SYSTEMATIC REVIEW OF DIETARY INTERVENTIONS IN AUTISM SPECTRUM DISORDER

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SUBMITTED: February 2013

A mini-dissertation submitted in the Faculty of Health Sciences, University of the Free State, in partial fulfilment of the requirements for the degree MSc. Dietetics

Bloemfontein, 2013

DECLARATION OF INDEPENDENT WORK

I, Cornelia King, identity number 8703220017082 and student number 2005065467, do hereby declare that the mini-dissertation hereby submitted by me for the M.Sc Dietetics degree at the University of the Free State (Systematic review of dietary interventions in autism spectrum disorders) is my independent effort and has not previously been submitted for a degree at another university/ Faculty. I furthermore waive copyright of the mini-dissertation in favour of the University of the Free State.

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Signature Date

ACKNOWLEDGEMENTS

I hereby wish to express my sincere appreciation and gratitude to the following persons that made this study possible:

My supervisor and co-supervisor, Prof C Walsh and Dr L van den Berg, for their competent guidance and mentorship. Thank you for your continual encouragement, constructive criticism, invaluable advice, support and friendship.

My parents, David and Coreen King, for all their guidance, love and support in the past three years. Thank you for the opportunity that you gave me to be able to study, and for encouraging me throughout my studies.

My brother, Ernest King, for your love and support, and for being the brother I can look up to.

All my friends, especially Chris and Yvette, for your invaluable support and friendship during this study.

My Heavenly Father, for Your unfailing love and grace, for the opportunity and blessings, for the friends that supported me and the courage to know that with You all things are possible. *"...man does not live from bread alone but on every word that comes from the mouth of the Lord." Deut. 8:3.* To You be all the glory and praise.

LIST OF ABBREVIATIONS

AA	Arachadonic acid
ABA	Applied Behavioural Analysis
ABC	Aberrant Behaviour Checklist
ADAH-IV	Attention-Deficit Hyperactivity Disorders – IV rating scale
ADDM	Autism and Developmental Disabilities Monitoring
ADHD	Attention-Deficit/ Hyperactivity Disorder
ADI-R	Autism Diagnostic Interview-Revised
ADOS-G	Autism Diagnostic Observation Scale-generic
ARS	Additional Rating Scale
ASAS	Australia Scale of Asperger's Syndrome
ASD	Autism Spectrum Disorders
ASSQ	Autism Spectrum Screening Questionnaire
ATEC	Autism Treatment Evaluation Checklist
BASC	Behaviour Assessment System for Children
BSE	Behaviour Summarized Evaluation
CAM	Complementary and Alternative methods of treatment
CAST	Childhood Asperger's Syndrome Test
CARS	The Childhood Autism Rating Scale
CBCL	Child Behaviour Checklist
CCDI	Chinese Child Developmental Inventory
CCTT	Child's Colour Trials Test
CDC	Centres for Disease Control and Prevention
CGI-I	Clinical Global Impression Scale of Improvement
CHAT	The Checklist for Autism in Toddlers
DA	D-arabinitol

DA/LA	D-/ L-arabinitol
DHA	Docohexanoic acid
DIPAB	Diagnosis of Psychotic Behaviour in Children
DMSA	Dimercapto Succunic acid
DMG	Dimethylglycine
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, Third Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text revision
EBP	Evidence-based practices
ECOS	Ecological Communication Orientation Scale
EEG	Eletroencephalogram
EPA	Eicosopentanoic acid
FPT	The Five Point Test
FOA/WHO	Food and Agricultural Organization of the United Nations and World Health Organization
GARS-2	The Gilliam Autism Rating-Scale – Second edition
GBRS	Global Behaviour Rating Scale
GERD	Gastro-oesophageal reflux disease
GFCF	Gluten-free, casein-free
GP	General Practitioner
ICD-10	International Classification of Diseases, Tenth Revision
IQ	Intelligence quotient
K-ABC	Kauffmann Assessment Battery for Children
MCDI	MacArthur Communication Developmental Inventory
M-CHAT	The Modified Checklist for Autism in Toddlers
MCT	Medium chain triglyceride
MMR	Measels-mumps-rubella

NICHD	National Institute of Child health and Human Development
PASS	Parental Satisfaction Questionnaire
PDD	Pervasive Developmental Disorders
PDD-BI	Pervasive Developmental Disorder Behaviour Inventory
PDD-NOS	Pervasive Developmental Disorder – Not Otherwise Specified
PDDST	The Pervasive Developmental Disorder Screening Test-Stage 1
PIA-CV	Parental Interview for Autism – Clinical Version
PPVT-III	Peabody Picture Vocabulary Test – Third Edition
PUFA	Polyunsaturated fatty acid
SALT	Systematic Analysis of Language Transcripts
SAS	Severity of Autism Scale
SCQ	Social Communication Questionnaire
SSRI	Selective serotonin reuptake inhibitors
STAT	Screening Tool for Autism in Toddlers and Young Children
ToC	The Tower of California Test
USA	United States of America
UPL	Urinary peptide level
UK	United Kingdom
VABS	Vineland Adaptive Behavioural Scale
WHO	World Health Organization

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Part A

PROTOCOL

TABLE OF CONTENTS

1. INTRODUCTION

Autism spectrum disorders (ASD) are a group of neurobiological developmental disabilities (NICHD, 2005: 2) characterized by, and diagnosed according to behavioural presentation (Martins *et al*., 2008: 1878). Generally diagnosed before the age of three years, ASD are likely to be visible throughout the lifespan of the affected individual (NICHD, 2005: 2). According to the Centers for Disease Control and Prevention (CDC), persons with ASD present with 'impairments in social interaction and communication and a wide array of restricted, repetitive and stereotyped patterns of behaviour' (CDC, 2012: 2). According to the most recent data published by the Autism and Developmental Disabilities Monitoring (ADDM) Network, an active surveillance system that estimates the prevalence of ASD in eight year old children in the United States of America (USA), one in every 88 children in the USA has an ASD (CDC, 2012: 1). This number varies around the globe with data from the latest epidemiologic studies conducted in Denmark, the United Kingdom (UK), Canada and Korea indicating a prevalence of: one in 188 children in Denmark (Ellefsen *et al.,* 2007: 437), one in 86 children in the UK (Baron-Cohen *et al*., 2009: 500), one in 126 children in Canada (Lazoff *et al*. 2010: 715) and one in every 38 children in Korea (Young *et al.,* 2011: 904). The prevalence in Australia is estimated to vary between one in 280 children and one in 1041 children (Williams *et al.*, 2008: 504); this variant being due to the diversity in the methods of diagnosis and treatment used by the different states and territories in Australia (Williams *et al.,* 2008: 505). No epidemiologic study to determine the prevalence of ASD has yet been conducted in South Africa (Bakare and Munir, 2010: 208).

