

REVIEW

Mediterranean diet during pregnancy and childhood for asthma in children: A systematic review and meta-analysis of observational studies

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Abstract

Objectives: To evaluate the relationship between high adherence to the Mediterranean diet in pregnancy and childhood and the risk of asthma and wheeze in children.

Methods: We conducted searches of PubMed, EMBASE, and Cochrane Central Register of Controlled Trials from inception to 30 October 2018. Observational studies providing risk estimates and corresponding confidence intervals on the association of high adherence to the Mediterranean diet in pregnancy or childhood and the risk of asthma or wheeze in childhood were included. The methodological quality of all included studies was assessed. Summary odds ratios (OR) were calculated using a random-effects model.

Results: Eighteen observational studies were included in this review. All studies were of moderate to high quality. The pooled data suggested high adherence to the Mediterranean diet during pregnancy was associated with a reduced incidence of wheeze in the first 12 months (OR, 0.92; 95% confidence interval [CI], 0.88–0.95; $P < 0.001$), and there was an inverse association between the Mediterranean diet during childhood and the incidence of wheeze in the history (OR, 0.51; 95% CI, 0.37–0.70; $P = 0.001$) and current wheeze (OR, 0.97; 95% CI, 0.95–0.99; $P = 0.013$). However, there was no significant association between high adherence of the Mediterranean diet in pregnancy and childhood and any of the other meta-analysis end points including diagnosed asthma.

Conclusion: High adherence to the Mediterranean diet during pregnancy and childhood may have short-term effects on wheeze in children in early life. However, these findings should be interpreted with caution owing to the heterogeneity of the studies.

KEYWORDS

asthma, children, Mediterranean diet, meta-analysis, wheeze

1 | INTRODUCTION

Asthma is a serious global health problem affecting all age groups. The incidence of asthma and wheeze has risen dramatically over

recent decades, which imposes an unacceptable burden on health-care systems and society.^{1–3} It has been suggested that changes in diet in the population, for example, change in the ratio of n-6/n-3 fatty acids, contribute to the increasing incidence of asthma.^{4,5} In

recent years, special attention was paid to the Mediterranean diet, which refers to a high intake of vegetables, fruits, cereals, bread, legumes, olives, and olive oil; a low to moderate intake of dairy, poultry, some fish, nuts, and seeds; a low intake of meat and sweets; and a regular intake of wine with meals.⁶ This diet is rich in monounsaturated fatty acids with a balanced ratio of n-3/n-6 essential fatty acids and high amounts of antioxidants, such as vitamins E and C, resveratrol, polyphenols, selenium, glutathione.^{6,7}

Published reviews discussing the effects of the Mediterranean diet on the primary prevention of asthma have been conducted.⁸⁻¹² But they were only qualitative summaries^{8,9,11,12} or meta-analysis¹⁰ including a small number of research. The only meta-analysis merely assessed the association between the Mediterranean diet in childhood and asthma/wheeze in the child, while the relationship between Mediterranean diet during pregnancy and asthma/wheeze in the child was not explored. Also, the lack of quality assessment is the main limitation that may influence the judgment of readers. The analysis showed that high adherence of Mediterranean diet in childhood was associated with a lower incidence of "asthma ever" and "current wheeze," which was inconsistent with the results of some studies published recently.^{13,14} In addition, early nutrient exposure in pregnancy was recently proved to influence early immune development and potentially prevent asthma and wheeze.¹⁵ But the relationship between adherence to the Mediterranean diet in pregnancy and asthma or wheeze in childhood has not been well established.

Considering the factors above and in view of the fact that more studies have emerged lately, we reviewed current evidence and performed a systematic review and meta-analysis to separately explore the relationship of high adherence to the Mediterranean diet in pregnancy and in childhood to the risk of asthma/wheeze in children. This systematic review and meta-analysis would provide new clue on the relationship between the Mediterranean diet and pediatric asthma and wheeze.

2 | METHODS

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The protocol was registered with the PROSPERO International Prospective Register of Systematic Reviews (CRD42018116739).

2.1 | Search strategy

Two investigators (YZ and JLL) independently searched the following databases from inception to 30 October 2018: PubMed (1966 to October 2018), EMBASE (1974 to October 2018), Cochrane Central Register of Controlled Trials (CENTRAL, through October, 2018), without any restriction. Search strategies were used as *Mediterranean AND (asthma OR asthmatic OR wheeze OR wheezing) AND (offspring OR infants OR neonates OR newborns OR toddlers OR child OR children OR*

adolescents OR pediatric). The reference lists of included studies and pertinent reviews were reviewed for supplementing the electronic search.

2.2 | Study selection

All observational studies (cohort, nested case-control, case-control, and cross-sectional studies) were eligible for inclusion if they evaluated the association of high adherence to the Mediterranean diet in pregnancy or childhood with the risk of asthma or wheeze in childhood. Conference abstracts were not included in this study in view of the fact that the results may change before formally published. On the basis of prespecified inclusion criteria, all of the studies identified were reviewed independently by two investigators (YZ and WLF). Any discrepancies were resolved by discussion.

2.3 | Outcomes

We evaluated the association of high adherence to the Mediterranean diet in pregnancy to the risk of asthma, wheeze in the first 12 months, wheeze in the history, current wheeze and atopic wheeze in childhood.

We also evaluated the association of high adherence to the Mediterranean diet in childhood to the risk of asthma, severe asthma, wheeze in the history, current wheeze, atopic wheeze, exercise-induced asthma or wheeze in childhood.

Asthma was defined according to a clinician diagnosis, parent report of symptoms, or parent report of a physician's diagnosis. Severe asthma was defined when there were greater than equal to 4 asthma attacks or when sleep was disturbed ≥ 1 nights/week or when there had been an episode of speech limitation. Wheeze in the first 12 months was defined as wheeze occurred in the first 12 months after birth. Wheeze in history was defined as wheeze occurred in history. Current wheeze was defined as wheeze occurred in the last 12 months. Atopic wheeze was defined as wheeze during the last 12 months with a positive skin prick test. Exercise-induced asthma or wheeze occurred in the last 12 months during or after exercise.

2.4 | Data extraction

Study characteristics were extracted independently by two reviewers (SL and CHG) using a self-designed data extraction sheet. Data were extracted including name of the first author, year of publication, location, study design, age of children participants, sample size, exposure assessing methods and main outcomes. We contacted each first author or corresponding author of included studies, asking for the data we needed. A discussion was held upon the differences until an agreement was reached between two reviewers.

