Project tile:

MATERNAL DIETARY MODIFICATION FOR PREVENTION OF FOOD SENSITISATION

A dissertation submitted in partial fulfilment for the award of the degree of Master of nutrition and dietetics, University of Wollongong.

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Abstract

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Introduction

Peanut and egg are the most common food allergies in Australia and may cause life threatening allergic reactions, anaphylaxis[1]. Since 1994, RPAH Allergy Unit has been advising maternal dietary modification (mainly peanut and tree nuts avoidance) during pregnancy in high-risk families to prevent children developing a food allergy. This study aims to investigate the effectiveness of this advice.

Method

Families with children (N=2114) with previously diagnosed food allergy were selected. Siblings of the index children were divided according to whether their mothers had avoided egg or peanut during late pregnancy and lactation. Siblings underwent skin prick tested for the common food allergens. Sensitization was defined as a SPT greater than 3x3mm. Results of egg and peanut SPT were analysed in those aged <1yr, 1-2 yrs, 2-4 yrs and >4yrs. Chi square tests were used for significance ($p<0.05$).

Results

Among the four age groups, there was no significant difference in the prevalence of egg sensitization whether the diet was modified or not. However, there was a significant difference in prevalence of peanut sensitization depending on whether peanut avoidance measures were adopted. The effect was much greater in the first year ($p=0.02$) and remained significant in most of the subsequent years. There was no significant difference in sensitization to other foods in relation to peanut avoidance.

Discussion

Although avoidance advice had no significant effect on egg sensitisation, maternal peanut avoidance measures significantly reduced the incidence of peanut sensitization, especially in the first year of life. The diminishing benefit of peanut avoidance measures after the first year of life suggests that subsequent sensitisation to peanut may be occuring through subtle environmental or dietary exposure.

Reference:

1. Bock SA, Furlong AM, Sampson Hugh, Fatalities due to anaphylactic reactions to foods. J Allergy Clin Immunol 2001; 107: 191-3.

Introduction

Natural history of food allergy and its prevalence

Food allergy usually begins in the first 1 to 2 years of life. Its prevalence peaks at about 6% to 8% at 1 year of age and then drops gradually until late childhood (Wood, 2003). Clinical allergy to milk, egg and soy frequently remit while allergy to peanut, nuts and fish persist during childhood (Wood, 2003). The prevalence of food allergy seems to be increasing at an alarming rate, particularly to peanut (Grundy et al, 2002). The increase is out of proportion to the increased prevalence of allergic disease such as asthma, rhinitis and eczema in western populations (Asher et al, 2006). In Australia, egg and peanut are the two most common food allergies. They were often associated with severe allergic reactions, such as anaphylaxis, which can be life threatening (Bock, Furlong & Sampson, 2001). The effect on quality of life of living with this risk is similar to that of other chronic diseases (Sicherer, Noone & Munoz, 2002).

Risk factors for food allergy

The cause of food allergy is multidimensional. Genetic, immunologic, dietary and environmental are all possible risk factors for food allergy (Sicherer & Sampson, 2007). Studies of the genetic influence on peanut allergy have shown that peanut allergy is more common in children of atopic mothers (Sicherer et al, 2000), and more common in siblings of peanut allergic patients (7%) than in the general population (1.3%) (Hourihane, 1996). It is much more common in monozygotic twins (64 %) than in dizygotic twins (7%).

Immature gastrointestinal (GI) and immunologic systems in infancy also contribute to the development of a food allergy. This is because allergenic proteins are more likely to be absorbed intact in infants than in older children and adults, due to the fact that infants have immature mucosal surface, with increased intestinal permeability and decreased production of gastric acid and pancreatic enzyme (Nowak & Sampson, 2006). Additionally, an infant's immune system can be biased either towards T helper cell type 2 (Th2) or T helper cell type 1 (Th1) mediated responses. The Th2 mediated response is predominant in atopic children, due to the increased secretion of interleukin (IL)-4, which stimulates IgE antibody production (Prescott et al, 1999). The Th1 mediated response is predominant in healthy children, due to production interon gamma (IFN- γ), which inhibits the growth of Th2 cells (Prescott et al,

1999). The Th2 response can also be influenced by environmental factors, with suppression by concomitant exposure to infection, or enhanced by concomitant exposure to air pollutants such as cigarette smoke. This is the basis of the 'hygiene hypothesis', according to which lack of exposure to environmental bacteria in the current Western environment and life style drives a Th2 mediated response that predisposes to allergic disease (Mosges, 2002).

Exposure to potential food allergens early in life is one of the big factors causing food sensitisation, raising the concerns about maternal ingestion of food allergens during pregnancy and breastfeeding. This is because environmental exposure to allergens may potentially occur early in life. Maternal dietary antigens including egg and peanut can cross the placenta and pass into breast milk, and infants are therefore exposed to the risk of becoming sensitised (ie producing IgE antibodies) in the perinatal period (Frank et al, 1999; Vadas et al, 2001).

