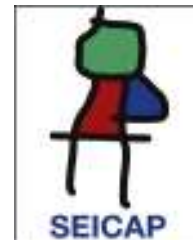




Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica,
Alergología y Asma Pediátrica

www.elsevier.es/ai



ORIGINAL ARTICLE

Mediterranean diet and childhood asthma



F.M. Calatayud-Sáez^{a,*}, B. Calatayud Moscoso del Prado^a,
J.G. Gallego Fernández-Pacheco^b, C. González-Martín^c, L.F. Alguacil Merino^{c,d}

^a Clínica "La Palma", Ciudad Real, Spain

^b Centro de Salud de Atención Primaria # 1, Ciudad Real, Spain

^c Unidad de Investigación Traslacional, Hospital General Universitario, Ciudad Real, Spain

^d Universidad San Pablo CEU, Madrid, Spain

Received 19 November 2014; accepted 2 April 2015

Available online 14 August 2015

KEYWORDS

Bronchial hyperreactivity;
Childhood asthma;
Dietary pattern;
Dietary programme;
Mediterranean diet;
Nutritional assessment

Abstract

Background: The incidence of bronchial hyperreactivity has increased to one-third of the population in developed countries, which requires the adoption of preventive and therapeutic measures. The objective of the present study was to assess the effects of a traditional Mediterranean diet on patients diagnosed with childhood asthma and determine if there is a beneficial effect from this dietary intervention.

Methods: Prospective before–after comparison study of 50 girls and 54 boys aged 1–5 years, who were enrolled in the 1-year programme "Learning to Eat from the Mediterranean", designed to promote the adoption of a traditional Mediterranean diet. We studied the clinical and therapeutic variables and anthropometric measurements.

Results: All studied symptomatic indicators (number and intensity of asthmatic attack, infections and hospital admissions) showed a positive and statistically significant evolution of bronchial hyperreactivity from the first weeks of the intervention onwards. Throughout the treatment, 32.2% of patients remained free of crisis, 35.3% of the patients only had one attack throughout the year and 24.9% had two episodes, compared to 4.73 episodes on average in the previous year. The use of inhaled corticosteroids markedly decreased from 3.92 ± 1.61 to 1.11 ± 1.09 times per patient per year ($P < 0.001$) and that of inhaled bronchodilators decreased from 4.14 ± 1.61 to 1.12 ± 1.40 ($P < 0.001$). As a result, the families involved in the programme reported a high level of satisfaction.

Conclusions: The adoption of a traditional Mediterranean diet could contribute significantly to the improvement of patients diagnosed with childhood asthma.

© 2014 SEICAP. Published by Elsevier España, S.L.U. All rights reserved.

* Corresponding author.

E-mail address: altayud@gmail.com (F.M. Calatayud-Sáez).

Introduction

The incidence of childhood asthma and bronchial hyperreactivity (BHR) has been progressively increasing in developed countries, reaching nearly one-third of the population.¹ This disease causes educational, economic and health problems for patients, their families, and society, which requires the adoption of preventive and therapeutic measures. The degree of asthma varies from patients who experience only a few episodes of wheezing, coughing with mild bronchospasm to patients with repeated episodes and persistent symptoms. The diagnosis of BHR in children is primarily clinical and can be complicated due to the subjective symptoms, which are sometimes difficult for their parents to assess.² There is no universal test to determine the exact diagnosis. It has been demonstrated that the fundamental pathophysiological basis is bronchial inflammation, which triggers hypersensitivity to a variety of stimuli such as upper respiratory tract infections, air pollution, tobacco, smoke, exercise, central heating, seasonal pollination and obesity.

