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Effect of dietary interventions on markers of type 2 inflammation in asthma: A systematic review

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A B S T R A C T

Introduction: Type 2 (T2) inflammation is a key mechanism in the pathophysiology of asthma. Diet may have immunomodulatory effects, and a role for diet in T2 inflammation has been suggested in the literature. Indeed, diet and food allergies play a role in children with atopic asthma, but less is known about diet in relation to adult asthma, which is often non-atopic.
Objective: To review the effect of dietary interventions on markers of T2 inflammation in adults with asthma.
Methods: The databases PubMed, Embase, Cochrane Library, and CINAHL were searched for eligible studies until December 2022. We included studies of all types of foods, nutrients, diets or supplements, either as an exposure or as an intervention, in adults and adolescents with asthma. Outcomes of interest included the T2 biomarkers FeNO, eosinophils, IL-4, IL-5, IL-13, eosinophil cationic protein and eosinophil peroxidase. The methodological quality of eligible studies was systematically evaluated, and the results were summarised according to dietary clusters.
Results: The systematic search identified studies on the dietary clusters antioxidants (n = 14), fatty acids, (n = 14), Mediterranean-style diets (n = 5), phytotherapy (n = 7), prebiotics & probiotics (n = 8), vitamin D (n = 7), and other dietary factors (n = 5). Studies within the phytotherapy and omega-3 poly-unsaturated fatty acids (PUFA) clusters showed possible improvements in T2 inflammation. Furthermore, we found little evidence for an effect of antioxidants, prebiotics & probiotics, and Mediterranean-style diets on T2 inflammation. However, heterogeneity in study protocols, methodological shortcomings and limited power of almost all studies make it difficult to fully determine the impact of different dietary approaches on T2 inflammation in asthma.
Conclusions: Overall, the current evidence does not support a specific dietary intervention to improve T2 inflammation in asthma. Interventions involving phytotherapy and omega-3 PUFA currently have the best evidence and warrant further evaluation in well-designed and adequately powered studies, while taking into account T2-high phenotypes of asthma.

1. Introduction

Asthma is a heterogeneous disease characterised by chronic airway inflammation and a history of respiratory symptoms, including recurrent episodes of dyspnoea, wheezing and cough [1]. A key mechanism in the pathophysiology of asthma is type 2 (T2) inflammation, leading to the current asthma classification of T2-high and T2-low asthma [2,3]. T2-high asthma is characterised by the cytokines IL-4, IL-5 and IL-13, which are released in the airways upon recognition of allergens and other irritants, leading to the accumulation of eosinophils, immunoglobulin E (IgE) and nitric oxide in the airways [3,4]. T2 inflammation is present in the majority of patients with difficult-to-treat or severe asthma [5,6], and can be identified by clinically available biomarkers, including eosinophils in blood or sputum, IgE in blood, and exhaled nitric oxide (FeNO) [2,5].

T2 inflammation has traditionally been associated with the atopic asthma phenotype, which often develops in childhood and drives IgE-mediated bronchoconstriction [4]. In recent decades, however, other forms of T2-high asthma have been recognised, characterised by the absence of atopy and disease onset in adulthood. This late-onset eosinophilic asthma phenotype is often severe and difficult to control [4,7],

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List of abbreviation

BALF	bronchoalveolar lavage fluid
BMI	body mass index
CINAHL	Cumulative Index to Nursing and Allied Health Literature
DASH	Dietary Approach to Stop Hypertension
DHA	docosahexaenoic acid
ECP	eosinophil cationic protein
EIB	exercise-induced bronchoconstriction
EPA	eicosapentaenoic acid
FeNO	fractional exhaled nitric oxide
IgE	immunoglobulin E
IL	interleukin
MSG	monosodium glutamate
MUFA	mono-unsaturated fatty acids
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PUFA	poly-unsaturated fatty acids
RCT	randomised controlled trial
SCFA	short-chain fatty acids
SFA	saturated fatty acids
Th cells	T-helper cells
T2	type-2

but the development of type 2-targeted biological therapy has led to new treatment options [5,6]. Still, it remains unclear what initiates T2 inflammation in patients with adult-onset onset eosinophilic inflammation [4].

Diet is increasingly recognised as a modifiable factor in lung health, as dietary metabolites play an important role in regulating immune responses [8,9]. Indeed, in-vivo studies have demonstrated potential inhibitory effects of vitamin E, flavonoids, and dietary fibre on markers of T2 inflammation [10–12]. Interestingly, food also acts as a trigger in the T2-related inflammatory disease eosinophilic esophagitis, in a non-IgE-mediated way [13]. Empiric elimination diets, such as the 6-food elimination diet (eliminating milk, eggs, soya, wheat, peanuts/tree nuts, and fish/shellfish), are commonly used as a drug-free therapy for eosinophilic esophagitis to induce clinical remission [13,14]. Atopic asthma is also often associated with food allergy, but it is unknown whether diet plays a role in T2 inflammation beyond this IgE-mediated food allergy. Although dietary interventions have been extensively studied in children with atopic asthma, less is known about diet in relation to adult asthma, which is often non-atopic. Therefore, we aimed to review the current evidence for an effect of dietary interventions on markers of T2 inflammation in adults with asthma, with a particular focus on eosinophilic inflammation.

2. Methods

2.1. Search strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15]. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO, record number CRD42021258825). After consultation with a medical information specialist, a comprehensive search of the electronic databases PubMed, Embase, Cochrane Library, and CINAHL was performed up to December 2, 2022, using medical subject headings and free text terms in the title/abstract. Search terms related to asthma, T2 inflammation and diet were combined using Boolean operators. The search was restricted to clinical and observational studies in adults and adolescents, and exclusion terms related to animals, children, and pregnancy were used, without losing studies in adults. The complete search query for each database can be found in the Supplementary Information. To ensure that all relevant studies were identified, reference lists of the included studies were manually searched for additional studies.

2.2. Eligibility criteria

Original peer-reviewed research articles and research letters were included in the review if they had the following study designs: randomised controlled trials, quasi-experimental studies, before-after studies, cohort studies, case-control studies and cross-sectional studies. Other types of publications or study designs were excluded. No language restriction was formulated.

Only studies in adults and adolescents ($\geq$12 years of age) with asthma were included. Studies evaluating the effect of the diet during pregnancy, or in infants or children ($<$12 years of age) were excluded.

Studies examining the intake of any type of food, nutrient, dietary pattern, or nutritional supplement, either as an exposure or as an intervention, were included. Studies evaluating the effects of food challenges, elimination diets, or a combination of treatments were also eligible for inclusion. Studies were excluded if the exposure was related to nutrients measured in blood, aerosol-related food particles, occupational exposure to food (e.g., bakery), or if the study was primarily concerned with food allergies or evaluated the effects of a weight-loss diet or calorie-restricted diet.

The outcome of interest was T2 inflammation as assessed by the following markers in blood, sputum, exhaled breath, bronchoalveolar lavage fluid, or bronchial biopsies: eosinophils, FeNO, IL-4, IL-5, IL-13, eosinophil cationic protein (ECP), and eosinophil peroxidase.

2.3. Study selection

After removing duplicates, the retrieved records were imported into Rayyan, a web-based program that facilitates collaboration among reviewers during the study screening process. A review team of six researchers independently assessed the relevance of studies based on title and abstract – EV screened all articles and the other five researchers each reviewed a part of the search results. Next, two researchers (EV and KJ) independently appraised all potentially eligible studies based on the full-text. This full-text screening was combined with the data-extraction and quality assessment. Disagreements were resolved by consensus and reasons for exclusion were documented at each stage.

