Article

Nonpharmacological Interventions for ADHD: Systematic Review and Meta-Analyses of Randomized Controlled Trials of Dietary and Psychological Treatments

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Objective: Nonpharmacological treatments are available for attention deficit hyperactivity disorder (ADHD), although their efficacy remains uncertain. The authors undertook meta-analyses of the efficacy of dietary (restricted elimination diets, artificial food color exclusions, and free fatty acid supplementation) and psychological (cognitive training, neurofeedback, and behavioral interventions) ADHD treatments.

Method: Using a common systematic search and a rigorous coding and data extraction strategy across domains, the authors searched electronic databases to identify published randomized controlled trials that involved individuals who were diagnosed with ADHD (or who met a validated cutoff on a recognized rating scale) and that included an ADHD outcome.

Results: Fifty-four of the 2,904 nonduplicate screened records were included in the analyses. Two different analyses were performed. When the outcome measure was based on ADHD assessments by raters closest to the therapeutic setting, all dietary (standardized mean differences=0.21–0.48) and psychological (standardized mean differences=0.40–0.64) treatments produced statistically significant effects. However, when the best probably blinded assessment was employed, effects remained significant for free fatty acid supplementation (standardized mean difference=0.16) and artificial food color exclusion (standardized mean difference=0.42) but were substantially attenuated to nonsignificant levels for other treatments.

Conclusions: Free fatty acid supplementation produced small but significant reductions in ADHD symptoms even with probably blinded assessments, although the clinical significance of these effects remains to be determined. Artificial food color exclusion produced larger effects but often in individuals selected for food sensitivities. Better evidence for efficacy from blinded assessments is required for behavioral interventions, neurofeedback, cognitive training, and restricted elimination diets before they can be supported as treatments for core ADHD symptoms.

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Attention deficit hyperactivity disorder (ADHD) is a common disorder that, although most frequently diagnosed during the school years, affects individuals across the lifespan (1). It is characterized by symptoms of inattention, overactivity, and/or impulsiveness that are age inappropriate, persistent, and pervasive (2). In the long term, ADHD is associated with a significant risk of educational failure, interpersonal problems, mental illness, and delinquency (3), creating a substantial burden on families as well as on health, social care, and criminal justice systems (4). Multimodal approaches are recommended for the treatment for ADHD (5), which normally begins during the school years. Pharmacological treatments are efficacious (6) and are widely used but may

This article is featured in this month's AJP Audio, is discussed in an Editorial by Dr. Galanter (p. 241) and is an article that provides Clinical Guidance (p. 289)

be limited in a number of ways: normalization is rare (6); long-term effectiveness remains to be established (7); adverse effects on sleep, appetite, and growth, although rarely serious, are common (8); and some parents and clinicians have reservations about medication use (9). A variety of nonpharmacological interventions are available to treat ADHD, and evidence for their efficacy has been supported in systematic reviews and meta-analyses (10–14). However, interpreting these reports, specifically in relation to impact on core ADHD symptoms, is complicated by the inclusion of trials using nonrandomized designs, non-ADHD samples, or non-ADHD outcome measures. Furthermore, estimates of efficacy are often based on assessments made by individuals who are likely to be aware of study allocation, which may inflate effect sizes (15).

Our aim was to address these limitations in six meta-analyses of randomized controlled trials to assess the effects of dietary and psychological treatments on ADHD symptoms for patients 3 to 18 years of age who had an ADHD diagnosis or met recognized symptom thresholds. This is the first meta-analysis to include both dietary and psychological domains of ADHD treatments. Our goal was to survey the field to prepare evidence-based clinical guidelines for the nonpharmacological treatment of ADHD. To build evidence-based guidelines, we needed to have a sense of the efficacy of treatments across domains using equivalent and equally stringent inclusion criteria and statistical approaches. Previous reviews have adopted very different approaches for the different domains, reflecting differences in research cultures. While recognizing the importance of other outcomes (e.g., oppositional symptoms) as treatment targets for children with ADHD, analyses of such measures were not viable in this study because an insufficient number of studies across the domains included these outcomes.

Our analyses covered three dietary domains—restricted elimination diets (exclusion of items associated with food hypersensitivity) (16), artificial food color exclusions (10), and free fatty acid supplementation (11)—and three psychological domains—cognitive training incorporating adaptive schedules that are hypothesized to strengthen ADHD-deficient neuropsychological processes (e.g., working memory) (12), neurofeedback using the visualization of brain activity to teach children to increase attention and impulse control (13), and behavioral interventions employing learning principles to target ADHD-related behaviors directly with the child or indirectly via an adult (14, 17). To address the issue of assessment blinding while at the same time allowing comparison with the results of previous reviews that included unblinded studies, we conducted two analyses. The first used a score from the rater (often unblinded) closest to the therapeutic setting. These ratings typically constituted a trial's own primary outcome measure and were therefore the assessment most available for analysis. They were termed the *most proximal assessment*. The second analysis was restricted to trials with a probably blinded assessment—either ratings clearly made under blind conditions (e.g., in a placebo-controlled trial) or ratings made by an adult unlikely to be aware of treatment allocation. This second analysis was considered especially important if the person responsible for the most proximal assessment either was involved in the delivery of the treatment—particularly where this involved a major investment of their own personal resources (e.g., it would be only natural for parents who had invested a lot of time and effort in parent training to overemphasize its beneficial effects)—or had strong beliefs about the efficacy of a particular treatment outcome (e.g., parents who believe in the importance of diet in ADHD may be especially likely both to volunteer for dietary trials and to rate the effects of the intervention positively).

Method

The review protocol is registered at PROSPERO (registration number CRD42011001393; http://www.crd.york.ac.uk/prospero/).

