

ORIGINAL ARTICLE

Influence of Mediterranean diet on asthma in children: A systematic review and meta-analysis

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Keywords

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Abstract

Background: There is epidemiological evidence that Mediterranean diet exposure is associated with lower asthma prevalence in children. We aimed to summarize the available data and to know whether the Mediterranean setting modifies this association.

Methods: The literature search, up to May 2012, was on epidemiological studies in the general population of children assessing whether adherence to Mediterranean diet (measured as a score) was associated with the prevalence of 'current wheeze'; 'current severe wheeze'; or 'asthma ever'. Odds ratios (OR) of the eight included studies compared the highest tertile of the score with the lowest. Random-effects meta-analyses for the whole group of studies and stratified by Mediterranean setting (centers <100 Km from the Mediterranean coast) were performed. Differences between strata were assessed using the *Q* test.

Results: For 'current wheeze', there was a negative significant association with the highest tertile of Mediterranean diet score (OR 0.85, 95% CI 0.75–0.98; *p* = 0.02), driven by Mediterranean centers (0.79, 0.66–0.94, *p* = 0.009), although the difference with the non-Mediterranean centers (0.91, 0.78–1.05, *p* = 0.18) was not significant. The results for 'current severe wheeze' were as follows: 0.82, 0.55–1.22, *p* = 0.330 (all); 0.66, 0.48–0.90, *p* = 0.008 (Mediterranean); and 0.99, 0.79–1.25, *p* = 0.95 (non-Mediterranean); with the difference between regions being significant. For 'asthma ever', the associations were as follows: 0.86, 0.78–0.95, *p* = 0.004 (all); 0.86, 0.74–1.01, *p* = 0.06 (Mediterranean); 0.86, 0.75–0.98; *p* = 0.027 (non-Mediterranean); with the difference between regions being negligible.

Conclusions: Adherence to the Mediterranean diet tended to be associated with lower occurrence of the three respiratory outcomes. For current and current severe wheeze, the association was mainly driven by the results in Mediterranean populations.

Asthma prevalence has increased dramatically over the past few decades with the highest incidence occurring in children (1). One of the potential environmental explanations of that increase relates to changes in diet (2). Modern diet is dominated by food which has been processed, modified, stored, and transported over great distances. Moreover, in the last decades, it has been a trend to consume higher amounts of sugar and saturated fats (e.g., burgers and soft drinks) (3). In contrast, traditional diet is produced and marketed locally and is eaten shortly after harvesting (4). The term 'Mediterranean diet' refers to dietary patterns found in olive-growing areas of

the Mediterranean region, which is low in saturated fatty acids; rich in carbohydrates, fiber, and antioxidants; and has a high content of monounsaturated fatty acids and n-3 polyunsaturated fatty acids (PUFA), which are primarily derived from olive oil, and in some regions from fish (5).

Some epidemiological studies reported a protective effect of adherence to Mediterranean diet on asthma in children/adolescents; however, others did not or they could not conclude anything definitive (6–12). These contradictory findings might be due to the use of different Mediterranean indexes, diverse asthma outcomes, dissimilar populations of

children (i.e., preschoolers, school children or adolescents), and unmatched categories of diet exposure. In addition, several studies were limited by small sample size. In contrast, several recent reviews have stated the importance of Mediterranean diet in the development of asthma in children (13–15), although no meta-analysis has yet been performed. Therefore, a systematic review with meta-analysis of this particular diet and its effect on asthma in children is of interest to summarize the current evidence. The aim of this systematic review and meta-analysis is to investigate whether adherence to Mediterranean diet might have some effect on asthma diagnosis and on current wheeze and severe current wheeze in childhood. Furthermore, as environmental risk or protective factors may be modified by the genetic background, the present meta-analysis explores the aforementioned effect when centers are stratified into Mediterranean and non-Mediterranean.

Methods

The literature search was centered on epidemiological studies in general population of children which assessed Mediterranean diet as an exposure factor associated with the prevalence of asthma or wheeze according to common definitions as follows: 'current wheeze' at least one wheeze episode during the year prior to the survey; 'current severe wheeze' defined in the International Study of Asthma and Allergies in Childhood (ISAAC) as ≥ 4 attacks of wheeze or ≥ 1 night per week sleep disturbance from wheeze or wheeze affecting speech in the past 12 months (16); and 'asthma ever' as an estimation of having received a diagnosis of asthma at any time of the individual's life prior to the survey.

Medline/Pubmed, Embase, Scopus, and ISI Web of Knowledge (for proceedings and abstracts from congresses) were included in the literature search, which was carried out in May 2012 and extended back to 1960. No restriction was made for publication language or publishing status. The search was completed using cross-referencing from the articles found. In those cases in which additional information was required, the authors of the specific article were contacted via email. The search terms were as follows: ['Mediterranean' AND 'diet' AND ('wheezing' OR 'wheeze' OR 'asthma' OR 'respiratory' OR 'airway' OR 'lung')]. To include a study, it was required to have some kind of Mediterranean diet score to have a measure of the exposure to the diet, which was put in relation with outcomes that were equivalent to the aforementioned definitions.

