Can a gluten-free and casein-free diet reduce symptoms in children with Autism Spectrum Disorders?

A systematic review

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Sammanfattning

Titel:	Kan en glutenfri och kaseinfri diet minska symptom hos barn med Autismspektrumtillstånd?
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Bakgrund: Autismspektrumtillstånd är en samling komplexa tillstånd som orsakar problem med bland annat kommunikation, uppmärksamhet, social interaktion och kognitiv funktion. Det finns idag inget känt botemedel, men det finns olika metoder för att minska symptomen. Barn med autismspektrumtillstånd har påvisat högre nivåer än andra barn av protein från gluten och kasein i urinen och det finns teorier om att dessa proteiner kan bidra och förvärrar en del av symptombilden.

Syfte: Syftet med denna översiktsartikel är att fastställa om en gluten- och kaseinfri diet kan reducera symptom och/eller förbättra sjukdomstillståndet hos barn med autismspektrumtillstånd.

Sökväg: Sökningar gjordes på databaserna PubMed och Scopus mellan den 15 och 19 februari 2012 för att hitta artiklar om ämnet. Sökord som användes var ”autism gluten casein”, ”autism diet”, och ”autism gluten free NOT review”.

Urvalskriterier: Inklusionskriterierna var randomiserad kontrollerad prövning eller klinisk prövning, utförd på barn 0-18 år med autismspektrumtillstånd, ha en gluten- och kaseinfri dietgrupp och en kontrollgrupp, samt vara skriven på engelska.

Datainsamling och analys: Åtta studier valdes ut genom ovan nämnda sökväg och granskades enligt SBUs granskningsmall för randomiserad kontrollerad prövning. Av dessa valdes fyra medium- eller högkvalitativa studier ut som uppfyllde alla inklusionskriterier. Resultaten och evidensen sammanställdes sedan enligt GRADE-systemet.

Resultat: Studierna visar, med låg vetenskaplig evidens, att en gluten- och kaseinfri diet inte ger någon positiv effekt på kommunikation, social interaktion eller kognitiv funktion hos barn med autismspektrumtillstånd. Det finns en måttlig vetenskaplig evidens för att dieten ger en positiv effekt på uppmärksamhet.

Slutsats: En gluten- och kaseinfri diet kan möjligtvis förbättra vissa symptom hos barn med autismspektrumtillstånd, men det finns idag en för låg vetenskaplig evidens för att kunna rekommendera dieten till alla barn med diagnosen.

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Abstract

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Background: Autism Spectrum Disorders (ASD) are complex developmental disabilities that cause problems with communication, attention, social interaction and cognitive function. There is no known cure for ASD but many different approaches are used to treat the symptoms of the disorders. Children with ASD have higher levels of peptides from gluten and casein in their urine, compared to other children, and there are theories that these proteins may contribute to and worsen the symptoms of ASD.

Objective: The purpose of this review was to determine whether a diet free from gluten and casein could reduce symptoms and/or improve the conditions of children with autism spectrum disorders.

Search strategy: A search for studies on the subject have been done in the data bases PubMed and Scopus between the 15th and 19th of February, 2012. The key words used were: ”autism gluten casein”, ”autism diet”, and ”autism gluten free NOT review”.

Selection criteria: Inclusion criteria was that the articles had to be randomized controlled trials or clinical trials, with children 0-18 years with autism spectrum disorders as participants, have one control and one diet (gluten and casein free) group, and be written in English.

Data collection and analysis: Eight articles were found in the search mentioned above and analysed with the template for randomized controlled trials from SBU. Out of these, four medium or high quality articles that met the inclusion criteria were chosen. The results and evidence were compiled with the GRADE evidence form.

Main results: There was low evidence for no effect of treatment with a GFCF diet on children with ASD on communication, social interaction and cognitive function, but medium evidence for a positive effect of the diet on attention.

Conclusions: A gluten free and casein free diet can possibly improve some of the symptoms in children with ASD, but the evidence is too low to make a general recommendation.

Abbreviations

ADHD – Attention-Deficit Hyperactivity Disorder
ADOS – Autistic Diagnostic Autism Schedule
ASD – Autism Spectrum Disorders
CARS – Childhood Autism Rating Scale
CBCL – Child Behaviour Checklist
GARS – Gilliam Autism Rating Scale
GFCF diet – Gluten-free and casein-free diet
ECO-scales – Ecological Communication Orientation Language Sampling Summary
ITPA – Illinois Test of Psycholinguistic Abilities
NS – Non significant
RCT – Randomized Clinical Trial
SBU – The Swedish Council on Health Technology Assessment
SD – Standard deviation
VABS – Vineland Adaptive Behaviour Scale

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Introduction

Background

What is Autism Spectrum Disorders?