Inclusion Criteria

We included randomized controlled trials (including studies with counterbalanced crossover designs) that were published in peer-reviewed journals at any time from the inception of the databases. We limited our search to published trials to ensure a level of methodological adequacy and rigor among included trials and to avoid the inevitable problems with securing access to a full set of unpublished trials and the bias that this would introduce (18). Participants (ages 3 to 18 years) had a diagnosis of ADHD of any subtype (DSM-defined ADHD or ICD-defined hyperkinetic disorder, as well as historic variants; we excluded minimal brain dysfunction) or met accepted criteria for clinical levels of symptoms on validated ADHD rating scales. Studies had to have an appropriate control condition. For studies that used two control conditions, we selected the most stringent, in the following order: sham/placebo, attention/active control, treatment as usual, waiting list. Treatment as usual could include medication, but trials were excluded if the nonpharmacological therapy was an adjunct to medication or if both interventions were combined into one therapeutic arm as part of the study design. For instance, studies evaluating the additional benefit of nonpharmacological therapies to already effective medication were excluded. Because allowing medication in treatment as usual may have reduced effect sizes for the nonpharmacological comparator, we conducted sensitivity analyses to compare effect sizes for those trials with low/no medication. Studies in which enrollment depended on the presence of rare comorbid conditions (e.g., fragile X syndrome) were excluded.

Search Strategy

A common search strategy was employed for all treatment domains, using a broad range of electronic databases: Science Citation Index Expanded; Social Sciences Citation Index; Arts and Humanities Citation Index; Conference Proceedings Citation Index–Science; Conference Proceedings Citation Index–Social Sciences and Humanities; Index Chemicus; Current Chemical Reactions; Current Contents Connect; Derwent Innovations Index; Biological Abstracts; BIOSIS Previews; CAB Abstracts and Global Health (both from CABI); Food Science and Technology Abstracts; Inspec; MEDLINE; Zoological Record; Ovid MEDLINE; PsycINFO; EMBASE Classic+EMBASE; Web of Science; ERIC; and CINAHL. Articles written in English, German, Spanish, Dutch,

and Chinese were included in the search. Common terms for participants (e.g., all variants of ADHD, hyperkinetic disorder, attention deficit) and study design terms were used across domains. The design terms were randomized controlled trial(s); cluster randomized controlled trial(s); clinical trial; controlled clinical trial; crossover procedure or crossover study; crossover design; double blind procedure; double blind method; double blind study; single blind procedure; single blind method; single blind study; random allocation; randomization; random assignment; and randomized controlled trial. Separate treatment terms were used: 1) restricted elimination diet: few foods diet, elimination diet, oligoantigenic diet, restriction diet, food intolerance, food allergy, and food hypersensitivity; 2) artificial food color elimination: food color, food dye, Feingold diet, Kaiser Permanente diet, K-P diet, tartrazine, azo dye, carmoisine, sunset yellow, brilliant blue, indigotine, allura red, quinoline yellow, and ponceau 4R; 3) free fatty acid supplementation: essential fatty acid, long-chain polyunsaturated fatty acids, omega-3, omega-6, docosahexaenoic acid, eicosapentaenoic acid, and arachidonic acid; 4) cognitive training: cognitive training, attention training, working memory training, cognitive remediation, executive function training, and cognitive control; 5) neurofeedback: neurofeedback, EEG biofeedback, neurotherapy, and slow cortical potentials; and 6) behavioral interventions: contingency management, management techniques, contingency techniques, psychosocial interventions, psychosocial treatment, psychosocial therapy, social skills training, social skills intervention, social skills treatment, problem solving intervention, problem solving treatment, problem solving training, problem solving therapy, behavior modification, cognitive behavior treatment, cognitive behavior therapy, cognitive behavior training, parent training, parent counseling, parent support, school-based, classroom-based, school intervention, classroom intervention, teacher training, after-school or remedial teaching, peer tutoring, computer assistance learning, task modification, curriculum modification, classroom management, education intervention, multimodal intervention, multimodal treatment, multimodal therapy, multimodal intervention, multimodal treatment, multimodal therapy, educational intervention, and verbal self-instruction training. Our search terms for behavioral interventions covered a wide variety of intervention types with the aim of being as thorough as possible. However, in the end all the trials that met our criteria involved some element of behavioral training based on social learning or operant techniques. For the specific syntax and language specific formulations used in different databases, see the published study protocol. Database searches were supplemented by manual searches of published reviews. Two coauthors (S. Cortese and M. Ferrin) separately conducted and cross-checked all searches, which were finalized on April 3, 2012.

Outcome Measure

The outcome measure was pre- to posttreatment change in total ADHD symptom severity measured at the first posttreatment assessment. Results from ADHD-specific symptom scales were used where available (e.g., the DSM-IV ADHD subscale of Conners' Parent and Teacher Rating Scales) (19). We also permitted questionnaire measures of ADHD-related dimensions (e.g., inattention on Rutter parents' and teachers' scales [20]) as well as direct observations.

Study Selection

Trials were blindly double-coded for eligibility. Articles were initially screened on the basis of titles and abstracts, and assessment of articles for final inclusion was based on full text. Disagreements not resolved by coders (N=6) were arbitrated by either of two authors (E. Sonuga-Barke or J. Sergeant) who were independent of the domain specific work groups. The process was independently validated by another author (E. Simonoff) on the basis of "near miss" cases. Study quality was assessed by two independent raters (with disagreements resolved by E. Simonoff) using the standard definitions for randomization, blinding, and treatment of missing data provided by Jadad et al. (21).

