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Gluten- and casein-free diets for autistic spectrum disorder

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Abstract

Background—It has been suggested that peptides from gluten and casein may have a role in the origins of autism and that the physiology and psychology of autism might be explained by excessive opioid activity linked to these peptides. Research has reported abnormal levels of peptides in the urine and cerebrospinal fluid of people with autism.

Objectives—To determine the efficacy of gluten and/or casein free diets as an intervention to improve behaviour, cognitive and social functioning in individuals with autism.

Search methods—The following electronic databases were searched: CENTRAL(The Cochrane Library Issue 2, 2007), MEDLINE (1966 to April 2007), PsycINFO (1971 to April 2007), EMBASE (1974 to April 2007), CINAHL (1982 to April 2007), ERIC (1965 to 2007), LILACS (1982 to April 2007), and the National Research register 2007 (Issue1). Review bibliographies were also examined to identify potential trials.

Selection criteria—All randomised controlled trials (RCT) involving programmes which eliminated gluten, casein or both gluten and casein from the diets of individuals diagnosed with an autistic spectrum disorder.

Data collection and analysis—Abstracts of studies identified in searches of electronic databases were assessed to determine inclusion by two independent authors. The included trials did not share common outcome measures and therefore no meta-analysis was possible. Data are presented in narrative form.

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CONTRIBUTIONS OF AUTHORS All reviewers contributed to the writing of the protocol and to the selection of trials. Graham Connell-Jones and Mike Ferriter extracted data. Claire Millward and Mike Ferriter wrote the text of the review.

DECLARATIONS OF INTEREST One of the reviewers (MF) is the parent of a son with autism.

Main results—Two small RCTs were identified ($n = 35$). No meta-analysis was possible. There were only three significant treatment effects in favour of the diet intervention: overall autistic traits, mean difference (MD) = -5.60 (95% CI -9.02 to -2.18), $z = 3.21$, $p = 0.001$ (Knivsberg 2002) ; social isolation, MD = -3.20 (95% CI -5.20 to 1.20), $z = 3.14$, $p = 0.002$) and overall ability to communicate and interact, MD = 1.70 (95% CI 0.50 to 2.90), $z = 2.77$, $p = 0.006$) (Knivsberg 2003). In addition three outcomes showed no significant difference between the treatment and control group and we were unable to calculate mean differences for ten outcomes because the data were skewed. No outcomes were reported for disbenefits including harms.

Authors' conclusions—Research has shown of high rates of use of complementary and alternative therapies (CAM) for children with autism including gluten and/or casein exclusion diets. Current evidence for efficacy of these diets is poor. Large scale, good quality randomised controlled trials are needed.

Medical Subject Headings (MeSH)

Autistic Disorder [*diet therapy; etiology; psychology]; Caseins [administration & dosage; adverse effects]; Glutens [administration & dosage; adverse effects]; Randomized Controlled Trials as Topic

MeSH check words

Child; Humans

BACKGROUND

This review is an update of a Cochrane Review published by the authors in 2004.

Description of the condition

The autistic spectrum disorders (ASD) are characterised by the triad of impairments identified by Wing, including impairments of social functioning, communication and lack of flexibility of thought and behaviour (Wing 1996a, Wing 1996b). These impairments persist from childhood to adulthood and can have a severe impact on learning and social integration. Fombonne's review of the epidemiology of autistic spectrum disorders reports that these disorders affect between 0.7 to 21.1 per 10,000 children (Fombonne 1999).

Description of the intervention

Diets in which all gluten, or casein or gluten and casein are excluded.

How the intervention might work

Reichelt et al hypothesised that peptides from gluten and casein have an aetiological role in the pathogenesis of the disorder of autism (Reichelt 1991). It has been suggested that the pathophysiology and psychology of autism can be explained by excessive opioid activity linked with the above (Israngkun 1986; Reichelt 1981). Urine samples of people with autism have been reported to show an increased 24-hour low molecular weight peptide excretion (Israngkun 1986; Reichelt 1986; Shattock 1990) and increased opioid levels in cerebrospinal fluid (Israngkun 1986; Reichelt 1981). Based on analysis of urine samples, dietary

intervention involving the exclusion of foods containing gluten or casein, or both, has been proposed to be effective in ameliorating some of the behavioural symptoms of autism. An investigation by Reichelt et al indicated that casein has a similar chemical structure to that of gluten (Reichelt 1991). Due to this similarity, it is hypothesised that if a person has a sensitivity to either they will have sensitivities to both, although these sensitivities need not be of equal severity. The inability to adequately process gluten and casein is proposed to result in or exacerbate a variety of disorders including postpartum psychosis, schizophrenia, and autism (Reichelt 1990; Reichelt 1991; Reichelt 1995).

Inadequately metabolised proteins are purported to breakdown into peptides that are absorbed across the dietary membranes into the body's systems. It is suggested that these peptides may become biologically active through binding with opioid receptors. The resulting excess of opioids is thought to lead to the behaviours noted in autistic spectrum disorders. Further, it is suggested that although high levels of peptides are appropriately deposited in the urine, a small proportion of the excess peptides will cross into the brain causing interference of signal transmission (Reichelt 1991). This can lead to a disruption of normal activity. One hypothesis surrounding the variation in behaviour of children and adults with autism is linked to food reactivity/sensitivity. It is postulated that the disruptive behaviour evidenced in many individuals with autism is directly linked to particular foods, for example, wheat and dairy products (Reichelt 1994). In addition to the various behavioural difficulties demonstrated, it is suggested that communicative ability and social and cognitive functioning are similarly affected (Knivsberg 2002).

Knivsberg et al have argued that the peptides probably derived from gluten and casein have a negative pharmacological effect on attention, brain maturation, social interaction and learning (Knivsberg 1995). Hence, they hypothesise that appropriate diets would facilitate learning, social behaviour, cognitive functioning and communicative skills in individuals with autism.

