

N-3 fatty acid supplementation in asthma management: A systematic review and meta-analysis

To the Editor,

Laboratory and epidemiological evidence suggests that n-3 fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are beneficial in asthma prevention and possibly treatment through their anti-inflammatory effect.¹ The mechanisms underlying the anti-inflammatory actions of n-3 fatty acids include activation of transcription factor peroxisome proliferator-activated receptor γ , binding to the G protein-coupled receptor, altered cell membrane phospholipid composition, inhibition of activation of the pro-inflammatory transcription factor nuclear factor kappa B, and inflammation resolving mediators called resolvins, protectins, and maresins.² However, evidence from randomized controlled trials remains inconsistent.³ Therefore, we aimed to examine the summarized effect of n-3 fatty acids on asthma control and management.

We conducted a systematic review and meta-analysis including randomized controlled trials on the effect of n-3 fatty acid supplementation in patients with asthma on lung function, fractional exhaled nitric oxide (FeNO), symptom score, bronchodilator use, and postexercise decline in forced expiratory volume in 1 s (FEV₁) (see Figure S1, Tables S1–S4 for detailed information). The scales used to evaluate symptoms varied across studies, but all of them reported their symptom scores as a number, with higher scores indicating severer asthma symptoms. In the subgroup analysis, participants aged >18 years were classified as adults; intervention ≥ 3 weeks was considered long duration. High dosage was defined as >4 g since it was the median number of dosages for all the included studies.

In the 16 trials included, four studies that compared n-3 fatty acid supplementation with placebo found that the decline in FeNO was more significant in the n-3 fatty acid group and decreased by 6.81 ppb (95% CI -11.94 to -1.97, $P < .01$; $I^2 = 23\%$) (Figure 1A). The change in FeNO exhibited no clear evidence of a difference in the subgroup analysis (Table 1). However, the effect of n-3 fatty acid supplementation on the decrease of FeNO was significant in the high-dosage group (-13.00, 95% CI -24.07 to -1.93), long-duration group (-11.82, 95% CI -18.80 to -4.83), and adult group (-5.82, 95% CI -11.10 to -0.54).

Four studies reported changes in FEV₁ decline after exercise. The pooled standardized mean difference (SMD) was -0.78 (95% CI

-1.28 to -0.28, $P < .01$; $I^2 = 47\%$; Figure 1B), showing protective effect of n-3 fatty acids in FEV₁ after exercise. Although subgroup analysis revealed no significant differences, the reduced decline in FEV₁ after exercise was more obvious in the high-dosage group (-0.99, 95% CI -1.89 to -0.09) (Table 1).

Nine studies displayed results on FEV₁, and no clear evidence of the benefit or harm of n-3 fatty acids on FEV₁ measurements was noted. The mean difference (MD) was 1.74% in predicted FEV₁ (95% CI -0.21 to 3.68, $P = .08$; $I^2 = 0\%$; Figure 1C). The subgroup analysis by dosage, duration, and age revealed no significant differences; however, an increase in FEV₁ was observed in the low-dosage group (MD = 2.13, 95% CI 0.03 to 4.23) (Table 1).

The effect of n-3 fatty acid supplementation on forced vital capacity (FVC), FEV₁/FVC, peak expiratory flow, asthma symptoms, or bronchodilator use remained inconclusive (Table 1).

Our most novel finding was the anti-airway inflammatory effect of n-3 fatty acids. The expression of inducible nitric oxide (NO) synthase can be increased by activating the NF- κ B transcription factor. The n-3 fatty acids, particularly EPA, inhibit NF- κ B activity directly, which may explain the observed fall in FeNO after n-3 fatty acid supplementation.⁴ Meijerink et al⁵ reported that adipocytes could rapidly and efficiently convert DHA to docosahexaenylethanolamine, suppressing both monocyte chemotactic protein-1 and inducible NO synthase mRNA. Although the relationship of n-3 fatty acids and NO production in the airway is not yet fully established, evidence strongly suggests that n-3 fatty acids may be effective in asthma treatment through NO inhibition, as indicated by our finding of a significant reduction in FeNO after n-3 fatty acid supplementation.