Data Extraction

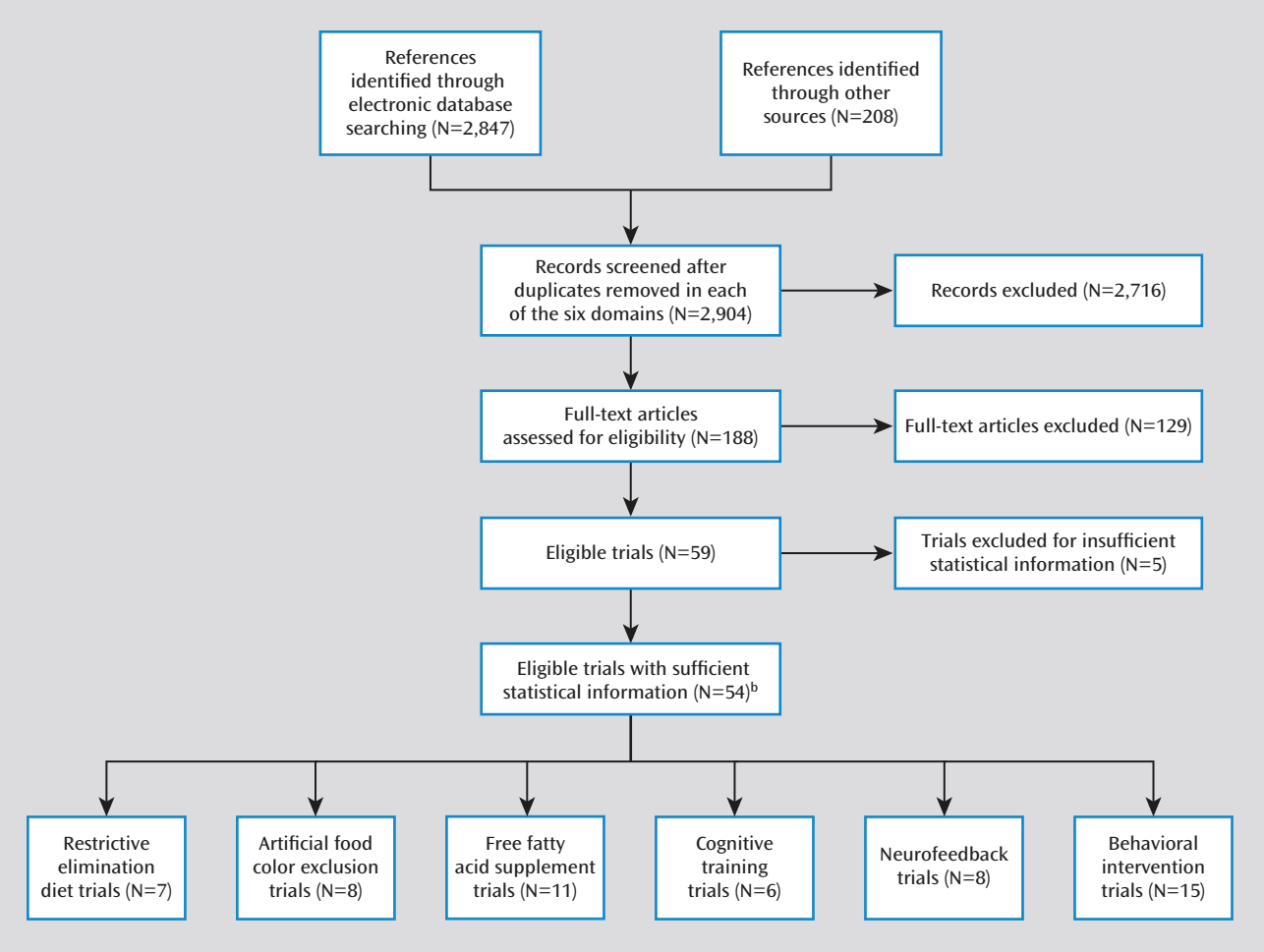
Sample and design information of included trials were entered into RevMan, version 5.0 (http://ims.cochrane.org/revman) to provide a systematic record of study features (22). Data were extracted by a single person in each domain and independently checked by another. See the published protocol for a list of data extracted.

Statistical Analysis

Individual effect sizes (the standardized mean difference) were based on the recommended formula: mean pre- to posttreatment change minus the mean pre- to posttreatment control group change divided by the pooled pretest standard deviation with a bias adjustment (23). Crossover trials were treated as parallel group trials because insufficient data were provided to permit analysis of within-individual change (e.g., there were no correlations of scores between conditions). This is a conservative approach, equivalent to setting the between-condition correlation to zero (24). In this case, the pretest (baseline) standard deviation was used as the denominator in the calculation of the standardized mean difference. When necessary, missing standard deviations were imputed separately for each of the outcome measures. The reported pretest standard deviations for each outcome measure were pooled across trials, and the value at the third quartile was adopted for studies with missing standard deviation values (25). Standardized mean differences for trials in each domain were combined using the inverse-variance method, in which the reciprocal of their variance is used to weight the standardized mean difference from each trial before being combined to give an overall estimate (26). Given the heterogeneity of ADHD assessments, sample characteristics, and implementation of treatments within domains in the included studies, we chose a priori to use random-effects models, as recommended by Field and Gillett (27). The I^2 statistic was calculated, a posteriori, as an estimate of between-trial heterogeneity in standardized mean difference, although given the number of trials included, the power to detect heterogeneity in these analyses is relatively low (28).

The *most proximal assessment* analysis used a report by the rater closest to the therapeutic setting as the outcome measure (i.e., parent ratings except for teacher-based interventions when teacher ratings or direct observations were used). If ratings of total ADHD symptoms (inattention, hyperactivity, and impulsivity) were not reported, then the next most appropriate available measure was used (e.g., ratings of one ADHD dimension). Ratings of non-ADHD-related dimensions were not included in the analyses. The *probably blinded assessment* analysis included both placebo- and non-placebo-controlled trials with an ADHD assessment made by an individual likely to be blind to treatment. In trials in which more than one such measure was available, the best blinded measure was selected. In nonplacebo or sham-treatment designs implemented in the home, these were either direct observations by an independent researcher or teacher ratings, as parent ratings were not considered probably blinded assessments. If the intervention was implemented at school, teacher ratings were not considered probably blinded assessments. When two measures were available, we considered independent direct observation as the best probably blinded assessment measure. In placebo or sham-treatment controlled trials, where all measures were likely to have some degree of blinding, parent ratings (home-implemented) and teacher ratings (school-implemented) were considered probably blinded

FIGURE 1. Combined PRISMA Flow Chart for All Six Treatment Domains Systematically Reviewed[a]



[a] PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses (www.prisma-statement.org).
[b] Data from one three-arm trial are included in both neurofeedback and cognitive training analyses.

assessments. For home-based interventions, direct observation or teacher ratings (in that order of preference) were considered better probably blinded assessments. Of the included studies, 93% of dietary and 54% of psychological trials had probably blinded assessments. Sensitivity analyses examined the impact of background ADHD medication use in trial samples on probably blinded assessments for which at least three trials in a domain had less than 30% of participants receiving medications (i.e., were no/low medication trials). Random-effects meta-regression was used to test whether lower-quality trials (as represented by total Jadad score) had larger effect sizes. Given the relatively small number of methodologically sound studies, the field is not yet mature enough for the investigation of publication bias using funnel plots—the interpretation of which, moreover, is equivocal when based on a small number of studies (29). In addition, it is problematic to distinguish between the effects of study heterogeneity and publication bias with sparse data (30).

