Allergologia et immunopathologia
Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica
www.all-imm.com

ORIGINAL ARTICLE

OPEN ACCESS

Mediterranean diet in the Castilian plains: Dietary patterns and childhood asthma in 6-7-year-old children from the province of Salamanca

María Domínguez[a]*, María Concepción Vega-Hernández[b], Teresa De la Calle Cabrera[c], Sonia Arriba-Méndez[d], Francisco Javier Pellegrini-Belinchón[e]

[a]Gerencia de Atención Primaria de Salamanca, Centro de Salud de San Juan, Avenida de Portugal, Salamanca, Spain
[b]Department of Statistics, Faculty of Medicine, University of Salamanca, Campus Miguel de Unamuno, Salamanca, Spain
[c]Gerencia de Atención Primaria de Salamanca, Centro de Salud de Tamames, Plaza del Ferial s/n, Tamames, Salamanca, Spain
[d]Department of Biomedical and Diagnostic Sciences, University Hospital of Salamanca, Paseo de San Vicente, Salamanca, Spain
[e]Department of Biomedical and Diagnostic Sciences, University of Salamanca, Centro de Salud de Pizarrales, Paseo de Canalejas, Salamanca, Spain

Received 19 November 2021; Accepted 21 December 2021
Available online: 1 September 2022

KEYWORDS
asthma;
children;
dietary patterns;
Global Asthma Network;
Mediterranean diet

ABSTRACT
Salamanca is the only Spanish center with no coastal line participating in the Global Asthma Network phase-I study. Questionnaires were collected from 6-7-year-old 2388 children and analyzed in particular for their diet and asthma symptoms as part of this study. The prevalence of current asthma (CA) was 9%, doctor-confirmed asthma (DCA) was 7%, and current severe asthma (CSA) accounted to 2.9%. Two Mediterranean Diet Scores (MDS) were performed to evaluate adherence of these children to the Mediterranean diet. Principal component analysis generated four dietary patterns. The relationship between asthma and each food type, MDS, and dietary patterns was assessed using multivariate adjusted logistic regression. Adherence to the Mediterranean diet by Salamanca's children and prevalence of asthma in Salamanca were similar to the findings of coastal located centers of other studies. High punctuation in MDS was associated with high prevalence of asthma. Higher scores for the pattern "Fats and sugar" was associated with less current asthma but not with DCA or CSA. These findings might be due to improvement in the diet of asthma children, reverse causation factor, how the questionnaire collected information about diet, and perhaps the manner in which the scores were constructed. The complexity of interconnections between nutrients, foods, and dietary patterns, and the heterogeneous nature of asthma, makes it difficult to identify single factor that affected its development. Our findings require corroboration by additional studies.

***Corresponding author:** María Domínguez Villoria, Gerencia de Atención Primaria, Centro de Salud de San Juan, Avenida de Portugal, 83, 37005 Salamanca, Spain. *Email address:* mariadomv@gmail.com

https://doi.org/10.15586/aei.v50i5.544

Introduction

Asthma is one of childhood's most prevalent chronic diseases in developed countries, where it affects approximately 10% of children.[1-3] Worldwide, asthma affects 334-million people of all ages, and presents significant physical, psychological and social burden.[4]

Salamanca is a Spanish province on the southwest border of Castilla y Leon region. In 2019, it had a population of 331,473 people, of whom 144,228 (40%) lived within the homonymous capital, and 5249 were 6–7 years old.[5] Climate is continental, with very cold winters and dry hot summers, as it is high above the sea level and far away from the sea. The economy is based on service class; and the University and the tourism industry are primary employers.

Salamanca was one of the centers in Spain that completed data collection for the Global Asthma Network (GAN) phase-I study. GAN was created in 2012 to continue the work of International Study of Asthma and Allergies in Childhood (ISAAC) to study asthma in children globally. The three-phase study evaluated the influence of food as a risk factor for the development of asthma in children, with questions with various subheadings as part of the primary questionnaire. Phase-I study of GAN has expanded by adding more food types.[6] GAN participating centers in Spain that completed data collection by 2020 were Cantabria, La Coruña, and Cartagena y Salamanca.[7]

There are some studies that evaluated how family diet, specific nutrients, and food groups, affect the development of asthma.[8,9] Possible mechanisms by which this can happen include changes in the intestinal microbiota, immune system, proinflammatory effects of some food types, food processing with additives and pasteurization, and presence of allergenic elements in foods.[10-12] Currently, no randomized controlled studies have been conducted to study relationship between diet and asthma and prevention of allergies in children. However, some observational studies have found that some micronutrients, such as vitamins A, D, and E and zinc, fruits and vegetables, and the Mediterranean diet protected from the development of asthma.[9]

The Mediterranean diet is one of the most studied dietary patterns in relation to protection against chronic diseases,[13] childhood asthma being one of these diseases. Characteristics of the Mediterranean diet are as follows: high consumption of fruits and vegetables, pulses and nuts, bread and other cereals, with wheat as the basic staple food, olive oil as the primary fat, and vinegar.[14] Various meta-analyses have evaluated effects of the Mediterranean diet on childhood asthma, but the results are not conclusive, probably because of the heterogeneity of available studies, although a protective tendency has been described regarding early wheezing and respiratory symptoms in early years of the disease.[14-16]

Recently, dietary patterns have been described as an alternative to evaluate the combination of foods that can be beneficial or deleterious in some chronic diseases.[17] In order to establish which foods belong to a particular dietary pattern, statistical tools, such as principal component analysis (PCA), have been used in nutritional epidemiology to explain the variability of food types in diet, and the relation of the amounts consumed in certain diseases.[8]

In Spain, regional variations exist regarding diet. According to the European Health Survey 2020, referred to those above 15 years of age, in Castilla y Leon, intake of daily fruit, vegetables, sweets and fish is higher but that of processed meats is lower than the average Spanish consumption.[18]

The objectives of this study were to evaluate, in 6–7-year-old children from Salamanca, severity of asthma in relation to their diet, whether they followed the Mediterranean diet, and whether any food type was associated with childhood asthma.