Autism Spectrum Disorders (hereby referred to as ASD) are complex developmental disabilities that cause problems with communication and social interaction. Symptoms can vary among people with Autism, therefore, healthcare professionals think of Autism as a spectrum disorder (1). Autism Spectrum Disorders include; Autistic disorder (also called classic autism), Asperger's Syndrome/ Asperger's Disorder, Atypical Autism (also called Pervasive Developmental Disorder), Rett's Disorder/ Rett's Syndrome and Childhood Disintegrative Disorder (2).

The aetiology of ASD is still unknown, but there are some different theories about the underlying causes. Some evidence supports the idea of genetic factors to be the primary cause, but whether there is one specific factor, or multiple combined, is not known. Environmental factors, such as viruses and vaccines, and neurological or metabolic factors have also been studied. ASD are equally common in all ethnic, racial and social groups (3). A study by Barnevik-Olsson *et al* (2008) have shown that children with a Somalian background living in Sweden has a 3 to 4 times higher risk of developing autism than children with a Swedish background, but this is not seen in Somalian children living in Somalia (4). This implies that the aetiology of ASD is both complex and probably multifactorial.

The prevalence of Autism Spectrum Disorders in Sweden is estimated to be at least 6 in 1000, the estimation is not certain since there are no registry over individuals with ASD (5). Boys have a three to four times higher risk of developing the disorder than girls (3). Symptoms usually appear before the age of three and consist through adulthood. As mentioned above, symptoms vary widely in individuals with Autism Spectrum Disorders, some children are mildly impaired, while others are severely disabled by their disorder. Symptoms of ASD are typically social impairment, communication difficulties and repetitive stereotypic behaviours (6).

How is Autism Spectrum Disorders treated?

There is no known cure for ASD, but many different approaches are used to treat the symptoms of the disorders, for example, visual aids are used to improve communication, social stories interventions are used to teach appropriate social behaviour, and medication is used to ameliorate specific symptoms like aggression (7). In the last few years, the gluten-free and casein-free diet (hereby referred to as GFCF diet) has been a popular approach in the treatment of ASD. Some parents have tried this diet, with what they consider good results regarding improvements in symptoms. Among other things, they report improvement in speech and behaviour (8). There is however no scientific evidence to support this.

Why a GFCF diet might work

The theory is that children with ASD have a hypersensitivity to foods that contain the proteins gluten and casein. Hypothetically, autistic children cannot digest these proteins properly, which results in a higher-than-normal level of urinary small peptides, and it is suggested that these peptides bind to opioid receptors and become biologically active. This then results in an excess of opioids, which are thought to lead to an increase of the behavioural difficulties seen in children with ASD. Dietary interventions with the exclusion of either gluten, casein or both is thought to have a positive effect on behavioural symptoms because of the elevated levels of peptides seen in the urinary analyses. Since the chemical

structure of gluten and casein are very similar to each other, it is very likely that having a sensitivity to one of them means having a sensitivity to both, even though one could be worse than the other (9) (10).

The impact of the diet on everyday life
The GFCF diet is a fairly restricted diet that can be hard to implement in a child's life. The child needs to avoid all dairy products, and all products that contain wheat, barley and rye. The concern is also that these children, that already often have a very restricted diet (because of aversions to certain textures and types of food), might suffer from nutritional deficiencies when excluding additional products (11). Some medical doctors are currently, based on their experience, recommending parents with autistic children to try the GFCF diet, while others are still questioning the theory behind the diet and request more research (12).

Why this review is important
A Cochrane review on this subject made by Millward *et al* was published in 2009 (13) where only two studies made by Elder *et al* (2006) and Knivsberg *et al* (2002) met the inclusion criteria (14) (15), and the conclusion made was that there was not enough evidence to support a GFCF diet as a standardised treatment. After this review was published in 2009, more research has been done, and since the diet is still used both in clinics and the homes of autistic children (8) (12), a new review to determine if there is evidence for the diet as a treatment for symptoms in children with ASD is needed.

Objectives
The purpose of this review was to determine whether a diet free from gluten and casein can reduce symptoms and/or improve the conditions of children with autism spectrum disorders.

Question at issue
Can a gluten-free and casein-free diet reduce symptoms related to social interaction, cognitive function, communication or attention in children with autism spectrum disorders?

Method
This review will summarise the literature published until February 2012 and what evidence there is to a gluten- and casein-free diet as a treatment of symptoms in children with autism spectrum disorder.
The effectiveness of a treatment with a gluten- and casein-free diet in this review was measured as the improvements of symptoms related to behaviour, attention, social interaction and cognitive function. The amount of urinary peptides has in some studies been used as a measure of how effective a treatment is, but will not be considered in this review since it is the symptoms of the disorder that are of interest for those concerned and not the urinary peptides.

