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Author manuscript

*Nutr Diet Suppl.* Author manuscript; available in PMC 2017 January 18.

Published in final edited form as:

*Nutr Diet Suppl.* 2015 ; 7: 87–101. doi:10.2147/NDS.S74718.

## A review of gluten- and casein-free diets for treatment of autism: 2005–2015

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### Abstract

**Background**—The gluten free, casein free (GFCF) diet is heralded by strong anecdotal parental reports to greatly improve and even “cure” symptoms of Autism Spectrum Disorders (ASD). Yet to date, little conclusive empirical evidence exists supporting its use.

**Objective**—The purpose of this paper is to provide an overview of the state of the recent evidence regarding use of GFCF diet for treatment of individuals with ASD.

**Methods**—Five database providers (PubMed, Web of Knowledge, EBSCO, ProQuest, and WorldCat) were used to search 19 databases yielding a total of 491 articles that were published through February 2015. Peer reviewed articles published between 2005 and February 2015 were included for review if study participants were identified as having ASD and investigated the effects of the GFCF diet on ASD behaviors or the relationship between the diet and these behaviors.

**Results**—Evaluation of search results yielded 11 reviews, 7 group experimental studies including 5 randomized controlled trials, 5 case reports, and 4 group observational studies published during the last 10 years. These studies represent a marked increase in number of reported studies as well as increased scientific rigor in investigation of GFCF diets in ASD.

**Conclusions**—While strong empirical support for the GFCF diet in ASD is currently lacking, studies point to the need for identifying subsets of individuals (e.g., those with documented

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Author contribution statement: JE, CK, NS contributed to the literature search. CK, NS, MD contributed to the data collection. JE, CK, NS, MD contributed to the data analysis and data interpretation. All authors contributed to the writing.

Declaration of interests and funding: The authors report no conflicts of interest. This work was supported in part by the National Institutes of Health – National Center for Medical and Rehabilitation Research (NICHD) and National Institute for Neurological Disorders & Stroke under grant number K12 HD055929. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

gastrointestinal abnormalities) who may be the best responders to the GFCF diet. Identifying these subsets is critically needed to enhance rigor in this research area. Until rigorous research supporting use of GFCF diet is reported, clinicians should continue use caution and consider several factors when advising regarding implementation of the GFCF diet for individuals with ASD.

### Keywords

GFCF diet; Autism Spectrum Disorders; review; gluten-free; casein-free; dietary intervention

Autism, or the broader category of Autism Spectrum Disorder (ASD), continues to pose challenges in determining the most efficacious and effective treatment approaches for managing associated social, communication, behavioral, and developmental symptoms.<sup>1</sup> First described in a 1943 case report by Leo Kanner,<sup>2</sup> intervention approaches for autism have been the subject of a vast number of clinical reports and case studies; less common are rigorous intervention trials. Recently, the thinking about ASD has expanded from a solely psychiatric condition to a multi-system inflammatory disorder that includes systemic inflammation of the gastrointestinal (GI) tract impacting the brain, immune system, and metabolism.<sup>3</sup>

One popular treatment for addressing possible systemic inflammation is the gluten free, casein free (GFCF) diet, heralded by strong anecdotal parental reports of greatly improved<sup>4</sup> and even “cured” symptoms of ASD such that the child no longer meets criteria for ASD.<sup>5</sup> The GFCF diet was first identified for use in schizophrenia<sup>6</sup> where a possible genetic defect may contribute to what has been referred to as a “leaky gut”, resulting in an overload of gluten (from wheat) and casein (from dairy). It is posited that this overload causes high peptide levels, which may produce an opioid-type effect that manifests in the behavioral symptoms commonly seen in ASD.<sup>7</sup> Others speculate that many individuals with ASD may have undiagnosed gastric conditions and sensitivities that are caused or aggravated by the ingestion of casein and gluten. This discomfort, or even severe pain in some cases, may result in externalizing behaviors (e.g., tantrums, screaming, and aggression) and inattention to tasks due to the distraction of pain.

Several systematic reviews<sup>8–14</sup> of GFCF studies have focused on the few existing intervention studies and reported inconclusive results.<sup>8–14</sup> However, as Kanner<sup>2</sup> noted in his case report, a thorough review must address case studies as well as reports of clinical trials to produce a “full view of the landscape” of what is currently known about the GFCF diet. Such comprehensiveness is needed to assist families and clinical professionals in making informed decisions about implementing the GFCF diet and can identify specific directions for future research.

The purpose of this paper is to provide an overview of the state of the recent evidence regarding use of GFCF diet for treatment of individuals with ASD as needed for directing future research and advancing clinical practice recommendations. As such, we reviewed the scientific literature published between 2005 and February 2015 and have organized our review into four sections: summaries of review articles, group experimental intervention studies including randomized clinical trials, case reports and group observational studies.

## Methods

We began our review with a scoping search of the literature in order to gain a broad overview of the existing relevant literature. Table 1 details our search strategies, which were constructed by the third author, a research librarian. Nineteen databases from five database providers (PubMed, Web of Knowledge, EBSCO, ProQuest, and WorldCat) were searched via subject headings and keywords, with the latter truncated and/or phrase-searched to capture various forms of gluten, casein, GFCF diet, autism, autism spectrum disorder, and Asperger's syndrome. Search efforts yielded a total of 491 articles. Removal of duplicates and non-English articles left 290 potential articles, whose titles (and abstracts when needed) were independently screened by two members of the research team. Additional screening was conducted for (a) publication date prior to 2005; (b) publication type, such as commentary, letter to the editor, book chapter, or thesis/dissertation; (c) publication in non-peer reviewed periodical (d) main topics unrelated to gluten or casein restricted diets; (e) main topics unrelated to ASD; (f) non-ASD research participants; and/or (g) non-English publications. Full texts of the remaining 61 publications were read and sorted by article type (i.e., review, experimental, case, group observational). Review articles focusing on GFCF diet in ASD were retained; all remaining articles were read for major focus on use of GFCF diet in ASD. Backward searches of references in the 11 included review articles yielded one additional published abstract, resulting in the 27 publications included in our review. At each step of the article reduction process two researchers discussed discrepancies in their independent evaluations until consensus was reached; when needed, a third member of the research team assisted with deliberations.