Materials and Methods

The present research, as a cross-sectional study of GAN phase I, followed the methods detailed in the GAN manual (http://globalasthmanetwork.org/surveillance/manual/methods.php)[19] and presented in Ellwood et al.[6] Participants of the study were children from the first and second year of primary schools in Salamanca. Their parents completed a questionnaire having 75 questions about life and health of the child; the participation rate was 74%. All schools with more than 20 pupils in the mentioned age range were contacted and with prior permission of the principal were included in the study. The questionnaire used was in Spanish provided by the coordination center of GAN phase-I study (Cartagena, Spain), and can be retrieved from: http://pediatria.imib.es/portal/instituto/pediatria_gan.jsf. No modifications were made to this version.

The questionnaire included demographic data, questions referring to asthma symptoms and its severity, food consumption, and other pre- and postnatal risk and protection factors for asthma.

Only children whose parents completed the question concerning food consumption (never or occasionally, 1–2 times/week, and >3 times/week) were included in this study. We compared the children who presented recent wheezing ("wheeze in the last 12 months"), referred to as current asthma (CA), those whose asthma was confirmed by a doctor (doctor-confirmed asthma; DCA), and those who suffered current severe asthma (CSA). CSA is a combined variable comprising children with current asthma that had suffered in the previous year more than four asthma attacks or their sleep was disturbed for more than one night/week, or there was at least one episode of speech limitation ("wheezing severe enough to limit your child's speech to only one or two words at a time between breaths?").

In order to evaluate the Mediterranean diet, we used the score from García-Marcos et al., developed on the basis of the score used by Psaltopoulou et al.[20-22] The scores were worked up as follows: foods considered ''pro-Mediterranean'' were rated 0, 1, or 2 points from less frequent to more frequent intake. Foods considered ''anti-Mediterranean'' were rated 0, 1, or 2 points from more frequent to less frequent consumption. We used two Mediterranean Diet Scores (MDS), the score based on the ISAAC phase-III questionnaire with 11 food types (MDS11),[20] and the one based on the GAN phase I that included 22 food types (MDS22).[21] MDS11 ranged from 0 to 22 points, while MDS22 ranged from 0 to 44 points; higher scores meant higher adherence to the Mediterranean diet.

The study was approved by the Ethics Committee of the Area of Salamanca in January 2016.

Statistical Analysis

Descriptive analyses were performed of variables, prevalence of asthma symptoms and diagnosis expressed as percentage and 95% confidence interval (95% CI), and possible risk and protection factors. As recommended by the GAN Manual, unanswered and incorrect answers were included in the denominators to calculate prevalence.

In order to evaluate the possibility of certain variables determining the manifestations of asthma, logistic regression was calculated with odds ratio (OR), 95% CI, and p-value.

A descriptive analysis of consumption of food types included in the questionnaire was prepared, with frequencies, percentage of consumption, and comparing those with and without current asthma, DCA, and CSA, looking for association with the Chi-squared test.

Both diet scores, MDS11 and MDS22, were calculated; PCA was performed with a promax rotation to identify dietary patterns. Calculation of the scores of the groups derived from dietary patterns was done by adding the values of 1, 2, and 3 from the parents' responses for each food, all in the same order: "Never or occasionally" = 1, and "More than 3 times per week" = 3. Higher scores for dietary pattern groups demonstrated more consumption of those foods. We analyzed possible differences between all scores for children with and without current asthma, DCA, and CSA using the Mann–Whitney U test.

Multivariate logistic regression was performed to calculate adjusted odds ratios (aOR) with 95% CI for current asthma, DCA, and CSA according to the consumption of each food. We adjusted for the variables that indicated following association: gender, maternal smoking during pregnancy, infections and antibiotics for respiratory pathology during the first year of life, use of paracetamol in the past 12 months, having ever suffered from pneumonia and age in months at the time of first attendance at childcare or school, except rhinoconjuntivitis and dermatitis because they present excessive collinearity with asthma and could distort results.

The significance level required was 5% ($p < 0.05$). Calculations were done with IBM SPSS Statistics for Windows, version 26 (IBM, Armonk, NY, USA).

Results

The parents of 2091 children from 51 schools in Salamanca province completed the food consumption questionnaire (87.6% of the 2388 questionnaires collected in this age group). Participants included 1046 girls, 1040 boys, and 5 did not specify gender. One-third of the participants, 33.3%, had wheeze at some point in their lives, but only 9.0% had wheeze in the preceding year, of whom 119 (5.7%) were boys. Asthma was diagnosed in 147 (7.0%) cases, and 61 (2.9%) met the criteria of severe asthma as described in the methods of the GAN manual.

Maternal smoking was found in 13.6% of pregnancies, and 86.2% of the children were breastfed at some point. Almost half of the children, 45.6%, had suffered from respiratory infections during the first year of life, for which 25.4% had received an antibiotic. Just 15% had suffered from pneumonia at some point in their lives. There was a personal history of rhinitis in 9.5% of the children, and 9.9% had dermatitis. The mean age of the children starting to attend childcare or school (hereafter, to simplify, we call both as "school") was 18.8 months (standard deviation [SD]: ±11.3), with the most children attending school by the age of 3 years. Regarding consumption of paracetamol, 78% children had had at least one dose during the previous year and 10.3% took it for at least one time a month. Exercise was carried out regularly (for more than one time a week) by 80.6% of the children (Table 1).