Search strategy
A search for studies on the subject have been done in the data bases PubMed and Scopus between the 15th and 19th of February, 2012. The results and key words from these searches are shown in table 1. Out of these, eight different articles where chosen for closer analysis.

Table 1 – Results and key words from data collection

Data base	Date	Key words	Limitations	Hits	Chosen articles	Final articles
PubMed	15-02-2012	Autism gluten casein	0-18, human, clinical trial, RCT, English	4	3	3
Scopus	15-02-2012	Autism gluten casein	Article, English	42	8 (3 duplicates)	4 (3 duplicates)
Pubmed	15-02-2012	Autism gluten free NOT review	0-18	21	3 (3 duplicates)	3 (3 duplicates)
Pubmed	19-02-2012	Autism, diet	0-18, human	130	5 (5 duplicates)	4 (4 duplicates)
Summary					**8**	**4**

Selection criteria

Inclusion criteria for studies to be chosen was that they had to be randomized controlled trials or clinical trials, with children (0-18 years) with Autism Spectrum Disorders as participants, have one control and one diet (gluten- and casein-free) group, and be written in English. Exclusion criteria were reviews, one case studies, cross-sectional studies, studies made only on gluten free or casein free diets, studies without control group, and studies that only look at urinary peptides.

Analysis

Eight articles were analysed separately by the two authors with the review template from SBU (The Swedish Council on Health Technology Assessment) that evaluate study population, study design, blinding, outcome measures, dropouts, results, and power (see appendix 1).

The grading of each article were then compared and compiled. Out of the eight original articles, two articles were made from the same study, and therefor one was excluded, one article lacked a non-diet control group, and two were rated as low-quality studies according the review templates from SBU. Three of the four remaining articles where graded as medium-quality studies and one as a high-quality study. They were all RCTs and lasted from twelve weeks up to two years. The strength of evidence was determined according to the GRADE evidence summary form (see appendix 2) and shown in table 3.

Results

Descriptions of all studies with their results are shown in table 2.

Description of studies

Knivsberg *et al* (2002) carried out a single blind controlled study with 10 children in a gluten- and casein-free diet group and 10 children in a control group continuing with their existing diet. All of the participating children had ASD and abnormal urinary peptide patterns.

Measures of symptoms were obtain at baseline and after one year of intervention with the following methods:

DIPAB (a standardized Danish scheme) – A scheme used to assess autistic behaviour, motor skills, communication and social contact.
Leiter International Performance Scale – A scale used to measure non-verbal communication and intelligence.
Illinois Test of Psycholinguistic Abilities (ITPA) – A test measuring linguistic abilities.
Rynells Språktest (a standardized Norwegian language test) – Also measured linguistic abilities.
Movement Assessment Battery For Children – A method used to assess motor abilities.
There is no mention of compliance in the article, but all participants completed the study (15).

The study made by **Elder *et al* (2006)** was made out of a total of 15 children, twelve males and three females, between 2 and 16 years with a mean age of 88 months. The children where diagnosed according to the DSM-IV criteria (made by the American Psychiatric Association in 2000). The children where divided into two groups where the first group (A) started with six weeks on a regular diet and then continued with six weeks (week seven through twelve) on a gluten- and casein-free diet. The second group (B) started with six weeks on a gluten- and casein-free diet, and continued with six weeks on a regular diet. The study was double blinded and the parents of the children were provided with all meals and snacks from the Metabolic Kitchen run by the study group. Everyone in the study, except the dietician and the data manager where blinded.
Measures was obtained at baseline, after six weeks and after twelve weeks in the following categories:
Childhood Autism Rating Scale (CARS) – A scale of 15 items that can be scored from one to seven, and a total score rating from 15 to 60. The scale covers: relationships with others, imitation, emotional expression, body use, peculiarities in object use, resistance to change, visual-, auditory-, and tactile responsiveness, anxiety, verbal and nonverbal communication, activity level, and intellectual ability. The child was in this study observed during a structured activity and then graded according to the scale by an evaluation team.
Ecological Communication Orientation Language Sampling Summary (ECO-scales) – A scale used to record child behaviour and collect interactive samples.
In-Home Observations – A research assistant videotaped each child in their home environment interacting with his/her primary caretaking parent for 15 minutes during an unstructured session. Blinded trained coders then obtained behavioural counts in the following categories: child initiating, child responding, intelligible words spoken, parent initiating, parent responding, and parent expectant waiting (a defined measure of parental signalling and waiting for a specific child response). Each tape was rated by two independent coders.
The only mention of compliance in the study was of children (not specified how many or how often) sneaking food from siblings or classmates.
Three of the 15 children lacked data on a major variable (CARS or ECOS) at six or twelve weeks, and a missing at random model was employed (14).

