Early Food Allergen Exposure May Be Protective Against Food Allergies: An Extension Of The Hygiene Hypothesis

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Citation

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Abstract

Background and Objective: Food allergy affects 6% of U.S. children and 4% of the overall U.S. population. Health officials have recommended food allergen avoidance to prevent food allergies, but according to the Hygiene Hypothesis, exposure to allergens and pathogens is necessary for an effective immune system. The purpose of this study was to challenge conventions and determine whether early exposure might be beneficial rather than detrimental. Participants: 258 teenagers between the ages of 14-18 from a regional high school in New England were studied. Of the 258 participants, 67 had allergies (cases) while 191 did not (controls). Methods: A Food Allergy & Diet History questionnaire was administered to the participants' parents. 2x2 contingency tables were constructed based on case and control exposure before and after a particular age cutoff for each of 6 common food allergens. Odds of exposure for the cases and controls were calculated and compared in an odds ratio (OR). Significance was evaluated with a P-value in a Chi-square test. Results: The types of food allergies within the 67 cases consisted of nuts (39%), dairy (25%), shellfish (19%), wheat/gluten (9%), eggs (6%), seeds (3%), and other (24%). Exposure to eggs (OR, 0.15 [95% CI, 0.08-0.27]), dairy (OR, 0.32 [95% CI, 0.18-0.57]), and wheat/gluten (OR, 0.18 [95% CI, 0.10-0.33]) before the age of 12 months was most protective against food allergies. Exposure to seeds (OR, 0.19 [95% CI, 0.10-0.36]) and peanuts/tree nuts (OR, 0.19 [95% CI, 0.10-0.36]) before 24 months was most protective, and exposure to shellfish (OR, 0.15 [95% CI, 0.08-0.30]) before 36 months was most protective. Conclusions: Exposure to dairy, eggs, and wheat/gluten before 12 months, peanuts/tree nuts and seeds before 24 months, and shellfish before 36 months of age may be protective factors against food allergies. The results from this study, which demonstrate that early exposure is indeed beneficial, are crucial to rewriting and improving the recommendations of health officials for future prevention of food allergies in children and young adults.

INTRODUCTION

Currently in the United States, 6% of children and 4% of the overall population are afflicted with some type of food allergy.[3] The most common food allergens are milk, eggs, peanuts, tree nuts, seafood, shellfish, soy, and wheat. In 2007, approximately three million children under 18 were reported to have a food or digestive allergy, and the prevalence of peanut allergy in children has doubled from 1997-2002.[3]

The increasing incidence of food allergies has put a strain on health care clinics nationwide. According to data collected by the National Center for Health Statistics, food allergies resulted in approximately 317,000 visits to hospital emergency rooms, clinics, and physician's offices from 2003 to 2006.[3] Food allergy-related hospital admissions more than tripled from 2,600 per year in the 1998-2000 period to 9,500 per year in the 2004-2006 period.[3]

There is no known cure for food allergies at this time, and treatment options (besides allergen avoidance) are limited. Researchers and health care professionals have instead focused on allergy prevention, which can be referred to in three stages. Primary prevention blocks immunologic sensitization to foods and seeks to avoid inappropriate immune responses to common allergens. Secondary prevention suppresses expression of allergic disease after sensitization, and tertiary prevention averts symptoms after allergic disease has developed.[13] In order to circumvent sensitization, the Committee on Nutrition of the American Academy of Pediatrics (AAP) published guidelines in 2000 for primary prevention, or prophylaxis, of food allergy in young children. The recommendation states that the least allergenic solid food is to be introduced at 6 months, cow's milk introduced at 12 months, eggs introduced no earlier than 24 months, and peanuts/tree nuts and fish avoided until

at least 36 months of age.[13]