Results

Figure 1 is a combined flow chart describing trial selection. (For domain-specific flow charts and individual justifications for the decision to exclude trials, see section I of the data supplement that accompanies the online edition of this article.) Overall, a higher proportion of behavioral interventions failed to meet the entry criteria for the present study than any other treatment domain, typically because of design limitations. Table 1 provides information about the retained trials, including overall Jadad ratings (for a detailed breakdown of Jadad scores, see section II of the online data supplement). Figures 2 and 3 present forest plots and their associated statistics.

Dietary Interventions

Restricted elimination diets. Seven studies examining restricted elimination diets met inclusion criteria; they included studies of known antigenic foods (31, 32), elimination of specific provoking foods (33, 34), general elimination diets (16, 35), and oligoantigenic diets (36). All were rated 3 (i.e., fair) or above on the Jadad scale. Five had probably blinded assessments. One study provided separate results for older and younger groups (34). Large and statistically significant effects with most proximal

TABLE 1. Summary of Characteristics of Studies Included in Meta-Analyses of Randomized Controlled Trials of Dietary and Psychological Treatments[a]

First Author (Reference)	Treatment	Control	Reported Design Quality[b]	Numbers Randomized		Characteristics		ADHD Measure	
				Treatment	Control	Age (Years; Mean or Range)	Male (%)	Most Proximal Assessment	Probably Blinded Assessment
Restricted elimination diets									
Pelsser (16)	Elimination diet	Waiting list	3	50	50	3–9	86	P-ARS	None
Boris (31)	Known antigenic foods	Placebo	5	16	16	7.5	69	CPRS	CPRS
Kaplan (32)	Known antigenic foods	Placebo	3	25	25	3–6	100	CPRS	CTRS
Carter (33)	Specific provoking food	Placebo	5	19	19	3–12	74	CPRS	Test session observation
Egger (34)	Specific provoking food	Placebo	5	31	31	3–12	88	Psychologist rating	Psychologist rating
Pelsser (35)	Elimination diet	Waiting list	3	15	12	3–9	81	CPRS	None
Schmidt (36)	Oligoantigenic diet	Control diet	4	49	49	7–12	96	CTRS	CTRS
Artificial food color exclusions									
Goyette (37)[c]	Certified food colors	Placebo	1	17	17	4–12	n.a.	CPRS	CTRS
Goyette (37)[d]	Certified food colors	Placebo	1	13	13	3–10	n.a.	CPRS	CTRS
Harley (38)	Certified food colors	Placebo	4	9	9	9.2	100	CPRS	CTRS
Williams (39)	Certified food colors	Placebo	4	29	29	6–14	93	CPRS	CTRS
Conners (40)	Kaiser Permanente diet	Control diet	4	17	17	6–13	n.a.	CPRS	CTRS
Harley (41)	Feingold diet	Control diet	3	36	36	6–13	100	CPRS	CTRS
Levy (42)	Tartrazine	Placebo	3	8	8	5.2	88	CPRS	CPRS
Adams (43)	Unspecified food colors	Placebo	3	18	18	4–12	83	Unstandardized parent rating	Unstandardized parent rating
Free fatty acid supplementation									
Bélanger (44)	Omega-3	Placebo	3	19	18	8.3	69	CPRS	CPRSC
Gustafsson (45)	Omega-3	Placebo	5	46	46	7–12	80	CPRS	CTRSD
Johnson (46)	Omega-3	Placebo	5	37	38	8–18	85	P-ARS	P-ARS
Stevens (47)	Omega-3	Placebo	3	25	25	6–13	87	P-CASQ	T-CASQ
Voigt (48)	Omega-3	Placebo	5	27	26	6–12	78	CBCL (attention)	CBCL (attention)
Aman (49)	Omega-6	Placebo	4	31	31	8.9	87	P-RBPC (attention)	CTRS
Arnold (50)	Omega-6	Placebo	4	18	18	6–12	100	CTRS average	CTRS average
Hirayama (51)	Omega-3, -6	Placebo	4	20	20	6–12	80	Symptom count[e]	Symptom count[e]
Manor (52)	Omega-3, -6	Placebo	5	137	63	6–13	70	CPRS	CTRS
Raz (53)	Omega-3, -6	Placebo	4	39	39	7–13	60	P-ARS	CTRS
Sinn (54)	Omega-3, -6	Placebo	4	—[f]	—[f]	7–12	74	CPRS	CPRS
Cognitive training									
Rabiner (55)	Attention training	Waiting list	2	25	25	n.a.	69	CTRS (inattention)	CTRS (inattention)

Continued

TABLE 1. Summary of Characteristics of Studies Included in Meta-Analyses of Randomized Controlled Trials of Dietary and Psychological Treatments[a] (*continued*)