The study made by **Whitely *et al* (2010)** had 72 participants when they started, 55 after one year and 35 after two years. The children (aged 4 years to 10 years 11 months) were randomly divided into one diet group and one control group continuing with their existing diet. Participants were tested at Baseline, 8 months, 12 months and 24 months with the following measures:
Autistic Diagnostic Autism Schedule (ADOS) – A schedule used to assess autistic behaviours such as communication, social skills, and repetitive behaviour.

Gilliam Autism Rating Scale (GARS) – A questionnaire used to assess communication, social interaction, stereotype behaviours, and developmental disturbances.
Vineland Adaptive Behaviour Scale (VABS) – A scale used to assess non-verbal communication and development.
ADHD-IV scale (Attention-Deficit Hyperactivity Disorder) – A scale used to determine inattention and hyperactivity.
Reports of dietary infractions in the experimental group were low, and the authors comment on that the long intervention period would reduce any extraneous effects associated with individual episodes of non-compliance (16).

The study made by **Johnson *et al* (2011)** was made out of a diet group of eight participants, seven males and one female, with a mean age of 40 months, and one control group of 14 participants, eleven males, and three females, with a mean age of 39.5 months. The children where diagnosed based on the *Autism Diagnostic Observation* Schedule (ADOS). The parents of the diet group were counselled by a nutritionist on how to follow a gluten- and casein-free diet, while the parents of the control group was counselled by a nutritionist on how to follow an overall healthy diet based on the food guide pyramid for young children. Measures was obtained at baseline and at a three months follow up visit in the following categories:
Mullen Scales of Early Learning AGS Edition – A measure of cognitive function for infants and young children 0-68 months. It provides standardized scales across five domains: visual reception (nonverbal problem solving skills), receptive language, expressive language, fine motor skills, and gross motor skills (for younger children).
Child Behaviour Checklist (CBCL) – A widely used behaviour rating tool appropriate for the age range in this sample and may be administered by parents, child caregivers and educators. The child is graded on the checklist and scores are calculated for different subscales: emotional regulation, anxious/depressed, somatic complaints, withdrawn, attention problems, aggressive behaviours, sleep problems, internalizing, externalizing, affectiveness and ADHD.
Direct Behaviour Observation Measure – Sessions where recorded during three activities from the ADOS, and then scored by blinded coders on three target behaviours: positive vocalizations, attending to task/activity, and social initiations.
The average adherence rate was reported for every other week, and was between 10 and 50% for the diet group and between 20 and 75% for the control group.
All participants completed the study (17).

None of the studies reported any side effects.

Outcomes

In the study by **Knivsberg *et al* (2002)** there were some significant improvements in ASD-symptoms in the diet group compared to the control group. The outcome measures that indicate improvement are shown in table 2. The reduction of autistic behaviour was significant in the diet group, but not in the control group, and a significant difference was found between the two groups before and after the study. For motor competence none of the changes within the groups were significant, but the development between the two groups was. For linguistic skills, the improvements for both groups were significant, but not between them.

A group analysis of the results from the study by **Elder *et al* (2006)** indicated no significant differences with CARS ($p=0.85$), ECO-scales ($p=0.29$), or behavioural frequencies ($P=0.32$ –

0.45). There was no significant difference observed in parent behaviour either (p=0.97 – 0.98), which indicates that there was no behavioural influence or confound by the parents. On the other hand parents of seven children reported that there were large improvements in their child's language, decreased hyperactivity and tantrums, and the parents of nine children decided to keep their children on a GFCF diet despite the lack of evidence from the study.

In the study by **Whiteley *et al* (2010)**, there were significant improvements ($p<0.01$) for the diet group compared to the control group after eight months on communication measured by GARS and ADOS, and for inattention on the ADHD-IV scale. After twelve months there were significant improvements in social interaction according to GARS, inattention and hyperactivity according to ADHD-IV. After 24 month there were no significant improvements in the children in the diet group, but the result of the study suggests that dietary intervention might have a positive effect on developmental outcome in Autistic Children.

The results from the study by **Johnson *et al* (2011)** based upon the Mullen Scales of Early Learning showed a gain for the GFCF diet group only on the receptive language subscale, but this result only approached statistical significance (P=0.061). The placebo group on the other hand showed a statistically significant improvement on the visual reception subscale (p=0.05). On the expressive language, and the fine motor subscales, no significant improvements were seen. On the CBCL-scales no particular pattern for improvement were seen for either group, except for the GFCF diet group on aggression (p=0.046) and ADHD (p=0.043) subscales. A two- and three-score decrease on the mean T-score was however not considered to be a clinically significant finding. The placebo group showed a similar improvement for the withdrawn subscale (p=0.04). In the direct observations by blinded raters, no statistically significant difference was noted between the groups.