Why it is important to do this review

Authors such as Hanson et al have reported high rates of use of complementary and alternative therapies (CAM) by parents of children with ASD including dietary supplements and restrictive diets (Hanson 2007/). In their survey of 112 families 74% reported using a CAM therapy. The main reasons reported for their use were concerns about the safety and side effects of prescribed medications. Wong and Smith compared the use of CAM therapy in fifty families with a child member with ASD and families with no ASD (Wong 2006). They found significantly higher rates of use of CAM therapies in the families with an autistic child. Six of the families with a child with autism were using or had used a casein free diet and nine of the families with a child with autism were using or had used a gluten free diet for their child (Wong 2006). The importance of this review in the light of evidence of widespread use of CAM therapies including exclusion diets is as follows. There is a need to assess the available evidence for the efficacy and effectiveness of diets that include gluten and/or casein free diet but also to identify any disbenefits associated with these diets. Gluten and/or casein are to be found to varying degrees in diets worldwide and are ubiquitous in Western diets which are in turn becoming more common throughout the world. The

consequences of this is that it is a challenge to parents to identify food products without gluten or casein and it can be a problem to source food products guaranteed to be without gluten or casein. Restriction diets often cost more than the standard diet and may involve extra effort in providing the special meals for the child with autism and normal meals for the rest of the family. For the child with autism the consequences are twofold. There may be physical health consequences of such elimination diets such as the loss of benefits of cow's milk for healthy growth in the child which must be supplemented in other ways. In addition, the child with autism is already restricted in lifestyle by her/his disorder but undergoes a further lifestyle restriction in terms of diet.

OBJECTIVES

To examine the effectiveness of gluten and/or casein free diets on the symptoms of individuals with autistic spectrum disorder and also to identify disbenefits including harms, costs and impact on quality of life.

METHODS

Criteria for considering studies for this review

Types of studies—Randomised controlled trials.

Types of participants—Children, adolescents and adults clinically diagnosed with an autism spectrum disorder, as per the DSM-IV (APA 1994) or ICD-10 (WHO 1993) criteria for autism.

Types of interventions—

- Gluten free diet versus placebo/no treatment.
- Casein free diet versus placebo/no treatment.
- Gluten and casein free diet versus placebo/no treatment.
- Gluten free diet versus casein free diet.

(NB: placebo can be particularly problematic in diet interventions; however, there are precedents for blinding participants to allocation. As an example of a blinded gluten free versus gluten challenge trial, see Vlisides 1986).

Types of outcome measures—

- Concentration of peptides in urine samples.
- Behavioural observations and standardised assessments of autistic behaviours.
- Communication and linguistic ability.
- Cognitive functioning.
- Motor ability (this is a change to our previously published protocol).
- Disbenefits including harms, costs and impact on quality of life.

Search methods for identification of studies

Electronic searches—The following electronic databases were searched:

1. The Cochrane Central Register of Controlled Trials -CENTRAL (The Cochrane Library Issue 2, 2007)
2. MEDLINE (1966 to April 2007)
3. EMBASE (1974 to April 2007)
4. CINAHL (1982 to April 2007)
5. PsycINFO (1971 to April 2007)
6. LILACS (1982 to April 2007)
7. ERIC (1965 to April 2007)

Search terms for the Cochrane Library were as follows:

- #1 CHILD-DEVELOPMENT-DISORDERS-PERVASIVE*: ME
- #2 COMMUNICATION*:ME
- #3 AUTIS*
- #4 PDD
- #5 (PERVASIVE and (DEVELOPMENTAL and DISORDER*))
- #6 (LANGUAGE near DELAY*)
- #7 COMMUNICAT*
- #8 (SPEECH near DISORDER*)
- #9(CHILDHOOD next SCHIZOPHRENIA)
- #10 KANNER*
- #11 ASPERG*
- #12 ((((((((((#1 or #2) or #3) or #4) or #5) or #6) or #7) or #8) or #9) or #10) or #11)
- #13 GLUTEN*:ME
- #14 CASEINS*:ME
- #15 GLUTEN*
- #16 CASEIN*
- #17 (#13 or #14 or #15 or #16)
- #18 (#12 and #17)

These terms were modified where appropriate for the other databases listed. The search strategies for MEDLINE, CINAHL, EMBASE and PsycINFO can be found in Table 1, Table 2, Table 3, Table 4. Filters for the identification of RCT's were used where necessary.

Searching other resources—The references of all studies identified from electronic and hand searches were inspected for further studies, and experts in the field as well as research and consumer groups with an interest in autism and nutrition were contacted.

Data collection and analysis

Selection of studies—Using titles and abstracts, the full text of all studies reporting treatment of autistic spectrum disorder with gluten or casein restricted diets were obtained. Once all potentially appropriate studies had been obtained, each trial was evaluated independently by two reviewers (MF and GCJ or CM and SC) for inclusion. Any disagreements were resolved by consensus decision between MF and GCJ. Reviewers were not blinded to the name(s) of the author(s), institution(s) or publication source at any level of review.

Data extraction and management—Two reviewers (MF and GCJ) independently extracted the data for trials meeting the inclusion criteria identified above, and authors were contacted for additional information.

Assessment of risk of bias in included studies

Assessment of methodological quality: Concealment of treatment allocation is important in minimising bias (Schulz 1995). Assessment and scoring were undertaken using standard Cochrane format where A = adequate, B = Inadequate and C = unclear, as described in *The Cochrane Collaboration Handbook for Systematic Reviews of Interventions* (Higgins 2005). Included trials were also critically appraised against the following criteria:

- Was the assignment to treatment condition truly random?
- Was allocation adequately concealed?
- How complete was the follow up?
- How were the outcomes of people who withdrew considered?
- Were those assessing outcomes blind to the treatment allocation?

Measures of treatment effect—If additional trials are identified in updates of this review, and report binary data, the odds ratio with a 95% confidence interval (CI) will be calculated. Continuous data will be analysed using weighted mean difference where the same outcome measures are reported in more than one study. If studies used different outcome measure of the same construct, standardised weighted mean difference will be used.