Review articles, intervention studies, case reports and group observational studies were included if the study participants were identified as having ASD and the study investigated either the effects of the GFCF diet on ASD behaviors or the relationship between the diet and behaviors of individuals with ASD. All articles included for review were published in peer-reviewed, English-language journals between January 2005 and February 2015. Studies were excluded if they did not focus on GFCF diet in ASD. However, because of the paucity of randomized controlled trials (RCTs) reported in the literature and because of the study's rigor, we chose to include the one double-blind randomized controlled trial (RCT) reported via published abstract<sup>15</sup> (no other published abstracts reported on a RCT testing GFCF diets in ASD).

## Results

### Reviews

A total of 11 review articles<sup>8-14,16-19</sup> from 10 research groups were included in this review and are summarized in Table 2. Hereafter, we will refer to these 11 review articles as 10 reviews because one review article was written as an addendum<sup>11</sup> of the group's review that was published in the prior year.<sup>10</sup> These authors reviewed a RCT reported in 2010 by Whiteley and colleagues<sup>20</sup> that was published shortly after the original review was released. Notably, six<sup>12-14,17-19</sup> of the 10 reviews were published during the last two years of our review period; of these six reviews, five<sup>13,14,17-19</sup> reported on multi-dimensional

considerations (e.g., safety, adherence to evidence based practice standards, diet allergies) informing the use of GFCF diets in the treatment of ASD.

Of the 10 reviews, two<sup>9,12</sup> limited their review to RCTs. The remaining reviews included uncontrolled studies, group descriptive/observational studies, and case reports in addition to RCTs. The most rigorous review of the GFCF diet in ASD is a 2008 Cochrane review by Millward, Ferriter, and Calver.<sup>9</sup> They identified only two small RCTs ( $n = 35$ ), which rendered a meta-analysis impossible. The authors concluded that despite the evidence of high use of this diet as well as other complementary and alternative therapies (CAM), insufficient evidence exists to support its efficacy. The review of GFCF diet studies conducted by Mulloy and colleagues<sup>10</sup> identified 14 reports published over the thirty years 1977–2007. These studies greatly varied in quality and scope; most lacked adequate control measures and sample sizes ranged from one individual to a group of 30. These authors used pre-established criteria to judge the evidence as *suggestive*, *preponderant* or *conclusive*; they found no studies providing conclusive level evidence and only three studies providing preponderant level evidence. In the most recent (2014) synthesis of the literature, Mari-Bauset, Zazpe, Marii-Sanchis, Llopis-Gonzalez, and Morales-Suarez-Varela<sup>14</sup> reviewed a total of 32 studies of various designs published between 1971 and 2012, of which 24 reported on effectiveness of GFCF diet in the treatment of ASD and 8 reported on the safety of the diet. Despite the breadth of evidence reviewed, these authors found the evidence supporting the effectiveness and safety of GFCF diets for treatment of ASD to remain limited and weak.

### Group Experimental Studies

A total of seven group experimental studies<sup>4,15,20–24</sup> testing the effect of GFCF diet in ASD were included for review, of which six were prospective studies<sup>4,15,20–23</sup> and one<sup>24</sup> a retrospective analysis of data from one<sup>4</sup> of the six prospective studies. Of the six prospective studies, two were double-blind RCTs.<sup>4,15</sup> Two studies<sup>20,21</sup> used a single-blind RCT design in which the parents provided the child's food while study personnel supported them with dietary guidance. Two studies<sup>22,23</sup> used an uncontrolled design to investigate the effect of GF-only, CF-only and GFCF diet conditions (3 separate interventions) on children's behaviors using non-blinded assessments of specific behaviors in the 3 intervention groups. Of the group experimental studies included for review, only two<sup>15,21</sup> restricted the age span of participants to an age range spanning 2 years; the remaining studies allowed study sample age ranges of up to 18 years. Additionally, only one study<sup>20</sup> tested an intervention that lasted longer than three months. Notably, this was the only study that reported statistically significant improvements in the GFCF diet group using blinded assessment. No other studies using blinded assessment found group differences for the GFCF diet. However, one study<sup>4</sup> did note positive anecdotal reports for some participants on the GFCF diet. Table 3 summarizes the 7 group experimental studies included in our review.

### Case Reports

A total of five case reports<sup>5,25–28</sup> were reviewed and are summarized in Table 4. Of these five cases, one employed a quasi-experimental design. Irvin<sup>25</sup> utilized a ABAB (2-phase design where A1 is the baseline, B1 is the introduction of the intervention, A2 is the

withdrawal of the intervention, and B2 is the reintroduction of the intervention) reversal design and measured the frequency of problem behaviors in a controlled setting while on and off the GFCF diet. No significant reduction in problem behaviors was found while the child was on the GFCF diet as compared to a regular diet. However, the remaining four case reports described positive changes in cognitive, behavioral, and language symptoms of the children with ASD following implementation of the GFCF diet. Additionally, in these four cases<sup>5,26–28</sup> parents reported positive results, such as improved language and cognitive development and satisfaction with the overall changes in their child. Three<sup>5,26,27</sup> of the five case reports noted that the GFCF diet improved the child's communication skills and cognitive scores so drastically that the children eventually no longer met the diagnostic criteria for ASD. Most notable amongst the five case reports reviewed was the presence of preexisting GI symptoms in the four cases<sup>5,26–28</sup> reporting improvement in ASD-related symptoms after the implementation of the GFCF diet.