2.5 | Assessment of quality

Two reviewers (YZ and JL) independently assessed the methodological quality of all included studies. An 11-item checklist which was

recommended by the Agency for Healthcare Research and Quality was used for assessing the quality of cross-sectional studies.¹⁶ An item would be scored "0" if the answer was "No" or "Unclear," if the answer was "Yes," the item scored "1." A total score of 0 to 3 was assessed as low quality; 4 to 7 as moderate quality and 8 to 11 as high quality. The quality of cohort studies and case-control studies was assessed using the Newcastle-Ottawa Scale.¹⁷ This scale uses a star system to evaluate the quality of studies on the basis of three perspectives: the selection of study cohort, the comparability of groups, and the ascertainment of either the exposure or outcome. A maximum of nine stars could be assigned to each study. A study with six or more stars was regarded to be of high quality.

2.6 | Statistical analysis

We analyzed the data using three or four levels of adherence and compared the lowest with the highest. We pooled the risk estimate from each study using a random-effects model because included studies varied markedly in terms of the methods, exposures and reported outcome measures. Odds ratio (OR) with 95% confidence interval (CI) was used to assess the effects of high adherence to the Mediterranean diet on the incidence of childhood asthma or wheeze. We used I^2 statistic to assess the statistical heterogeneity within studies. A percentage of less than 50% ($I^2 \leq 50$) indicates a low heterogeneity.¹⁸ Sensitivity analysis was conducted by repeating meta-analysis with a fixed-effects model to determine the stability of summary risk estimates. We did not test publication bias with the formal statistical tests, because some data were from the same study. Data synthesis and analysis were performed with STATA 12.0 (StataCorp., College Station, Texas). $P < 0.05$ was considered statistically significant unless otherwise specified.

3 | RESULTS

3.1 | Search results

Detailed information was shown in Figure 1. Nine hundred sixteen records were obtained from electronic searching. Seven hundred twenty-three records remained after 193 duplicate records were removed. Six hundred ninety-one studies were removed after reading titles and abstracts by two independent reviewers, resulting in 32 studies which needed be read in full-text. Fourteen studies were excluded. No study was included in manual retrieval. Eighteen observational studies were included in the qualitative analysis in this study.^{13,14,19-34} To assess the association between high adherence to the Mediterranean diet in pregnancy and wheeze in the first 12 months in the child, children at the age of 1.5 years in one study¹⁴ were from the population in another included study.¹⁹ To obtain complete data on the relationship between the Mediterranean diet during pregnancy and wheeze in the first 12 months in childhood, we extracted relevant data from one of the two studies.¹⁹ Consequently, 5 of the 18 studies,^{19,21,23-25} explored the relationship between high adherence of Mediterranean diet in pregnancy and prevalence of

asthma/wheeze; 11 studies^{13,14,26-34} assessed the effects of the Mediterranean diet in childhood on risk of asthma/wheeze; while two studies researched on the effects of Mediterranean diet in both pregnant and childhood period.^{20,22} Consequently, 16 studies^{14,19-24,26-34} were included in the meta-analysis, while two studies^{13,25} were only included in the qualitative description because of the lack of sufficient data.

3.2 | Characteristics of included studies

Detailed information was shown in Tables 1 and 2. Eighteen observational studies published in 2005-2017 were included in this systematic review and meta-analysis. Studies were conducted in countries including Turkey, Spain, Greece, Peru, Mexico, USA, and etc. Included children were aged from 0 to 14 years old. The sample size ranged from 208 to 50 004. 9488 mother-child pairs were enrolled to assess the relationship between pregnant adherence to the Mediterranean diet and childhood asthma/wheeze, while 102 627 children were enrolled to assess the relationship between childhood adherence to the Mediterranean diet and asthma/wheeze in later life. The measurement of adherence to the Mediterranean dietary pattern in pregnancy and childhood was different among studies. Four studies used the Mediterranean diet score developed by Trichopoulou et al^{21-23,34}; 10 studies used the Mediterranean diet score developed by Psaltopoulou et al^{13,14,19,24,25,28,30-33}; 4 studies used the KIDMED index developed by Serra-Majem et al^{20,26,27,29}. Outcomes of "asthma," "wheeze in the first 12 months," "wheeze in the history," "current wheeze," "atopic wheeze" occurred in children whose mothers were adhered to the Mediterranean diet in pregnant period and "asthma," "severe asthma," "wheeze in the history," "current wheeze," "atopic wheeze," and "exercise-induced wheeze" occurred in children who adhered to the Mediterranean diet in childhood were reported.

3.3 | Methodological quality assessment

All of the included studies were assessed for methodological quality. The quality of 12 cross-sectional studies^{13,19,22,24-32} was assessed in terms of the checklist which was recommended by the Agency for Healthcare Research and Quality, 11 of which were considered as moderate quality and one³² as high quality. The methodological quality of five cohort studies^{14,20,21,23,34} and one case-control study³³ was assessed according to the Newcastle-Ottawa Scale, all of which were considered as high quality. The quality score of each study was presented in Table S-1.

3.4 | Outcomes

3.4.1 | High adherence to the Mediterranean diet in pregnancy

Asthma

Two studies reported the association between high adherence to the Mediterranean diet during pregnancy and asthma in the