As the definition of using the Mediterranean diet score and the method to calculate it were not uniform for all included studies, the authors of the studies where scores had been used as a continuous variable were asked to re-analyze their data comparing the lowest tertile of the score with the highest one. Thus, all included studies offered the comparison of a group of highest adherence (highest tertile of the Mediterranean diet score used) with a group of lower adherence (lowest tertile of the score). This would minimize the effects of using different types of scores, namely those based on Psaltopoulou (17), Trichopoulou (18), and KIDMED (19), and would allow including all studies found in the literature that had previously analyzed the data using three levels of adherence and had

compared the lowest with the highest. The three aforementioned scores are arbitrary ones and measure adherence to Mediterranean diet after obtaining information about consumed diet from previously validated food frequency questionnaires (20). Those three scores assign an arbitrary low value to the group of non-Mediterranean group of foods, and a higher one to Mediterranean group of foods. The scores by Trichopoulou (18) and Psaltopoulou (17) are built identically although the group of foods vary very slightly.

In two studies (10, 11), several centers (corresponding generally to city districts) were included. In those centers, a re-analysis was performed, and the data from each center were analyzed and reported separately to facilitate a stratified analysis between Mediterranean vs. non-Mediterranean centers; however, the cutoff points for the tertiles of the Mediterranean diet score were calculated from the whole population and not from each center separately to obtain a better distribution. Those two studies had several geographical areas in common, but the individuals included in the studies and the time they were carried out were different.

It is quite well established that Mediterranean countries adhere to Mediterranean diet better than non-Mediterranean ones, and although this adherence has been decreasing for the past decades, the difference was still substantial in the period of 2000–03 (21). However, within a particular Mediterranean country, diet may differ considerably, especially if it has a large geographical area far from the Mediterranean shore, such as that of France or Spain (22). For instance, in the 2009 Health European Survey in Spain (23), fruits and vegetables were reported to be consumed two or more times per day by 19.5% of individuals in those autonomous regions on the Mediterranean coast (Valencia, Murcia, and Cataluña), while the same consumption frequency was only reported by 9.9% of individuals living in autonomous regions on the Bay of Biscay (Galicia, Asturias, Cantabria, and País Vasco). Therefore, Mediterranean centers were arbitrarily defined as centers close to the Mediterranean coast (<100 Km), which are considered to consume traditional Mediterranean diet and where olive trees grow (22). Furthermore, in Spain, which was the most problematic country in which to classify centers into Mediterranean and non-Mediterranean, 100 km is a distance enough to get from the coast to the central plateau where Mediterranean culture tend to disappear.

Two investigators (LGM and JCR) collected the relevant articles, whereas the other authors independently reviewed the literature, and disagreements were solved by consensus, if necessary. MOOSE checklist was followed as best as possible in every stage of the meta-analysis (24).

Statistical analysis

Three different random-effects meta-analyses with the three aforementioned outcomes (current wheeze, current severe wheeze, and asthma ever), for all centers and stratified by Mediterranean setting were performed by means of Comprehensive Meta-Analysis (CMA) v2.2 software (Borenstein M, Hedges L, Higgins J, Rothstein H. Comprehensive Meta-analysis Version 2; Biostat, Englewood, NJ, USA, 2005).

Combined odds ratios for the whole group and for the two strata were calculated. As an index of heterogeneity, I^2 was also calculated both for the whole group of studies and for the two strata. This statistic indicates what proportion of the observed variance reflects real differences in effect size. Values of 25%, 50%, and 75% might be considered as low, moderate, and high, respectively (25). Differences between strata were assessed using the Q test for heterogeneity (26), which considers subgroups as single studies and assesses them for heterogeneity, by testing the dispersion of single studies about the summary effect. As a sensitivity test, an automated one-pass analysis (i.e., leaving one of the studies out and re-analyzing the data without it until all studies had been out once) was carried out. Additionally, and in order to know to what extent adjustment for BMI might have affected the results, a subgroup comparison of those studies adjusted for this factor with those non-adjusted was carried out by means of the Q test previously described.