N-3 fatty acids seem to be an effective nonpharmacological treatment for exercise-induced bronchoconstriction (EIB), which may facilitate physical activity. In patients with asthma who experience EIB, cysteinyl leukotrienes (leukotriene C₄, D₄, and E₄) and prostaglandin D₂ are continuously released into the airways after an exercise challenge, corresponding to acute bronchoconstriction development.⁶ Because EIB in asthma has an inflammatory basis, it is reasonable that n-3 fatty acid supplementation may reduce its severity. A study showed that, compared with individuals receiving

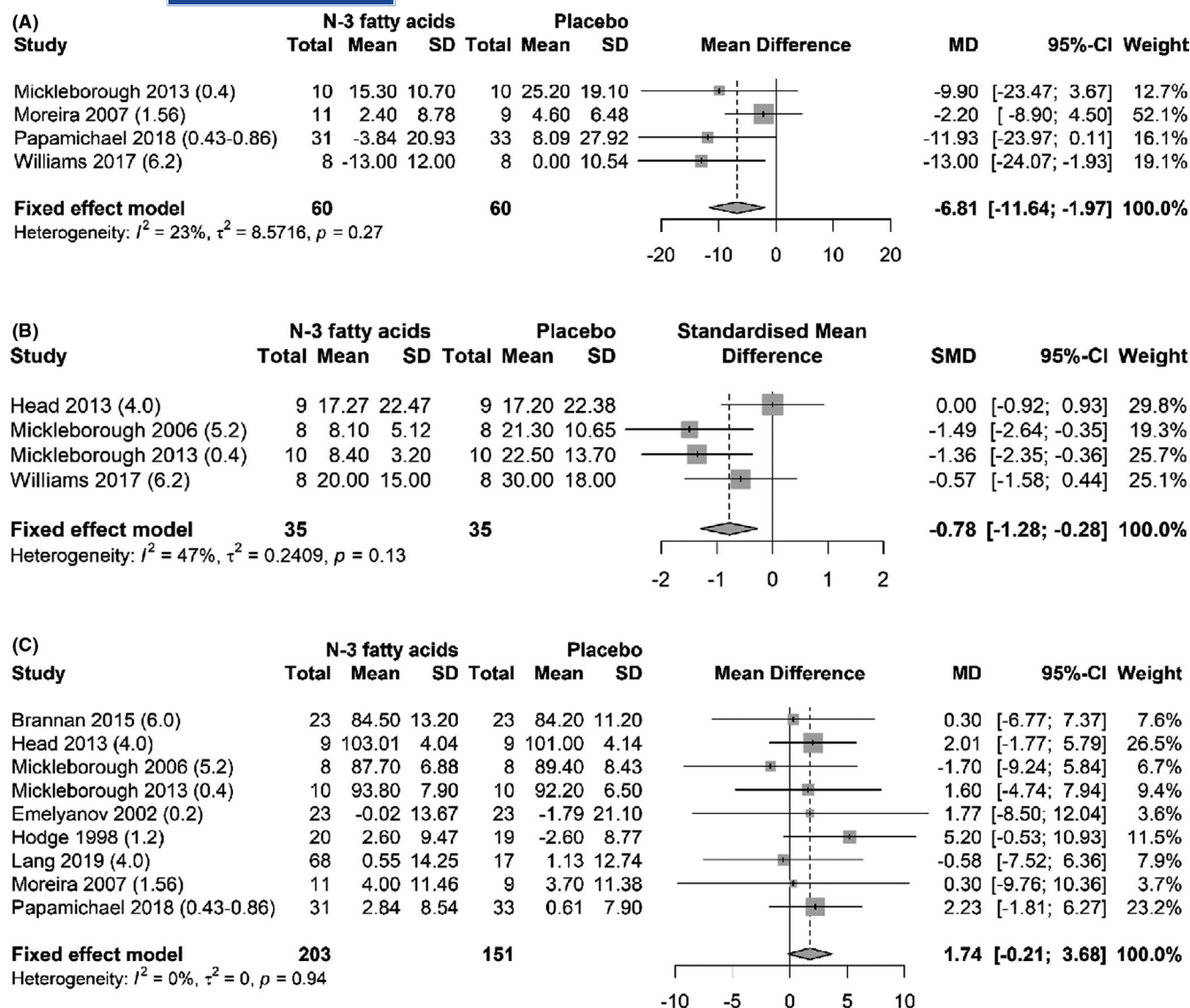


FIGURE 1 Summarized differences of FeNO (A), the exercise challenge test (B), and FEV₁ (C) under N-3 Fatty Acid Supplementation. The dose (g/d) used in each study was presented in the bracket after the study name. Definition of abbreviation: CI, confidence interval; MD, mean difference; SD, standard deviation; SMD, standardized mean difference