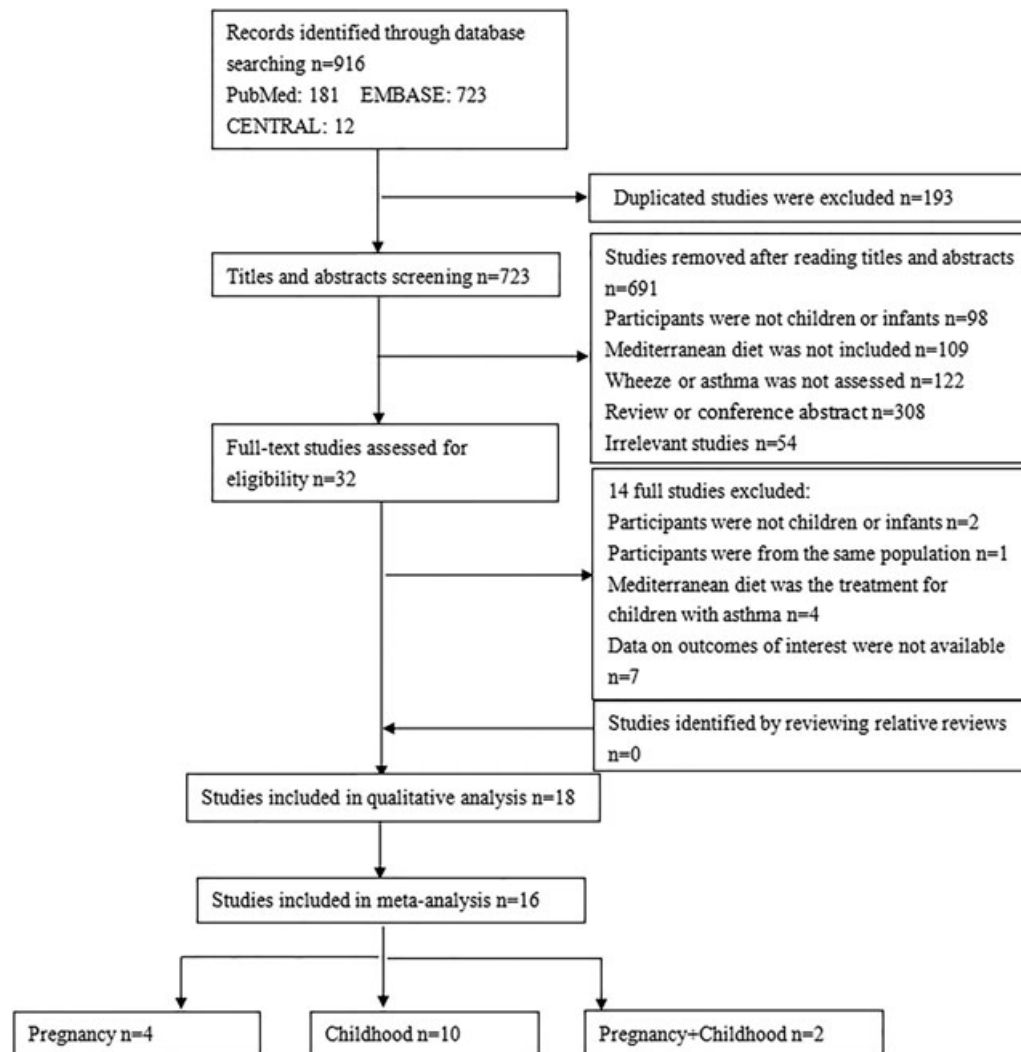


FIGURE 1 The flow diagram of identifying relevant studies

offspring.^{22,23} The pooled data suggested high adherence to the Mediterranean diet during pregnancy was not associated with the risk of asthma in the offspring (OR, 1.01; 95% CI, 0.94-1.09; $P = 0.78$) with insignificant heterogeneity ($I^2 = 0\%$).

Wheeze

Four studies reported the association between high adherence to the Mediterranean diet during pregnancy and wheeze in the first 12 months in the offspring.^{19,21,24,25} One study²⁵ suggested no association was detected between higher adherence to the Mediterranean diet and wheeze in the first 12 months ($P = 0.348$), while the pooled data of three studies^{19,21,24} suggested there was an inverse association between high adherence to the Mediterranean diet during pregnancy and the risk of wheeze in the first 12 months (OR, 0.92; 95% CI, 0.88-0.95, $P = 0.000$) with insignificant heterogeneity ($I^2 = 0\%$). Three studies reported on current wheeze in the offspring.^{20,22,23} The pooled data suggested that high adherence to the Mediterranean diet during pregnancy was not associated with the risk of current wheeze (OR, 0.76; 95% CI, 0.45-1.29; $P = 0.3$) with

significant heterogeneity ($I^2 = 77.6\%$). One study²⁰ suggested that there was an inverse association between high adherence to the Mediterranean diet during pregnancy and the risk of atopic wheeze of the offspring (OR, 0.34; 95% CI, 0.12-0.97). One study suggested there was no association between the Mediterranean diet and wheeze in the history in children²² (Figure 2).

3.4.2 | High adherence to the Mediterranean diet in childhood

Asthma

Eight studies reported the association between high adherence to the Mediterranean diet in childhood and asthma.^{13,22,26,27,31-34} The pooled data of seven studies^{22,26,27,31-34} suggested there was no association between high adherence to the Mediterranean diet during childhood and the risk of asthma in children (OR, 0.87; 95% CI, 0.72-1.04; $P = 0.121$) with significant heterogeneity ($I^2 = 71.7\%$). One study also suggested there was no association between Mediterranean diet and pediatric asthma ($P = 0.85$).¹³ Two studies reported on severe

TABLE 1 The characteristics of studies exploring the relationship between high adherence to the Mediterranean diet in pregnancy and asthma/wheeze in childhood

Study	Location	Study design	Age	Sample size	Exposure	Exposure assessment	Outcomes	Adjusted confounders
Castro-Rodriguez ¹⁹	Spain	Cross-sectional	16.6 ± 2.5 mo	1409	Mediterranean diet FFQ (number of item unreported)	Questionnaire with MD score based on Psaltopoulou et al	Wheeze in the first 12 mo (OR, 0.96; 95% CI, 0.8, 1.1)	Sex, exclusive breastfeeding, day care attendance, eczema, maternal asthma, smoking during pregnancy, siblings, mould stains on household wall, preterm birth, olive oil for cooking or dressing salads during pregnancy
Chatzi ²⁰	Spain	Cohort	6.5 y	460	Mediterranean diet 96-item FFQ	Questionnaire with KIDMED score	Current wheeze (OR, 0.23; 95% CI, 0.09, 0.60) Atopic wheeze (OR, 0.34; 95% CI, 0.12, 0.97) at an average follow-up of 6.5 y	Sex, maternal and paternal asthma, maternal social class and education, BMI and total energy intake
Chatzi ²¹	Spain, Greece	Cohort	13.6 ± 1.4 mo	2516	Mediterranean diet 100-item FFQ	Questionnaire with MD score based on Trichopoulou et al	Wheeze in the first 12 mo (OR, 0.97; 95% CI, 0.77, 1.24) at an average follow-up of 12 mo	Maternal age, education, maternal history of asthma, smoking during pregnancy, parity, duration of breastfeeding, child's age at assessment, child's sex
De Batlle ²²	Mexico	Cross-sectional	6–7 y	1476	Mediterranean diet 70-item FFQ	Questionnaire with KIDMED score	Asthma (OR, 1.03; 95% CI, 0.67, 1.56) Current wheeze (OR, 1.02; 95% CI, 0.65, 1.60)	Sex, maternal education, physical exercise, current tobacco smoking at home, maternal asthma, and maternal rhinitis
Lange ²³	United States	Cohort	3 y	1376	Mediterranean diet 166-item FFQ	Questionnaire with MD score based on Trichopoulou et al	Asthma (OR, 1.01; 95% CI, 0.94, 1.09) Current wheeze (OR, 0.98; 95% CI, 0.89, 1.08) at an average follow-up of 3 y	Child's sex, maternal race, maternal education level, household income, maternal and paternal history of asthma, presence of children less than 12 y of age at home, maternal prepregnancy BMI, breast-feeding duration, and passive smoke exposure
Pellegrini-Belinchon ²⁴	Spain	Cross-sectional	1.5 y	1164	Mediterranean diet FFQ unreported	Questionnaire with MD score based on Psaltopoulou et al	Wheeze in the first 12 mo (OR, 0.91; 95% CI, 0.87, 0.95)	Not adjusted
Zallo ²⁵	Europe and Latin America	Cross-sectional	12.11 ± 0.57 mo	1087	Mediterranean diet FFQ (number of item unreported)	Questionnaire with MD score based on Psaltopoulou et al	Wheeze in the first 12 mo (P = 0.372)	Age, sex, breastfeeding, mother education and parental smoking taking as reference no consumption

