Dietary Interventions for Autism Spectrum Disorder: A Meta-analysis

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abstract

CONTEXT: Dietary interventions such as restrictive diets or supplements are common treatments for young people with autism spectrum disorder (ASD). Evidence for the efficacy of these interventions is still controversial.

OBJECTIVE: To assess the efficacy of specific dietary interventions on symptoms, functions, and clinical domains in subjects with ASD by using a meta-analytic approach.

DATA SOURCES: Ovid Medline, PsycINFO, Embase databases.

STUDY SELECTION: We selected placebo-controlled, double-blind, randomized clinical trials assessing the efficacy of dietary interventions in ASD published from database inception through September 2017.

DATA EXTRACTION: Outcome variables were subsumed under 4 clinical domains and 17 symptoms and/or functions groups. Hedges' adjusted g values were used as estimates of the effect size of each dietary intervention relative to placebo.

RESULTS: In this meta-analysis, we examined 27 double-blind, randomized clinical trials, including 1028 patients with ASD: 542 in the intervention arms and 486 in the placebo arms. Participant-weighted average age was 7.1 years. Participant-weighted average intervention duration was 10.6 weeks. Dietary supplementation (including omega-3, vitamin supplementation, and/or other supplementation), omega-3 supplementation, and vitamin supplementation were more efficacious than the placebo at improving several symptoms, functions, and clinical domains. Effect sizes were small (mean Hedges' g for significant analyses was 0.31), with low statistical heterogeneity and low risk of publication bias.

LIMITATIONS: Methodologic heterogeneity among the studies in terms of the intervention, clinical measures and outcomes, and sample characteristics.

CONCLUSIONS: This meta-analysis does not support nonspecific dietary interventions as treatment of ASD but suggests a potential role for some specific dietary interventions in the management of some symptoms, functions, and clinical domains in patients with ASD.

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Dr Fraguas conceived and planned the original idea of the study, double screened all articles in 3 phases, double checked data extraction from each eligible study, performed the analysis, wrote the first draft, and approved the manuscript; Dr Díaz-Caneja conceived and planned the original idea of the study, double checked data extraction from each eligible study, and wrote the manuscript; (Continued)

To cite: Fraguas D, Díaz-Caneja CM, Pina-Camacho L, et al. Dietary Interventions for Autism Spectrum Disorder: A Meta-analysis. *Pediatrics.* 2019;144(5):e20183218

Autism spectrum disorder (ASD) is a group of complex neurodevelopmental disabilities, characterized by a set of core symptoms involving social interaction and communication impairment, restricted interests, and repetitive behaviors.[1] Educational, psychosocial, and pharmacologic interventions appear to improve associated psychiatric symptoms and functioning in people with ASD, especially if applied at early developmental stages.[1,2] Yet few treatments are efficacious for the core symptoms of autism, with only early and intensive treatments revealing improvements on dyadic and/or social interaction deficits.[3,4] Many patients with ASD and their relatives seek alternative medicine and nonmedicine treatment strategies. For example, some 25% of people with ASD use dietary interventions such as restrictive diets (the most common being gluten- and casein-free diets) and nutritional supplements such as vitamins, minerals, amino acids, omega-3, and herbal compounds.[5] However, results on the efficacy of dietary interventions in ASD are still controversial.[6–9] This may be because authors of most studies assess dietary interventions as a whole, without differentiating specific interventions, or they assess treatment response as a global measure, without focusing on specific ASD core or associated symptoms or clinical domains.[10]

Using a meta-analytic approach, we sought to assess the efficacy of specific dietary interventions (ie, restrictive diets or nutritional supplements) relative to placebo on specific symptoms, functions, and clinical domains in subjects with ASD.

METHODS

Search Strategies

Using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, we conducted a systematic 2-step literature search to identify appropriate studies.[11] To detect restrictive diet and nutritional supplement studies in patients with ASD, we first performed a computerized Ovid Medline, PsycINFO, and Embase database search from inception through September 2017. We used 2 sets of search terms, detailed in Supplemental Table 4: (1) ASD terms and (2) dietary intervention terms. These searches were limited to [clinical trial or randomized controlled trial or controlled clinical trial] and [English language]. Second, we conducted a manual search of the reference lists of the articles included in the meta-analyses for any studies not identified by the computerized literature search.

Study Selection Criteria

The flowchart of the systematic literature search strategy is shown in Figure 1. The initial literature search yielded 2631 studies. After removing 348 duplicates, we evaluated 2283 potential studies.

Two consultant psychiatrists and a biochemistry specialist (D.F., M.d.M., and E.G.-V.) double screened all articles in 3 phases with discrepancies resolved through discussion and consensus. In phase 1, we screened the titles and abstracts of the retrieved articles. We excluded articles if they met any of the following hierarchical exclusion criteria: (1) they were not published in English as original peer-reviewed articles; (2) they did not include patients with a diagnosis of ASD, pervasive development disorder

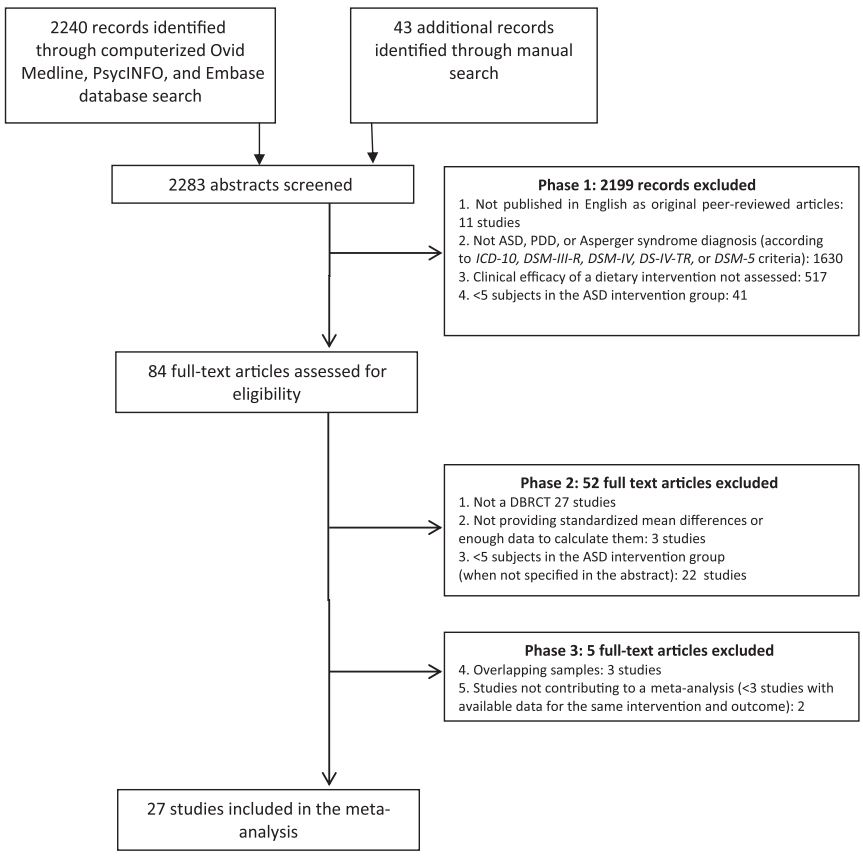

FIGURE 1
PRISMA flow diagram of the systematic literature search strategy. DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; *ICD-10*, *International Classification of Diseases, 10th Revision*.