Following were the risk factors for at least one of the asthma variables studied: male gender, maternal smoking

Table 1 Participants' characteristics and associations with current asthma, doctor-confirmed asthma, and current severe asthma (n = 2091).

			Current asthma (n = 188)		Doctor-confirmed asthma (n = 147)		Current severe asthma (n = 61)	
	n	%	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Gender: Males	**1040**	**49.9**	**0.5 (0.4-0.7)**	**<0.001**	0.5 (0.4-0.8)	0.001	0.7 (0.4-1.2)	0.235
Maternal smoking during pregnancy	**284**	**13.6**	**1.5 (1-2.2)**	**0.043**	1.4 (0.9-2.2)	0.149	1.4 (0.7-2.7)	0.355
Rhinitis	**198**	**9.5**	**7.8 (5.5-11.1)**	**<0.001**	**8.1 (5.6-11.8)**	**<0.001**	**8.6 (5.1-14.7)**	**<0.001**
Dermatitis	**206**	**9.9**	**2.5 (1.7-3.7)**	**<0.001**	**2.6 (1.7-3.9)**	**<0.001**	**3.4 (1.9-6.2)**	**<0.001**
Breastfeeding ever	1803	86.2	1 (0.6-1.5)	0.946	1 (0.6-1.7)	0.899	0.7 (0.4-1.5)	0.404
Infections during the first year of life	**954**	**45.6**	**1.8 (1.3-2.5)**	**<0.001**	**1.9 (1.3-2.7)**	**<0.001**	**1.9 (1.1-3.2)**	**0.017**
Physical exercise	1686	80.6	0.9 (0.6-1.3)	0.489	0.9 (0.6-1.3)	0.516	0.6 (0.3-1)	0.050
Paracetamol in the past 1 year								
Never	**227**	**10.9**		**<0.001**		**<0.001**		**<0.001**
At least for one time a year	1632	78.0	1 (0.6-1.7)	0.944	0.8 (0.5-1.3)	0.357	1.3 (0.5-3.7)	0.628
At least for one time per month	**215**	**10.3**	**3.4 (1.9-6.1)**	**<0.001**	**2.3 (1.2-4.2)**	**0.010**	**5.1 (1.7-15.3)**	**0.004**
Antibiotics for respiratory infections	**532**	**25.4**	**2.2 (1.3-3.7)**	**0.003**	**3.7 (1.9-7.1)**	**<0.001**	**3.8 (1.3-11)**	**0.013**
Pneumonia	**313**	**15.0**	**4.4 (3.1-6.1)**	**<0.001**	**4 (2.8-5.7)**	**<0.001**	**4.7 (2.8-8)**	**<0.001**

during pregnancy, past history of rhinitis or dermatitis, respiratory infections and/or use of antibiotics for respiratory infections during the past 1 year of life, paracetamol in the past 1 year, history of pneumonia, and age in months at the time of first school attendance.

Age in months at the time of starting school attendance was significantly associated to current asthma (p = 0.024) but not to DCA (p = 0.922) and CSA (p = 0.227).

Table 2 shows all food types included in the questionnaire, with absolute frequencies, percentages of consumption, and their use in the scores as included in "pro-Mediterranean" or "anti-Mediterranean" groups. We observed that most children had consumed meat, fruit, bread, olive oil, milk, and dairy products for "more than three times per week" in the past 12 months. However, they consumed only fish, cooked and raw vegetables, pulses, rice, pasta, eggs, potatoes, and sugar "once or twice per week," and butter, margarine, nuts, fast food, and sugary drinks "never or occasionally."

In addition, according to the PCA results, food types based on their components were divided into the following four groups: Group 1 "Fats and sugar," Group 2 "Veg and sea," Group 3 "Carbs," and Group 4 "Western." In Group 1, there were foods rarely consumed by the children, such as fast food, fatty foods, and sugars. Group 2 represented more of the Mediterranean diet as it contained fruit, vegetables, fish, and olive oil among its components. This group and Groups 3 and 4 represented foods that were consumed more frequently by the children. Group 3 included carbohydrates, pulses, and eggs whereas Group 4 represented somehow the Western diet with meat, milk and dairy, and bread. The frequency of consumption depending upon asthma symptoms is described in Table 3.

Mean value for MDS22 was 24 points (range 14–34 points) with SD = ±2.8. Mean value for MDS11 was 11.6 points (range 3–18 points). Significant differences were found for the children with and without current asthma in Group 1 "Fats and sugar" (Mann–Whitney U test = 156,047; p = 0.007).

Table 3 presents the frequency of consumption for the children with current asthma, DCA, and CSA. Association was found between the frequency of consumption of pulses and sugar and current asthma (p = 0.023 and 0.009, respectively), and between fast food (excluding burgers) and DCA (p = 0.023).

Odds ratios and aOR scores for gender, maternal smoking, respiratory infections and/or antibiotics for respiratory infections before 1 year of age, use of paracetamol in the past 12 months, pneumonia, and age in months at the time of first school attendance, each food type, and PCA food groups for current asthma, DCA, and CSA are presented in Table 4.

Foods with a protective effect before adjustment, for current asthma, were nuts and sugar whereas seafood appeared to be a risk factor. This effect did not appear after adjustment. As per DCA, fast food appeared as a

Table 2 Description of food types included in the GAN questionnaire and their use in the MDS (as "pro-Mediterranean" [+] or "anti-Mediterranean" [-]) and grouping according to PCA.