2.4. Quality assessment

Study quality of eligible studies was assessed independently by two review authors (EV and KJ) using the standardised critical appraisal checklist developed by the American Academy of Nutrition and Dietetics [16]. The checklist combined four relevance questions about the applicability to practice and ten validity questions about scientific soundness. All studies were rated as having positive, negative, or neutral quality. Studies without strong evidence – that is a “no (not valid)” answer – to at least one of the four critical validity questions (i.e. selection of subjects, randomisation and comparability of study groups, description of intervention/exposure, and valid outcome assessment) were given a neutral rating. Studies with negative quality – that is a “no (not valid)” answer to six or more validity questions – were excluded from the review. The risk of bias assessment was presented visually for the ten validity questions. Only studies rated as positive are included in the results tables in the main paper to improve clarity given the large amount of data. The results of the studies of neutral quality are summarised in the main text and further details are provided in the tables in the Supplementary Information.

2.5. Data extraction

The following data were extracted from the included studies independently by two review authors (EV and KJ) using a standardised data extraction form, including information on: first author, publication year, country, study design, population description, method of asthma diagnosis, sample size, sex, age, BMI, intervention/exposure details, control treatment (if applicable), study duration, effect of intervention/exposure on the primary study outcome and on the outcome of interest, i.e. markers of T2 inflammation.

Because our outcome of interest was often a secondary outcome, we also reported the primary outcome of the study to assess whether a study was successful at all. The effect of the intervention/exposure on the primary outcome and the outcome of interest was reported as an increase (↑), decrease (↓) or no effect (↔) on markers of T2 inflammation, as compared to the control treatment (between-group effect), or compared to baseline if no control treatment was available (within-group effect).

Included studies were clustered according to the dietary intervention/exposure described. If a study examined multiple interventions/exposures belonging to different clusters, the study was described in each cluster. On the other hand, multiple articles that were based on the same study, were described only once. Studies were sorted by type of dietary intervention. Due to the heterogeneity of study designs, asthma definitions, dietary approaches and outcome markers, a meta-analysis was not considered appropriate. Instead, a summary figure of all studies was derived for each cluster, showing the percentage of studies that had a statistically significant positive, negative or no effect between groups on T2 inflammation. Given the exploratory and hypothesis-generating nature of this systematic review, a two-colour pattern was used when 1) a single study reported conflicting between-group results (i.e. a positive and no effect, or a negative and no effect) for multiple outcome markers, or 2) when the results were obtained from studies with a design other than an RCT (e.g. cross-sectional, before-after study). If only a significant within-group effect was reported, but the between-group effect was not significant, the study was classified as having no effect.

3. Results

The search strategy identified 4031 articles after removal of duplicates (Fig. 1). These were assessed on the basis of title and abstract, after which 199 articles were retrieved for full-text review. After full-text review, 134 articles were excluded because they did not meet the inclusion criteria and 3 articles could not be evaluated due to language barriers [17–19]. The quality assessment and data-extraction was performed for 63 studies, after which 4 studies were excluded due to negative quality [20–23]. Finally, 59 articles were included in this review, which describe 57 individual studies.

3.1. Description of studies and methodological quality

The following seven clusters were identified: antioxidants (n = 14) [24–37], fatty acids (n = 14) [27,38–51], Mediterranean-style diets (n = 5) [49,52–55], phytotherapy (i.e. herbal medicine, n = 7) [56–63], prebiotics & probiotics (i.e. non-digestible carbohydrates and health-beneficial microbiota, n = 8) [50,64–70], vitamin D (n = 7) [71–77], and other dietary factors (n = 5) [78–82]. The results for the studies in each cluster are described in Tables 1–7 for the studies with a positive quality assessment and in Tables S1–S7 in the Supplementary Information for the studies with a neutral quality assessment. Of the 57 described studies, 50 (88 %) were RCTs, five (9 %) were non-randomised intervention studies, and two (4 %) were observational cross-sectional studies. Most studies were conducted in North America (n = 22, 39 %), followed by Europe (n = 12, 20 %), Australasia (n = 11, 19 %), the Middle East (n = 6, 11 %), Asia (n = 5, 9 %) and Central America (n = 1, 2 %). The year of publication ranged from 1997 to 2022.

Overall, 26 (44 %) studies had a positive methodological quality, with the main strengths being the selection of study subjects, randomisation and comparability of study groups, clear description of intervention and outcomes, and appropriate statistical analyses (Fig. 2). The remaining 33 studies (56 %) were of neutral quality, with methodological shortcomings described by cluster below. Table S8 in the Supplementary Information shows the quality assessment for each included study.

3.2. Antioxidants

Fourteen studies investigated the effect of dietary factors with antioxidant properties, which are summarised in Table (S)1. There were eleven RCTs, of which five had a crossover design, two were before-after studies, and one was a cross-sectional study. Study duration ranged from 6 h (acute effects) to 6.5 months. T2 markers were a primary outcome in five studies, of which only two studies were adequately powered [35,37]. Six studies had a positive quality rating. The methodological shortcomings of the eight studies of neutral quality were mainly related to the randomisation and comparability of study groups, unclear handling of withdrawals, blinding, and over-interpretation of results (Fig. 3).

In two well-conducted studies from Australia in patients with stable asthma, lycopene, a potent antioxidant, did not affect FeNO or sputum eosinophils, either as a supplement or by ingestion of tomato juice [24,25]. Similarly, Wood et al. showed that an antioxidant-rich diet for 3 months did not affect FeNO or sputum eosinophils in patients with stable asthma [25]. In contrast, consumption of a pro-inflammatory meal increased sputum %eosinophils after exercise compared with an anti-inflammatory meal, suggesting that an anti-inflammatory meal may attenuate the post-exercise increase in sputum eosinophils [26]. However, a major limitation of this neutral-quality study was the self-directed, non-randomised choice of meal. Regarding individual antioxidants, in patients with mild asthma and exercise-induced bronchoconstriction (EIB), high-dose vitamin C supplementation significantly reduced FeNO compared with baseline and placebo [28], but dietary vitamin C intake was not associated with FeNO in a well-conducted cross-sectional study of 174 (un)controlled asthma patients [27]. Next, in a high-quality RCT, sputum eosinophils were significantly reduced after 2 weeks of γ-tocopherol supplementation compared with placebo [29]. RCTs of neutral quality found no effect of tocopherol supplementation on eosinophil levels in either sputum or BALF [30–32]. Finally, in a well-conducted RCT, FeNO levels did not change after intervention with polyphenols in patients with high FeNO (>400 ppb) [35] or after treatment with magnesium citrate [34]. Intervention studies with either choline or sulforaphane showed no effect on IL-4 or FeNO, IL-4 and IL-13, respectively, although these studies had methodological shortcomings [33,36,37].

Overall, five of the fourteen studies showed an improvement in markers of T2 inflammation (Fig. 4), most of which had inconsistent results with regard to the various T2 markers assessed (possible improvement). Nine studies (64 %) found no effect.

3.3. Dietary fatty acids

Table (S)2 lists the results of studies on dietary fats. We found nine articles that examined the effect of omega-3 polyunsaturated fatty acids (PUFA) [27,38–45], four on omega-6 PUFA [27,47,48,50], four on saturated fatty acids (SFA) [27,46,50,51], and one study described in two publications, on monounsaturated fatty acids (MUFA) [27,49]. Barros et al. and Wood et al. evaluated different types of fatty acids and were therefore listed multiple times [27,46]. Thirteen studies were RCT's, of which seven with a cross-over design, and two studies had a cross-sectional design. T2 markers were a primary study outcome in only two studies, one of which seemed to be adequately powered for FeNO

