The role of antioxidants, fatty acids and maternal diet to children with asthma and allergy

Maria Emporiadou, Dimitrios Papandreou

2nd Pediatric Department, Aristotle University of Thessaloniki, School of Medicine, Ahepa General Hospital, Thessaloniki, Greece

ABSTRACT: The increase in the prevalence of asthma and allergic diseases highlights the need for devising effective preventing strategies. Although the genetics of these disorders are being investigated, manipulation of known environmental risk factors and diet is an effective approach to this problem. Avoidance of cow's milk protein with exclusive breast-feeding (with or without maternal avoidance of allergenic foods) or hydrolyzed formula has been suggested for infants at risk of allergy. It has also been proposed that introduction of other highly allergenic foods, such as eggs and nuts, to the infant is delayed. Currently it has been hypothesized that decreasing antioxidant (vit A, vit C, selenium), increasing n-6 polysaturated fatty acid (PUFA; vegetable oil, margarine), and decreasing n-3 PUFA (oil fish) intakes, all have contributed to the recent increases in asthma and atopic disease. However, epidemiologic studies in adults and children have reported beneficial associations between dietary antioxidants, lipids and parameters of asthma and atopic disease. In this review, we analyze the role of diet in children and adults with allergies, atopy and asthma.

Key Words: Diet, Asthma, Allergy, Atopy, Children, Adults.

1. INTRODUCTION

Asthma is a chronic, complex, obstructive lung disease characterized by acute symptomatic episodes of varying bronchial constriction that occurs in response to viral infections or other triggers such as allergens and exercise[1,2].

The term 'allergy' was originally introduced in 1906 by Von Pirquet from the Greek words (ἄλλο=other and ἔργον=action). Gell and Coomps proposed a general classification of immunological reactions involved in respiratory allergy. These immunological mechanisms are classified as a type I hypersensitivity reaction, associated with increased synthesis of allergy-specific IgE. The disorders and syndromes associated with immediate-onset allergy are classified as atopic and non-atopic disorders[3].

The term «atopy» in the early 1920s by Coca and Cooke explain a series of syndromes (asthma, rhinitis, eczema) with hereditary transmission[4]. Currently atopy is characterized by the following:

a) Syndromes including allergic asthma, allergic rhinitis and atopic eczema,

b) Hereditary transmission,

c) Increased synthesis of IgE antibody against environmental allergens and primary pharmacological anomalies or secondary to the interaction of cell-bound IgE with allergens[3].

There has been a dramatic increase in the prevalence of asthma and other allergic diseases over the last few decades. They are now major public health problems[2,4] and an enormous burden on health care recourses[5]. Severe asthma and systemic allergic reactions are potentially life-threatening conditions. Additionally, these diseases adversely affect the quality of life of millions of children and adults. Common clinical manifestations of allergy include asthma, allergic rhinitis, atopic dermatitis, and food allergy. Subjects with allergic diseases are often atopic, manifested by sensitization to common allergens. However, atopy is only one of many factors involved in the pathogen-

Corresponding author: Papandreou Dimitrios, Tsimiski 54, TK 54623, Thessaloniki, Greece, Tel.: +30 2310 230000, Fax: +30 2310 994803, E-mail: vellada@otenet.gr

esis of these disorders. The contribution of atopy and atopy-related genes might vary with the disease in question. For example, atopy plays a dominant role in IgE-mediated food allergy, such as peanut allergy, but alternate immunologic pathways, driven directly by T lymphocytes, assume significance in conditions such as nonatopic asthma. A number of risk factors have been identified, including early introduction of solid foods, different types of nutrients (e.g. Vitamin A, Vitamin C, Lipids etc.), infections, allergens, pollutants, and tobacco smoke. The definition and diagnosis of asthma and rhinitis in early childhood is most challenging in view of the lack of uniform criteria and availability of objective tests to support the diagnosis. Another consequence is that early childhood allergic manifestations are often transient, and yet many studies report short term (<5 years follow up) periods. Most studies suggest that an intervention such as exclusive breast-feeding prevents wheeze in early childhood[6], but recently, it has been reported that it might increase the risk of asthma in early adult life[7].