Table 2 – Results[1] and descriptions of articles.

Article	Design	Population[2]	Intervention	Communication	Attention	Social interaction	Cognitive function	Other	Quality
Knivsberg *et al* (2002)	RCT Single blinded (project leader)	**Diet group** 10 children. 91 months (62-120) **Control group** 10 children. 86 months (59-127) **Drop outs** 0%	**Diet group** GFCF-diet **Control group** Regular diet **Measures** at baseline and after 1 year.	**P<0.05** Non-verbal. Reaction when spoken to. Language peculiarities. Communicative factors. Eye contact. **NS** Verbal. Repetitive and peculiar language. Echolalia.	**P<0.05** Attention. Number of interests.	**P<0.05** Peer relationships. Empathy. Social and emotional factors. Aloofness. **NS** Sharing of emotions. Reaction to physical contact. Interaction with other children.	**P<0.05** Cognitive factors. Judgement of dangerous situations. Responses to learning. **NS** Behaviour in learning situations.	**P<0.05** Abnormalities in extraordinary restlessness and passiveness. Physical contact. Anxiety. Routines and rituals. **NS** Unusual emotional expression. Adult dependency. Rigidity. Peculiar handling of toys. Attachment to particular items. Peculiar gate or movement.	Medium
Elder *et al* (2006)	RCT Cross over Double blinded (children, parents, project leader).	**Diet group** 15 children 89 months (24-192) **Control group** 15 children 89 months (24-192) **Drop outs** 13% (2 children)	**Diet group** GFCF-diet **Control group** Regular diet **Measures** at baseline, after six weeks of GFCF-diet and after six weeks of regular diet (week 12) or vice versa.	**NS** Imitation. Emotional expression. Intelligible words spoken.	**No outcomes measured**	**NS** Relationship with others. Visual, auditory and tactile responsiveness. Child initiating. Child responding.	**NS** Resistance to change. Intellectual ability.	**NS** Body use. Anxiety. Peculiarity in object use. Activity levels.	Medium

[1] Significant results are for difference between the diet and control group, with improvements for the diet group.
[2] Shows number of children, their mean age and range or SD (depending on what is reported in the original article).

Table 2 – Results[1] and descriptions of articles.

Article	Design	Population[2]	Intervention	Communication	Attention	Social interaction	Cognitive function	Other	Quality
Whiteley *et al* (2010)	RCT Single blinded (all study members except nutritionist)	**Diet group** 38 children 94 months (77-118) **Control group** 34 children 96 months (76-120) **Drop outs** **8 months** Diet: 24% (9 children) Control: 12% (4 children) **12 months** Diet: 32% (12 children) Control: 15% (5 children) **24 months** Diet: 53% (20 children) Control: 50% (17 children)	**Diet group** GFCF-diet for 24 months. **Control group** Regular diet for 12 months, followed by GFCF-diet for 12 months. **Measures** at baseline, after 8, 12 and 24 months.	**8 months** **P<0.01** Communication (ADOS). **NS** Communication (GARS, VABS) **12 months** **NS** Communication (ADOS, VABS, GARS) **24 months** **NS** Communication (ADOS, VABS, GARS)	**8 months** **P<0.01** Inattention (ADHD). **NS** Hyper activity (ADHD) **12 months** **P<0.05** Inattention (ADHD). Hyper activity (ADHD). **24 months** **NS** Inattention (ADHD). Hyper activity (ADHD).	**8 months** **NS** Social interaction (ADOS, GARS, VABS) **12 months** **P<0.05** Social interaction (GARS). **NS** Social interaction (ADOS, VABS) **24 months** **NS** Social interaction (ADOS, VABS, GARS).	**No outcomes measured**	**8 months** **NS** Repetitive behaviour (ADOS). Stereotyped (GARS). Daily living (VABS). **12 months** **NS** Repetitive behaviour (ADOS). Stereotyped (GARS). Daily living (VABS). **24 months** **NS** Repetitive behaviour (ADOS). Stereotyped (GARS). Daily living (VABS).	High
Johnson *et al* (2011)	RCT Single blinded (study coders)	**Diet group** 8 children 40 months (SD 9.26) **Control group** 14 children 39.5 months (SD 8.72) **Drop outs** 0%	**Diet group** GFCF-diet **Control group** Healthy diet **Measures** at baseline and after 3 months.	**NS** Communications. Receptive language. Expressive language. Positive vocalizations.	**P<0.05** ADHD. **NS** Attention problems. Attending to task.	**P<0.05** Withdrawn[3] **NS** Social behaviours. Social communications. Emotional regulation. Social initiations.	**P<0.05** Visual reception[4]	**P<0.05** Aggression. **NS** Restricted repetitive behaviour. Fine motor skills. Gross motor skills. Anxious/ depressed. Aggressive. Sleep problems. Somatic problems.	Medium

[1] Significant results are for improvements in the diet group within each area of symptoms.
[2] Shows number of children, their mean age and range or SD (depending on what is reported in the original article).
[3] This shows a significant improvement for the control group.
[4] This shows a significant improvement for the control group.