Current treatment is based on the use of bronchodilator β_2 -agonists (which reduce bronchial muscle spasticity), anti-inflammatory corticosteroids and anti-leukotrienes (which reduce BHR and clinical symptoms). All are effective upon acute application, but prolonged use is more questionable due to the limited evidence supporting efficacy and the emergence of adverse effects such as abnormal growth in children.³ It has been suggested that dietary interventions could be of potential use based on a number of publications that have linked the disease with the loss of traditional dietary patterns. Some of these results, however, are controversial.⁴⁻⁷ One of our recent studies on overweight and obese children supports this idea because patients with BHR improved considerably after controlling the quality of their diet.⁸ We therefore hypothesise that restoring traditional, healthy diets such as the Mediterranean diet could help decrease bronchial hyperreactivity significantly. In accordance with this idea, a meta-analysis has recently been published supporting the positive influence of Mediterranean diets on respiratory outcomes in children.⁹ The present study aims to extend knowledge in this direction by studying the effects of a traditional Mediterranean diet (TMD), on patients diagnosed with childhood asthma through a food re-education programme developed in the family sphere. The study diet was based on the Decalogue proposed by the Mediterranean Diet Foundation.¹⁰ The Mediterranean diet was proclaimed an Intangible Cultural Heritage of Humanity by UNESCO in 2010 and is characterised by a high intake of unrefined plant-based foods such as fruits and fresh vegetables, whole grains, legumes, olive oil and nuts; low to moderate consumption of foods of animal origin such as fermented milk, fish, eggs and lean meats; and by a low intake of sugar, refined flour and fast food.

Methods

Study design

The study was approved by the Research and Ethics Committees of the General University Hospital of Ciudad Real, Spain. The research design was an analytical, before-after

comparison study, which consecutively enrolled patients 1-5 years of age who met childhood asthma criteria¹¹ and who attended a consultation at a primary care practice between May 2009 and September 2013. It was considered necessary to include the medical history of at least 1 year prior to the study and informed consent signed by their parents or guardians. The intervention focused on dietary re-education based on the TMD by a nutritional education programme named "Learning to Eat from the Mediterranean". This programme is based on a series of visits to the nutritionist and paediatrician that are designed to assist the entire family. The visits were monthly during the first 4 months and bimonthly the rest of the year. To start the programme a 7-day recall questionnaire was required. On the first visit, we evaluated the food choices of each child and family. Based on the problems identified, we proposed dietary changes by providing dietary patterns, recipes, sample menus, etc. An anthropometric assessment was also performed and key health issues were explained, such as the importance of a good breakfast, variability in menus, the balance between food consumption and energy expenditure, the quality of fats, proteins and carbohydrates, understanding labels and creating a healthy shopping list. The patients were followed-up for 1 year to evaluate growth, clinical evolution, treatment needs, adherence to the TMD and the degree of family satisfaction. The conventional treatment remained initially unchanged and the drugs were reduced only when clinical improvements were observed.

Study variables

Clinical parameters and treatment

Primary end point: The number of BHR episodes and childhood asthma attacks per person per year (relapses or exacerbations). The Third International Pediatric Consensus has defined childhood asthma as a condition in which there are three or more episodes of wheezing and/or coughing in a clinical setting in which the diagnosis of asthma is the most likely after excluding other less common conditions. This conceptually strategic definition is still in use (2008 PRAC-TALL consensus) because it includes the expression of the disease (wheezing, coughing), recurrent episodes (three or more) and the absence of other conditions (wheezing and coughing unrelated to asthma).¹²

Secondary end points: Intensity of attacks, evaluated according to the protocols of the Spanish Pediatrics Association (1 - mild, 2 - moderate, 3 - severe),¹³ upper respiratory tract infections (URTIs), bacterial complications, emergency room visits, hospital admissions, drugs administered (inhaled corticosteroids, oral corticosteroids, short-acting bronchodilators, antibiotics and symptomatic treatment).

Clinical and therapeutic evaluation index

To evaluate the patients' clinical outcome, in addition to clinical assessment made by the paediatrician, we have developed a questionnaire given to the parents or guardians that assessed symptoms related to childhood asthma. Ten questions concerning the past 4 weeks were evaluated and scored from a minimum of 0 (poor control) to a maximum of

30 (asymptomatic). It was considered that the patient was well controlled when the sum of the 10 items was greater than 20.