While some health care professionals have followed these guidelines, many others have questioned their validity. The guidelines are in direct opposition to the Hygiene Hypothesis, a theory that has received much attention in the field of immunology in recent years. First proposed by David P. Strachan in the British Medical Journal in 1989, the Hygiene Hypothesis states that a lack of early childhood exposure to infectious agents and bacterial infections increases susceptibility to allergic diseases by suppressing natural development of the immune system.[10, 11] Strachan noted an increase in worldwide allergic disease in recent years, particularly in affluent and developed countries, and attributed it to the modern, widespread use of vaccinations, antibiotics, pasteurized milk, and an industrial lifestyle with fewer children per family. Strachan based his reasoning on biological evidence that a balance between the T helper (T_h) cytokine response and the T regulatory (T_{reg}) cytokine response is necessary for a healthy immune system. Without proper stimulation, the T_{reg} pathway becomes underused and ineffective in curbing inappropriate responses driven by the T_h pathway, such as the allergic reaction.

Strachan derived the Hygiene Hypothesis from a 1989 study of environmental allergens and hay fever and eczema, and the theory has held up in subsequent studies which have found a correlation between airborne allergen exposure and the likelihood of children developing asthma, wheeze, and other respiratory diseases.[11, 12] However, studies on food allergies and food allergen exposure have just begun to generate attention. Studies in Israel, the United Kingdom, and Australia in recent years have demonstrated beneficial effects of early consumption of cow's milk, peanuts, and eggs, prompting further questions about the validity of food allergen avoidance as a means of allergy prevention in the United States.[1, 6, 7]

As an extension of the Hygiene Hypothesis, which has dealt primarily with pathogens and environmental factors, this case-control study focuses on exposure to food allergens. The question we examined is whether teenagers with and without food allergies differ in their age of first exposure to common food allergens in attempt to determine whether early allergen exposure may be advantageous. We hypothesized that teenagers with food allergies will have been exposed to the common food allergens relatively late while teenagers without food allergies will have been exposed to a variety of foods at an early age. The results from this study will be valuable in reconsidering and improving the conventional, largely believed to be outdated, recommendations of health officials for children to avoid food allergens to prevent food allergies later in life.

METHODS AND MATERIALS

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Ethics. This study was approved by the participating school's Scientific Review Committee. Permission was obtained from the school principal and nurses to collect data on medical history, provided that no identifying information appeared on the survey besides grade, age, and sex. A consent form was signed by parents or legal guardians of the participants, indicating their willingness to participate in the study. The project proposal, consent form, and survey were all approved by the Scientific Review Committee prior to data collection. The appropriate ethical guidelines pertaining to this study were identified by members of the Scientific Review Committee, and ethical clearance was granted provided that those guidelines were adhered to.

The Food Allergy & Diet History survey. The Food Allergy & Diet History survey was designed after significant literature review and asked for grade, age, sex, medical history, allergy symptoms, diet history, past and current food allergies, and age of first exposure to common food allergens. The survey was pretested on a group of twelve teenagers aged 16-17 to check for clarity in the wording of the questions and adequate length and content of responses. The data collected in this trial was not included in the final report. The researcher visited the classrooms of willing teachers at a regional high school that covers three nearby towns to describe the purpose and nature of the study and answer any questions prospective participants may have had. The consent form and Food Allergy & Diet History survey was then distributed to students to be filled out by their parents on their behalf. It was made clear that the return of the consent form and survey were completely optional. Participants included freshman, sophomore, junior, and senior students aged 14-18. There was no preference for any grade, gender, race/ethnicity, or academic achievement level. This age group was selected primarily because of the rising incidence of food allergies in children and young adults age 18 and under.[3] Also, childhood allergies that are commonly outgrown during adolescence will have been outgrown by the time one reaches high school. The surveys were filled out by the parents of the participants, as many teenagers do not remember facts about their own diet and allergy

histories.