ASD occur in all racial/ ethnic groups with only a slightly higher prevalence in non-Hispanic white children than in other racial/ ethnic groups in the USA (CDC, 2012: 16 - 17). The ADDM network has, as was indicated by the same group in 2009 (CDC, 2009: 1), confirmed the significantly higher prevalence of ASD in males. According to the ADDM network one in 54 boys have an ASD, whereas only one in 252 girls have an ASD (CDC, 2012: 16). Males are thus four to five times more likely than females to be autistic (CDC, 2012: 16).

The prevalence (or diagnosis) of ASD is thought to be increasing. When compared to data previously published by the ADDM network (in 2007 and 2009) an increase of 78% was noted, in the six year time period between 2002 and 2008 when the epidemiologic studies were conducted (CDC, 2012: 13 - 14). Researchers are, however, doubtful whether there truly has been an increase in the prevalence, and whether the greater awareness (both in the medical profession and by the public), better diagnostic criteria and easier access to services have not contributed to the greater number of persons diagnosed with ASD annually (CDC, 2012: 1; NICHD, 2005: 4). Irrespective of the increased prevalence of ASD, the causes and risk factors for these disorders are still largely unknown. Once thought to be due to bad parenting, psychological trauma and physical abuse (Ritvo, 1983: 103), extensive research over the past two decades has identified environmental, biologic and genetic factors to be the most likely causes of ASD (NICHD, 2005: 3). Measles-mumps-rubella (MMR) vaccines and mercury poisoning were also recently thought to be the potential causes of ASD, but further epidemiological studies have not confirmed this link (Taylor *et al.,* 2002: 393 - 396; Madsen *et al.,* 2002: 1477 - 1482). More research in this regard is thus required.

ASD are part of the broader category of Pervasive Developmental Disorders (PDD) and include autistic disorder (classic autism), Asperger's syndrome, Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS), Rett's syndrome and childhood disintegrative disorder (Muhle *et al.,* 2004: 473; WHO, 1992: 40). Although the signs and symptoms of this group of disorders are similar, the disorders vary slightly from one another according to the time of onset, the developmental areas affected and the severity of the symptoms (Muhle *et al.,* 2004: 473). Behavioural symptoms with which children with ASD can present can be divided into the following categories: communication issues, social issues, bizarre or repetitive behaviour, motor issues, sensory overload, sensory issues, self-injurious behaviour and safety issues (Help Autism Now Society, 2011: 7). Examples of these behavioural traits include the lack of imaginative play, the inability to initiate social interaction and thus no or little interest in play with other children, the avoidance of affection, flapping of hands, rocking from side to side, head-banging, self-biting and an unwillingness to change daily activities and routine (Help Autism Now Society, 2011:7 - 28).

With as many as 40% of autistic children being unable to talk, and a further 25% to 30% of children presenting with a deterioration in their language skills after the age of 12 to 18 months, impairments in communication skills, together with impairments in social skills, might be some of the first warning signs for ASD (Johnson, 2004: 115). Literature suggests that behavioural problems, such as self-injury, aggression and an overall change in the state of well-being, are closely related to the presence of pain and discomfort (Buie *et al.,* 2010: S7 - S8). Even though many other reasons (for example biochemical imbalances, genetic reasons, sensory stimulation and frustration) can be stated for the occurrence of behavioural problems (Edelson, [n.d]: online.), these should be regarded as a possible indication of illness, pain or discomfort (since autistic children are unable to communicate their needs effectively) (Buie *et al.,* 2010: S7 - S8).

Persons with ASD might also present with gastrointestinal related symptoms. In a review paper published in 2005 by Erickson *et al.* the question whether gastrointestinal symptoms should be regarded as one of the set signs and symptoms with which persons with ASD can present, was assessed (Erickson *et al.,* 2005: 713 - 727). In 2010 a multidisciplinary panel, led by gastroenterologist Dr Timothy Buie, came to the same conclusion as Erickson *et al*., namely that even though the presence of gastrointestinal related symptoms are slightly higher (varying between 1% to 20% for the different gastrointestinal symptoms (Kushak *et al.,* 2005)) in autistic individuals than their non-autistic peers, no clear relation can be made between gastrointestinal upset and ASD (Buie *et al.,* 2010: S3). The gastrointestinal symptoms with which children with ASD can present are similar to those seen in non-autistic children and include chronic constipation and encopresis due to constipation, abdominal pain, diarrhoea, gastro-oesophageal reflux disease (GERD), abdominal bloating, and pathologic problems such as inflammation of the gastrointestinal tract and abnormalities of the enteric nervous system (Buie *et al.,* 2010: S3).

With about a 10% greater occurrence of feeding problems or food selectivity in children on the autism spectrum (Ibrahim *et al.,* 2009: 682), it is commonly believed that children with ASD have a poor nutritional status. According to studies conducted by Johnson *et al.* (2008: 437 - 488), Lindsay *et al.* (2006: 204 - 209), Field *et al.* (2003: 299 - 304), Ahearn *et al.* (2001: 505 - 511), and Raiten and Massaro (1986: 133 - 143) this is not the case. Results of

these studies indicate that children with ASD, even when following a restricted or selective diet, are able to have a daily intake sufficient to meet their nutrient requirements. Lindsay *et al.* (2006:208) have however found variability in the calcium intake, and Johnson *et al.* (2008:445) established that autistic children consumed fewer vegetables, resulting in an insufficient vitamin K intake. The limitations and the relatively small sample sizes of these studies should however be taken into consideration. Johnson *et al*. (2008:446) concluded that larger studies with more direct measures of food intake are required to determine the true nutritional status of children with ASD. A thorough nutrition evaluation (including weight, length or stature, behavioural symptoms and changes in behaviours, and a thorough diet history) is thus required (Buie *et al*., 2010:S3).