### Group Observational Studies

Four group observational studies<sup>29–32</sup> were reviewed that contribute evidence informing more nuanced aspects of future GFCF diet trials; these studies are summarized in Table 5. An observational study by Patel and Curtis<sup>29</sup> incorporated pre- and post-testing of 10 children who received a comprehensive, multi-faceted treatment regime, which for some children included a GFCF diet. These authors reported improved behavioral, social, motor and GI symptoms after 3 to 6 months. In a survey of 293 parents of children with ASD on a GFCF diet, Pennesi and Klein<sup>30</sup> found greatest improvements in the subgroups of children with GI symptoms, allergy symptoms, and those on the GFCF diet for longer than 6 months. In a post-hoc analysis of the ScanBrit trial data, Pederson et al.<sup>31</sup> reported that children with the strongest probability of responding to a GFCF diet are those aged 7 to 9 years who have clinically significant ADHD-IV scores.

### Discussion

Our review of the recent literature on gluten- and/or casein- restricted diets for treatment of ASD yielded 11 reviews, 7 group experimental studies including 5 randomized controlled trials, 5 case reports, and 4 group observational studies published during the last 10 years (January 2005 through February 2015). As previously mentioned, the earliest reports within the literature on gluten- and/or casein- restricted diets in ASD have been case studies, with gradual movement toward more rigorous research over the last 10 years. Perhaps this review's strongest contribution to the literature informing GFCF dietary interventions in ASD is the contextual overview of the scientific literature published during the past 10 years. Of the reviews included in our study, the review conducted by Mari-Bauset and colleagues (2014)<sup>14</sup> included the largest number of primary (non-review) studies informing on the effect of gluten and/or casein restricted diets in the treatment of individuals with ASD ( $n = 24$ ). Of its 24 relevant studies, 4 (16 %) were published in the 1970s, 10 (42%) were published in the 12 year span of 1990 and 2002, and the remaining 10 studies (42%) were published during the 7 year period of 2005 through 2012. This observation, in conjunction with the number of reviews focusing on GFCF in ASD published in 2012 and 2013 (6 of 10 included in our review) indicates an increased interest in GFCF treatments for ASD over the

past ten years. Researchers' collective understanding of the questions at hand has refined to reflect an incomplete but multifaceted understanding of gluten- and/or casein- restricted diets in the treatment of ASD. Some studies point to a child's age at diet introduction,<sup>31</sup> while others suggest duration of diet<sup>20,30</sup> as well as possible food sensitivities and allergies<sup>10–12,14,18</sup> as potential factors impacting efficacy of GFCF diet in ASD. Others note physiological abnormalities in ASD that may help to elucidate potential responders.<sup>33–37</sup> These findings are highly significant and similar to our conclusions about the state of the science related to the GFCF intervention in ASD.

### Limitations

Findings were limited by our specific question investigating the current state of evidence regarding use of the GFCF dietary intervention in ASD. That is, we were seeking information about results of the GFCF diet itself and not necessarily what patient characteristics might suggest the best responders. Resultantly, only eight studies included for review contributed evidence as to who may be best responders to a GFCF diet for treatment of ASD.<sup>10–12,14,18,20,30, 31</sup>

### Future direction: Targeting subgroups of likely responders

The recent literature indicates a need for future GFCF diet trials to target likely responders. Case report descriptions of positive effects in the four (of five) cases included in our study reporting GI symptoms are consistent with conclusions drawn from reviews published between 2005 and 2015. Specifically, Mulloy et al.<sup>10,11</sup> and Mari-Bauset and colleagues<sup>14</sup> recommended consideration of the GFCF diet only when food allergy and/or sensitivities have been diagnosed. In their reviews of the scientific literature, Dosman et al.,<sup>18</sup> Hurwitz<sup>12</sup> and Mari-Bauset et al.<sup>14</sup> recommended screening for celiac disease and/or food allergies prior to implementation of the GFCF diet. Conclusions drawn in at least two reviews,<sup>13,17</sup> analysis of two clinical trials,<sup>15,20</sup> and one observational cross-sectional study<sup>30</sup> suggest the existence of a sub-group of responders to GFCF dietary interventions. Empirically derived information suggestive of subgroups that may be responsive to GFCF dietary interventions has only recently come to light and has not yet been incorporated into the published clinical trials included in our review.

### Summary

Despite its lack of empirical validation, there is enough interest in the GFCF diet that the treatment strategy remains widely used with individuals with ASD. The GFCF diet serves as a strong exemplar of science lagging behind in its ability to inform the practices of a community of interest. Some reasons for this paucity of empirical support are discussed in the reviewed literature and include challenges related to conducting clinical trials that must ensure dietary compliance and experimental blinding in naturalistic, day-to-day settings and interactions. In short, well-controlled GFCF dietary trials are difficult to conduct but remain desperately needed in order to inform clinical treatment decisions. Further concerted efforts must be made to identify subsets of individuals (e.g., those with documented GI abnormalities) who may be the best GFCF diet "responders". Finally, until such evidence is available, clinicians should advise those wishing to implement the GFCF diet that it is not



likely to be a “miraculous cure” as some claim. As such, clinicians should use caution and consider a number of factors, such as the individual’s overall nutritional status as well as potential added family burden related to cost and time commitments, when advising regarding implementation of the GFCF diet for individuals with ASD.

## Acknowledgments

The authors acknowledge Caroline S. Mikael for assistance with initial data analysis.