(PDD), or Asperger syndrome (according to *International Classification of Diseases, 10th Revision*; *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* [*DSM-III-R*]; *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [*DSM-IV*]; *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision* [*DSM-IV-TR*]; or *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, criteria); (3) they did not assess clinical efficacy of a dietary intervention or they assessed the efficacy of foods not present in nature; and (4) there were <5 subjects in the ASD intervention group. Of the 2283 studies, 84 did not fulfill any exclusion criterion and qualified for phase 2.

Phase 2 consisted of a comprehensive review of the full text of the articles. We excluded studies if they met any of the following hierarchical exclusion criteria: (1) the study did not provide standardized mean differences or odds ratios or they could not be calculated on the basis of correlations, independent group means, risk ratios, or 2 × 2 contingency tables; (2) there were <5 subjects in the ASD intervention group (for studies in which that information was missing from the abstract); and (3) the study design was not a parallel or crossover placebo-controlled, double-blind randomized clinical trial (DBRCT). Of the 84 studies, 32 qualified for phase 3.

In phase 3, we used the following hierarchical criteria to determine the inclusion of studies with overlapping samples to ensure that only independent samples were included in each of the meta-analyses: study with (1) the largest sample and (2) the most recent publication. When data from at least 3 independent studies assessing the efficacy of the same type of intervention on the same outcome variable (ie, "symptom/function" or "clinical domain") were available, we included the study for meta-analysis. Of the 32 studies, 27 original independent studies met criteria for inclusion in the final meta-analysis database.[12–38]

Data Extraction

Two researchers (M.d.M. and E.G.-V.) extracted data from each eligible study and 2 different researchers (D.F. and C.M.D.-C.) double checked it. Data extracted included publication year, type of dietary intervention (predictor variable), symptoms and/or functions groups and clinical domains (outcome variable), duration of the intervention, sample characteristics (clinical diagnosis, proportion of girls and/or women, age at baseline, age group (ie, child and adolescent sample, adult sample, mixed sample), clinical and/or functional severity at baseline, and intellectual functioning), concomitant pharmacologic treatment, baseline nutritional deficits, country (or countries) where the study was conducted, number of sites, and statistics to calculate effect sizes (ESs) for the meta-analyses. In studies with a crossover design, we extracted data from just the first phase of the study to avoid a carryover effect.[39]

Classification of Dietary Interventions

We divided dietary interventions into restrictive diets and nutritional supplements. There were <3 independent studies assessing the same predictor variable and the same clinical outcome in the case of restrictive diets, so we excluded them from phase 3. There were enough studies to contribute to an independent meta-analysis on the clinical effect of 2 types of nutritional supplements: omega-3 polyunsaturated fatty acids (including α-linolenic acid, eicosapentaenoic acid, docosahexaenoic acid, and a combination of them) and vitamins (including vitamin B_6, vitamin B_{12}, vitamin C, vitamin D, folic acid, folinic acid, and combinations of different vitamins). Thus, we conducted a meta-analysis on the global efficacy of "dietary supplementation" (including "omega-3/vitamin supplementation/other supplementation") and 2 additional subgroup meta-analyses on the efficacy of "omega-3 supplement" and "vitamin supplement." The interventions assessed in each of the studies included in the meta-analyses are shown in Table 1.

Classification of Outcome Variables: Symptomatic Groups and Clinical Domains

The 27 original independent studies used 206 different instruments to assess the various outcome variables. To add evidence to the important question of the efficacy of diets and supplements for improving problem behaviors in individuals with ASD and the impossibility of conducting a more straightforward analysis of multiple studies with one sole end point, we decided to combine end points in a predefined and expert-consensus manner. Two qualified reviewers (M.P. and C.M.), both consultant child and adolescent psychiatrists with extensive clinical and research experience in ASD, independently classified the instruments into a manageable number of outcome variables, with discrepancies resolved by discussion. This allowed us to consolidate outcome variables into 4 clinical domains and 17 symptoms and/or functions groups, on the basis of a balance of (1) how symptoms are organized in recent nosological classifications and (2) the design (target symptoms and subscales) of the most common instruments used to assess autistic symptoms and associated psychopathology. Each clinical domain included a range of symptomatic groups: (1) "core symptoms," including pragmatic language deficits, social deficits, stereotypes, and restricted or repetitive behaviors; (2) "associated

TABLE 1 Characteristics of Included Studies

Study, y	Intervention	Outcome (Symptoms and/or Functions Groups)	Outcome (Clinical Domains)	Diagnostic Criteria	Quality Assessment Score (0–6)	Total Sample Size	Intervention Sample Size	Length of Intervention, wk	Age of Participants, y, Range	Mean Age, y, Intervention Group	Mean Age, y, Control Group	Female Intervention Group, %	Female Control Group, %
Adams and Holloway, 2004[12]	Vitamin	3-6-9-12-13-14	A-B-D	Not reported	3	20	11	12	3–8	5.20	5.40	9.00	11.10
Adams et al, 2011[13]	Vitamin and/or mineral supplement	2-3-4-7-9-12-13	A-B-D	Not reported	5	141	72	12	5–60	11.70	9.89	11.10	11.60
Al-Ayadhi and Elamin, 2013[14]	Camel milk	13	D	*DSM-IV-TR*	3	36	25	2	2–12	N/A	N/A	N/A	N/A
Al-Ayadhi et al, 2015[15]	Camel milk	2-4-9-13-14	A-B-D	*DSM-IV-TR*	3	40	25	2	2–12	7.80	7.80	N/A	N/A
Amminger et al, 2007[16]	Omega-3	7-9-13-14	A-D	*DSM-IV*	6	12	7	6	5–17	10.50	12.10	0	0
Bent et al, 2011[17]	Omega-3	1-2-3-6-7-8-9-13-14	A-B-C-D	*DSM-IV-TR*	5	25	13	12	3–8	5.80	5.80	N/A	N/A
Bent et al, 2014[18]	Omega-3	2-4-7-9-13-14	A-B-D	*DSM-IV-TR*	6	57	29	6	5–8	7.30	7.10	10.30	14.30
Bertoglio et al, 2010[19]	Vitamin B_{12}	2-6-9-13	C-D	*DSM-IV-TR*	2	30	13	6	3–8	N/A	N/A	N/A	N/A
Chez et al, 2002[20]	L-carnosine	5-6-13-14	A-D	*DSM-IV-TR*	3	31	14	8	3–12	N/A	N/A	N/A	N/A
Dolske et al, 1993[21]	Vitamin C	1-2-9-11-13	A-B-D	*DSM-III-R*	2	18	9	10	6–19	N/A	N/A	N/A	N/A
Fahmy et al, 2013[22]	L-carnitine	13	D	Not reported	4	30	16	24	2–9	5.75	5.71	21.40	12.50
Findling et al, 1997[23]	Vitamin B_6 + Mg	2-6-7	A-B-D	*DSM-III-R*	5	20	10	4	3–17	6.30	6.30	10.00	10.00
Frye et al, 2016[24]	Folinic acid	1-2-3-4-7-8-9-10-11-13-14	A-B-D	*DSM-IV-TR*	5	48	23	12	3–14	7.60	7.20	22	20
Geier et al, 2011[25]	L-carnitine	2-3-4-6-9-13	A-B-C-D	Not reported	6	27	16	12	3–10	6.30	6.70	12.50	18.20
Hasanzadeh et al, 2012[26]	Ginkgo biloba	7-9-13-14	A-D	*DSM-IV-TR*	5	47	23	10	4–12	6.04	6.76	17.40	16.70
Kerley et al, 2017[27]	Vitamin D	2-6-7-9-13-14	A-B-C-D	*DSM*	6	42	22	20	N/A	7.90	6.90	17.00	10.00
Kern et al, 2001[28]	Dimethylglycine	7-9-13-14	A-D	*DSM-IV*	2	37	18	4	3–11	N/A	N/A	N/A	N/A
Klaiman et al, 2013[29]	Tetrahydrobiopterin	2-6-7-9-13-14	A-B-C-D	*DSM-IV-TR*	6	39	23	16	3–7	5.01	5.02	13.04	21.70