Assessment of heterogeneity—Should studies be included in future updates of this review, we plan to assess the extent to which between-trial differences are apparent and assess consistency of results both visually and by examining I^2 (Higgins 2002), a quantity which describes approximately the proportion of variation in point estimates that is due to heterogeneity rather than sampling error. I^2 below 30% will be considered low heterogeneity, and I^2 in excess of 70% will indicate high levels of heterogeneity. This will be supplemented with a test of homogeneity, to determine the strength of evidence that the

heterogeneity is genuine. Where heterogeneity is found, a random effects model will be used. Every attempt will be made to determine the source of heterogeneity, which we anticipate may include the degree to which the integrity of the diet has been maintained between studies.

Assessment of reporting biases—If, in the future, further trials are identified, funnel plots will be evaluated to assess the relationship between effect size and trial precision. Such a relationship could be due to publication or related biases or due to systematic differences between small and large studies. If a relationship is identified, clinical diversity of the studies will be further examined as a possible explanation (Egger 1997).

Data synthesis—All data analyses were conducted using RevMan 4.2.

Sensitivity analysis—In future updates if there is sufficient data, the authors plan to assess the impact of study quality using sensitivity analysis.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Two randomised control trials met the criteria for inclusion. Knivsberg et al's study was a small single phase trial and Elder et al's study was a small pilot, randomised, crossover trial.

Participants—Both studies recruited children who met criteria for autistic spectrum disorder.

In Knivsberg et al's study participants had been recruited from all parts of Norway via journal announcements and school psychological services, and participation was based on written consent. Mean age range of the intervention group was 91 months (range 62 to 120); mean age range of the control group was 86 months (range 59 to 127). Entry criteria included a diagnosis of autism and the presence of abnormal urinary patterns of peptides. There were 10 participants in each arm of the trial (Knivsberg 2002).

In Elder et al's study fifteen child participants (mean age 7.32 years, SD=4.1 years, range 2-16 years) were recruited into the trial (Elder 2006). Inclusion criteria were meeting the DSM-IV diagnostic criteria for autism disorder and a score above cut off on each symptom domain of the Autism Diagnostic Interview Revised (ADI-R). Exclusion criteria were medical history or physical examination indicating physical or sensory impairment or significant medical problems including celiac disease. Twelve boys and three girls were recruited into the trial with one child of Asian origin and the remainder described by the authors as Caucasian.

Intervention and comparator—Both studies compared gluten and casein free diet versus normal diet.

Outcomes—Knivsberg et al reported on four outcome measurements in their first paper: number of autistic traits (see below for fuller description), linguistic age in months, non-verbal cognitive level and motor problems. Data were presented as both group means and standard deviations and individual patient data for both before and after scores, and standard deviations were calculated and presented below. The four outcomes reported in their second paper were the four subscales of the DIPAB, a Danish instrument for measuring autistic traits (Haracopos 1975) the four subscales are: resistance to communication, bizarre behaviour, communication and interaction and social isolation.

Elder et al (Elder 2006) reported on the following outcome measures: the Childhood Autism rating Scale (CARS), Urinary Peptide Levels (UPL), Ecological Communication Orientation (ECO) Language Sampling Summary; and in-home observations based on samples of video tape of the child interacting with his/her primary care-taking parent. The interactions were rated in six categories: child initiating, child responding, intelligible words spoken, parent initiating, parent responding and parent expectant waiting (for the child's response).

Duration of trial—In Knivsberg et al's study the duration of the trial was 12 months (Knivsberg 2002). Elder et al's study lasted twelve weeks with crossover after six weeks (Elder 2006).

Excluded studies—Thirty three studies were excluded from the review, principally because they did not meet the criteria for study design. Reasons for exclusion are detailed in the Table of excluded studies.

Ongoing studies—We identified one ongoing study sponsored by the US National Institute of Mental Health at the University of Rochester Medical Center, Rochester, New York. Details of this study are shown in the 'Characteristics of ongoing studies' table.

Risk of bias in included studies

See Table 5 and Table 6 for 'Risk of Bias' tables.

Both included trials were small scale studies. Knivsberg et al's trial (Knivsberg 2002) consisted of twenty participants and Elder et al's trial had fifteen participants (Elder 2006).

The method of randomisation in Knivsberg et al was pair-wise matching by severity of autistic symptoms and randomly allocate, within each pair, to treatment or control group. Methods of randomisation and allocation concealment were not described in the published papers, but we established through contact with the authors that coin-tossing had been used and that both randomisation and allocation had been undertaken independently of the project team conducting the trial (Knivsberg 2004). The trial reported by Elder et al was a double blind, crossover trial. The method of randomisation was not described.

In the Knivsberg 2002 trial the outcomes assessors were blinded. In the Elder 2006, the child participants, parents and investigative team, with the exception of the data manager and dietician, were blind to allocation.

Knivsberg et al reported baseline scores for all outcomes (Knivsberg 2002). One participant is described as “not responding to the cognitive and linguistic tasks” and scores are not reported for these two outcomes for this participant. There was no loss to follow up. Elder et al reported urinary Peptide Levels measures at baseline and weeks three, six, nine and twelve. All other outcome measures were carried out at baseline and weeks six and twelve. The authors employed a missing at random model for the three participants whose data was incomplete (CARS and ECO) at week six or week twelve.

Effects of interventions

There was not sufficient homogeneity of participants interventions comparators and outcomes to carry out meta-analysis and therefore it was also not possible to carry out funnel plots. There were not sufficient studies and data to assess the impact of study quality using sensitivity analysis. We have presented the results for the two included studies, individually.

Treatment effect sizes were not calculated for continuous data that were skewed, skewedness being defined as when the mean is less than twice the standard deviation. Elder et al (Elder 2006) report the results of a crossover trial and although the authors’ report that they were advised that a “wash out” period would not be necessary we adopted the more prudent strategy of reporting on only the results of the first phase of the trial.