The survey first asked whether or not participants had food allergies and whether those allergies had been confirmed via a blood test for antibodies to food allergens, a skin test reaction to food allergens, and/or another form of confirmation by a health care professional. The survey then listed six of the most common food allergens (nuts, seeds, dairy, wheat/gluten, eggs, and shellfish – determined from literature review) and participants were asked to select whether they had a past allergy to the food, a current allergy to the food, or had never had an allergy to the food.[3] The survey asked for the participant's age of first exposure to those six common foods. Exposure was defined as first consumption in any amount. The age categories were 0-12 months, 13-24 months, 25-36 months, and later than 36 months. The age categories were selected based partly on AAP recommendations and partly on the findings of previous studies.[1,6,7,12] At the end, participants were asked on a scale of 1-5 (5 being the highest) how confident they were in the accuracy of the answers they provided.

Study design. The participants were divided into two groups: food allergy (cases) and no food allergy (controls). No distinction was made between the types of food allergy within the cases. For each of the six common food allergens, the participants were divided into the cases and controls. Within the cases and controls, the data was then divided into two groups based on exposure before or exposure after a particular age. Because there were four age categories that participants chose from, three age cutoffs were possible: up to and including 12 months vs. after 12 months, up to and including 24 months vs. after 24 months, and up to and including 36 months vs. after 36 months. Three 2x2 contingency tables were then created to compare the cases vs. controls in terms of exposure before vs. exposure after the cutoff age (one table for each age cutoff).

Data Analysis and Statistics. The odds of exposure among the cases and controls were calculated and compared in an odds ratio (OR), which contrasts the chances of exposure before the particular age in the cases with the chances of exposure before the particular age in the controls. If OR is greater than 1, the exposure is likely a risk factor for developing the disease. If OR is less than 1, the exposure is likely a protective factor against developing the disease. 95% confidence intervals were calculated using VassarStats: Website for Statistical Computation.[8] From the actual, or "observed" data, the "expected" data was calculated as what one could expect if the two variables were statistically independent of each other. Each "expected" value was calculated by multiplying its column and row totals (in the 2x2 contingency tables) and dividing the product by the total sample size. With the "observed" and the "expected" data, a chi-square test was performed using Microsoft Excel 2007, producing p-values that were used to determine the data's statistical significance. Significance was accepted if $p<0.05$. For each food, the age cutoff with the lowest OR that was statistically significant was deemed most protective.

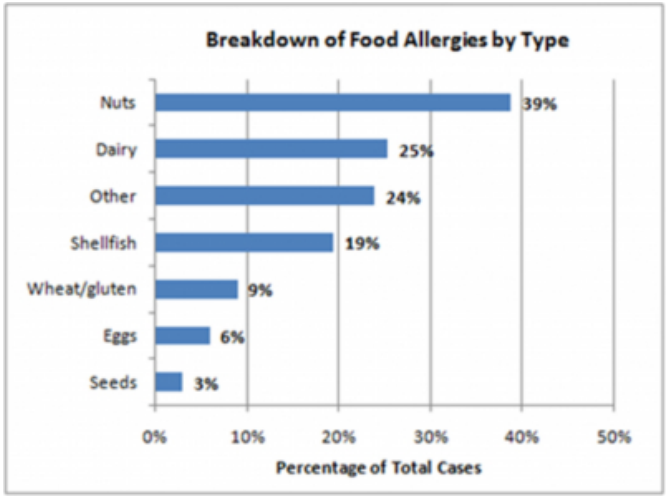
RESULTS

To determine the relationship between food allergies in teenagers and their age of first exposure to common allergens, 258 total high school students were surveyed. 67 participants were found to have food allergies, and these participants made up the "cases" group. 191 participants did not have any food allergies, so these participants composed the "controls" group.

The six major food allergens in the survey were peanuts/tree nuts, seeds, dairy, shellfish, eggs, and wheat/gluten. Within the 67 cases of food allergies, a breakdown of the relative prevalence of each allergy is given in Figure 1. Peanut/tree nut, dairy, and shellfish allergies were the most prevalent, each composing 19% or more of the total cases of allergies. Seed, egg, and wheat/gluten allergies were less prevalent, each comprising less than 10% of the total cases.