Evidence

Using the GRADE evidence scale, the conclusions are that there is low evidence for no effect of treatment with a GFCF diet on children with ASD on communication, social interaction and cognitive function, but medium evidence for an effect of the diet on attention. See table 3 for grading of the studies and outcome measures.

Table 3 – Strength of evidence for a GFCF diet according to GRADE

Outcome measures	Communication	Attention	Social interaction	Cognitive function
Included studies	4 RCT	3 RCT	4 RCT	3 RCT
Study design	Certain limitations	Certain limitations	Certain limitations	Certain limitations
Conformity of results	Strong limitations	Certain limitations	Strong limitations	Strong limitation
Study population	Certain limitations	Certain limitations	Certain limitations	Certain limitations
Unclear support	No limitations	No limitations	No limitations	No limitations
Strength of evidence	Low (++) No effect	Medium (+++) Effect	Low (++) No effect	Low (++) No effect

Discussion

To summarize the results from this review, one article showed no significant improvements for the diet group compared to the control group, while the other three showed some significant improvements on different symptoms in children with ASD.

Strengths and weaknesses of the included articles

The strengths of the article by **Knivsberg *et al* (2002)** are that the intervention period was long (twelve months), the project leaders were blinded, there were no drop outs, and the article included many different outcome measures which makes sure all ASD symptoms were looked at. The weaknesses of the article are that the parents and children were not blinded, the size of the intervention group is small (only 10 children in each group), there is no mention of compliance, and no measures of outcomes between baseline and twelve months.

The strengths of the article by **Elder *et al* (2006)** are that it is a cross over study, and it is double blinded were the project leaders administered the food. The weaknesses of the article are that the size of the intervention group is small (only 15 children), non-compliance is mentioned but not specified, and the intervention period was short (six weeks of diet), which might be too short to produce significant results.

The strengths of the article by **Whitely *et al* (2010)** are that the size of the intervention group is relatively large (72 children), the intervention period was long (24 months), and the outcomes were measures at 8, 12 and 24 months. The weaknesses of the article are that the parents and children were not blinded, they do not measure compliance, and the drop out rate was high after 12 months and even higher after 24 months.

The strengths of the article by **Johnson *et al* (2011)** are that the intervention period was rather long (three months), there were no dropouts, and both the diet group and control group were counselled by a dietician. The weaknesses of the article are that the size of the intervention group was small (22 children), and the compliance was very low.

In conclusion, these four studies represent the best research available in the area investigated, but there are however some serious limitations to the articles. The sample size in all articles is very small, with 72 participants at the most, which makes it difficult to see results because of large individual variations, and also to draw general conclusions from the results shown. The parents and children were only blinded in one study, in the other three studies the result may have been effected by the knowledge of being on a diet. Only one article reported data on non-compliance, two only mention that there were events of non-compliance, and one did not mention compliance at all. This makes it difficult to determine weather the children actually followed a strict diet during the whole intervention, and whether this may have effected the results. In the study that measured the outcomes at four different times (Whiteley *et al* 2010), less significant improvements were seen after 24 months than after 12 months, and also the dropout rate in this long study was a lot higher than in the shorter ones. This implies that the diet might be hard to follow over a longer period of time.

Strengths and weaknesses of this review article

The strength of this review is that the four best articles published were selected and analysed, which gives the best available evidence on the subject. While analysing the articles, standardized templates and methods have been used to ensure an objective result. The main weakness of this review is that all the articles evaluate different outcome measures, and use different scales to assess these outcomes, which makes it very to difficult to draw compiled conclusions from the four articles. In order to be able to overview the results, the outcome measures were divided into different sub-groups. The way the outcome measures were divided might have effected the results, and a different result might have been seen with different or fewer/additional sub-groups.

