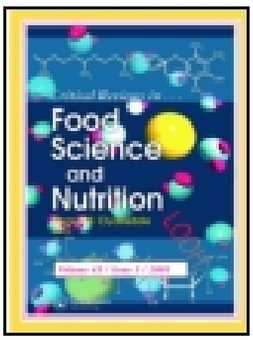

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DIET EFFECTS IN THE ASTHMA TREATMENT: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Obesity in asthmatic patients has important relationships with asthma control, pulmonary function, and quality of life. The objective of this study was to conduct a systematic review of the literature on the effect of diet on asthma management in adults. Methods: We searched PubMed, Embase, and Scopus (January 1948--October 2014) for randomized clinical trials that evaluated the effects of diet in adults with asthma. Results: Of 12,215 studies identified, 21 were included. A reduction in weight of at least 7.5% from baseline as a result of caloric restriction can be beneficial for improving disease control, quality of life, and pulmonary function in obese patients with asthma. A dietary pattern rich in foods with potential antioxidant effect had an impact in improving asthma control, but with little clinical significance. Studies involving antioxidant supplementation showed improvements in asthma control with magnesium supplementation and less decline in lung function with vitamin C supplementation. Studies of fatty acid supplementation demonstrated effects on weight loss and improvement of asthma control and lung function. Studies of supplementation with propolis and caffeine reported significant increases in FEV1. Conversely, studies of high dietary salt intake reported greater declines in lung function. Conclusions: The evidence shows that, for obese adults with asthma, the best dietary intervention seems to be caloric restriction, regardless of specific dietary components.

Keywords: nutrition, asthma, DIET, SYSTEMATIC REVIEW

INTRODUCTION

Asthma is a chronic inflammatory disease characterized by increased responsiveness of the lower airways leading to recurrent, typically reversible airflow limitation (SBPT, 2012). Obesity and asthma are multifactorial, chronic diseases that feature interactions between genetics and the environment (Beuther et al., 2007). In addition, both have a great impact on public health and are highly prevalent in many countries, especially in Brazil. Currently, the prevalence of asthma in Brazilian adults is 10% (SBPT, 2012), whereas overweight is present in 50.1% of men and 48% of women (Portal de Saúde, 2013).

In Brazil, the prevalence of asthma in obese subjects is higher than in individuals with normal weight (Beuther et al., 2007). In a cross-sectional study of 508 patients with severe asthma admitted to the Asthma Control Program Referral Center in the state of Bahia, approximately 30% of subjects were obese (Barros et al., 2011). In another cross-sectional study conducted in Pelotas, state of Rio Grande do Sul (Mehraban et al., 2003), of 119 adults with current asthma symptoms, 65 (54.6%) were overweight. In Porto Alegre, 64.8% of 176 adult asthma patients followed at a university hospital from March 2007 to November 2008 were overweight (Forte et al., 2013). In addition, a dose-dependent association between the severity of overweight and the prevalence of asthma was observed in a meta-analysis of seven prospective studies (Beuther et al., 2007).

According to the Brazilian Thoracic Society Guidelines for Asthma Management (SBPT, 2012) and the Global Initiative for Asthma (GINA, 2015), there is insufficient evidence to suggest that the management of asthma in obese patients should be different from management of patients with normal weight (BMI 18.5--24.99 kg/m^2). However, randomized clinical trials

(RCTs) have demonstrated that a 5 to 10% reduction in weight improves lung function, quality of life, and morbidity (Stenius-Aarniala et al., 2000; Scott et al., 2013). Moreover, in the last decade, evidence has mounted in support of an association between dietary components (alone or combined) and asthma, particularly as a result of foods that are sources of antioxidants, such as vitamins A, C and E, selenium, and magnesium, as well as omega-3 polyunsaturated fatty acids (Beuther et al., 2007; Castro-Rodriguez et al., 2007; Reisman et al., 2006; Nagel et al., 2005; Saint-Pierre et al., 2005). On the other hand, diets characterized by high fat and calorie intake and low in foods with potential antioxidant effects tend to increase the prevalence of the disease and lead to deterioration of symptoms (Devereux et al., 2005; Lavoie et al., 2006). However, the effect of these components (alone or combined in dietary patterns) on asthma-related outcomes is not well established, and thus warrants further investigation for better understanding and to support recommendations. In this context, the objective of the present study was to conduct a systematic review of the literature about the effects of diet on asthma management in adults.

METHODS

This systematic review was carried out using a protocol constructed according to Cochrane Collaboration recommendations (Higgins et al., 2008). The MEDLINE (via PubMed), Embase, and Scopus databases were searched for articles published from January 1948 to October 2014.