placebo supplements, those receiving n-3 fatty acid supplements exhibited significant decreases in sputum differential cell count percentage and concentrations of cysteinyl leukotrienes, prostaglandin D₂, interleukin-1 β , and tumor necrosis factor- α before and after exercise.⁷ Therefore, we suggest that n-3 fatty acid supplementation represents a potentially beneficial nonpharmacologic intervention in patients with asthma with EIB.

Our study had some limitations. In the analysis, the effect of fatty acid supplementation on symptom scores was borderline. The result was possibly affected by the small size of the studies, and the different dosage, duration, and the questionnaire used in the studies. More large-scale studies using the same questionnaire were needed to confirm the effect of n-3 fatty acid on symptom score. As pointed out by Venter et al, the effect of n-3 fatty acid on asthma is influenced by a wide range of genetic polymorphisms.

Although our research showed that n-3 fatty acid has no significant protective effect other than feno and EIB, future studies including genetic analyses may better define the effect of n-3 fatty acid on asthma.²

N-3 fatty acid supplementation may provide a protective effect on FeNO and a decrease in postexercise FEV₁ decline. We found that high-dose supplementation (4000 mg/d) for 3 weeks leads to reduced FeNO production and exercise-induced bronchoconstriction. The amount of omega-3 fatty supplementation that seemed to have a beneficial effect was higher than current EU recommendations (250mg/d) regarding EPA and DHA intake in this age group (>2 years). Therefore, high-dose supplementation for over 3 weeks was suggested for patients with asthma, particularly those with elevated FeNO and exercise-induced bronchoconstriction.

TABLE 1 Summarized mean difference and 95% confidence interval of outcomes and subgroup analysis

Outcome	Dosage			Duration			Age		
	N-3 fatty acids vs. placebo			N-3 fatty acids vs. placebo			N-3 fatty acids vs. placebo		
	Total	High	Low	P value ^a	Long	Short	P value ^b	Adult	Children
FEV ₁ (%)	1.74 [-0.21, 3.68]	-0.64 [-5.80, 4.52]	2.13 [0.03, 4.23]	.33	1.79 [-0.19, 3.78]	0.30 [-9.76, 10.36]	.78	1.16 [-1.41, 3.73]	2.52 [-0.46, 5.50]
FVC (%)	1.24 [-1.21, 3.68]	-0.50 [-8.74, 7.74]	1.40 [-1.16, 3.96]	.67	1.19 [-1.3, 3.68]	2.58 [-11.62, 16.78]	.85	0.61 [-2.36, 3.57]	2.57 [-1.75, 6.89]
FEV ₁ /FVC (%)	0.01 [-0.03, 0.05]	-2.90 [-11.94, 6.14]	0.01 [-0.03, 0.03]	.53	—	—	—	-2.90 [-11.94, 6.14]	0.02 [-0.03, 0.05]
PEF (L)	21.83 [-19.39, 63.04]	6.95 [-16.62, 30.51]	35.25 [-22.93, 93.43]	.38	—	—	—	24.49 [-22.10, 71.08]	10.20 [6.77, 13.63]
PEF (%)	-1.37 [-4.78, 2.04]	—	—	—	—	—	—	-1.42 [-5.06, 2.21]	-1.00 [-10.94, 8.94]
FeNO (ppb)	-6.81 [-11.64, -1.97]	-13.00 [-24.07, -1.93]	-5.35 [-10.72, 0.03]	.22	-11.82 [-18.80, -4.83]	-2.20 [-8.90, 4.50]	.05	-5.82 [-11.10, -0.54]	-11.93 [-23.97, 0.11]
Symptom score	-0.55 [†] [-1.09, -0.002]	-0.01 [-0.53, 0.51]	-0.82 [-1.56, -0.08]	.08	-0.64 [-1.23, -0.04]	0.14 [-0.75, 1.02]	.16	-0.49 [-1.14, 0.15]	-0.74 [-1.97, 0.50]
Bronchodilator use (puffs/ dosages per day)	-1.35 [-3.05, 0.36]	0.16 [-1.94, 2.27]	-2.82 [-6.00, 0.37]	.13	—	—	—	—	—
Changes in FEV ₁ decline after exercise (%)	-0.78 [-1.28, -0.28]	-0.99 [-1.89, -0.09]	-0.66 [-2.00, 0.67]	.69	—	—	—	—	—

Note: All values are presented as mean difference [95% CI] unless otherwise indicated.