Results

Selection of studies

A total of 55 studies were retrieved electronically using the search strategy previously indicated. Only seven of them were eligible for inclusion in the analysis, and 48 were rejected due to the following reasons: abstract published afterward as a full paper ($n = 1$); population study only including asthmatics and assessing asthma control ($n = 2$); lung function as the only outcome without information about the prevalence of symptoms of asthma ($n = 1$); editorial or comment ($n = 4$); effect of Mediterranean diet assessed prenatally ($n = 2$); review ($n = 18$); not specifically assessing Mediterranean diet (but specific foods or other diets) or asthma symptoms (eczema or atopy, for instance; $n = 17$); and data previously reported in a larger study which is included in the meta-analysis ($n = 3$). Additionally, one further study that met the inclusion criteria was found manually, published as a congress abstract (Fig. 1). No extra publication which might have been eligible was found by cross-referencing. The characteristics of the eight studies included (6, 8–11, 27–29) are shown in Table 1. Five studies were performed exclusively in Mediterranean regions (6, 8, 27–29); two studies included centers both in Mediterranean and non-Mediterranean regions (10, 11); and one was performed only in a non-Mediterranean center (9). Those studies not included and the reasons why they were excluded are listed in web Table 1.

Meta-analyses for 'current wheeze', 'severe current wheeze', and 'asthma ever'

A negative significant association between the highest tertile (as compared with the lowest) of Mediterranean diet consumption with lower occurrence of 'current wheeze' was found (OR: 0.85; 95% CI 0.75–0.98; $p = 0.02$; Fig. 2). However, the result seemed mainly driven by the Mediterranean centers (OR: 0.79; 95% CI 0.66–0.94; $p = 0.009$; Fig. 2), although the difference with the non-Mediterranean centers (OR: 0.91; 95% CI 0.78–1.05; $p = 0.184$) was not statistically significant ($Q = 1.38$; $p = 0.241$).

With respect to 'severe current wheeze', the results were similar, the association being statistically significant for Mediterranean centers (OR: 0.66; 95% CI 0.48–0.90; $p = 0.008$) but not so for non-Mediterranean centers (OR: 0.99; 95% CI 0.79–1.25; $p = 0.95$). The overall combined OR was not statistically significant (OR: 0.82; 95% CI 0.55–1.22; $p = 0.330$), and the difference between the two groups (Mediterranean vs. non-Mediterranean centers) was statistically significant (Q : 4.33; $p = 0.037$; Fig. 3).

In contrast with those results, a lower prevalence of 'asthma ever' was significantly associated with the highest tertile of Mediterranean diet in non-Mediterranean centers (OR: 0.86; 95% CI 0.75–0.98; $p = 0.027$). The result for the Mediterranean centers had a very similar value and was in the same direction although it did not reach full statistical significance (OR: 0.86; 95% CI 0.74–1.01; $p = 0.063$). However, there was no statistical difference between the two strata of centers Mediterranean vs. non-Mediterranean ($Q = 0.001$; $p = 0.980$), and considering all centers together, Mediterranean diet was significantly associated with a lower prevalence of 'asthma ever' (OR: 0.86; 95% CI 0.78–0.95; $p = 0.004$; Fig. 4).

Sensitivity analyses using the one-pass analysis showed that results were quite consistent and independent of any particular study (Table S2). Similarly, adjusting for BMI did not seem to modify the overall summary effect for any of the outcome variables (Table S3).

Discussion

The results of the present meta-analysis show that adherence to Mediterranean diet during childhood is a protective factor for 'current wheeze', and 'asthma ever' but not for 'severe current wheeze' when considering all studies together. However, there seems to be an effect of the geographical area where the children were recruited: Mediterranean centers tended to have a protective effect from the diet on all conditions, while in non-Mediterranean centers, there was only an inverse association with 'asthma ever' but not to the other two conditions. Those results come from the limited number of studies published and fulfilling eligibility criteria which were retrieved after searching the main medical databases, abstracts from congresses and cross-references. Although limited in number ($n = 8$), two of the studies included a very numerous population of children (20,106 and 13,441, respectively) coming from very different centers and by design not being subject to publication bias, therefore allowing to have quite robust information.

One of the most important environmental changes worldwide in the past decades has been diet patterns. Regarding diet, Black and Sharpe (30) postulated that changes in dietary fat intake by increasing n-6 PUFAs and decreasing n-3 PUFAs have contributed to the increase in the prevalence of asthma worldwide: incrementing the ratio of dietary n-6/n-3 PUFA might cause the production of higher levels of prostaglandin (PG) E₂. PGE₂ suppresses T-helper (Th)1 differentiation (reduces IFN- γ secretion) and promotes Th2 phenotype, which is associated with asthma and atopic diseases, by increasing IgE isotype switching. On the other hand, Seaton et al. (31) postulated that diets low in antioxidants may have