	Frequency of weekly consumption						Scores used		Grouping according to PCA
	Never		1 or 2 times		>3 times		MDS11	MDS22	
Food types	n	%	n	%	n	%			
Meat	8	0.4	642	30.7	1441	68.9	(-)	(-)	4
Sea food	189	9.0	1667	79.7	235	11.2	(+)	(+)	2
Fruit	107	5.1	436	20.9	1548	74.0	(+)	(+)	2
Cooked veg	169	8.1	1186	56.7	736	35.2	(+)*	(+)	2
Raw veg	801	38.3	918	43.9	372	17.8		(+)	2
Pulses	62	3.0	1681	80.4	348	16.6	(+)	(+)	3
Cereals	526	25.2	789	37.7	776	37.1	(+)	(+)	2
Bread	93	4.4	282	13.5	1716	82.1		(+)	4
Pasta	66	3.2	1870	89.4	155	7.4	(+)	(+)	3
Rice	134	6.4	1840	88.0	117	5.6	(+)	(+)	3
Margarin	1806	86.4	262	12.5	23	1.1		(-)	1
Butter	1711	81.8	322	15.4	58	2.8		(-)	1
Olive oil	65	3.1	341	16.3	1685	80.6		(+)	2
Milk	79	3.8	70	3.3	1942	92.9	(-)	(-)	4
Dairy	31	1.5	331	15.8	1729	82.7		(-)	4
Eggs	110	5.3	1840	88.0	141	6.7		(-)	3
Nuts	1359	65.0	681	32.6	51	2.4		(+)	1
Potatoes	129	6.2	1635	78.2	327	15.6	(+)	(+)	3
Sugar	374	17.9	1114	53.3	603	28.8		(-)	1
Burger	1604	76.7	481	23.0	6	0.3		(-)	1
Fast food	1728	82.6	357	17.1	6	0.3	(-)**	(-)	1
Soft drink	1655	79.1	377	18.0	59	2.8		(-)	1

GAN: Global Asthma Network; MDS: Mediterranean diet scores; PCA: principal component analysis.
*Combination of two vegetable questions was used, taking the highest consumption.
**Combination of two fast food questions was used, taking the highest consumption.

Table 3 Weekly frequency of consumption of all food types by 6-7-year-old children with current asthma, DCA, and CSA.

	Current asthma (n = 188)				Doctor-confirmed asthma (DCA, n = 147)				Current severe asthma (CSA, n = 61)			
	Never	1 or 2 times	>3 times		Never	1 or 2 times	>3 times		Never	1 or 2 times	>3 times	
	n (%)	n (%)	n (%)	p	n (%)	n (%)	n (%)	p	n (%)	n (%)	n (%)	p
Meat	1 (0.59)	62 (33.0)	125 (66.5)	0.741	1 (0.7)	38 (25.9)	108 (73.5)	0.365	1 (1.6)	17 (27.9)	43 (70.5)	0.249
Seafood	11 (5.9)	150 (79.8)	27 (14.4)	0.128	14 (9.5)	113 (76.9)	20 (13.6)	0.620	6 (9.8)	47 (77.0)	8 (13.1)	0.862
Fruit	12 (6.4)	33 (17.6)	143 (76.1)	0.379	8 (5.4)	25 (17.0)	114 (77.6)	0.478	2 (3.3)	10 (16.4)	49 (80.3)	0.509
Cooked veg	15 (8.0)	105 (55.9)	68 (36.2)	0.948	12 (8.2)	81 (55.1)	54 (36.7)	0.907	5 (8.2)	36 (59.0)	20 (32.8)	0.922
Raw veg	73 (38.8)	72 (38.3)	43 (22.9)	0.102	56 (38.1)	60 (40.8)	31 (21.1)	0.493	24 (39.3)	26 (42.6)	11 (18.0)	0.979
Pulses	**8 (4.3)**	**137 (72.9)**	**43 (22.9)**	**0.023**	5 (3.4)	113 (76.9)	29 (19.7)	0.540	2 (3.3)	43 (70.5)	16 (26.2)	0.119
Cereals	47 (25.0)	69 (36.7)	72 (38.3)	0.946	35 (23.8)	57 (38.8)	55 (37.4)	0.915	11 (18.0)	26 (42.6)	24 (39.3)	0.417
Bread	4 (2.1)	26 (13.8)	158 (84.0)	0.269	11 (7.5)	19 (12.9)	117 (79.6)	0.187	2 (3.3)	7 (11.5)	52 (85.2)	0.795
Pasta	8 (4.3)	160 (85.1)	20 (10.6)	0.120	7 (4.8)	123 (83.7)	17 (11.6)	0.060	4 (6.6)	52 (85.2)	5 (8.2)	0.290
Rice	11 (5.9)	160 (85.1)	17 (9.0)	0.100	7 (4.8)	126 (85.7)	14 (9.5)	0.082	5 (8.2)	52 (85.2)	4 (6.6)	0.790
Margarin	161 (85.6)	24 (12.8)	3 (1.6)	0.792	130 (88.4)	15 (10.2)	2 (1.4)	0.647	54 (88.5)	7 (11.5)	0 (0.0)	0.677
Butter	161 (85.6)	23 (12.2)	4 (2.1)	0.431	119 (81.0)	23 (15.6)	5 (3.4)	0.891	53 (86.9)	6 (9.8)	2 (3.3)	0.468
Olive oil	2 (1.1)	33 (17.6)	153 (81.4)	0.223	7 (4.8)	22 (15.0)	118 (80.3)	0.440	2 (3.3)	14 (23.0)	45 (73.8)	0.356
Milk	8 (4.3)	10 (5.3)	170 (90.4)	0.272	5 (3.4)	3 (2.0)	139 (94.6)	0.645	5 (8.2)	3 (4.9)	53 (86.9)	0.139
Dairy	3 (1.6)	26 (13.8)	159 (84.6)	0.762	3 (2.0)	23 (15.6)	121 (82.3)	0.850	2 (3.3)	14 (23.0)	45 (73.8)	0.136
Eggs	10 (5.3)	165 (87.8)	13 (6.9)	0.975	9 (6.1)	127 (86.4)	11 (7.5)	0.810	4 (6.6)	54 (88.5)	3 (4.9)	0.774
Nuts	136 (72.3)	47 (25.0)	5 (2.7)	0.067	101 (68.7)	41 (27.9)	5 (3.4)	0.348	43 (70.5)	15 (24.6)	3 (4.9)	0.212
Potato	11 (5.9)	146 (77.7)	31 (16.5)	0.918	7 (4.8)	111 (75.5)	29 (19.7)	0.318	7 (11.5)	44 (72.1)	10 (16.4)	0.203
Sugar	**49 (26.1)**	**93 (49.5)**	**46 (24.5)**	**0.009**	34 (23.1)	75 (51.0)	38 (25.9)	0.210	15 (24.6)	27 (44.3)	19 (31.1)	0.265
Burger	148 (78.7)	39 (20.7)	1 (0.5)	0.628	108 (73.5)	39 (26.5)	0 (0.0)	0.451	47 (77.0)	13 (21.3)	1 (1.6)	0.130
Fast food	152 (80.9)	36 (19.1)	0 (0.0)	0.534	**110 (74.8)**	**37 (25.2)**	**0 (0.0)**	**0.023**	48 (78.7)	13 (21.3)	0 (0.0)	0.619
Soft drink	154 (81.9)	33 (17.6)	1 (0.5)	0.148	112 (76.2)	32 (21.8)	3 (2.0)	0.410	48 (78.7)	12 (19.7)	1 (1.6)	0.816