TABLE 1 Continued

Study, y	Intervention	Outcome (Symptoms and/or Functions Groups)	Outcome (Clinical Domains)	Diagnostic Criteria	Quality Assessment Score (0–6)	Total Sample Size	Intervention Sample Size	Length of Intervention, wk	Age of Participants, y, Range	Mean Age, y, Intervention Group	Mean Age, y, Control Group	Female Intervention Group, %	Female Control Group, %
Levine et al, 1997[30]	Inositol	13	D	*DSM-III-R*	2	20	10	4	5–7	5.60	5.60	10.00	10.00
Mankand et al, 2015[31]	Omega-3	1-2-3-9-10-11-13-14	A-B-D	*DSM-IV-TR*	4	37	18	24	2–5	3.90	3.50	22.20	31.60
Munasinghe et al, 2010[32]	Proteolytic enzyme	3-9-12	A-D	*DSM-IV*	5	27	11	12	3–8	5.70	5.80	14.00	18.00
Parellada et al, 2017[33]	Omega-3	2-4-6-9-13-14	A-B-C-D	*DSM-IV-TR*	6	77	40	8	5–17	9.39	10.03	24.25	8.58
Pusponegro et al, 2015[35]	Gluten and casein supplementation	13	D	*DSM-IV-TR*	3	47	23	1	2–10	5.40	5.10	12.50	11.50
Rimland et al, 1978[34]	Vitamin B_6	3	A	Not reported	2	32	16	N/A	8–19	12.40	12.40	25.00	25.00
Singh et al, 2014[36]	Sulforaphane	1-2-3-7-9-11-13-14	A-B-C-D	*DSM-IV*	1	37	26	18	13–30	17.90	16.60	N/A	N/A
Voigt et al, 2014[37]	Omega-3	2-13-14	C-D	*DSM-IV*	1	38	22	24	3–10	5.80	6.50	16.70	16.70
Yui et al, 2012[38]	Omega-3	4-7-9-13-14	A-D	*DSM-IV*	2	13	7	16	6–28	13.90	15.50	14.30	0.00

Symptoms and/or functions groups: 1: Anxiety and/or affect; 2: autistic general psychopathology; 3: behavioral problems and impulsivity; 4: cognition; 5: communication; 6: global severity; 7: hyperactivity and irritability; 8: inflexible behavior; 9: language (general); 10: language (pragmatic); 11: sensory and motor; 12: sleep; 13: social-autistic; 14: stereotypies and restricted and repetitive behavior. Clinical domains: A: associated symptoms; B: autism global; C: clinical global impression; D: nuclear symptoms. *DSM, Diagnostic and Statistical Manual of Mental Disorders*; N/A, not available.

symptoms," including deficits in attention, irritability, behavioral difficulties, cognition, language (not pragmatic), anxiety and/or affect, sleep, and sensory sensitivities; (3) "autism global," including "autistic general psychopathology"; and (4) "clinical global impression," including Clinical Global Impressions (CGI) Scale[40] ratings. Therefore, we decided to use composite end points with mutually exclusive categories of symptoms that contribute to either a full understanding of the clinical picture of ASD (eg, language, nonverbal communication, social responsiveness) or functionally relevant comorbidities (eg, irritability, hyperactivity). We conducted meta-analyses for each of the 4 clinical domains and each of the 17 symptoms and/or functions groups. For further details of the classification of the outcome variables, see Supplemental Table 5.

Quality Assessment

We assessed the quality of the 27 included studies using an item checklist constructed for this review inspired by the Cochrane Collaboration's tool for assessing risk of bias[41] and in previously published quality assessments.[42,43] The assessment evaluated the following categories: (1) study design, such as selection bias (random sequence generation, allocation concealment), attrition bias, role of the funding source, and sample size; (2) demographic and clinical characteristics, such as clearly reported inclusion and exclusion criteria, accurate method of ASD diagnosis, age, and sex reported; and (3) results, such as reported drop-out rates, clinical assessments, statistical thresholds, and reporting bias. We scored categories on a scale of 0 to 2 and each study on a scale of 0 to 6, with higher values representing greater quality (see Table 1, Supplemental Table 6).

Statistical Analysis

We entered data into an electronic database and analyzed them with a quantitative meta-analytical approach using Comprehensive Meta-Analysis Software version 2 (Biostat, Inc, Englewood, NJ).[44] Standardized mean differences using Hedges' adjusted g were used as estimates of the ES of each dietary intervention (nutritional supplementation) relative to placebo. Pooled 95% confidence intervals (CIs) were calculated. The magnitude of Hedges' g can be interpreted by using Cohen's convention as small (0.2–0.5), moderate (0.5–0.8), or large (>0.8).[45] We included as outcomes the mean overall differences between dietary intervention and placebo groups in change (ie, the score change between end point and baseline in the clinical test or scale during the trial) in symptoms and/or functions and clinical domains (as a mean score of the symptoms and/or functions comprising each domain). If the change value was not available for a certain scale, we used end-point differences between intervention and control conditions. We minus transformed tests or scales for which low scores indicate better performance so that higher scores always correspond to better clinical outcomes. When pre-post correlation value was not available and could not be calculated, we used an imputed default r value of 0.5. Although the bias is notably small for every scenario of imputation strategies for pre-post correlation,[46] we decided to use an imputation of $r = 0.5$ because this is a conservative approach. On the basis of the known clinical heterogeneity of ASD and the methodologic heterogeneity of study designs and outcome measures, we expected that the estimates would vary substantially between studies, so we ran random-effects models. In the random-effects analysis, each study was weighted by the inverse of its variance and the between-studies variance.[47] To explore if particular studies influenced the random weighted mean, we conducted an "influence analysis" by studying the effect of each individual study on the overall estimate by excluding 1 study at a time.[48]

We assessed statistical heterogeneity through visual inspection of forest plots and using the Q statistic (a magnitude of statistical heterogeneity) and the I^2 statistic (a measure of the proportion of variance in summary ES attributable to heterogeneity).[49] I^2 values <30% correspond to an irrelevant amount of statistical heterogeneity.[50] We assessed publication bias by visually inspecting funnel plots and using Orwin's fail-safe N,[51] with criterion for a "trivial" standardized difference in means as 0.1 and mean standardized difference in means in missing studies as 0. This generated the number of unpublished studies required to move estimates to a nonsignificant threshold. Furthermore, we used the linear regression method of Egger et al[52] to quantify the bias captured by the funnel plot. When the funnel plot or test statistics suggested publication bias, we used the Duval and Tweedie[53] trim-and-fill method to estimate an ES corrected for publication bias.

We used meta-regressions with a random-effect model with unrestricted maximum likelihood to test effects of potential moderators (study quality, year of publication, duration of intervention, sample size, mean age of the intervention group, and percentage of girls and/or women in the intervention group) on ES estimates for significant meta-analyses. We performed meta-regressions for moderator variables if at least 4 studies assessing the same predictor and outcome variable were available.

We performed a meta-analytic subgroup analysis including studies assessing only children and adolescents (all participants <18 years old). Because authors of recent studies on the efficacy of pharmacologic and dietary supplement interventions in ASD have reported a relevant moderator effect of geographical location,[10] we performed a meta-analytic subgroup analysis by region (classifying studies into 3 groups: studies conducted in the United States, in Europe, and in other regions) instead of just including this variable as a potential moderator in the meta-regressions.