3. Maternal Diet

3.1 Maternal diet during pregnancy

Several studies have investigated the preventive effect of maternal avoidance of highly allergenic foods, such as cow's milk, egg, and nuts, during pregnancy to protect the fetus from the effect of food allergens ingested by the mother. A randomized controlled trial showed that maternal diet (excluding cow's milk and egg) during late pregnancy does not protect against the development of allergies manifestation in genetically predisposed children[8]. Additionally there was some concern regarding maternal and fetal weight gain. Zeiger et al[9] evaluated the effect of maternal avoidance of allergenic food (cow's milk, egg, nuts, fish and soy) during late pregnancy and lactation, supplementation with extensive hydrolysate, and avoidance of solids up to 6 months. There was a reduction in food sensitization on skin prick tests, food allergic manifestations, and atopic dermatitis at the age of 2 years. However, no long-term benefit beyond early childhood was observed[10]. Lack of weight gain during the third trimester was again a concern in mothers who practiced an avoidance diet[15]. In contrast, children with high weight either at birth or later in childhood are at increased risk for future asthma[11].

3.2 Maternal diet during lactation

In a randomized controlled trial maternal avoidance of highly allergenic foods (dairy produce, egg, fish, peanut, and soy) during lactation in high risk infants led to a reduction in the prevalence of atopic dermatitis at 18 months[12]. In a Japanese study infants in the intervention group were exclusively breast fed or given whey hydrolysate, whereas the lactating mothers were given the same whey hydrolysate as the only source of protein. These infants were compared for the development of allergy with 2 other groups of children. One group was breast fed with the mother consuming cow's milk, while the other group was given cow's milk formula. The active group infants showed lower incidence of atopic dermatitis and cow's milk allergy[13]. In another trial maternal avoidance diet (cow's milk, egg and fish) during the first 3 months of lactation reduced atopic dermatitis in early childhood, but there was no long-tern benefit[14-16].

4. Exclusive breast-feeding

The duration of the preventive effect of breast-feeding on allergic diseases remains controversial. Exclusive breast-feeding does seem to prevent wheeze and atopic dermatitis during early childhood[6,17]. However, long-term prospective studies have produced conflicting data. Despite that many studies report short term (<5 years follow up) periods, a relatively small study of at-risk children with 15 years' prospective follow-up did show a reduction in allergic manifestations in the breast-fed children compared with those fed cow's milk or soy milk[18]. However, several large observational studies failed to show a long-term prospective effect of exclusive breast-feeding on asthma or other allergic manifestations[7,19,20]. Two systematic reviews showed that exclusive breast feeding seems to have some prospective effect on the development of allergy[21,22]. This effect might be due to avoidance of cow's milk protein allergen, other dietary constituents of breast milk, an immunomodulatory effect, or a combination of these. It was recently suggested that the effect of exclusive breast-feeding might be dependent on atopic heredity. Those with a genetic predisposition had a lower incidence of sensitization and allergic rhinitis, whereas children without such a predisposition had an increased risk[23,24].

5. Hydrolyzed milk formulae

In an attempt to avoid exposure to cow's milk protein early in life, hydrolyzed (casein or whey) formulae are suggested as a replacement for or supplement to breast feeding. A number of trials have been done over the last 2 decades to assess the preventive effect of replacing cow's milk formula with hydrolysate or soy milk formulae. Chandra et al[25,26] compared the development of allergies (asthma, atopic dermatitis, and food allergy) in groups of children fed breast milk, hydrolyzed formula, cow's milk formula, and soy formula. A significant preventive effect of breast milk and partially hydrolyzed formula was shown consistently up to the age of 5 years. Another study, comparing cow's milk formula and whey hydrolysate, showed a reduction in cow's milk allergy and atopic dermatitis in the first year of life[27]. In a study by Marini et al[28], exclusive breast-feeding combined with hydrolysate supplementation led to a significant reduction in various allergic manifestations up to the age of 3 years. Another trial showed prevention of atopic dermatitis, but not asthma, with the use of hydrolysate formula[29]. Proteins can be extensively or partially hydrolyzed in the infant formulae. For secondary prevention, in children with cow's milk allergy, it is generally agreed that only extensive hydrolysate should be used to avoid any reaction in highly sensitized infants.

