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REVIEW

Gluten- and casein-free diet and autism spectrum disorders in children: a systematic review

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Abstract
Purpose Effective treatments for core symptoms of autism spectrum disorders (ASD) are lacking. We systematically updated evidence on the effectiveness of a gluten-free and casein-free (GFCF) diet as a treatment for ASD in children.
Methods The Cochrane Library, MEDLINE, and EMBASE databases were searched up until August 2016, for randomized controlled trials (RCTs); additional references were obtained from reviewed articles.
Results Six RCTs (214 participants) were included. With few exceptions, there were no statistically significant differences in autism spectrum disorder core symptoms between groups, as measured by standardized scales. One trial found that compared with the control group, in the GFCF diet group there were significant improvements in the scores for the 'communication' subdomain of the Autism Diagnostic Observation Schedule and for the 'social interaction' subdomain of the Gilliam Autism Rating Scale. Another trial found significant differences between groups in the post-intervention scores for the 'autistic traits', 'communication', and 'social contact' subdomains of a standardized Danish scheme. The remaining differences, if present, referred to parent-based assessment tools or other developmental/ASD-related features. No adverse events associated with a GFCF diet were reported.
Conclusions Overall, there is little evidence that a GFCF diet is beneficial for the symptoms of ASD in children.

Keywords Randomized controlled trial · Autism spectrum disorders · Children · Gluten · Casein

Introduction

The American Psychiatric Association defines autism spectrum disorders (ASD) as biologically based neurodevelopmental disorders characterized by (1) persistent deficits in social communication and social interaction, and (2) restricted, repetitive patterns of behavior, interests, or activities, with severity based on impairments and symptoms present when social demands exceed limited capacities [1]. The World Health Organization estimates that 1 in 160 children have an autism spectrum disorder [2]. The etiology of ASD remains unknown. However, genetics as well as environmental factors may be relevant [3]. The most common approaches to the treatment of ASD include behavioral, educational, and pharmacological interventions. While these approaches allow children with ASD to function better, a major step forward is still lacking. A substantial number of parents of children with ASD express interest in complementary or alternative methods of treatment [4]. Recently, we systematically updated evidence on the use of omega-3 fatty acids to manage ASD in children [5]. Due to the limited number of included studies and

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the small sample sizes, no firm conclusions were drawn. However, these limited data suggest that omega-3 fatty acid supplementation does not benefit the performance of children with ASD. Other alternative treatments include melatonin, vitamins, probiotics, and the use of a gluten-free and/or casein-free diet [4]. An interest in the role of gluten and casein in children with ASD was prompted by the hypothesis that abnormal metabolism of those two proteins may result in excessive opioid activity in the central nervous system, altering its function [6]. Another potential mechanism is an increased intestinal permeability or 'leaky gut'. According to that model, abnormal function of the gut barrier (and possibly, blood–brain barrier) leads to the increased passage of gluten, casein, and their metabolites into the bloodstream and the central nervous system. That, combined with a metabolic defect, may contribute towards development of autistic symptoms [7]. Consequently, a gluten-free and casein-free (GFCF) diet was proposed as being potentially beneficial for patients with ASD.

A 2008 Cochrane review (search date: April 2007) found only two small, randomized controlled trials (RCTs) involving overall 35 children that evaluated the efficacy of following a GFCF diet for management of ASD. One trial indicated that a combined GFCF diet reduced autistic traits; however, the second trial found no difference in outcome measures between groups [8]. As new studies have been published, our aim was to systematically update evidence on the effects of use of a GFCF diet for the management of ASD in children.

Methods

Only RCTs were eligible for inclusion. Participants had to be children diagnosed with ASD according to established criteria such as those described in the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) [9], the DSM-IV—Text Revision (DSM-IV-TR) [10], or Manual of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [11]. Studies that compared a GFCF diet with a regular diet were eligible for inclusion. All behavioral and ASD-related outcome measures reported by the investigators were considered, if relevant to the current review.