Figure 1

Figure 1. Percentage breakdown of observed food allergies in cases by allergen type



The results for the six common food allergens are reported in Figure 2. For shellfish, the particular age for exposure was

36 months. The number of cases and controls exposed to shellfish by 36months and the number exposed after 36 months are reported. The odds of exposure for both cases and controls are included along with the odds ratio and the p-value from the chi-square test. In parenthesis are the "expected" data that was used in the chi-square analysis. Similar data for dairy exposure (most protective at 12 months) is reported. It is worth noting that all 258 participants were first exposed to dairy between 0-24 months; there were no cases or controls first exposed to dairy between 24-36 months or after 36 months. The results for peanuts/tree nuts, eggs, seeds, and wheat/gluten exposure in the cases and controls are similarly reported along with the odds of exposure for each group, the odds ratios, and the corresponding p-values calculated from the chi-square analysis.

Figure 2

Figure 2. Odds of exposure, OR, and P-value for the six common food allergens at the most protective age cutoffs

Shellfish – Age Cutoff: 36 months

	Cases (Expected)	Controls (Expected)	Total
Exposed	12 (32.46)	113 (92.54)	125
Nonexposed	55 (34.53)	78 (98.46)	133
Total	67	191	n=258
Odds of exposure	0.2182	1.4487	

OR = 0.15 (95% CI, 0.08-0.30) P-value < 0.001

Eggs – Age Cutoff: 12 months

	Cases (Expected)	Controls (Expected)	Total
Exposed	21 (42.85)	144 (122.15)	165
Nonexposed	46 (24.15)	47 (68.85)	93
Total	67	191	n=258
Odds of exposure	0.4565	3.0638	

OR = 0.15 (95% CI, 0.08-0.27) P-value < 0.001

Dairy – Age Cutoff: 12 months

	Cases (Expected)	Controls (Expected)	Total
Exposed	26 (39.73)	127 (113.27)	153
Nonexposed	41 (27.27)	64 (77.73)	105
Total	67	191	n=258
Odds of exposure	0.0634	1.9998	

OR = 0.32 (95% CI, 0.18-0.57) P-value < 0.001

Seeds – Age Cutoff: 24 months

	Cases (Expected)	Controls (Expected)	Total
Exposed	16 (35.06)	119 (99.94)	135
Nonexposed	51 (31.94)	72 (91.06)	123
Total	67	191	n=258
Odds of exposure	0.3137	1.6528	

OR = 0.19 (95% CI, 0.10-0.36) P-value < 0.001

Wheat/gluten – Age Cutoff: 12 months

	Cases (Expected)	Controls (Expected)	Total
Exposed	18 (38.17)	129 (108.83)	147
Nonexposed	49 (28.83)	62 (82.17)	111
Total	67	191	n=258
Odds of exposure	0.3673	2.0806	

OR = 0.18 (95% CI, 0.10-0.33) P-value < 0.001

Peanuts/tree nuts – Age Cutoff: 24 months

	Cases(Expected)	Controls (Expected)	Total
Exposed	22 (41.29)	137 (117.71)	159
Nonexposed	45 (25.71)	54 (73.29)	99
Total	67	191	n=258
Odds of exposure	0.4889	2.5370	

OR = 0.19 (95% CI, 0.10-0.35) P-value < 0.001

In summary, the most protective age cutoff for eggs, dairy, and wheat/gluten was 12 months. For peanuts/tree nuts and seeds it was 24 months, and for shellfish it was 36 months. These age cutoffs for the six food allergens produced the lowest odds ratios that were statistically significant, as demonstrated in Figure 3.