1.1 Rationale for the study

ASD are a treatable, but unfortunately not curable group of disorders (Baron-Cohen *et al.*, 2001:5). Current treatment includes educational intervention (such as applied behavioural analysis, structured teaching programmes, speech and language therapy and occupational therapy), medical treatment (which involves the treatment of certain symptoms, such as irritability, hyperactivity and impulsivity with medication), dietary treatment, and complementary and alternative methods (Myers and Johnson, 2007:1163 - 1174). The treatment options of parents are almost limitless due to on-going desperate attempts to cure ASD, especially when taking complementary and alternative methods into considerations. The following dietary interventions have been recommended in the popular media for the treatment of ASD: gluten/ casein-free diet, yeast-free diet, specific carbohydrate diet, elimination diet, ketogenic diet, low oxalate diet, avoidance of food colourants, detoxification diet and detoxification therapies such as chelation, and supplementation of antifungal agents, digestive enzymes, probiotics, omega-3 fatty acids, vitamin A, vitamin C, vitamin B_6 together with magnesium, folic acid, vitamin B_{12}, carnosine, inositol and/ or other minerals (Myers and Johnson, 2007:1173; Autism Nutrition, 2012: online; Health Communities, 2012: online; Treating Autism: 2012: online; Wisconsin Institute of Nutrition, 2012: online; Wikipedia, 2012: online).

In the light of the Hippocratic Oath taken by health care practitioners, particularly in terms of nonmaleficence, scientifically (or evidence) based guidelines for the dietary treatment of children with ASD are required. As the main objective of this study, a systematic search strategy will be applied to assess the above mentioned dietary treatment methods for ASD using peer-reviewed scientific studies in order to ensure that dietary guidelines and interventions are evidence-based. Relevant recommendations for dietary management of children with ASD and further research will also be made.

1.2 Aim of the study

The aim of the review is to identify and critically appraise dietary interventions currently being suggested in peer-review literature for the treatment of the signs and symptoms related to ASD in children aged birth to 18 years.

1.3 Objectives

The primary objective of this review is to compare the impact of dietary interventions on the signs and symptoms with which children with ASD present. Secondary objectives include ascertaining whether differences exist between the dietary interventions in terms of growth and development, nutritional status and general well-being of the child; as well as, the sustainability of the diet.

2. METHODS AND DESIGN

2.1 Study design

A systematic review of peer-reviewed scientific studies investigating the dietary treatment of children with ASD will be conducted. If appropriate, a meta-analysis will also be undertaken.

2.2 Criteria for selecting studies

The following inclusion and exclusion criteria will be taken into account when identifying all relevant studies. In order to ensure that all possible studies are included in this review, broad inclusion criteria with regards to the study design will be used:

Inclusion criteria:

- *Type of study*: Both randomized and non-randomized controlled trials will be included. The number of studies conducted as randomized controlled trials might be limited due to the relatively small amount of research done on this topic. Even though randomized controlled trials are the 'gold standard' in assessing the effects of an intervention, both types of trials will be included to thus ensure a sufficient study sample. Randomized and non-randomized data will however be interpreted separately to limit the possibility of research bias.
- *Population*: Infants, children and adolescents (up to the age of 18 years) who have participated in a study designed to evaluate the impact of a specific dietary intervention on the signs and symptoms related to ASD will be included.
- *Types of intervention*: All studies designed to evaluate the impact of a specific dietary intervention on the signs and symptoms related to ASD will be included.
- *Types of outcome measures*:
  - The primary outcome variables will be those related to the overall impact of the dietary intervention on the signs and symptoms related to ASD.
  - The secondary outcomes include those variables which are likely to respond to changes in the diet, namely growth and development, nutritional status and the general well-being of the child (as perceived by the study authors). The sustainability of the diet (as perceived by the authors) will also be noted.
- *Language of publication:* Only studies published in English will be included in this review; translation of non-English articles might not be viable in the time period allocated for this systematic review. Non-English articles with an English abstract will also be excluded due to the possibility of the abstract not containing sufficient information.
- *Other data*: All relevant studies published between January 1990 and July 2012 will be included in this review.

Exclusion criteria:

- All studies focused on persons with ASD older than the age of 18 years.
- All studies with a study population which includes children on the autistic spectrum with medical conditions not related to ASD.
- All non-English studies.
- All studies published outside of the given time period.

2.3 Identification of eligible studies and data extraction

2.3.1 Search strategy, screening and review process

The following three-part search strategy will be used to identify all eligible studies: Firstly, electronic bibliographic databases will be searched for published articles. Secondly, search trial registers will be searched for ongoing and recently completed trails, and finally the reference lists of all eligible studies will be screened for any possible appropriate trials. Databases which will be used will include EbscoHost (including MEDLINE, HealthSource (academic edition) and CINAHL), Cochrane (Cochrane Database of Systematic reviews, Cochrane controlled trials register), Pubmed and Science Direct. The following search terms will be used to seek eligible studies from these databases: autism OR autistic OR "autism spectrum disorders" OR ASD AND "dietary intervention" OR "dietary treatment" OR diet OR nutrition OR supplementation OR "gluten-casein-free diet" OR "vitamin and mineral supplementation" OR "omega-3 supplementation" OR "elimination diet" OR "food colorants" OR "yeast-free diet" OR "ketogenic diet" OR "low oxalate diet" OR "specific carbohydrate diet" OR "detoxification diet" OR chelating OR "antifungal agents" OR "digestive enzymes" OR probiotics OR "folic acid" OR "vitamin B_6 and magnesium" OR "vitamin A" OR "vitamin C" OR "vitamin B_{12}" OR carnosine OR inositol AND signs OR symptoms OR behaviour AND child OR children OR "birth to 18 years".