The GFCF diet is a very restrictive diet, which can be hard to follow, especially when the diet does not give an immediate reaction. As a parent it might be easier to make sure your child avoids all products containing dairy and gluten if the child has an allergic reaction when they ingest it, compared to a gradual and uncertain reduction of symptoms. Therefor we think that there can have been major issues of non-compliance in these studies, which has effected the results. Also, the implementation of the diet in a child's life requires educated and motivated parents with the financial capability to replace the excluded products with appropriate substitutes. Since the GFCF diet is so hard to follow, should clinical professionals recommend it even though it might work when strictly followed?

Conclusions

The conclusions are that there is low evidence for no effect of treatment with a GFCF diet on children with ASD on communication, social interaction and cognitive function, but medium evidence for an effect of the diet on attention, meaning that a gluten-free and casein-free diet can possibly improve some of the symptoms in children with ASD. But since a gluten- and casein-free diet has a large impact on a child's life, the evidence is too low to support a general recommendation for all children with ASD.

More research is needed with high quality studies where the intervention is over a longer period of time, with a larger intervention population, and preferably double blinded where compliance is assured.

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Appendix 1

Review template from SBU

Granskningsmall för randomiserad kontrollerad prövning

Författare, år alternativt SBU:s identifikationsnummer:

Total bedömning av studiekvalitet:		
Hög ☐	Medelhög ☐	Låg ☐

Anvisningar:

- Alternativet ”oklart” används när uppgiften inte går att få fram från texten.
- Alternativet ”ej tillämpligt” väljs när frågan inte är relevant.
- Det finns förtydligande kommentarer till vissa delfrågor. Dessa anges med en fotnot.

Studiekvalitet	Ja	Nej	Oklart	Ej tillämpligt
1. Studiepopulation				
a) Framgår det hur många personer som exkluderades före randomiseringen?	☐	☐	☐	☐
b) Är redovisningen av personer som inte randomiserades, trots att de var valbara, adekvat?	☐	☐	☐	☐
2. Tilldelning av åtgärd/intervention/behandling				
a) Användes en randomiseringsmetod som på ett acceptabelt sätt minimerar risken för manipulation?	☐	☐	☐	☐
b) Utfördes randomiseringen så att fördelningen blev oförutsägbar och slumpmässig? [1]	☐	☐	☐	☐
c) Påbörjade samtliga deltagare, som randomiserades, behandlingen? [2]	☐	☐	☐	☐
3. Gruppernas jämförbarhet				
a) Var grupperna vid baseline rimligt lika avseende egenskaper som kan påverka resultatet (t ex ålder, kön, sjukdoms svårighetsgrad)?	☐	☐	☐	☐
4. Blindning (maskering) [3]				
Blindades följande på tillfredsställande sätt:				
a) Patienter	☐	☐	☐	☐
b) Prövare/behandlare	☐	☐	☐	☐
c) Utvärderare av resultat	☐	☐	☐	☐
5. Bortfall (antalet randomiserade deltagare som inte har följts upp enligt studieprotokollet) [4]				
a) Går det att följa deltagarnas väg genom studien t ex i ett flödesschema?	☐	☐	☐	☐

Studiekvalitet	Ja	Nej	Oklart	Ej tillämpligt
b) Är storleken på bortfallet efter randomisering acceptabelt?	☐	☐	☐	☐
c) Är orsakerna till bortfallet acceptabla?	☐	☐	☐	☐
6. Följsamhet (”compliance, adherence, concordance”) [5]				
a) Framgår det i vilken utsträckning deltagarna fullföljde behandlingen?	☐	☐	☐	☐
b) Var andelen som fullföljde behandlingen acceptabel?	☐	☐	☐	☐
7. Rapportering av effektmått och biverkningar				
a) Var det primära effektmåttet definierat i förväg och adekvat rapporterat?	☐	☐	☐	☐
b) Var de sekundära effektmåtten definierade i förväg och adekvat rapporterade?	☐	☐	☐	☐
c) Baserades slutsatserna på enbart i förväg definierade effektmått och subgruppsanalyser? [6]	☐	☐	☐	☐
d) Har utfallen av samtliga viktiga effektmått redovisats på ett adekvat sätt? [7]	☐	☐	☐	☐
e) Rapporterades biverkningar/komplikationer på ett tillfredsställande sätt?	☐	☐	☐	☐
8. Resultat och precision				
a) Redovisas resultaten på ett adekvat sätt? [8]	☐	☐	☐	☐
b) Har resultaten beräknats med lämplig analysmetod? [9]	☐	☐	☐	☐
c) Var den minsta kliniskt relevanta effekten definierad på förhand?	☐	☐	☐	☐
d) Är den valda minsta kliniskt relevanta effekten av rimlig storlek?	☐	☐	☐	☐
e) Har man använt acceptabla metoder för att mäta effekterna?	☐	☐	☐	☐
f) Mättes observatörsöverensstämmelsen på ett acceptabelt sätt? [10]	☐	☐	☐	☐
g) Är de överväganden och beräkningar som ligger till grund för antal deltagare acceptabla (”power”-analys)? [11]	☐	☐	☐	☐
9. Bindningar och jäv				
a) Anges eventuella bindningar och jäv (”conflicts of interest”)?	☐	☐	☐	☐
b) Bedömer du att studiens resultat inte påverkats av intressekonflikter?	☐	☐	☐	☐
Total bedömning av studiekvalitet				
Hög ☐	Medelhög ☐	Låg ☐		