Figure 3

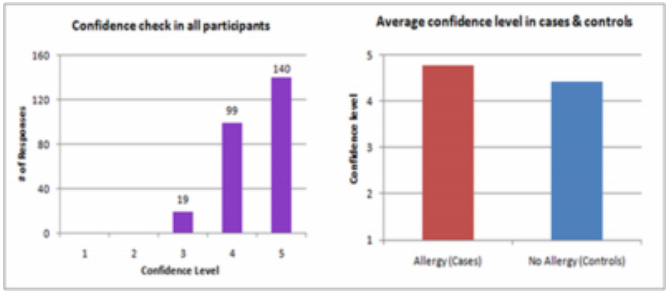
Figure 3. The most protective age cutoffs, ORs, and P-values for the six common food allergens

Food Allergen	Age Cutoff	Odds ratio (95% CI)	P-value
Eggs	12 months	0.15 (0.08-0.27)	>0.001
Dairy	12 months	0.32 (0.18-0.57)	>0.001
Wheat/gluten	12 months	0.18 (0.10-0.33)	>0.001
Peanuts/tree nuts	24 months	0.19 (0.10-0.35)	>0.001
Seeds	24 months	0.19 (0.10-0.36)	>0.001
Shellfish	36 months	0.15 (0.08-0.30)	>0.001

To determine the relative accuracy of the responses recorded, participants were asked on a scale of 1-5 how confident they were in the answers they provided, with 1 being "not confident" and 5 being "very confident." The results of the confidence check are reported in Figure 4 along with the average confidence levels for the cases and controls.

Figure 4

Figure 4. Overall confidence level in all participants; confidence level between cases & controls



DISCUSSION

Despite the AAP recommendation of allergen avoidance for prevention of food allergies, a number of recent studies on feeding habits of small children and their food allergies have shown just the opposite. A 2008 study of peanut consumption and peanut allergy in children in Israel and the United Kingdom revealed that Israeli infants consume as much as 7.1g of peanut protein as often as eight times per month, while infants in the UK consume virtually no peanuts. Correspondingly, children in the UK had a 10-fold higher prevalence of peanut allergy than Israeli children.[1] Similarly, a 2010 study of infants in Israel has confirmed the protective benefits of cow's milk and soy formulas as supplements to breast milk.[6] In addition, a study conducted in Melbourne, Australia also in 2010 found reduced risk of

egg allergy in infants exposed to eggs within 4-6 months of age as opposed to markedly higher risk of egg allergy in infants exposed at 10-12 months or after 12 months.[7] Based on the Hygiene Hypothesis and the mounting evidence in these studies, we hypothesized that teenagers without food allergies will have been exposed to a variety of foods relatively early whereas teenagers with food allergies will have been exposed to the allergens late.

The results for shellfish exposure demonstrate that most of the participants with food allergies (cases) were exposed to shellfish late whereas the majority of the participants without food allergies (controls) were exposed to shellfish early. For shellfish, the age cutoff for exposure that was most protective was 36 months. The odds of exposure in the cases was 0.22, which represents little chance that the cases had been exposed to shellfish before 36 months. On the other hand, the odds of exposure in the controls was 1.45, suggesting a much greater chance that the controls had been exposed to shellfish before 36 months. This yields an odds ratio of 0.15 [95% CI, 0.08-0.30], or 85% smaller odds of exposure among the cases than the controls. Because the odds ratio is less than 1, exposure to shellfish prior to 36 months can be considered a potential protective factor against food allergies. The chi-square test yielded χ^2 (1, N = 258) = 33.8, p <0.001 so these results are statistically significant.

The results for dairy were similar. The age cutoff that was most protective for dairy exposure was 12 months. The odds of exposure before 12 months for the cases and controls were 0.06 and 2.00, respectively. Again, the chances of dairy exposure before 12 months were much smaller in the cases than in the controls, which is confirmed in the odds ratio of 0.32 [95% CI, 0.18-0.57). This indicates roughly 68% smaller odds of exposure before 12 months in the cases than the controls. Because 0.32 is less than 1, exposure to dairy before 12 months may also be a protective factor against food allergies. The chi-square test yielded χ^2 (1, N = 258) = 15.75, p <0.001 confirming the statistical significance of the results.