We implemented false discovery rate (FDR) correction for multiple comparisons (37 analyses for meta-analyses and 132 analyses for meta-regressions) (https://brainder.org/2011/09/05/fdr-corrected-fdr-adjusted-p-values/). This function computes the FDR threshold for a vector of P values. The percentage of tolerated false-positives was 5% ($q < 0.05$).

RESULTS

General Characteristics of the Included Studies and Study Samples

This meta-analysis includes 27 DBRCT studies,[12–38] comprising an overall sample of 1028 participants with ASD, of which 542 were in intervention groups and 486 in placebo groups. The participant-weighted average (PWA) intervention duration was 10.6 weeks (range 1–24 weeks). PWA female percentage was 10.9% (range 0%–25%). All the studies included children and adolescents (<18 years old) and 4 of them included mixed samples of children, adolescents, and adults (age range 2–60 years). The PWA age was 7.1 years. The main characteristics of the included studies are shown in Table 1, with further details in Supplemental Table 7.

Meta-analysis of the Efficacy of Dietary Supplementation on Clinical Outcomes (Specific Symptoms and/or Functions Groups and Clinical Domains)

We performed a total of 37 meta-analyses, with 25 on the effect of dietary intervention on symptoms and/or functions groups (see Table 2) and 12 on the effect of dietary intervention on clinical domains (see Table 3).

Meta-analyses revealed the following:

1. Dietary supplementation (omega-3, vitamin supplementation, and/or other supplementation) was more effective than placebo in treating the following symptoms and/or functions groups: anxiety and/or affect, autistic general psychopathology, behavioral problems and impulsivity, global severity, hyperactivity and irritability, language (general), and social-autistic and stereotypies, restricted and repetitive behaviors (see Table 2). Dietary supplementation (omega-3, vitamin supplementation, and/or other supplementation) was more effective than placebo in treating the following clinical domains: core symptoms, associated symptoms, autism global, and clinical global impression (see Table 3).
2. Omega-3 supplementation was more effective than placebo in treating the following symptoms and/or functions groups: language (general) and social-autistic (see Table 2). Omega-3 supplementation was more effective than placebo in treating the following clinical domains: core symptoms and associated symptoms (see Table 3).
3. Vitamin supplementation was more effective than placebo in treating the following symptoms and/or functions groups: global severity, language (general), stereotypies, restricted and repetitive behaviors, behavioral problems and impulsivity, and hyperactivity and irritability (see Table 2). Vitamin supplementation was more effective than placebo in treating the following clinical domains: core symptoms, associated symptoms, and clinical global impression (see Table 3).

For all types of dietary intervention, significant meta-analyses revealed small ES relative to placebo, low statistical heterogeneity, and low risk of publication bias (see Tables 2 and 3). Forest plots of meta-analyses are shown in Fig 2.

Meta-regression analyses revealed that none of the putative moderators (study quality, year of publication, length of intervention, sample size, mean age of the intervention group, and percentage of girls and/or women in the intervention group) had a significant effect on the ES estimates (see Supplemental Table 8).

Efficacy of Dietary Supplementation in the Subsample of Children and Adolescents

Twenty-three of the 27 DBRCT studies included only children and adolescents, comprising an overall sample of 802 children and adolescents with ASD, of which 411 were in intervention groups and 391 in placebo groups. Meta-analysis including only these 23 studies revealed comparable results (in terms of the magnitude and direction of the effect and statistical significance) to those found using the whole group of studies (see Supplemental Tables 9 through 10).

Meta-analytic Subgroup Analysis by Geographic Region

The meta-analytic subgroup analysis by location (United States, Europe, and other regions) revealed that the effect of dietary supplementation (omega-3, vitamin supplementation, and/or other supplementation) on 2 symptoms and/or functions (social-autistic, and stereotypies, restricted and repetitive behaviors) and 2 clinical domains (core symptoms and associated symptoms) remained significant only for studies conducted in the United States but not in those conducted in Europe. The magnitude of the effect was similar in the European and US studies for the symptom and/or function stereotypies, restricted and repetitive behaviors and the associated symptoms clinical domain, whereas European studies revealed smaller ESs than those of US studies in social-autistic symptom and/or function and core symptoms clinical domain. For the symptom and/or function language (general), the magnitude and significance of the effect was similar in both regions. Some studies conducted in other regions were similar to those conducted in United States and others were more similar to studies conducted in Europe (see Supplemental Fig 3).

DISCUSSION

This meta-analysis revealed that in people with ASD, dietary supplementation (omega-3, vitamin supplementation, and/or other supplementation), omega-3 supplementation, and vitamin supplementation were more efficacious than placebo for improving particular symptoms and/or functions and clinical domains. Most of the effective dietary interventions had small ESs relative to placebo. There was low study statistical heterogeneity and low risk of publication bias. For dietary supplementation strategies as a whole, we found the largest ES for various ASD-associated symptoms (eg, anxiety-affect, behavioral problems and impulsivity; Hedges' g ~0.5) and a significant improvement (Hedges' g ~0.3–0.4) in core symptoms (eg, social-autistic symptoms and stereotypies, restricted and repetitive behaviors). Omega-3 and vitamin supplementation revealed similar ESs

TABLE 2 Meta-analyses of Effect of Dietary Supplementation on Symptoms and/or Functions Groups in People With ASD

Clinical Outcome (Symptoms and/or Functions Groups)	k	Intervention Group, *n*	Control Group, *n*	Meta-analysis		Heterogeneity				Publication Bias	
				Hedges' g (95% CI)	*P* (FDR Correction)	Q Value	df (Q)	*P* (Q)	I^2, %	Orwin's Fail-Safe *N*	Egger's Regression Intercept (Uncorrected *P*)
Dietary supplementation (omega-3, vitamin supplementation, and/or other supplementation)											
Anxiety and/or affect	5	88	75	0.482 (0.167 to 0.797)	.007[a]	2.713	4	.607	0.000	20	.244
Autistic general psychopathology	13	326	282	0.289 (0.133 to 0.445)	.002[a]	6.427	12	.893	0.000	25	.388
Behavioral problems and impulsivity	9	206	188	0.482 (0.242 to 0.721)	.001[a]	10.903	8	.207	26.629	34	.669
Cognition	7	212	191	0.198 (0.006 to 0.390)	.062	1.998	6	.920	0.000	7	.139
Global severity	11	210	176	0.337 (0.121 to 0.554)	.006[a]	8.821	10	.549	0.000	27	.835
Hyperactivity and irritability	12	272	244	0.286 (0.115 to 0.457)	.004[a]	5.529	11	.903	0.000	23	.283
Language (general)	19	406	368	0.342 (0.202 to 0.483)	<.001[a]	9.097	18	.957	0.000	46	.162
Sensory and motor	4	76	64	0.159 (−0.195 to 0.512)	.400	1.771	3	.621	0.000	3	.135
Sleep	3	94	94	0.148 (−0.129 to 0.425)	.331	0.196	2	.907	0.000	2	.201
Social-autistic	24	505	444	0.369 (0.230 to 0.508)	<.001[a]	26.056	23	.298	11.728	62	.128
Stereotypies and restricted and repetitive behaviors	16	318	277	0.269 (0.106 to 0.432)	.004[a]	8.130	15	.918	0.000	28	.011[a]
Omega-3 supplementation											
Autistic general psychopathology	4	100	96	0.285 (0.005 to 0.565)	.062	0.699	3	.873	0.000	8	.679
Global severity	3	75	65	0.074 (−0.330 to 0.479)	.746	0.374	2	.829	0.000	0	.970
Cognition	3	76	71	0.155 (−0.166 to 0.476)	.375	0.156	2	.925	0.000	2	.777
Hyperactivity and irritability	4	56	51	0.223 (−0.127 to 0.574)	.244	0.566	3	.904	0.000	5	.522
Language (general)	6	114	107	0.313 (0.056 to 0.571)	.031[a]	1.111	5	.953	0.000	13	.486
Social-autistic	7	136	123	0.311 (0.069 to 0.554)	.023[a]	1.838	6	.934	0.000	15	.859
Stereotypies and restricted and repetitive behaviors	7	133	121	0.231 (−0.019 to 0.481)	.090	1.921	6	.927	0.000	10	.028[a]
Vitamin supplementation											
Autistic general psychopathology	5	136	133	0.206 (−0.023 to 0.434)	.093	1.534	4	.821	0.000	6	.795
Behavioral problems & impulsivity	4	122	119	0.402 (0.155 to 0.648)	.005[a]	0.310	3	.958	0.000	13	.418
Global severity	4	56	56	0.464 (0.065 to 0.864)	.038[a]	3.594	3	.309	16.527	16	.488
Hyperactivity and irritability	4	127	124	0.426 (0.182 to 0.669)	.003[a]	1.374	3	.712	0.000	14	.142
Language (general)	6	150	149	0.351 (0.126 to 0.575)	.006[a]	2.241	5	.815	0.000	16	.994
Social-autistic	6	150	149	0.226 (0.003 to 0.450)	.062	2.721	5	.743	0.000	8	.691
Stereotypies, restricted & repetitive behaviors	3	56	54	0.531 (0.167 to 0.896)	.009[a]	1.664	2	.435	0.000	13	.263