The search strategy included the following descriptors (MeSH headings and other entry terms) related to asthma and diet: *asthma OR status asthmaticus OR asthma, exercise-induced OR asthma, occupational AND micronutrients OR antioxidant micronutrient OR antioxidant vitamins OR vitamins OR antioxidants OR food OR vitamin A OR beta carotene OR pro-vitamin*

A OR vitamin C OR acid ascorbic OR vitamin E OR diet OR nutrition therapy OR diet therapy OR diet fat-restriction OR diet, Mediterranean OR diet, reducing OR diet, sodium-restricted OR diet, vegetarian OR energy intake OR caloric restriction OR dietary pattern OR alfa-tocopherol OR vitamin D OR vitamin B complex OR minerals OR antioxidant minerals OR zinc OR copper OR manganese OR chromium OR selenium OR magnesium OR sodium, dietary OR sodium chloride, dietary OR sodium glutamate OR caffeine OR lipids OR fats OR dietary fats OR fats, unsaturated OR fatty acids, omega-6 OR linoleic acid OR fatty acids, omega-3 OR fatty acid OR fatty acid, unsaturated OR oils OR fish oils.

The search strategy described above was used to identify studies in PubMed. Similar queries were employed for the other databases. There was no restriction on the language of publication. In addition, the references of articles included in this review were hand-searched for other potentially eligible studies. The proceedings of select conferences from January 2010 to November 2014 (Brazilian Pulmonology Congress, Brazilian Asthma, Tobacco, and Chronic Obstructive Pulmonary Disease Congresses, American Thoracic Society and European Respiratory Society conferences) were also reviewed.

Only RCTs conducted with adults of both sexes diagnosed with chronic asthma were included. Unpublished or ongoing studies were excluded, as were studies in which participants had other comorbidities, such as chronic obstructive pulmonary disease and chronic bronchitis, unless data were reported separately, and pregnant women. RCTs of weight loss by caloric restriction, exercise or physical activity, behavior modification or medication (either alone or in combination) and intervention trials of intake of specific dietary patterns (such as the Mediterranean or Western diet) or specific nutrient supplementation were included. The primary

outcome of interest was the degree of asthma control; secondary outcomes included quality of life, lung function, use of bronchodilators, inhaled corticosteroids, exacerbations, and changes in body weight.

Two investigators (M.L.H. and D.T.R.) independently reviewed the titles and abstracts of each article identified in the literature search. All articles that clearly did not meet the inclusion criteria were rejected. The selected articles were retrieved for full-text analysis and eligible articles were identified. In case of disagreement, the articles were reviewed aiming at a consensus position, and if no consensus could be achieved, the matter was referred to a third investigator (G.C.F.). Agreement between the researchers was investigators was calculated by the kappa coefficient ($\kappa = 0.70$).

Extraction of data from each study included in this review was also conducted independently by two investigators (M.L.H. and D.T.R.), using a standardized instrument. The following data were extracted: journal, study design, sample size, intervention time, general characteristics of participants (gender, age, body mass index), intervention characteristics, and outcomes of interest.

The methodological quality of each study included in the review was assessed against the Cochrane Collaboration criteria (Higgins et al, 2008), based on a study by Carvalho et al. (Carvalho et al, 2013). This assessment was performed by a third reviewer (G.C.F.). The questionnaire included questions related to selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and providers), detection bias (blinding of outcome assessors), attrition bias (incomplete outcomes), reporting bias (selective outcome reporting), and other biases (such as non-similarity of groups at an early stage and

sample loss >20%). This tool classifies studies as low-risk (if most of the information is classified as having a low risk of bias), uncertain-risk (if reporting is insufficient to allow assessment), or high-risk (if the proportion of high-risk information is sufficient to affect interpretation of study results). In the present review, we also include a description of evidence level according to GINA (GINA, 2014), which considers that the best evidence is provided by those studies best able to prevent the occurrence of systematic error or bias.

RESULTS

The initial search strategy yielded 12,215 articles, of which 447 were excluded as duplicates. After analysis of titles and abstracts, 11,667 records were excluded for failing to meet the inclusion criteria and 101 were selected for full-text review. Of these, 80 studies were excluded (41 that were not RCTs, 25 for including children and adolescents, 2 studies conducted in pregnant women, 7 that did not assess the outcome of interest, and 5 for other causes), resulting in a final sample of 21 studies. Our search of annals of relevant conferences did not yield any unpublished abstracts of interest (Figure 1).

The studies were organized into five sections by type of dietary intervention: “weight loss” (low-calorie diets or calorie restriction), “dietary pattern” (Mediterranean-type diet, antioxidant-rich versus antioxidant-poor), “antioxidants” (isolated supplementation or combinations of micronutrients with potential antioxidant effect), “lipids” (omega-6 and omega-3 polyunsaturated fatty acids, conjugated linoleic acid [CLA]), and “miscellaneous” (dairy, vitamin D, salt, propolis, and caffeine).

In the selected studies, the degree of disease control was assessed by the Asthma Control Questionnaire (ACQ) (Juniper et al., 1999), which measures the intensity and duration of

symptoms and use of rescue medications in the preceding 7 days. A 0.5-point or greater change in total score is considered clinically significant. Quality of life was assessed using a generic instrument (SF-36) (Espinosa et al., 2002), a specific questionnaire for asthma (Asthma Quality of Life Questionnaire - AQLQ) (Juniper et al., 2001), (0.5-point or greater change deemed significant), or a specific questionnaire for respiratory diseases (Saint George Respiratory Questionnaire - SGRQ) (4-point or greater change deemed clinically significant). In the first two questionnaires, higher scores denote better quality of life. In the SGRQ, the lower the score, the better the quality of life. Pulmonary function was measured by spirometry and results presented as forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1). Changes in body weight were presented as % mass in relation to baseline.