Maternal dietary advice debate

Since 1994, it has been standard practice at the Royal Prince Alfred Hospital (RPAH) Allergy Unit to advise maternal dietary modification in high-risk families (particularly peanut and tree nut avoidance) to prevent children becoming sensitised to food allergens. Hourihane et al (1996) & Frank et al, (1999) also found that the ingestion of peanut or peanut products during pregnancy and lactation may increase the risk of subsequent peanut allergy, and suggested that maternal avoidance may prevent peanut sensitisation. As a result, the UK and United States Department of Health recommended that women with infants at risk for atopy, should avoid peanut during pregnancy and lactation from 1998. Despite this, the prevalence of peanut allergy in children has doubled since this advice was initiated, although this does not indicate a cause and effect relationship (American Academy of Pediatrics, 2000).

The effect of the maternal avoidance dietary advice is very controversial. Zeiger et al (1989 & 1992) have shown that the maternal avoidance measures reduced food sensitisation and food allergy primarily during the first year of life, but the protective effect reduced by 2 years and vanished at ages 3 and 4 years. Grimshaw et al (2003) have found a significant reduction in the rate of egg sensitisation in 18 month old infants with strict maternal egg avoidance. However, several studies have found no effect of the prevalence of food allergies as a result of avoidance

of egg or peanut during the third trimester of pregnancy and lactation (Lilja et al, 1989; Hermann et al, 1996; Kramer & Kakuma, 2006; Hourihane et al, 2007).

Aim

The aim of this study was to investigate the effectiveness of the maternal dietary modification in preventing food sensitization in high risk children attending the RPAH Allergy Unit.

Methods

Ethics

This study was approved by the Ethics Review Committee of the Sydney South West Area Health Service.

Subjects

Subjects were selected from a total cohort of 2114 children with eczema and possible food allergy and their siblings who were seen by Dr Velencia Soutter at the RPAH allergy unit from 1992 to 2007.

The inclusion criteria were:

- Children aged 0 to 18 years old.
- Children who were breastfed.
- Family records including siblings with at least one food allergy.
- Family records including skin prick tests (SPT) results on all siblings.

The exclusion criteria were:

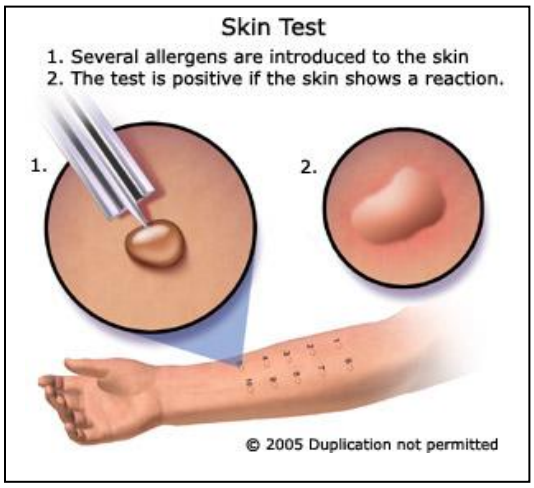
- Only one child in the family.
- Children without SPT results.
- Children with unknown maternal dietary status.
- Children lost to follow-up.

Skin prick tests (SPT)

SPT were performed by dropping protein extracts (allergen) on the forearm, and gently pricking the skin through the protein extracts (Figure 1)

Positive SPT results were taken as a weal of 3mm or greater response to the reference (1% histamine).

