Nutritional and Dietary Interventions for Autism Spectrum Disorder: A Systematic Review

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abstract

CONTEXT: Children with autism spectrum disorder (ASD) frequently use special diets or receive nutritional supplements to treat ASD symptoms.

OBJECTIVES: Our objective was to evaluate the effectiveness and safety of dietary interventions or nutritional supplements in ASD.

DATA SOURCES: Databases, including Medline and PsycINFO.

STUDY SELECTION: Two investigators independently screened studies against predetermined criteria.

DATA EXTRACTION: One investigator extracted data with review by a second investigator. Investigators independently assessed the risk of bias and strength of evidence (SOE) (ie, confidence in the estimate of effects).

RESULTS: Nineteen randomized controlled trials (RCTs), 4 with a low risk of bias, evaluated supplements or variations of the gluten/casein-free diet and other dietary approaches. Populations, interventions, and outcomes varied. Ω-3 supplementation did not affect challenging behaviors and was associated with minimal harms (low SOE). Two RCTs of different digestive enzymes reported mixed effects on symptom severity (insufficient SOE). Studies of other supplements (methyl B_{12}, levocarnitine) reported some improvements in symptom severity (insufficient SOE). Studies evaluating gluten/casein-free diets reported some parent-rated improvements in communication and challenging behaviors; however, data were inadequate to make conclusions about the body of evidence (insufficient SOE). Studies of gluten- or casein-containing challenge foods reported no effects on behavior or gastrointestinal symptoms with challenge foods (insufficient SOE); 1 RCT reported no effects of camel's milk on ASD severity (insufficient SOE). Harms were disparate.

LIMITATIONS: Studies were small and short-term, and there were few fully categorized populations or concomitant interventions.

CONCLUSIONS: There is little evidence to support the use of nutritional supplements or dietary therapies for children with ASD.

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Ms Sathe helped to conceptualize and design the review, helped to acquire, analyze, and interpret data, and drafted and helped to revise the initial manuscript; Drs Andrews, McPheeters, and Warren helped to conceptualize and design the review, helped to acquire, analyze, and interpret data, and helped to draft the initial manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Autism spectrum disorder (ASD) is characterized by impairments in social interaction, communication, and behavior as well as sensory challenges. Substantial evidence supports benefits of specific behavioral, educational, and some pharmacologic interventions for children with ASD. However, given the limits of available treatments in improving core and associated ASD symptoms, substantial resource challenges in accessing evidence-based treatment approaches, and perceptions regarding lessened risks of treatment, many families, if not a majority of families, pursue dietary and nutritional approaches as components of treatment.[1–11] Given limitations in the existing research base, families and providers alike often struggle to understand the safety and potential benefit of such approaches.

Proponents of the frequently used gluten/casein-free (GFCF) diet posit varied theories (eg, excess opioid peptide levels) regarding why individuals with ASD may have altered metabolism of gluten or casein proteins that may negatively affect behavior.[12–14] Evidence to support specific theories, however, is lacking.[15,16] Studies have also explored differences in nutrient status in children with and without ASD and potential correlations with ASD symptoms as well as the effects of vitamin supplementation. The results of these studies have been inconclusive.[3,17–28]

Despite limited evidence and limited understanding of the potential mechanisms underlying variations in nutrition and metabolism that may affect behavior, specialized or restricted diets and nutritional supplementation are frequently used treatments in children with ASD. In the present review, a component of an Agency for Healthcare Research and Quality–commissioned update of a comparative effectiveness review of therapies for children with ASD conducted by the Vanderbilt Evidence-based Practice Center,[29] we examine the evidence specifically for nutritional or dietary interventions in children with ASD. The full comparative effectiveness review update[30] and review protocol (PROSPERO registry number: CRD42016033941) are available at www.effectivehealthcare.ahrq.gov.