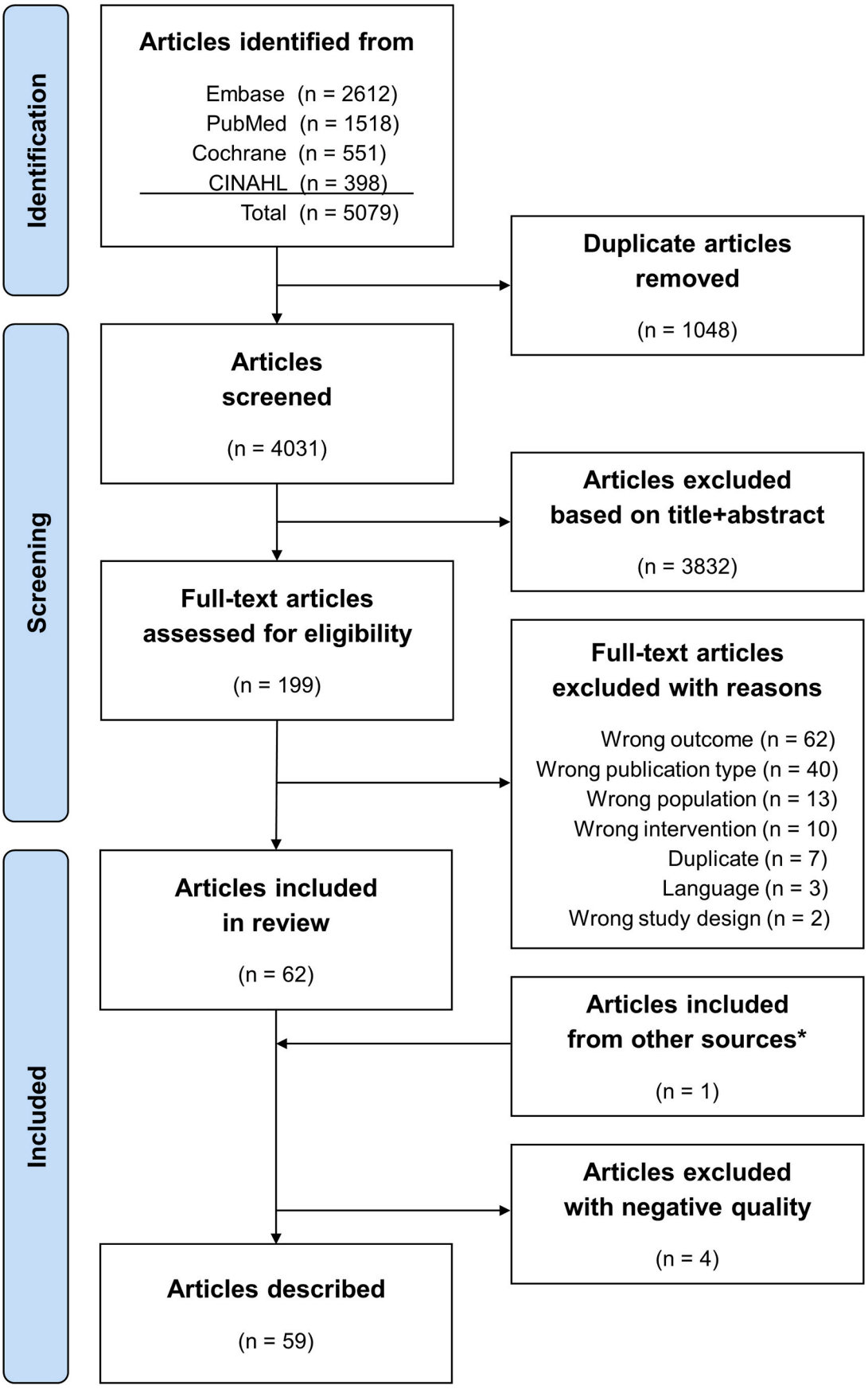

Fig. 1. PRISMA flowchart of study selection.
CINAHL, Cumulative Index to Nursing and Allied Health Literature
* From screening reference lists.

Table 1
Study characteristics and T2 inflammation outcomes for studies examining antioxidants.

Ref.	Author, year	Study design	Country	Population description	Asthma diagnosis	N	Female (%)	Age (y)	BMI (kg/m^2)	Intervention/ exposure	Control	Study duration	Result primary outcome	Result T2 inflammation	Quality
Antioxidant diets															
[24]	Wood, 2008	X-RCT	Australia	Stable asthma	Physician diagnosed, current respiratory symptoms, and AHR to hypertonic saline	22 o/w 10 with sputum	64	52	NA	Low-antioxidant diet + 1] Tomato juice 2] Tomato extract Both 45 mg/d lycopene	Low-anti oxidant diet + placebo (soybean oil)	1 w	↓ Neutrophils (S) ↔ Asthma control, pulmonary function	1 & 2] ↔ FeNO,[a] Eos (S)[a]	+
[25]	Wood, 2012	RCT	Australia	Stable asthma	Physician diagnosed, current respiratory symptoms, and AHR to hypertonic saline	137	55	57	31	1] Low-antioxidant diet + 45 mg/d lycopene 2] High-antioxidant diet + placebo	Low-anti oxidant diet + placebo (soybean oil)	3 mo	↔ Neutrophils (S)	1 & 2] ↔ FeNO,[a] Eos (S)[a]	+
Vitamins and minerals															
[27]	Barros, 2011	CS	Portugal	(Un) controlled asthma	Physician diagnosed	174	82	40	27	Consumption of 1] Carotene; 2] Retinol; 3] Vit E; 4] Vit C; 5] Magnesium; 6] Zinc	NA	NA	↔ Asthma control	1-6] ↔ FeNO[c]	+
[28]	Tecklenburg, 2007	X-RCT	USA	Mild asthma with EIB	Physician diagnosed	8	75	25	NA	Vit C 1500 mg/d	Placebo	2 w	↑ FEV_1 post-exercise, asthma symptom score	↓ FeNO[a b]	+
[29]	Burbank, 2018	X-RCT	USA	Mild asthma	Physician diagnosed or history of asthma symptoms, and BCT	23, o/w 13 with sputum	83	26	26	γ-tocopherol 1200 mg/d	Placebo (Safflower oil)	2 w	↓ Eos(S) ↓ Neutrophils (S)	↓ Eos(S)[a]	+
Other dietary antioxidants															
[35]	Power, 2017	X-RCT	New-Zealand	Mild asthma with FeNO >40 ppb	Physician diagnosed	28	39	42	27	Berry fruit polyphenolic extract 1000 mg/d	Placebo	1 mo	↔ FeNO	↔ FeNO,[a b] Eos(B)[a b]	+

(B), blood; (S), sputum; AHR, airway hyperresponsiveness; BCT, bronchial challenge test; CS, cross-sectional study; EIB, exercise-induced bronchoconstriction; Eos, eosinophils; FeNO, fractional exhaled nitric oxide; NA, not applicable; (X)-RCT, (cross-over) randomized controlled trial. +, positive study quality; ↓ decrease; ↑ increase; ↔ no change.

[a] Between-group effect (intervention vs control).

[b] Within-group effect (intervention group).

[c] Regression coefficient, adjusted for confounders.

Table 2
Study characteristics and T2 inflammation outcomes for studies examining dietary fatty acids.