Figure 1



www.allergy.health.ivillage.com

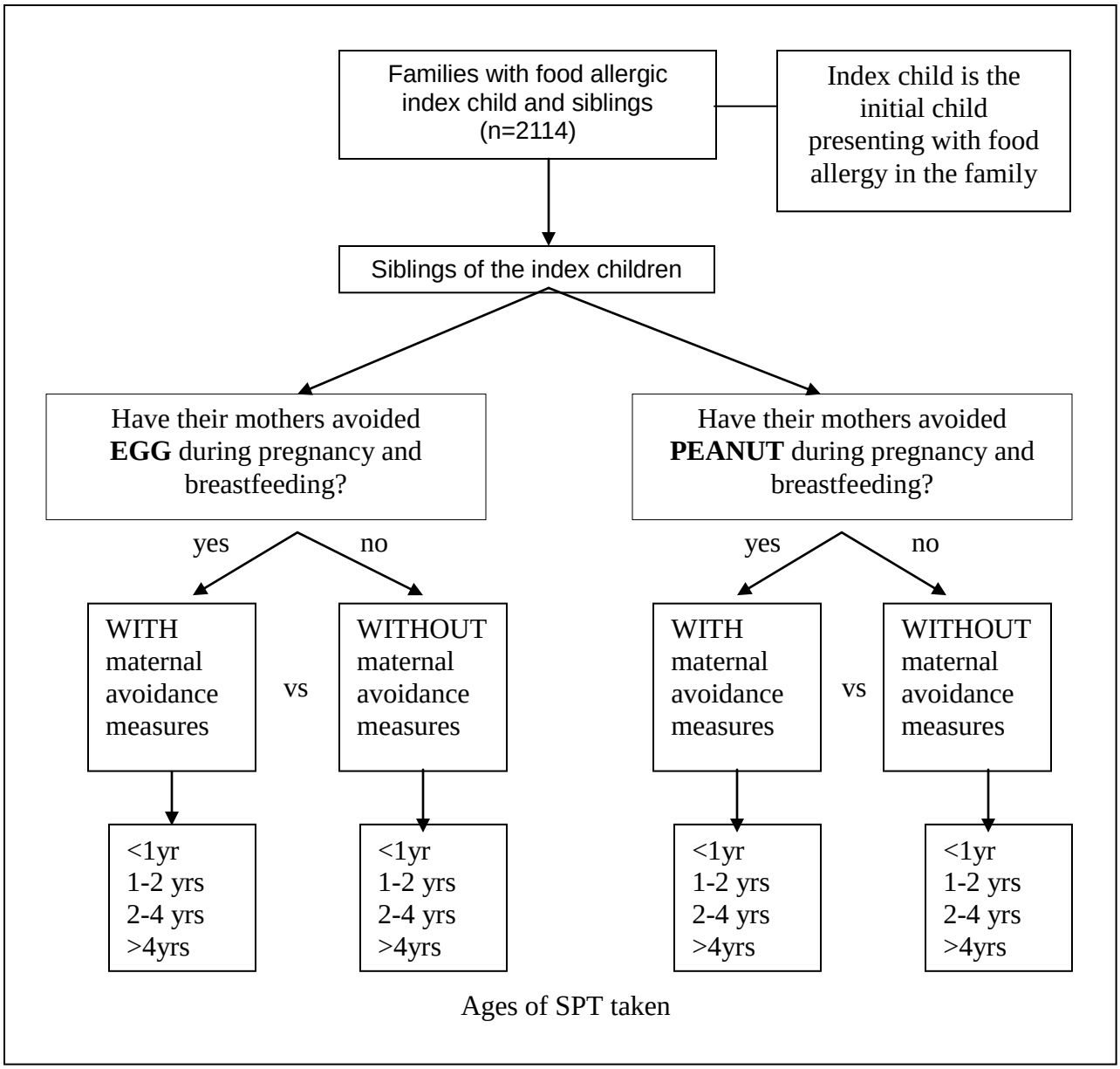
Procedure

'Index children' were defined as the initial child in the family presenting with food sensitisation. Index children and their siblings were seen for follow-up and retested at vearying intervals. Egg and peanut SPT results up to 2007 were extracted from the Allergy Unit database, and relevant aspects of maternal diet were recorded. Siblings of the index children were then divided into two groups: those with and those without maternal modification/avoidance measures during pregnancy and breastfeeding. SPT results of egg and peanut were analysed, according to the age at which SPT was taken, which were: <1yr, 1-2yr, 2-4yrs, and >4 yrs. (Figure 2).

Statistical analysis

Chi square tests were used in order to test the difference in prevalence of egg or peanut sensitisation between those with and without maternal avoidance measures. The SPSS software package (version 10 for Windows, Chicago, IL, USA) was used, and a p-value of <0.05 was considered statistically significant. Also, independent sample t tests were used to see the difference in the number of food allergens in children with or without peanut sensitisation, and $p<0.05$ was considered significant.