Given the wide heterogeneity among studies regarding the type and form of dietary interventions, as well as with regard to the assessed outcomes, we could not perform meta-analysis of the extracted data. The following sections provide additional detail on the included studies, grouped by type of intervention.

Low-calorie Diets for Weight Loss

We found three RCTs that assessed the effect of low-calorie diets for weight loss in asthma (Stenius-Aarniala et al., 2000; Scott et al., 2013; Dias-Junior et al., 2014). The main characteristics of these three studies are described in Table 1. One study was conducted in Brazil (Dias-Junior et al., 2014), one in Australia (Scott et al., 2013), and one in Finland (Stenius-Aarniala et al., 2000). The sample size ranged from 33 participants (Dias-Junior et al., 2014) to 46 participants (Scott et al., 2013), who were overweight (Scott et al., 2013) or obese (Stenius-Aarniala et al., 2000, Dias-Junior et al., 2014). The age of participants ranged from 20 to 68

years. Only one study had a similar gender distribution in the sample (Scott et al., 2013). Another was conducted mainly in women (93.3% of the sample) (Dias-Junior et al., 2014), and Stenius et al. did not report gender information (Stenius-Aarniala et al., 2000).

In all three studies, the intervention consisted of offering caloric restriction (Stenius-Aarniala et al., 2000) or a low-calorie diet (Scott et al., 2013, Dias-Junior et al., 2014), whether in isolation (Stenius-Aarniala et al., 2000) or combined with regular physical activity (Scott et al., 2013) or anti-obesity medication (Dias-Junior et al., 2014). The intervention period ranged from 8-10 weeks in weekly meetings (Stenius-Aarniala et al., 2000; Scott et al., 2013) up to 6 months with fortnightly sessions (Dias-Junior et al., 2014). Despite the short intervention period in the study of Stenius et al. (Stenius-Aarniala et al., 2000), outcomes were evaluated 1 year after the intervention.

The outcome measures were body weight, degree of asthma control (Scott et al., 2013; Dias-Junior et al., 2014), lung function (Stenius-Aarniala et al., 2000; Scott et al., 2013; Dias-Junior et al., 2014), and quality of life (Stenius-Aarniala et al., 2000; Scott et al., 2013; Dias-Junior et al., 2014). Weight loss from baseline was observed in all three studies (Stenius-Aarniala et al., 2000; Scott et al., 2013; Dias-Junior et al., 2014), ranging from approximately 7.5% to 11.3%. Clinically significant improvement in degree of disease control (ACQ score) in the low-calorie diet arm was observed in the two studies that assessed this outcome (Scott et al., 2013; Dias-Junior et al., 2014). FEV_1 (% predicted) increased approximately 7.6% (95%CI 1.5% to 13.8%) (Stenius-Aarniala et al., 2000), which reflects a clinically significant improvement in lung function in this population. Regarding quality of life, clinically significant improvement

was observed in all three studies, at approximately 0.9 points on the AQLQ (Scott et al., 2013) and 10 to 14 points on the SGRQ (Stenius-Aarniala et al., 2000, Dias-Junior et al., 2014).

Loss of at least 7.5% of initial body weight as a result of calorie restriction can be beneficial to improving disease control, quality of life, and pulmonary function in obese patients with asthma. However, the quality of the evidence is limited by the small number of RCTs with dietary intervention, small sample size, short follow-up, and heterogeneity in type of intervention (time, prescribed diet, diet alone or combined with other strategies).

Dietary Pattern

Only two RCTs evaluating the effect of specific dietary patterns of asthma in adults were found. The characteristics of these studies are shown in Table 2. One study was conducted in the United States, with 38 patients (Sexton et al., 2013), and the other in Australia, with 137 participants (Wood et al., 2012).

Both assessed dietary patterns that are rich in antioxidants; however, the U.S. study used the term "Mediterranean-type" diet, whereas the Australian study used the term "rich in antioxidants." The Mediterranean-type dietary pattern consisted of high intake of fruits, vegetables, legumes, nuts, whole grains, and olive oil; moderate to high consumption of fish oil; moderate intake of dairy products; and low intake of red meat, chicken, and omega-6 fatty acids (Sexton et al., 2013). The antioxidant-rich dietary pattern consisted of daily intake of at least five servings of vegetables and two servings of fruit with or without lycopene supplementation (from tomato extract) (Wood et al., 2012). The intervention period was 2 weeks in the Australian study (Wood et al., 2012) and 12 weeks in the U.S. study (Sexton et al., 2013).