df, degrees of freedom; k, number of studies; *N*, number of subjects.

[a] Indicates significant *P* values (after FDR correction).

TABLE 3 Meta-analyses of Effect of Dietary Supplementation on Clinical Domains in People With ASD

Clinical Outcome (Clinical Domains)	k	Intervention Group, *n*	Control Group, *n*	Meta-analysis		Heterogeneity				Publication Bias	
				Hedges' g (95% CI)	*P* (FDR Correction)	Q Value	df (Q)	*P* (Q)	I^2, %	Orwin's Fail-Safe N	Egger's Regression Intercept (Uncorrected P)
Dietary supplementation (omega-3, vitamin supplementation, and/or other supplementation)											
Associated symptoms	20	419	377	0.266 (0.132 to 0.400)	<.001[a]	7.734	19	.989	0.000	34	.235
Autism global	13	326	282	0.289 (0.133 to 0.445)	.002[a]	6.427	12	.893	0.000	25	.388
Clinical global impression	11	210	176	0.337 (0.121 to 0.554)	.006[a]	8.821	10	.549	0.000	27	.835
Core symptoms	25	516	460	0.331 (0.209 to 0.454)	<.001[a]	10.937	24	.989	0.000	58	.037
Omega-3 supplementation											
Associated symptoms	6	114	107	0.276 (0.027 to 0.525)	.046[a]	2.502	5	.776	0.000	11	.342
Autism global	4	100	96	0.285 (0.005 to 0.565)	.062	0.699	3	.873	0.000	8	.679
Clinical global impression	3	75	65	0.074 (-0.330 to 0.479)	.739	0.374	2	.829	0.000	0	.970
Core symptoms	7	136	123	0.268 (0.031 to 0.505)	.042[a]	0.746	6	.993	0.000	12	.401
Vitamin supplementation											
Associated symptoms	7	163	158	0.308 (0.100 to 0.517)	.009[a]	1.022	6	.985	0.000	15	.685
Autism global	5	136	133	0.206 (-0.023 to 0.434)	.093	1.534	4	.821	0.000	6	.795
Clinical global impression	4	56	56	0.403 (0.049 to 0.757)	.042[a]	3.146	3	.370	4.643	13	.091
Core symptoms	6	150	149	0.308 (0.090 to 0.526)	.011[a]	2.216	5	.819	0.000	13	.489

df, degrees of freedom; k, number of studies; *N*, number of subjects.

[a] Indicates *P* values (after FDR correction).

(relative to placebo) for most symptoms and/or functions except for stereotypies, restricted and repetitive behaviors, for which a larger ES was found for vitamins. The effect of both supplementation strategies on the 4 ASD clinical domains was also similar.

Our results are consistent with a recent meta-analysis[10] and a single-blind study[54] supporting a potential role for dietary supplementation in global improvement in people with ASD, although our results add granularity to the previous meta-analysis[10] by providing information on specific ASD symptoms and/or functions and clinical domains (including autism core symptoms) that might be more sensitive to change with these kinds of interventions. However, the small ESs limit the clinical utility. The relatively small ES for supplementation strategies should be appraised in the light of a lack of effective pharmacologic treatments for most core and associated symptoms in ASD.[2,3] A number of positive studies of other treatments, such as using oxytocin to target nuclear symptoms of ASD (eg, social cognition, emotion recognition, or empathy), also reveal small ESs.[55,56]

Our results suggest that dietary supplements might exert a nonspecific and small effect in ASD. These findings are consistent with the reported clinical efficacy of omega-3 supplementation in other neurodevelopmental disorders such as attention-deficit/hyperactivity disorder (ADHD), with similar ESs.[57]

Authors of a recent clinical trial in young people with ASD found that omega-3 supplementation increases the omega-3/omega-6 ratio in the erythrocyte membrane,[33] which might be an indirect measure of neuronal membrane integrity.[58,59] In our meta-analyses, omega-3 supplementation was associated with improvements in language and social