Ref.	Author, year	Study design	Country	Population description	Asthma diagnosis	N	Female (%)	Age (y)	BMI (kg/m^2)	Intervention/ exposure	Control	Study duration	Result primary outcome	Result T2 inflammation	Quality
Omega-3 poly-unsaturated fatty acids (PUFA)															
[27]	Barros, 2011	CS	Portugal	(Un) controlled asthma	Physician diagnosed	174	82	40	27	Consumption of 1] n-3 PUFA; 2] ALA; 3] EPA; 4] DHA	NA	NA	1, 2] ↑ Asthma control 3, 4] ↔ Asthma control	1, 2] ↓ FeNO[c] 3, 4] ↔ FeNO[c]	+
[38]	Brannan, 2015	X-RCT	Canada	Stable asthma, with AHR to mannitol	Physician diagnosed, and current respiratory symptoms	23 o/w 11 with sputum	39	28	28	4.0 g/d EPA and 2.0 g/d DHA	Placebo (n-6 and n-9 blend)	3 w	↔ AHR post-mannitol challenge	↔ Eos(S)[a]	+
[39]	Mickleborough, 2006	X-RCT	USA	Mild to moderate asthma with EIB	Physician diagnosed	16	38	23	23	3.2 g/d EPA and 2.0 g/d DHA	Placebo (olive oil)	3 w	↑ FEV_1 post-exercise	↓ Eos(S)[a]	+
[40]	Mickleborough, 2013	X-RCT	USA	Mild to moderate asthma with EIB	Physician diagnosed	20	40	23	NA	Marine lipid fraction PCSO-524™ with 400 mg/d n-3 PUFA o/w 72 mg/d EPA and 48 mg/d DHA	Placebo (1.2 g/d olive oil)	3 w	↑ FEV_1 post eucapnic voluntary hyperpnoea test	↓ FeNO[a b]	+
[41]	Moreira, 2007	RCT	Portugal	Stable asthma	Physician diagnosed	20	100	38	27	455 mg/d EPA and 325 mg/d DHA + 10 mg/d vit E	Placebo	2 w	↔ FeNO	↔ FeNO[a b]	+
Omega-6 poly-unsaturated fatty acids (PUFA)															
[27]	Barros, 2011	CS	Portugal	(Un) controlled asthma	Physician diagnosed	174	82	40	27	Consumption of 1] n-6 PUFA; 2] n-6:n-3 ratio	NA	NA	1] ↔ Asthma control 2] ↓ Asthma control	1] ↔ FeNO[c] 2] ↑ FeNO[c]	+
Mono-unsaturated fatty acids (MUFA)															
[27,49]	Barros, 2008; Barros, 2011	CS	Portugal	(Un) controlled asthma	Physician diagnosed	174	82	40	27	Consumption of 1] MUFA 2] MUFA:SFA ratio	NA	NA	↔ Asthma control	1] ↔ FeNO[c] 2] ↑ FeNO[c]	+
Saturated fatty acids (SFA)															
[27]	Barros, 2011	CS	Portugal	(Un) controlled asthma	Physician diagnosed	174	82	40	27	Consumption of SFA	NA	NA	↑ Asthma control	↓ FeNO[c]	+
[50]	Berthon, 2013	CS	Australia	Stable asthma	Physician diagnosed, current respiratory symptoms, and AHR to hypertonic saline	110	59	56	28	Consumption of 1] Total fat 2] SFA	NA	NA	↑ Asthma severity	1 & 2] ↑ Eos(S)[c]	+

(S), sputum; AHR, airway hyperresponsiveness; CS, cross-sectional study; EIB, exercise-induced bronchoconstriction; Eos, eosinophils; FeNO, fractional exhaled nitric oxide; NA, not applicable; (X)-RCT, (cross-over) randomized controlled trial. +, positive study quality; ↓ decrease; ↑ increase; ↔ no change.

[a] Between-group effect (intervention vs control).

[b] Within-group effect (intervention group).

[c] Regression coefficient, adjusted for confounders.

Table 3
Study characteristics and T2 inflammation outcomes for studies examining Mediterranean-style diets.

Ref.	Author, year	Study design	Country	Population description	Asthma diagnosis	N	Female (%)	Age (y)	BMI (kg/m^2)	Intervention/exposure	Control	Study duration	Result primary outcome	Result T2 inflammation	Quality
[52]	Toennesen, 2018	RCT	Denmark	Non-obese asthma	BCT or BRT	125	69	40	25	1] High-protein diet with low glycemic index 2] Diet of 1] + high-intensity interval training	Usual care	2 mo	1] ↔ Asthma control 2] ↑ Asthma control	1 & 2] ↔ FeNO,[a b] Eos (B),[b a] Eos(S)[b a]	+
[53]	Bseikri, 2018	RCT	USA	Uncontrolled asthma with obesity	Physician diagnosed	56	45	15	NA	Nutrient- and fibre-dense CHORI-bar 2 bars/d + weekly nutrition and exercise classes	Weekly nutrition and exercise classes, no placebo	2 mo	↔ Asthma control	↔ FeNO[a b]	+
[54]	Nygaard, 2021	RCT	USA	Uncontrolled asthma	Physician diagnosed or BRT	64	67	52	28	Counselling sessions to improve diet quality based on DASH diet	Usual care	6 mo	↑ Asthma control	↓ IL-4(B),[c] IL-5 (B)[c] at 3 mo ↔ IL-4(B),[c] IL-5 (B),[c] IL-13(B)[c] at 6 mo	+
[49]	Barros, 2008	CS	Portugal	(Un)controlled asthma	Physician diagnosed	174	82	40	27	Consumption of 1] Mediterranean diet; 2] Fruit; 3] Pulses; 4] Nuts; 5] Whole grains; 6] Fish; 7] Red meat; 8] Ethanol	NA	NA	1,2] ↑ Asthma control 3-7] ↔ Asthma control 8] ↓ Asthma control	1-8] ↔ FeNO[d]	+

(B), blood; (S), sputum; BCT, bronchial challenge test; BRT, bronchodilator reversibility test; CS, cross-sectional study; Eos, eosinophils; FeNO, fractional exhaled nitric oxide; IL, interleukin; NA, not applicable; RCT, randomized controlled trial. +, positive study quality; ↓ decrease; ↑ increase; ↔ no change.

[a] Between-group effect (intervention vs control).

[b] Within-group effect (intervention group).

[c] Correlation between change in DASH-score and change in inflammatory markers.

[d] Regression coefficient, adjusted for confounders.

Table 4
Study characteristics and T2 inflammation outcomes for studies examining phytotherapy.

Ref.	Author, year	Study design	Country	Population description	Asthma diagnosis	N	Female (%)	Age (y)	BMI (kg/m^2)	Intervention/ exposure	Control	Study duration	Result primary outcome	Result T2 inflammation	Quality
[56]	Koshak, 2017	RCT	Saudi Arabia	(Un)controlled asthma	GINA guideline	80	59	41	29	*Nigella sativa* oil 1000 mg/d	Placebo (olive oil)	1 mo	↓ Asthma control	↓ Eos(B)[a]	+
[57]	Salem, 2017	RCT	Saudi Arabia	(Un)controlled asthma	NIH guideline	76	66	38	30	1] *Nigella sativa* 1 g/d 2] *Nigella sativa* 2 g/d	Placebo	3 mo	1: ↑ PEF ↔ FEV_1, FEV_1/FVC 2: ↑ FEV_1, PEF ↔ FEV_1/FVC	1] ↓ FeNO[b] ↔ IL-4(B)[b] 2] ↔ FeNO[b] ↔ IL-4(B)[b]	+
[58]	Zilaee, 2019	RCT	Iran	Mild and moderate atopic asthma	GINA guideline	76	42	41	27	Saffron 100 mg/d	Placebo	2 mo	↑ Clinical symptoms ↔ Asthma severity	↓ Eos(B)[b] ↔ Eos(B)[a]	+

(B), blood; Eos, eosinophils; FeNO, fractional exhaled nitric oxide; GINA, Global Initiative for Asthma; IL, interleukin; NIH, National Institutes of Health; RCT, parallel randomized controlled trial. +, positive study quality; ↓ decrease; ↑ increase; ↔ no change.
[a] Between-group effect (intervention vs control).
[b] Within-group effect (intervention group).

Table 5
Study characteristics and T2 inflammation outcomes for studies examining prebiotics and probiotics.

Ref.	Author, year	Study design	Country	Population description	Asthma diagnosis	N	Female (%)	Age (y)	BMI (kg/m^2)	Intervention/exposure	Control	Study duration	Result primary outcome	Result T2 inflammation	Quality
Probiotics															
[64]	Satia, 2021	X-RCT	Canada	Mild asthma	BCT	15	53	27	26	*Limosilactobacillus reuteri* DSM-17938 1 x 10^9 CFU/d	Placebo	1 mo	↔ Number of capsaicin-evoked coughs	↔ Eos(S)[b]	+
Prebiotics and probiotics															
[67]	McLoughlin, 2019	X-RCT	Australia	Stable asthma	Physician diagnosed	17	53	43	30	Soluble fibre meal with inulin 12 mg/d and 3 probiotics[a] >25 x 10^9 CFU	Placebo (maltodextrin)	1 w	↔ Plasma short-chain fatty acids	↔ Eos(S),[b] FeNO[b c]	+
Prebiotics															
[67]	McLoughlin, 2019	X-RCT	Australia	Stable asthma	Physician diagnosed	17	53	43	30	Soluble fibre meal with inulin 12 mg/d	Placebo (maltodextrin)	1 w	↔ Plasma short-chain fatty acids	↓ Eos(S)[c] ↔ Eos(S),[b] FeNO[b c]	+
[50]	Berthon, 2013	CS	Australia	Stable asthma	Physician diagnosed, current respiratory symptoms, and AHR to hypertonic saline	110	59	56	28	Dietary fibre consumption	NA	NA	↓ Asthma severity, FEV_1/FVC	↓ Eos(S)[d]	+

(S), sputum; AHR, airway hyperresponsiveness; BCT, bronchial challenge test; CS, cross-sectional study; Eos, eosinophils; FeNO, fractional exhaled nitric oxide; NA, not applicable; (X)-RCT, (cross-over) randomized controlled trial. +, positive study quality; ↓ decrease; ↑ increase; ↔ no change.
[a] *Lactobacillus acidophilus* strain LA5, *Bifidobacterium lactis* strain Bb12, and *Lactobacillus rhamnosus* strain GG.
[b] Between-group effect (intervention vs control).
[c] Within-group effect (intervention group).
[d] Regression coefficient, adjusted for confounders.