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Table 1

## Search Strategies Used

Database (Provider)	Search Strategy	Limits	Date Searched	Number of Results
PubMed	((diet OR dietary) AND (restrict OR restricts OR restricted OR restriction OR restrictions OR limit OR limits OR limited OR limitation OR limitations)) AND (“ASD”[tiab] OR “Child Development Disorders, Pervasive”[Mesh] OR “Asperger Syndrome”[Mesh] OR Asperger[tiab] OR Asperger’[tiab] OR Asperger’s[tiab] OR Aspergers[tiab] OR Aspergers’s[tiab] OR autism[tiab] OR autistic[tiab] OR “Autistic Disorder”[Mesh])	Clinical Trial; Review; Evaluation Studies; Journal Article; Twin Study // published in the last 10 years // English	2/28/15	86
PubMed	((“gluten free” AND “casein free”) OR “GFCF”[tiab] OR “gluten free casein free”) AND (“ASD”[tiab] OR “Child Development Disorders, Pervasive”[Mesh] OR “Asperger Syndrome”[Mesh] OR Asperger[tiab] OR Asperger’[tiab] OR Asperger’s[tiab] OR Aspergers[tiab] OR Aspergers’s[tiab] OR autism[tiab] OR autistic[tiab] OR “Autistic Disorder”[Mesh] OR “Child Development Disorders, Pervasive”[Mesh]))	Published in the last 10 years; English	2/28/15	42
Academic Search Premier (EBSCO)	(DE “Gluten-free diet” OR DE “Casein-free diet” OR (“gluten free diet*” OR “gluten free” OR “casein free diet*” OR “casein-free” OR GFCF OR GFD OR “gluten* and casein-free diet*” OR ((gluten OR casein) AND (“restricted diet*” OR “diet* restriction*”)))) AND AB (autis* OR ASD OR ASC OR “autism spectrum disorder*” OR “autism spectrum condition*”) OR TI (autis* OR ASD OR ASC OR “autism spectrum disorder*” OR “autism spectrum condition*”))	Scholarly (Peer-Reviewed Journals)	3/17/15	43
CINAHL (EBSCO)	(MH “Autistic Disorder” OR MH “Asperger Syndrome” OR autis* OR ASD OR ASC OR Asperger*) AND MH “Diet, Gluten-Free” OR GFD OR ((MH “Diet” OR “diet* restriction*” OR “restricted diet*” OR “limited diet*” OR “diet* limit*”) AND (“gluten free” OR gluten OR casein OR “casein free” OR GFCF))	2004–2014; academic journals; English	3/18/15	22
Education FullText (H.W. Wilson on EBSCO)	GFD OR ((gluten OR “gluten free” OR “gluten-free” OR casein OR “casein free” OR “casein-free” OR GFCF) AND (diet* OR “diet* restriction*” OR “restricted diet*” OR “limited diet*” OR “diet* limit*”)) AND (DE “Autism spectrum disorders” OR DE “Asperger’s syndrome” OR DE “Autism” OR DE “Autism spectrum disorders in women” OR DE “Pervasive developmental disorder	2003–2014; Scholarly, Peer-reviewed Academic journals	3/18/15	5

Database (Provider)	Search Strategy	Limits	Date Searched	Number of Results
Health Source: Nursing/Academic Edition (EBSCO)	not otherwise specified" OR ASD OR ASC OR autis*) (DE "Autism spectrum disorders" OR DE "Autism" OR DE "Pervasive developmental disorder not otherwise specified" OR autis* OR Asperger* OR ASD OR ASC) AND ((DE "Gluten-free diet" OR DE "Casein-free diet" OR ((gluten OR "gluten free" OR casein OR "casein free" OR GFCF) AND (diet* OR "diet* limit*" OR "limited diet*" OR "diet* restriction*" OR "restricted diet*"))))	Peer-reviewed academic journals or reviews, 1997–2014	3/18/15	24
Psychology and Behavioral Sciences Collection (EBSCO)	(DE "Autism spectrum disorders" OR DE "Asperger's syndrome" OR DE "Autism" OR autis* OR ASD OR ASC) AND (((DE "Diet" OR DE "Diet therapy") AND (gluten OR "gluten-free" OR casein OR "casein-free" OR GFCF)) OR GFD OR DE "Casein-free diet" OR DE "Gluten-free diet")	1978–2014 publication date; Peer-reviewed and academic journals	3/18/15	34
PsycINFO (EBSCO)	(DE "Aspergers Syndrome" OR DE "Autism" OR "autism spectrum disorder*" OR "autism spectrum condition*" OR ASD OR ASC OR autis*) AND ((DE "Dietary Restraint" OR DE "Diets" OR "diet* restriction*" OR "restricted diet*" OR "diet* limitation*" OR "limited diet*") AND (gluten OR casein OR GFCF OR GFD OR "gluten-free" OR "casein free"))	Academic Journals, Books and Dissertations	3/18/15	35
SportDiscus (EBSCO)	(DE "Casein-free diet" OR DE "Gluten-free diet" OR (DE "Diet in disease" OR DE "Diet therapy" OR DE Nutritionally induced diseases" OR DE "Diet" OR "diet* restriction*" OR "restricted diet*" OR "diet* limitation*" OR "limited diet*") AND (DE "Gluten-free foods" OR gluten OR "gluten free" OR casein OR "casein free")) AND (Asperger* OR ASD OR ASC OR autis* OR "autism spectrum disorder*" OR "autism spectrum condition*")	Academic journals, 2002–2014	3/18/15	8
Web of Science (Web of Knowledge)	("gluten* and casein-free diet*" OR ("gluten free" OR "casein free" OR GFCF OR gluten OR casein) AND("restricted diet*" OR "diet* restriction*" OR "limited diet*" OR "diet* limit*")) AND TOPIC: (autis* OR ASD OR ASC OR "autism spectrum disorder*" OR Asperger*)	No limits set	3/18/15	21
ASSIA (ProQuest)	((SU.EXACT("Diet" OR diet*) AND (gluten* OR casein* OR GFC OR GFCF)) AND ((SU.EXACT.EXPLODE("Autistic spectrum disorders") OR SU.EXACT EXPLODE ("Autism" OR "infantile autism") OR SU.EXACT.EXPLODE("Asperger's syndrome")) OR ASD OR autis* OR Asperger*)	No limits set	3/27/15	6