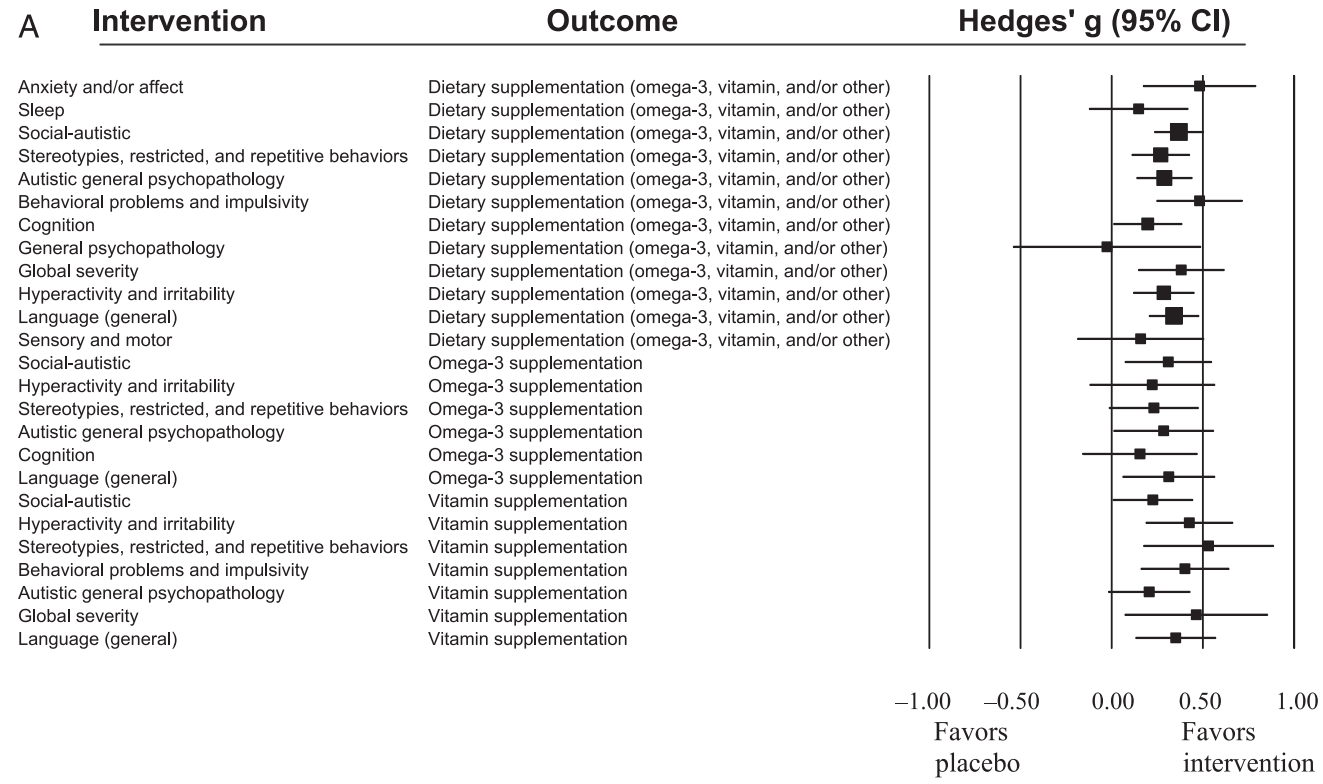

FIGURE 2

Meta-analysis of dietary interventions on clinical outcomes in people with ASD. Uncorrected Hedges' g values and 95% CIs are shown. Because of differences in the number of studies assessing each kind of intervention, the size of boxes is comparable between meta-analyses of the same intervention but not between meta-analyses of different interventions. Significance and CIs are comparable between all the meta-analyses, regardless of the outcome and the type of intervention. A, Meta-analysis of dietary interventions on symptoms and/or functions in people with ASD. B, Meta-analysis of dietary interventions on clinical domains in people with ASD.

deficits and in associated symptoms. Vitamins are active organic compounds needed in small quantities to sustain a healthy life.[60] In our meta-analyses, vitamin supplementation was associated with statistically significant albeit small improvements in most of the outcome measures evaluated. Our findings are not easy to interpret, but they highlight the need for further investigation into the various,

nuanced factors that might influence the efficacy of these interventions, particularly for the nutraceuticals with the largest effects because our knowledge of the pathophysiology of autism is still incomplete.

The efficacy of dietary supplementation was not moderated by study quality, year of publication, length of intervention, sample size, mean age of the intervention group, or percentage of girls and/or women in the intervention group. Along the lines of the above-mentioned meta-analysis of pharmacologic and dietary supplement interventions in pediatric autism,[10] we found some differences in the efficacy of interventions between regions where the study was conducted. In addition to between-region differing methodologic aspects or baseline differences in the severity of symptoms in different regions cohorts, we cannot rule out the possibility that US and European samples have different nutritional statuses at baseline. Authors of 1 of the European studies included in our meta-analyses reported that patients in the lower 50 percentile of omega-3/omega-6 ratio at baseline show a treatment effect with the intake of omega-3 that is not found in patients in the higher percentiles or in the whole sample.[33]

Our work was subject to several limitations. First, there was great methodologic heterogeneity among the included studies in terms of the intervention itself (eg, dosage, duration), clinical outcome measures, and sample characteristics. Most of the outcome variables were not clearly defined as primary or secondary outcomes in the original studies, and they were highly heterogeneous. It was not easy to classify them in a manageable number of variables. Second, there were small numbers of DBRCTs for some of the dietary interventions, which precluded performing meta-analyses on the efficacy of diet restriction interventions. Third, most studies (74.9%) did not assess the presence of baseline nutritional deficits or intolerances, which may be present in a significant percentage of children with ASD,[61–63] nor other relevant demographic or clinical baseline variables (including levels of biochemical parameters to stratify patients) that are associated with distinct efficacy of dietary interventions.[64,65] Designers of future trials testing dietary interventions in ASD should account for these factors. Fourth, we analyzed outcome variables regardless of whether they were primary or secondary outcomes in the original studies. This could have led to an underestimation of the ES for secondary variables. We decided to include secondary outcome variables to be able to conduct a clinically relevant and comprehensive assessment of the efficacy of dietary interventions on specific nuclear and associated symptoms in people with ASD. Fifth, ESs were strikingly similar for most symptoms and/or functions groups and clinical domains between omega-3 and vitamins. It is unclear whether this reflects a nonspecific effect of these kinds of strategies or whether further benefits could be expected from combining both types of supplements. The source data did not make it possible to assess potential interactions between different supplementation strategies. Sixth, the 4 clinical domains and the 17 symptoms and/or functions groups were constructed by combining different scales and tests on the basis of a balance of the organization of symptoms in recent nosological classifications and the design of assessment instruments. Despite this, there might be some heterogeneity among the resulting categories in terms of internal validity. Finally, most studies did not report concomitant pharmacologic treatment, and we could not control for this important variable. However, because we only included DBRCTs, we do not expect significant differences in concomitant pharmacologic treatment between intervention and placebo groups.

Because of the complexity and clinical heterogeneity of ASD, there is no 1-size-fits-all treatment.[66] This meta-analysis does not support a general recommendation of dietary interventions in ASD but suggests that some well-defined interventions could have a potential role in the management of some core and associated symptoms in these patients. In this study, we also highlight the need for better-designed clinical trials assessing dietary interventions in this population.

ABBREVIATIONS

ADHD: attention-deficit/hyperactivity disorder
ASD: autism spectrum disorder
CGI: Clinical Global Impressions
CI: confidence interval
DBRCT: placebo-controlled, double-blind randomized clinical trial
DSM-III-R: *Diagnostic and Statistical Manual of Mental Disorders, Revised, Third Edition*
DSM-IV: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*
DSM-IV-TR: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*
ES: effect size
FDR: false discovery rate
PDD: pervasive development disorder
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses
PWA: participant-weighted average

Drs Pina-Camacho and Arango and Mr Hendren conceived and planned the original idea of the study and approved the manuscript; Drs Moreno and Parellada conceived and planned the original idea of the study, classified instruments into the outcome variables, and approved the manuscript; Dr Durán-Cutilla performed the analysis and wrote the manuscript; Dr Ayora performed the analysis and approved the manuscript; Drs González-Vioque and de Matteis double screened all articles in 3 phases and approved the manuscript; and all authors reviewed the manuscript and approved the final manuscript as submitted.

DOI: https://doi.org/10.1542/peds.2018-3218

Accepted for publication Aug 5, 2019

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by the Spanish Ministry of Science, Innovation, and Universities, Instituto de Salud Carlos III (PI14/00397, PI14/02103, PIE16/00055, PI17/00819, PI17/00481); cofinanced by European Regional Development Fund "A way of making Europe," Centro de Investigación Biomédica en Red Salud Mental, Madrid Regional Government (B2017/BMD-3740 AGES-CM-2); European Structural Funds, European Seventh Framework Program under grant agreements FP7-HEALTH-2009-2.2.1-2-241909 (project EU-GEI), FP7-HEALTH-2009-2.2.1-3-242114 (project OPTiMISE [Optimization of Treatment and Management of Schizophrenia in Europe]), FP7-HEALTH-2013-2.2.1-2-603196 (project PSYSCAN), and FP7-HEALTH-2013-2.2.1-2-602478 (project METSY [Neuroimaging platform for characterization of metabolic co-morbidities in psychotic disorders]); European Horizon 2020 Program under the Innovative Medicines Initiative 2 Joint Undertaking under grant agreements 115916 (project Psychiatric Ratings using Intermediate Stratified Markers) and 777394 (project Autism Innovative Medicine Studies-2-Trials); European Research Area Network's Network of European Funding for Neuroscience Research; Fundación Familia Alonso; Fundación Alicia Koplowitz; and Fundación Mutua Madrileña.