Difference between baseline and end of trial scores—Individual patient data were available for Knivsberg et al’s study for the four outcomes of number of autistic traits, linguistic age in months, non verbal cognitive level and motor problems (Knivsberg 2002). This enabled us to calculate the more sensitive measure of difference score; that is to say, we could subtract the baseline score from the end of trial score for each individual patient and calculate the mean and standard deviation for each arm of the trial from this. However, in all cases the data could not be used because it was skewed.

The results for the difference scores were as follows. For the number of autistic traits (data on ten participants in each arm of the trial) the diet group showed a mean reduction in the number of traits of 6.90 (standard deviation (SD) = 2.42) and the control group a mean reduction of 0.30 (SD = 3.94). For linguistic age (data on nine participants in each arm of the trial) in months the diet group showed a mean increase of 11.11 (SD = 8.79) and the control group a mean increase of 7.89 (SD = 10.03). For non verbal cognitive level (data on nine participants in each arm of the trial) the diet group showed a mean increase of 5.67 (SD = 6.54) and the control group a mean decrease of 10.44 (SD = 13.59). For motor problems (data on ten participants in each arm of the trial) the diet group showed a mean decrease of 3.00 (SD = 6.19) and the control group a mean increase of 3.10 (SD = 6.21).

All other results below are based on end of trial scores only:

1. Concentration of peptides in urine samples: Knivsberg et al did not report investigations of peptide concentrations in the urine samples of participants (Knivsberg 2002). In Elder et al’s trial data was not reported in a usable form for urinary peptide levels but the authors report that there was no significant difference between groups for this outcome.

2. Behavioural observations and standardised assessments of autistic behaviours:

Knivsberg et al assessed overall autistic traits by combining the social isolation and bizarre behaviour sub scores of the DIPAB. The sub scores are described in more detail below. Post intervention, the diet group had a mean autistic trait score of 5.60 (SD = 2.41) compared to the control group mean score of 11.20 (SD = 5.00). Mean difference (MD) = -5.60 (95% CI -9.02 to -2.18), $z = 3.21$, $p = 0.001$ (Knivsberg 2003). The results favour the intervention group.

The sub score results for social isolation were calculated from the questions related to resistance to communication and interaction and questions related to ability to interact and communicate. At the end of the trial the mean score for the diet group was 3.0 (SD= 1.4) and for the control group the mean was 6.2 (SD=2.9). MD = -3.20 (95% CI -5.20 to 1.20), $z = 3.14$, $p = 0.002$). The results favoured the intervention group.

Resistance to communication and interaction was computed from scores for verbal and nonverbal communication, reaction when spoken to, resistance to learning, sharing of feelings, reaction to physical contact, eye contact and peer relationship. A decrease in score shows positive development. At the end of the trial the mean score for the diet group was 0.2 (SD=0.4) and for the control group the mean was 1.9 (SD=1.4). MD was not calculated for this outcome as the data were skewed.

Knivsberg et al measured bizarre behaviour using the bizarre behaviour score for the DIPAB which measures compulsive or stereotypic communication, echolalia, adult dependency, strange emotional reactions, abnormal anxiety, reactions to changes in the environment or routines peculiar handling of toys and playing materials, attachment/affinity for special items and unusual movements or motor behaviour (Knivsberg 2003). At the end of the trial the mean score for the diet group was 2.6 (SD=1.7) and for the control group the mean was 4.8 (SD=2.6). MD was not calculated for this outcome as the data were skewed.

Elder et al used the CARS scale which rates a number of behaviours including relationship with others; imitation; emotional expression; body use; peculiarities in object use; resistance to change; visual, auditory and tactile responsiveness; anxiety; verbal and non verbal communication; activity level and intellectual ability. At the end of the first phase the mean score for the diet group was 33.60 (SD=8.60) and for the control group the mean was 31.20 (SD= 8.70). MD = 2.40 (95% CI -6.66 to 11.46), $z = 0.52$, $p = 0.60$); this was non-significant.

3. Communication and linguistic ability: Knivsberg et al assessed linguist age using one of two tests depending on the age and functional level of the participants (Knivsberg 2002). The tests were the Illinois Test of Psycholinguistic Ability (ITPA) (Gjessing 1975), as standardised for Norwegian children, or the Reynells språktest (language-test) (Hagtvet 1986). Post intervention, the diet group had a mean linguistic age in months of 66.60 (SD = 35.10) compared to the control group mean age of 55.70 (SD = 28.30). MD was not calculated for this outcome as the data were skewed.

Knivsberg et al assessed the child's overall ability to communicate and interact from the computed scores for verbal and non verbal communication, reaction when spoken to, resistance to learning, sharing of feelings, reactions to physical contact, eye contact, peer relationship, and handling of toys and play materials (Knivsberg 2003). An increase in score shows positive development. At the end of the trial the mean score for the diet group was 6.20 (SD=1.10) and for the control group the mean was 4.50 (SD=1.60). MD = 1.70 (95% CI 0.50 to 2.90), $z = 2.77$, $p = 0.006$). This result favoured the intervention group. Elder et al also used the Ecological Communication Orientation (ECO) Language Sampling Summary to record the child's behaviour and collect interactive samples. At the end of the first phase the mean score for the diet group was 175.80 (SD=86.40) and for the control group the mean was 174.40 (SD=86.00). MD was not calculated for this outcome as the data were skewed.

In addition, Elder et al recorded the following scores for which we were not able to calculate a standardised treatment effect size because the data was skewed:

In-home observations-child initiating: at the end of the trial the mean score for the diet group was 9.5 (SD=9.6) and for the control group the mean was 7.5 (SD=6.1).

In-home observations-child responding: at the end of the trial the mean score for the diet group was 27.7 (SD=21.8) and for the control group the mean was 14.3 (SD=6.5).

In-home observations-intelligible words spoken: at the end of the trial the mean score for the diet group was 26.8 (SD=35.1) and for the control group the mean was 24.0 (SD=43.5). In-home observations-parent initiating: at the end of the trial the mean score for the diet group was 61.2 (SD=37.0) and for the control group the mean was 71.6 (SD=34.9). In-home observations-parent responding: at the end of the trial the mean score for the diet group was 15.2 (SD=11.6) and for the control group the mean was 20.1 (SD=13.6). In-home observations-parent expectant waiting (for the child's response): at the end of the trial the mean score for the diet group was 2.3 (SD=1.4) and for the control group the mean was 1.9 (SD=2.7).