TABLE 1 Inclusion Criteria

Category	Criteria
Study population	Children ages 2–12 y with ASD (mean age + SD is ≤12 y and 11 mo)
Publication languages	English only
Admissible evidence (study design and other criteria)	Admissible designs RCTs, prospective and retrospective cohort studies with comparison groups, and non-RCTs Other criteria Original research studies published from 2010 to the present Studies must have relevant population and ≥20 participants with ASD (non-RCTs) or at least 10 total participants (RCTs) Studies must address ≥1 of the following for ASD: Outcomes of interest Treatment modality of interest Predictors or drivers of treatment outcomes (eg, biomarkers, clinical changes) Maintenance of outcomes across environments or contexts Sufficiently detailed methods and results to enable data extraction Reporting of outcome data by target population or intervention

METHODS

Search Strategy and Study Selection

We searched the Medline database via PubMed, Embase, and the Cochrane Library from January 2010 to September 2016 using a combination of controlled vocabulary and key terms related to interventions for ASD (eg, autism, ASD, therapy). We note that the original review,[31] which the current report updates, included studies published from January 2000 to 2011. We also hand-searched the reference lists of included articles and recent reviews addressing ASD therapies to identify potentially relevant articles.

We developed inclusion criteria in consultation with an expert panel of clinicians and researchers (Table 1). We included comparative study designs (eg, randomized controlled trials [RCTs] and prospective or retrospective cohort studies) and studies published in English. We required that eligible RCTs have a total minimum sample size of 10. We required a higher minimum sample size (n = 20) for other comparative studies because they typically have fewer controls for bias than RCTs.

Data Extraction and Analysis

One investigator extracted data regarding study design, descriptions of study populations, intervention and comparison groups, and baseline and outcome data using a standardized form. A second investigator independently verified the accuracy of the extraction and made revisions as needed. Significant heterogeneity in interventions and outcomes reported precluded meta-analysis; thus, we synthesized studies qualitatively.

Assessment of Study Risk of Bias and Strength of Evidence

Two investigators independently evaluated the overall methodologic risk of bias of individual studies using the ASD-specific assessment approach developed and used in previous reviews of interventions for ASD.[29,32,33] Senior reviewers resolved discrepancies in risk of bias assessment, and we used an

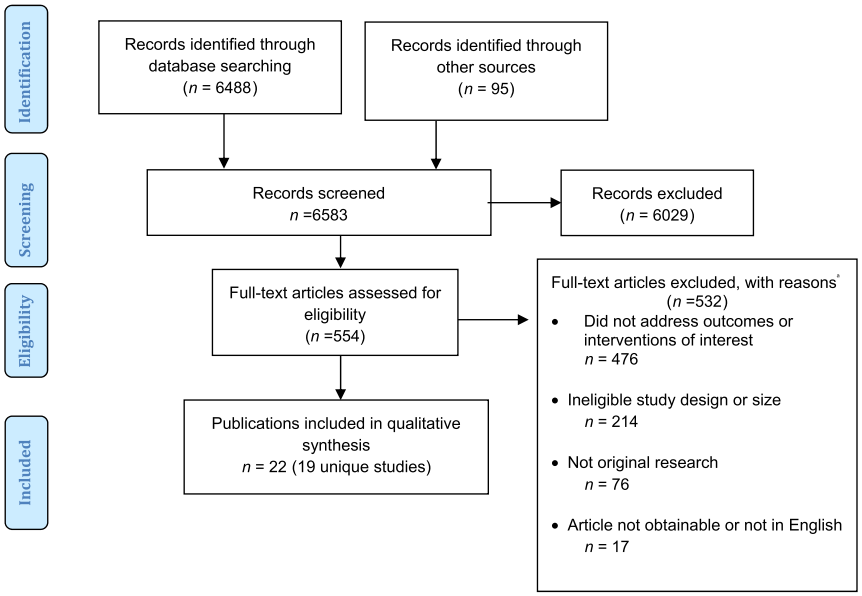

FIGURE 1
Disposition of studies identified for this review. Numbers do not tally because studies could be excluded for multiple reasons.[a]

approach described in the full review[34] to determine low, moderate, or high risk of bias ratings.