Database (Provider)	Search Strategy	Limits	Date Searched	Number of Results
Dissertations & Theses (ProQuest)	diet* AND (gluten* OR casein* OR GFC OR GFCF) AND (autis* OR ASD OR Asperger*). Narrowed by Subject: biochemistry; genetics; microbiology; cellular biology; food science; medicine; autism; livestock; toxicology; analytical chemistry; anatomy and physiology; biology; health care management; nursing; occupational therapy; alternative medicine; parents and parenting; rehabilitation; therapy	No limits set	3/27/15	5
ERIC (ProQuest)	(SU.EXACT.EXPLODE("Pervasive Developmental Disorders") OR ASD OR autism* OR Asperger*) AND ((SU.EXACT.EXPLODE("Dietetics") OR diet*) AND (gluten* OR casein* OR GFD OR GFCF))	No limits set	3/27/15	23
Agricola (ProQuest)	(gluten* OR casein* OR GFD OR GFCF) AND (autis* OR Asperger* OR ASD) AND diet*	No limits set	3/29/15	9
SportDiscus (EBSCO)	((DE "Diet" OR DE "Diet in disease" OR DE "Diet therapy" OR DE "Nutritionally induced diseases") OR diet*) AND (gluten* OR casein* OR GFD OR GFCF) AND (autis* OR Asperger* OR ASD)	Academic journals, 2002–2014	3/29/15	9
AltHealthWatch (EBSCO)	(DE "DIET" OR DE "NUTRITIONALLY induced diseases" OR DE "DIET in disease" OR DE "Diet therapy" OR diet*) AND (gluten* OR casein* OR GFD OR GFCF) AND (DE "Autism spectrum disorders" OR DE "ASPERGER'S syndrome" OR DE "AUTISM" OR autis* OR Asperger* OR ASD)	No limits set	3/29/15	6
PubAg	(gluten* OR casein* OR GFCF OR GFD) AND diet* AND (autis* OR ASD OR Asperger*)	No limits set	3/29/15	0
BIOSIS (Web of Knowledge)	TOPIC: (gluten* OR casein* OR GFD OR GFCF) AND TOPIC: (diet*) AND TOPIC: (autis* OR Asperger* OR ASD)	No limits set	3/29/15	57
CABI (Web of Knowledge)	TOPIC: (diet*) AND TOPIC: (autis* OR ASD OR Asperger*) AND TOPIC: (casein* OR gluten* OR GFC OR GFCF)	No limits set	3/29/15	27
Dissertations & Theses (WorldCat)	(kw: gluten* OR kw: casein* OR kw: GFD OR kw: GFCF) AND kw: diet* AND (kw: autis* OR kw: ASD OR kw: Asperger*)	No limits set	3/29/15	29
Web of Science	Backward referencing from 11 review articles selected for inclusion	Not applicable (na)	9/8–9/14/15	1

Table 2

## Review Articles

First Author, Year	Review Type and Topic(s)	Age of Participants	Publication Years	Number and Types of Studies Included	Author's Conclusions regarding GF/CF Diet in ASD
Christison, 2006 <sup>8</sup>	Systematic review: published trials of gluten and/or casein elimination in children with ASD	Authors did not report ages included in search. Participant ages in included studies: 3 – 22 years.	Authors did not report years searched. Years of included studies: 1990–2002.	N = 7 6 uncontrolled clinical trials 1 single-blind RCT	Inadequate evidence to clearly support or refute use of GF/CF for ASD symptom alleviation. Outcome assessments should include measurement of nonverbal cognition.
Elder, 2008 <sup>16</sup>	Narrative overview review. Topics: historical background GF/CF diets; GI abnormalities in ASD; evidence informing GF/CF effect in ASD	Author did not report ages included in search or review.	Author did not report years searched or years of included studies.	N = unreported n = 3 studies regarding effectiveness of GF/CF diet in treatment of ASD 1 Systematic review 2 RCTs	Great need for additional research exists on order to address remaining questions from both researchers and families; great needs exist for patients with ASD and their families.
Millward, 2008 <sup>9</sup>	Systematic review: published RCTs examining effectiveness of gluten and/or casein free diets on symptoms of individuals with ASD	Children, adolescents and adults included in search. Participant ages in included studies: 2 – 16 years.	Years searched: 1965 to April 2007. Years of included studies: 2002 – 2006.	N = 2 1 single-blind RCT 1 double-blind RCT	Authors cannot recommend gluten and/or casein exclusion diets as standard treatment of individuals with ASD. Larger well-controlled trials are needed.
Mulloy, 2010 <sup>10</sup>	Systematic review: all available studies where gluten and/or casein was removed or reduced to treat ASD	Authors did not report ages included in search. Participant ages in included studies: 2 – 17 years.	Authors did not report years searched. Years of included studies: 1978–2007.	N = 14 studies 2 case observational studies 4 group observational studies 2 single-subject experimental studies 6 group experimental studies	Evidence is limited and weak in supporting use of GF/CF diets for treatment of ASD. GF/CF diets should only be used when behavioral changes appear to be associated with diet changes and/or in the presence of confirmed allergy to gluten and/or casein.
Mulloy, 2011 <sup>11</sup>	Addendum to earlier published systematic review	Participant ages in included study: 4 years – 10 years 11 months.	Year of included study: 2010.	N = 1 1 single-blind RCT	Researchers maintain their position as published in 2010; no new conclusions in light of the newly published study reviewed in this addendum to the systematic review conducted by Mulloy et al., 2010.
Butie, 2013 <sup>17</sup>	Narrative review: the literature evaluating use of GF diets in patients with ASD. Topics: gluten sensitivity, celiac disease, diet allergies, gut permeability, and opioid peptide theory and ASD; evidence of GF/CF diet effect in treatment of ASD.	Author did not report ages included in search or review	Years searched: 1990 – 2012. Author did not report years of included studies.	N = unreported n = 4 clinical trials of GF/CF diet in treatment of ASD	Insufficient evidence to support GF diet as treatment for ASD. Gluten sensitivity can present with a variety of symptoms. Identification of a subgroup of characteristic presentation may help predict response to dietary interventions. Additional considerations are needed as to what may constitute response to interventions (e.g. better sleep, improved task performance) in individuals with ASD.
Dosman, 2013 <sup>18</sup>	Narrative exploratory review. Topics: current evidence for potential	Authors did not report ages included in search or review.	Authors did not report years searched or years of included studies.	Authors did not report total number or types of articles reviewed.	Inconclusive evidence regarding GF/CF diet effectiveness due to methodological