4. Cognitive functioning: Knivsberg et al measured the participants non-verbal cognitive level using the Leiter International Performance Scale (LIPS) (Leiter 1979). Post intervention, the diet group had a LIPS mean score of 86.7 (SD = 38.5) compared to the control group mean score of 74.30 (SD = 31.40). MD = 12.40 (95% CI -20.06 to 44.86), $z = 0.75$, $p = 0.45$ (Knivsberg 2002); result not significant.

5. Motor problems: The published protocol for this systematic review (Millward 2002) did not pre-specify that outcomes concerning motor ability would be sought; however, we will include this information both here and in future updates of the review. Knivsberg et al reported that motor problems were assessed using the Movement Assessment Battery for Children (Henderson 1992). Post intervention, the mean score for the diet group was 26.3 (SD = 11.50) compared to the control group mean score of 27.80 (SD = 12.20). MD = -1.50 (95% CI -11.89 to 8.88), $z = 0.28$, $p = 0.78$ (Knivsberg 2002), result not significant.

6. Disbenefits including harms, costs and impact on quality of life: None reported.

DISCUSSION

This review identified two studies and there was not sufficient homogeneity of outcomes to undertake meta-analysis. One study showed significant lower autistic traits in the intervention group compared to the control group and the other study showed no difference between the intervention and the control group.

Knivsberg et al reported results on four outcomes in their first paper (Knivsberg 2002). Unfortunately we were not able to use the data on one of the outcomes, linguistic age, because the data were skewed. Unsurprisingly in such a small scale study, the results for two of these outcomes (cognitive skills and motor ability) had wide confidence intervals that spanned the line of nil effect. However, the third outcome, reduction in autistic traits, showed a beneficial treatment effect for the combined gluten and casein free diet. The second paper (Knivsberg 2003) reported the results of the four subscales of the DIPAB but unfortunately we were unable to use the results for two of the scales, resistance to communication and bizarre behaviour, because the data were skewed. The results for the other two outcomes, communication and interaction and social isolation, all showed a significant treatment effect size in favour of the diet intervention. However, when interpreting these results it should be born in mind that the data for one of the significant outcomes in the second paper, social isolation, is also a component of the data on the significant outcome in the first paper, autistic traits.

The second trial (Elder 2006) reported usable data on the Childhood Autism Rating Scale (CARS) but there was no significant difference between the diet and control group for this outcome. They reported data on the Ecological Communication Orientation (ECO) Language Sampling Summary and all six outcomes of the in-home observation but in every case the data were skewed. Data was not reported in a usable form for urinary peptide levels but the authors report that there was no significant difference between groups for this outcome.

Elder 2006 was particularly well designed both in its formal structure (double blind with adequate concealment of allocation) and the care with which the diets were tailored to individual participant's needs and preferences. The authors acknowledge two significant problems with there study. This was a small scale study, intended only as a pilot for a much larger study and the authors declared their suspicions that the integrity of the diet may have been breached by participants requesting food from siblings and peers.

Neither study report a washout period which might be an important factor in this area, particularly in short term trials. If gluten and/or casein peptides have a long term residual effect, after their elimination from the diet, the impact in short duration trails would be to minimise the treatment effect size between the intervention and control group. This less of a problem in Knivsberg et al's study than in Elder et al's shorter term study and one way round this would be that future trails should commence with a washout period of the exclusion diet for both intervention and control groups. Neither study reported disbenefits including harms and costs of these diets.

Four years on from the first version of this review (Millward 2002) we were only able to identify one paper providing extra information on the trials included in the first review, one new trial and one ongoing trial. This is disappointing bearing in mind the extent to which these diets are being used by parents of children with autism. In the first version of this review we said that “Researcher’s in the field are attempting to explore the effectiveness of these dietary interventions on persons with autistic spectrum disorder but to date there has not been evidence of sufficiently rigorous methodology to eliminate other explanations for these beneficial changes. Only well conducted and adequately powered RCTs will resolve this issue and we await, with interest, further developments in this field”. Elder 2006 answers the first need by providing the blueprint for a well designed trial in this area though thought needs to be given to the provision of a washout period prior to the commencement of the trial proper. The second problem of adequate power is still to be addressed.

AUTHORS’ CONCLUSIONS

Implications for practice

In the first version of this review we argued that exclusion diets are not without cost in terms of inconvenience and extra financial cost and limitations on foods of choice for the affected family member and that we could not recommend their use as a standard treatment on the basis of the limited data available. The only trial identified since the first review shows no significant difference between the intervention and control group and, again, we cannot recommend these exclusion diets as standard treatment.

Implications for research

Well-conducted and adequately-powered randomised controlled trials are urgently needed in this area. Elder’s et al’s pilot trial provides a useful model which needs to be replicated with an adequate sample size.

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External sources

- NHS Cochrane Collaboration Programme Grant Scheme, UK.

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Elder 2006

Methods	Randomised, double blind crossover trial	
Participants	Fifteen children with autistic spectrum disorder (DSM-IV criteria), 12 boys and 3 girls, age range 2-16 years and mean age 7.32 years	
Interventions	Gluten and casein free diet adapted to the individual child's food preference v matched diet but containing gluten and casein. duration of the study, 12 weeks	
Outcomes	Childhood Autism rating Scale (CARS) Urinary Peptide Levels (UPL) Ecological Communication Orientation (ECO) Language Sampling Summary In-home observation of child behaviours rated as: child initiating, child responding, intelligible words spoken and also parent initiating, parent responding and parent expectant waiting	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Knivsberg 2002