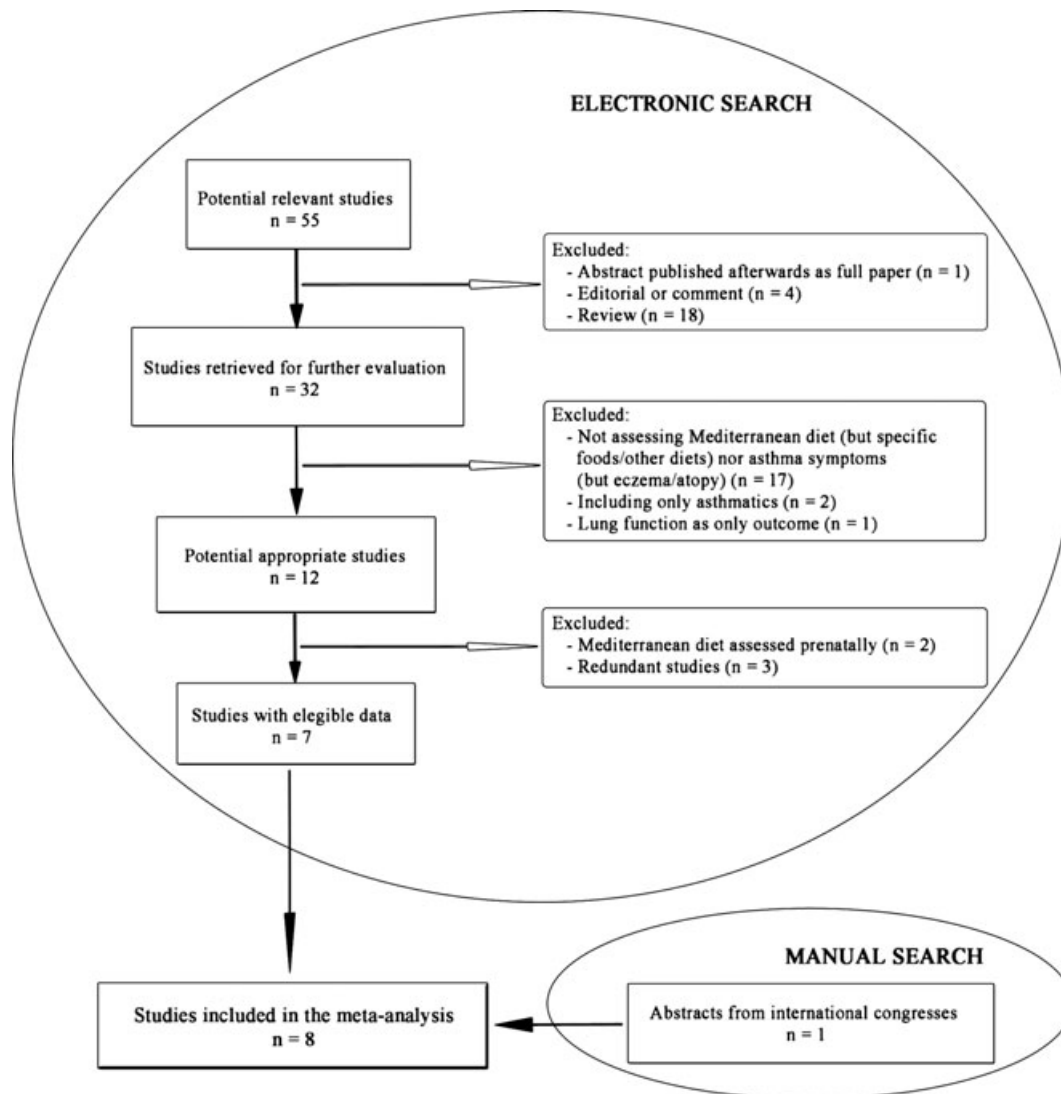


Figure 1 Process of study selection.

increased the susceptibility to develop asthma. The proposed mechanism involves the decline of lung antioxidant defences, resulting in increased oxidant-induced airway damage.

There has been considerable new information from recent studies as to how individual nutrients or foods may be associated with asthma. Several of those studies have reported on the beneficial effect of single foods rich in antioxidants or n-3 PUFA, such as flavonoids (32); citrus/kiwi fruit (33); whole milk, apples, and pears (34); vegetables, tomatoes, and fruit (35, 36); nuts (8); and oily fish (37) on asthma or wheeze. Conversely, a meta-analysis of primary prevention of asthma with n-3 and n-6 PUFA failed to show a beneficial effect on asthma and other allergic diseases (38). However, the included studies were performed in selected populations, mainly of high-risk individuals, and not in the general one; furthermore, none of those studies were performed in the Mediterranean area. Furthermore, the meta-analysis could only include four studies

using n-3 PUFA and two using n-6 PUFA as interventions, with a limited number of individuals, thus making small effects difficult to detect.