Table 6
Study characteristics and T2 inflammation outcomes for studies examining vitamin D.

Ref.	Author, year	Study design	Country	Population description	Asthma diagnosis	N	Female (%)	Age (y)	BMI (kg/m^2)	Intervention/ exposure	Control	Study duration	Result primary outcome	Result T2 inflammation	Quality
[71]	Castro, 2014	RCT	USA	Symptomatic asthma, vit D < 30 ng/ml	Physician diagnosed, BRT or BCT	408	68	40	32	Vit D_3 100,000 IU once, then 4000 IU/d + inhaled ciclesonide	Placebo + inhaled ciclesonide	7 mo	↔ First treatment failure	↔ Eos(S)[a]	+
[72]	de Groot, 2015	RCT	The Netherlands	Non-atopic asthma	BRT or BCT	44	41	56	27	Vit D_3 400,000 IU (single dose, long acting) in yogurt	Plain yogurt	9 wk	↔ Neutrophils(S), Eos(S)	↔ FeNO,[a b] Eos (S),[b a] Eos(B)[b a] ↓ Eos(S)[b a] in subgroup with high eos	+
[73]	Martineau, 2015	RCT	United Kingdom	Asthma	Physician diagnosed and BRT	250, o/w 50 with sputum	56	48	NA	Vit D_3 120,000 IU (Vigantol oil) every 2 mo	Placebo (Miglyol oil)	12 mo	↔ Time to first exacerbation or respiratory infection	↔ FeNO,[a] Eos (S),[a] IL-4(S),[a] IL-13(S)[a]	+

(B), blood; (S), sputum; BCT, bronchial challenge test; BRT, bronchodilator reversibility test; Eos, eosinophils; FeNO, fractional exhaled nitric oxide; IL, interleukin; NA, not applicable; RCT, randomized controlled trial. +, positive study quality; ↓ decrease; ↑ increase; ↔ no change.
[a] Between-group effect (intervention vs control).
[b] Within-group effect (intervention group).

Table 7
Study characteristics and T2 inflammation outcomes for studies examining other dietary factors.

Ref.	Author, year	Study design	Country	Population description	Asthma diagnosis	N	Female (%)	Age (y)	BMI (kg/m^2)	Intervention/exposure	Control	Study duration	Result primary outcome	Result T2 inflammation	Quality
[78]	Mickleborough, 2005	X-RCT	USA	Mild, atopic asthma with EIB	Physician diagnosed	24	38	24	27	Low-salt diet of 1500 mg/d sodium and 2250 mg/d chloride + 10 capsules of salt 1 g/capsule	Low-salt diet with placebo	2 w	↓ FEV_1 post-exercise	↔ Eos(S),[a b] ECP (S)[b a] pre-exercise ↑ Eos(S),[b a] ECP (S)[b a] 6h post-exercise	+
[79]	Woods, 1998	X-RCT	Australia	Stable atopic asthma, MSG sensitive	History of BRT	12	58	35	28	1] MSG challenge 1 g 2] MSG challenge 5 g	Placebo (lactose)	12 h	↔ FEV_1	1 & 2] ↔ ECP(B)[c]	+
[80]	Smith, 2015	RCT	USA	Uncontrolled asthma	Physician diagnosed	386	66	36	28	Soy isoflavones 100 mg/d	Placebo	6 mo	↔ FEV_1	↑ FeNO[d] ↔ FeNO,[b] Eos(B)[a,b]	+

(B), blood; (S), sputum; BRT, bronchodilator reversibility test; Eos, eosinophils; ECP, eosinophil cationic protein; FeNO, fractional exhaled nitric oxide; MSG, monosodium glutamate; (X)-RCT, (crossover) randomized controlled trial. +, positive study quality; ↓ decrease; ↑ increase; ↔ no change.
[a] Between-group effect (intervention vs control).
[b] Within-group effect (intervention group).
[c] Not statistically tested, only descriptive data.
[d] Between-group effect, because of an decrease in FeNO in placebo group.

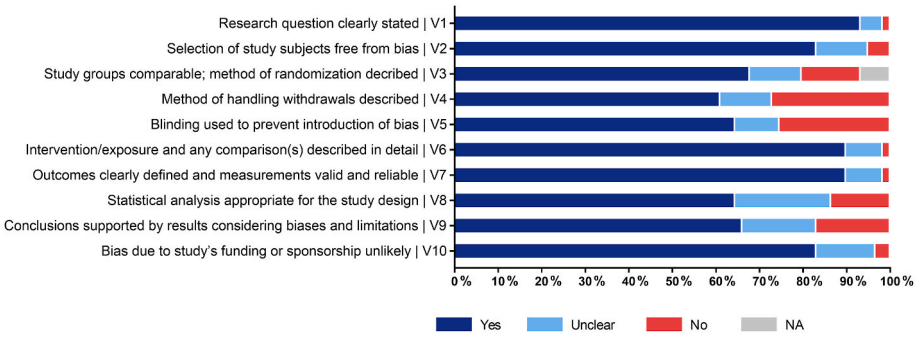

Fig. 2. Summary of quality assessment.
Y, yes (=good quality); N, no (=insufficient quality); U, unclear; NA, not applicable.

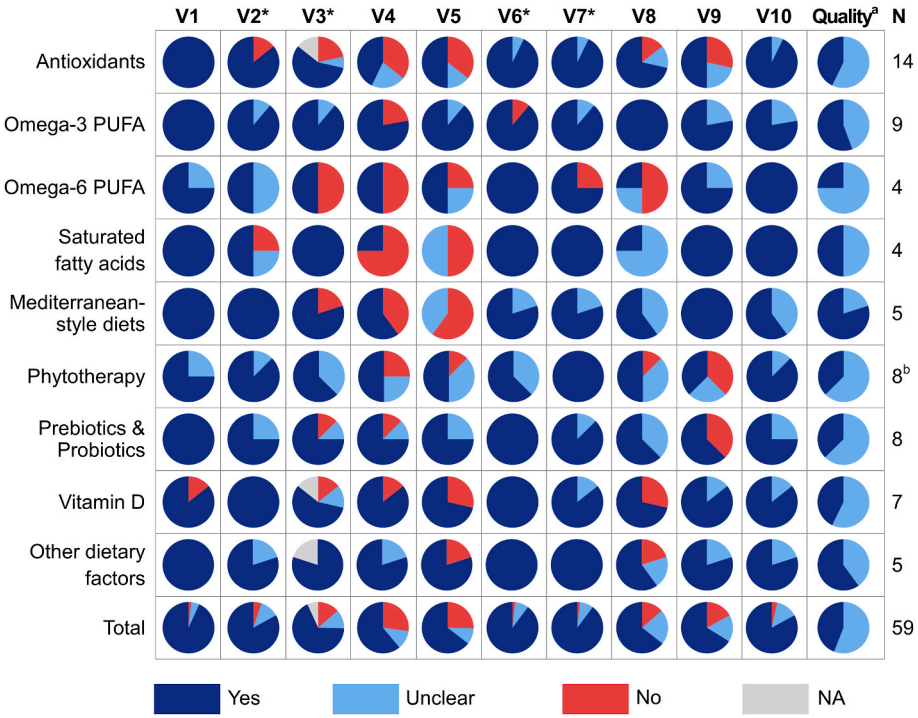

Fig. 3. Summary of quality assessment for each cluster.
Y, yes (=good quality); N, no (=insufficient quality); U, unclear; NA, not applicable. PUFA, poly-unsaturated fatty acids.
Critical validity questions.a Dark blue = positive quality; Light blue = neutral quality. b One study described in two separate publications; quality assessment was performed for both publications
V1 Research question clearly stated – V2 Selection of study subjects free from bias – V3 Study groups comparable, method of randomisation described – V4 Method of handling withdrawals described – V5 Blinding used to prevent introduction of bias – V6 Intervention/exposure and any comparison(s) described in detail – V7 Outcomes clearly defined and measurements valid and reliable – V8 Statistical analysis appropriate for the study design – V9 Conclusions supported by results considering biases and limitations – V10 Bias due to study's funding or sponsorship unlikely. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