Searches of the Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library), MEDLINE, and EMBASE electronic databases from April 2007 (end date of last search in the Cochrane review) to August 2016 were performed. There were no language restrictions. The search strategy, which was part of a broader project to assess some complementary and alternative medicines for ASD, included use of a validated filter for identifying controlled trials, which was combined with a topic-specific strategy. In brief, the following search terms were used: (diet OR elimination diet OR gluten free diet OR gluten-free casein-free diet OR dairy free diet) AND (autism OR autism spectrum disorder OR ASD OR Asperger syndrome OR pervasive developmental disorder OR PDD). The search was carried out independently by three reviewers (AH, JŁ, AP). Additionally, reference lists of identified studies, key review articles, and previous systematic reviews were searched. An attempt was made to obtain additional data from the authors of one of the included studies; however, with no success. Three registers for clinical trials (www.clinicaltrials.gov; www.clinicaltrialsregister.eu; www.anzctr.org.au) were screened.

Three reviewers (AP, JŁ, AH) initially screened the title, abstract, and keywords of every record identified with the search strategy, and they retrieved the full text of potentially relevant trials and of records for which the relevance was unclear. The same reviewers independently applied the inclusion criteria to each potentially relevant trial to determine its eligibility. If differences in opinion existed, they were resolved by discussion until a consensus was reached. Data extraction was performed using standard data-extraction forms. Information about sample size calculation and the funding of each study was also collected. The Cochrane Collaboration's tool for assessing risk of bias was used to establish the risk of bias [12]. No meta-analysis was undertaken, as the included trials differed in their methods.

Results

Figure 1 documents the identification process for eligible trials. In addition to the two randomized controlled trials (RCTs) identified in the Cochrane review [13, 14], four new trials were included [16–18]. Table 1 summarizes characteristics of all of the included RCTs, and Online Resource 1 summarizes characteristics of the excluded trials, including the reasons for exclusion. Moreover, three registered trials were identified. Among them, two RCTs were completed but no publication was found (ClinicalTrials.gov NCT01116388; NCT00090428), and one RCT had an unclear status (ClinicalTrials.gov, NCT01625299).

The six selected trials recruited a total of 214 participants (107 in the experimental groups and 107 in the control groups), aged 2–16 years. With one exception, the diagnosis of ASD was made according to the DSM-IV or DSM-IV-TR criteria and confirmed using the Autism Diagnostic Interview-Revised (ADI-R) [19] and/or the Autism Diagnostic Observation Schedule (ADOS) [20]. In the remaining study, no details regarding the diagnostic criteria were described; it was only stated that the diagnosis was made by *'professionals working with child psychiatry or child neurology'* [14].