At the same time, other studies have described a deleterious effect of foods related to dietary fat composition such as margarine and butter (35, 39, 40) or fast food (10, 41) or fish (42) contradicting previous studies (37), although the difference between oily and whitefish might be important. A recent meta-analysis summarized many of those studies related to dietary antioxidants intake and concluded that increased consumption of zinc, vitamins A, D, and E, and also of fruits and vegetables is associated with lower prevalence of asthma and/or wheeze in children and adolescents (15). However, those studies fail to account for the interactions between nutrients, and they do not take into consideration that some nutrients are correlated between them (43). As our normal eating behavior is to follow certain diet patterns that contain

Table 1 Characteristics of the studies included in the meta-analyses

Study	Year(s) performed	Age group (years)	n	Study type	Outcome 1 (Prevalence %)	Outcome 2 (Prevalence %)	Outcome 3 (Prevalence %)	Covariates	Mediterranean diet score
Garcia-Marcos et al. (10)	2001–03	6–7	20106	Cross-sectional	CW (10.3)	AE (13.1)	CSW (2.3)	Gender, BMI, current smoker mother, siblings, exercise	Mean $\pm$ SD: 13.2 $\pm$ 1.9 Range: 4–20*
Sanchez-Solis et al. (29)	2005	6–8	1174	Cross-sectional	CW (13.3)	AE (14.4)	CSW (9.4)	Gender, percent body fat, maternal asthma, indoor humidity, current smoker mother	Mean $\pm$ SD: 24.7 $\pm$ 3.8 Range: 12–36†
Chatzi et al. (8)	2001	7–18	690	Cross-sectional	CW (4.6)	AE (16.8)	NA	Age, gender, BMI, parental asthma, older siblings	$\leq$ 3: 27.9% 4–5: 43.8% 6–10: 28.3%‡
Chatzi et al. (28)	1997–2004	6.5	460	Cross-sectional	CW (13.2)	NA	NA	Gender, BMI, parental asthma, maternal social class and education, total energy intake	$\leq$ 3: 9.3% 4–5: 53.7% 6–10: 37.0%‡
Castro-Rodriguez et al. (27)	2004–05	3–4	1757	Cross-sectional	CW (20.1)	AE (10.2)	CSW (7.2)	Gender, BMI, current smoker mother, siblings, exercise	Mean $\pm$ SD: 24.9 $\pm$ 3.7 Range: 14–36†
De Batlle et al. (9)	2004	6–7	1476	Cross-sectional	CW (25.0)	AE (12.0)	NA	Gender, maternal education, exercise, current tobacco smoking at home, maternal asthma, maternal rhinitis	$\leq$ 3: 44.3% 4: 27.7% 5–8: 28.0%§
Nagel et al. (11)	1995–2005	8–12	13441	Cross-sectional	CW (10.4)	AE (9.2)	CSW (3.8)	Age, gender, current tobacco smoking at home, parental atopy, siblings, exercise	Mean $\pm$ SD: 8.5 $\pm$ 2.0 Range: 0–16*
Anvaniti et al. (6)	2005–06	10–12	700	Cross-sectional	NA	AE (23.7)	NA	Age, sex, BMI, energy intake and physical activity status	$\leq$ 3: 30.4% 4–7: 59.0% 8–12: 10.6%¶

CW, current wheeze; AE, asthma ever; CSW, current severe wheeze; NA, not available.

*Modified from Psaltopoulou (17) (min-max score: 0–20).

†Modified from Psaltopoulou (17) (min-max score: 0–36).

‡Modified from KIDMED (19).

§Adapted from Trichopoulou (18).

¶KIDMED (19).