The results for peanuts/tree nuts, eggs, seeds, and wheat/gluten all point to the same conclusion that the participants with allergies had a smaller chance of having been exposed to the food allergen before their respective age cutoffs. Correspondingly, the participants without allergies had a higher chance of having been exposed to the food allergen before the age cutoff, suggesting that early exposure may be a protective factor against food allergies. The most protective age cutoff for nuts and seeds was found to be 24 months while the most protective age cutoff for eggs and wheat/gluten was 12 months. The odds ratios for nuts, eggs, seeds, and wheat/gluten were 0.19 [95% CI, 0.10-0.35], 0.15 [95% CI, 0.08-0.27], 0.19 [95% CI, 0.10-0.36], and 0.18 [95% CI, 0.10-0.33], respectively, representing over 80% smaller chances of exposure in the cases than in the controls. Because odds ratios are all less than 1, exposure to each of these foods before their respective age cutoffs may be possible protective factors against the development of food allergies. The chi-square tests returned χ^2 (1, N = 258) = 31.73, p <0.001 for peanuts/tree nuts, χ^2 (1, N = 258) = 41.75, p <0.001for eggs, χ^2 (1, N = 258) = 29.35, p <0.001for seeds, and χ^2 (1, N = 258) = 33.47, p <0.001for wheat/gluten, verifying the statistical significance of the results.

LIMITATIONS

Despite the strong evidence in this study that exposure to food allergens prior to a certain age may be beneficial rather than harmful in terms of allergic disease, there are many limitations that must be considered. One of the greatest limitations was the sample size. With a total of 258 participants, there may not have been enough data to draw a wide-ranging conclusion for the general United States population. It is worthy to note, however, that the participants did come from a variety of backgrounds, as the regional high school covered urban, suburban, and rural neighborhoods. The low number of cases also prevented further division into the different types of food allergies as there were not enough cases to meaningfully compare peanut allergy to peanut exposure and egg allergy to egg exposure, etc. However, there has been evidence in the past of cross-sensitization and co-occurrence of allergies to foods with similar proteins, such as peanuts and sesame seeds.[1] Thus it may have been beneficial to examine food allergies as a whole rather match each type of allergy to its specific allergen.

Environmental exposure was another confounding variable that may have impacted results. Environmental allergens were excluded from the scope of this study because they are extremely difficult to control and assess, but this does not mean that environmental factors are not related to food allergies. In fact, 34 of the 67 cases (or 43%) had some sort of seasonal allergy in addition to their food allergies, opening up an interesting avenue for future research.

As with all studies involving self-report methodology, there

is the risk of recall bias. Recall bias arises when individuals with a disease (cases) remember past exposures more completely or accurately than those individuals without the disease (controls).[5] It is natural that people with a disease might try to determine the cause of their disease and remember more events from their past than people without disease, who have no reason to keep track of past exposures. Family history for a disease or increased risk for developing a disease might also influence how well people remember their past exposures. In a confidence check depicted in Figure 4, the overwhelming majority chose 4 or 5 on a scale of 1-5, signifying that they were "very confident" in their responses. Only 8% chose 3 and not a single participant chose 2 or 1. The average confidence level for the cases was 4.78/5 while the average for the controls was 4.36/5, indicating that there was little difference in confidence level between the two groups.