First Author, Year	Review Type and Topic(s)	Age of Participants	Publication Years	Number and Types of Studies Included	Author's Conclusions regarding GFCE Diet in ASD
Hurwitz, 2013 <sup>12</sup>	benefits of GFCE diet in children with ASD; risks of GFCE diet in children with ASD	Age of participants included in search: < 18 years. Participant ages in included studies: 2 – 16 years.	Years searched: 1999 – 2012. Years of included studies: 2003 to 2011.	<i>n</i> = 7 testing effect of GFCE diet in treatment of ASD 2 systematic reviews 3 single-blind RCTs 2 double-blind RCTs	limitations. Studies suggest existence of a sub-group of responders to GFCE diet.
Whiteley, 2013 <sup>13</sup>	Systematic review: RCTs of GFCE diet in treating ASD	Age of participants included in search: < 18 years. Participant ages in included studies: 2 – 16 years.	Years searched: 1999 – 2012. Years of included studies: 2003 to 2011.	<i>N</i> = 5 1 open RCT 2 single-blind RCTs 2 double-blind RCTs	Effect of GFCE diet on behavior of children with ASD is inconclusive; GFCE diet does not significantly change functioning or behavior.
Zhang, 2013 <sup>19</sup>	Narrative review. Topics: summary of main experimental research of GFCE in ASD; main effects of GFCE diet in ASD; highlight of safety issues with dietary interventions; discussion of current explanations regarding potential dietary effect	Authors did not report ages included in search or review.	Authors did not report years searched or years of included studies.	Author did not report total number or types of articles reviewed. <i>n</i> = 12 regarding effectiveness of GFCE diet in treatment of ASD 1 survey 3 open clinical trials 3 single-blind RCTs 2 double-blind RCTs 4 systematic reviews	Experimental studies suggest improved symptoms and improved development for some individuals with ASD. Dietary studies do not yet adequately measure GFCE diet effects having clinical significance (as opposed to statistical significance) such as effects that, if exist, positively increase quality of life and overall daily functioning.
Marf-Bauset, 2014 <sup>14</sup>	Systematic research synthesis: adherence to EBP standards and effectiveness of GFCE diet for treatment of ASD	Authors did not report ages included in search or review.	Authors did not report years searched. Years of included studies: 1977 – 2010.	<i>N</i> = 23 7 group comparison studies 2 single subject designs 7 AB designs 7 studies did not identify research design	Evidence insufficient to draw firm conclusions as to efficacy of GFCE diets for individuals with ASD.
Marf-Bauset, 2014 <sup>14</sup>	Systematic review: Gluten-free, casein-free type restrictive diets' treatment effectiveness and safety in ASD	All ages included in the search. Participant ages in included studies: 2 years - adults.	Years searched: 1970 to September 30, 2013. Years of included studies: 1971 – 2012.	<i>N</i> = 32 total <i>n</i> = 24 regarding effectiveness of GFCE diet in treatment of ASD 3 observational case reports/case series 2 experimental case reports 1 experimental cohort study 1 open-label study 2 open-label experimental studies 2 open-label cohort studies 1 open-label experimental cohort study 1 open-label double-blind controlled cohort study 1 open-label randomized experimental study 1 double-blind randomized experimental cohort study 1 retrospective double-blind randomized trial 2 single-blind RCTs 3 double-blind RCTs 3 systematic reviews	Evidence is limited and weak in supporting use of GFCE diets for treatment of ASD. Authors advise against introduction of gluten-free and/or casein-free diets unless gluten and/or casein intolerance or allergy has been diagnosed. Future research can target identification of a diet-related phenotype and/or discovery of a marker for responsiveness to GFCE dietary intervention.