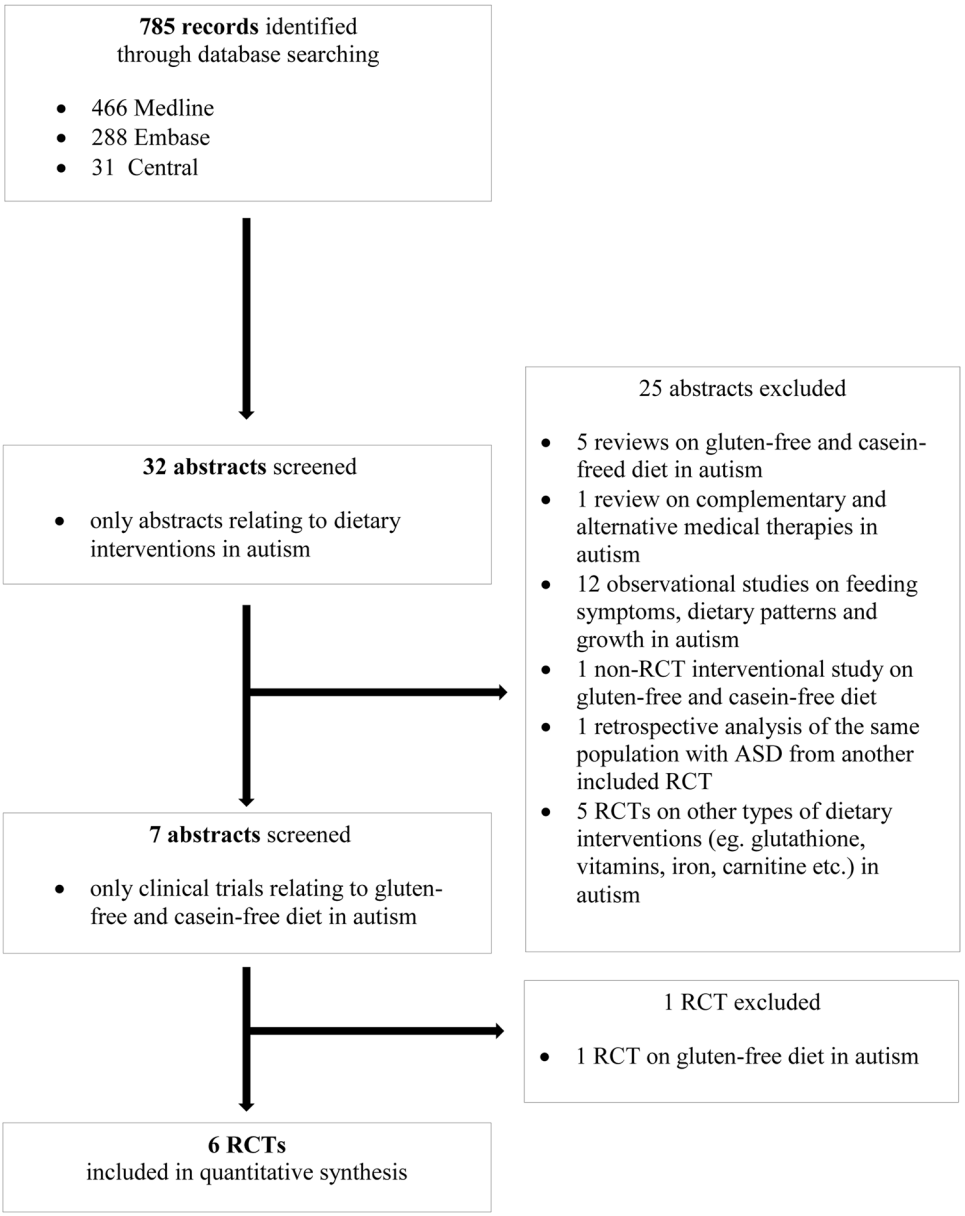

Fig. 1 Gluten- and casein-free diet in children with autism spectrum disorders—identification process for eligible trials

Included trials were performed in high-income industrialized countries (three in the USA, one in Denmark, and one in Norway), except for one performed in a low-income country (Indonesia). The evaluated diets varied with respect to the way they were administered. In one study [13], the research center's metabolic kitchen provided each participant with the type of food adequate for his or her group affiliation (either a GFCF diet or a regular diet) in accordance with Recommended Dietary Allowances for age. In one study [17], participants received daily either 11 g of gluten and 12 g of casein or a placebo (rice meal) in addition to following a GFCF diet. In another RCT [16], after a 2-week washout period of following a gluten-free diet, one group followed a GFCF diet but received a daily supplementation of gluten (0.5 g/kg) and non-fat dried milk (0.5 g/kg) (gluten-dairy-containing diet), while the other group followed a GFCF diet and received 1 g/kg/day of brown rice flour (gluten-dairy-free diet). In the three remaining trials [14, 15, 18], study nutritionists or dieticians provided parents with guidelines on following a GFCF diet or a regular, healthy diet. Interventions lasted from 7 days to 24 months; in four included trials, the duration was 3 months or less [13, 15–17]. There was variability in how a change in autism spectrum disorder symptoms was assessed (see Online Resource 2). Each of the scales, measuring different aspects of autistic symptoms, cognitive functioning, adaptive behavior, and coexisting behavior or emotional problems, was used only once, with the exception of the Child Behavior Checklist (CBCL), which was used in two studies [15, 16]. In three studies [15–17],

Table 1 Gluten- and casein-free diet in children with autism spectrum disorders—characteristics of the included studies