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

TABLE 2 The characteristics of studies exploring the relationship between high adherence to Mediterranean diet in childhood and asthma/wheeze in childhood

Study	Location	Study design	Age	Sample size	Exposure	Exposure assessment	Outcomes	Adjusted confounders
Akay ¹³	Turkey	Cross-sectional	13-14 y	9991	Mediterranean diet FFQ (number of item unreported)	Questionnaire with MD score based on Psaltopoulou et al	Asthma ($P = 0.85$)	Not adjusted
Castro-Rodriguez ¹⁴	Spain	Cohort	4 y	1000	Mediterranean diet FFQ unreported	Questionnaire with MD score based on Psaltopoulou et al	Current wheeze (OR, 0.78; 95% CI, 0.49, 1.25) at a follow-up of about 3 y	Unreported
Chatzi ²⁰	Spain	Cohort	6.5 y	460	Mediterranean diet 96-item FFQ	Questionnaire with adjusted KIDMED score	Current wheeze (OR, 0.46; 95% CI, 0.10, 2.17). Atopic wheeze (OR, 0.64; 95% CI, 0.10, 4.06) at an average follow-up of 6.5 y	Sex, maternal and paternal asthma, maternal social class and education, BMI and total energy intake
De Batlle ²²	Mexico	Cross-sectional	6-7 y	1476	Mediterranean diet 70-item FFQ	Questionnaire with MD score based on Trichopoulou et al	Asthma (OR, 0.61; 95% CI, 0.36, 1.02) Wheeze in the history (OR, 0.52; 95% CI, 0.35, 0.78) Current wheeze (OR, 0.80; 95% CI, 0.45, 1.42)	Sex, maternal education, exercise, current environmental tobacco smoke at home, maternal asthma and rhinitis
Antonogeorgos ²⁶	Greece	Cross-sectional	10-12 y	1125	Mediterranean diet FFQ (number of item unreported)	Questionnaire with KIDMED score	Asthma: rural children (OR, 0.29; 95% CI, 0.09, 0.96); urban children (OR, 0.15; 95% CI, 0.05, 0.41)	Age, gender, and parental history of atopy
Arvaniti ²⁷	Greece	Cross-sectional	10-12 y	700	Mediterranean diet 63-item FFQ	Questionnaire with KIDMED score	Asthma (OR, 0.22; 95% CI, 0.05, 0.90) Wheeze in the history (OR, 0.31; 95% CI, 0.13, 0.72) Exercise-induced wheeze (OR, 0.05 95% CI, 0.00, 0.91)	Age, sex, BMI, physical activity status, energy intake
Castro-Rodriguez ²⁸	Spain	Cross-sectional	4.08 ± 0.8 y	1784	Mediterranean diet FFQ unreported	Questionnaire with MD score based on Psaltopoulou et al	Current wheeze (OR, 0.54; 95% CI, 0.33, 0.88)	Age, birth weight, livestock during pregnancy, cesarean, antibiotic and acetaminophen consumption during the previous 12 mo, rhinoconjunctivitis, dermatitis, paternal and maternal asthma, maternal age and education level, current paternal and maternal smoking, vigorous physical activity, and cats at home in the last 12 mo.
Chatzi ²⁹	Greece	Cross-sectional	7-18 y	690	Mediterranean diet 58-item FFQ	Questionnaire with KIDMED score	Wheeze in the history (OR, 0.67; 95% CI, 0.34, 1.32) Current wheeze (OR, 0.64; 95% CI, 0.20, 2.05) Atopic wheeze (OR, 0.53; 95% CI, 0.16 to 1.80)	Age, sex, BMI, parental asthma, number of older siblings

(Continues)

TABLE 2 (Continued)

Study	Location	Study design	Age	Sample size	Exposure	Exposure assessment	Outcomes	Adjusted confounders
García-Marcos ³⁰	Spain	Cross-sectional	6-7 y	20106	Mediterranean diet 15-item FFQ	Questionnaire with MD score based on Psaltopoulou et al	Girls: Current wheeze (OR, 0.97; 95% CI, 0.92, 1.01) Severe asthma (OR, 0.90; 95% CI, 0.82, 0.98) Boys: current wheeze (OR, 0.98; 95% CI, 0.95, 1.04) Severe asthma (OR, 0.98; 95% CI, 0.91, 1.06)	Sex, older and younger siblings, BMI, maternal smoking and level of exercise
Gonzalez-Barcala ³¹	Spain	Cross-sectional	6-7 and 13-14 y	14700	Mediterranean diet FFQ unreported	Questionnaire with MD score based on Psaltopoulou et al	6-7 y old: Girls: asthma (OR, 1.04; 95% CI, 0.84, 1.30) Severe asthma (OR, 1.52; 95% CI, 0.79, 2.94) Current wheeze (OR, 1.03; 95% CI, 0.74, 1.44) Exercise-induced asthma (OR, 1.02; 95% CI, 0.61, 1.71) Boys: Asthma (OR, 1.12; 95% CI, 0.91, 1.38) Severe asthma (OR, 1.18; 95% CI, 0.75, 1.88) Current wheeze (OR, 0.94; 95% CI, 0.71, 1.23) Exercise-induced asthma (OR, 1.21; 95% CI, 0.82, 1.78) 13-14 y old: Girls: asthma (OR, 1.26; 95% CI, 0.96, 1.65) Severe asthma (OR, 1.09; 95% CI, 0.67, 1.77). Current wheeze (OR, 1.28; 95% CI, 0.92, 1.77). Exercise-induced asthma (OR, 1.07 95% CI, 0.80, 1.42) Boys: asthma (OR, 0.84; 95% CI, 0.61, 1.15) Severe asthma (OR, 1.36; 95% CI, 0.77, 2.41). Current wheeze (OR, 0.88 95% CI, 0.58, 1.33). Exercise-induced asthma (OR, 1.32; 95% CI, 0.95, 1.83)	Parent smoking habits, BMI of the children and maternal education level