Assessment of the strength of the evidence (SOE) reflects the confidence that we have in the stability of treatment effects in the face of future research. The degree of confidence that the observed effect of an intervention is unlikely to change in additional research, the SOE, is presented as insufficient, low, moderate, or high. Assessments are based on consideration of study limitations, consistency in the direction of the effect, directness in measuring intended outcomes, precision of effect, and reporting bias.[35] We determined the strength of evidence separately for major intervention-outcome pairs using a prespecified approach described in detail in the full review.[34]

RESULTS

Our searches (conducted for the broader systematic review update[30]) identified 6583 citations, of which 19 RCTs (reported in multiple publications) met inclusion criteria and addressed diet or nutritional therapies (Fig 1).[36–58] Seventeen of these studies were published after the completion of our initial review of therapies for children with ASD,[29] and 2 were included in the previous review.[49,50] Four RCTs had low risk of bias,[38,41,43,47] 10 had moderate,[36,37,39,40,46,49–51,53,56–58] and 5 had high risk.[42,44,45,48,52,54,55] Table 2 outlines study characteristics and risk-of-bias assessments. Study treatment durations ranged from 7 days to 2 years, and sample sizes ranged from 12 to 92 (total $N = 732$). Follow-up occurred immediately posttreatment in all studies.

Ω-3 Fatty Acid Supplementation

Little evidence supports the effectiveness of Ω-3 supplementation to improve core or associated ASD symptoms. Three RCTs of Ω-3s versus placebo (low[41] and moderate[39,40] risk of bias) reported no significant group differences on most measures of challenging behavior, communication, language, and adaptive behavior.[39–41] One study reported significantly improved scores in the placebo group compared with the Ω-3 group in externalizing behaviors after 6 months of treatment,[39] and another reported a significant improvement in parent ratings of stereotypy and lethargy in children receiving Ω-3 supplements compared with those receiving placebo; teacher ratings were not significantly different.[40] Another RCT (moderate risk of bias) of dietary docosahexanoic acid (DHA) supplementation versus placebo reported improvement in parent-rated social skills in children receiving placebo versus those receiving docosahexanoic acid, whereas teachers rated communication as more improved in the treatment group compared with placebo.[37] Scores on other measures did not differ significantly between groups. Supplemental Table 3 reports outcome data for all studies.

Digestive Enzyme Supplementation

Evidence is inadequate to assess the effects of short-term digestive enzyme supplements. Two RCTs (moderate risk of bias) addressed digestive enzyme supplements compared with placebo: 1 evaluated a proteolytic enzyme supplement (Peptizyde)[49] and the other a digestive enzyme supplement (Neo-Digestin)[36]; both supplements contained papain and pepsin or peptidase. The Peptizyde RCT reported no significant differences in measures of behavior, sleep quality, or gastrointestinal symptoms, and no significant differences in adverse effects.[49] In a 3-month trial of Neo-Digestin versus placebo, symptom severity scores improved significantly in the treatment group compared with placebo.[36]

Other Supplements

Two RCTs (low[38] and moderate[58] risk of bias) addressed methyl B_{12} supplementation. Clinical Global Impression (CGI) scores improved significantly in the methyl B_{12} group in 1 RCT (effect size = 0.84, $P = .005$), but studies

TABLE 2 Overview of Studies (k = 19)