Figure 2: Diagram of Study Methodology



Results

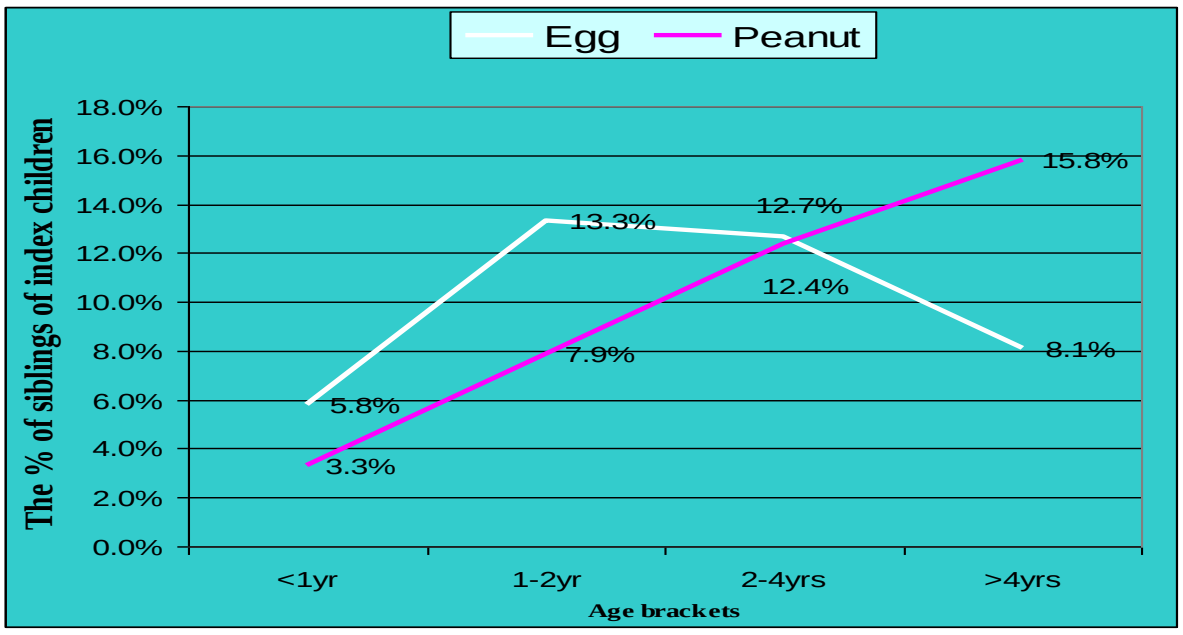
Egg and peanut sensitisation in siblings of index children

Table 1: Egg and peanut sensitisation in siblings of index children by age

Sensitisation	<1yr	1-2yrs	2-4yrs	<4yrs
Egg	22/381 (**5.8%**)	55/359 (**13.3%**)	53/418 (**12.7%**)	34/422 (**8.1%**)
Peanut	19/568 (**3.3%**)	44/554 (**7.9%**)	72/579 (**12.4%**)	74/474 (**15.8%**)

Egg and peanut sensitisation were analysed separately. At ages <1yr, 1-2yrs, 2-4yrs, >4yrs, there were (respectively) 381, 359, 418, 422 siblings of the index children in the egg analysis group, while there were 568, 554, 579, 474 in the peanut analysis group. The percentages of egg sensitisation in siblings by age were shown in Table 1, which were 5.8%, 13.3%, 12.7% and 8.1% respectively, while the percentages of peanut sensitisation in siblings by age were 3.3%, 7.9%, 12.4%, 15.8% respectively.

Figure 3: The pattern of egg and peanut sensitisation in siblings of index children by age.



Regarding the pattern of egg and peanut sensitisation in siblings by age, Figure 3 has shown that egg sensitisation peaked at 1-2 yrs of age, and was subsequently diminished in the older groups, whereas peanut sensitisation increased progressively over time.

Food allergen sensitisation with and without maternal avoidance measures

Egg sensitisation

Figure 4: The prevalence of egg sensitisation in siblings of index children with or without maternal avoidance measures