Although the nature of allergic disease eliminates any uncertainty as to whether allergen exposure or disease occurred first, this case-control study was limited in that it was retrospective and collected information about the disease in the present and the exposure in the past. There could have been many other factors contributing to the development of food allergies besides age of first food allergen exposure, but case-control studies allow for examination of only one factor at a time. With unlimited resources, future directions may include conducting a longitudinal, prospective cohort study with a sample size based on a power calculation to determine the true effects of early vs. late allergen exposure on the development of allergies. If in fact early exposure proves to be beneficial, subsequent studies can be conducted to optimize the amount and manner of exposure necessary to reduce sensitization and prevent allergy development.

CONCLUSIONS

Despite the limitations of sample size, recall bias, and temporality, analysis of the ages of first exposure to six common food allergens in 67 cases and 191 controls yielded the strong conclusion that those with no food allergies were much more likely to have been exposed to the food allergens early than those who did have food allergies. The definition of "early," however, varies for each food. Based on the most protective age cutoffs determined for each food, it may be beneficial for parents to expose their children to dairy, eggs, and wheat/gluten by 12 months, peanuts/tree nuts and seeds by 24 months, and shellfish by 36 months as a means of preventing sensitization and subsequent food allergies.

The evidence from this study supports the Hygiene Hypothesis, which states early exposure to pathogens and various allergens is necessary to develop a balanced immune system between the T_h and T_{reg} responses. Additional research into environmental, viral, and bacterial factors is needed to confirm such a theory, but it does appear that the Hygiene Hypothesis can be applied to food allergies in addition to other disorders of the immune system.

The results from this study are consistent with those of previous studies demonstrating the benefits of early consumption of peanuts, cow's milk, and egg, but they are inconsistent with the recommendations of the American Academy of Pediatrics. Whereas the AAP viewed early allergen exposure as a risk factor for allergy development and advised parents to avoid prematurely exposing their children to certain allergens, we demonstrate that early allergen exposure may actually be protective in preventing food allergies.

Research into allergic disease and food allergies is essential in improving the quality of life for millions of Americans. This new insight into the benefits and protective potential of early allergen exposure is crucial to correcting a decade's worth of misguided recommendations regarding allergy prevention. In an evolving society where the incidence of allergic disease is rising concurrently with the quality of health care and hygiene, it is urgent that effective methods of allergy prevention are found before too many lives are jeopardized by severe diet restrictions and life-threatening allergic reactions. It is clear that the Hygiene Hypothesis is a promising path that must be further explored.

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APPENDIX 1

Allergy Study Consent Form

Dear Parent/Guardian,

My name is Zizi Yu and I am enrolled in the Authentic Science Research program at Amity Regional High School. As part of the program, I am conducting a study on food allergies and food allergen exposure in high school teenagers.

Food allergy is a problem that has become more and more prevalent in recent years, especially in the United States. After reading the common recommendations of health officials for prevention of food allergies, I became interested in allergy epidemiology and devised this study on food allergies in high school teenagers.

I am asking for your participation in hopes that you will fill out a quick questionnaire and provide information about your child's diet and allergy history. Please note that participation involves minimal risk. Please be assured that all information you provide will be kept completely confidential and will be used for research purposes only. The results from this study could be valuable in evaluating and perhaps improving the current methods for allergy prevention.

If you would like to participate, please sign the following form, fill out the attached questionnaire, and return it to me or my Science Research teacher Ms. Deborah Day. Be sure to discuss with your child the reasons for participating and obtain his/her permission as well. If you have any questions about the study, please do not hesitate to contact me at zizi262@yahoo.com. Thank you for your participation.

Please sign and return

I, _____, have discussed this study with my child and agree to participate in this study with the knowledge that any information I provide will be kept completely confidential and will be used for research purposes only. The answers I provide cannot and will not be connected to me or my child in any way, shape, or form.

I understand that I may participate to any degree with which I am comfortable. I may choose which questions to answer and can skip any that I am not comfortable answering. If I have any questions about the study, I may contact Zizi Yu at zizi262@yahoo.com or Ms. Deborah Day at chemqueen1988@sbcglobal.net.

Student Signature_____ Date _____

Parent Signature _____ Date _____

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