Abbreviations: FeNO, fraction of exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; FEV₁/FVC, ratio of forced expiratory volume in 1 s to forced vital capacity; FVC, forced vital capacity; PEF, peak expiratory flow; ppb, parts per billion; SD, standard deviation.

[†]The effect of n-3 fatty acid on symptom score was borderline (95% CI -1.02 to -0.002, $P = .049$, $I^2 = 80\%$). Due to the high heterogeneity and probable publication bias revealed by Egger's test (Table S3), it was not reported as a significance finding in the main text.

^a P value for the subgroup analysis examining the difference in intervention effect between high- and low-dosage study groups.

^b P value for the subgroup analysis examining the difference in intervention effect between long- and short-duration groups.

^c P value for the subgroup analysis examining the difference in intervention effect between adult and children groups.

FUNDING INFORMATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Yu-Hsin Wang performed systematic searching, study selection, quality assessment, data extraction, and meta-analysis and wrote the manuscript with help from Dr. Yang-Ching Chen. Mr. Hsien-Yu Fan, Prof. Shih-Yi Huang, and Dr. Han-Pin Kuo assisted in data interpretation and critical review for important intellectual content. Dr. Yang-Ching Chen reviewed the study design, collected data, interpreted data, supervised the study, and revised the manuscript critically for valuable academic content. André Moreira and Maria Michelle Papamichael shared original data and helped with the analysis. All authors have approved the final manuscript and agree to be accountable for all aspects of the work.

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SUPPORTING INFORMATION

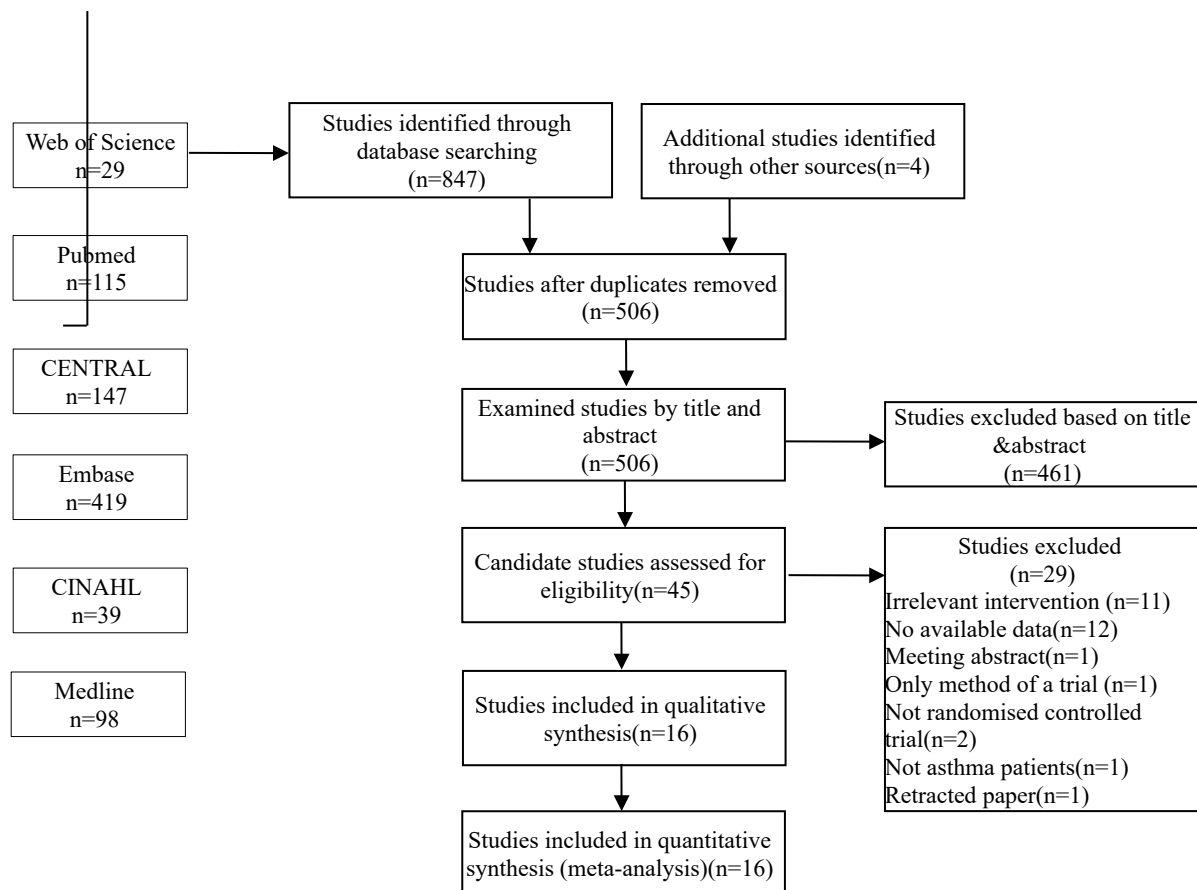
Additional supporting information may be found online in the Supporting Information section.