Methods	Single-blind, randomised trial (method: coin-tossing).	
Participants	Twenty children with autistic syndrome and abnormal urinary peptide patterns. Mean age range of the intervention group was 91 months (range 62 - 120); mean age range of the control group was 86 months (range 59-127)	
Interventions	Gluten and casein free diet v normal diet. Duration of the study, 12 months	
Outcomes	Autistic traits (as measured by the DIPAB). Cognitive skills (Leiter International Performance Scale). Linguistic ability (ITPA & Reynells språktest). Motor ability (Movement Assessment Battery for Children).	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Adams 1997	Review article
Ashkenazi 1980	Letter
Baghdadli 2002	Review of research on intervention for autism including diet
Bird 1977	Case study
Bowers 2002	Audit
Brudnak 2001	Not RCT
Christison 2006	Review
Cocchi 1996	Discussion paper

Study	Reason for exclusion
Cook 1997	Review article
Cornish 2002	Non random postal survey
Ellis 1999	Review article
Fitzgerald 1999	Not RCT, not dietary intervention.
Garvey 2002	Review of diet and autism
Gemmell 1997	Allocation between diet group and control group at parental discretion
Grace 1999	No control group
Howling 1997	Review article
Howling 1999	Editorial
Israngkun 1986	Not RCT
Kidd 2002a	Review
Kidd 2002b	Review
Knivsberg 1990	Not RCT
Knivsberg 1995	Not RCT
Knivsberg 2001	Review
Lucarell 1995	'Control' group did not have ASD; no randomisation
O'Banion 1978	Case study
Pontino 1998	Summarises the results of studies reported by Gemmell et al (1997) and later reported by Grace et al (1999) q.v
Reichelt 1991	Not RCT
Reichelt 1997	Not RCT
Shattock 2002	A review of the opioid-excess theory.
Sponheim 1991	Groups were of different ages, received different interventions, no separate controls
Torisky 1993	Not RCT
Whitely 1999	A non-randomised controlled trial of gluten-free diet. Controls did not have autistic spectrum disorder
Whitely 2000	Qualitative analysis of feeding problems of a random sample of persons with autistic spectrum disorder

Characteristics of ongoing studies [ordered by study ID]

NIMH 2004

Trial name or title	Diet and Behavior in Young Children with Autism Clinical trials no.: NCT00090428
Methods	
Participants	Expected enrollment: 30. Ages eligible: 30 to 54 Months, both genders eligible; Inclusion Criteria: Autism spectrum disorder or pervasive developmental disorder Participation in applied behavioral analysis classes for at least 4 months, with at least 20 hours per week of service, and at least 1 hour of service in the home A score higher than 30 on the Mullen Early Learning scale Ability to maintain a gluten- and casein-free diet during the study

	In order to maintain study integrity, and due to frequent child assessments, enrollment is limited to a select population within the Rochester NY (USA) area
Interventions	Gluten- and casein-free diet
Outcomes	Primary Outcomes: Safety and Efficacy of the gluten free casein free diet
Starting date	Study start: January 2004; Expected completion: April 2008
Contact information	University of Rochester Medical Center, Rochester, New York, 14642, United States; Recruiting Carol Stamm carol.stamm@urmc.rochester.edu
Notes	Sponsored by the NIMH

DATA AND ANALYSES

Comparison 1

Gluten and casein free diet versus normal diet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Autistic traits (social isolation plus bizarre behaviour sub scores of the DIPAB) at 12 months	1	20	Mean Difference (IV, Fixed, 95% CI)	-5.6 [-9.02, -2.18]
2 Cognitive skills at 12 months	1	18	Mean Difference (IV, Fixed, 95% CI)	12.40 [-20.06, 44.86]
4 Motor ability at 12 months	1	20	Mean Difference (IV, Fixed, 95% CI)	-1.5 [-11.88, 8.88]
5 Ecological Communication Orientation (ECO) Language Sampling Summary at week 6	1	13	Mean Difference (IV, Fixed, 95% CI)	1.40 [-92.61, 95.41]
6 Childhood Autism Rating Scale (CARS) at week 6	1	14	Mean Difference (IV, Fixed, 95% CI)	2.40 [-6.66, 11.46]
7 DIPAB sub score - communication and interaction at 12 months (note low score indicates deficit)	1	20	Mean Difference (IV, Fixed, 95% CI)	1.70 [0.50, 2.90]
8 DIPAB sub score - social interaction at 12 months (note high score indicates deficit)	1	20	Mean Difference (IV, Fixed, 95% CI)	-3.2 [-5.20, -1.20]

HISTORY

Protocol first published: Issue 1, 2002

Review first published: Issue 2, 2004

Date	Event	Description
20 February 2008	New citation required and conclusions have changed	Substantive amendment. This review contains results from one new trial (Elder 2006) and further data from a previously included study (Knivsberg 2002).

Date	Event	Description
		In addition, we have learned of an ongoing USA-based Phase I randomized, double-blind, placebo controlled, parallel assignment, safety/efficacy study, which is now within the references of this review. The study is anticipated to be completed in April 2008

WHAT'S NEW

Last assessed as up-to-date: 1 April 2007.

Date	Event	Description
4 July 2008	Amended	Converted to new review format.

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- * *Indicates the major publication for the study*

PLAIN LANGUAGE SUMMARY

Gluten and casein-free diets for autism spectrum disorder

It has been suggested that peptides from gluten and casein may have a role in the origins of autism and that the physiology and psychology of autism might be explained by excessive opioid activity linked to these peptides.

An extensive literature search was carried out to identify any randomised control trials of gluten and/or casein free diet as an intervention to improve behaviour, cognitive and social functioning in individuals with autism. Only three papers reporting on two randomised control trial were identified, two small scale trials the first with ten participants in each arm of the trial and the second with fifteen participants recruited into the trial. The results for the first study indicated that a combined gluten and casein free diet reduced autistic traits and the second study showed no significant difference in outcome measures between the diet group and the control group. This is an important area of investigation and large scale, good quality randomised control trials are needed. None of the studies reported on adverse outcomes or potential disbenefits.