7. Antioxidants and Asthma

Some observational studies link intake of antioxidants, such as vitamins C, E, A and selenium, and vitamin A with the occurrence of atopy and asthma[27,30]. Observational studies consistently show a protective effect of omega-3 polyunsaturated fatty-acids (omega-3 PUFAs) and an increased risk with high intake of omega-6 PUFAs[31,32] . Thus dietary modifications of supplementation with fish oil, rich in omega-3 PUFAs, might be of some benefit.

7.1 Vitamin C

Many epidemiologic studies have demonstrated that dietary vitamin C intake or serum ascorbate is positively associated with ventilatory function (FEV1) in children and adults[33-37]. In the First National and Nutrition Examination Survey (NHANES I) dietary vitamin C intake was positively associated with FEV1 in adults, with a mean 40-ml FEV1 difference between subjects with the highest and lowest centiles of vitamin C intake[37]. In NHANES III serum, but not dietary, vitamin C was positively associated with Forced Expiratory Volume (FEV1) in a cross-sectional adult study, with a Standard Deviation (SD) increase in serum vitamin C being associated with an average 17-ml increase in FEV1[35] . Dietary vitamin C has been less frequently associated with asthma and wheezing symptoms in children and adults[37-39]. In NHANES III a negative association between serum ascorbate and asthma was reported in children aged 4 to 16 years, with a SD increase in serum ascorbate being associated with a 19% reduction in asthma prevalence[38].

7.2 Vitamin E

Lipid-soluble vitamin E is the principal defense mechanism against oxidant-induced membrane injury. In contrast to vitamin C, it has also non-antioxidant effects on immune function that might account for differences in its epidemiologic associations. Studies have consistently demonstrated beneficial associations between dietary vitamin E and ventilatory function[35,36,40] and a few have demonstrated beneficial associations with asthma and atopy[41,42].

In a cross sectional study among children aged 11 to 19 years, dietary vitamin E intake was positively associated with ventilatory function[36]. These associations were more marked in boys, with dietary vitamin E intakes in the lowest centiles being associated with reduced FEV25-75 (8.9%), FEV1/forced vital capacity ratio (2.3%), and peak expiratory flow rate (5.1%) when compared with intakes greater than the lowest centiles. The Caerphilly heart disease study[40] reported that dietary vitamin E intake was positively associated with FEV1 in a cross-sectional analysis. A 5-year longitudinal analysis indicated that the protective effect of vitamin E was not reversible because there was no significant association between change in FEV1 over a 5-year period in change in dietary vitamin E intake or average dietary vitamin E intake[40]. Dietary vitamin E intake was negatively associated with asthma and wheezing in a case-control study of 12-year-old Saudi Arabian children[41].

7.4 Selenium

The trace element selenium enters the food chain through plants, but there is wide geographic variation in soil selenium content. Selenium is an important antioxidant, principally because of its incorporation into glutathione peroxidase, an enzyme that plays a key role in protective cells against oxidative damage. Selenium status has been negatively associated with asthma, respiratory symptoms, and ventilatory function[35,38,43]. A negative association between asthma and serum selenium content in children aged 4 to 16 years has been demonstrated in NHANES III, with a SD increase in serum selenium being associated with a 10 % reduction in asthma prevalence[38].

7.5 Fruits

Potential advantages of investigating dietary fruit are that intake tends to be easily remembered, portion size is obvious, and fruits contain many potential important antioxidants that cannot be currently quantified. Furthermore, by demonstrating associations with fruit, the nature of potential intervention studies and public health measures are obvious and more acceptable. Beneficial associations have been reported between fruit intake and asthma[43,44], ventilatory function[40] , and respiratory symptoms[45] in children and adults.