Weight and height evolution parameters

Taking into account that the intervention performed involved a limitation of certain types of high-energy food, it was considered necessary to carefully evaluate the patients' anthropometric development. Thus, we collected anthropometric data such as weight, height, skin folds and circumferences of the arm, abdomen and waist to calculate the body mass index (BMI), lean mass and fat mass following the procedures routinely used by our group.⁸

Parameters of adherence to the TMD

All participants received identical nutritional information intended for the whole family and whose characteristics are condensed in the Decalogue of the Mediterranean diet.¹⁰ To evaluate the new habits acquired by the patients and their families, we used the KIDMED test, which assesses the degree of adherence to the Mediterranean dietary pattern among children and adolescents.¹⁴

The 10 basic Mediterranean diet recommendations are: (1) use olive oil as your main source of added fat. (2) Eat plenty of fruits and vegetables; fruits, vegetables, legumes and nuts. (3) Bread and other grain products (pasta, rice, and whole grains) should be a part of your everyday diet. (4) Foods that have undergone minimal processing, that is fresh and locally produced are best. (5) Consume dairy products on a daily basis, mainly yoghurt and cheese. (6) Red meat should be consumed in moderation and if possible as a part of stews and other recipes. (7) Consume fish abundantly and eggs in moderation. (8) Fresh fruit should be your everyday dessert and, sweets, cakes and dairy desserts should be consumed only on occasion. (9) Water is the beverage par excellence in the Mediterranean diet. (10) Be physically active every day, since it is just as important as eating well.

For the sample size calculation, a significance level of 0.05 and a power of 85% were used, assuming a decrease in the mean number of childhood asthma attacks of one unit per patient per year, with a standard deviation of four units, adjusted for a 25% loss. The resulting sample size was 115 patients. For the analysis of the results, SPSS 15.0 was employed. We performed a descriptive statistical analysis of central tendency and dispersion for quantitative variables and absolute and relative frequencies for qualitative variables. After checking for normality with the Shapiro-Wilk test, the results of the different variables before and after treatment intervention were compared with Student's *t*-test for paired data, when the variables followed a normal distribution, and Wilcoxon's test otherwise.

Results

According to the sample size calculation, the families of the 137 patients who met the inclusion criteria were invited to participate in the programme "Learning to Eat from the Mediterranean", of whom 24 families refused to

Table 1 Characteristics of the sample.

	Boys (n=54)	Girls (n=50)
Weight (kg)	14.06 ± 3.32	13.58 ± 3.77
Height (m)	0.92 ± 0.11	0.91 ± 0.10
BMI (kg/m ²)	16.50 ± 1.50	15.13 ± 1.39
Fat mass (%)	14.11 ± 3.13	15.67 ± 3.49
Lean mass (%)	12.08 ± 2.96	11.38 ± 2.87

participate. Of the 113 patients initially enrolled in the programme, 6 gave up the project after the first session and 3 after the fifth session. Five of these patients left due to social or personal difficulties in implementing the diet and four due to disagreement with the limitation of certain foods. Therefore, a total of 104 patients completed the study, of whom 50 were girls and 54 were boys, with a mean age of 2.74 years (Table 1). The results were similar for both sexes and are therefore presented together. Fig. 1 shows the evolution of the indicators studied in symptomatic patients (number and severity of attacks, respiratory infections, emergency and hospital admissions). All of them showed a positive and statistically significant change in the BHR from the first weeks of the intervention onwards. This clinical improvement was maintained until the end of the treatment year. There were no episodes of BHR in 32.2% of children during the year of treatment, 35.3% had only one attack during the year and 24.9% had two episodes, compared to 4.73 episodes on average in the previous year. The intensity of the crisis was assessed by the paediatrician and decreased from mild-moderate to low-mild. This positive evolution of symptoms was accompanied by a significant decrease in the URTIs, bacterial complications, ER admissions and emergency assistance. Moreover, the need for anti-asthma therapy, antibiotic use and other symptomatic medications was also dramatically reduced (Table 2). In the year of study, none of the patients required treatment with anti-leukotrienes, or oral corticosteroids. The degree of family satisfaction was very high, as seen in the questionnaire regarding the improvement observed (Table 3). Air pollution and smoke snuff was not object of study, so we interpret that the results are mainly due to nutritional changes. The anthropometric variables measured before the intervention,

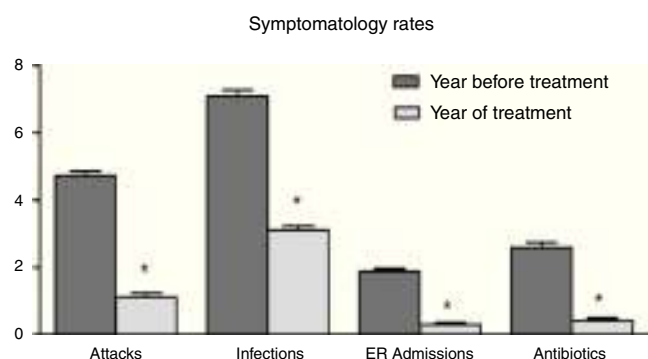


Figure 1 Evolution of parameters indicative of BHR symptomatology in the year before intervention (baseline) and during the year of intervention (1 year). Error bars.