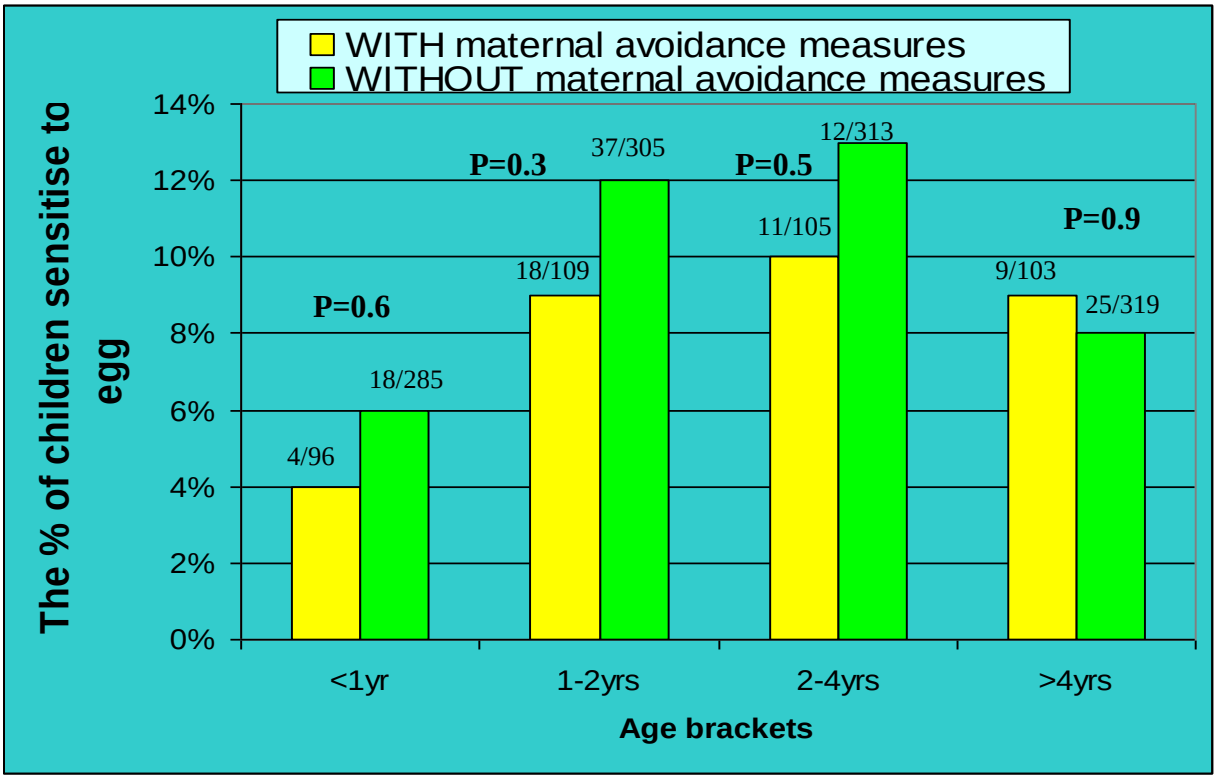
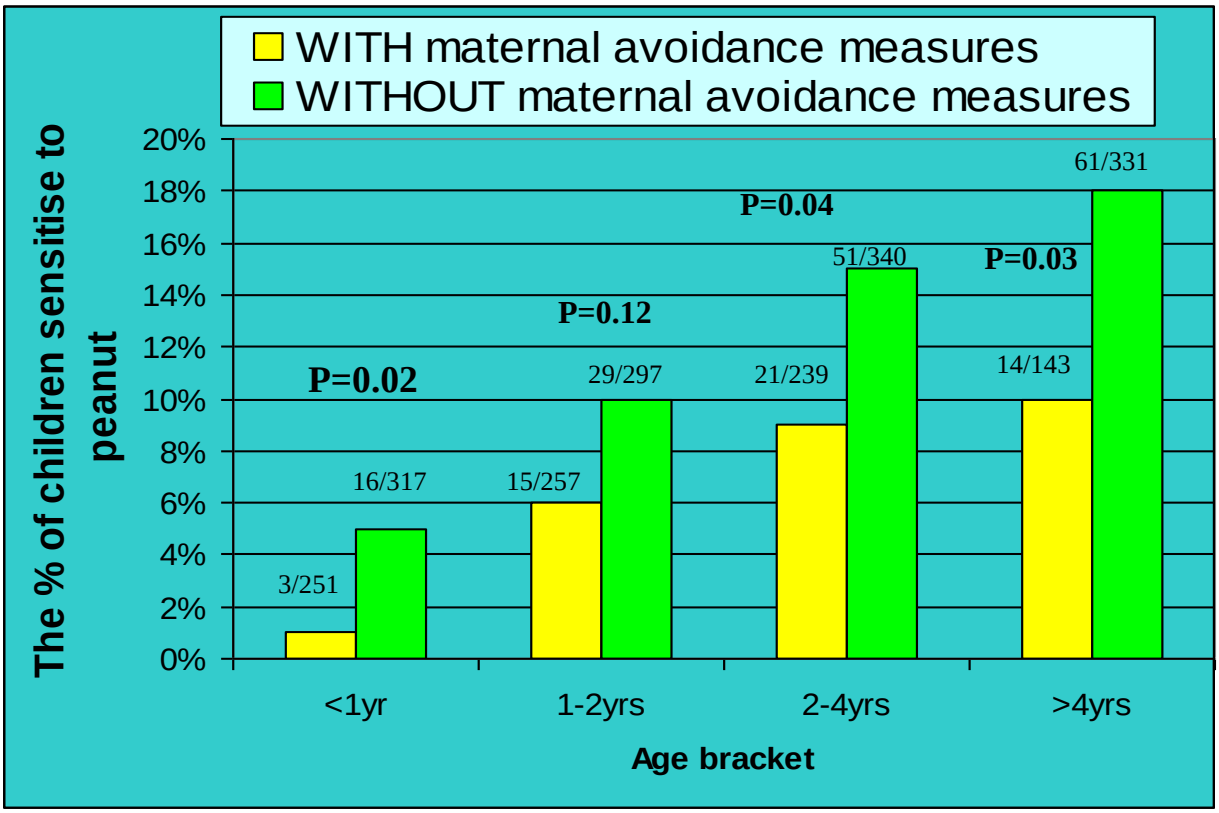


Figure 4 shows the prevalence of egg sensitization in siblings with and without maternal avoidance measures. At <1yr of age, 4% (4/96) of siblings with maternal avoidance measures were sensitized to egg, compared to 6% (18/285) siblings without maternal avoidance measures. There was no significant difference between these two groups (p=0.6). Likewise, among the other age groups, maternal egg avoidance measures did not produce any significant reduction in egg sensitization (all p values >0.05). However, there was a trend for siblings with maternal avoidance measures to have a lower incidence of egg sensitization in the first four years of life (Figure 4).