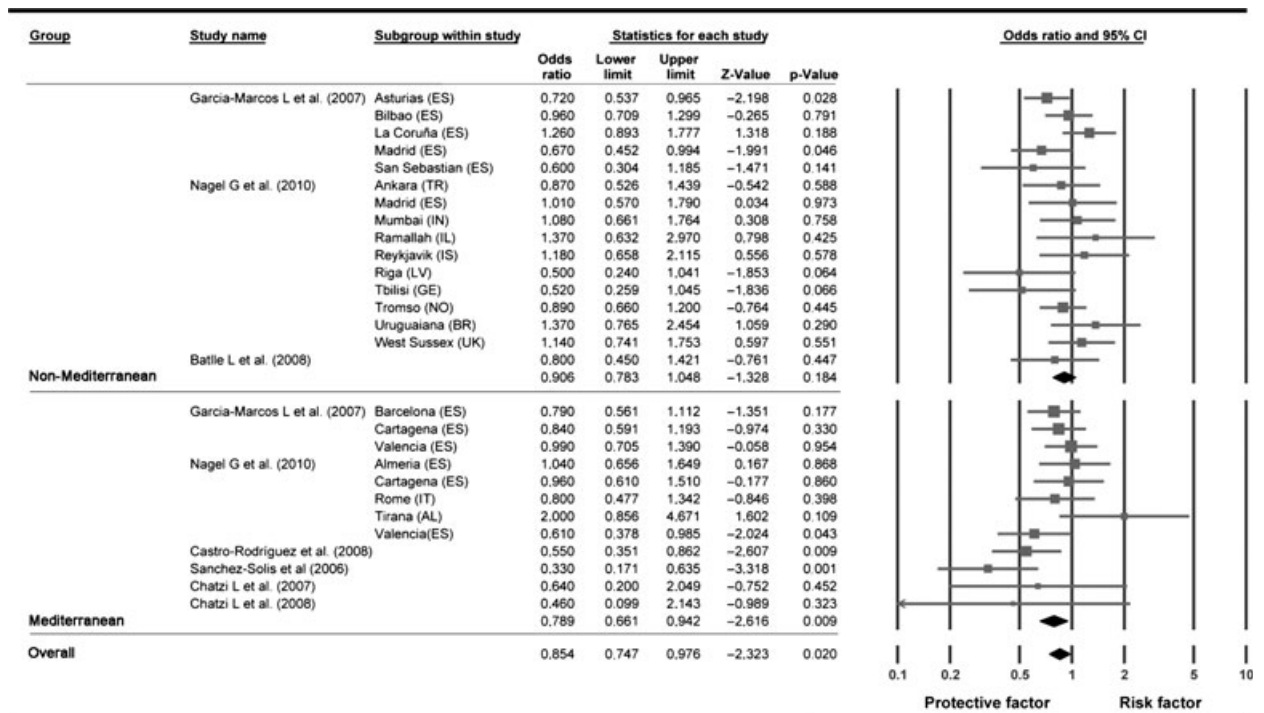


Figure 2 Summary plot of studies including 'current wheeze' as outcome. I^2 : Non-Mediterranean centers 26.5%; Mediterranean centers 43.6%; total 35.4%. Q between groups 1.38; $p = 0.24$.

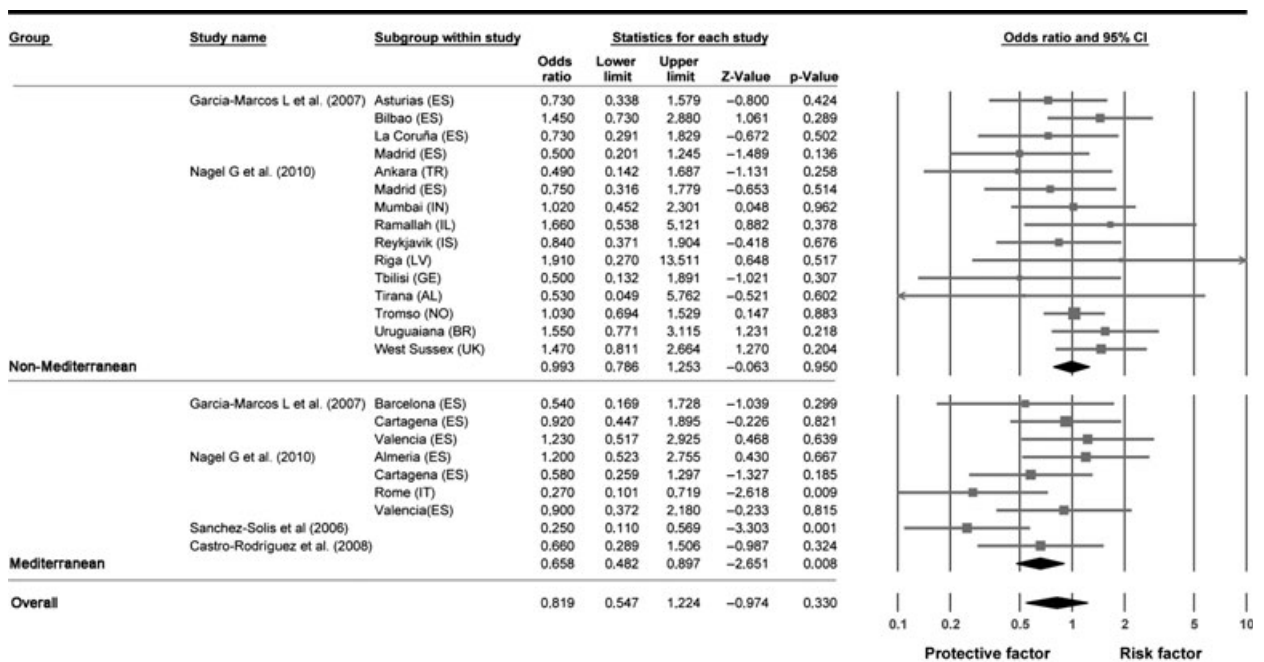


Figure 3 Summary plot of studies including 'current severe wheeze' as outcome. I^2 : Non-Mediterranean centers 0%; Mediterranean centers 42.9%; total 27.2%. Q between groups 4.33; $p = 0.037$.