Table 2 Evolution of drug treatments.

	Year before intervention	Year of intervention	P
Treatment with inhaled corticosteroids	3.92 ± 1.61	1.11 ± 1.09	0.001
Treatment with short acting bronchodilators	4.14 ± 1.61	1.11 ± 1.11	0.001
Treatment with leukotrienes	0.20 ± 0.42	0.01 ± 0.09	0.001
Symptomatic treatment	7.50 ± 2.88	3.40 ± 1.24	0.001

Table 3 Questionnaire answers from parents or guardians about improvements in bronchial hyperreactivity. (3) A lot; (2) considerably; (1), a bit; (0) nothing.

	4 Months of intervention	1 Year of intervention
Did asthma recurrence decrease?	2.31	2.41
Have you noticed lower intensity of asthma attacks?	2.58	2.95
In your opinion, did emergency room and hospitalisation need decrease?	2.84	2.95
Have you noticed cough improvements?	2.80	2.95
Have you noticed a decline in respiratory distress (whistles, catcalls, fatigue, shortness of breath)?	2.31	2.95
Have you noticed a greater recovery of normal state?	2.42	2.95
Have you noticed less use of inhaled corticosteroids and bronchodilators?	2.97	2.95
Have you found the diet well tolerated and linked to reduced asthma symptoms?	2.95	2.95
Have culinary changes been simple or easy?	2.35	2.5
Are you satisfied with the results?	2.58	2.95
Total score	26.11	28.96

at 4 months, and after 1 year revealed an adequate evolution of parameters related to growth and development, with a significant increase of lean mass (Table 4). The patient's dietary habits had also improved in the entire sample by the end of the programme (Table 5). As a result, there were an increased number of patients who had breakfast and consumed fruits, vegetables, fish, whole grains and fermented milk, while the proportion of those who ate sweets daily and bakery products for breakfast decreased. According to these data, the KIDMED index positively evolved from an upper-middle score at the beginning of the programme to a good-optimal value by the end.

Discussion

The overall results reflect a fast and positive evolution of patients enrolled in the programme, as shown by the various study variables. Thus, the number of attacks had notably decreased by the conclusion of the study, as had their intensity and associated complications. There was a very favourable start within weeks of dietary treatment, even in younger children and in those with more intense

involvement response. Of particular importance is the marked decrease observed in the need for bronchodilators and inhaled corticosteroids, given that one of the main goals of the treatment according to the Global Initiative for Asthma is the prevention of exacerbations and the avoidance of adverse effects of antiasthma medication.¹⁵⁻¹⁷ There was a significant decrease in symptomatic drugs as a result of fewer illnesses and their lesser intensity degree. It is important to note that the use of anti-leukotrienes, and oral corticosteroids was not necessary during the study period. Significant improvements with respect to the previous year's situation were observed within the first 4 months of the intervention, which led to a high adherence to the programme and greatly enhanced monitoring. There was good tolerance of the proposed diet, with an easy adaptation and a lack of relevant culinary difficulties. The evolution of the height and weight of the patients was also satisfactory. There was a slight decrease in BMI and fat mass, and a significant increase in lean mass which happened in a similar way in our previous study of childhood obesity.⁸ The clinical outcome was assessed by a paediatrician when there was disease and by periodic inspections. The lack of a control group is the major weakness in our study and prevents

Table 4 Anthropometric assessments.

	Before intervention	4 Months of intervention	1 Year of intervention	P
BMI (kg/m ²)	16.15 ± 1.45	15.67 ± 2.28	15.35 ± 2.47	0.14
Fat mass (%)	15.12 ± 3.04	14.95 ± 3.10	14.81 ± 2.95	0.24
Lean mass (%)	11.60 ± 3.38	12.27 ± 3.46	13.54 ± 3.50	0.01

Table 5 KIDMED test (percentage).