(Continues)

TABLE 2 (Continued)

Study	Location	Study design	Age	Sample size	Exposure	Exposure assessment	Outcomes	Adjusted confounders
Nageh ³²	20 countries	Cross-sectional	8-12 y	50004	Mediterranean diet FFQ (number of items unreported)	Questionnaires with the MD score based on Psaltopoulou et al	Asthma (OR, 0.95; 95% CI, 0.92, 0.99) Current wheeze (OR, 0.97 95%CI, 0.94, 0.99) Atopic wheeze (OR, 1.00 95% CI, 0.95, 1.04)	Age, sex, environmental tobacco smoke, parental atopy, exercise and number of siblings
Rice ³³	Peru	Case-control	9-19 y	383	Mediterranean diet 170-item FFQ	Questionnaires with the MD score based on Psaltopoulou et al	Asthma (OR, 0.55 95% 0.33, 0.92)	Age, sex, BMI category, and maternal education
Romieu ³⁴	Mexico	Cohort	6-14 y	208	Mediterranean diet 108-item FFQ	Questionnaires with the MD score based on Trichopoulou et al	Asthma (OR, 1.39; 95% CI, 0.59, 3.24) at an average follow-up of 22 wk	Sex, BMI, previous day min. temperature, corticoid use, chronological time

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

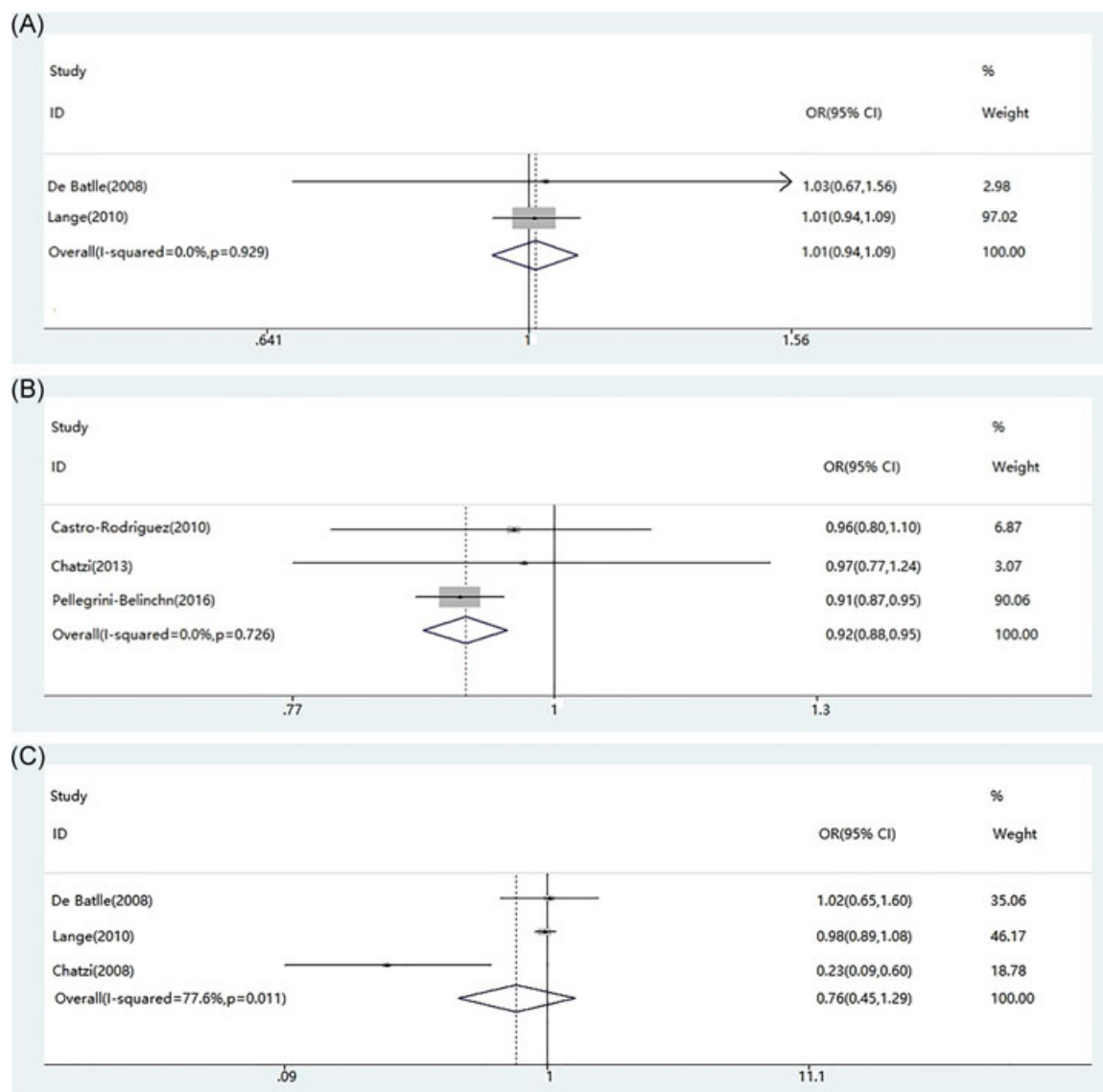


FIGURE 2 High adherence to the Mediterranean diet during pregnancy and the odds ratio and 95% confidence intervals of (A) asthma; (B) wheeze in the first 12 months; (C) current wheeze in childhood [Color figure can be viewed at wileyonlinelibrary.com]

asthma.^{30,31} The pooled data suggested that high adherence to Mediterranean diet during childhood was not associated with the risk of severe asthma (OR, 0.97; 95% CI, 0.89-1.06; $P=0.47$) with insignificant heterogeneity ($I^2=24.6\%$). One study reported on exercise-induced asthma.³¹ The pooled data suggested that high adherence to Mediterranean diet during childhood was not associated with the risk of exercise-induced asthma (OR, 1.16; 95% CI, 0.97-1.39; $P=0.10$) with insignificant heterogeneity ($I^2=0\%$) (Figure 3).