At first all studies will be screened on the basis of their title, after which abstracts for eligible studies will be obtained. Two other reviewers with experience in conducting systematic reviews, namely Professor C Walsh and Doctor L van den Berg (both registered dietitians), will also conduct the three-part search strategy to ensure that no studies are overlooked. Full-text articles will be retrieved for all studies which adhere to the inclusion criteria. All eligible studies will be evaluated and discussed by the three reviewers to ensure relevance.

A table detailing all studies excluded during the systematic search process, as well as the reason for exclusion, will be compiled.

2.3.2 Quality assessment

The quality of each eligible study will be assessed using an evaluation tool designed by Reichow *et al.*, (2008: 1311-1319): Evaluative Method for Evaluating and Determining Evidence-based practices in Autism. This tool was designed with the aim of supporting researchers and practitioners in determining evidence-based practices (EBP) for autistic children (Reichow *et al.*, 2008: 1312). The tool consists of three instruments: 1) Rubrics for the evaluation of research report rigor, (2) guidelines for the evaluation of research report strength, and (3) criteria for the determination of EBP (Reichow *et al.*, 2008: 1312)'. Below is a short description of each instrument:

1) *Rubrics for the evaluation of research report and rigor:* Two rubrics are used to assess the rigor (quality) of the methodological elements of a study, namely a rubric for group research and a rubric for single subject research. The two rubrics are further divided into a primary quality indicators level (assess elements which are deemed critical to assess the validity of a study), and a secondary quality indicators level (assess elements not deemed necessary for evaluating the validity of a study) (Reichow *et al.*, 2008: 1312-1313).
2) *Guidelines for the evaluation of research report strength:* Using the outcome of the first instrument, each study is classified into one of three report strength groups using this instrument. The three groups include: strong research report strength (the study contains solid evidence of high quality reporting), adequate research report strength (study contains strong evidence of good reporting in most areas, but not all), and weak research report strength (study has many missing elements or contains flaws) (Reichow *et al.*, 2008: 1313).
3) *Criteria for the determination of EBP:* In this part the research report strength ratings from all studies evaluated are combined to determine whether the practice is evidence-based (Reichow *et al.*, 2008: 1315).

The tool is attached in appendix A (Reichow, 2011: 38-39). The three instruments will be used as presented; the EBP will however be determined separately for the different methods of dietary intervention being assessed.

2.3.3 Data extraction

Data will be extracted using a screening- and data extraction form (preliminary forms are attached in appendix B and appendix C), and will be summarized in table format using an Excel spread sheet. The data which will be extracted will include study design, method of randomization, study setting and population, inclusion and exclusion criteria, dietary intervention used, other interventions and outcome. An attempt will be made to contact the corresponding author in the case of not all required data reported in the publication.

2.4 Data analysis

The results from the included studies will be stratified according to:

1. Study design:
    - Trial design and quality;
    - The data collection methods and techniques used;
    - Statistical analysis and other methods of analysis used, and the
    - Conflict of interest.

2. Participants (intervention group and control group):
    - Socio-economic and demographic characteristics (for example the age, gender and ethnicity);
    - Type of autism spectrum disorder with which participants is diagnosed;
    - Health status and overall well-being of the participant;
    - Behavioural problems and other symptoms noted, and the
    - Setting and recruitment methods.
3. Intervention
    - Description of dietary intervention used;
    - Frequency, intensity and duration of the intervention, and the
    - Interventions, other than the dietary interventions used.
4. Outcomes
    - Primary outcome, namely the impact that intervention has on the signs and symptoms related to autism spectrum disorders, and

- Secondary outcomes, namely the differences noted in growth and development, nutritional status and general well-being of the participant, as well as the sustainability of the diet.

The various dietary interventions will be assessed and compared according to this analysis. The impact of each dietary intervention will be determined statistically in a meta-analysis, provided that there is sufficient homogeneity across the studies with regards to the target population, intervention, comparison groups, and outcomes measured. As different dietary interventions will be assessed, the homogeneity of each type of intervention will be assessed individually.

3. ETHICS AND COMMUNICATION

3.1 Ethics

This protocol will be submitted for ethical approval to the Ethics Committee of the Faculty of Health Sciences, University of the Free State (South Africa).

3.2 Reporting and implementation

The final report will be compiled in the form of a scientific article (taking the publisher's instructions to authors into consideration) to be submitted for publication in two international- and one South African peer-reviewed scientific journals. These journals include the *Journal of Autism and Developmental Disorders*, *Autism*, and *South African Journal of Clinical Nutrition.* The article will be submitted for publication within six months after completion and authorship will be as follows: Miss C King as first author, and Prof. C. Walsh and Dr. L. van den Berg as fellow authors.

All attempts will be made to avoid plagiarism during the research process and in the writing of the dissertation and scientific article. Recognition will be given to all authors.

4. LOGISTICS

4.1 Timeline

Estimates on the start and end dates for the conduct of the systematic review (please note that some of the stages do overlap):

Stages of writing the dissertation	Time period allocated to each stage
Proposal development	03 January 2012 - 30 June 2012
Ethical approval	01 July 2012 - 31 July 2012
Writing of literature review	01 August 2012 - 31 August 2012
Data search	01 August 2012 - 17 August 2012
Analysis	18 August 2012 - 14 September 2012
Writing of results and dissertation	01 September 2012 - 05 October 2012
Writing of journal article	01 October 2012 - 19 October 2012
Editing and submission	20 October 2012 - 31 October 2012

4.2 Budget

All financial expenses will be the responsibility of the first author, Miss. C. King.