	At the beginning	After 4 months	After 1 year
Eat 1 fruit per day?	81	99	100
Eat more than 1 fruit per day?	24	71	88
Eat 1 vegetable per day?	88	98	100
Eat more than 1 vegetable per day?	15	38	67
Eat fresh fish regularly (2–3 times/week)?	84	96	96
Attend fast food centres once a week or more?	30	7	4
Eat legumes regularly (1–2 times/week)?	88	98	98
Eat pasta and rice weekly?	96	98	98
Breakfast cereals or derivatives?	92	99	99
Eat raw nuts regularly? ^a	21	38	48
Use olive oil at home?	100	100	100
No breakfast	12	7	3
One dairy breakfast?	98	98	100
Consume bakery at breakfast?	33	13	9
Eat two yoghurts or 40 g cheese daily?	98	98	97
Eat sweets frequently?	22	6	4

^a Not recommended for children under 3 years.

us from categorically affirming that the dietary intervention was the direct cause of the observed improvements. However, the clinical history of the patients included in the study did not permit to expect a spontaneous favourable evolution of the symptoms¹⁸ and therefore the therapeutic efficacy of the diet seems obvious. Furthermore, our results agree with those of other studies that tend to show the beneficial effects of adherence to the TMD and the increased consumption of fruits, vegetables, legumes, oily fish and whole grains.^{4,6,19,20} In contrast, the consumption of fast food and sugar has been associated with childhood asthma and counteracts the protective effect of breastfeeding. Junk food²¹ and excessive salt consumption²² have also been linked with asthma. Despite these findings, a number of other studies do not support the idea that healthy food intake and/or avoidance of certain foods can play an important role in the control of childhood asthma.²³ Thus, a recent review and meta-analysis concluded that nutritional factors responsible for the increase in these diseases are unclear.^{24,25} Of note is the cross-sectional study of 14,700 Spanish children that found no protective effect of the TMD on the prevalence and severity of asthma.⁵ Among the possible causes that could explain the lack of effectiveness of these studies related to the dietary intervention, we highlight the lack of an exhaustive follow up and inadequate diet control. We consider that the beneficial effect of our intervention is due to the implementation of a very specific and well-controlled TMD. The positive results of interventions such as ours on childhood asthma could depend on the effects of the TMD; we highlight the implementation of a very specific and well-controlled TMD on inflammation and the immune processes underlying the disease. This was previously proposed after a prospective study of children with asthma in Mexico City in which the strict adherence to the TMD appeared to have a beneficial effect on airway inflammation and lung function.⁷ In a recent clinical trial in adults with asthma, consistent improvements were seen in the clinic and spirometry in those who adhered to the TMD.²⁶ In patients with mild asthma, it has been shown

that inflammation remains asymptomatic for long periods from the start of the disease.²⁷ The bronchial mucus inflammation will condition bronchial hyperresponse to stimuli, causing a major airflow limitation due to smooth muscle contraction, mucous oedema and mucus hypersecretion. The putative anti-inflammatory properties of the TMD could be partially attributed to a proper intake of carbohydrates. By limiting the intake of white bread, refined flour, sugar and bakery products, our dietary intervention decreases the amount of carbohydrates with a high glycaemic index and glycaemic load, which could prevent an excess of circulating insulin from interfering with the proper formation of eicosanoids. It is known that hyperinsulinaemia stimulates the delta-6-desaturase enzyme, which favours the formation of arachidonic acid and type II eicosanoids, which are strongly proinflammatory.²⁸

In addition to limiting simple carbohydrates, reducing the intake of unhealthy fats appears to be a highly beneficial aspect of the TMD and could significantly contribute to limiting inflammation. Before participating in the study, most of our patients ate little in the way of vegetable fats and consumed significant amounts of animal or industrial fats. By limiting the intake of meat and animal derivatives, fatty and fermented dairy, butter, margarine, bakery products and precooked meals, patients can reduce their intake of saturated fats, trans-fats and arachidonic acid, as well as reduce certain sensitising proteins²⁹ that could interfere with the proper function of cell membranes that are more hyperreactive to triggers. The TMD also provides a correct balance of omega-3 and omega-6 fatty acids, which can decrease the levels of inflammatory cytokines (already high in patients with asthma)³⁰ and affect the differentiation of T helper cells.⁴