Characteristic	Ω-3 Fatty Acids	Digestive Enzymes	Other Supplements	GFCF Diets	Other Dietary Intervention	Total
Treatment duration						
<1–4 wk	0	0	0	0	3	3
5–8 wk	1	0	1	0	1	3
9–12 wk	1	2	2	2	0	7
≥13 wk[a]	2	0	1	2	1	6
Primary outcomes addressed						
Attention/attention-deficit/hyperactivity disorder symptoms	2	0	0	0	1	3
Adaptive behavior	1	0	0	1	0	2
ASD symptom severity	3	1	4	3	2	13
Challenging behaviors	3	0	2	1	3	9
Communication	2	1	1	2	2	8
Medical symptoms (eg, sleep, gastrointestinal)	0	2	1	0	3	6
Neurocognitive skills	0	0	0	1	0	1
Social skills	2	0	1	1	1	5
Harms	4	2	4	1	1	12
Region of study conduct						
Asia or Africa	0	1	1	0	2	4
Australia	0	1	0	0	0	1
Europe	1	0	0	2	1	4
North America	3	0	3	2	2	10
Risk of bias						
Low	1	0	1	0	2	4
Moderate	3	2	2	2	1	10
High	0	0	1	2	2	5
Total N participants	167	135	136	82	212	732

[a] Two studies were >52 weeks' duration.[44,45,54,55]

reported few other significant group differences in measures of behavior or communication.[58] Two RCTs of levocarnitine (moderate[51] and high[42] risk of bias) reported improvements in symptom severity in the levocarnitine group compared with placebo, but scores on other behavioral measures or adverse effects did not differ between groups.[42] In the second RCT, symptom severity did not differ between groups after 6 months of treatment.[51]

GFCF Diets

Data to assess the effects of GFCF diets are limited because dietary approaches and outcome measures varied among studies as did control diets and monitoring of adherence to GFCF diets. Four RCTs (in multiple publications) compared GFCF diets to either an unaltered diet[44,45,54–57] or a low-sugar diet (total N across studies = 82).[53] One RCT (moderate risk of bias) reported no significant differences between groups on measures of development or behavior, although the control group improved significantly from baseline on visual reception, withdrawal, aggression, and attention subscales (P values < .05) Another crossover RCT (moderate risk of bias) similarly reported no statistically significant differences between groups on measures of symptom severity or language, although parents of 7 of the 15 children participating in the study reported improvements in language.[56,57] In a retrospective analysis of videotapes recorded during the study period, investigators found no significant group differences in verbal communication between children in the diet or control groups or between children whose parents reported language improvements after the study period and those whose parents did not.

One RCT (high risk of bias) reported significant parent-rated improvements in communication, resistance to communication, social isolation, repetitive or challenging behavior, and overall impairment in children on a GFCF diet compared with those on a usual diet (P values ≤ .007).[54,55] Children on the GFCF diet also improved significantly on tests of cognitive skills, motor skills, verbal and social communication, anxiety, and reaction to changes in environment and routine compared with control children (P values < .05). Another high risk of bias RCT with 24-month follow-up of participants reported few differences in behavioral measures between children on a GFCF diet and those with no dietary restrictions[44,45]; ASD symptoms improved significantly in participants in the GFCF diet group versus the no diet group at 12 months, but were not different on any measure in a subset of participants followed for 24 months.

Other Dietary Approaches

One RCT (high risk of bias) compared a gluten-free diet to a usual diet and reported significant improvements in gastrointestinal symptoms (stomachache, bloating, constipation) from baseline in the gluten-free diet group, but not in the control group. Diarrhea did not improve significantly in either group. Stereotyped behavior and communication improved significantly in the gluten-free group compared with control children (P values $\leq .005$).[52] Another small RCT (low risk of bias) comparing a gluten- and dairy-free diet with a diet including both gluten and dairy reported no significant group differences in challenging behavior (hyperactivity, irritability, inattention).[47]

Two small RCTs (low[59] and moderate[46] risk of bias) evaluated the "challenges" of gluten- or casein-containing foods, but the evidence is inadequate to determine if short-term gluten- or casein-containing foods affect ASD symptoms or gastrointestinal function. One RCT that randomized children who were maintaining GFCF diets to foods with gluten, gluten and casein, or placebo foods reported no significant group differences in measures of challenging behaviors or measures of sleep quality and stool frequency.[43] Another RCT (moderate risk of bias) assessing the effects of introducing gluten/casein-containing foods versus placebo foods similarly reported no significant effects of added gluten or casein on behavior or gastrointestinal symptoms.[46] Finally, a single RCT (high risk of bias) compared boiled or raw camel's milk with cow's milk and reported no significant differences in ASD severity between groups after 2 weeks of treatment.[48]

Harms

Studies that reported harms either reported no significant difference between the intervention group and the control group, or reported 0 harms for each group. Harms were disparate and the clinical significance was generally difficult to assess (Supplemental Table 4).