risk factor only before adjustment, but after adjustment, consumption of raw vegetables once or twice per week and intake of nuts for more than three times per week appeared as risk factors, while bread appeared as a protective factor. For CSA, consumption of nuts for more than 3 days per week appeared as a risk factor after adjustment, and consumption of potatoes for one time or twice per week appeared as a protective factor. High points in MDS and Group 3 (Veg and sea) appeared as risk factors for current asthma, while Group 1 (Fats and sugar) appeared as a protective factor. For DCA, both MDS11 and MDS22 appeared as risk factors, and Group 4 (Western) was a protective factor. We found that for CSA, only high scores in MDS22 were risk factors.

Discussion

The prevalence of current asthma in 6-7-year-old children in Salamanca province was 9%, similar to the results of recent

Table 4 Odds ratio and adjusted odds ratio of food types, MDS, and PCA food groups for current asthma, DCA, and CSA. Only food types with statistically significant results are shown.

	Current asthma							
	1 or 2		>3		1 or 2		>3	
	OR (95% CI)	p	OR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p
Seafood	1.6 (0.8-2.9)	0.168	**2.1 (1.0-4.3)**	**0.048**	1.5 (0.5-4.2)	0.435	1.3 (0.4-4.9)	0.654
Nuts	**0.7 (0.5-0.9)**	**0.022**	1.0 (0.4-2.7)	0.945	0.6 (0.3-1.1)	0.129	2.0 (0.5-8.9)	0.348
Sugar	**0.6 (0.4-0.9)**	**0.008**	**0.6 (0.4-0.8)**	**0.006**	0.7 (0.4-1.3)	0.281	0.5 (0.2-1.1)	0.082
MDS11	**1.1 (1.0-1.2)**	**0.022**			**1.2 (1.1-1.4)**	**0.001**		
MDS22	**1.1 (1.0-1.1)**	**0.037**			**1.2 (1.1-1.3)**	**< 0.001**		
G 1, Fats & sugar	**0.9 (0.8-1.0)**	**0.028**			**0.8 (0.7-0.9)**	**0.003**		
G 2, Veg & sea	1.0 (1.0-1.1)	0.225			1.1 (1.0-1.3)	0.069		
G 3, Carbs	1.1 (1.0-1.3)	0.105			**1.3 (1.1-1.6)**	**0.006**		
G 4, Western	1.0 (0.9-1.2)	0.947			0.9 (0.7-1.2)	0.459		
	Doctor-confirmed asthma							
	1 or 2		>3		1 or 2		>3	
	OR (95% CI)	p	OR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p
Raw Veg	0.9 (0.6-1.4)	0.705	1.2 (0.8-1.9)	0.392	**2.4 (1.2-4.8)**	**0.014**	1.8 (0.7-4.3)	0.223
Bread	0.5 (0.2-1.2)	0.121	0.5 (0.3-1.1)	0.074	**0.2 (0.1-0.7)**	**0.012**	**0.2 (0.1-0.5)**	**0.001**
Nuts	0.8 (0.5-1.2)	0.228	1.4 (0.5-3.5)	0.511	1.0 (0.5-1.9)	0.937	**7.6 (1.9-29.8)**	**0.004**
Fast food	**1.7 (1.1-2.5)**	**0.008**	0.0 (0.0-0.0)	0.999	1.5 (0.7-3.4)	0.337	0.0 (0.0-0.0)	1.000
MDS11	1.0 (1.0-1.1)	0.376			**1.2 (1.0-1.3)**	**0.013**		
MDS22	1.0 (1.0-1.1)	0.379			**1.2 (1.1-1.3)**	**0.001**		
G 1, Fats & sugar	1.0 (0.9-1.1)	0.932			0.9 (0.8-1.1)	0.272		
G 2, Veg & sea	1.0 (0.9-1.1)	0.517			1.1 (1.0-1.3)	0.056		
G 3, Carbs	1.1 (1.0-1.3)	0.062			1.2 (1.0-1.5)	0.072		
G 4, Western	1.0 (0.8-1.2)	0.987			**0.7 (0.6-0.9)**	**0.007**		
	Current severe asthma							
	1 or 2		>3		1 or 2		>3	
	OR (95% CI)	p	OR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p
Nuts	0.7 (0.4-1.2)	0.220	1.9 (0.6-6.4)	0.292	1.2 (0.4-3.6)	0.751	**7.4 (1.0-55.3)**	**0.050**
Potato	0.5 (0.2-1.1)	0.081	0.5 (0.2-1.5)	0.235	**0.2 (0.0-0.9)**	**0.036**	0.6 (0.1-4.1)	0.630
MDS11	1.1 (0.9-1.2)	0.324			1.2 (0.9-1.4)	0.160		
MDS22	1.0 (1-1.1)	0.336			**1.2 (1.0-1.3)**	**0.030**		
G 1, Fats & sugar	1.0 (0.8-1.1)	0.614			0.8 (0.7-1.0)	0.105		
G 2, Veg & sea	1.0 (0.9-1.2)	0.739			1.1 (0.9-1.3)	0.604		
G 3, Carbs	1.0 (0.8-1.2)	0.907			1.3 (0.9-1.8)	0.171		
G 4, Western	0.9 (0.7-1.1)	0.203			0.8 (0.6-1.2)	0.261		