Item	Total cost
Interlibrary loans and postage	R 500-00
Stationary	R 150-00
Printing	R 500-00
Binding	R 1000-00
Total	***R 2150-00***

5. STRUCTURE OF DISSERTATION

The mini-dissertation will include the following sections:

- Part A: Protocol.
- Part B: Literature review. This section will provide information on the different ASD's, the prevalence of these disorders and the signs and symptoms related to these disorders. The methods of diagnosis, as well as current methods of treatment, this including educational therapy, medical treatment, dietary intervention and alternative and complementary methods, will be discussed.
- Part C: Systematic review. This is the research publication, and will include a description of the systematic review process, as well as a presentation and discussion of the findings.
- Part D: Summary.

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APPENDIX A

Evaluative Method for Evaluating and Determining Evidence-based practices in Autism

(Reichow 2011: 38-39; Reichow *et al.*, 2008: 1311 -1319)

EVALUATIVE METHOD FOR DETERMINING EVIDENCE-BASED PRACTICES IN AUTISM

INSTRUMENT 1: Rubrics for the Evaluation of Research Report Rigor

RATING FORM FOR STUDIES USING GROUP RESEARCH DESIGN STUDIES:

Study	Essential Quality Indicators							Desirable Quality Indicators								Research Report Strength
	PART	IV	CC	DV	LRQ	STAT		RA	IOA	BR	FID	ATR	G/M	ES	SV	

*High **(H)** quality rating:* Study meets all criteria
*Acceptable **(A)** quality rating*: Study meets the most of the criteria but omits specific details
*Unacceptable **(U)** quality rating***:** Study does not meet the criteria

Definition of group research quality indicators

Quality indicator	Definition

PART: Participant characteristics	• Age and gender were provided for all participants;
	• Specific diagnostic information was provided for all participants with autism;
	• And if applicable,
	  • standardized test scores were provided, and
	  • information on the characteristics of the interventionist was provided

DV: Dependent variable	• Dependent measures were described with operational and replicable precision; • Showed a clear link to the treatment outcome, and • Were collected at appropriate times.
IV: Independent variable	• Information about the treatment was provided with replicable precision (if a manual was used, this was always given a high quality rating).
BSLN: Baseline condition	All baselines: • Encompassed at least three measurement points; • Appeared through visual analysis to be stable; • Had no trend or a counter therapeutic trend, and • Were operationally defined with replicable precision.
CC: Comparison condition	• The conditions for the comparison group were defined with replicable precision, including, at a minimum, a description of any other interventions participants received.

LRQ: Link between research question and data analysis	• Data analyses were strongly linked to the research question(s), and • The data analysis used correct units of measure (i.e., child level, teacher level, etc.) on all variables.
STAT: Use of statistical test	• Proper statistical analyses were conducted for each statistical measure with an adequate power and a sample size of n C 10
RA: Random assignment	• Participants were assigned to groups using a random assignment procedure
IOA: Interobserver Agreement	• IOA was collected across all conditions, raters, and participants with inter-rater agreement at or above .80, and a minimum of Good reliability (j C .60). Psychometric properties of standardized tests were reported and were equal or greater than .70 agreement with a j C .40
BR: Blind raters	• Raters were blind to the treatment condition of the participants
FID: Fidelity	• Procedural fidelity or treatment fidelity was continuously assessed across participants, conditions, and implementers, and if applicable, had measurement statistics at or greater than .80
ATR: Attrition	• Articulation was comparable (did not differ between groups by more than 25%) across conditions and less than 30% at the final outcome measure
G/M: Generalisation or maintenance	• Outcome measures were collected after the final data collection to assess generalization and/or maintenance
ES: Effect size	• Effect sizes were reported for at least 75% of the outcome measures and were equal or greater than .40
SV: Social validity	The study contained at least four of the following: • DVs were socially important (i.e., would society value the changes in outcome of the study), • The intervention was time and cost effective (i.e., did the ends justify the means), • Comparisons were made between individuals with and without disabilities, • The behavioural change was large enough for practical value (clinically significant), • Consumers were satisfied with the results, • People who typically come in contact with the participant manipulated the IVs, • The study occurred in natural contexts

Rubric for studies using single subject experimental designs continues of following page...

RATING FORM FOR STUDIES USING SINGLE SUBJECT EXPERIMENTAL DESIGNS:

Study	Essential Quality Indicators							Desirable Quality Indicators						Research Report Strength
	PART	DV	IV	BSLN	VIS ANAL	EXP CON		IOA	KAP	BR	FID	G/M	SV	

*High **(H)** quality rating:* Study meets all criteria
*Acceptable **(A)** quality rating*: Study meets the most of the criteria but omits specific details
*Unacceptable **(U)** quality rating***:** Study does not meet the criteria

Definition of single subject research quality indicators

Quality indicator	Definition
PART: Participant characteristics	• Age and gender were provided for all participants; • Specific diagnostic information was provided for all participants with autism; • If applicable, standardized test scores were provided, and, • Information on the characteristics of the interventionist was provided.
DV: Dependent variable	• Dependent measures were described with operational and replicable precision; • Showed a clear link to the treatment outcome, and • Were collected at appropriate times.
IV: Independent variable	• Information about the treatment was provided with replicable precision (if a manual was used, this was always given a high quality rating)
BSLN: Baseline condition	All baselines: • Encompassed at least three measurement points, • Appeared through visual analysis to be stable, • Had no trend or a counter therapeutic trend, and • Were operationally defined with replicable precision
CC: Comparison condition	• The conditions for the comparison group were defined with replicable precision, including, at a minimum, a description of any other interventions participants received
VIS ANAL: Visual analysis	All relevant data for each participant was graphed. Inspection of the graphs revealed : • All data appeared to be stable (level and/or trend), • contained less than 25% overlap of data points between adjacent conditions, unless behavior was at ceiling or Floor levels in previous condition, and • Showed a large shift in level or trend between adjacent conditions which coincided with the implementation or removal of the IV (note, if there was a delay in change at the manipulation of the IV, the delay was similar across different conditions and/or participants [±50% of delay])