There is evidence of widespread use by parents of complementary and alternative therapies (CAM) including exclusion diets for their children with autism. Despite this, there is a lack of evidence to support the use of gluten and/or casein free diet as an effective intervention for persons with autism and also a lack of research on potential harms and disbenefits of such diets. Despite the problems of maintaining the integrity of such diets in the community it is possible to carry out randomised control trials to address these questions and more and adequately powered trials are needed in this area.

Table 1

Medline searched 1966 to April 2007

MEDLINE
MEDLINE searched via OVID 1966 to April 2007
1 exp Child Development Disorders, Pervasive/
2 exp COMMUNICATION/
3 autism.tw.
4 PDD.tw.
5 pervasive developmental disorder\$.tw.
6 (language adj3 delay\$.tw.
7 communicat\$.tw.
8 (speech adj3 disorder\$.tw.
9 childhood schizophrenia.tw.
10 kanner\$.tw.
11 asperg\$.tw.
12 or/1-11
13 exp Gluten/
14 exp Caseins/
15 gluten\$.tw.
16 casein\$.tw.
17 or/13-16
18 randomized controlled trial.pt.
19 controlled clinical trial.pt.
20 randomized controlled trials.sh.
21 random allocation.sh.
22 double blind method.sh.
23 single blind method.sh.
24 or/18-23
25 (animals not humans).sh.
26 24 not 25
27 clinical trial.pt.
28 exp Clinical Trials/
29 (clin\$ adj25 trial\$.ti,ab.
30 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.
31 placebos.sh.
32 placebo\$.ti,ab.
33 random\$.ti,ab.
34 research design.sh.
35 or/27-34
36 35 not 25
37 36 not 26
38 comparative study.sh.

MEDLINE

39 exp Evaluation Studies/

40 follow up studies.sh.

41 prospective studies.sh.

42 (control\$ or prospectiv\$ or volunteer\$).ti,ab.

43 or/38-42

44 43 not 25

45 44 not (26 or 37)

46 26 or 37 or 45

47 12 and 17 and 46

Table 2

CINAHL searched 1982 to April 2007

CINAHL
CINAHL searched via OVID 1982 to April 2007
1 autis\$.tw.
2 PDD.tw.
3 pervasive developmental disorder\$.tw.
4 (language adj3 delay\$).tw.
5 communicat\$.tw.
6 (speech adj3 disorder\$).tw.
7 childhood schizophrenia.tw.
8 kanner\$.tw.
9 asperg\$.tw.
10 exp Autism/
11 exp COMMUNICATION/
12 or/1-11
13 exp GLUTEN/
14 (gluten\$ or casein\$).tw.
15 or/13-14
16 randomi\$.mp. [mp=title, subject heading word, abstract, instrumentation]
17 clin\$.mp. [mp=title, subject heading word, abstract, instrumentation]
18 trial\$.mp. [mp=title, subject heading word, abstract, instrumentation]
19 (clin\$ adj3 trial\$).mp. [mp=title, subject heading word, abstract, instrumentation]
20 singl\$.mp. [mp=title, subject heading word, abstract, instrumentation]
21 doubl\$.mp. [mp=title, subject heading word, abstract, instrumentation]
22 tripl\$.mp. [mp=title, subject heading word, abstract, instrumentation]
23 trebl\$.mp. [mp=title, subject heading word, abstract, instrumentation]
24 mask\$.mp. [mp=title, subject heading word, abstract, instrumentation]
25 blind\$.mp. [mp=title, subject heading word, abstract, instrumentation]
26 (20 or 21 or 22 or 23) and (24 or 25)
27 crossover.mp. [mp=title, subject heading word, abstract, instrumentation]
28 random\$.mp. [mp=title, subject heading word, abstract, instrumentation]
29 allocate\$.mp. [mp=title, subject heading word, abstract, instrumentation]
30 assign\$.mp. [mp=title, subject heading word, abstract, instrumentation]
31 (random\$ adj3 (allocate\$ or assign\$)).mp.
32 Random Assignment/
33 exp Clinical Trials/
34 exp Meta Analysis/
35 31 or 27 or 26 or 19 or 16 or 32 or 33 or 34
36 12 and 15 and 35

Table 3**EMBASE searched to April 2007**

EMBASE
EMBASE searched via OVID 19 to April 2007
1 autis\$.tw.
2 PDD.tw.
3 pervasive developmental disorder\$.tw.
4 (language adj3 delay\$).tw.
5 communicat\$.tw.
6 (speech adj3 disorder\$).tw.
7 childhood schizophrenia.tw.
8 kanner\$.tw.
9 asperg\$.tw.
10 exp Developmental Disorder/
11 exp Interpersonal Communication/
12 or/1-11
13 exp GLUTEN/
14 exp CASEIN/
15 (gluten\$ or casein\$).tw.
16 or/13-15
17 clin\$.tw.
18 trial\$.tw.
19 (clin\$ adj3 trial\$).tw.
20 singl\$.tw.
21 doubl\$.tw.
22 trebl\$.tw.
23 tripl\$.tw.
24 blind\$.tw.
25 mask\$.tw.
26 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).tw.
27 randomi\$.tw.
28 random\$.tw.
29 allocat\$.tw.
30 assign\$.tw.
31 (random\$ adj3 (allocat\$ or assign\$)).tw.
32 crossover.tw.
33 32 or 31 or 27 or 26 or 19
34 exp Randomized Controlled Trial/
35 exp Double Blind Procedure/
36 exp Crossover Procedure/
37 exp Single Blind Procedure/
38 exp RANDOMIZATION/