8. Lipids and Asthma

An attractive feature of the hypothesis is the proposed mechanism by which atopic sensitization and inflammation could be promoted by decreasing dietary intakes of n-6 PUFAs from margarine and vegetable oils and increasing intake of n-3 Polyunsaturated fatty acids (PUFAs) from oily fish[46]. The most common dietary PUFAs are linoleic-acid (n-6) and a-linolenic acid (n-3), both of which can be converted to longer-chain PUFAs by a single desaturation and elongation enzyme pathway. Linoleic acid is converted into arachidonic acid that can be metabolized by cyclooxygenase (COX) and lipoxygenase enzymes ultimately to produce 2-series prostaglandins, thromboxanes, and 4-series leukotrienes, lipoxins that are of particular pertinence to asthma and atopic disease. Four-series leukotrienes have pro-inflammatory activity[46], and the two series prostaglandin E2 (PGE2) is known to have immunomodulatory properties, promoting the TH2 immunoresponse phenotype associated with asthma and atopic disease.

Several studies have related cord blood PUFA composition to the subsequent development of atopic disease[47,48], with the largest of them finding no association between cord blood PUFA intake and subsequent childhood eczema and wheezing[48]. Galli et al[47] reported significant reductions in cord blood plasma dihomo-γ-linolenic acid and arachidonic acid concentrations in neonates who subsequently had atopic dermatitis. A modest but insignificant increase in linoleic-acid was also reported. These findings were interpreted as evidence of reduced Δ-6 desaturase activity predating the development of atopic dermatitis.

Margarine contains up to 20 times more n-6 linoleic acid than butter, and an increased dietary intake of margarine has been associated with an increased likelihood of atopic sensitization and atopic disease[49]. Dunder et al[49] reported the results of a case-control study of 3 to 18p year old children recruited in 1980 and re-examined in 1986 and 1989. Children with atopic disease consumed more margarine and less butter than non-atopic control subjects. There is an extensive literature relating the concentration of PUFA in serum, erythrocytes, and adipose tissue to atopic disease, particularly atopic dermatitis. Much of the work originated from observations in the 1930s that rats fed a diet deficient in unsaturated fats experienced a scaly dermatitis similar to atopic dermatitis. In a longitudinal analysis of dietary data in 1980 related to the development of atopic disease by 1989, children who had atopic disease consumed less butter and fish than those who remained non-atopic[49].

Several cross-sectional studies have reported beneficial associations between dietary fish intake, asthma, and atopic disease[32,49,50]. Hodge et al[50] reported that in children aged 8 to 11 years the risk of current asthma was significantly reduced in those who included fresh oily fish in their diet

9. CONCLUSION

In conclusion, restriction of proposed allergenic foods (cow's milk, eggs, peanuts, fish and soy) during pregnancy may not prevent allergy. However, ma-

ternal food allergen avoidance may be of some benefit during lactation. The effect of exclusive breast feeding on allergy may be dependent on children's predisposition. The associations with n-6 and n-3 PUFA appear to be very complex and might differ between asthma and atopic dermatitis. Dietary antioxidants probably have antioxidant and non-antioxidant immunomodulatory effects. Dietary lipids have numerous complex effects on pro-inflammatory and immunologic pathways. Atopic dermatitis is associated with an enzyme defect in lipid metabolism. In spite of this, the results of supplementation studies in established disease have been disappointing. Recently there is an increasing interest on the possibility that dietary antioxidant and lipid intakes might be important in modifying the disease expression during pregnancy and early childhood and that dietary interventions should be targeted at these groups. It also seems likely that there is individual variation in the responses. Further research to determine whether dietary intervention can reduce the risk of asthma and atopic disease is needed.