EXP CON: Experimental control	There were: • At least three demonstrations of the experimental effect, • At three different points in time, and • Changes in the DVs covaried with the manipulation of the IV in all instances of replication (note, if there was a delay in change at the manipulation of the IV, the delay was similar across different conditions or participants [±50% of delay]).
IOA: Interobserver Agreement	• IOA was collected on at least 20% of sessions across all conditions, raters, and participants with inter-rater agreement at or above .80
BR: Blind raters	• Raters were blind to the treatment condition of the participants.
FID: Fidelity	• Procedural fidelity and/or treatment fidelity was continuously assessed across participants, conditions, and implementers with reliability at or greater than .80
G/M: Generalisation or maintenance	• Outcome measures were collected after the conclusion of the intervention to assess generalization and/or maintenance.
SV: Social validity	The study contained at least four of the following: • DVs were socially important (i.e., would society value the changes in outcome of the study), • The intervention was time and cost effective (i.e., did the ends justify the means), • Comparisons were made between individuals with and without disabilities, • The behavioral change was large enough for practical value (clinically significant), • The consumers were satisfied with the results, • People who typically come in contact with the participant manipulated the IVs, (g) the study occurred in natural contexts
KAP: Kappa	• Kappa was calculated on at least 20% of sessions across all conditions, raters, and participants with a score at or greater than .60 (Good reliability)

Instrument 2 and 3 continues on the following page...

INSTRUMENT 2: Guidelines for the evaluation of the Research Report Strength

Strength of research report	Group research
Strong	Received high quality ratings on all primary quality indicators and showed evidence of four or more secondary quality indicators
Adequate	Received high quality ratings on four or more primary quality indicators with no unacceptable quality ratings on any primary quality indicators, and showed evidence of at least two secondary quality indicators
Weak	Received fewer than four high quality ratings on primary quality indicators or showed evidence of less than two secondary quality indicators

INSTRUMENT 3: Criteria for the determination of EBP

EBP STATUS WORKSHEET:

***Type of dietary intervention:*_____**

Study	Research method	Rigor rating	Successful *N*

Number of group *studies* with strong rigor ratings	= $Group_S$
Number of group *studies* with adequate rigor ratings	= $Group_A$
Number of *participants* from SSED studies with strong rigor ratings	= $Group_S$
Number of *participants* from SSED studies with adequate rigor ratings	= $Group_A$

Formula for determining EBP status

$$(Group_S * 30) + (Group_A * 15) + (SSED_S * 4) + (SSED_A * 2) = Z$$

Points (*Z*)	**0**	**10**	**20**	**30**	**31**	**40**	**50**	**59**	**60+**
EBP Status	Not an EBP				Probable EBP				Established EBP

APPENDIX B

Initial Screening Form

INITIAL SCREENING FORM

A systematic review of dietary interventions in autism spectrum disorder.

Authors: _____

Title: _____

Reference: _____

Level 1: Initial screening

1. Is this paper about the effect of a specific dietary intervention on the signs and symptoms related to autism spectrum disorders (perhaps in addition to other topics):

☐	1.Yes	☐ 1
☐	2.No	
☐	3.Can't tell	

2. What kind of article is this?

☐	1.Dietary intervention outcome evaluation	☐ 2
☐	2.Review of dietary intervention outcome studies (and other research)	
☐	3.Case study	
☐	4.Theoretical or position statement, editorial or book review	
☐	5.Practical guidelines or treatment protocol	
☐	6.Other, specify _____	
☐	7.Can't tell	

If excluded at this level, do not list in table as excluded

Level 2: Eligibility Decisions

1. Does this study include two or more parallel cohorts (groups that received different treatments and were assessed at the same time)?

☐	1.Yes	☐ 3
☐	2.No	
☐	3.Can't tell	

2. Is the experiment a:

☐	1.Randomized controlled trial?	☐ 4
☐	2.Non-randomized controlled trial?	
☐	3. Can't tell	

3. Does this study include the use of a clearly described dietary intervention?

☐	1.Yes: (namely:_____)	☐ 5
☐	2.No	
☐	3.Can't tell	

4. Does it include a study population of children aged birth to 18 years?

☐	1.Yes	☐ 6
☐	2.No	
☐	3.Can't tell	

5. Is the primary presenting problem sign(s) and/ or symptom(s) related to autism spectrum disorders?

☐	1.Yes	☐ 7
☐	2.No	
☐	3.Can't tell	

6. Was the study published between January 1990 and July 2012?

☐	1.Yes	☐ 8
☐	2.No	
☐	3.Can't tell	

7. Was the study published in English?

☐	1.Yes	☐ 9
☐	2.No	

If the study falls out here, it should be listed in the table of excluded studies

Appendix C

Initial data extraction form

INITIAL DATA EXTRACTION FORM

A systematic review of dietary interventions in autism spectrum disorder

Authors: _____

Title: _____

Reference:_____

Level 1: Data Extraction: Study level

Research methods

1. How were comparison/ control groups formed?

☐	1.Random assignment	☐ 1
☐	2.Other, specify_____	
☐	3. Can't tell	

2. If random assignment, specify design

☐	1.Simple/ systematic (individuals)	☐ 2
☐	2.Stratified/ blocked (identify stratifying variables)	
☐	3.Matched pairs (identify matching variables)	
☐	4.Cluster (group) randomised	
☐	5.Other, specify_____	
☐	6.Can't tell	

3. Who performed group assignment?

☐	1.Research staff	☐ 3
☐	2.Medical/ Treatment staff	
☐	3.Can't tell	
☐	4.Other, specify_____	

4. How was random assignment performed?

☐	1.Computer generated	☐ 4
☐	2.Random numbers table	
☐	3.Coins or dice	
☐	4.Other, describe_____	
☐	5.Can't tell	

5. How many separate sites were included in the study?

☐	1.One	☐ 5
☐	2.Two	
☐	3.Three	
☐	4.Four	
☐	5.Five or more	
☐	6.Can't tell	

6. Was random assignment performed in the same way in all sites?

☐	1.Yes	☐ 6
☐	2.No, explain_____	
☐	3.Can't tell	

7. How many intervention groups were there?

☐	1.One (Specialized diet)	☐ 7
☐	2.Two (Specialized diet + what?)_____	
☐	3.Three (Specialized diet + what?)_____	
☐	4.Can't tell	