Fresh and seasonal foods contain numerous vitamins, minerals, enzymes, yeasts and antioxidants, and many of these are important co-factors in the formation of the eicosanoids involved in bronchial inflammation.³¹ We have encouraged the use of raw and steamed foods and foods heated at low temperatures so as to avoid modification

by excess heat. By promoting fresh, seasonal foods, many of the additives in processed foods have been eliminated, additives that might be involved in the enzymatic block of bronchial inflammatory mediators. The TMD is rich in antioxidants that can counteract the reduced intake of these substances, which have been associated with increased asthma prevalence.^{31,32} Additionally, plant foods, acting as symbiotic, favour intestinal flora fermentation, which has co-evolved with the human race since ancient times.³³ Intestinal microbiota depends on the food we eat and have a critical role in modulating the immune system. The immune response also depends on the consumption of significant amounts of fibre,³⁴ which is present in the TMD. The significant decrease of URTIs and their complications are remarkable in our study, which suggests a protective immune effect. Intestinal microbiota is essential for initiating individual IgA production in children younger than 1 year and influence the development of the entire IgA system.³⁵ IgA is abundant in most mucous membranes, where harmless antigens are neutralised and prevented from entering the epithelium.³⁶ Therefore, low levels of IgA in infancy might be the cause of the lack of a significant response to innocuous antigens, namely the induction of oral tolerance. This could be important in the prevention of allergic diseases. Microbiota have a symbiotic relationship with the host, and if this relationship is not adequate, it can cause immune dysregulation and pathological response to environmental antigens (atopy).³⁷

It is noteworthy that the patients in our study showed a high score in the KIDMED test at the beginning of the intervention, before they had started undergoing dietary changes. In our opinion, the KIDMED test, which measures the quality of the Mediterranean diet, is not sensitive to all the nutritional factors proposed in the Decalogue of the Mediterranean diet.^{38,39} Thus, it does not take into account whether the cereals are whole grain or refined grain, the percentage of fresh or processed food, the kind of dairy products or the proportion of meat and sausages. A reformulation of this tool could be useful. In addition to the lack of a randomised control group, our study has a number of other limitations that should be mentioned. In the course of the study, it was impossible to make a clinical classification as proposed by the GEMA⁴⁰ because the intervention began from the third crisis of BHR, and therefore the possible evolution of the patients could not be known. No additional systematic tests were conducted, which is why we have no asthma predictive index values. We did not use the Asthma Control Questionnaire (ACQ) in children proposed by the Spanish consensus because it does not include nutritional questions.

In conclusion, our study supports the hypothesis that a diet of high nutritional quality such as the Traditional Mediterranean Diet can contribute to a better control of asthma in children, possibly impacting the underlying immune and inflammatory pathophysiology. The study protocol presented here is easily reproducible in any primary care clinic and can significantly contribute to a better understanding of the therapeutic effects of diet on respiratory diseases, being thus complementary to the use of modern technologies in cross-sectional studies and clinical trials that also address childhood asthma but require much larger budgets.

Ethical disclosures

Protection of human subjects and animals. The authors state that the procedures followed were in accordance with the regulations of the Ethics Committee for Clinical Research responsibly and in accordance with the World Medical Association and the Declaration of Helsinki.

Confidentiality of data. The authors declare that they have followed the protocol of the workplace in the publication of patient data and all patients included in the study have received sufficient information and gave written informed consent to participate in this study.

Right to privacy and informed consent. The authors declare that there is no patient data displayed on this article.

Conflict of interest

The authors have no conflict of interest to declare.