The outcome measures were degree of asthma control (Sexton et al., 2013; Wood et al., 2012), lung function (Sexton et al., 2013; Wood et al., 2012), and quality of life (Sexton et al., 2013). A dietary pattern rich in foods with potential antioxidant effect had a positive impact on asthma control (ACQ score); however, the observed result, although statistically significant, was of little clinical significance (Wood et al., 2012). Some methodological issues may have contributed to the absence of a positive result, such as sample size, good lung function among participants (FEV_1 >60%), lack of control of daily caloric intake, and lack of monitoring of food choices. Thus, although both studies reported a healthy eating pattern and the Mediterranean diet is clearly beneficial to cardiovascular health because of its potential anti-inflammatory effect (Serra-Majem et al., 2006), there is insufficient scientific evidence to state that these eating patterns are associated with clinical improvement of asthma in adults.

Supplementation with Antioxidant Micronutrients

Seven RCTs (Nadi et al., 2012; Tecklenburg et al., 2007; Pearson et al., 2004; Fogarty et al., 2003; Fogarty et al., 2006; Kazaks et al., 2010; Shaheen et al., 2007) that evaluated the effect of supplementation with antioxidant vitamins and minerals on asthma-related outcomes were included. The characteristics of these studies are presented in Table 3. Four studies were undertaken in the UK (Pearson et al., 2004; Fogarty et al., 2003; Fogarty et al., 2006; Shaheen et al., 2007), two in the United States (Tecklenburg et al., 2007; Kazaks et al., 2010) and one in Iran (Nadi et al., 2012). The sample size ranged from eight patients (Tecklenburg et al., 2007) to 300 participants (Fogarty et al., 2003).

The interventions consisted of supplementation, alone or in combination, with vitamins C and E and the minerals magnesium and selenium. The effect of vitamin C supplementation alone

(1 to 1.5 g/day) was evaluated in four RCTs (Nadi et al., 2012; Tecklenburg et al., 2007; Fogarty et al., 2003; Fogarty et al., 2006). Another study (Pearson et al., 2004) evaluated the isolated effect of vitamin E supplementation (250 mg/day). Three studies (Fogarty et al., 2003; Fogarty et al., 2006; Kazaks et al., 2010) evaluated the effects of magnesium supplementation alone (340 to 450mg/day), and one study (Shaheen et al., 2007) evaluated the effect of 100 μg selenium supplementation. The intervention period ranged from 2 weeks (Tecklenburg et al., 2007) to 6.5 months (Kazaks et al., 2010).

The outcome measures were degree of asthma control (Fogarty et al., 2003; Kazaks et al., 2010), lung function (Nadi et al., 2012; Tecklenburg et al., 2007; Pearson et al., 2004; Fogarty et al., 2003; Kazaks et al., 2010; Shaheen et al., 2007), quality of life (Fogarty et al., 2003; Kazaks et al., 2010; Shaheen et al., 2007), and bronchodilator use (Fogarty et al., 2006). Clinical improvement in degree of asthma control (ACQ score) was observed only in one study in which magnesium supplementation was compared to placebo (Kazaks et al., 2010). Regarding pulmonary function, only one study (Tecklenburg et al., 2007) of isolated vitamin C supplementation reported a significant result, with a smaller drop in post-exercise FEV_1 compared to usual diet or placebo. The other five studies found no difference in FEV_1 after supplementation with vitamins or minerals. There was no statistically significant improvement in quality of life (AQLQ) (Fogarty et al., 2003; Kazaks et al., 2010) compared with placebo intervention. Similarly, supplementation was not associated with any significant reduction in use of bronchodilators (inhaled corticosteroids) as compared with placebo (Pearson et al., 2004; Fogarty et al., 2003; Shaheen et al., 2007).

The results of this review were inconsistent regarding supplementation with antioxidants (vitamins C and E and minerals selenium and magnesium), with five studies reporting no change. Although a systematic review with meta-analysis of observational studies has shown an association between antioxidant nutrients and asthma (Allen et al., 2009), the RCTs available to date do not support a possible beneficial effect of antioxidant supplementation.

Supplementation with Fatty Acids

Four RCTs that assessed the effect of fatty acid intake on asthma-related outcomes were included. The characteristics of these studies are shown in Table 4. One was conducted in Japan (Okamoto et al., 2000), one in the U.S. (Surette et al., 2008), one in Australia (Wood et al., 2011), and one in Canada (MacRedmond et al., 2010). The sample size ranged from 14 to 72 patients.

The study interventions were fat intake (Wood et al., 2011), conjugated linoleic acid (CLA) supplementation, perilla oil supplementation (Okamoto et al., 2000), and supplementation of gamma-linolenic acid (GLA) in combination with eicosapentaenoic acid (EPA). The intervention period ranged from 4 hours (Wood et al., 2011) to 12 weeks (MacRedmond et al., 2010).

The outcome measures were body weight (MacRedmond et al., 2010), degree of asthma control (Surette et al., 2008; Wood et al., 2011), quality of life (Mini AQLQ), (Surette et al., 2008; MacRedmond et al., 2010) and pulmonary function (FEV_1) (Okamoto et al., 2000; Wood et al., 2011; MacRedmond et al., 2010). A significant weight reduction was observed in subjects treated with CLA compared to placebo-treated patients (MacRedmond et al., 2010). Clinical improvements in degree of asthma control and quality of life were observed in only one study,

which assessed supplementation with GLA and EPA (Surette et al., 2008). Significant improvement in pulmonary function was reported in subjects who received perilla oil compared to placebo (Okamoto et al., 2000).