Wheeze

Three studies reported the association between high adherence to the Mediterranean diet in childhood and wheeze in history.^{22,27,29} The pooled data suggested there was an inverse association between high adherence to the Mediterranean diet during childhood and the risk of

wheeze in the history (OR, 0.51; 95% CI, 0.37-0.70; $P=0.001$) with insignificant heterogeneity ($I^2=0\%$). Eight studies reported on current wheeze.^{14,20,22,28-32} The pooled data suggested that there was an inverse association between high adherence to the Mediterranean diet during childhood and the risk of current wheeze (OR, 0.97; 95% CI, 0.95-0.99; $P=0.013$) with insignificant heterogeneity ($I^2=4.1\%$). Three studies reported on atopic wheeze.^{20,29,32} The pooled data suggested high adherence to the Mediterranean diet during childhood was not associated with the risk of atopic wheeze (OR, 1.00; 95% CI, 0.95-1.05; $P=0.96$) with insignificant heterogeneity ($I^2=0\%$). One study reported on exercise-induced wheeze.²⁷ The number of children with exercise-induced wheeze was reduced significantly in the group with high adherence to the Mediterranean diet compared with the control group (Figure 4).

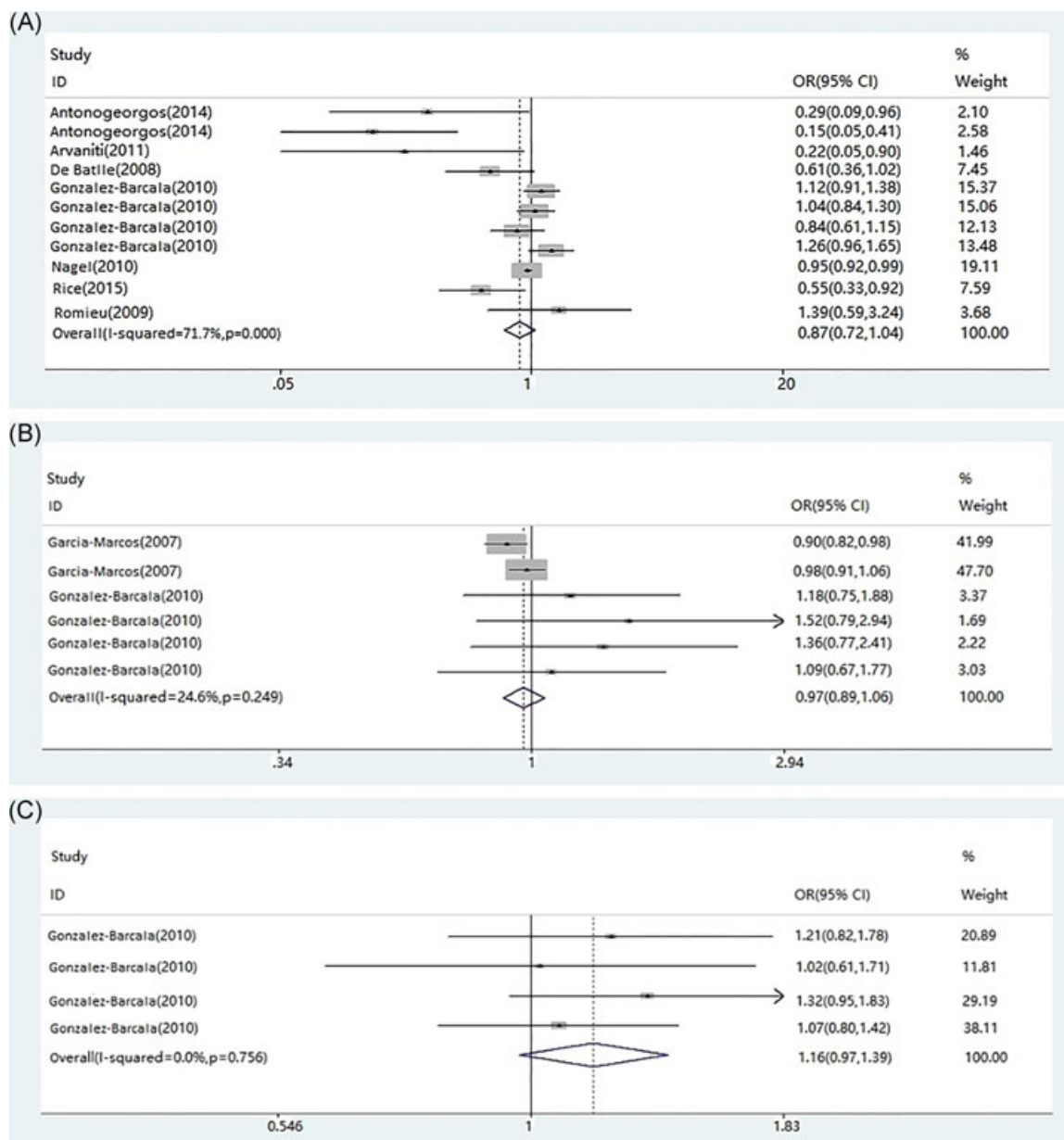


FIGURE 3 High adherence to Mediterranean diet during childhood and the odds ratio with 95% confidence intervals of (A) asthma; (B) severe asthma; (C) exercise-induced asthma in childhood [Color figure can be viewed at wileyonlinelibrary.com]

3.5 | Sensitivity analysis

Sensitivity analysis was conducted by repeating meta-analysis with a fixed-effects model to determine the stability of summary risk estimates. The association between asthma and high adherence to the Mediterranean diet during childhood was changed significantly from (OR, 0.87; 95% CI, 0.72-1.04) to (OR, 0.95; 95% CI, 0.92-0.99) when transferring random-effects to fixed-effects model. It indicated the result was unstable. The effects of high adherence to the Mediterranean diet during childhood on asthma should be focused on more in the future research to obtain the accurate evidence. Changing the pooling model for other outcomes did not change the results. Details were shown in Tables 3 and 4.