Reference (country)	Population (diagnosis of ASD)	Intervention (group size)	Control (group size)	Duration of intervention	Outcomes	Sample size calculation	Funding
Navarro (2015) (USA) [16]	4–7 years, ASD[a] (DSM-IV-TR[b], (ADI-R[c], ADOS[d])	GFCF[e] diet + daily supplementation of gluten powder (0.5 g/kg) and non-fat dried milk (0.5 g/kg) ($n = 6$)	GFCF[e] diet + daily supplementation of brown rice flour (1 g/kg) ($n = 6$)	4 weeks	ABC[f], CBCL[g], CPRS-R[h], SCQ[i], GI[j] symptoms, Intestinal permeability (the urine lactose/mannitol ratio)	Not reported	Not reported
Pusponegoro (2015) (Indonesia) [17]	4–7 years, ASD[a], severe maladaptive behavior, abnormal urinary I-FABP[k] level (DSM-IV-TR[b])	GFCF[e] diet + daily supplementation of Gluten (11 g) and Casein (12 g) in the form of six biscuits ($n = 38$)	GFCF[e] diet + daily supplementation of 30 g of rice meal in the form of six biscuits ($n = 36$)	7 days	AWPC-score[l] subtest of PDDBI[m], GI[j] symptoms, Urinary I-FABF[k]	Not reported	Authors declare no funding
Johnson (2011) (USA) [15]	3–5 years, ASD[a] (DSM-IV[n] and ADOS[d])	GFCF[e] diet ($n = 8$)	Regular diet ($n = 14$)	3 months	Mullen Scales of early learning (measures intellectual development, not ASD symptoms), CBCL[g], Direct Behavior Observation Measure, GI[j] symptoms, nutritional status, side effects	Not reported	Supported by the John and Nancy Emmerling fund/ The Pittsburgh foundation
Whiteley (2010) (Denmark) [18]	4–10 years, ASD[a] (ADOS[d], ADI-R[c])	GFCF[e] diet ($n = 38$)	Regular diet ($n = 34$)	8 months (1st stage) 12 months (2nd stage) 24 months (3rd stage)	ADOS[d], GARS[o], VABS[p], ADHD-IV[q], adverse effects, urinary compounds co-eluting with exogenous opioid peptide standards and/or IAG[r]	Not reported	Part of IMGSAC[s]; grants from the Center for Autisme, the Nils O. seim Family Fond, the Norwegian Protein Intolerance Association, the Robert Luff Foundation
Elder (2006) (USA) [13]	2–16 years, ASD[a] (DSM-IV[n], ADI-R[c])	GFCF[e] diet ($n = 7$)	Regular diet ($n = 7$)	12 weeks (6 weeks-crossover-6 weeks)	CARS[t], ECOS[u], ADI-R[c], in-home observation, urinary peptide levels	Not reported	Supported by the University of Florida's College of Nursing Biobehavioral NINR-funded research grant P20 NR 07791-03 and GCRC grant M01RR00082 from the National Institute of Research Resources, National Institutes of Health

Table 1 continued

Reference (country)	Population (diagnosis of ASD)	Intervention (group size)	Control (group size)	Duration of intervention	Outcomes	Sample size calculation	Funding
Knivsberg (2002) (Norway) [14]	5–10 years, ASD[a], abnormal urinary peptide levels (ASD diagnostic criteria not described)	GFCF[e] diet ($n = 10$)	Regular diet ($n = 10$)	12 months	DIPAB[v], LIPS[w], ITPA[x], Reynells spraktest, MABC[y], TOMI[z]	Not reported	Funding from The country council of Rogaland, Sigval Bergesen d.y. og hustru Nanki's almennyttige stiftelse, and Seim Family Foundation

[a] Autism spectrum disorders

[b] Diagnostic and statistical manual of mental disorders-IV—text revision

[c] Autism diagnostic interview-revised

[d] Autism diagnostic observation schedule

[e] Gluten- casein-free diet

[f] Aberrant behavior checklist

[g] Child behavior checklist

[h] Conners parent rating scale-revised

[i] Social communication questionnaire

[j] Gastrointestinal

[k] Intestinal fatty acids binding protein

[l] The approach withdrawal problems composite

[m] Pervasive developmental disorder-behavior inventory

[n] Diagnostic and statistical manual of mental disorders-IV

[o] Gilliam autism rating scale

[p] Vineland adaptive behavior scale

[q] Attention-deficit hyperactivity disorder

[r] Trans-indolyl-3-acryloylglycine

[s] The international molecular genetic study of autism consortium

[t] Childhood autism rating scale

[u] Ecological communication orientation scale

[v] Standardized Danish scheme

[w] Leiter international performance scale

[x] Illinois test of psycholinguistic abilities

[y] Movement assessment battery for children

[z] Test of motor impairment

gastrointestinal symptoms were assessed. Five of the included studies measured certain laboratory parameters [13, 14, 16–18]; however, these measurements were not included in our review. The risk of bias assessment is presented in Online resource 3. Sample size calculations were not available in any of the included trials.

Effects of interventions

Behavior

The authors of two trials [13, 18] reported statistically significant differences in autism spectrum disorder core symptoms between groups, as measured by standardized scales. The clinical importance of the findings was reported for a few individuals in only one trial [18].