First Author (Reference)	Treatment	Control	Reported Design Quality[b]	Numbers Randomized		Characteristics		ADHD Measure	
				Treatment	Control	Age (Years; Mean or Range)	Male (%)	Most Proximal Assessment	Probably Blinded Assessment
Shalev (56)	Attention training	Computer game	2	20	16	6–13	83	CPRS	CPRS
Steiner (57)	Attention training	Waiting list	3	13	15	12.4	52	CPRS	CTRS
Johnstone (58)	Working memory training	Easy training	3	20	20	8–12	85	Purpose-designed rating scale, parents	Purpose-designed rating scale, parents
Johnstone (59)	Working memory training	Waiting list	2	22	20	7–12	86	Purpose-designed rating scale, parents	None
Klingberg (60)	Working memory training	Easy training	5	26	27	7–12	82	CPRS	CTRS
Neurofeedback									
Steiner (57)	Theta-beta training	Waiting list	3	13	15	12.4	52	CPRS	CTRS
Bakhshayesh (61)	Theta-beta training	EMG biofeed-back	3	18	17	6–14	74	P-FBB-HKS	T-FBB-HKS
Beauregard (62)	Theta-beta training	No treatment	1	15	5	8–12	55	CPRS	None
Holtmann (63)	Theta-beta training	Cognitive exercise	2	20	14	7–12	91	P-FBB-HKS	None
Linden (64)	Theta-beta training	Waiting list	1	9	9	5–15	n.a.	P-SNAP	None
Heinrich (65)	Slow cortical potential training	Waiting list	2	13	9	7–13	95	P-FBB-HKS	None
Gevensleben (66)	Theta-beta and slow cortical potential training	Cognitive exercise	2	64	38	8–12	82	P-FBB-HKS	T-FBB-HKS
Lansbergen (67)	IFBT	Placebo neurofeed-back	4	8	6	8–15	93	P-ARS	P-ARS
Behavioral interventions									
Bor (68)	Parent training	Waiting list	2	26	37	3.6	73	ECBI (inattention)	None
Hoath (69)	Parent training	Waiting list	1	9	11	5–9	76	P-CAPS	T-CAPS
Jones (70)	Parent training	Waiting list	3	50	29	3.8	68	CPRS	None
Pisterman (71)	Parent training	Waiting list	2	23	22	4.1	91	Home observation	Home observation
Sonuga-Barke (72)	Parent training	Attention control	4	30	28	2–4	62	PACS	Home observation
Sonuga-Barke (73)	Parent training	Waiting list	4	59	30	2–4	n.a.	PACS	None
Thompson (74)	Parent training	Waiting list	5	21	20	2–6	73	PACS	Home observation
van den Hoofdakker (75)	Parent training	Treatment as usual	2	48	48	4–12	76	CPRS	None
Evans (76)	Parent and child training	Treatment as usual	1	31	18	11–13	71	P-ARS	None

Continued

TABLE 1. Summary of Characteristics of Studies Included in Meta-Analyses of Randomized Controlled Trials of Dietary and Psychological Treatments[a] (*continued*)

First Author (Reference)	Treatment	Control	Reported Design Quality[b]	Numbers Randomized		Characteristics		ADHD Measure	
				Treatment	Control	Age (Years; Mean or Range)	Male (%)	Most Proximal Assessment	Probably Blinded Assessment
Fehlings (77)	Parent and child training	Nondirective therapy and/or support	2	13	13	8–11	100	P-WWAS	None
Horn (78)	Parent and child training	Placebo	2	16	16	7–11	n.a.	CPRS	None
Webster-Stratton (79)	Parent and child training	Waiting list	3	49	50	6.4	75	CPRS	CTRS
Bloomquist (80)	Child, parent, and teacher training	Waiting list	2	20	16	8.5	69	CTRS	None
MTA (81)	Child, parent, and teacher training	Treatment as usual	3	144	146	8.3	80	P-SNAP	Classroom observation
Brown (82)	Child training	Nondirective therapy and/or support	2	10	8	5–13	85	CPRS (hyperactivity)	ACTRS

[a] See the online data supplement for more detailed information on intervention and measures. ACTRS=Abbreviated Conners' Teachers Rating Scale; CBCL=Child Behavior Checklist; CPRS=Conners' Parent Rating Scale; CTRS=Conners' Teachers Rating Scale; ECBI=Eyberg Child Behavior Inventory; EMG=electromyographic; IFBT=individualized frequency band training; n.a.=not available; PACS=Parental Account of Child Symptoms; P-ARS=Parent ADHD Rating Scale; P-CAPS=Parent–Child Attention Problem Rating Scale; T-CAPS=Teacher–Child Attention Problem Rating Scale; P-CASQ=Parent–Conners' Abbreviated Symptom Questionnaire; T-CASQ=Teacher–Conners' Abbreviated Symptom Questionnaire; P-FBB-HKS=German Parent ADHD Rating Scale; T-FBB-HKS=German Teacher ADHD Rating Scale; P-RBPC=Parent–Revised Behavior Problem Checklist; P-SNAP=Parent SNAP ADHD rating scale; P-WWAS=Parent Werry-Weiss Activity Scale.
[b] Reported quality of design based on Jadad ratings; 5=excellent, 4=good, 3=fair, 2=poor, 1=very poor.
[c] Experiment 1 in Goyette (37).
[d] Experiment 2 in Goyette (37).
[e] Combined parent and teacher DSM-IV symptom count.
[f] Numbers allocated to each arm not specified; a total of 167 children were randomized, and data were available for 104.

assessments (Figure 2A) were reduced substantially in the analysis of probably blinded assessments, which fell just short of statistical significance (Figure 3A; drop in standardized mean difference=0.98). In both analyses, there was statistically significant between-study heterogeneity in standardized mean differences. Sensitivity analysis was not possible, as only two trials with probably blinded assessments had no/low medication.