MDS: Mediterranean diet scores; PCA: principal component analysis; OR: odds ratio; aOR: adjusted odds ratio (adjusted for gender, maternal smoking, respiratory infections, and/or antibiotics for respiratory infections before 1 year of age, paracetamol in the last 12 months, pneumonia, and age of first school attendance, in months).

studies conducted in Salamanca,[23] and the prevalence of severe asthma was 2.9%, similar to the prevalence of severe asthma found by García-Marcos et al. in ISAAC phase III in Spain.[21] DCA in 7% of the children was a lower percentage than encountered by García-Marcos Barbero et al. in Cartagena in the GAN phase-I study.[22]

As described, personal history of rhinitis and dermatitis, having ever suffered from pneumonia, having suffered from respiratory infections in the first year of life and/or having an antibiotic for the same, and frequent use of paracetamol were associated with current asthma, DCA, and CSA. Curiously, male gender was associated with current asthma and DCA but not CSA, and maternal smoking during pregnancy and age in months at the time of starting school were associated only with current asthma.

Breastfeeding and amount of exercise per week were not associated with any of the asthma parameters in our sample, in contrast to what was found in ISAAC phase III.[21]

MDS22 score was similar to the one calculated by García-Marcos Barbero et al. using the data of GAN phase I in Cartagena.[22] MDS11 score was also similar to the one published by two previous Spanish studies.[21,24] In 2007, García-Marcos et al. presented the data from the Spanish ISSAC phase III, with approximately 17,000 children, and concluded that the Mediterranean diet appeared to be protective, particularly for 6–7-year-old girls.[21] However, our data demonstrated that higher scores in MDS were associated with current asthma. A similar result was also described in a Galician study conducted by Gonzalez Barcala et al.; the authors found that higher scores were associated with high prevalence of severe asthma in 6–7-year-old girls.[24] As a possible explanation, we believe, like Gonzalez Barcala et al.[24] that perhaps families of asthmatic children try to improve their diet, creating a reverse causality bias.

In addition, a meta-analysis conducted by García-Marcos et al. depicted that the protective effect of the Mediterranean diet was primarily for current asthma and CSA, but not for "asthma ever," and was limited to the studies conducted at the centers of the Mediterranean area.[14] This might be explained by the fact that other factors, such as climate, affect the development of asthma more than that of food, which is also supported by the fact that MDS in our children was similar to those in Cartagena. Hence, we believe that nowadays children probably consume similar foods all over the country.

Other possible factors include a response bias from parents, even though other studies have found that the use of questionnaires to gather this information was reliable.[25] Also, some of the food types included in the score, and/or the way they are included as "pro-Mediterranean" or "anti-Mediterranean", do not relate to asthma at all, and act as confusion factors because of their high relative frequencies. For example, in the score we included foods such as potatoes, eggs, and milk, which were are clearly linked to the Mediterranean diet. This was supported by the fact that score with 22 food items appeared as a risk factor for all three asthma parameters, while score with 11 food items did not appear as a risk factor for severe asthma. Perhaps, the amount of each food item consumed was not accounted for properly to observe its risk or protective effect; for example, having nuts every day was not necessary or was even damaging in terms of asthma, but consuming them once or twice a week was beneficial, and adding an extra point to the score for consumption on most days did not add value to the model. It could also be the case that some food types were included as beneficial or damaging when in fact they are the opposite. Both MDS were based on *a priori* knowledge about foods belonging to the traditional Mediterranean diet. In this study, we presented our PCA, *a posteriori* analysis, on how groups are formed from the foods consumed by children; this was another recognized manner to study the variability of food types in nutritional epidemiology scientific literature.[8,26] As such, food types were grouped to explain variability of the sample; for example, the group "Fats and sugar" sorted foods that children in Salamanca appeared to consume rather infrequently according to our data, while the group "Western" contained food items that most children consumed on daily basis. According to this analysis, data in the first group, "Fats and sugar," was associated with the lower scores of MDS to appear as being protective for asthma, because higher consumption of Group 1 foods appeared to be protective of asthma. When we evaluated separately the effect of food types, only sugar consumption for more than one time per week and nuts consumed once or twice per week appeared to protect against current asthma, while seafood appeared as a risk factor. All those effects disappeared after adjusting for possible confounders. Other foods, such as nuts consumed once or twice a week that appeared significant in the ISAAC phase III[21] did not appear as protective in our sample after adjustment. For CSA, potatoes consumed once or twice a week appeared to be protective, while nuts consumed thrice a week were a risk factor.