Based on the findings from one RCT [18] ($n = 72$), compared with the control group, in the GFCF group there was improvement in both the score for the 'communication' subdomain of the ADOS at 8 months (no data provided; $P = 0.002$) and the score for the 'social interaction' subdomain of the Gilliam Autism Rating Scale (GARS) at 12 months (no data provided; $P = 0.0001$).

In the parent-based reports, there was a statistically significant improvement in the score for the 'daily living skills' subdomain of the Vineland Adaptive Behavior Scale (VABS) at 12 months (no data provided; $P = 0.0208$) in favor of the GFCF group. Finally, there were statistically significant improvements in the scores for the 'inattention' (no data provided; $P = 0.0007$) and 'hyperactivity' (no data provided; $P = 0.0188$) subscales of the Attention-Deficit Hyperactivity Disorder (ADHD)-IV scale at 12 months in favor of the GFCF group.

Based on the findings from one RCT [14] ($n = 20$), there was a statistically significant difference between groups in the post-intervention scores for the 'autistic traits' subdomain of the standardized Danish scheme (DIPAB) (mean difference, MD, −5.6, 95% CI −9.02 to −2.18; $P = 0.001$). Additionally, as reported in the previous Cochrane review [8] (based on additional information obtained from the authors), there were also significant differences between groups in the post-intervention scores for the 'communication' (MD 1.7, 95% CI 0.5–2.9; $P = 0.006$) and 'social contact' (MD −3.2, 95% CI −5.2 to −1.2; $P = 0.002$) subdomains of the DIPAB. All of these differences were in favor of the GFCF group.

In the Cochrane review [8], further analysis of data from the same study [14] revealed no significant difference between the groups in the non-verbal cognitive level at the end of the intervention (MD 12.4, 95% CI −20.06 to 44.86; $P = 0.45$), as assessed with the Leiter International Performance Scale (LIPS). However, the authors reported a statically significant difference in change in the non-verbal cognitive level (no data provided; $P = 0.004$) in favor of the GFCF group.

In the Cochrane review [8], further analysis of data from the same study revealed no significant difference between groups in motor problems at the end of the intervention (MD −1.5, 95% CI −11.89 to 8.89; $P = 0.78$), as assessed with the Movement Assessment Battery for Children (MABC). However, the authors reported a statistically significant difference in change in motor problems (no data provided; $P = 0.04$) in favor of the GFCF group.

Finally, the authors of one trial [15] ($n = 22$) reported that, compared with the GFCF group, in the control group there were statistically significant improvements in both the 'visual reception' subscale of the Mullen Scales of Early Learning (no data provided; $P = 0.005$) and the 'withdrawn' subscale of the Child Behavior Checklist (no data provided; $P = 0.04$) between baseline and the 3-month follow-up. Authors of the same study reported that compared with the control group, in the GFCF group there were reductions in both the 'aggression' (no data provided; $P = 0.046$) and 'ADHD' (no data provided; $P = 0.043$) subscale scores on the Child Behavior Checklist between baseline and the 3-month follow-up. However, comparison of post-intervention mean scores revealed no significant differences between groups for any subdomains of the scales.

Gastrointestinal symptoms

In three included studies [15–17], data concerning gastrointestinal disturbances, such as abdominal pain, nausea/vomiting, bowel movements, bloating, and borborygmi, were assessed. No significant differences between groups were found.

Adverse events

No differences between groups in adverse events were found in the two trials that reported data on adverse events [15, 18].

Discussion

Summary of evidence

Although not routinely recommended, a GFCF diet is commonly used as a treatment for ASD in children. The current systematic review documents that overall, there is little evidence that following a GFCF diet is beneficial for managing the symptoms of ASD in children and adolescents. With few exceptions in some subdomains, there were no statistically significant differences in autism spectrum disorder

core symptoms between groups, as measured by standardized scales. Furthermore, the clinical importance of the results cannot be reliably established, as no individuals' data were provided. Based on the findings from one trial, compared with the control group, in the GFCF group there were significant improvements in the scores for the 'communication' subdomain of the Autism Diagnostic Observation Schedule and for the 'social interaction' subdomain of the Gilliam Autism Rating Scale. Based on the findings from one trial, there were statistically significant differences between groups in the post-intervention scores for the 'autistic traits', 'communication', and 'social contact' subdomains of the standardized Danish scale (DIPAB). With regard to parent-based assessments, there were significant improvements in scores for the 'daily living skills' subdomain of the Vineland Adaptive Behavior Scale, as well as for the 'inattention' and 'hyperactivity' subscales of the ADHD-IV scale, in favor of the GFCF group. Some trials reported significant differences between groups in scores reflecting change in other developmental features from baseline to end of the trial. Compared with the regular diet group, in the GFCF diet group there were significant differences in the Leiter International Performance Scale and Movement Assessment Battery for Children scores (nonverbal cognitive level and motor problems, respectively) and in two subdomains of the Child Behavior Checklist ('aggression' and 'ADHD'). In one study, there were significant improvements in the 'withdrawn' subscale of the Child Behavior Checklist and in the 'visual reception' subscale of the Mullen Scales of Early Learning in favor of the control group. No adverse events associated with following a GFCF diet were reported. All of these results should be interpreted with caution due to limited evidence available.