Table 3

## Group Experimental Studies

First Author, Year	Design	Participant Diagnoses	No. Enrolled; No. Included in Analysis; Ages	Intervention; Duration	Comparator	Diet Provision/Monitoring	Behavioral/Developmental Outcome Measures	Results
Elder, 2006 <sup>4</sup>	Double-blind RCT, repeated measures cross-over	ASD	<i>N</i> = 15 enrolled & analyzed 2 – 16 years	GFCF diet; 6 weeks	Regular diet 6 weeks	Study provided food for GFCF and non-GFCF diet.	Ecological Communication Orientation Scale (ECOS); Childhood Autism Rating Scale (CARS); Behavioral response frequencies	No group differences on behavioral/developmental measures. Positive anecdotal reports for subgroup.
Mageshwari, 2006 <sup>23</sup>	Observational description of entire study sample with dietary intervention study of subgroup.	ASD	<i>N</i> = 25 enrolled <i>n</i> = 10 descriptive analysis <i>n</i> = 15 dietary intervention analysis 3 – 18 years	CF diet (group 1) GF diet (group 2) GFCF diet (group 3); 3 months	No control group	Parents oversaw child's diet per assigned group. Parents received diet counseling and written dietary guide books per assigned group.	Food intake & behavior ratings recorded daily by parents and collected weekly by investigator. Parents rated eye contact, socialization, attention, comprehension, speech, digestion, sleep, hyperactivity, anxiety/depression.	Statistical significance in pre- and post-intervention behavioral ratings not reported. 80% of intervention subgroup had behavioral improvements with majority improving in hyperactivity and digestion.
Seung, 2007 <sup>24</sup>	Retrospective/secondary analysis of 1-group pre-post data from double-blind RCT <sup>4</sup>	ASD	<i>N</i> = 13 analyzed 2 – 16 years	GFCF diet; 6 weeks	No control group	Study provided food for GFCF diet.	Direct observation & frequency counts of: verbal responses to questions; verbal imitations; different words produced; total utterances	No group differences in verbal communication variables measured pre and post 6 week intervention.
Nazmi, 2008 <sup>22</sup>	Observational description of entire study sample with dietary intervention study of subgroup.	ASD	<i>N</i> = 50 enrolled with descriptive analysis <i>n</i> = 30 dietary intervention analysis 3 – > 11 years	CF diet (group 1) GF diet (group 2) GFCF diet (group 3); 2 months	No control group	Parents oversaw child's diet per assigned group. Parents received diet counseling and written dietary guide books per assigned group.	Food intake & behavior ratings recorded daily by parents and collected weekly by investigator. Parents rated attention span, repetitive body movements, need for sameness, tantruming, perseveration, aggression, passiveness, eye contact, socialization, attention, comprehension, speech, digestion, sleep, hyperactivity, anxiety/compulsion	Significant differences in pre- and post-intervention behavioral ratings.
Hyman, 2010 <sup>15</sup>	Double-blind RCT	ASD	<i>N</i> = 21 enrolled <i>n</i> = 14 included in analysis 30 – 54 months	GFCF diet with weekly double-blind snack challenges; 12 weeks	Placebo: snacks that did not contain wheat flour or nonfat milk	Researchers did not report who provided the GFCF diet food. Study provided snack challenges.	Ritvo Freeman Real Life Rating Scale (RFRLRS); Bristol Stool Scale; Sleep Diaries; Actigraphy; Conners Abbreviated Rating Scale; Target Symptoms Scale	No group differences in frequency or quality of stools, sleep, activity, attention/activity ratings. Group RFRLRS data were higher 2 hours post placebo, but not different 24 hours post challenge.
Whiteley, 2010 <sup>20</sup>	Two-stage, Single-blind RCT using an adaptive design with interim analysis	PDD (ICD-10 code F84)	<i>N</i> = 72 started the trial <i>n</i> = 55 analyzed at 12 months <i>n</i> = 35 analyzed at 24 months 4 years – 10 years 11 months	GFCF diet; Intervention group: 24 months GFCF diet Control group: 12 months GFCF diet	Control group continued their regular diet.	Parents oversaw the child's diet. Study nutritionists monitored participants receiving GFCF diet for dietary compliance and nutritional intake.	Autism Diagnostic Observation Schedule (ADOS); Gilliam Autism Rating Scale (GARS); Vineland Adaptive Behaviour Scale (VABS); Attention-Deficit Hyperactivity Disorder - IV rating scale (ADHD-IV);	Statistically significant improvements above pre-determined threshold for subjects in the GFCF diet group warranted reassignment of control participants to the intervention group at 12 months.
Johnson, 2011 <sup>21</sup>	Parallel 3-group, single-blind RCT	ASD	Authors did not report number of participants enrolled. <i>n</i> = 22 completed study 3 – 5 years	GFCF diet; 3 months	2 comparison groups: Healthy low-sugar diet group & Omega 3 supplementation group	Parents provided food per group assignment. Parents received prepared instructional materials regarding assigned diet, and verbal and written	Mullen Scales of Early Learning AGS Edition; Child Behavior Checklist 1 1/3–5 (CBCL/1 1/2–5); Direct Behavior Observation Measure	No significant gains in development for dietary intervention group. No clinically significant differences in behavioral outcomes for dietary

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First Author, Year	Design	Participant Diagnoses	No. Enrolled; No. Included in Analysis; Ages	Intervention; Duration	Comparator	Diet Provision/Monitoring	Behavioral/Developmental Outcome Measures	Results
						instruction regarding potential problems.		intervention group. No group differences in behavioral outcome scores.

Note: No. = Number

**Table 4**

Case Reports

First Author, Year	Age & Diagnosis	Previous/ Additional Therapies	Behavioral/ Developmental Symptoms Preceding Intervention	Gastrointestinal/ Physiologic Symptoms Preceding Intervention	Intervention	Behavioral Outcome	Gastrointestinal Outcome
Irvin, 2006 <sup>25</sup>	12 year-old male ASD and intellectual disability	GCCF diet for one year prior to initial trial.	Extreme self-injury, physical aggression, property destruction, and self-restraint	None reported	Single case ABAB quasi-experimental design A1: 1 year GFCE diet B1: 12 days regular diet A2: 10 days GFCE diet B2: 30 months regular diet	No change in problem behaviors. Behaviors measured during attention, demand, and play conditions.	None reported.
Hsu, 2009 <sup>28</sup>	42 month-old male ASD and CHARGE syndrome	Speech, occupational, physical, and sensory integration therapy	Delayed motor, language, social concept, social comprehension, and general development. 3rd percentile height and weight.	Postprandial vomiting and long-term constipation	GFCE diet	Improved eye contact after 2.5 months. Improved physiological biometry and interpersonal relations after 5 months. Improved development within 11 months.	Improved appetite, and reduced postprandial vomiting and constipation within 2.5 months.
Gannage, 2010 <sup>26</sup>	3 year-old male Regressive autism at 18 months old	Previous therapies - Supplements: probiotics, essential fatty acids, B vitamins. Additional therapies - Behavioral therapies	Language loss, self-stimulatory behavior, hyperactivity.	Abnormal stool color and consistency	CAM interventions: Dietary: GFCE diet Medication: anti-fungal & anti-viral medications. Heavy metal toxicity treatment: chelation therapy. dimercaptosuccinic acid, alpha-lipoic acid, zinc, selenium, vitamin C, methylsulfonylmethane, taurine, & vitamin E Nutrition supplementation: glutathione, carosine.	At 3 years following CAM interventions, which included GFCE diet, child had greatly improved language, toilet training, increased play interaction, lowered hyperactivity. At age 11, functions as a neurotypical child without symptoms of ASD.	Improved stool consistency, 3 months after implementation of GFCE diet.
Genuis, 2010 <sup>27</sup>	5 year-old male Regressive autism diagnosed at 3 years old; language disorder, positive screen for celiac disease at 5 years old	Speech language therapy, intensive educational programming	Developmental delay, language and communication impairment, difficulty sleeping, depressed mood,	Abdominal bloating/pain, belching, nausea, vomiting, diarrhea, chronic upper respiratory infections, chronic congestion.	Gluten restricted diet with nutritional supplementation (omega 3 & omega 6 fatty acids, folic acid)	After 3 months of initiating gluten restricted diet, the child's functioning improved enough to enable enrollment in a typical classroom without an aide; the individualized	Gastrointestinal symptoms were relieved within 1 month of initiating gluten restricted diet.

