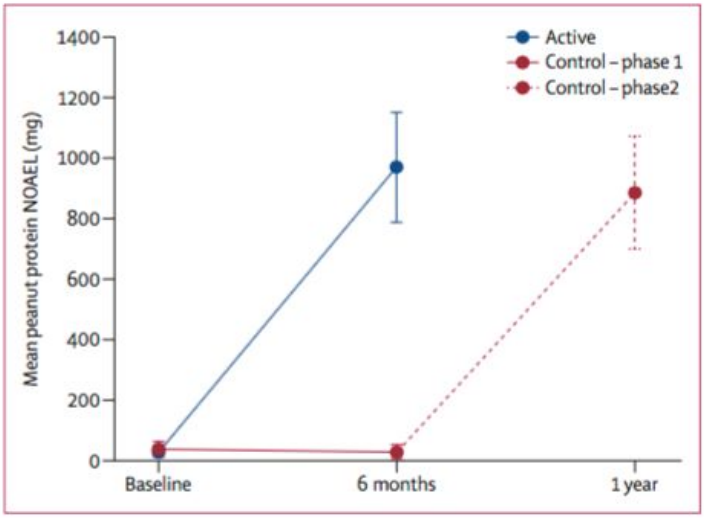
A peanut allergy specifically is present in 0.6% of the U.S population and is the leading cause of food allergy deaths[1]. This allergen presents a unique epidemiological concern as unlike other food sensitivities, a peanut allergy is rarely outgrown as the child ages. Additionally, when a severe attack is underway, an immediate epinephrine injection with a rescue pen is vital and in

2016, the Mylan brand EpiPen faced a price hike of more than 600%[2]. Because of the inconvenience, cost and danger of having this allergy, the focus of the medical community must be aimed towards promising prevention methods.

Previously, children that were identified as "high risk" for the development of a peanut allergy, such as those that have other identified food allergies or those with a family history, were instructed to avoid exposure with the allergen until they were grown. The theory was to avoid an over sensitization to the allergen, and to ensure the safety of any potentially allergic infants. Shockingly though, despite the intention to reduce the incidence of this allergy, the Fare Allergy Research and Education (FARE) reports that between 1997 and 2011, the incidence of food allergies in children under 18 has actually increased by 50%[3]. Another important observation that historically, these allergies are less prevalent in developing countries than they are in the United States[4]. Peanut allergies are also more common in first children than in younger siblings[4] and less common in immigrant children raised outside of the U.S[5]. One theory to explain all of these findings is the Hygiene Hypothesis or the "biome depletion theory." This theory states that avoiding potential irritants with extreme "cleanliness" actually dampens the development of a healthy immune system in infants and results in the increase in autoimmune and allergic responses. Under this hypothesis, a more frequent exposure to potential microbiological irritants can build a tolerance and would result in less incidence of these conditions.

This theory has stepped into the spotlight of the scientific community and is well accepted. However, the exact timing of the first exposure to a peanut allergen that is both effective and safe for a developing child has been investigated recently. In children 7 years and

older, oral immunotherapy (OIT) has been tested as a prevention method for allergic reactions. The principle is that repeated exposure to a small amount of the allergen will result in a desensitization to the allergen without causing an actual allergic reaction. This immunotherapy technique can theoretically increase the body's tolerance for the allergen slowly. In one study, 39 children aged 7-16 years with diagnosed peanut allergy were divided into two groups. One group that completed to the OIT for 6 months and the other group that avoided the allergen completely to act as the control. Both groups were then tested with an oral food tolerance test to 800 mg of peanut protein. Of those that underwent OIT, 62% did experience peanut protein desensitization as determined by a negative test, while zero members of the control group got the same result. For the second phase of the study, the control group then followed the oral immunotherapy technique for another 6 months, and 54% of those participants had achieved desensitization by the end of that period [6]. Below is the graphical summary of the statistical analysis from the treatment and control groups, showing the deviance from baseline of the treatment and control groups at the first six months in regards to mean amount of peanut protein tolerated.