POTENTIAL CONFLICT OF INTEREST: Dr Fraguas has been a consultant and/or has received fees from Angelini, Eisai, IE4 Lab, Janssen, Lundbeck, and Otsuka. He has also received grant support from Instituto de Salud Carlos III (Spanish Ministry of Science, Innovation, and Universities) and from Fundación Alicia Koplowitz. Drs Díaz-Caneja and Pina-Camacho have received grants from Instituto de Salud Carlos III (Spanish Ministry of Science, Innovation, and Universities) and from Fundación Alicia Koplowitz. Dr Moreno reports grants from European Union Funds, Instituto de Salud Carlos III (Spanish Ministry of Science, Innovation, and Universities), and consultancy for Janssen, Servier Laboratories, Lundbeck, Nuvelution, and Otsuka unrelated to the submitted work. Drs Durán-Cutilla and Ayora hold a Río-Hortega grant from Instituto de Salud Carlos III (Spanish Ministry of Science, Innovation, and Universities). Dr de Matteis has been a consultant and/or has received fees from Servier, Qualigen, Otsuka, Lunbeck, Janssen, and Fundación Patología Dual. Mr Hendren has received research grants from Curemark, Roche, Sunovion, and Shire in the past year and is a consultant for Curemerk, BioMarin, Janssen, and Axial Therapeutics. Dr Arango has been a consultant to or has received honoraria or grants from Acadia, Abbot, Ambrosetti, Amgen, AstraZeneca, Bristol-Myers Squibb, Sumitomo Dainippon Pharma, Forum, Gedeon Richter, Janssen-Cilag, Lundbeck, Merck, Otsuka, Pfizer, Roche, Servier, Shire, Schering-Plough, Sunovio, and Takeda. Dr Parellada has received educational honoraria from Otsuka, research grants from Fundación Alicia Koplowitz and Mutua Madrileña, and travel grants from Otsuka and Janssen. Dr González-Vioque has indicated he has no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2019-1680.

REFERENCES

1. Lai MC, Lombardo MV, Baron-Cohen S. Autism. *Lancet*. 2014;383(9920):896–910
2. Tachibana Y, Miyazaki C, Ota E, et al. A systematic review and meta-analysis of comprehensive interventions for pre-school children with autism spectrum disorder (ASD). *PLoS One*. 2017;12(12):e0186502
3. Ameis SH, Kassee C, Corbett-Dick P, et al. Systematic review and guide to management of core and psychiatric symptoms in youth with autism. *Acta Psychiatr Scand*. 2018;138(5):379–400
4. Green J, Garg S. Annual Research Review: the state of autism intervention science: progress, target psychological and biological mechanisms and future prospects. *J Child Psychol Psychiatry*. 2018;59(4):424–443
5. Salomone E, Charman T, McConachie H, Warreyn P; Working Group 4, COST Action 'Enhancing the Scientific Study of Early Autism'. Prevalence and correlates of use of complementary and alternative medicine in children with autism spectrum disorder in Europe. *Eur J Pediatr*. 2015;174(10):1277–1285
6. Marí-Bauset S, Zazpe I, Mari-Sanchis A, Llopis-González A, Morales-Suárez-Varela M. Evidence of the gluten-free and casein-free diet in autism spectrum disorders: a systematic review. *J Child Neurol*. 2014;29(12):1718–1727
7. Millward C, Ferriter M, Calver S, Connell-Jones G. Gluten- and casein-free diets for autistic spectrum disorder. *Cochrane Database Syst Rev*. 2008;(2):CD003498
8. Buie T. The relationship of autism and gluten. *Clin Ther*. 2013;35(5):578–583
9. Alanazi AS. The role of nutraceuticals in the management of autism. *Saudi Pharm J*. 2013;21(3):233–243
10. Masi A, Lampit A, DeMayo MM, Glozier N, Hickie IB, Guastella AJ. A comprehensive systematic review and meta-analysis of pharmacological and dietary supplement interventions in paediatric autism: moderators of treatment response and recommendations for future research. *Psychol Med*. 2017;47(7):1323–1334

11. Shamseer L, Moher D, Clarke M, et al; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation [published correction appears in *BMJ*. 2016;354: i4086]. *BMJ*. 2015;350:g7647

12. Adams JB, Holloway C. Pilot study of a moderate dose multivitamin/mineral supplement for children with autistic spectrum disorder. *J Altern Complement Med*. 2004;10(6):1033–1039

13. Adams JB, Audhya T, McDonough-Means S, et al. Effect of a vitamin/mineral supplement on children and adults with autism. *BMC Pediatr*. 2011;11:111

14. Al-Ayadhi LY, Elamin NE. Camel milk as a potential therapy as an antioxidant in autism spectrum disorder (ASD). *Evid Based Complement Alternat Med*. 2013; 2013:602834

15. Al-Ayadhi LY, Halepoto DM, Al-Dress AM, Mitwali Y, Zainah R. Behavioral benefits of camel milk in subjects with autism spectrum disorder. *J Coll Physicians Surg Pak*. 2015;25(11):819–823

16. Amminger GP, Berger GE, Schäfer MR, Klier C, Friedrich MH, Feucht M. Omega-3 fatty acids supplementation in children with autism: a double-blind randomized, placebo-controlled pilot study. *Biol Psychiatry*. 2007;61(4): 551–553

17. Bent S, Bertoglio K, Ashwood P, Bostrom A, Hendren RL. A pilot randomized controlled trial of omega-3 fatty acids for autism spectrum disorder. *J Autism Dev Disord*. 2011;41(5):545–554

18. Bent S, Hendren RL, Zandi T, et al. Internet-based, randomized, controlled trial of omega-3 fatty acids for hyperactivity in autism. *J Am Acad Child Adolesc Psychiatry*. 2014;53(6):658–666

19. Bertoglio K, Jill James S, Deprey L, Brule N, Hendren RL. Pilot study of the effect of methyl B12 treatment on behavioral and biomarker measures in children with autism. *J Altern Complement Med*. 2010;16(5):555–560

20. Chez MG, Buchanan CP, Aimonovitch MC, et al. Double-blind, placebo-controlled study of L-carnosine supplementation in children with autistic spectrum disorders. *J Child Neurol*. 2002;17(11): 833–837

21. Dolske MC, Spollen J, McKay S, Lancashire E, Tolbert L. A preliminary trial of ascorbic acid as supplemental therapy for autism. *Prog Neuropsychopharmacol Biol Psychiatry*. 1993;17(5):765–774

22. Fahmy SF, El-hamamsy MH, Zaki OK, Badary OA. L-carnitine supplementation improves the behavioral symptoms in autistic children. *Res Autism Spectr Disord*. 2013;7:159–166

23. Findling RL, Maxwell K, Scotese-Wojtila L, Huang J, Yamashita T, Wiznitzer M. High-dose pyridoxine and magnesium administration in children with autistic disorder: an absence of salutary effects in a double-blind, placebo-controlled study. *J Autism Dev Disord*. 1997;27(4): 467–478

24. Frye RE, Slattery J, Delhey L, et al. Folinic acid improves verbal communication in children with autism and language impairment: a randomized double-blind placebo-controlled trial. *Mol Psychiatry*. 2018; 23(2):247–256