ONLINE SUPPLEMENT APPENDIX

N-3 Fatty Acid Supplementation in Asthma Management: A Systematic Review and Meta-analysis

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Figure S1. Studies selection flowchart



We conducted a literature search of publications up to May 2021 using the following databases: CENTRAL, CINAHL (EBSCO), PubMed, Web of Science, MEDLINE, and EMBASE. The literature search identified 840 potential RCTs, and 4 additional citations were retrieved by manual checking of reference lists. After removing duplicates, two reviewers independently screened the 503 eligible papers by scanning titles and abstracts. Of them, 458 were excluded and 29 were considered to be inappropriate, leaving 16 relevant trials, which were analyzed.

TABLE S1. Baseline characteristics of the included studies

Study, authors, year	Design	Country	Mean [SD] age, years	Males, %	[†] N-3 fatty acids, n	[†] Control, n	N-3 fatty acids, g/day	[†] Duration, weeks	Control oil
Arm et al, 1988	Parallel	United Kingdom	25.4 [—]	50	12	8	5.4	10	Olive oil
Arm et al, 1989	Parallel	United Kingdom	26 [—]	41	9	8	5.4	10	Olive oil
Brannan et al, 2015	Crossover	Canada	28 [8.86]	61	23	23	6	3	Omega-6+omega-9 oil
Emelyanov et al,	Parallel	United	39.1	26	23	23	0.2	8	Olive oil

2002		Kingdom	[3.26]						
Hodge et al, 1998	Parallel	Australia	10.26	41	20	19	1.2	24	Omega-6 oil+olive oil
			[0.72]						
Head et al, 2013	Crossover	United States	22.36	67	9	9	4	3	Corn and soy oil
			[1.31]						
Lang et al, 2019	Parallel	United States	14.6	48	77	21	4	24	Soy oil
			[2.2]						
McDonald et al, 1990	Crossover	Australia	^a —	NA	15	15	4.5	10	Olive oil
Mickleborough et al, 2006	Crossover	United States	23 [1.6]	63	8	8	5.2	3	Olive oil
Mickleborough et al, 2013	Crossover	United States	22.6	60	20	20	0.4	3	Olive oil
			[2.1]						
Moreira et al, 2007	Parallel	Portugal	37.85	0	11	9	1.56	2	Amide
			[—]						
Nagakura et al, 2000	Parallel	Japan	11.02	52	11	12	0.72–1.44	40	Olive oil
			[3.98]						
Papamichael et al, 2018	Parallel	Australia	7.99	52	31	33	*0.43–0.86	24	Normal diet
			[2.24]						
Stenius-Aarniala et al, 1989	Crossover	Finland	40 [—]	34	29	29	3.2	10	Olive oil
Thien et al, 1993	Parallel	United Kingdom	^b —	52	15	10	5.4	24	Olive oil
Williams et al, 2017	Crossover	United Kingdom	27.5	100	8	8	6.2	3	medium chain triacylglycerols
			[8.32]						

[†] In the crossover-design trials, half of the patients start with n-3 fatty acids, and the other half start with placebo.

[‡] Duration of either n-3 fatty acids or placebo for crossover trials.