8. How many intervention groups were relevant for this review?

☐	1.One (Specialized diet)	☐ 8
☐	2.More than one (Explain)_____	

9. How many different control/ comparison groups were there? (i.e. groups that received different treatments)

☐	1.One	☐ 9
☐	2.More than one, explain_____	

10. How many control/ comparison groups are relevant for this review?

☐	1.One	☐ 10
☐	2.More than one, explain_____	

Settings:

11. Location of interventions

☐	1.Developed country	☐ 11
☐	2.Developing country	
☐	3.Both	
☐	4. Can't tell	

12. Location of interventions:

	1.Urban	12
	2.Rural	
	3.Can't tell	

13. Location of interventions

	1.Home	13
	2.Hospital	
	3. Clinic	
	4. School (Preschool/ Primary school/ Secondary School)	
	5.Other, specify_____	

14. Location details

Country:_____ 14

15. Sample size

Number (n) of cases	*Specialized diet*	*Comparison group*	*Total*	*p. and notes*	
Referred to study					15-18
Consented					19-22
Randomly assigned					23-29
Started treatment					30-36
Completed treatment					37-43
Completed post treatment data					44-50
Completed follow-up					51-57

16. Sample characteristics

	Specialized diet	*Control*	*Total*	*p. and notes*	
Gender (% male)					58-64
Age range (years)	-	-	-		65- 76

Race ethnicity

☐	1.White	☐ 77
☐	2.Black	☐ 1
☐	3.Mixed origin	☐ 2
☐	4.Indian	☐ 3
☐	5.Other,_____	☐ 4
☐	6.Not mentioned	☐ 5

Socioeconomic status

☐	1. High	☐ 6
☐	2.Medium	☐ 7
☐	3.Low	☐ 8
☐	4.Not mentioned	☐ 9

17. Were there any differences between the intervention groups and comparison groups at baseline?

☐	1.Yes, describe differences_____	☐ 10
☐	2. No (how do we know?)_____	
☐	3.Can't tell	

18. Was there any analysis of differences between programme treatment completers and drop-outs?

☐	1.Yes	☐ 11
☐	2.No	
☐	3.Can't tell	

If yes, what were the differences?_____ ☐ 12

19. Was there any analysis of differences between control treatment completers and drop-outs?

☐	1.Yes	☐ 13
☐	2.No	
☐	3.Can't tell	

If yes, what were the differences?_____

20. Dietary intervention characteristics

	Min	*Max*	*Mean*	*SD*	*p. and notes*	
Duration of dietary intervention diet:						
Days				.		14-22
Weeks				.		
Months						

Dietary intervention/ specialized diet:_____ 23-24

Description of diet:

1_____ 25-26
2_____ 27-28
3_____ 29-30
4_____ 31-32
5_____ 33-34
6_____ 35-36
7_____ 37-38
8_____ 39-40
9_____ 41-42
10_____ 43-44

21. Where was the food consumed:

- 1.At home 45
- 2.On site 46
- 3.Other, specify_____ 47
- 4.Can't tell 48

22. Describe methods used to ensure that all food was consumed

_____ 49
_____ 50

23. Is there any information on feeding programme adherence?

- 1.Yes, describe_____ 51
- 2.No
- 3.Not sure

Level 2: Outcome measures

1. When was data collected? Mark all that apply (1=yes, 2=no)

☐	Baseline: _____	☐ 52
☐	1st follow-up: _____	☐ 53
☐	2nd follow-up: _____	☐ 54
☐	3rd follow-up: _____	☐ 55
☐	4th follow-up: _____	☐ 56
☐	Post treatment: _____	☐ 57
☐	1st follow-up: _____	☐ 58
☐	2nd follow-up: _____	☐ 59
☐	3rd follow-up: _____	☐ 60
☐	4th follow-up: _____	☐ 61
☐	5th follow-up: _____	☐ 62
☐	Other: _____	☐ 63

2. Who collected data?

☐	1.Research staff	☐ 64
☐	2.Medical/ Treatment staff	
☐	3.Both	
☐	4.Other, specify_____	

3. Were data collected in the same manner for intervention groups and control groups?

☐	1.Yes	☐ 65
☐	2.No (what were the differences?)_____	
☐	3.Can't tell	

Part B

LITERATURE REVIEW

TABLE OF CONTENTS

List of tables included:

1. INTRODUCTION

Autism spectrum disorders (ASD) are a group of complex neurodevelopmental disorders characterized by and diagnosed according to its behavioural presentation (Elder, 2008: 583; Martins *et al.,* 2008: 1878). Likely to manifest before the age of three years (NICHD, 2005: 2), ASD (also referred to as pervasive developmental disorder) are lifelong disorders which effect every area of the affected individual's life (Elder, 2008: 583). According to the Centers for Disease Control and Prevention (CDC) (2012: 2), persons with ASD present with 'impairments in social interaction and communication' and 'restricted, repetitive and stereotyped patterns of behaviour'. No two individuals are, however, the same as evidenced by the wide array of abilities and disabilities reported. These abilities and disabilities vary from being severely impaired to being gifted; being socially aloof and passive to active, but odd; and from being non-verbal to being verbal. Whereas some individuals might be hyposensitive to sensory stimuli, others are hypersensitive; motor-coordination might also vary between being clumsy and being well co-ordinated. Persons with ASDs' behavioural presentation can furthermore be interpreted as intensely abnormal or mildly so (Venter, 2011: 12).

The prevalence of this group of disorders is thought to be escalating. According to the most recent data published by the Autism and Developmental Disabilities Monitoring (ADDM) network the prevalence has increased by 78% during a six year time period between 2002 and 2008 (CDC, 2012: 13 - 14). Researchers are, however, doubtful whether there truly is an increase in the prevalence and whether the greater awareness (both by the medical profession and the public), better diagnostic criteria and easier access to services have not contributed to the greater number of persons diagnosed with ASD annually (CDC, 2012: 1; NICHD, 2005: 4). Regardless, what was once thought to be a rare disability is now globally becoming one of the most frequent childhood neurodevelopment disorders (Fombonne, 2009: 591).