Appendix 2

GRADE evidence summary form

GÖTEBORGS UNIVERSITET

Sahlgrenska akademin
Institutionen för medicin
Avdelningen för klinisk näringslära
Dietistprogrammet, 2012/AW

Sammanfattande Evidensformulär **Effektmått:**

RCT utgår från ++++, kohortstudier utgår från ++. Sänk eller höj därefter graderingen utifrån studiekvalitet, överensstämmelse, överförbarhet, oprecisa data, risk för publikationsbias och effektstorlek.

Tillstånd:	
Åtgärd:	
Effektmått:	
Ingående studier: RCT ☐ (++++) Kohortstudier ☐ (++) Alla eller några av studierna sammanfattade i en systematisk översikt ☐ Antal studier: Antal pt:	+ 4 alt. +2
Studiedesign - Intern validitet (Randomiseringsförfarande, blindning, uppföljning, bortfall, intention-to-treat, vid kohortstudier – hantering av confounders) ☐ Inga begränsningar ☐ Vissa begränsningar (*men inte nog för nedgradering*[1]) ☐ Allvarliga begränsningar (*minska ett steg*) ☐ Mycket allvarliga begränsningar (*minska två steg*) Kommentera begränsningar eller grundvalen för nedgradering:	 ☐ 0 ☐ ? ☐ -1 ☐ -2
Överensstämmelse (Estimat av relativa effekten lika storlek och riktning mellan studierna? Överlappande konfidensintervall?) ☐ Inga problem ☐ Viss heterogenicitet (*men inte nog för nedgradering*[1]) ☐ Bekymmersam heterogenicitet (*minska ett steg*)	 ☐ 0 ☐ ? ☐ -1

Kommentera brist på överensstämmelse eller grundvalen för nedgradering:	
Studiepopulation – extern validitet(överförbarhet) Interventionen (effektmåttets relevans, relevans av jämförelsemetod, sjukvårdsmiljö, adekvat uppföljningstid)	
☐ Ingen osäkerhet	☐ 0
☐ Viss osäkerhet (*men inte nog för nedgradering*[1])	☐ ?
☐ Osäkerhet (*minska ett steg*)	☐ -1
☐ Påtaglig osäkerhet (*minska två steg*)	☐ -2
Kommentera viss osäkerhet eller grundvalen för nedgradering:	
Oprecisa data (Få händelser, vida konfidensintervall som infattar möjlig ogynnsam effekt) - kohort	
☐ Inga problem	☐ 0
☐ Vissa problem med precision (*men inte nog för nedgradering*[1])	☐ ?
☐ Oprecisa data (*minska ett steg*)	☐ -1
Kommentera viss osäkerhet eller grundvalen för nedgradering:	

Osäkert underlag (Få och små studier från samma forskargrupp eller företag som alla visar samma sak) ☐ Inga problem ☐ Vissa problem (men inte nog för nedgradering[1]) ☐ Klar risk för publikationsbias (*minska ett steg*) Kommentera grundvalen för nedgradering	 ☐ 0 ☐ ? ☐ -1
Effektstorlek Vid stor effekt eller mycket stor effekt kan man uppgradera evidensstyrkan (Kohort) ☐ Ej relevant ☐ Stor effekt (RR<0,5 eller >2) (öka ett steg) ☐ Mycket stor effekt (RR<0,2 eller >5) (öka två steg) Kommentera grundvalen för uppgradering	 ☐ 0 ☐ +1 ☐ +2
Kommentera andra viktiga aspekter som ska beaktas vid kategorisering av evidensstyrka/bedömning av vetenskapligt underlag, t.ex. stark dos-respons, allt-eller-inget-effekter, confounders som maskerar del av effekt kan uppgradera evidensstyrkan. (kohort)	☐ +1
Räcker summan av smärre brister under flera punkter till en nedgradering med ett helt steg? (beräkna antal ? i ovanstående frågor) ☐ Ja ☐ Nej	 ☐ -1 ☐ 0
Evidensstyrka ☐ Hög (++++) ☐ Måttlig (+++) ☐ Låg (++) ☐ Mycket låg (+) (= saknas vetenskapligt underlag)	