Ο ρόλος των αντιοξειδωτικών, λιπαρών οξέων και μητρικής διατροφής σε παιδιά με άσθμα και αλλεργία

Μαρία Εμποριάδου, Δημήτριος Παπανδρέου

Β΄ Παιδιατρική Κλινική, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης, Τμήμα Ιατρικής, Πανεπιστημιακό Νοσοκομείο ΑΧΕΠΑ

ΠΕΡΙΛΗΨΗ: Η αύξηση της συχνότητας του άσθματος και των αλλεργικών παθήσεων κορυφώνουν την ανάγκη για εύρεση αποτελεσματικών προληπτικών στρατηγικών. Παρόλο που η γενετική αυτών των παθήσεων βρίσκεται υπό εξέταση, ο χειρισμός των γνωστών περιβαλλοντικών παραγόντων κινδύνου και της δίαιτας αποτελεί σημαντικό παράγοντα πρόληψης της νόσου. Η αποφυγή της πρωτεΐνης του αγελαδινού γάλακτος με αποκλειστικό θηλασμό (με ή χωρίς μητρική αποφυγή αλλεργιογόνων τροφών) ή με υδρολυμένη φόρμουλα έχουν προταθεί για βρέφη με κίνδυνο εμφάνισης αλλεργιών. Έχει επίσης προταθεί ότι η σύσταση άλλων υψηλά αλλεργιογόνων τροφών, όπως τα αυγά και τα φυστίκια, στα βρέφη θα πρέπει να καθυστερείται. Σήμερα έχει γίνει αποδεκτή η υπόθεση ότι η μείωση των αντιοξειδωτικών ουσιών (βιταμίνη Α, βιταμίνη C, σελήνιο), η αύξηση των n-6 πολυακόρεστων λιπαρών οξέων (πολυακόρεστα: φυτικό λάδι, μαργαρίνη) και η μείωση τα n-3 πολυακόρεστων (λίπη ψαριού), έχουν συνεισφέρει στην πρόσφατη αύξηση στο άσθμα και στις ατοπικές παθήσεις. Όμως, επιδημιολογικές μελέτες σε ενήλικες και παιδιά έχουν αναφέρει θετικές συσχετίσεις μεταξύ των διαιτητικών αντιοξειδωτικών, των λιπιδίων και των παραμέτρων του άσθματος και των ατοπικών παθήσεων. Σε αυτό το άρθρο, προσπαθήσαμε να αναλύσουμε τη συσχέτιση και το ρόλο της δίαιτας σε παιδιά και ενήλικες με αλλεργίες, ατοπία και άσθμα.

Λέξεις Κλειδιά: Δίαιτα, Άσθμα, Αλλεργία, Ατοπία, Παιδιά, Ενήλικες.