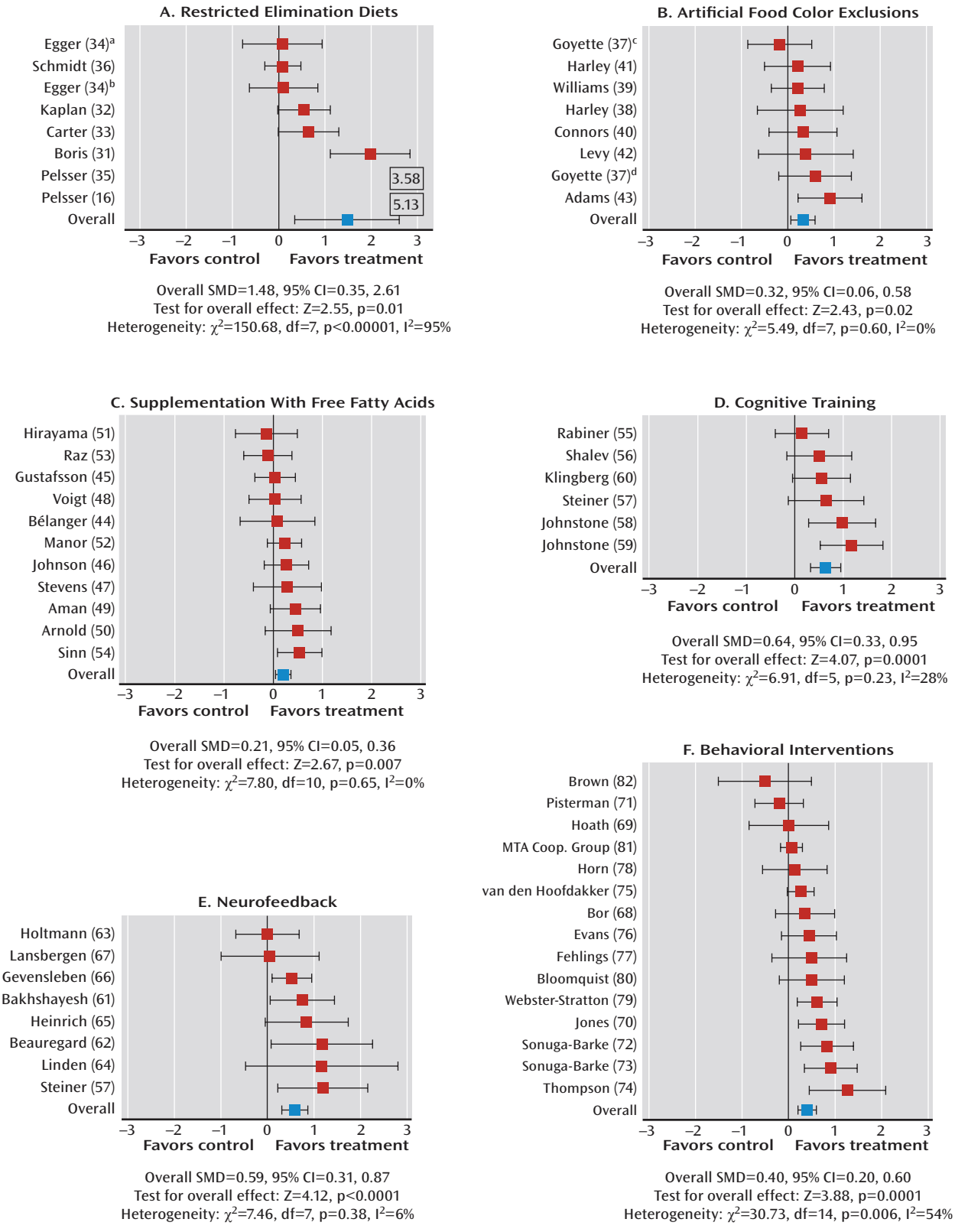
Artificial food color exclusions. Eight trials provided sufficient data for a meta-analysis of most proximal assessments, all of which also had probably blinded assessments. Four trials excluded certified food colors (37–39), two implemented Feingold-type diets (40, 41), one excluded tartrazine (42), and one excluded unspecified food colors (43). Six trials (75%) had Jadad ratings of 3 or more. Both approaches to analysis indicated significant positive treatment effects (Figures 2B and 3B). Restricting the probably blinded assessment analysis to the four no/low medication trials reduced the standardized mean difference (0.32) to nonsignificant levels (95% CI=–0.13, 0.77).

Free fatty acid supplementation. Eleven free fatty acid supplementation trials met inclusion criteria. Five involved omega-3 supplements (44–48), two involved omega-6 supplements (49, 50), and the remainder used both omega-3 and omega-6 supplements (51–54). All had probably blinded assessments and scored 3 or more on the Jadad scale. Treatment effects were significant for both analyses (Figures 2C and 3C). The probably blinded assessment effects remained significant when the analysis was limited to the nine trials with no/low medication (standardized mean difference=0.17; 95% CI=0.01, 0.34).

Psychological Interventions

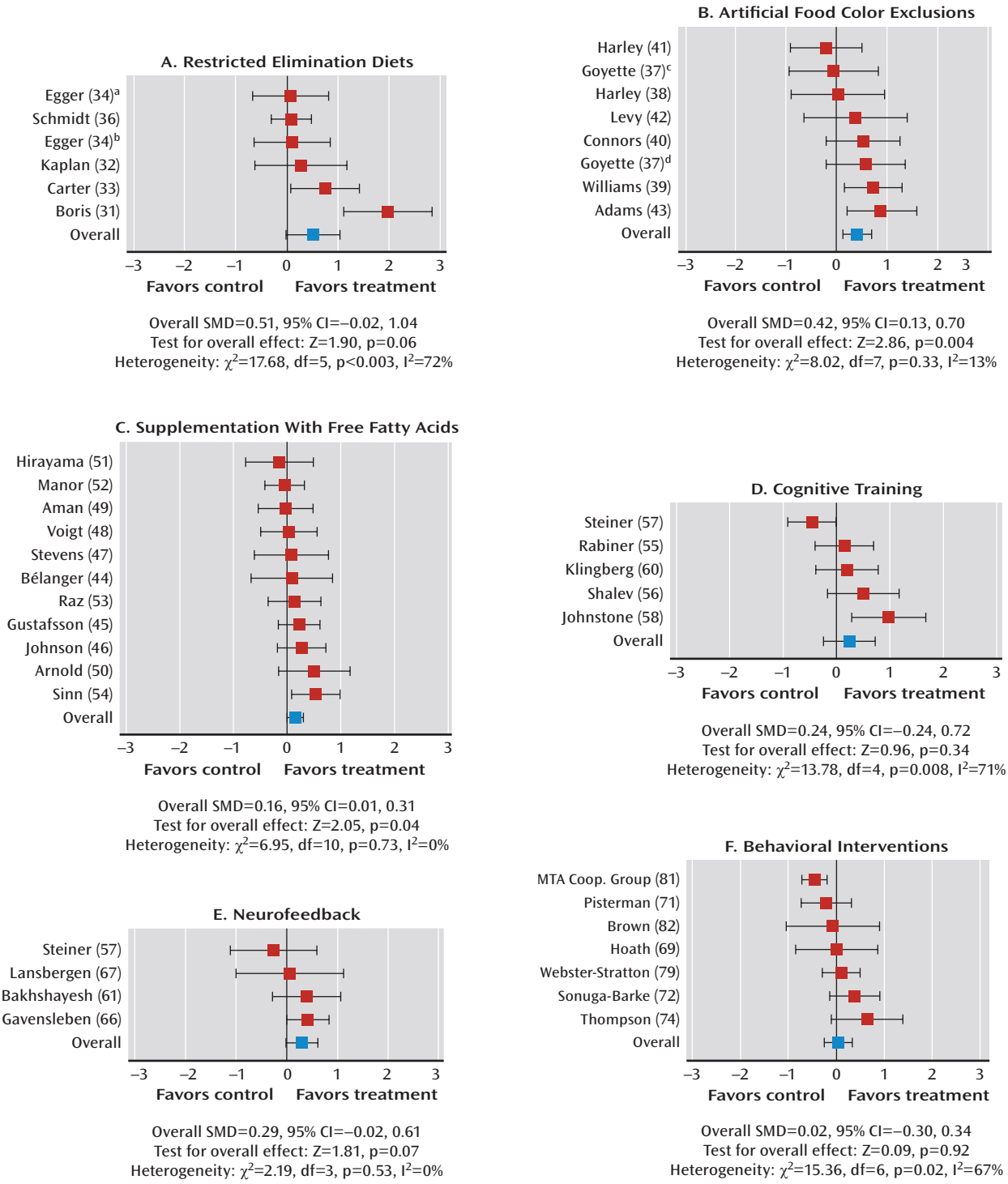
Cognitive training. Six trials (three focusing on attention [55–57] and three on working memory training [58–60]) provided sufficient data for the most proximal assessment analysis; all but one had probably blinded assessments. Three were rated 3 or more on the Jadad scale. While significant treatment effects were identified using the most proximal assessments (Figure 2D), these were lost when probably blinded assessments were analyzed (Figure 3D; drop in standardized mean difference=0.40), and this effect remained unaltered when the analysis was restricted to the three no/low medication trials (standardized mean difference=0.26; 95% CI=–0.08, 0.60)].