[41], while the other did not report details on the power calculation [43]. The study durations ranged from 4 h (acute effects) to 12 months. Overall, the studies on omega-3 PUFA had only few methodological problems, although four of the nine studies were of neutral quality because of deficiencies in one of the critical validity points (Fig. 3). Three omega-6 studies and two SFA studies were of neutral quality, with potential biases related to the subject selection, incomparability of study groups, missing data, lack of blinding, and inappropriate statistical analyses.

All studies of omega-3 PUFA have examined the fish fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), with mixed results. In a study of patients with mild to moderate asthma and EIB, supplementation with EPA and DHA attenuated the increase in sputum eosinophils seen in the control group following an exercise challenge [39]. Similarly, a reduction in FeNO was found in patients with asthma and EIB following supplementation with an EPA/DHA-rich marine lipid fraction [40]. In contrast, no effect of EPA/DHA supplementation on sputum eosinophils or FeNO was found in two other high-quality trials in patients with stable asthma but without EIB [38,41]. Next, consumption of omega-3 PUFA, but not EPA and DHA, was associated with lower FeNO levels in a large, well-conducted cross-sectional study [27]. Other studies of neutral quality have reported both reductions [43,45], and no effect of fish fatty acids on FeNO in patients with asthma [42,44].

Regarding other fatty acids, a higher dietary omega-6:omega-3 ratio and a higher MUFA:SFA ratio, were associated with higher FeNO, but a

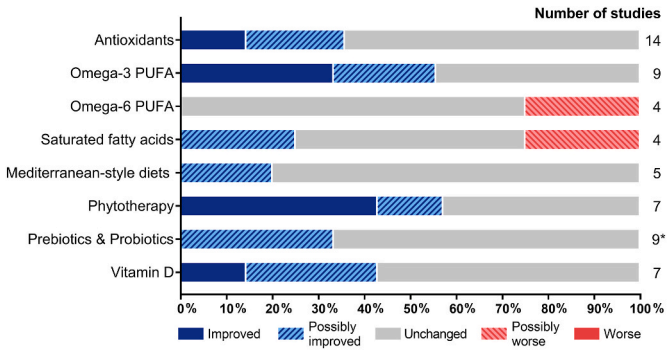

Fig. 4. Overview of evidence of the effect of dietary interventions on markers of T2 inflammation.
PUFA, poly-unsaturated fatty acids. Percentage of studies in each cluster showing a statistically significant between-group effect, either positive (blue) or negative (red), on markers of T2 inflammation. Studies with no significant between-group effects, despite within-group effects in RCT, are classified as unchanged (grey). A two-colour pattern was used when 1) a single study reported conflicting between-group results for multiple outcome markers; i.e. a positive and no effect (dashed blue) or a negative and no effect (dashed red); 2) the results were obtained from studies with a design other than an RCT (e.g. cross-sectional, before-after study).
* One publication evaluated both prebiotics and the combination with probiotics, and was therefore included twice. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

higher dietary intake of either omega-6 PUFA or MUFA was not associated with FeNO [27,49]. Consistent with this, results from neutral-quality RCTs also show no clear effect of omega-6-rich interventions on various markers of T2 inflammation [46–48].

High-quality cross-sectional data showed that a higher total fat and SFA intakes were associated with higher sputum eosinophils [50], but SFA intake was also associated with lower FeNO [27]. However, no changes in FeNO or blood and sputum eosinophils were observed in data from RCTs of neutral quality that investigated the acute effects of high-fat and SFA-rich meals [46,51].

Overall, five out of the nine omega-3 PUFA studies reported a (possible) improvement in markers of T2 inflammation, while one omega-6 PUFA study showed a possible worsening (Fig. 4). For SFA, the results were mixed, with one study showing a possible improvement, one study showing a possible worsening and two studies showing no effect on T2 inflammatory markers.

3.4. Mediterranean-style diets

The results for the cluster on Mediterranean-style diets are shown in Table (S)3. Despite the heterogeneity in the type of interventions, all studies have focused on a predominantly plant-based and Mediterranean-style diet. The dietary intervention was combined with exercise in two studies [52,53]. One study used a cross-sectional design [49], the others were RCT's with a study duration of 2–6 months [52–55]. None of these studies assessed T2-related markers as the primary study outcome. Four out of five studies were of positive quality (Fig. 3), but due to the nature of the intervention, all studies were either open-label or single-blind.

Neither intervention with a high-protein, low-glycemic index diet, nor supplementation with a nutrient-dense bar – whether or not combined with exercise – had an effect on FeNO levels [52,53], or on blood and sputum eosinophils [52]. Both interventions had compositional similarities to the Mediterranean diet. Furthermore, Nygaard et al. studied the effect of the DASH (Dietary Approach to Stop Hypertension) diet, using counselling sessions for 6 months to promote high intake of fruits and vegetables, and low intake of total fat and sodium [54]. A higher DASH-score was significantly correlated with lower levels of the T2-related markers IL-4 ($r = -0.29$) and IL-5 ($r = -0.31$) at 3 months, but not at 6 months. Last, consumption of a Mediterranean diet or its components, was not associated with FeNO in a cross-sectional study [49], nor did it change blood eosinophils in an intervention study of neutral quality using dietary counselling to adopt a Mediterranean diet [55].

Overall, in this cluster focusing on Mediterranean-style diets, only one study showed a possible improvement in T2-related markers (Fig. 4), but the results were not sustained over time.

3.5. Phytotherapy

Table (S)4 summarises the results and characteristics of the phytotherapy (herbal medicine) studies. All studies were parallel RCT's with a study duration of 1–3 months. None of the studies assessed T2-related markers as the primary study outcome. The articles by Alavinezhad et al. and Ghorani et al. described the same study and have been combined in the table [61,62]. Five of the eight articles were of neutral quality, with methodological shortcomings related to the handling of missing data, blinding, statistical analysis, and study limitations and biases not taken into account (Fig. 3).

A well-conducted study in patients with (un)controlled asthma using *Nigella sativa* oil for 1 month showed a small reduction in blood eosinophil count of -0.05×10^9 cells/L (95 % CI: 0.15; 0.00×10^9 cells/L), which was significantly different from the placebo group [56]. FeNO levels were also reduced after an intervention with 1 g/d *Nigella sativa*, but differences between groups were not tested and the effect on FeNO was not shown in the group receiving a higher dose of 2 g/d *Nigella sativa* [57]. Next, in patients with mild to moderate asthma, blood eosinophils were reduced after intervention with saffron, although not significantly different from the control group [58], and after supplementation with curcumin, although the control group did not receive a placebo and the overall quality of the study was poor [59]. Other studies of neutral quality in patients with moderate to severe asthma have shown a reduction in blood eosinophils after intervention with high-dose *Zataria multiflora* extract [60] and its main constituent, carvacrol [61,62]. Supplementation with a herbal supplement containing extracts of *Boswellia serrata* gum resin and *Aegle marmelos* fruit reduced blood IL-4 levels, but this study also had methodological shortcomings and was assessed as neutral quality study [63].