Although positive effects on asthma-related outcomes were demonstrated in these studies, given the small sample sizes and different types of fatty acids evaluated, a possible beneficial effect of fatty acid supplementation is not supported by the literature available to date.

Miscellaneous Interventions

Five RCTs that assessed intake or supplementation of other components were found. Due to the heterogeneity of these interventions, these studied have been grouped in a "miscellaneous" section, as we believe this potential new evidence warrants discussion. The characteristics of these studies are shown in Table 5. Two studies were conducted in the U.S. (Mickleborough et al, 2005; Castro et al., 2014), one in Australia (Woods et al., 1998), one in Egypt (Khayyal et al., 2003), and one in Israel (Kivity et al., 1990). The sample size ranged from 13 patients (Kivity et al., 1990) to 408 patients (Castro et al., 2014), all of whom were adults.

The study interventions were dairy intake (Woods et al., 1998), propolis extract (Khayyal et al., 2003), dietary salt (Mickleborough et al, 2005), vitamin D supplementation (Castro et al., 2014), and caffeine (Kivity et al., 1990). The intervention period ranged from 2 weeks (Kivity et al., 1990) to 28 weeks (Castro et al., 2014).

The evaluated outcomes were asthma exacerbations (Castro et al., 2014) and lung function at the end of the intervention (Woods et al., 1998; Khayyal et al., 2003) and after exercise (Mickleborough et al, 2005; Kivity et al., 1990). A protective effect against exacerbations was reported in patients who received vitamin D3 supplementation compared with

the placebo group (Castro et al., 2014). Regarding lung function, a significant increase in FEV_1 at the end of the intervention was reported in one study (Khayyal et al., 2003). Among studies that analyzed change in post-exercise lung function (Mickleborough et al, 2005; Kivity et al., 1990), we observed a greater decline in lung function in the group that consumed a salt-rich diet compared to those who ate low or normal amounts of salt (Mickleborough et al, 2005). A smaller decline in FEV_1 was observed in patients receiving high-dose caffeine supplementation compared to placebo recipients (Kivity et al., 1990).

In conclusion, and according to the evidence available, data on the effects of intake or supplementation with miscellaneous dietary components on asthma-related outcomes (frequency of exacerbations and lung function) in adults are too scarce to determine any real effect.

Methodological Quality Assessment of Studies

Our assessment of the methodological quality of the included studies is shown in Table 6. None of the included studies satisfied all areas established by the Cochrane Collaboration for methodological quality assessment. However, all studies were designed to answer a clear and focused question. Ten studies provided detailed descriptions of the method used for random sequence generation, while only seven studies described the method used for allocation concealment in detail. The methods used for participant and provider blinding were reported in 16 studies. Blinding of outcome assessors was described in 14 studies, but these did not describe all measures used for blinding. Outcomes were evaluated completely in 19 of 21 studies. Other sources of bias, such as heterogeneity across groups at baseline, were found in only one study, and sample loss greater than 20% was not reported in any of the studies.

Regarding the level of evidence, two trials provided Category A evidence (due to study design and large sample size), while 19 studies provided Category B evidence (due to the small sample size).

The limitations of this review include the short follow-up period of some included studies and the generally small sample sizes. Another limitation was the great methodological heterogeneity of the studies, which made it impossible to conduct meta-analysis. Therefore, we limited our review to a descriptive presentation of data.

The current evidence shows that, for obese adults with asthma, the best dietary intervention appears to be energy restriction, regardless of the specific dietary components or dietary pattern. Data on the intake of specific nutrients, alone or combined, are still too scarce to determine a real effect on asthma management in adults. Additional RCTs with larger sample sizes and longer follow-up should be conducted to explore the real effect of nutrients on asthma-related outcomes. The results of this review should help researchers interested in this subject develop their hypotheses, and can support the development of dietary and nutrition education programs for this population.

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Table 1 Characteristics of intervention studies of low-calorie diets in patients with asthma