Strengths and limitations

An important strength of this systematic review is the use of rigorous methodology developed by the Cochrane Collaboration. We employed several methods to reduce bias (i.e., comprehensive literature search, pre-specified criteria for methodological assessment and analysis, and no restrictions by language or year of publication). However, we cannot exclude the risk of bias. There were some methodological limitations in the trials, including unclear allocation concealment, unclear blinding, and no intention-to-treat analysis; this may result in selection, performance, and/or attrition biases and, eventually, invalidate the results. Additional limitations include small sample sizes and the lack of sample size calculations in all of the trials. The included studies were likely to be underpowered for addressing some outcomes (also adverse events).

A further limitation was that the included studies differed in the diagnostic criteria for ASD and other inclusion criteria; thus, participants may have differed in the level of core autism features and cognitive level. Participants in the included studies varied widely in age. The large age ranges, at least in some of the studies, as well as the small sample sizes in all of the included studies, may not allow one to reliably detect a clinically important difference in the performance of children with ASD, even if one actually exists.

The age of children when the GFCF diet was introduced may also be a critical factor, because of brain plasticity in younger children [21]. Additionally, we can suspect that the ability to comply with the diet may differ with age. In the included studies, the only trial that assessed dietary compliance found lower adherence in the GFCF diet group compared with the regular diet group. A dietary evaluation by a trained dietician is considered the best method to assess dietary compliance [22]. However, this was not systematically done in any of the included trials. On the other hand, Elder et al. [13] noted that some parents continue GFCF-diet despite lack of clinical effect. One can hypothesize that dietary adherence, especially in younger children, may depend on parents/care-givers approach.

Additionally, the changes in behavior may be associated with puberty onset, pharmacotherapy (more commonly used in older children with ASD), and the presence of ASD-comorbidities such as anxiety or depression [23]. While all of these factors may confound the findings, they were not well described in the included studies.

The studies might have been too short to demonstrate a benefit. In four trials, the interventions lasted for 3 months or less, while some data suggests that a GFCF diet should be implemented for at least 6 months to assess the response to that diet [24]. Moreover, for validated psychometric tests, to detect relevant changes in performance of children with ASD, the observation period should last at least 4 months [25].

Finally, we can speculate that a parental placebo effect may have had an impact on the assessment of the effectiveness of the GFCF diet. This placebo effect should be taken into account when interpreting the results of parent-reported scales such as the Child Behavior Checklist or the Vineland Adaptive Behavior Scale [26]. Taken together, while some findings are promising, they must be interpreted with caution and the generalizability of the results is limited. Given the lack of clear evidence, the GFCF diet should be considered only on a case-by-case basis.

Conclusions

The current systematic review was designed to resolve uncertainty regarding the role of a GFCF diet in children with ASD. Even if new data have become available, the overall conclusions made previously did not change. The

limited available evidence suggests that there is no consistent evidence to support the use of a GFCF diet in children with ASD. However, caution is needed when interpreting current evidence, as the evidence is limited. Large, high-quality RCTs, involving multidisciplinary teams, are still needed to further clarify the effects of following a GFCF diet, if any, on performance and functional outcomes in children with ASD.

Author's Contribution AH initially conceptualized this study. AP and JŁ were responsible for data collection. HS and AH assumed the main responsibility for the writing of this manuscript. All authors were responsible for data analysis and data interpretation. All authors contributed to (and agreed upon) the final version of this manuscript.

Compliance with ethical standards

Conflict of interests AH and AP are the recipients of a grant from the Fundacja Nutricia (Nutricia Foundation) under Grant RG8/2013 to carry out the study on ASD and a gluten-free diet. Other authors declare no conflict of interests.

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