SOE

Ω-3 fatty acid supplementation and placebo did not affect challenging behaviors and was associated with minimal harms. Our confidence in these conclusions is low (low SOE). Despite the number of RCTs with low or moderate risk of bias addressing other supplements, data were inadequate to make conclusions about all clinical efficacy and harms outcomes because only a few small studies addressed each supplement (insufficient SOE). Similarly, although multiple RCTs evaluated variations of a GFCF diet, studies addressed different outcomes and different approaches to restricted and control diets; thus, data were inadequate to make conclusions about the body of evidence (insufficient SOE) or about other dietary interventions (challenge foods, camel's milk).

DISCUSSION

Despite their widespread reported use, little evidence supports the effectiveness of nutritional supplements or the GFCF diet for improving ASD symptoms. Harms reported in studies were generally considered mild, but the long-term effects of these therapies are not well understood. Although the conduct of studies generally improved from those reported in our 2011 review, evidence remains insufficient for most interventions given the small sample sizes, lack of longer term follow-up, and heterogeneous agents and populations. Few studies assessed the effect of concomitant behavioral or other therapies, although many children with ASD receive multiple interventions.

These findings generally align with conclusions in recent reviews addressing specific diets or supplements. One Cochrane review evaluating Ω-3 fatty acids reported no evidence for effects on social interaction, communication, hyperactivity, or stereotypy.[27]

Another review of GFCF diets included 32 studies, typically with high risk of bias, and noted scarce evidence for GFCF diets, with positive effects reported only in lower quality studies.[60]

Even without a clear evidence base documenting safety and efficacy, many families of children with ASD use diet and nutritional approaches.[61,62] Parents have cited better alignment with their personal views as well as perceived fewer side effects than conventional medications as reasons for using "complementary or alternative" therapies, including restricted diets and nutritional supplements.[5–9] Caregivers have also reported making treatment decisions about such therapies without a clinician's input, noting a perceived unwillingness to consider potential benefits among clinicians, even in the face of few evidence-based effective therapies.[63] These findings continue to highlight the need for shared decision-making among providers and families, including understanding of family motivations for using specific therapies and discussion of balancing potential benefits with potential risks and resource and time costs to families.[64,]

Limitations of the Review Process

We included studies published in English only and did not include unpublished data. Although our preliminary scan of non-English publications identified few potential eligible studies, we recognize that some nutritional supplements may have been studied only in non-Western countries and will not be addressed in the current review. We also included only comparative

studies of medical interventions with at least 10 children with ASD. Given the heterogeneity in treatment regimens, outcomes addressed in each study, and patient populations, we were limited in our ability to meta-analyze findings or identify potential subgroups that may respond more favorably to specific treatments. Finally, we used a nonvalidated tool to assess risk of bias; this tool evaluates constructs similar to those assessed by organizations such as the Cochrane Collaboration, with the addition of ASD-specific domains.

CONCLUSIONS

Overall, studies of nutritional supplements or specialized diets were typically small and short-term (<6 months) and provided little evidence regarding the potential effects of these approaches. Several agents were addressed in single studies, which limit conclusions about their effects. These findings can help to inform shared caregiver and clinician decision-making about therapies for children with ASD.

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ABBREVIATIONS

ASD: autism spectrum disorder
CGI: Clinical Global Impression
GFCF: gluten/casein-free
RCT: randomized controlled trial
SOE: strength of the evidence

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