Author, journal, year	Population	Design Follow-up	Intervention	Variables	Results
Dias-Junior et al. *Eur Respir J* (2014)	N = 33 93.9% women 20-68 years BMI >30kg/m²	Parallel-group RCT 6 months	1.Intervention: low caloric intake + sibutramine (10 mg/day) and orlistat (max. 120 mg/day) 2. Usual diet	BMI Asthma control (ACQ) Quality of life (St George's Questionnaire) Pulmonary function (FEV_1)	**BMI** (P<0.001) 1. 39.68±1.31 to 36.71±1.37 2. 37.29±1.07 to 36.85±1.06 **Asthma control** (P<0.001) 1. 3.04±0.25 to 1.64±0.19 2. 2.91±0.25 to 2.90±0.16 **Quality of life** (P = 0.011) 1. 65.12±3.02 to 45.47±4.42 2. 67.29±3.37 to 62.42±3.27 **Pulmonary function** = NS
Scott et al. *Clin Exp Allergy* (2013)	N = 46 54.3% women 22-60 years BMI 28-40 kg/m²	Parallel-group RCT 10 weeks	1. Reduced calorie diet 2. Usual diet + exercise intervention (1 h/week) 3. Reduced-calorie diet + exercise intervention (1 h/week)	Weight (kg) Pulmonary function (FEV_1) Asthma control (ACQ) Quality of life (AQLQ)	**Weight loss** (P = 0.001) 1. -8.5 ± 4.2% 2. -1.8 ± 2.6% 3. -8.3 ± 4.9% **Pulmonary function** = NS **Asthma control** (P<0.001) 1. -0.6 ± 0.5 2. unchanged 3. -0.5 ± 0.7 **Quality of life** = NS
Stenius-Aarniala et al. *BMJ* (2000)	N = 38 % women = ND 18-60 years BMI 30-42 kg/m²	Parallel-group RCT 1 year	1. Very-low-energy diet (8 weeks) 2. Control: usual diet	Weight (kg) Pulmonary function (FEV_1) Quality of life (St George's Questionnaire)	**Weight loss** (P = ND) 1. -11.3% 2. +2.2% **Pulmonary function** (P = 0.02) 1. 4.9 (-0.5 - 10.3) 2. -2.7 (-5.9 - 0.5) **Quality of life** (P = 0.02) Very-low-energy diet vs. usual diet = -10 (-18 to -1)

BMI = body mass index, RCT = randomized clinical trial, ACQ = Asthma Control Questionnaire, FVC = forced vital capacity, FEV_1 = forced expiratory volume in first second, AQLQ = Asthma Quality of Life Questionnaire, ND = not described, NS = not significant.

Table 2 Characteristics of intervention studies of specific dietary patterns in patients with asthma

Author, journal, year	Population	Design Follow-up	Intervention	Variables	Results
Sexton et al. *J Asthma* (2013)	N = 38 48.6% women 25-52 years BMI 18.5-29.9 kg/m²	Parallel-group RCT 12 weeks	1. Mediterranean diet, high-intervention 2.. Mediterranean diet, low-intervention 3. Control: usual diet	Asthma control (ACQ) Pulmonary function (FEV_1) Quality of life (AQLQ)	There was no statistically significant difference in the analyzed variables
Wood et al. *Am J Clin Nutr* (2012)	N = 137 55.5% women > 18 years BMI 30.5 ± 7.2 kg/m²	Parallel-group RCT 14 days	1. Low-antioxidant diet 2. Low-antioxidant diet + lycopene 45 mg 3. High-antioxidant diet	Asthma control (ACQ) Pulmonary function (FEV_1)	**Asthma control** (P = 0.042) 1. 0.9 (0.4-1.4) to 0.9 (0.4 -- 1.6). P>0.05 2. NS 3. 0.7 (0.4-1.4) to 0.9 (0.4 -- 1.4), P>0.05 **Pulmonary function** = NS

BMI = body mass index, RCT = randomized clinical trial, ACQ = Asthma Control Questionnaire, FVC = forced vital capacity, FEV_1 = forced expiratory volume in first second, AQLQ = Asthma Quality of Life Questionnaire, NS = not significant.

Table 3 Characteristics of intervention studies of antioxidant micronutrient supplementation in patients with asthma

Author, journal, year	Population	Design Follow-up	Intervention	Variables	Results
Vitamins					
Nadi et al. *Acta Medica Iranica* (2012)	N = 60 % women = ND 18 -- 50 years BMI 25±4.2 kg/m²	Parallel-group RCT 1 month	1. Vitamin C 1 g 2. Placebo	Pulmonary function (FEV_1)	There was no statistically significant difference in the analyzed variables
Tecklenburg et al. *Respir Med* (2007)	N = 8 75% women >18 years BMI = ND	Crossover RCT 2 weeks	1. Vitamin C 1.5 g/day 2. Usual diet 3. Placebo	Pulmonary function (FEV_1)	**Pulmonary function** (P<0.05) 1. -6.4±2.4%[a] 2. -14.3±1.6%[b] 3. -12.9±2.4%[b]
Pearson et al. *Thorax* (2004)	N = 72 54% women 18-60 years	Parallel-group RCT 6 weeks	1. Vitamin E 250 mg 2. Placebo	Pulmonary function (FEV_1) Bronchodilator use	There was no statistically significant difference in the analyzed variables
Minerals					
Fogarty et al. *Clin Exp Allergy* (2003)	N = 300 53% women 18-60 years BMI = ND	Parallel-group RCT 16 weeks	1. Vitamin C 1 g/day 2. Magnesium 450 mg/day 3. Placebo	Pulmonary function (FEV_1) Quality of life (SF-36) Bronchodilator use	There was no statistically significant difference in the analyzed variables
Fogarty et al. *Respir Med* (2006)	N = 92 % women = ND 18-60 years BMI = ND	Parallel-group RCT 26 weeks	1. Vitamin C 1 g/day 2. Magnesium 450 mg/day 3. Placebo	Bronchodilator use	There was no statistically significant difference in the analyzed variables
Kazaks et al. *J Asthma* (2010)	N = 52 30.7% women 21-55 years BMI 28.5±1 kg/m²	Parallel-group RCT 6.5 months	1. Magnesium 340 mg/day 2. Placebo	Asthma control (ACQ) Quality of life (AQLQ) Pulmonary function (FEV_1)	**Asthma control** (P = ND) 1. -0.3 (0.6 to 0.1), P = 0.05 2. 0.1 (-0.3 to 0.5), P = 0.68 **Quality of life = NS** **Pulmonary function** = NS
Shaheen et al. *Thorax* (2007)	N = 197 62.4% women 18-54 years BMI = ND	Parallel-group RCT 24 weeks	1. Selenium 100 µg/day 2. Placebo	Pulmonary function (FEV_1) Bronchodilator use	There was no statistically significant difference in the analyzed variables