REFERENCES

1. Bethesda MD. Global Strategy for Asthma management and Preventions Natural History of Asthma. National Heart, Lung and Blood institute, NIH 2002; 18-19.
2. Sennhauser FH., Brann-Falizländer C, Wildhaber JH. The burden of asthma in children: a European perspective. Paed Res Rev 2005; 6: 2-7.
3. Bousquet J, Demoly P, Issel H. Atopy in: Bousquet J, Dutau G, Grimfeld A, Ives de Prost eds: From Atopic Dermatitis to Asthma. Expansion Sciantifique Francaise, PARIS (FRANCE), 2002; 5-17.
4. Bethesda MD. National heart, Lung, and Blood Institute, Asthma statistics. National Institutes of health, Public Health Service 1999.
5. Weiss KB, Sullivan SD. The health economics asthma and rhinitis. I. Assessing the economic impact. J Allergy Clin Immunol 2001; 107: 3-8.
6. Kull I, Almqvist C, Lilja G, Pershagen G, Wickman M. Breast feeding reduses the risk of asthma during the first 4 years of life. J Allergy Clin Immunol 2004; 114: 755-760.
7. Sears MS, Green J M, Willan AR, et al. Long term relation between breast feeding and development of atopy and asthma in children and young adults: a longitudinal study. Lancet 2002; 360: 901-907.
8. Falth-Magnusson K, Kjellman NI. Allergy prevention by maternal elimination diet during late pregnancy-a 5-year follow-up of a randomised study. J Allergy Clin Immunol 1992; 89: 709-713.
9. Zeiger RS, Heller S, Mellon MH, et al. Effect of combinated maternal and infant food-allergen avoidance on development of atopy in early infancy: a randomized study. J Allergy Clin Immunol 1989; 84: 72-89.
10. Zeiger RS, Heller S. The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomozed study of combinated maternal and infant food allergen avoidance. J Allergy Clin Immunol 1995; 95: 1179-1190.
11. Flaherman V, Rutherford GW. Ameta-analysis of the effect of high weight on asthma. Arch Dis Child 2006; 91 (4):334-9.
12. Chandra RK, Puri S, Hamed A. Influence of maternal diet during lactation and use of formula feeds on development of atopic eczema in high risk infants. BMJ, 1989; 299: 228-230.
13. Fukushima Y, Iwamoto K, Takeuchi-Nakashima A, et al. Preventive effect of whey hydrolysate formulas for mothers and infants against allergy development in infants for the first 2 years. J Nutr Sci Vitaminoln (Tokyo) 1997; 43: 397-411.
14. Sigurs N, Hattevig G, Kjellman B. Maternal avoidance of eggs, cow's milk, and fish during lactation: effect on allergic manifestations, skin-prick tests, and specific IgE antibodies in children at age 4 years. Pediatrics 1992; 89:735-739.
15. Hattevig G, Sigurs N, Kjellman B. Effects of maternal dietary avoidance during lactation on allergy in children at 10 years of age. Acta Paediatrical 1999; 88: 7-12.
16. Hermann ME, Dannemann A, Gruters A, et al. Prospective study of the atopy preventive effect of maternal avoidance of milk and eggs during pregnancy and lactation. Eur J Pediatr 1996; 155: 770-774.
17. Schoetzau A, Filipiac-Pittroff B, Franke K, et al. Effect of exclusive breast-feeding and early solid food avoidance on the incidence of atopic dermatitis in high risk infants at 1 year of age. Pediatr Allergy Immunol 2002; 13: 234-242.
18. Gruskay FL. Comparison of breast, cow, and soy feedings in the prevention of onset of allergic disease: a 15-year old prospective study. Clin Pediatr (Phila) 1982; 21: 486-491.
19. Wright AL, Holberg CJ, Taussig LM, Martinez FD. Factors anfluencing the relation of infant feeding to asthma and recurrent wheeze in childhood. Thorax 2001; 56: 92-197.
20. Arshad SH, Kurukulaaratchy RJ, Fenn M, Matthews S. Early life risk factors for current wheeze, asthma, and bronchial hyperesponsiveness at 10 years of age. Chest 2005; 127: 502-508.
21. Gdalevich M, Mimouni D, Mimouni M. Breastfeeding and the risk of bronchial asthma in childhood: a systemic review with meta-analysis of prospective studies. J Pediatr 2001; 139: 261-266.
22. Mimouni BA, Mimouni D, Mimouni M, Gdalevich M. Does breast feeding protect against allergic rhinitis during childhood? A meta-analysis of prospective studies. Acta Paediatrica 2002; 91: 275-279.
23. Siltanen M, Kajosaari M, Poussa T, Saarinen KM, Savilahti E. A dual long-term effect of breast feeding on atopy in relation to heredity in children at 4 years of age. Allergy 2003; 58: 524-530.
24. Friedman NJ, Zeiger RS. The role of breast feeding in the development of allergies and asthma. J Allergy Clin Immunol 2005; 115: 1238-1248.
25. Chandra RK, Hamed A. Cumulative incidence of atopic disorders in high risk infants fed whey hydrolysate, soy, and conventional cow milk formulas. Ann Allergy 1991; 67: 129-132.
26. Chandra RK. Five-year follow-up of high-risk