Sugar deserves a special mention, as it appeared as a protective factor for current asthma in our sample. Only 28.8% of the parents responded that their children took sugar for more than three times a week. However, we considered that there was a bias in that result, as in Spain, in general, most children don't take milk without sugary cocoa (70% sugar), take yogurt products with a lot of sugar,[27] and also consume sugar in juices, milkshakes, and breakfast cereals—all these were "hidden" from their parents' knowledge.[28] In our population, 92.9% took milk for more than thrice a week, and 82.7% consumed dairy products, while 37.1% parents said that their children had cereals on most of the days. Taking this into account, we believed that real sugar consumption was not represented reliably by parents in their answers to questionnaires, and that if it was properly accounted for might not show the protective effect. In a similar manner, consumption of nuts that appeared as a protective factor in other studies was a risk factor for DCA and CSA in the present study; this could be due to the fact that some parents might assume some fried corn snacks and other such processed snacks as "nuts."

This was a limitation to this type of questionnaire. Another limitation was not considering quantities consumed but only weekly frequency of consumption. In addition, very low frequency of consumption of some food items could account for statistical bias in the results of this analysis.

However, this questionnaire, and both MDS, allowed us to analyze interactions between food types, and "weekly frequency of consumption" is easily answered by the

parents, and as a part of international studies, we could make comparisons between and within countries. Another limitation of the present study was not having collected the weight and height of the participating children. Our sample comprised more than 2000 children from only one province of Spain, which was another limitation. As a strength, this study provided the first GAN phase-I results published for the Mediterranean diet in 6-7-year-old children from Salamanca. This was the only center having no coastline. We performed a multivariate logistic analysis adjusted for possible confusion and risk factors to evaluate foods that affected manifestation of asthma, and a PCA to compare food groups that could affect the presence of asthma in these children.

Conclusions

The complexity of interactions between nutrients, foods, and dietary patterns and their effect on the development of asthma, by itself a syndrome with complex etiology and presentation, means that it is very difficult to reliably identify foods or food types that by themselves influence development of asthma. Lack of randomized controlled trials with restrictive diets before a child is conceived, which would be extremely difficult if not impossible, to put into practice epidemiological results based on questionnaires of international level such as GAN help us to establish dietary patterns that could minimize development of asthma. Our data established an association of asthma with higher MDS. More studies are required to compare with other geographical areas and cultures whether adherence to the Mediterranean diet is related to the prevalence of asthma.

Acknowledgments

Dr. Félix Lorente is acknowledged for his advice, direction, and support during all the phases of the study and for his amazing field work; all this would not have been possible without his assistance. Eduard Baladia and Julio Basulto are thanked for their advice in the early stages of the research. Padraig Mac an Bhaird and Julie Lucey are acknowledged for revising the English translation and advice. Moreover, we won't forget to thank the parents for completing the questionnaires, and the teachers for collecting the same.

Funding

This study was partially funded by the Gerencia Regional de Salud de la Consejería de Sanidad de la Junta de Castilla y León. It also received funding by means of a research grant adjudicated by the Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica (SEICAP).

Conflict of interest

The authors declare no potential conflict of interest with respect to research, authorship, and/or publication of this study.