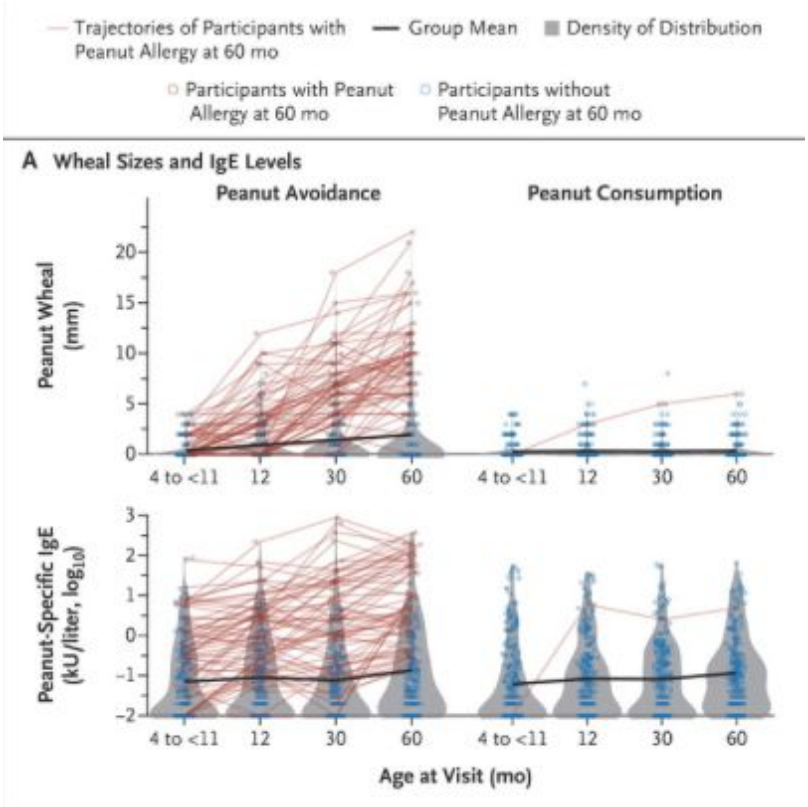
[6]Anagnostou K, Islam S, King Y, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): A phase 2 randomised controlled trial Figure 1. *The Lancet*. 2014;383(9925):1297-1304.

While beyond age 7 OIT desensitization can be successful, other studies have sought to investigate the effect of peanut consumption in the first two years of life on the development of future allergies. In an analysis of 300 children with asthma or allergic rhinitis, one study collected data using skin prick tests, food frequency surveys and oral food challenges to collect data. One goal was to statistically analyze the age of first exposure to peanut protein against the incidence of positive peanut allergies. A multivariate analysis was conducted and revealed that the median age of first exposure in children with a positive peanut allergy result was 2 years whereas the median age of first exposure in children without peanut allergies was just 1 year. The results confirmed that an earlier exposure to the peanut allergen in at-risk children was correlated with less frequent allergies later[7].

While it is still considered the gold standard for infant nutrition to breastfeed exclusively for at least 6 months, results have also been promising when exposing at-risk children to potential peanut allergens as early as 4 months of age. In a randomized UK study, 640 at-risk children were identified as either currently having a different food allergy or present eczema and assigned to either of two groups: an exposure group or an avoidance group. The exposure group of children consumed 2 grams of peanut protein three times weekly and the avoidance group avoided peanut protein entirely. After five years, the food oral tolerance test was given to each child and the results analyzed. The results were astonishing, as 13.7% of the infants that avoided peanut protein exposure had a positive peanut allergy result after 5 years and only 1.9% of those that received regular peanut protein exposure had the same positive allergy response[8]. The stark

difference in the results of two groups of high-risk infants heavily implies that an early exposure to the potential allergen is in fact, a better method at preventing future allergies than avoidance.

Additionally, the result from the skin-prick test ("wheal size") and serum IgE levels were also measured for the participants and results are reflected in the figure below. Significant findings include that the skin-prick wheal size result of the avoidance group of infants was more sharply increased from the initial measurement than those in the exposure group. Furthermore, infants in the exposure group also had lower levels overall of peanut-specific IgE at 1-5 years.



[8]Figure 3. Early Peanut Consumption Associated with Lower Risk of Peanut Allergy in High Risk Children. *Health Library: Evidence-Based Information* [serial online]. March 2015;Available from: Nursing Reference Center Plus, Ipswich, MA. Accessed February 7, 2017

While the data pointing to exposure in infants as an effective method for preventing future allergies is overwhelming, it is possible that the effect is even useful before the child is conceived. In a study published in the Journal of Allergy and Clinical Immunology, 1277 mothers and their children were asked to provide food frequency questionnaire responses detailing foods they frequently consumed during each trimester of their pregnancy. When the children were born, blood tests were analyzed for serum protein-specific IgE levels. Levels above 0.35 kU/L were considered a "positive result" for the peanut allergy. Regression models were created factoring in many possible variables such as family history of allergies, breastfeeding, ethnicity, and gender. Although this mathematical analysis has obvious limitations due to the inevitability of other factors influencing the development of allergies, the results were quite significant. With each increasing z-score of higher maternal peanut consumption ranging from, particularly in the first trimester of pregnancy, showed a decrease in 47% of future peanut allergies of the offspring[9].