4 | DISCUSSION

Previous research indicated that the intake of a balanced ratio of n-3/n-6 fatty acids and high amounts of n-3 fatty acids could potentially reduce the risk of asthma and wheeze.³⁵ Therefore, we conducted a systematic review and meta-analysis to explore the relationship of high adherence to the Mediterranean diet during pregnancy and childhood separately to the risk of asthma/wheeze in children.

As for high adherence to the Mediterranean diet in pregnancy, one previous review indicated that adherence to the Mediterranean diet in pregnancy may have protective effects on asthma or wheeze in the first year of life in the offspring without pooled data,⁸ while our

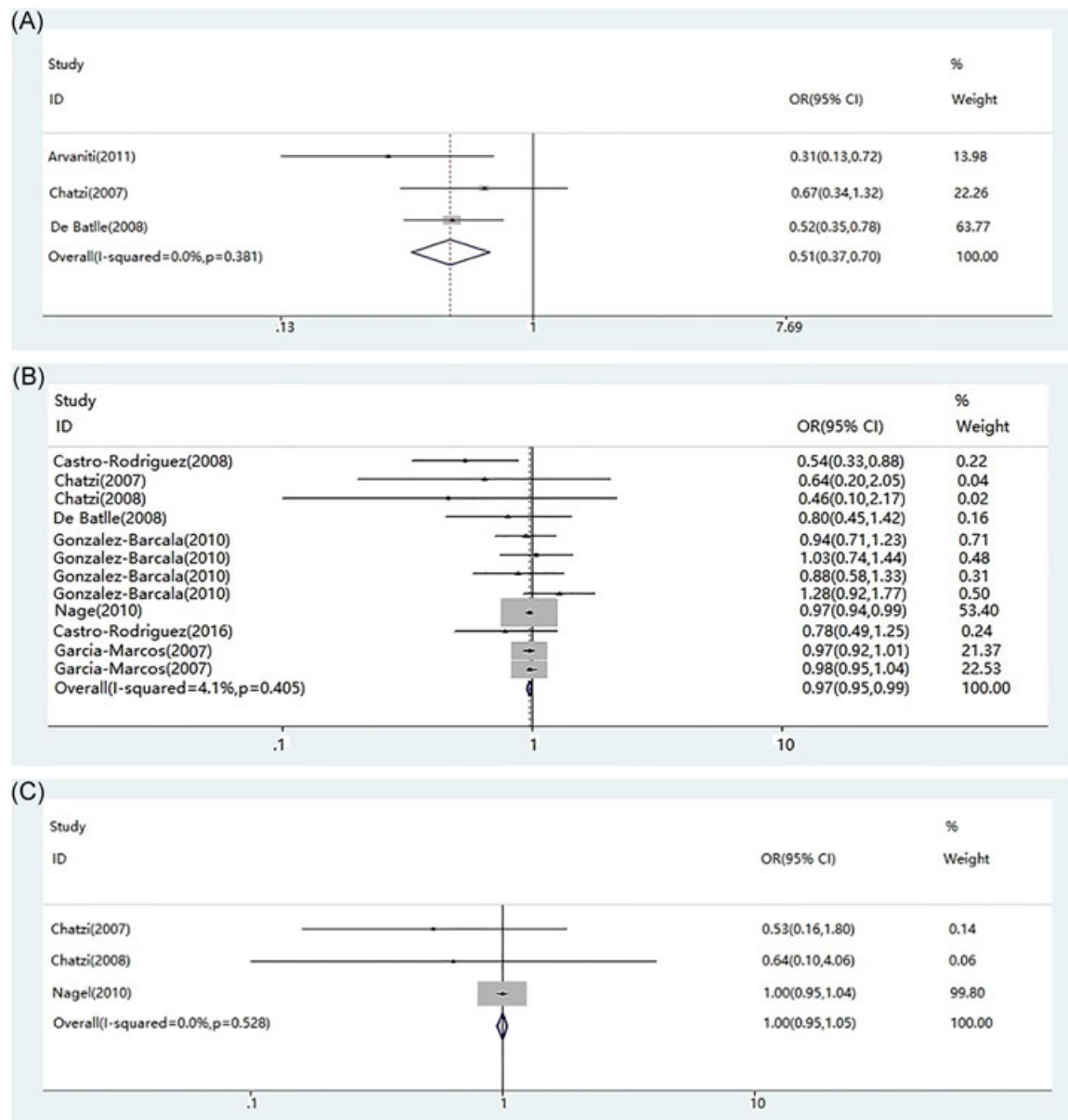


FIGURE 4 High adherence to the Mediterranean diet during childhood and the odds ratio with 95% confidence intervals of (A) wheeze in the history; (B) current wheeze; (C) atopic wheeze in childhood [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Sensitivity analysis for high adherence to the Mediterranean diet during pregnancy

	n	OR (95% CI)	I ² (%)
Asthma			
Random effects	2	1.01 (0.94, 1.09)	0
Fixed effects	2	1.01 (0.94, 1.09)	0
Wheeze in the first 12 mo			
Random effects	3	0.92 (0.88, 0.95)	0
Fixed effects	3	0.92 (0.88, 0.95)	0
Current wheeze			
Random effects	3	0.76 (0.45, 1.29)	77.6
Fixed effects	3	0.97 (0.88, 1.06)	77.6

Abbreviations: CI, confidence interval, OR, odds ratio.

meta-analysis validated the association with statistical evidence. The present meta-analysis showed that the exposure may have an inverse association with the risk of wheeze in the first 12 months in the offspring, but the inverse association with asthma, current wheeze or atopic wheeze in the child was not observed. These analyses indicated that high adherence to the Mediterranean diet during pregnancy may have short-term effects on risk of wheeze in children in early life, but not long-term effects on risk of wheeze or asthma.

As for high adherence to the Mediterranean diet in childhood, this meta-analysis indicated an inverse association between the exposure and the risk of wheeze in the history and current wheeze. However, the inverse association between the exposure and asthma, severe asthma, atopic wheeze, exercise-induced asthma or wheeze in childhood were not obtained.