References

1. Pearce N, Ait-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, et al. Worldwide trends in the prevalence of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax*. 2007;62:758–66.
2. Soto-Quirós ME. Tratamiento práctico del asma basado en el control de la enfermedad: actualización de guías GINA. *An Pediatr (Barc)*. 2008;68:317–9.
3. Kelly HW, Sternberg AL, Zeiger RS, Fuhlbrigge AL, Williams P, Zeiger RS, et al., CAMP Research Group. Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med*. 2012;367:904–12.
4. Battle J, Garcia-Aymerich J, Barraza-Villarreal A, Antó JM, Romieu I. Mediterranean diet is associated with reduced asthma and rhinitis in Mexican children. *Allergy*. 2008;63:1310–6.
5. González Barcala FJ, Pertega S, Bamonde L, Garnelo L, Perez Castro T, Sampedro M, et al. Mediterranean diet and asthma in Spanish school children. *Pediatr Allergy Immunol*. 2010;1021–7.
6. Nagel G, Weinmayr G, Kleiner A, Garcia-Marcos L, Strachan DP, ISAAC Phase Two Study Group. Effect of diet on asthma and allergic sensitisation in the International Study on Allergies and Asthma in Childhood (ISAAC) phase two. *Thorax*. 2010;65:516–22.
7. Romieu I, Barraza-Villarreal A, Escamilla-Núñez C, Texcalac-Sangrador JL, Hernandez-Cadena L, Díaz-Sánchez D, et al. Dietary intake, lung function and airway inflammation in Mexico City school children exposed to air pollutants. *Respir Res*. 2009;10:122.
8. Calatayud F, Calatayud B, Gallego JG. Efectos de una dieta mediterránea tradicional en niños con sobrepeso y obesidad tras un año de intervención. *Rev Pediatr Aten Primaria*. 2011;13:553–69.
9. Garcia-Marcos L, Castro-Rodriguez JA, Weinmayr G, Panagiotakos DB, Priftis KN, Nagel G. Influence of Mediterranean diet on asthma in children: a systematic review and meta-analysis. *Pediatr Allergy Immunol*. 2013;24:330–8.
10. Bach-Faig A, Berry EM, Lairon D, Reguant J, Trichopoulos A, Dernini S, et al. Mediterranean diet pyramid today. Science and cultural updates. *Public Health Nutr*. 2011;14:2274–84.