The mechanism by which this sensitization occurs is still up for debate. It has been posited that regulatory T-cells may hold the key. One prospective birth cohort study with 856 children analyzed food diversity of pregnant mothers and of childhood diet on the development of asthma allergic rhinitis and common food allergies. They analyzed the cord blood at birth and again as children aged 4-6 years old. Diet variance was given a score 1-3, with 3 being the most variable, and a multivariate analysis was run examining the correlations. Key results showed that children with the least diet variance had an increased incidence of food allergies at 6 years of age, compared to children with the highest diet variability. Figure 2 below compares the results

graphically. Graph A depicts food variance for all participants of the study. Graph B depicts food variance in children that did not avoid any foods because of allergies. Graph C depicts the variance of food for all food items and all participants in the population. “The solid line represents the predicted value of asthma as a function of the score, and dashed lines represent the CI. The y-axis is the linear logit of food allergy, and the values are centered on 0 (50/50 odds) and extended to both positive and negative values”[10]

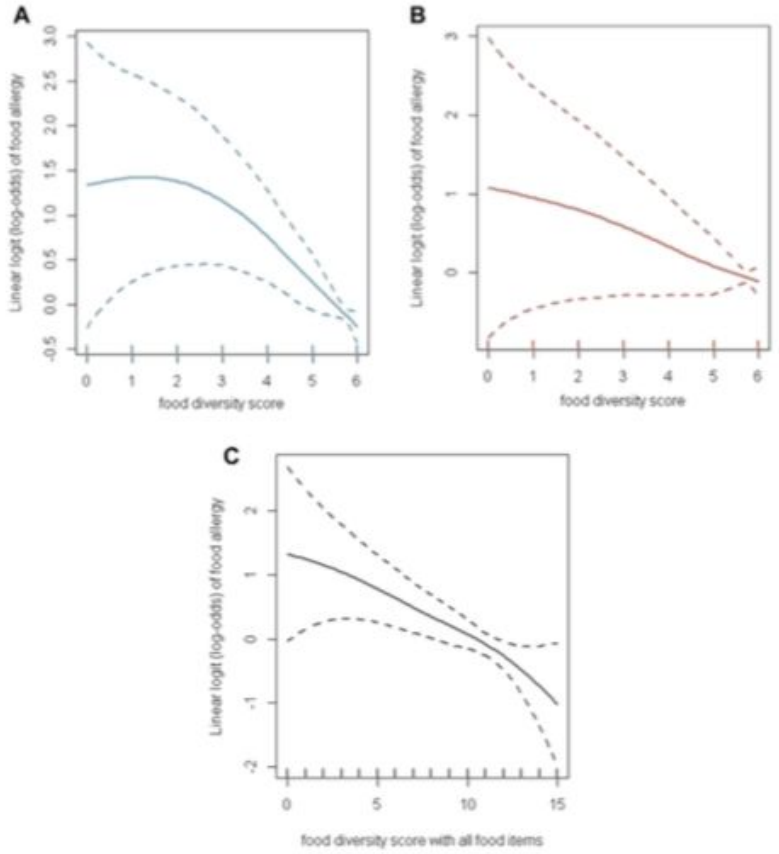


Figure 2. Roduit C, Frei R, Depner M, et al. Increased food diversity in the first year of life is inversely associated with allergic diseases. *J Allergy Clin Immunol*. 2014;133(4):1056-64.

Additionally, blood analysis investigated more detailed mechanisms for the trend in participants. By 6 years of age, unsuccessful oral tolerance tests for food allergies were

associated with a depletion in Foxp3 transcription factor for regulatory T-cells or suppressor T-cells. Regulatory T-cells help the body recognize "self-antigens" and prevent autoimmune disease. One hypothesis is that these T-cells prevent an isotype from becoming IgE and thus prevent the dangerous allergic response[10] . This study showed that early environmental exposure actually influences the gene expression in children and can protect against the development of future allergies by modulating the development of the immune system.

The results of the recent findings regarding early exposure to potential allergens in at-risk children has been so overwhelming that the American Academy of Pediatrics changed their recommendations for infant and childhood exposure[11]. In the past, at-risk infants were encouraged to avoid potential allergen triggers until it was confirmed that they are non-allergic. However, with recent evidence confirming that there is no protective effect of avoidance, they lifted this recommendation. It now appears that the opposite may be true and more exposure may be a preventative but perhaps that the more exposure may be preventative. Once an allergy has already developed, allergen avoidance is the only way to manage the condition. However, because of the severe and life-threatening consequences of mounted allergic reaction, there is a huge incentive to prevent allergies from developing. Because of its close association with the immune system, medical research focused on the development of the immune system seems to hold the key. Early exposure, both in utero, during breastfeeding and into the early childhood years to the peanut allergen in at-risk children serves as an effective method of preventing the development of future allergies and recommendations should reflect this new fact.

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