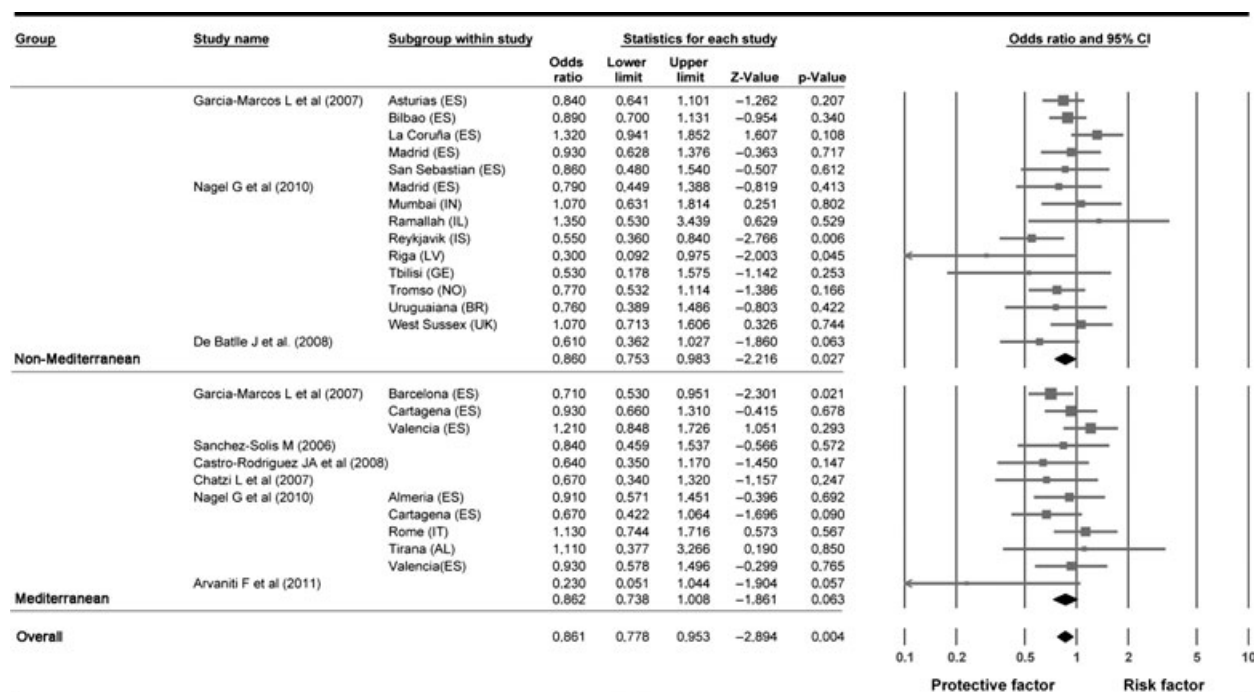


Figure 4 Summary plot of studies including 'asthma ever' as outcome. I^2 : Non-Mediterranean centers 27.7%; Mediterranean centers 14.7%; total 19.4%. Q between groups 0.001; $p = 0.98$

many specific foods, our attention should probably better be on those patterns or diets.

Mediterranean diet is rich in both antioxidants and cis-monounsaturated fatty acids. Moreover, among its components, cereals (particularly wholegrain) are rich in vitamin D, phenolic acids, and phytic acid; and fruits, vegetables, and legumes are rich in vitamin C, E, carotenoids, selenium, and flavonoids (5). Therefore, it may be reasonable to assume that a higher adherence to Mediterranean diet might have some protective effects on asthma in childhood. This diet might affect asthma development through its ability to counteract oxidative stress (44).

The present meta-analysis also offers some evidence that Mediterranean diet is protective only in the Mediterranean area. There is no straightforward explanation for this finding. However, the difference in protection seems only applicable for symptoms but not for 'asthma' labeling. To what extent the different diagnostic criteria in the different studies, or centers within studies, might be responsible for this discrepancy, is difficult to say. Moreover, 'asthma' labeling might reflect not only current wheeze due to current asthma but also a past diagnosis of wheeze in the early years, which is a different condition from asthma in school years. This possible misclassification might also account for the discrepancy.

Apart from this potential classification error, which may be increased due to the diverse age groups included in the meta-analyses, the present study has several important limitations that should be considered. Firstly, it is a meta-analysis, and thus, the inherent limitations of the individual studies included

(cross-sectional and observational) might be amplified. Specifically, heterogeneity is probably increased by the use of different scoring methods of measuring adherence to the Mediterranean diet. The way the different scoring systems were dealt with in the different meta-analyses was the main issue to be agreed upon by the authors. It was thought that using tertiles of the different scores and comparing the highest with the lowest was the best possible way to minimize the aforementioned heterogeneity. As those studies are cross-sectional, no causal relationship between Mediterranean diet and asthma can be drawn; but although no causal relationship can be derived, any association found – in either direction – could be an interesting starting point for new and better controlled studies on this issue. Secondly, not every study was controlled for exactly the same covariates. Thirdly, Mediterranean diet was measured according to different scores, although using the highest vs. the lowest tertile instead of a different approach such as using the median as a cutoff point, probably minimized the effect of the different scoring systems across studies. To end, factors such as exposure to the sun and vitamin D levels (45, 46), which may be related to asthma prevalence, were not controlled for in the meta-analyzed studies. On the other hand, we cannot rule out publication bias. However, there is some evidence that clinical trials not funded by the industry are less affected to this bias than funded ones (47), and thus, it is quite possible that epidemiological studies usually non-funded by industry (as it may be the case with studies leading with the association between diet and asthma) are even less subject to publication bias. Furthermore,

a major strength in this respect is the availability of two multicenter studies, where the selection of the numerous centers was independent of the research question and outcome.