^a Age range 28–72 years old

^b Age range 19–42 years old

*Intake from fatty fish

Of the 16 trials, 7 were crossover-design trials,¹⁻⁷ and 9 were parallel-design trials (Table 1).⁸⁻¹⁶ The median study size was 21.5 participants; in total, this meta-analysis included 464 individuals treated with n-3 fatty acids or placebo for 7766 person-weeks. The mean ages of the study populations ranged from 8 to 40 years. Of the intervention groups, three included exercise-induced bronchoconstriction (EIB) with asthma^{2,4,5} and one comprised obese individuals with asthma.⁷ The median n-3 fatty acid dosage was 4 (range, 0.2–6.2) g/day, and the median treatment duration was 10 (range, 2–40) weeks. A study using the Mediterranean diet was also included in the analysis because the main difference between the intervention and control group was the consumption of fatty fish. Table S1 and S2 describe the detailed characteristics and quality assessment of included studies, respectively.

TABLE S2. Quality assessment of the included studies using the revised Cochrane risk-of-bias tool for randomized trials

Study ID	Experimental	Comparator	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Arm 1988	N-3 fatty acids	Placebo	●	●	●	●	●	●
Arm 1989	N-3 fatty acids	Placebo	●	●	●	●	●	●
Brannan 2015	N-3 fatty acids	Placebo	●	●	●	●	●	●
Emelynov 2002	N-3 fatty acids	Placebo	●	●	●	●	●	●
Head 2013	N-3 fatty acids	Placebo	●	●	●	●	●	●
Hodge 1998	N-3 fatty acids	Placebo	●	●	●	●	●	●

Lang 2019	N-3 fatty acids	Placebo	●	●	●	●	●	●
Mickleborough 2006	N-3 fatty acids	Placebo	●	●	●	●	●	●
Mickleborough 2013	N-3 fatty acids	Placebo	●	●	●	●	●	●
Moreira 2007	N-3 fatty acids	Placebo	●	●	●	●	●	●
Nagakura 2000	N-3 fatty acids	Placebo	●	●	●	●	●	●
Papamichael 2018	N-3 fatty acids	Placebo	●	●	●	●	●	●
Stenius-Aarniala 1989	N-3 fatty acids	Placebo	●	●	●	●	●	●
Thien 1993	N-3 fatty acids	Placebo	●	●	●	●	●	●
Williams 2017	N-3 fatty acids	Placebo	●	●	●	●	●	●
Legend:			●	Low risk				
			●	Some concerns				
			●	High risk				

McDonald et al was not include in the quality assessment due to lack of enough information

TABLE S3. Analysis of publication bias using the Egger’s test

Outcome	Intercept	SE	slope	t Test	df	P value
FEV ₁ (%)	3.83	0.61	−0.74	−1.22	7	0.26
FVC (%)	1.29	0.87	−0.02	−0.02	3	0.98
FEV ₁ /FVC	0.02	0.22	−0.42	−1.89	1	0.31
PEF (L)	27.78	5.88	0.90	0.15	4	0.89
PEF (%)	−1.32	0.23	−0.02	−0.09	1	0.95
FeNO (ppb)	8.06	1.02	−3.14	−3.09	2	0.09
Symptom score	1.14	1.67	−4.07	−2.44	8	0.04
Bronchodilator use	−1.05	4.38	−0.58	−0.17	4	0.90
Exercise challenge test	5.52	6.93	−12.27	−1.77	2	0.22

Abbreviations: SE = standard error; %pred, %predicted; FEV₁= forced expiratory volume in 1 s; FVC = forced vital capacity; FEV₁/FVC, ratio of forced expiratory volume in 1 s to forced vital capacity; PEF = peak expiratory flow; FeNO = fraction of exhaled nitric oxide

High heterogeneity was observed between the studies reporting symptom score. Clear differences were noted in studies by Nagakura et al and Mickleborough et al, which favored n-3 fatty acids. Publication bias assessed using Egger’s test revealed potential publication bias. Therefore, the trim and fill analysis was performed, which revealed similar findings.¹⁷

TABLE S4. Meta-regression analysis on potentially confounding factors in included studies on obesity categories and pulmonary function