Peanut sensitisation

Figure 5: The prevalence of peanut sensitization in siblings of index children with or without maternal avoidance measures



In contrast, there was a significant difference in the prevalence of peanut sensitisation depending on whether peanut avoidance measures were adopted (Figure 5). For example, at <1yr of age, 1% (3/251) siblings with maternal avoidance measures were sensitized to peanut, compared to 5% (16/317) siblings without maternal avoidance measures. The effect was greatest in the first year (p=0.02), but remained significant in subsequent years. Although the difference in the 1-2 yr age group was not statistically significant (p=0.12), fewer siblings with maternal avoidance measures were sensitised to peanut.

Any food sensitisation

Figure 6: The prevalence of any food sensitization in siblings of index children with or without maternal avoidance measures

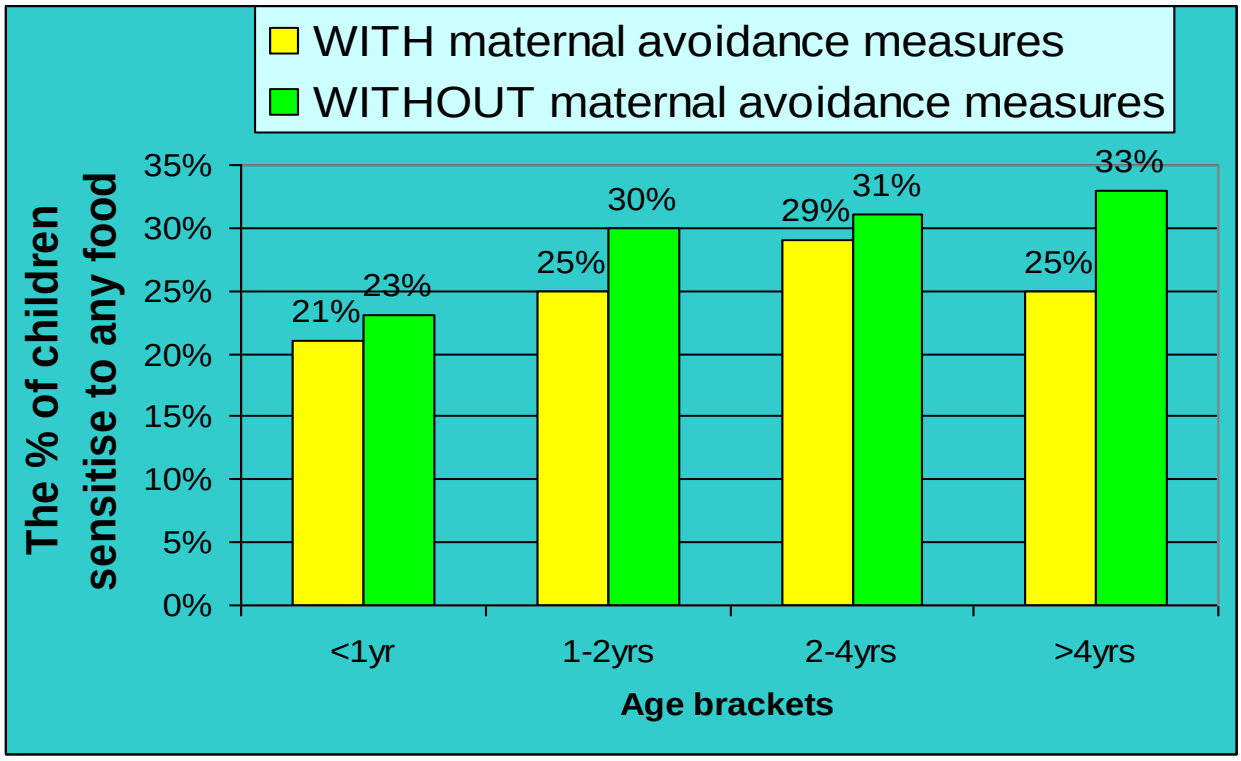


Figure 6 shows the prevalence of sensitization to any food in siblings of children according to age. Maternal peanut avoidance measures did not show a significant reduction in food sensitisation overall ($p>0.05$).

Is preventing peanut sensitisation worthwhile?