FIGURE 2. Forest Plots With Standardized Mean Difference (SMD), Effect Size, and Homogeneity Statistics for Meta-Analyses of the Six Domains Using Most Proximal Assessment



[a] Younger group in Egger et al. (34).
[b] Older group in Egger et al. (34).
[c] Experiment 1 in Goyette et al. (37).
[d] Experiment 2 in Goyette et al. (37).

FIGURE 3. Forest Plots With Standardized Mean Difference (SMD), Effect Size, and Homogeneity Statistics for Meta-Analyses of the Six Domains Using Probably Blinded Assessments



[a] Younger group in Egger et al. (34).
[b] Older group in Egger et al. (34).
[c] Experiment 1 in Goyette (37).
[d] Experiment 2 in Goyette (37).

Neurofeedback. Of the eight trials with data for most proximal assessments, four reported probably blinded assessments and three had Jadad ratings of 3 or more. Five trials studied theta-beta training (57, 61–64), one used the training of slow cortical potentials (65), one included a combination of both of these (66), and one used individualized frequency band training (67). Significant treatment effects were seen for most proximal assessments

(Figure 2E). These were substantially reduced and fell short of statistical significance for probably blinded assessments (Figure 3E; drop in standardized mean difference=0.30). Sensitivity analysis to test for medication effects was not possible because of the small number of no-medication trials.

Behavioral interventions. Eight trials evaluated behavioral parent training (68–75), four focused on a combination of child and parent training (76–79), and two included a teacher-related component along with child- and parent-related components (80, 81). One trial used child-focused training only (82). Of the 15 trials with sufficient most proximal assessment data, seven had probably blinded assessments and six scored 3 or more on the Jadad scale. The overall standardized mean difference in the analysis of the most proximal assessments was significant (Figure 2F) but reduced to near zero for probably blinded assessments (Figure 3F; drop in standardized mean difference=0.38). Heterogeneity was significant in both analyses. Restricting the probably blinded assessments analysis to the five trials with low/no medication removed the heterogeneity (χ^2=4.61; I^2=13%; p=0.26) and increased the effect (standardized mean difference=0.15; 95% CI=–0.11, 0.42), which nevertheless still fell short of significance.

Effect of study quality. Meta-regression did not support the assertion that large effect sizes were more likely in trials with low Jadad ratings, although statistical power to identify such effects was relatively low.

Discussion

Dietary interventions had small beneficial effects on ADHD symptoms. Evidence supporting psychological interventions was strongly influenced by whether the analysis was for most proximal or probably blinded assessments. Nonpharmacological standardized mean differences were substantially smaller than those reported for ADHD medications (around 0.9 for stimulants in meta-analyses of placebo-controlled randomized trials) (83). These results are less supportive of nonpharmacological interventions for ADHD than results of previous meta-analyses have been (10–14). Unlike the present analyses, however, previous analyses have rarely been limited to ADHD case subjects or focused exclusively on ADHD outcomes; nor have they addressed the issue of assessment blinding systematically by including an analysis limited to probably blinded assessments.

All three of the psychological interventions produced statistically significant reductions in symptoms according to the most proximal assessment analyses, using ratings often provided by parents who were not blind to treatment allocation. This finding mirrors those of previous meta-analyses, although the effects reported here are smaller than those reported earlier by Arns et al. for neurofeedback (13) and by Fabiano et al. (14) and Lee et al. (17) for behavioral interventions. This may be a consequence of the more stringent entry criteria used here. Most notably, the standardized mean differences for all psychological interventions dropped considerably, to nonsignificant levels, when analyses were restricted to trials with probably blinded assessments. This was most striking for behavioral interventions, where the value dropped to zero. Some of this attenuation may reflect the lower reliability—and consequently lesser sensitivity to treatment-related change—of some of the probably blinded assessments (e.g., if pre- and posttreatment ratings were supplied by different teachers). However, doubt is cast on this explanation by the fact that the size of the attenuation seen between parent-based most proximal and teacher-based probably blinded assessments differed across treatment domains. In some domains, teacher-based measures were clearly sensitive to change. This effect is therefore perhaps more likely due to the fact that estimates of effects based on most proximal assessments, most of which were based on unblinded assessments, may be inflated significantly because raters have an investment in the treatment being a success. Trials of behavioral interventions may be especially prone to this bias, as the individuals supplying these assessments (e.g., parents) are often directly involved in treatment delivery. Another possibility is that parents' unblinded most proximal assessments accurately captured treatment effects established in the therapeutic setting but that these effects did not generalize to the settings in which probably blinded assessments were made. If so, we would expect the four behavioral intervention trials that had blind assessments made by independent trained observers within the home-based therapeutic setting to show significant treatment effects. This was not the case, although it is also possible that these assessment themselves lacked ecological validity, as they are based on only a snapshot of the child's behavior.