BMI = body mass index, RCT = randomized clinical trial, ACQ = Asthma Control Questionnaire, FVC = forced vital capacity, FEV_1 = forced expiratory volume in first second, AQLQ = Asthma Quality of Life Questionnaire, ND = not described, NS = not significant.

Table 4 Characteristics of intervention studies of fatty acids in patients with asthma

Author, journal, year	Population	Design Follow-up	Intervention	Variables	Results
Wood et al. *J Allergy Clin Immunol* (2011)	N = 72 59.7% women >18 years BMI 18-40 kg/m²	Parallel-group RCT 4 hours	1. Non-obese asthmatics: high-fat 2. Non-obese asthmatics: low-fat 3. Obese asthmatics: high fat 4. Healthy control: high-fat	Asthma control (ACQ) Pulmonary function (FEV_1)	There was no statistically significant difference in the analyzed variables
MacRedmond et al. *Clin Exp Allergy* (2010)	N = 26 50% women 19-40 years BMI 27.9 kg/m²	Parallel-group RCT 12 weeks	1. CLA 4.5 g/day 2. Placebo	Body mass Pulmonary function (FEV_1) Quality of life (AQLQ)	**Weight** (P = 0.002) 1. Δ -2.0±1.5 2. Δ 2.3±0.4 **Pulmonary function** = NS **Quality of life** = NS
Okamoto et al. *Intern Med* (2000)	N = 14 57.1% women 22-84 years BMI = ND	Parallel-group RCT 4 weeks	1. Perilla oil supplementation (10-20 g/day) 2. Corn oil supplementation (10-20 g/day)	Pulmonary function (FEV_1)	**Pulmonary function** (P<0.05) 1: ND 2: ND
Surette et al. *Cur Med Res Opinion* (2008)	N = 65 65% women 22-55 years BMI = ND	Parallel-group RCT 28 days	1. GLA 0.75 g + EPA 0.5 g/day 2. Placebo	Asthma control (ACQ) Quality of life (AQLQ)	**Asthma control**(P = ND) 1. 1.0±0.1, P<0.001 2. ND **Quality of life** (P = ND) 1. 1.5±0.2, P<0.001 2. ND

RCT = randomized clinical trial, ACQ = Asthma Control Questionnaire, FEV_1 = forced expiratory volume in first second, BMI = body mass index, AQLQ = Asthma Quality of Life Questionnaire, CLA = conjugated linoleic acid, GLA = gamma-linolenic acid, EPA = eicosapentaenoic acid, ND = not described, NS = not significant.

Table 5 Characteristics of studies of miscellaneous dietary interventions in patients with asthma

Author, journal, year	Population	Design Follow-up	Intervention	Variables	Results
Castro et al. *JAMA* (2014)	N = 408 % women = ND >18 years BMI 31.75 kg/m²	Parallel-group RCT 28 week	1. Vitamin D3 (100,000 IU; 4,000 IU) 2. Placebo	Exacerbation	**Exacerbations** (P = 0.05) OR: 0.63 (95CI% 0.39 to 1.01)
Mickleborough et al. *Clin Invest* (2005)	N = 24 37.5% women 24±1.8 years BMI = ND	Crossover RCT 5 weeks	1. Low-salt diet (usual diet + placebo) 2. High-salt diet (usual diet + Na: 4000 mg, Cl: 6000 mg) 3. Normal-salt diet (usual diet + Na: 1500 mg, Cl: 2250 mg)	Pulmonary function (FEV_1)	**Pulmonary function** (P<0.05) 1. -7.9% (-0.10 to 0.38)[a] 2. -27.4% (-0.35 to -1.13)[b] 3. -18.3% (-0.21 to -0.83)[c]
Khayyal et al. *Fund Clin Pharmacol* (2003)	N = 46 21.7% women 19-52 years BMI = ND	Parallel-group RCT 2 months	1. Propolis extract 2. Placebo	Pulmonary function (FEV_1)	**Pulmonary function** (P = ND) 1. + 29.5%, p<0.001 2. NS
Woods et al. *J Allergy Clin Immunol* (1998)	N = 20 65% women 35.4 years BMI 25.7 kg/m²	Crossover RCT 2 weeks	1. Intervention: 300 ml UHT skim milk + 600 mg calcium 2. Placebo: 300 ml UHT rice milk + 600 mg calcium	Pulmonary function (FEV_1)	There was no statistically significant difference in the analyzed variables
Kivity et al. *Chest* (1990)	N = 13 30% women 19-22 years BMI = ND	Parallel-group RCT 2 weeks	1. Caffeine 3.5 mg/kg 2. Caffeine 7 mg/kg 3. Placebo	Pulmonary function (FEV_1)	**Pulmonary function** Intervention 1 versus placebo = NS Intervention 2 versus placebo = P<0.05 Intervention 2: 3.61±0.17 to 3.26±0.15 Placebo: 3.23±0.18 to 2.41±0.18