11. Castillo JA, De Benito J, Escribano A, Fernández M, García de la Rubia S, Garde J. Grupo de trabajo para el Consenso sobre Tratamiento del Asma Infantil: Consenso sobre tratamiento del asma en pediatría. *An Pediatr (Barc)*. 2007;67:253–73.
12. Bacharier LB, Boner A, Carlsen KH, Eigenmann PA, Frischer T, Götz M, et al. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. *Allergy*. 2008;63:5–34.
13. Sánchez-Etxaniz J, Mintegi-Raso S. Crisis asmática. Protocolos diagnóstico-terapéuticos de la Asociación Española de Pediatría, de Urgencias pediátricas. Available from: http://www.aeped.es/sites/default/files/documentos/crisis_asma.pdf
14. Serra-Majem L, Ribas L, Ngo J, Ortega RM, García A, Perez-Rodrigo C, et al. Food, youth and the Mediterranean diet in Spain. Development of KIDMED, Mediterranean Diet Quality Index in children and adolescents. In: Serra L, Aranceta J, editors. *Infant and child feeding. Study EnKid*. Barcelona: Masson; 2002.
15. Soto-Martínez ME, Ávila L, Soto-Quirós ME. Nuevas pautas para el diagnóstico y manejo del asma en niños menores de 5 años: Guías GINA 2009. *An Pediatr (Barc)*. 2009;71:91–4.
16. National Heart, Lung and Blood Institute, National Institutes of Health. Global strategy for the diagnosis and management of asthma in children 5 years and younger. NHLBI/WHO Workshop report 2009. Bethesda, MD, US: NHLBI; 2009.
17. Guidelines for the Diagnosis and Management of Asthma [Internet]. National Asthma Education and Prevention Program. Expert panel report. Available from: <http://www.nhlbi.nih.gov/guidelines/asthma/index.htm>
18. Castro-Rodríguez JA, García-Marcos L. Wheezing and asthma in childhood: an epidemiology approach. *Allergol Immunopathol*. 2008;36:280–90.
19. Chatzi L, Torrent M, Sunyer J, Garcia-Esteban R, Ferrer C, Vioque J, et al. Diet, wheeze, and atopy in school children in Menorca, Spain. *Pediatr Allergy Immunol*. 2007;18:480–5.
20. Nagel G, Weinmayr G, Kleiner A, Garcia-Marcos L, Strachan DP. Effect of diet on asthma and allergic sensitisation in the International Study on Allergies and Asthma in Childhood (ISAAC) phase two. *Thorax*. 2010;65:516–22.
21. Mai XM, Becker AB, Liem JJ, Kozyrskyj AL. Fast food consumption counters the protective effect of breastfeeding on asthma in children? *Clin Exp Allergy*. 2009;39:556–61.
22. Romieu I, Trenga C. Diet and obstructive lung diseases. *Epidemiol Rev*. 2001;23:268–87.
23. Brown MA. A tough nut to crack. *J Pediatr*. 2008;152:749–50.
24. Torres-Borrego J, Moreno-Solis G, Molina-Terán AB. Diet for the prevention of asthma and allergies in early childhood: much ado about something? *Allergol Immunopathol (Madr)*. 2012;40:244–52.
25. Lv N, Xiao L, Ma J. Dietary pattern and asthma: a systematic review and meta-analysis. *J Allergy Asthma*. 2014;7:105–21.
26. Sexton P, Negro P, Metcalf P, Wall CR, Ley S, Wu L, et al. Influence of mediterranean diet on asthma symptoms, lung function, and systemic inflammation: a randomized controlled trial. *J Asthma*. 2014;50:75–81.
27. Vignola AM, Chanez P, Campbell AM, Souques F, Lebel B, Enander I, et al. Airway inflammation in mild intermittent and persistent asthma. *Am J Respir Crit Care Med*. 1998;157:403–9.
28. Simopoulos AP. Essential fatty acids in health and chronic disease. *Am J Clin Nutr*. 1999;70:560–9.
29. Calderón TE, Ferrero M, Marino GM, Cordoba A, Beltramo D, Muino JC, et al. Meat-specific IgG and IgA antibodies coexist with IgE antibodies in sera from allergic patients: clinical association and modulation by exclusion diet. *J Biol Regul Homeost Agents*. 2010;24:261–71.
30. Broide DH, Lotz M, Cuomo AJ, Coburn DA, Federman EC, Wasserman SI. Cytokines in symptomatic asthma airways. *J Allergy Clin Immunol*. 1992;89:958–67.
31. Nurmatov U, Devereux G, Sheikh A. Nutrients and foods for the primary prevention of asthma and allergy: systematic review and meta-analysis. *J Allergy Clin Immunol*. 2011;127:724–33.
32. Blaser MJ. Who are we? Indigenous microbes and the ecology of human diseases. *EMBO Rep*. 2006;7:956–60.
33. Romeo J, Nova E, Wärnberg J, Gómez-Martínez S, Díaz Ligia LE, Marcos A. Immunomodulatory effect of fibres, probiotics and symbiotic indifferent life-stages. A review. *Nutr Hosp*. 2010;25:341–9.
34. Romeo J, Nova E, Wärnberg J, Gómez-Martínez S, Díaz LE, Marcos A. Fibre, probiotics and the immune system in different life-stages. In: van der Kamp JW, Jones JM, McCleary BV, Topping DL, editors. *Dietary fibre: new frontiers for food and health*. Wageningen: Wageningen Academic Publishers; 2010. p. 167–76.
35. Park JH, Um JI, Lee BJ, Goh JS, Park SY, Kim WS, et al. Encapsulated *Bifidobacterium bifidum* potentiates intestinal IgA production. *Cell Immunol*. 2002;219:22–7.
36. Penders J, Stobberingh EE, van den Brandt PA, Thijs C. The role of the intestinal microbiota in the development of atopic disorders. *Allergy*. 2007;62:1223–36.
37. Guarner F. Papel de la flora intestinal en la salud y en la enfermedad. *Nutr Hosp*. 2007;22 Suppl. 2:14–9.
38. Mediterranean dieta decalogue [Internet]. Fundación de la Dieta Mediterránea [cited 2012 May 12]. Available from: <http://dietamediterranea.com/dieta-mediterranea/decalogo>
39. Bach-Faig A, Berry EM, Lairon D, Reguant J, Trichopoulou A, Dernini S, et al., Mediterranean Diet Foundation Expert Group. Mediterranean diet pyramid today. Science and cultural updates. *Public Health Nutr*. 2011;14:2274–84.
40. Guía Española para el manejo del Asma (GEMA 2009) [Internet] [cited 2013 July 18]. Available from: <http://www.gemasma.com/images/stories/GEMASMA/Documentos/GEMA%202009/index.html>