EMBASE

39 34 or 35 or 36 or 37 or 38 or 33

40 12 and 16 and 39

Table 4

PsycINFO searched 1971 to April 2007

PsycINFO
PsycINFO searched via Silverplatter 1971 to April 2007
#11 (((random*)or(trial*)) and (((gluten)or(casein*)) and (((language near delay*)or(communicat*)or(speech near disorder*)) or ((autis*)or(pdd)or(pervasive developmental disorder*)) or ("Communication-" in MJ,MN) or (explode "Pervasive-Developmental-Disorders" in MJ,MN) or ((childhood schizophrenia)or(kanner*)or(asperg*)))
#10 ((random*)or(trial*))
#9 ((gluten)or(casein*)) and (((language near delay*)or(communicat*)or(speech near disorder*)) or ((autis*)or(pdd)or(pervasive developmental disorder*)) or ("Communication-" in MJ,MN) or (explode "Pervasive-Developmental-Disorders" in MJ, MN) or ((childhood schizophrenia)or(kanner*)or(asperg*)))
#8 (((language near delay*)or(communicat*)or(speech near disorder*)) or ((autis*)or(pdd)or(pervasive developmental disorder*)) or ("Communication-" in MJ,MN) or (explode "Pervasive-Developmental-Disorders" in MJ,MN) or ((childhood schizophrenia)or(kanner*)or(asperg*)))
#7 ((language near delay*)or(communicat*)or(speech near disorder*)) or ((autis*)or(pdd)or(pervasive developmental disorder*)) or ("Communication-" in MJ,MN) or (explode "Pervasive-Developmental-Disorders" in MJ,MN) or ((childhood schizophrenia)or(kanner*)or(asperg*))
#6 (childhood schizophrenia)or(kanner*)or(asperg*)
#5 (language near delay*)or(communicat*)or(speech near disorder*)
#4 (autis*)or(pdd)or(pervasive developmental disorder*)
#3 "Communication-" in MJ,MN
#2 explode "Pervasive-Developmental-Disorders" in MJ,MN
#1 (gluten)or(casein*)

Table 5

Risk of bias - Knivsberg 2002

Item	Description	Reviewers' judgment
Sequence generation	Quote: 'twenty children were matched pairwise according to age, cognitive level and severity of autistic behavior' (p.248, col.1). '... the participating children were matched pair-wise and then randomly assigned to a group' (p.248, col.2). Comment: Random allocation. Though not reported in paper, reviewers established via contact with authors that allocation was by tossing of a coin	Allocation sequence adequately generated
Allocation concealment	Quote: 'Professionals outside the project randomly assigned children to the diet group or the control group' (p.250, col.1). Comment: Assignments could not have been predicted based on the result of coin tosses by external personnel	Allocation was adequately concealed
Blinding of participants, personnel and outcomes Assessments should be made for each main outcome (or class of outcomes)	Participants not blinded. Personnel - the project leader 'met parents and children in their homes' (p.249, col.3) and matched participants on age, cognitive level and severity of autistic symptoms, but 'had no contact with the families during the experimental period and did not know which children belonged to which group until the formal testing and interviews had been repeated' (p.250, col.2). Outcomes - the identity of the person(s) carrying out the endpoint assessments was not stated specifically in the paper but may have been the project leader, nor whether they were blind to allocation status of the participants. It was unclear who performed the statistical analysis and whether he/she was blind to allocation status of the participants	Knowledge of the allocated interventions was to some extent prevented during the study
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes)	Quote: Outcomes are derived using an observation scheme: the Diagnosis of Psychotic Behavior in Children (DIPAB). Authors report 'for Child 2 in the diet group and Child 12 in the control group, Questions 1, 2, and 3 could not be answered and were consequently registered as missing' (p. 250, col.3). However, no details are given about how this missing data was handled	It was unclear how incomplete outcome data were addressed
Selective outcome reporting	There was no indication that outcomes were reported selectively	The report of the study were free of suggestion of selective outcome reporting
Other sources of bias	Authors note a number of limitations to the study including that 'monitoring of the compliance with diet was not carried out' (p.254, col.1), difficulty deciding whether 'changes are due to intervention or maturation' (p.254, col.1), and the possibility of a placebo effect. Each of these has the potential to introduce bias	Apart from the potential sources bias acknowledged by the authors the study was apparently free of other problems that could put it at a high risk of bias

Table 6

Risk of bias - Elder 2006

Item	Description	Reviewers' judgment
Sequence generation	Quote: '... following a screening evaluation, the GCRC data manager randomly assigned participants who met the inclusion criteria to either the GFCF or a placebo diet' (p.417, col.3). No further details given. Comment: Sequence generation probably done adequately, although no information available on method of randomization	It seems probable that the allocation sequence was adequately generated
Allocation concealment	Comment: Not possible to assess since no details given on method of randomization	Insufficient information to decide whether allocation was adequately concealed
Blinding of participants, personnel and outcomes Assessments should be made for each main outcome (or class of outcomes)	Quote: 'Children, parents, and all of the investigative team except for the data manager and dietician were blind to the dietary order' (p.417, col.2). Quote: 'Before unblinding, parents were asked to comment on whether they thought their child was on the GFCF diet the first or second 6 weeks. Five were correct, two had 'no idea', and six were incorrect' (p.418, col.2). Comment: Probable that all except data manager and dietician were blind to allocation. Adequacy of blinding was tested satisfactorily for the parents	Knowledge of the allocated interventions was adequately prevented during the study
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes)	Quote: The authors state that, of the 15 randomized, 'thirteen of the children completed the 12-week protocol' (p.416, col.1). They '... employed a missing at random model for the three of 15 subjects whose week 12 or week 6 data were incomplete on a major variable' (p.418, col.2). Comment: Additional information that might support the use of a 'missing at random' model was not provided	Unclear
Selective outcome reporting	There was no indication that outcomes were reported selectively	The report of the study were free of suggestion of selective outcome reporting
Other sources of bias	Authors note a number of limitations to the study including that: (a) the sample was small in size and was heterogeneous 'possibly contributing to a Type 2 error' (p. 419, col.1) (b) there was occasional noncompliance with 'several reports of children 'sneaking food' from siblings or classmates' (p.419, col.1) (c) the duration of treatment was relatively short (12 weeks), given that there are 'clinical reports of some children who respond to the GFCF diet quickly, while others take several weeks before behavioral effects are detectable' (p.419, col. 2). (d) the possibility of a placebo effect Each of these has the potential to introduce bias	Apart from the potential sources of bias acknowledged by the authors, the study was apparently free of other problems that could put it at a high risk of bias