First Author, Year	Age & Diagnosis	Previous/ Additional Therapies	Behavioral/ Developmental Symptoms Preceding Intervention	Gastrointestinal/ Physiologic Symptoms Preceding Intervention	Intervention	Behavioral Outcome	Gastrointestinal Outcome
Herbert, 2013 <sup>5</sup>	5 year-old female Regressive autism at 4 years old; seizure onset at puberty (12 years old)	Speech and physical therapy	Escalating tantrums, no eye contact, lack of social awareness, hypersensitivity to sensory stimulation, hypotonia, stereotypies	Foul smelling orange diarrhea, abdominal distension, daily morning moaning; Asthma, recurrent otitis media, recurrent sinusitis	Parents implemented GFCF diet when the child was 5 years old. Recurrent illness treated with intravenous immunoglobulins; asthma with nutritional supplements and pharmacological supports. Treatment for inflammatory bowel disease. Seizures at 12 years; non-responsive to pharmacological therapy, ketogenic GFCF diet implemented.	Language improvements immediately after implementation of GFCF diet. Gradual improvement in auditory sensitivity; gradual reduced tantrum severity. Autism symptoms reduced over time to non-autistic range on Childhood Autism Rating Scale. Seizures were significantly improved several weeks after GFCF-ketogenic diet was implemented.	Following implementation of GFCF diet, gastrointestinal symptoms improved but did not resolve.

Group Observational Studies

Table 5

First Author, Year	Diagnoses	Number of Subjects; Age	Design/Description of the Study	Measures	Results
Patel, 2007 <sup>29</sup>	ASD plus ADHD, Asperger syndrome plus ADHD	N = 10 Authors did not state how many received GFCF diet Age: 4 – 10 years	Design: Open label observational study Description: 3 – 6 month comprehensive multidimensional treatment program including: environmental control, organic diet or organic GFCF diet if child had gluten or casein sensitivities, gastrointestinal support, antigen injection therapy, nutritional supplements, chelation therapy, injections with glutathione and methylcobalamin, and usual therapies (e.g., speech therapy, occupational therapy, physical therapy, behavioral/educational therapies).	Parents, teacher, and physician pre- and post-intervention reports regarding child's: Motor capabilities Behavioral capabilities Educational capabilities ASD & ADHD symptoms Urinary metal concentration	Improved behavior, social, motor, and GI symptoms; statistically significant reduction of urinary lead levels; 4 participants able to attend mainstream classes
Harris, 2012 <sup>32</sup>	ASD	N = 13 n = 7 Age: 5 – 12 year	Design: Cross-sectional survey Description: Correlation analysis of adherence to GFCF diet to (a) severity of gastrointestinal symptoms, and (b) behavior patterns. Group difference testing (GFCF diet vs. non-GFCF diet) in (a) number of gluten/casein containing foods consumed per week, (b) gastrointestinal symptoms, and (c) autism symptoms.	Food Frequency Questionnaire (FFQ) - Adapted Gastrointestinal Symptoms Rating Scale (GSRS) Childhood Autism Rating Scale (CARS)	No statistically significant relationships found between consumption of gluten- and casein-containing foods and (a) gastrointestinal symptoms or (b) behavior patterns. Positive anecdotal reports for improved GI symptoms and behavior patterns.
Pennessi, 2012 <sup>30</sup>	ASD (49.4%), HFA (16.8%) AS (15.8%) PDD (4.9%) PDD-NOS (28.4%) RS (0.3%) CDD (0.3%)	N = 387 n = 293 on GFCF diet Age not reported	Design: Cross-sectional survey Description: Examination of group differences in (a) degree of GFCF diet implementation, (b) length of diet implementation, (c) physical symptoms (e.g. gastrointestinal symptoms), and (d) reported diet effectiveness.	90-question survey including inquiry of demographics, diagnoses, parental familiarity with GFCF diet, parental implementation of GFCF diet, parental report of GFCF diet effectiveness, observable changes in autism-related symptoms and autism-related behaviors.	Statistically significant reduction of ASD behaviors, and physiological and social symptoms for: <b>1</b> subgroup with GI symptoms - especially constipation & diarrhea <b>2</b> subgroup with allergy symptoms <b>3</b> subgroup of GFCF diet implementation greater than 6 months
Pedersen, 2014 <sup>31</sup>	ASD	N = 72 n = 27 potential responders	Design: Post-hoc analysis of data from ScanBrit trial (Whiteley et al., 2010)	ADHD-IV total baseline score VABS total baseline standard score	Statistically significant regression analysis indicate children, ages 7 – 9 years, who have clinically significant ADHD-IV scores at baseline have strongest probability of benefiting from GFCF diet.

First Author, Year	Diagnoses	Number of Subjects; Age	Design/Description of the Study	Measures	Results
		Age: 4 – 12 years	Description: Exploration of potential explanatory variables for predicting GF/CF diet responder status.	ADOS total baseline raw score Age at baseline Laboratory status Continued use of GF/CF diet post study completion Parent evaluation of effect of dietary intervention	

Note: ASD = Autism Spectrum Disorder; HFA = High Functioning Autism; AS = Asperger's Syndrome; PDD = Pervasive Developmental Delay; PDD-NOS = Pervasive Developmental Delay – Not Otherwise Specified; RS = Rett's Syndrome; CDD = Childhood Disintegrative Disorder