In summary, the present meta-analysis shows a clear trend to an inverse association between adherence to the Mediterranean diet and the occurrence of asthma as defined by symptoms or diagnosis in childhood. With respect to current symptoms and current severe symptoms, the association was mainly driven by the results coming from Mediterranean

populations. The results warrant future and better controlled studies, which establish the apparently protective effect of Mediterranean diet on asthma prevalence as well as to what extent this protection may vary in different geographical areas.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Studies not included in the meta-analyses and reasons for exclusion.

Table S2. Highest and lowest summary effect sizes (odds

ratio) obtained with one-pass sensitivity analysis in each of the meta-analyses.

Table S3. Comparison of the summary effect size (odds ratio) of those studies adjusting and not adjusting for BMI according to *Q* test for heterogeneity.

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Gonzalez Barcala FJ et al. (46), Grigoropoulou D et al. (47), Kosti et al. (48)	Data previously reported in a wider study which is included in the meta-analysis

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Web table 2. Highest and lowest summary effect sizes (odds ratio) obtained with one-pass sensitivity analysis in each of the meta-analyses.

	Current wheeze		Current severe wheeze		Asthma ever	
	Highest	Lowest	Highest	Lowest	Highest	Lowest
	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)
Non-Mediterranean	0.93 (0.79-1.04)	0.87 (0.77-0.99)	1.05 (0.85-1.29)	0.96 (0.77-1.91)	0.89 (0.79-1.01)	0.83 (0.74-0.93)
Mediterranean	0.82 (0.67-0.99)	0.76 (0.61-0.94)	0.75 (0.54-1.04)	0.60 (0.40-0.89)	0.91 (0.77-1.06)	0.82 (0.71-0.95)
Overall	0.88 (0.79-0.97)	0.84 (0.75-0.94)	0.92 (0.78-1.09)	0.81 (0.66-0.99)	0.87 (0.79-0.95)	0.86 (0.77-0.79)

Web table 3. Comparison of the summary effect size (odds ratio) of those studies adjusting and not adjusting for BMI according to Q test for heterogeneity.

	Adjusted for BMI	Non-adjusted for BMI		
	(95% CI)	(95% CI)	Q	p-value
Current wheeze	0.814 (0.764-0.963)	0.895 (0.765-1.046)	0.653	0.419
Current severe wheeze	0.833 (0.585-1.186)	0.845 (0.652-1.094)	0.004	0.950
Asthma ever	0.897 (0.784-1.027)	0.822 (0.710-0.951)	0.750	0.386

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Web table 2. Highest and lowest summary effect sizes (odds ratio) obtained with one-pass sensitivity analysis in each of the meta-analyses.~~Summary of point estimate variation (OR) for one-pass sensitivity analysis in each of the overall and stratified meta-analyses.~~

	Current wheeze		Current severe wheeze		Asthma ever	
	Highest (95%CI)	Lowest (95%CI)	Highest (95%CI)	Lowest (95%CI)	Highest (95%CI)	Lowest (95%CI)
Non-Mediterranean	0.93 (0.79-1.04)	0.87 (0.77-0.99)	1.05 (0.85-1.29)	0.96 (0.77-1.91)	0.89 (0.79-1.01)	0.83 (0.74-0.93)
Mediterranean	0.82 (0.67-0.99)	0.76 (0.61-0.94)	0.75 (0.54-1.04)	0.60 (0.40-0.89)	0.91 (0.77-1.06)	0.82 (0.71-0.95)
Overall	0.88 (0.79-0.97)	0.84 (0.75-0.94)	0.92 (0.78-1.09)	0.81 (0.66-0.99)	0.87 (0.79-0.95)	0.86 (0.77-0.79)

Web table 3. Comparison of the summary effect size (odds ratio) of those studies adjusting and not adjusting for BMI according to Q test for heterogeneity.

	Adjusted for BMI	Non-adjusted for BMI		
	(95% CI)	(95% CI)	Q	p-value
Current wheeze	0.814 (0.764-0.963)	0.895 (0.765-1.046)	0.653	0.419
Current severe wheeze	0.833 (0.585-1.186)	0.845 (0.652-1.094)	0.004	0.950
Asthma ever	0.897 (0.784-1.027)	0.822 (0.710-0.951)	0.750	0.386