25. Geier DA, Kern JK, Davis G, et al. A prospective double-blind, randomized clinical trial of levocarnitine to treat autism spectrum disorders. *Med Sci Monit*. 2011;17(6):PI15–PI23

26. Hasanzadeh E, Mohammadi MR, Ghanizadeh A, et al. A double-blind placebo controlled trial of Ginkgo biloba added to risperidone in patients with autistic disorders. *Child Psychiatry Hum Dev*. 2012;43(5):674–682

27. Kerley CP, Power C, Gallagher L, Coghlan D. Lack of effect of vitamin D_3 supplementation in autism: a 20-week, placebo-controlled RCT. *Arch Dis Child*. 2017;102(11):1030–1036

28. Kern JK, Miller VS, Cauller PL, Kendall PR, Mehta PJ, Dodd M. Effectiveness of N,N-dimethylglycine in autism and pervasive developmental disorder. *J Child Neurol*. 2001;16(3):169–173

29. Klaiman C, Huffman L, Masaki L, Elliott GR. Tetrahydrobiopterin as a treatment for autism spectrum disorders: a double-blind, placebo-controlled trial. *J Child Adolesc Psychopharmacol*. 2013; 23(5):320–328

30. Levine J, Aviram A, Holan A, Ring A, Barak Y, Belmaker RH. Inositol treatment of autism. *J Neural Transm (Vienna)*. 1997;104(2–3):307–310

31. Mankad D, Dupuis A, Smile S, et al. A randomized, placebo controlled trial of omega-3 fatty acids in the treatment of young children with autism. *Mol Autism*. 2015;6:18

32. Munasinghe SA, Oliff C, Finn J, Wray JA. Digestive enzyme supplementation for autism spectrum disorders: a double-blind randomized controlled trial. *J Autism Dev Disord*. 2010;40(9): 1131–1138

33. Parellada M, Llorente C, Calvo R, et al. Randomized trial of omega-3 for autism spectrum disorders: effect on cell membrane composition and behavior. *Eur Neuropsychopharmacol*. 2017; 27(12):1319–1330

34. Rimland B, Callaway E, Dreyfus P. The effect of high doses of vitamin B6 on autistic children: a double-blind crossover study. *Am J Psychiatry*. 1978; 135(4):472–475

35. Pusponegoro HD, Ismael S, Firmansyah A, Sastroasmoro S, Vandenplas Y. Gluten and casein supplementation does not increase symptoms in children with autism spectrum disorder. *Acta Paediatr*. 2015;104(11): e500–e505

36. Singh K, Connors SL, Macklin EA, et al. Sulforaphane treatment of autism spectrum disorder (ASD). *Proc Natl Acad Sci USA*. 2014;111(43): 15550–15555

37. Voigt RG, Mellon MW, Katusic SK, et al. Dietary docosahexaenoic acid supplementation in children with autism. *J Pediatr Gastroenterol Nutr*. 2014;58(6):715–722

38. Yui K, Koshiba M, Nakamura S, Kobayashi Y. Effects of large doses of arachidonic acid added to docosahexaenoic acid on social impairment in individuals with autism spectrum disorders: a double-blind, placebo-controlled, randomized trial. *J Clin Psychopharmacol*. 2012;32(2): 200–206

39. Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol*. 2002;31(1):140–149

40. Guy W. *ECDEU Assessment Manual for Psychopharmacology*. Rockville, MD: US Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration; 1976

41. Higgins JP, Altman DG, Gøtzsche PC, et al; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928

42. Paulson JF, Bazemore SD. Prenatal and postpartum depression in fathers and its association with maternal depression: a meta-analysis. *JAMA*. 2010;303(19):1961–1969

43. Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S. Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. *Neurosci Biobehav Rev*. 2013;37(8):1680–1691

44. Borenstein MHL, Higgins J, Rothstein H. *Comprehensive Meta-Analysis Version 2*. Englewood, NJ: Biostat; 2005

45. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: Lawrence Earlbaum Associates; 1988

46. Azzolina D, Baldi I, Minto C, Bottigliengo D, Lorenzoni G, Gregori D. Handling missing continuous outcome data in a Bayesian network meta-analysis. *Epidemiol Biostat Public Health*. 2018; 15(4):e12985-1–e12985-10

47. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. *Introduction to Meta-Analysis*. Chichester, United Kingdom: John Wiley and Sons; 2009

48. Sterne J. *Meta-Analysis in Stata: An Updated Collection From the Stata Journal*. College Station, TX: Stata Press; 2009

49. Lipsey M, Wilson D. *Practical Meta-Analysis*. Thousand Oaks, CA: Sage Publications; 2000

50. Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. GRADE guidelines: 7. Rating the quality of evidence–inconsistency. *J Clin Epidemiol*. 2011;64(12):1294–1302

51. Orwin RG. A fail-safe N for effect size in meta-analysis. *J Educ Stat*. 1983;8(2): 157–159

52. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629–634

53. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000; 56(2):455–463

54. Adams JB, Audhya T, Geis E, et al. Comprehensive nutritional and dietary intervention for autism spectrum disorder-a randomized, controlled 12-month trial. *Nutrients*. 2018;10(3):E369

55. Ooi YP, Weng SJ, Kossowsky J, Gerger H, Sung M. Oxytocin and autism spectrum disorders: a systematic review and meta-analysis of randomized controlled trials. *Pharmacopsychiatry*. 2017;50(1): 5–13

56. Keech B, Crowe S, Hocking DR. Intranasal oxytocin, social cognition and neurodevelopmental disorders: a meta-analysis. *Psychoneuroendocrinology*. 2018;87: 9–19

57. Sonuga-Barke EJ, Brandeis D, Cortese S, et al; European ADHD Guidelines Group. Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. *Am J Psychiatry*. 2013; 170(3):275–289

58. du Bois TM, Deng C, Huang XF. Membrane phospholipid composition, alterations in neurotransmitter systems and schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005;29(6):878–888

59. Haag M. Essential fatty acids and the brain. *Can J Psychiatry*. 2003;48(3): 195–203

60. Combs GF Jr. *The Vitamins*. 3rd ed. London, United Kingdom: Academic Press; 2007

61. Vinkhuyzen AAE, Eyles DW, Burne THJ, et al. Gestational vitamin D deficiency and autism-related traits: the Generation R Study. *Mol Psychiatry*. 2018;23(2):240–246

62. Liu X, Liu J, Xiong X, et al. Correlation between nutrition and symptoms: nutritional survey of children with autism spectrum disorder in Chongqing, China. *Nutrients*. 2016;8(5): E294

63. Berding K, Donovan SM. Microbiome and nutrition in autism spectrum disorder: current knowledge and research needs. *Nutr Rev*. 2016;74(12): 723–736

64. Losurdo G, Principi M, Iannone A, et al. Extra-intestinal manifestations of non-celiac gluten sensitivity: an expanding paradigm. *World J Gastroenterol*. 2018; 24(14):1521–1530

65. Pennesi CM, Klein LC. Effectiveness of the gluten-free, casein-free diet for children diagnosed with autism spectrum disorder: based on parental report. *Nutr Neurosci*. 2012;15(2):85–91

66. European Medicines Agency. *Guideline on the Clinical Development of Medicinal Products for the Treatment of Autism Spectrum Disorder (ASD)*. London, United Kingdom: European Medicines Agency; 2007

Dietary Interventions for Autism Spectrum Disorder: A Meta-analysis

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Pediatrics originally published online October 4, 2019;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Dietary Interventions for Autism Spectrum Disorder: A Meta-analysis

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Pediatrics originally published online October 4, 2019;