infants with family history of allergy who were exclusively breast-fed or fed partial whey hydrolysate, soy, and conventional cow's milk formulas. J Pediatr Gastroenterol Nutr 1997; 24: 380-388.
27. Vandenplas Y, Hauser B, Van den Borre C, Sacre L, Dad I. Effect of whey hydrolysate prophylaxis of atopic disease. Ann Allergy 1992; 68: 419-424.
28. Marini A, Agosti M, Motta G, Mosca F. Effects of a dietary and environmental prevention programme on the incidence of allergic symptoms in high atopic risk infants: three years' follow up. Acta Paediatrica Suppl 1996; 414: 1-21.
29. Mallet E, Henocq A. Long-term prevention of allergic diseases by using protein hydrolysate formula in at-risk infants. J Pediatr 1992; 121: 95-100.
30. Shidfar F, Baghai N, Keshavarz A, Ameri A, Shidfar S. Comparison of plasma and leukocyte vitamin C status between asthmatic and healthy subjects. East Mediterr Health J 2005; 11: 87-95.
31. Fogarty A, Britton J. The role of diet in the aetiology of asthma. Clin Exp Allergy 2000; 30: 615-627.
32. Mickleborough TD, Lindley MR, Ionescu AA, Fly AD. Protective effect of fish oil supplementation on exercise-incluced bronchoconstriction in asthma. Chest 2006; 129: 39-49.
33. Schwartz J, Weiss ST. Relationship between dietary vitamin C intake and pulmonary function in the First National Health and Nutrition Examination Survey (NHANES I). Am J Nutr 1994; 59: 110-114.
34. Britton JR, Pavord ID, Richards KA, et al. Dietary antioxidant vitamin intake and lung function in the general population. Crit Care Med Am J Respir 1995; 151: 1383-1387.
35. Hu G, Cassano P. Antioxidants and pulmonary function: the third National Health and Nutrition Examination Survey (NHANES III). Am J Epidemiol 2001; 151: 975-981.
36. Gilliland FD, Berhane KT, Li YF, Gauderman J, McConnell R, Peters J. Childrens' lung function and antioxidant vitamin, fruit, juice and vegetable intake. Am J Epidemiol 2003; 158: 576-584.
37. Soutar A, Seaton A, Brown K. Bronchial reactivity and dietary antioxidants. Thorax 1997; 52: 166-170.
38. Rubin RN, Navon L, Cassano PA. Relationship of serum antioxidants to asthma prevalence in youth. Am J Respir Crit Care Med 2004; 169: 393-398.
39. Haric-Khan RI, Muller DC, Wise RA. Serum vitamin levels and the risk of asthma in children. Am J Epidemiol 2004; 15: 351-357.
40. Butland BK, Fehily AM, Elwood PC. Diet, lung function and lung function decline in a cohort of 2512 middle aged men. Thorax 2000; 55: 102-108
41. Hijazi N, Abalkhail B, Seaton A. Diet and childhood asthma in a society in transition: a study in urban and rural Saudi Arabia. Thorax 2000; 55: 775-779.
42. Fogarty A, Lewis S, Weiss S, Britton J. Dietary vitamin E, IgE concentrations and atopy. Lancet 2000; 365: 1573-1574.
43. Shaheen SO, Sterne JAC, Thompson RL, Songhurst CE, Margetts BM, Burney PGJ. Dietary antioxidants and asthma in adults. Population based case-control study. Am J Respir Crit Care Med 2001; 164: 1823-1828.
44. Romieu I, Varraso R, Avenel V, Leynaert B, Kauffmann F, Clavel-Chapelon F. Fruit and vegetable intakes and asthma in the E3N study. Thorax 2001; 61: 209-15.
45. Forastiere F, Pistelli R, Sentini P, et al. Consumption of fresh fruit rich in vitamin C and wheezing symptoms in children. Thorax 2000; 55: 283-288.
46. Thien FCK, Walters EH. Eicosanoids and asthma: an update. Prostagladins Leukot Essent Fatty Acids 1995; 52: 271-288.
47. Galli E, Ricardo M, Chini L, et al Analysis of polyunsaturated fatty acids in newborn sera: a Screening tool for atopic disease. Br J Dermatol 1994; 130: 752-756.
48. Newson RB, Shaheen SO, Henderson AJ, Emmet PM, Sherriff A, Calder PC. Umbilical cord and maternal blood red cell fatty acids and early childhood wheezing and eczema. J Allergy Clin Immunol 2004; 114: 531-537.
49. Dunder T, Kuikka L, Turtinen J, Rasanen L, Uhari M. Diet, Serum fatty acids, and atopic diseases in childhood. Allergy 2001; 56: 425-428.
50. Hodge L, Salome CM, Peat JK, Haby MM, Xuan W, Woolcock AJ. Consumption of oily fish and childhood asthma risk. Med J Aust 1996; 164: 137-140.