Overall, four out of seven studies reported (possible) improvements in markers of T2 inflammation after treatment with herbal supplements, while three-studies did not observe or examine between-group effects (Fig. 4).

3.6. Prebiotics and probiotics

The results for the prebiotics and probiotics cluster are shown in Table (S)5. Three studies focused on probiotics [64–66], three studies evaluated prebiotics [50,67,70], and three studies examined the combination of prebiotics and probiotics [67–69]. McLoughlin et al. evaluated both prebiotics and the combination with probiotics in the same study, and was therefore listed twice [67]. With the exception of Berthon et al., who used a cross-sectional design [50], all other studies were (randomised) clinical controlled trials with either a placebo or control treatment, and study durations ranged from 4 h (acute effects) to 3 months. A T2-related parameter was the primary outcome in two studies, of which one was adequately powered for sputum eosinophils [69], and the other did not describe the sample size calculation [68]. Three of the eight studies had a positive quality rating (Fig. 3). Potential biases were related to the randomisation procedure and missing data, and in some studies the results seemed over-interpreted.

McLoughlin et al. reported a significant reduction in sputum eosinophils of −1.0 % (median; IQR: 2.5; 0.0) in patients with stable asthma after intervention with the prebiotic fibre inulin, but this was not

statistically significantly different from the placebo group [67]. Consistent with this, higher dietary fibre intake was also associated with lower sputum eosinophil levels in a cross-sectional study (β±SE -0.36 ± 0.026 %/g) [50]. However, two well-conducted crossover RCTs in patients with mild and stable asthma showed no effect on blood eosinophils after intervention with probiotics alone [64] or after daily consumption of a meal containing both probiotics and prebiotics for one week [67]. Other intervention studies of neutral quality also showed no significant effect of probiotic treatment – whether or not combined with prebiotics – on sputum or blood eosinophils [65,66,68,69]. Last, results from neutral-quality studies show that supplementation with prebiotic oligosaccharides had no effect on FeNO [70], but when combined with the probiotic strain *Bifidobacterium breve* it attenuated the increase in serum IL-5 levels after HDM-challenge [69].

Overall, in this cluster focusing on prebiotics & probiotics, the majority (67 %) showed no effect on T2 inflammation, while three studies reported possible improvements in T2 inflammation, due to inconsistent results or results from cross-sectional data (Fig. 4).

3.7. Vitamin D

Table (S)6 lists the characteristics and results of the seven vitamin D intervention trials. Five trials examined the effect of vitamin D_3 [71–75], one trial assessed 1,25-$(OH)_2D_3$ (the bioactive form of vitamin D) [77], and one trial did not specify the type of vitamin D [76]. Study duration ranged from 2 months to 1 year. Only one study assessed T2 inflammation as the primary outcome and was adequately powered for sputum eosinophils [72]. Four studies were of neutral quality, with the most common quality issues related to an unclear study question, incomparability of study groups, lack of blinding, and inappropriate statistical analyses (Fig. 3).

In a subgroup of non-atopic asthma patients with prominent eosinophilia, a reduction in sputum eosinophils from a median of 41.1 %–11.8 % was observed 9 weeks after a single high-dose of long-acting vitamin D3 [72], but no effect on FeNO or blood eosinophils was reported. In contrast, two other high-quality trials with much longer study durations, but with different populations and dosing regimens, found no effect of vitamin D3 on sputum eosinophil counts [71,73]. Results from studies of neutral quality show that long-term vitamin D3 supplementation reduces blood eosinophils in patients with vitamin D deficiency [75], and daily supplementation with 1,25-(OH)2D3 for 6 months reduces blood eosinophils, IL-5 and IL-13 in patients with atopic asthma [77]. Other studies of vitamin D interventions have shown no effect on T2 inflammatory markers [73,74,76].

Overall, three of the seven studies on vitamin D showed a statistically significant decrease in one or more markers of T2 inflammation, but results were inconsistent in two of them (Fig. 4).

3.8. Other dietary factors

Table (S)7 summarises the results and characteristics of studies examining dietary interventions other than those described in the clusters above. Due to the heterogeneity of interventions, these studies were not included in the overview figure. One study assessed FeNO as primary outcome and was adequately powered [81]. Two of the five studies were rated with neutral quality, with methodological shortcomings related to blinding and statistical analysis (Fig. 3).

In a well-conducted cross-over study of adults with asthma and EIB, dietary salt supplementation had no effect on sputum eosinophils and ECP concentrations [78]. However, in the same study, 6 h after an exercise challenge, both eosinophils (pre: 7.6 %, post: 31.4 %) and ECP (pre: ±150 ng/ml, post: 354 ng/ml) increased in the intervention group, which was significantly different from the placebo group. Furthermore, Woods et al. showed that neither a high- nor low-dose monosodium glutamate (MSG) challenge had an effect on blood ECP levels in MSG-sensitive asthmatic subjects [79]. Next, in a large, high-quality RCT (n = 386) neither FeNO nor blood eosinophils changed 6 months after intervention with soy isoflavones [80]. Results from a pilot study using the same intervention but for only 4 weeks, showed a significant reduction in FeNO [81]. However, this latter finding was questionable given the reported standard deviations. Finally, higher serum plant stanol concentrations during a 2-month plant stanol ester intervention were significantly associated with lower IL-13 production, but this was attenuated after adjustment for cholesterol levels [82].

4. Discussion

In this systematic review we examined the effect of dietary interventions on markers of T2 inflammation in adult asthma, beyond IgE-mediated food allergy. To our knowledge, such a comprehensive and systematic evaluation has not been done before. Possible improvements in T2 inflammation were shown by the majority of studies within the clusters phytotherapy and omega-3 PUFA. On the other hand, we found little evidence for an effect of antioxidants, prebiotics & probiotics, and Mediterranean-style diets on T2 inflammation. Furthermore, most of the studies had insufficient statistical power for these outcome measures, many did not have a proper between-group comparison in the RCT design, and the results were often inconsistent across all T2 markers evaluated in a study. This makes it difficult to determine the effect of different dietary approaches on T2 inflammation in asthma. Overall, there is no clear evidence for a role of diet in T2 inflammation from studies that are often underpowered, but the results of this review provide leads for further research.

Our findings are consistent with a review by Van Brakel et al. that summarised the current evidence for dietary interventions showing simultaneous improvements in asthma-related outcomes and immunological parameters [83]. Despite differences in the study question and selection criteria compared to the current review, Van Brakel et al. found that studies within the clusters 'herbs, herbal mixtures and extracts' and 'omega-3 PUFA' were identified as the most promising. The authors hypothesised that the beneficial effect of herbal interventions on asthma-related outcomes was due to the restoration of the Th1/Th2 balance [83]. Although we did not assess T1 inflammatory markers, the majority of studies in the phytotherapy cluster showed improvements in one or more T2 markers, but most studies were of poor quality and the results were often not statistically different from the control treatment. Interventions involving *Nigella sativa*, curcumin and the combination of *Boswellia serrata* gum resin and *Aegle marmelos* fruit require further research to fully elucidate the effect on T2 inflammation.

For omega-3 PUFA, more than half of the studies showed improvements in at least one marker of T2 inflammation after supplementation with EPA and DHA. These fish fatty acids are considered anti-inflammatory through several cellular mechanisms, including the incorporation into cell membranes and the resulting altered synthesis of eicosanoids, thereby inhibiting T-cell proliferation and altering the production of Th1 and Th2 cytokines [84,85]. Interestingly, the majority of studies have been conducted in patients with EIB [38–40,42,44,45], suggesting that the increased concentration of omega-3 PUFA in cell membranes may specifically protect against inflammatory responses following exercise or comparable bronchial provocation challenges [39,40,45]. However, not all studies have shown such an effect in patients with EIB [38,42,44] and the number of studies in patients without EIB was limited. On the other hand, omega-6 PUFA intake has been associated with possibly higher T2 inflammation, although the evidence was weak [27]. The omega-6 PUFA linoleic acid, the main component of safflower oil, is a precursor of the Th2-promoting prostaglandin E2 (PGE2), and is therefore considered to be pro-inflammatory [86]. However, both conjugated- and gamma-linoleic acid may compete with linoleic acid in the synthesis of PGE2, thereby inhibiting T2 cytokine production [87,88]. Indeed, studies using either conjugated- or gamma-linoleic acid have shown no effect on markers of T2 inflammation, but were only of neutral quality [47,48].