Table 2: The mean number of food allergens in siblings of index children with and without peanut sensitisation

	Mean number of food allergen ± SD (N*)			
	<1yr	1-2yrs	2-4yrs	<4yrs
Peanut sensitisati	**2.8** ± 1.7 (19)	**3.0** ± 1.6 (44)	**2.9** ± 1.9 (72)	**3.1** ± 2.6 (75)
No peanut sensitisation	**0.3** ± 0.8 (549)	**0.4** ± 0.9 (510)	**0.3** ± 0.8 (507)	**0.3** ± 0.9 (402)

*N=the total number of siblings with or without peanut sensitisation by age

Table 2 shows the impact of peanut sensitisation on other food allergies. Among the four age groups, those with peanut sensitisation were sensitized to more foods (all p values <0.001). For example, at age <1yr, the mean number of SPT positive foods in siblings with peanut sensitisation (2.8) was greater than those without peanut sensitisation (0.3). Clinically therefore, it seemed worthwhile to prevent peanut sensitisation.

Discussion

The natural history of egg and peanut sensitisation

The results of this study have shown that in the age groups <1yr, 1-2yrs, 2-4yrs and >4yrs, 5.8%, 13.3%, 12.7% and 8.1% (respectively) of siblings of those children with food allergy were sensitised to egg (Figure 3). It was shown that egg sensitisation peaked at 13% at 1-2yrs of age, and was diminished in the subsequent groups. These results were similar to findings in a large German cohort study on 4028 children (Kulig et al, 1999), in which the prevalence of food sensitisation (egg predominantly) peaked at 10% at 1 year and declined to 3% at 6 years of age. Both findings lend credibility to the long established statement that egg allergies are most frequently outgrown by school age, which was consistent with the clinical observation. This is supported by other studies on the natural history of egg allergy. Dannaeus & Inganas (1981) found that 36% of children became egg tolerant and an additional 44% of children had become less sensitive by age of 5. Similarly, Ford & Taylor (1989) followed 25 children from 7 months to 9 years of age with challenge-confirmed egg allergy for 2 to 2.5 years, and found that egg allergy had resolved in 44% of children.

By contrast, the prevalence of peanut sensitisation increased with age (Figure 3). The rate of peanut sensitisation increased progressively over time, supporting the previous finding that peanut allergies are rarely outgrown and usually persist for life (Bock & Atkin, 1989). On the other hand, a small proportion of young children with peanut allergy early in life can lose their sensitivity in a similar way to egg allergy in infants and preschool children (Hourihane et al, 1998). It was suggested that the size of SPT weal may predict which children were tolerant when challenged with peanut (Hourihane, 1998). In the 20% of children who had resolution of peanut allergy this was more likely to happen in those who were successfully able to avoid peanuts strictly (Fleischer et al, 2004). However, 8% of those who outgrow their peanut allergy suffer from a recurrence, and the risk was found to be higher for those who continue to avoid peanut after passing a food challenge (Fleischer et al, 2004). In this study, there was no resolution of peanut allergy at all. The mechanism of peanut resolution is unkown, although it has been suggested that it may be a function of the physical structure of peanut protein related to the linear or conformational configuration of individual T-cell and IgE epitopes (Wood, 2003).

Outcome of maternal avoidance measures

Maternal egg avoidance measures

This study has shown that maternal egg avoidance advice had no significant effect on egg sensitisation in siblings of the index children at all ages (Figure 4). This result was similar to the findings in previous studies. For example, in 1989, Lilja et al and Hattevig et al both have examined infants at risk for atopy up to 18 months of age, and found that the number of SPT positive to egg was not influenced by the differences in maternal diet during late pregnancy. Another prospective control study in high-risk German newborns also showed that the rates of sensitisation to eggs at 6 and 12 months were not significantly different between those with and without maternal avoidance measures in the last trimester of pregnancy and during the period of exclusive breastfeeding (Hermann et al, 1996). Recently, a meta-analysis was published in Cochrane (Kramer & Kakuma, 2006), showing that maternal restriction of egg may also cause disturbances in maternal weight gain during the third trimester of pregnancy and infant birth weight. However, one study (Grimshaw et al, 2003) has reported a significant reduction in the rate of egg sensitisation in 18 month old infants with strict maternal egg avoidance (abstract only). Due to the lack of positive studies on the protective effect of maternal egg avoidance measures during pregnancy and lactation, combined with the potential for harmful nutritional effects of such diets on mother and fetus, a position statement summary published at *Medical Journal of Australia* does not recommend institution of a maternal egg avoidance diet, as egg was an essential food in the diet (Prescott, Tang & Bjorksten, 2007).

Maternal peanut avoidance measures

Unlike staple foods, peanut is not an essential food and can easily be removed from the diet without any risk to maternal or infant wellbeing. This study showed that maternal peanut avoidance measures produced a significant reduction in incidence of peanut sensitisation in siblings of the index children (Figure 5). Although no significant ($p=0.06$) reduction was found in the maternal avoidance group in Frank's study (1999), a strong trend was also shown as frequent consumption of peanuts (more than once a week) by mothers during pregnancy were almost four times as likely to produce peanut sensitisation in the unborn child. The non-

significant reduction in Frank's study may be due to its small sample size (n=43), as compared to the population in the present study (n>500).