References

1. Carvajal-Uruena I, Garcia-Marcos L, Busquets-Monge R, Morales Suarez-Varela M, Garcia de Andoin N, Batlles-Garrido J, et al. Geographic variation in the prevalence of asthma symptoms in Spanish children and adolescents. International Study of Asthma and Allergies in Childhood (ISAAC) Phase 3, Spain]. Arch Bronconeumol. 2005 Dec;41(12):659–62. https://doi.org/10.1016/s1579-2129(06)60333-9
2. Asher MI. Worldwide variations in the prevalence of asthma symptoms: The International Study of Asthma and Allergies in Childhood (ISAAC). Eur Respir J. 1998;12(2):315–35. https://doi.org/10.1183/09031936.98.12020315
3. Pearce N, Sunyer J, Cheng S, Chinn S, Bjorksten B, Burr M, et al. Comparison of asthma prevalence in the ISAAC and the ECRHS. ISAAC Steering Committee and the European Community Respiratory Health Survey. International Study of Asthma and Allergies in Childhood. Eur Respir J. 2000;16(3):420–6. https://doi.org/10.1183/9031936.00.16337700
4. Global Asthma Network. The Global Asthma Report 2018 [Internet]. Auckland, New Zealand; 2018. [cited 2021 Jun 15]. Available from: www.globalasthmareport.org
5. Instituto Nacional de Estadística. Demografía y población. Tablas del Instituto Nacional de Estadística [Internet]. 2020 [cited 2021 Jun 11]. Available from: www.ine.es
6. Ellwood P, Asher MI, Billo NE, Bissell K, Chiang C-YY, Ellwood EM, et al. The Global Asthma Network rationale and methods for phase I global surveillance: Prevalence, severity, management and risk factors. Eur Respir J. 2017;49(1):1601605. https://doi.org/10.1183/13993003.01605-2016
7. Ellwood P, Ellwood E, Rutter C, Perez-Fernandez V, Morales E, García-Marcos L, et al. Clinical Medicine Communication Global Asthma Network phase i surveillance: Geographical coverage and response rates. J Clin Med. 2020;9(11):3688. https://doi.org/10.3390/jcm9113688
8. Lv N, Xiao L, Ma J. Dietary pattern and asthma: A systematic review and meta-analysis. J Asthma Allergy. 2014;7:105–21. https://doi.org/10.2147/JAA.S49960
9. 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 Mar;127(3):724-33.e1-30. https://doi.org/10.1016/j.jaci.2010.11.001
10. Statovci D, Aguilera M, MacSharry J, Melgar S. The impact of western diet and nutrients on the microbiota and immune response at mucosal interfaces. Front Immunol. 2017;8:838. https://doi.org/10.3389/fimmu.2017.00838
11. Sozańska B, Sikorska-Szaflik H. Diet modifications in primary prevention of asthma. Where do we stand? Nutrients. 2021;13(1):173. https://doi.org/10.3390/nu13010173
12. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature. 2014;505(7484):559–63. https://doi.org/10.1038/nature12820
13. Sofi F, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: An updated systematic review and meta-analysis. Am J Clin Nutr. 2010;92(5):1189–96. https://doi.org/10.3945/ajcn.2010.29673
14. García-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 Jun;24(4):330–8. https://doi.org/10.1111/pai.12071
15. Zhang Y, Lin J, Fu W, Liu S, Gong C, Dai J. Mediterranean diet during pregnancy and childhood for asthma in children: A systematic review and meta-analysis of observational studies. Pediatr Pulmonol. 2019;54(7):949–61. https://doi.org/10.1002/ppul.24338

16. Castro-Rodriguez JA, Garcia-Marcos L. What are the effects of a Mediterranean diet on allergies and asthma in children? Front Pediatr. 2017;5:72. https://doi.org/10.3389/fped.2017.00072
17. Tapsell LC, Neale EP, Satija A, Hu FB. Foods, nutrients, and dietary patterns: Interconnections and implications for dietary guidelines. Adv Nutr. 2016;7(3):445–54. https://doi.org/10.3945/an.115.011718
18. Instituto Nacional de Estadística. Encuesta Europea de Salud 2020 [Internet]. [cited 2021 May 21]. Available from: https://www.ine.es
19. Global Asthma Network. Methods. [Internet] 2016. [cited 2021 Jun 21]. Available from: http://globalasthmanetwork.org/surveillance/manual
20. Psaltopoulou T, Naska A, Orfanos P, Trichopoulos D, Mountokalakis T, Trichopoulou A. Olive oil, the Mediterranean diet, and arterial blood pressure: The Greek European Prospective Investigation into Cancer and Nutrition (EPIC) study. Am J Clin Nutr. 2004;80(4):1012–8. https://doi.org/10.1093/ajcn/80.4.1012
21. García-Marcos L, Canflanca IM, Garrido JB, Varela ALS, Garcia-Hernandez G, Grima FG, et al. Relationship of asthma and rhinoconjunctivitis with obesity, exercise and Mediterranean diet in Spanish schoolchildren. Thorax. 2007;62(6):503–8. https://doi.org/10.1136/thx.2006.060020
22. García-Marcos Barbero P. Epidemiología del asma y dermatitis atópica en escolares de Cartagena: "Global Asthma Network." Dissertation, Universidad de Murcia (University of Murcia), Murcia, Spain; 2017. Available from: https://digitum.um.es/digitum/handle/10201/55479
23. De la Calle Cabrera T. Evolución de las sibilancias en los primeros 10 años de vida en la provincia de Salamanca. Factores de riesgo asociados. Dissertation, Universidad de Salamanca, Salamanca, Spain; 2020. Available from: https://gredos.usal.es/handle/10366/145325
24. Gonzalez Barcala FJ, Pertega S, Bamonde L, Garnelo L, Perez Castro T, Sampedro M, et al. Mediterranean diet and asthma in Spanish schoolchildren. Pediatr Allergy Immunol. 2010;21(7):1021–7. https://doi.org/10.1111/j.1399-3038.2010.01080.x
25. Byers T, Treiber F, Gunter E, Coates R, Sowell A, Leonard S, et al. The accuracy of parental reports of their children's intake of fruits and vegetables: Validation of a food frequency questionnaire with serum levels of carotenoids and vitamins C, A, and E. Epidemiology. 1993;4(4):350–5. PMID: 8347746. Available from: https://journals.lww.com/epidem/Abstract/1993/07000/The_Accuracy_of_Parental_Reports_of_Their.11.aspx
26. Hoffmann K, Schulze MB, Schienkiewitz A, Nöthlings U, Boeing H. Application of a new statistical method to derive dietary patterns in nutritional epidemiology. Am J Epidemiol. 2004;159(10):935–44. https://doi.org/10.1093/aje/kwh134
27. Bernadette Moore J, Sutton EH, Hancock N. Sugar reduction in yogurt products sold in the UK between 2016 and 2019. Nutrients. 2020;12(1):171. https://doi.org/10.3390/nu12010171
28. Boulton J, Hashem KM, Jenner KH, Lloyd-Williams F, Bromley H, Capewell S. How much sugar is hidden in drinks marketed to children? A survey of fruit juices, juice drinks and smoothies. BMJOpen. 2016;6(3):e010330. https://doi.org/10.1136/bmjopen-2015-010330