Despite the large number of studies, we found limited evidence for a beneficial effect of antioxidants on T2 inflammation, although studies were often underpowered. Dietary antioxidants – such as vitamins E and C, carotenoids, flavonoids, and selenium – may help to protect against the damaging effects of oxidative stress in the airways caused by reactive oxygen species [84]. More specifically for T2 inflammation, vitamin C affects the release of arachidonic acid, a prostaglandin precursor, thereby inhibiting PGE2 synthesis [86]. We found one study that did show a reduction in FeNO with vitamin C supplementation [28], but also studies with no association with T2 inflammation [27,31]. In-vivo studies have also suggested inhibitory effects of vitamin E and flavonoids on markers of T2 inflammation [8], but the results of the clinical studies we found were again inconclusive. The lack of efficacy in supplementation studies is often attributed to the fact that only a single nutrient is studied, whereas whole foods or dietary patterns may be more effective. Indeed, people do not consume individual foods or nutrients, but rather meals and diets that may have different effects due to the combination of nutrients [89,90]. The Mediterranean diet in particular is thought to be anti-inflammatory, because it is high in plant foods, antioxidants, dietary fibre and omega-3 PUFA. However, we also found very little evidence on the effect of the Mediterranean diet and other plant-based diets on T2 inflammation, although none of the studies was adequately powered for these outcomes measures, as were most studies on single antioxidants. Interestingly, in children, the Mediterranean diet was associated with a lower risk of developing asthma, but did not affect the development of allergies [91]. This may suggest that the Mediterranean diet has protective properties against asthma through a mechanism other than T2 inflammation.

Furthermore, only three of the nine studies in the cluster of prebiotics and probiotics showed a potential reduction in one or more markers of T2 inflammation, which was not different between studies using either prebiotics, probiotics or the combination treatment. Prebiotics are non-digestible carbohydrates, such as dietary fibres and oligosaccharides, that regulate the balance of the gut microbiome and stimulate the growth of presumed beneficial bacteria. Prebiotics are fermented by the gut microbiota into short-chain fatty acids (SCFAs) that bind to the receptors GPR41 and GPR43. SCFAs promote the development of dendritic cells from the bone marrow by activating GPR41, which then circulate to the lungs where they impair the differentiation of naive T cells into Th2 cells [9]. Probiotics are live microorganisms that can confer health benefits on the host, while dysbiosis of the gut microbiota impairs immune responses and pulmonary homeostasis, due to cross-talk between the lungs and gut [8]. The species *Bifidobacterium* and *Lactobacillus* are among the most potent producers of SCFAs [92], and these are often used as probiotics. However, the mechanisms of action are still largely unknown. However, other than in children with allergic airways disease, where probiotics have been shown to have the potential to reduce T2 responses (i.e. atopy) [93,94], results in adults do not clearly indicate a T2 inhibitory effects of prebiotics or probiotics, although studies may have been underpowered to show between-group effects.

Last, vitamin D plays an important role in Treg responses and may suppress IgE synthesis, but there is little evidence on the effect of vitamin D on innate lymphoid cells and eosinophils [95]. We found one study showing a significant between-group effect of 1,25-$(OH)_2D_3$, the active form of vitamin D, on blood eosinophils, IL-5 and IL-13 in atopic asthma patients [77], while the other six intervention studies in this vitamin D cluster showed no or inconsistent effects on markers of T2 inflammation. Interestingly, de Groot et al. showed a significant reduction in sputum eosinophils after vitamin D supplementation in non-atopic asthma patients with prominent eosinophilia [72]. The authors hypothesised that vitamin D improves steroid sensitivity, thereby reducing eosinophilic inflammation. Furthermore, these results suggest that vitamin D may be most beneficial in patients with a T2-high phenotype. In fact, it could be imagined that the effect of diet on T2 inflammation would generally apply only to patients with T2-high asthma. Unfortunately, other studies included in this review did not distinguish between asthma phenotypes and hence it is unclear whether this is the reason for the discrepancy in results between studies.

In terms of the quality of the articles reviewed, the majority of the studies were double-blind, placebo-controlled randomised trials, although details of the randomisation procedure and the blinding of both patients and outcome assessors were often missing. Given the objective nature of our outcome of interest, the latter is unlikely to have influenced the results. However, some studies had incomparable study groups or lacked a control group, while other placebo-controlled trials only reported within-group effects. This often led to conclusions that were not sufficiently supported by the results. Furthermore, most studies were not primarily designed to investigate T2 inflammation, and lack of power was a major issue in almost all included studies. Also attrition bias may have influenced the results, because of frequent missing data and lack of details on the handling of withdrawals. For example, it is well-known that sputum induction is not always successful or that the sputum sample is of poor quality. Yet, whether the number of samples analysed to assess sputum eosinophils differed from the overall sample size was often not reported. Finally, although we did not formally assess reporting bias, some studies did not report numerical results for each of the measures mentioned in the methods or results sections.

The current review also has its strengths and limitations. We conducted a comprehensive literature search in several databases using pre-specified criteria. We excluded studies evaluating the effects of a weight-loss diet or nutrients measured in blood, as we were only interested in the effect of dietary intake. Furthermore, the quality of all included studies was systematically assessed, and most of the studies were RCT's, which was more than expected. Limitations include the heterogeneity of the included studies in terms of asthma population, sample characteristics, type and dose of dietary intervention, and study duration. This inhibited the ability to perform a meta-analysis and further complicated comparability of study findings. The outcome of interest was T2 inflammation, as assessed by FeNO, eosinophils, IL-4, IL-5, IL-13, ECP and eosinophil peroxidase, although no results were found for the latter outcome marker. However, the T2 inflammatory cascade is much broader and also includes, for example, eotaxin and periostin [6]. But as this field is relatively new and still evolving, we have only included the most common ones.

To conclude, the results presented in this review highlight potential dietary interventions that may affect the T2 inflammatory process present in certain asthma subtypes. The heterogeneity of study protocols, methodological shortcomings and limited power of almost all studies make it difficult to determine the impact of different dietary approaches on T2 inflammation in asthma. However, interventions involving phytotherapy and omega-3 fatty acids have the best evidence to warrant further evaluation in well-designed, prospective studies. Furthermore, we found little evidence for an effect of antioxidants, prebiotics & probiotics, and Mediterranean-style diets on T2 inflammation, but this does not rule out the possibility that these dietary factors may play a role in the management of asthma, perhaps through a mechanism other than T2 inflammation. Methodologically, more attention needs to be paid to adequate statistical power, appropriate comparisons with a control group, and the handling of missing data. Reliable dietary assessment in observational studies and achieving blinding in experimental studies also remain challenges in nutrition research. Last, future research should consider asthma endotypes or T2-high phenotypes, as some subgroups of patients are more likely to benefit from dietary interventions than others.

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CRediT authorship contribution statement

Edith Visser: Conceptualization, Data curation, Investigation,

Methodology, Project administration, Visualization, Writing – original draft. **Anneke ten Brinke:** Conceptualization, Data curation, Methodology, Supervision, Writing – review & editing, Investigation. **Dionne Sizoo:** Data curation, Investigation. **Janneke J.S. Pepels:** Data curation, Investigation. **Lianne ten Have:** Data curation, Investigation. **Erica van der Wiel:** Data curation, Investigation. **Tim van Zutphen:** Conceptualization, Supervision, Writing – review & editing. **Huib A.M. Kerstjens:** Conceptualization, Supervision, Writing – review & editing. **Kim de Jong:** Conceptualization, Data curation, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

There is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2023.107504.

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