TABLE 4 Sensitivity analysis for high adherence to the Mediterranean diet during childhood

	n	OR (95% CI)	I ² (%)
Asthma			
Random effects	11	0.87 (0.72, 1.04)	71.7
Fixed effects	11	0.95 (0.92, 0.99)	71.7
Severe asthma			
Random effects	6	0.97 (0.89, 1.06)	24.6
Fixed effects	6	0.96 (0.90, 1.01)	24.6
Wheeze in the history			
Random effects	3	0.51 (0.37, 0.71)	0
Fixed effects	3	0.51 (0.37, 0.71)	0
Current wheeze			
Random effects	8	0.97 (0.95, 0.99)	4.1
Fixed effects	8	0.97 (0.95, 0.99)	4.1
Exercise-induced wheeze			
Random effects	4	1.16 (0.97, 1.39)	0
Fixed effects	4	1.16 (0.97, 1.39)	0
Atopic wheeze			
Random effects	3	1.0(0.96, 1.05)	0
Fixed effects	3	1.0(0.96, 1.05)	0

Abbreviations: CI, confidence interval, OR, odds ratio.

The previous meta-analysis including eight cross-sectional studies focusing on the adherence to Mediterranean diet during childhood suggested the exposure during childhood was associated with decreased risk of asthma and current wheeze in children.¹⁰ Although we found there is a trend for high adherence to the Mediterranean diet in childhood to prevent current wheeze in later life, our meta-analysis, with more evidence, indicated that the risk of pediatric asthma was not significantly decreased. This meta-analysis also failed to prove the association of high adherence to the Mediterranean diet in childhood and reduced risk of severe asthma, atopic wheeze, exercise-induced asthma, or wheeze in childhood. Several reasons should not be ignored for these results. First, results may be influenced by many factors which caused obvious heterogeneity of studies, such as inconsistent criteria of studies. Second, the random-effects model for pooling the small number of data may lead to more conservative outcomes which might figure out insignificant outcomes.

The strength of this meta-analysis should be noted. This is the first quantitative analysis exploring the relationship between adherence to the Mediterranean diet in pregnancy and prevalence of asthma and wheeze in childhood. More evidence assessing the effects of Mediterranean diet in childhood on asthma and wheeze were also considered.^{13,14,26,31,33,34} Further, the outcome measures of this meta-analysis were classified more appropriately compared with the previous study,¹⁰ which could avoid data heterogeneity of the included studies to provide a more accurate clinical clue. Rigorous and transparent methods were used in this systematic review and meta-analysis. Quality assessment was conducted and all studies were of moderate to high quality according to corresponding scales. Sensitivity analyses were undertaken to assess the stability of results.

This meta-analysis also has limitations. Obvious heterogeneity was obtained in some results. However, subgroup analysis and meta-regression analysis were not carried out. Sensitivity analysis showed that a small number of results were not stable and the risk of publication bias cannot be excluded. Although we contacted the authors, we did not have access to the original data sets. Also, the included studies were all observational studies including cross-sectional studies, no causal relationship between the Mediterranean diet and asthma/wheeze could be assessed. However, this study would provide new clue about the relationship between the Mediterranean diet and childhood asthma/wheeze in clinical practice. Randomized controlled trials are needed to provide more accurate evidence.

5 | CONCLUSION

High adherence to the Mediterranean diet during pregnancy and childhood may have short-term effects on wheeze in children in early life as the exposure in pregnancy was associated with the reduced risk of wheeze in the offspring in the first 12 months and there is an inverse association between the exposure during childhood and the risk of wheeze in the history in children. Although there is a trend for high adherence to the Mediterranean diet in childhood to prevent current wheeze in later life, the relationship between the Mediterranean diet and pediatric asthma was not confirmed. However, these findings should be interpreted with caution owing to heterogeneity of the studies. Randomized controlled trials are needed to provide more accurate evidence.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Quality indicators for cross-sectional studies

	Akca 2014	Antonog eorgos2014	Arvaniti2011	Castro-Ro driguez2008	Chatzi 2007	De Batlle2008	Garcia-Ma rcos2007	Gonzalez-B arcala2010	Grigoropou lou2011	Nagel2010	Castro-Rod riguez2010	Pellegrini- Belinchn2016	Zallo2017
1) Define the source of information (survey, record review)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2) List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous	N	Y	Y	Y	Y	Y	N	Y	N	Y	N	Y	N

publications

3) Indicate time period used for identifying patients	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4) Indicate whether or not subjects were consecutive if not population-b ased	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

5) Indicate if
 evaluators of
 subjective
 components
 of study
 were masked U
 to other
 aspects of
 the status of
 the
 participants

U U U U U U U U U U U U U

6) Describe
 any
 assessments
 undertaken for
 quality
 assurance U
 purposes (e.g.,
 test/retest of
 primary
 outcome
 measurements

N N N N N N N N U N N N N

)

7) Explain
any patient
exclusions
from analysis

N	N	Y	N	Y	Y	Y	N	Y	Y	Y	N	Y
---	---	---	---	---	---	---	---	---	---	---	---	---

8) Describe
how
confounding
was assessed
and/or
controlled.

Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
---	---	---	---	---	---	---	---	---	---	---	---	---

9) If
applicable,
explain how
missing data
were handled

N	N	N	N	N	N	Y	N	Y	Y	Y	N	Y
---	---	---	---	---	---	---	---	---	---	---	---	---

in the analysis

10)

Summarize
patient
response
rates and
completeness
of data
collection

Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
---	---	---	---	---	---	---	---	---	---	---	---	---

11) Clarify

what
follow-up, if
any, was
expected and
the
percentage of
patients for
which
incomplete
data or

U	U	U	U	U	U	U	U	U	U	U	U	U
---	---	---	---	---	---	---	---	---	---	---	---	---

follow-up
was obtained

Total score	5	6	7	6	7	7	7	6	7	8	7	5	7
-------------	---	---	---	---	---	---	---	---	---	---	---	---	---

Quality indicators from Newcastle-Ottawa Scale for cohort studies

Study	Representativeness of the exposed cohort	Selection		Comparability		Outcome		Total scores
		Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur? Adequacy of follow-up of cohorts	
Chatzi 2008	*	*		*	**	*	*	8
Castro-Roriguez 2016	*	*		*		*	*	6
Chatzi 2013	*	*		*	**	*	*	8
Lange 2010	*	*		*	**	*	*	8
Romieu 2009	*	*			**	*	*	7

Quality indicators from Newcastle-Ottawa Scale for case-control studies

Study	Selection			Comparability		Enposure		Total scores	
	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls		Non-Response rate
Rice 2015		*	*	*	**	*	*	*	8