In this study, the effect of maternal peanut avoidance measures on peanut sensitisation was shown to be greatest in the first year of life (p=0.02), and the protective effect remained in most of the subsequent age groups. Zeiger (1989 & 1992) also reported a significant reduction in food sensitisation and food allergy primarily in the first year of life (p=0.03) and the protective effect diminished in the second year. However, the protective effect disappeared at ages 3 and 4 years (Zeiger, 1989 & 1992). The difference between the present study and Zeiger's studies may be due to the fact that the present study was focused specifically on sensitisation to peanut, while Zeiger's study was on food sensitisation generally.

In the present study, maternal peanut avoidance measures during pregnancy and lactation showed a small reduction in the number of foods to which children were sensitised at all ages, but this was not statistical significance (Figure 6). In contrast, Hide et al (1996) has reported that there was a significant reduction in sensitisation to dietary allergens in infants at risk of atopy whose mothers excluded highly antigenic foods during pregnancy and lactation. The difference may be due to avoidance measures that were specific to peanut alone in the present study, whereas in the previous study (Hide et al, 1996) avoidance measures included all highly allergenic foods such as milk, egg and fish. In addition, egg was shown to be the most prevalent food causing sensitisation whether or not peanut was avoided in the present study. Maternal peanut avoidance measures did not produce a significant difference in food sensitisation overall, as the majority of siblings became sensitised to other highly allergenic foods that were not avoided.

<u>Is preventing peanut sensitisation worthwhile?</u>

The increased prevalence of peanut sensitisation in at risk children

In the general population, the prevalence of peanut sensitisation in children has increased from 1.1% to 3.3% during the past decade (Grundy et al, 2002). Most recently, the Isle of Wight study has shown the prevalence of peanut sensitisation in the general population was 0.6%, 2% and 3% at 1yr, 2yr, and 3 yrs of age respectively (Dean et al, 2007). The rate of peanut

sensitisation in high-risk families in the present study was 3.3%, 7.9%, 12.4% and 15.8% at aged <1yr, 1-2yrs, 2-4yrs and >4yrs, respectively (Table 1). Both studies indicate that the prevalence of peanut sensitisation increases with age. The rate of peanut sensitisation in the present study was higher, because the selected population was siblings at risk for atopy, as compared to the general population in the Isle of Wight's study. This is supported by the finding by Hourihane (1996) that siblings of people with peanut sensitisation (7%) were more likely to be sensitised to peanut than the general population (1.3%).

The impact of peanut sensitisation on other food allergies

This study also showed that siblings who were sensitised to peanut were sensitised to significantly more foods than those without peanut sensitisation (Table 2). This indicated that peanut sensitisation was associated with other food sensitisation, although the cause and effect relationship was unclear. Tariq (1996) suggested that egg sensitisation during the first two years of life was a significant risk factor for peanut sensitisation. Dean et al (2007) also found that those sensitised to egg were 6 times more likely to be sensitized to peanut, but the increase in risk failed to reach statistical significance. The present study did not look at the interaction between each food allergen, but it did show a trend for those with peanut sensitisation to be sensitised to more foods, among which egg was the most common. Therefore prevention of peanut sensitisation may reduce the likelihood of sensitisation to other foods.

Conclusion

During the first four years of life there was a non-significant trend for less egg sensitisation in siblings of the index children with maternal egg avoidance measures, but overall maternal egg avoidance advice had no long-term effect on egg sensitisation. This may be a reflection of the natural history of egg allergy which is usually outgrown over time.

By contrast, maternal peanut avoidance measures were found to significantly reduce the incidence of peanut sensitization, especially in the first year of life. The reduction in benefit of peanut avoidance measures after the first year of life strongly suggests that sensitisation to peanut may have occurred through subtle environmental or dietary exposure in some children.

Children not sensitised to peanut were found to be sensitised to fewer foods overall. Additionally, since peanut sensitisation tends to be life long, maternal peanut avoidance measures are likely to have a lasting impact on the quality of life for children in whom sensitisation was prevented.

Study limitation and future direction

In this study, mothers' maternal dietary status was evaluated retrospectively by phone. The results may be unreliable due to recall bias. It is recommended that future evaluations of maternal dietary avoidance are conducted prospectively and that a formal assessment tool be developed to assess mother's dietary intake.

In this study sensitisation was defined as a SPT result greater than or equal to 3x3mm. No significant difference was shown in egg sensitisation between those with, and those without maternal egg avoidance diet. This may indicate that the definition of sensitisation to egg was not stringent enough to detect a difference in relation to maternal avoidance measures. Repeating the analysis using a larger SPT weal size to define egg sensitisation may show significant differences.

Finally, peanut sensitisation was found to be associated with sensitisation to other foods, but the cause and effect relationship was not examined in this study. Further studies would be required to investigate the interaction between peanut and other highly allergenic foods.

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