A number of caveats are needed in relation to these negative behavioral intervention results. First, there was significant heterogeneity of effects in both the most proximal and probably blinded assessments analyses. The sensitivity analysis suggested that the inclusion of two trials with high levels of ADHD medication was important in this regard. The Multimodal Treatment of ADHD study (81) in particular had high medication levels in its treatment-as-usual arm (over 70% of patients were taking medication for ADHD). The inclusion of this trial may have biased the overall meta-analysis result because of its large size and its negative findings. However, excluding this trial in the no/low medication sensitivity analysis did not change the overall pattern of standardized mean differences for behavioral interventions. In order to rule out completely the possibility that medication exposure during trials biases results against behavioral interventions, future trials should be conducted using medication-naive patients—although this itself may introduce certain

biases into analyses. Second, the included trials differed greatly with respect to several important treatment parameters. For instance, the largest standardized mean differences were observed with trials with preschool children—a finding consistent with the proposition that behavioral interventions may be most effective as part of early intervention strategies (84). Third, although not effective for ADHD symptoms themselves, behavioral interventions may result in other positive effects (e.g., reducing oppositional behavior [68]).

For both neurofeedback and cognitive training, effects were substantially lower for probably blinded than for most proximal assessments, despite attempts in some trials to blind parents to treatment allocation by using sham and/or active control conditions. However, the standardized mean differences for these still relatively novel approaches were higher than those for the more traditional behavioral interventions. Both sets of analyses included trials that used a range of different approaches to treatment. Cognitive training trials addressed either working memory or attention deficits, and neurofeedback trials targeted several different electrophysiological correlates of ADHD. Neither analysis had sufficient power to identify whether any approach was better than the others. Based on these results, the value of psychological approaches that directly target neuropsychological processes should be further investigated.

Artificial food color exclusion had statistically significant but modest effects on ADHD symptoms. The effects for free fatty acid supplementation were also significant but small. Restricting analyses to trials with probably blinded assessments did not change the results—probably because of the use of placebo-controlled designs, which meant that most proximal assessments were often blinded. Restricting the analyses to trials with no/low medication levels reduced the effects on ADHD of artificial food color exclusions but not of free fatty acid supplementation. The standardized mean differences for free fatty acid supplementation reported here are smaller than those reported by Bloch and Qawasmi (11), who included trials with non-ADHD populations. However, the effects were generally similar to those reported recently in a meta-analysis by Gillies et al. (85). The Gillies et al. protocols and the present study differed in important ways in inclusion criteria, the number of studies included, and the statistical model employed, especially in relation to the choice of random- versus fixed-effects models. These differences between values reported in recent reviews highlight the sensitivity of meta-analytical findings to relatively small variations in protocol and the need for caution when interpreting the clinical significance of small effects for the free fatty acid supplementation reported here. The artificial food color exclusion effects were similar in magnitude to those reported by Nigg et al. (10). The restricted elimination diets produced strong effects in the most proximal assessment analysis, which dropped markedly to marginally nonsignificant levels when the analysis was restricted to probably blinded assessments. This change was largely due to the exclusion of two trials with very large effects from the analysis of probably blinded assessments—the first (35) because it was an open-label trial and the second (16) because the reported blind assessment by a pediatrician was based in part on unmasked parental accounts of behavior. Participants in restrictive elimination diets and the artificial food color exclusion trials were often preselected to be adverse responders before entering the controlled phase of the trial, so these effects may be limited to individuals with suspected food sensitivities.

Despite using a common search and selection protocol, our ability to directly compare different nonpharmacological approaches was hindered by methodological variations across domains linked to different research traditions in each area. There were also differences between domains in terms of ratings of reported study quality. The included trials used a range of different control conditions, and these varied considerably in the extent to which they allowed for control of extraneous and potentially biasing factors, such as the effects of nonspecific attention by therapists. While the use of strict placebo control was common only in dietary domains, the best-designed psychological trials included active, attention, or sham comparators. Trials also differed considerably in the intensity and duration of therapy. An analysis of these factors was not possible because of the limited number of trials in each treatment domain. Our exclusion of trials that included individuals with subclinical levels of ADHD and the fact that few trials included analyses of the predictors of treatment response meant that we were unable to test the hypothesis that patients with less severe ADHD are more responsive to psychological interventions (86).

Conclusions

Free fatty acid supplementation and artificial food color exclusions appear to have beneficial effects on ADHD symptoms, although the effect of the former are small and those of the latter may be limited to ADHD patients with food sensitivities. Evidence for the value of behavioral interventions is limited to unblinded ratings made by individuals likely to have an investment in treatment success. While the most proximal assessment data on neurofeedback, cognitive training, and restrictive elimination diets were potentially more positive, evidence of efficacy from blinded assessments is required before they are likely to be supported as ADHD treatments. The challenge for the future is to improve the efficacy of nonpharmacological interventions on the basis of a growing understanding of ADHD pathophysiology and to better integrate these interventions with pharmacological approaches. Properly powered, randomized controlled trials

with blinded, ecologically valid outcome measures are urgently needed, especially in the psychological treatment domain. Future trials should focus across a broader range of child-, parent-, and family-related functional outcomes. It is important that implementation of adequately blinded designs in future studies does not compromise the quality of the treatment being evaluated.

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Clinical Guidance: Nonpharmacological ADHD Treatments Have Limited Efficacy

The only dietary or psychological treatments that improve core symptoms of attention deficit hyperactivity disorder (ADHD) are supplementation with omega-3/omega-6 free fatty acids and elimination of artificial food colorings. Even these effects are small, limited to food-sensitive individuals, or dependent on coadministration of medication. Other meta-analyses by Sonuga-Barke et al. of blinded studies provided no evidence of improvement from cognitive training, neurofeedback, behavioral interventions, or exclusion of foods associated with hypersensitivity. However, Galanter notes in an editorial (p. 241) that behavioral treatments may improve symptoms of co-occurring conditions or behaviors specific to the home.