Outcome	Confounding factors	Estimate	±SE	P value
FEV ₁ (%pred)	Dosage (g)	−0.48	0.51	0.35
	Duration (week)	0.07	0.10	0.49
	Latitude (°)	−0.03	0.03	0.30
	Age (years)	−0.09	0.11	0.45
	Publication (year)	−0.11	0.15	0.46
	Males (%)	0.03	0.05	0.62
	Sample size (n)	0.00	0.04	1.00
FVC (%pred)	Dosage (g)	0.09	0.13	0.47
	Duration (week)	−0.78	0.68	0.25
	Latitude (°)	−0.03	0.03	0.46
	Age (years)	−0.10	0.17	0.56
	Publication (year)	0.23	0.35	0.51
	Males (%)	−0.01	0.07	0.94
	Sample size (n)	0.05	0.05	0.37
FEV ₁ /FVC (%)	Dosage (g)	0.05	0.34	0.89
	Duration (week)	0.14	0.22	0.53
	Latitude (°)	0.00	0.02	0.85
	Age (years)	−0.00	0.17	0.99

	Publication (year)	0.22	0.34	0.51
	Males (%)	0.06	0.11	0.61
	Sample size (n)	0.01	0.03	0.61
PEF (L)	Dosage (g)	−9.77	8.89	0.27
	Duration (week)	−1.64	3.44	0.63
	Latitude (°)	0.25	0.47	0.59
	Age (years)	0.58	1.42	0.68
	Publication (year)	4.14	3.02	0.17
	Males (%)	−1.08	0.83	0.19
	Sample size (n)	−0.05	0.67	0.94
PEF (%pred)	Dosage (g)	0.03	0.21	0.90
	Duration (week)	0.09	1.36	0.95
	Latitude (°)	−0.00	0.06	0.96
	Age (years)	−0.00	0.24	0.98
	Publication (year)	−0.01	0.17	0.97
	Males (%)	−0.07	0.53	0.90
	Sample size (n)	0.01	0.13	0.92
FeNO (ppb)	Dosage (g)	−0.87	1.50	0.56
	Duration (week)	−0.26	0.37	0.47
	Latitude (°)	0.04	0.10	0.66
	Age (years)	0.36	0.23	0.11
	Publication (year)	−0.99	0.51	0.05
	Males (%)	−0.12	0.06	0.06
	Sample size (n)	−0.09	0.18	0.62
Symptom score	Dosage (g)	0.29	0.15	0.05
	Duration (week)	−0.02	0.03	0.41
	Latitude (°)	−0.01	0.01	0.40
	Age (years)	0.02	0.02	0.37
	Publication (year)	−0.03	0.02	0.25
	Males (%)	−0.01	0.01	0.59
	Sample size (n)	0.01	0.01	0.36
Bronchodilator use (dosages/puffs per day)	Dosage (g)	0.85	0.41	0.04
	Duration (week)	0.17	0.14	0.20
	Latitude (°)	0.33	0.16	0.03
	Age (years)	0.11	0.17	0.55
	Publication (year)	−0.27	0.07	<0.01
	Males (%)	−0.04	0.06	0.56
	Sample size (n)	−0.00	0.09	0.97
Exercise challenge test	Dosage (g)	0.09	0.19	0.62
	Latitude (°)	0.02	0.07	0.73
	Age (years)	0.05	0.22	0.83
	Publication (year)	0.09	0.10	0.36
	Males (%)	0.01	0.01	0.29
	Sample size (n)	−0.04	0.08	0.66

Abbreviations: SE = standard error; %pred, %predicted; FEV₁ = forced expiratory volume in 1 s; FVC = forced vital capacity; FEV₁/FVC, ratio of forced expiratory volume in 1 s to forced vital capacity; PEF = peak expiratory flow; FeNO = fraction of exhaled nitric oxide

Meta-regression revealed relationships between the bronchodilator use and n-3 fatty acid dosage, publication year, and latitude. Significant heterogeneity was found between the studies reporting bronchodilator use. This was attributable to the study of Mickleborough et al (2013), which indicated an obvious reduction in medication use, in contrast to the other studies. After excluding the study of Mickleborough et al (2013), the heterogeneity decreased, and the meta-regression indicated that the significance only existed in duration of n-3 fatty acid supplementation. Because the types of bronchodilator vary with age, the

effect of n-3 fatty acid supplementation on bronchodilator use may be related to the year the studies published.

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