RCT = randomized clinical trial, ACQ = Asthma Control Questionnaire, FEV_1 = forced expiratory volume in first second, BMI = body mass index, AQLQ = Asthma Quality of Life Questionnaire, ND = not described, NS = not significant.

Table 6 Cochrane tool for assessment of methodological quality or risk of bias

	Días-Junior et al. (2014)	Scott et al. (2013)	Stenius-Aarniala et al. (2014)	Sexton et al. (2013)	Wood et al. (2012)	Nadi et al. (2012)	Tecklenburg et al. (2007)	Pearson et al. (2004)	Fogarty et al. (2003)	Fogarty et al. (2006)	Kazaks et al. (2010)
Random sequence generation	Low risk	Low risk	Low risk	Unclear risk	Low risk	High risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk
Allocation concealment	Unclear risk	Low risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk
Blinding of participants and personnel	Low risk	Low risk	Unclear risk	High risk	High risk	High risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Blinding of outcome assessment	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	High risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Incomplete outcome data	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Selective reporting	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Other sources of bias	Low risk	Low risk	Unclear risk	Low risk	Low risk	High risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
	Shaheen et al. (2007)	Wood et al. (2011)	MacRedmond et al. (2010)	Okamoto et al. (2000)	Surette et al. (2008)	Castro et al. (2014)	Woods et al. (1998)	Khayyal et al. (2003)	Mickleborough et al. (2005)	Kivity et al. (1990)	
Random sequence generation	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk	
Allocation concealment	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk	
Blinding of participants and personnel	Low risk	High risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	
Blinding of outcome assessment	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	
Incomplete outcome data	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	
Selective reporting	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk	High risk	Unclear risk	
Other sources of bias	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	

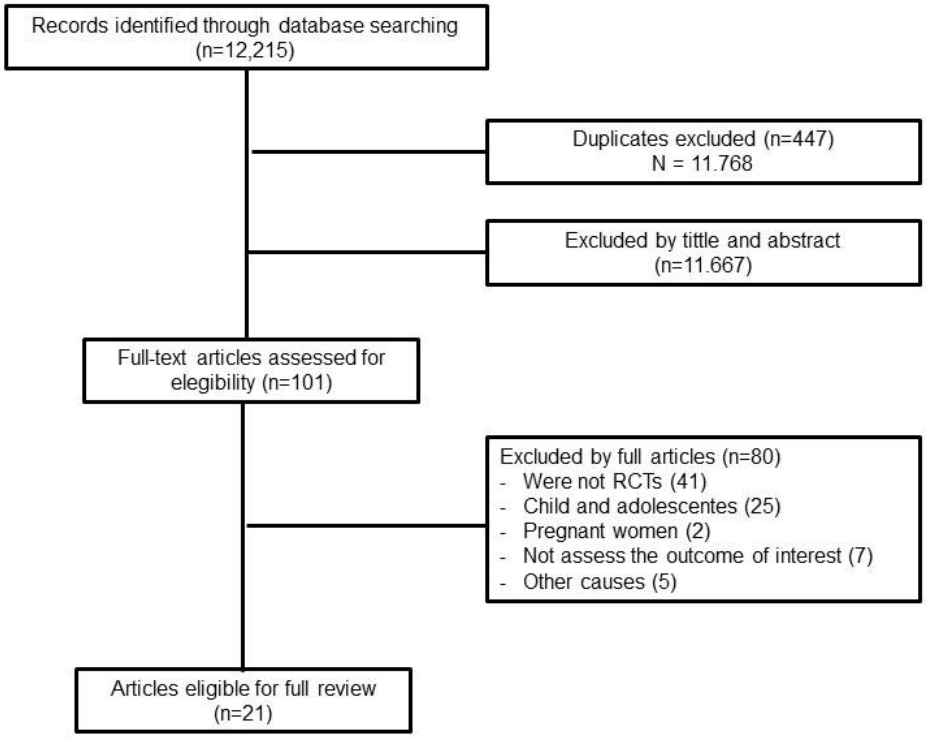

Figure 1. Study-flow diagram showing the number of studies screened, assessed for eligibility, and included in the review.