One in every 88 children in the USA has an ASD (CDC, 2012: 1). This number varies around the globe with data from the latest epidemiologic studies conducted in Denmark, the United Kingdom (UK), Canada and Korea indicating a prevalence of one in 188 children in

Denmark (Ellefsen *et al.,* 2007: 437), one in 86 children in the UK (Baron-Cohen *et al*., 2009: 500), one in 126 children in Canada (Lazoff *et al*. 2010: 715) and one in every 38 children in Korea (Young *et al.,* 2011: 904). The prevalence in Australia is estimated to vary between one in 280 children and one in 1041 children (Williams *et al.,* 2008: 504); this variation being due to the diversity in the methods of diagnosis and treatment used by the different states and territories in Australia (Williams *et al.,* 2008: 505). No epidemiologic study has yet been conducted in South Africa (Bakare and Munir, 2010: 208) and the prevalence of ASD is thus, as in many countries around the globe, still unknown in this country.

ASD occur in all racial/ ethnic groups with only a slightly higher prevalence in non-Hispanic white children than in other racial/ ethnic groups (CDC, 2012:16 - 17). The ADDM network has confirmed the significantly higher prevalence of ASD in males (CDC, 2009: 1). According to the ADDM network, one in 54 boys has an ASD, whereas only one in 252 girls have an ASD (CDC, 2012: 16). Males are thus four to five times more likely than females to be autistic (CDC, 2012: 16).

As a life-long disorder which influences every aspect of the individual's life, persons with ASD have greater life- and medical costs than persons without ASD. This was indicated by three separate studies conducted in the UK (Knapp *et al.,* 2009: 317- 336), the USA (Shimabukuro *et al.,* 2007: 546 – 552) and China (Wang *et al.,* 2012: 1 – 7). Knapp *et al.* (2009: 317) studied the economic impact of ASD for the UK as a whole. The costs were shown to be influenced by the prevalence of ASD in the country, the level of intellectual disability of the persons with ASD, the place of residence, medical costs, as well as the total cost of lost productivity due to the disability. Total annual costs amounted to an estimated £2.7 billion (R32.2 billion at an exchange rate of R13.73 for one British Pound Sterling (January 5th 2013) for children (birth to 17 years) and £25 billion (R343.25 billion) for adults (18 years and older) (Knapp *et al.,* 2009: 317). In the USA and China medical expenditures were found to be 4.1 – 6.2 times (Shimabukuro *et al.,* 2007: 546) and 60.8% to 74.7% (Wang *et al.,* 2012: 1) greater in persons with ASD than in persons without ASD. In China behavioural therapy accounted for the greatest portion of the medical costs (Wang *et al.,* 2012: 1). Wang *et al.* (2012: 1) also indicated that up to 38.2% of households with

members diagnosed with an ASD had medical expenses greater than the total annual household income.

ASD are a treatable, but unfortunately not curable group of disorders (Baron-Cohen *et al.,* 2009: 500). Current treatment options include educational interventions, medical treatment, dietary treatment, and complementary and alternative methods of treatment (Myers and Johnson, 2007: 1163 – 1174). This literature review precedes the systematic review and is structured according to the following objectives:

- Defining ASD,
- Understanding the related signs and symptoms,
- Exploring the aetiology of ASD,
- Exploring the methods of diagnosis, and
- Exploring the methods currently suggested for the treatment of ASD.

2. HISTORY OF AUTISM SPECTRUM DISORDERS

The term "autism", from Greek origin and meaning 'living in self', was first used in 1911 by the Swiss psychiatrist Eugen Bleuler to describe 'self-absorption due to poor social relatedness in schizophrenia' (Gupta, 2004a: 14). ASD, as it is known today, was first described by Leo Kanner, a Jewish American psychiatrist and physician, and Hans Asperger, a Viennese paediatrician (Gupta, 2004a: 14). Kanner adopted the term "autism" in 1943 to portray 11 children who he described as 'oblivious to other people, did not talk or who parroted speech, used idiosyncratic phrases, who lined up toys in long rows, and who remembered meaningless facts' (Kanner, 1943: 217). In 1944, Asperger described a condition similar to that portrayed by Kanner, but referred to the condition as 'autistic psychopathy' due to 'severe and characteristic difficulties of social integration' (Gupta, 2004a: 15). Aspergers' work, however, remained unknown until the early 1980's due to the fact that his research papers were ignored by the global academic community as they were written in Germany during the Second World War (Gupta, 2004a: 15).

Controversy and confusion surrounded the use of the term "autism," as this term was initially used to refer to conditions related to schizophrenia (Gupta, 2004a: 15). Both Kanner and Asperger, however, individually accentuated the differences perceived between the new disorder being studied and schizophrenia. Asperger noted that whereas 'both autistic children and schizophrenics have complete shutting off of relations between self and the outside world, the latter have a gradual disintegration of personality while the former have social withdrawal from the start' (Gupta, 2004a: 16). ASD yet remained to be regarded as a type of childhood psychosis or childhood schizophrenia; it was only in the late 1960's that ASD was considered as a condition in itself and not related to schizophrenia. In 1978 Micheal Rutter recommended the first criteria for the diagnosis of ASD. This was incorporated in the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (DSM-III) under the category of infantile autism and the criteria included: '1) social delay or deviance that was not just a function of mental retardation, (2) communication problems, again not as a function of mental retardation, (3) unusual behaviours such as stereotypic movement and mannerisms, and (4) onset before the age of 30 months' (Gupta, 2004a: 17). These diagnostic criteria have been adjusted through the years. The current diagnostic criteria for ASD are discussed in section 6.

3. DEFINITION AND CLASSIFICATION OF AUTISM SPECTRUM DISORDERS

ASD are defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text revision,* (DSM-IV-TR) (a guide to the standard classification of all mental disorders) and the *International Classification of Diseases, Tenth Revision* (ICD-10) (a World Health Organization publication which forms part of the DSM system, stating for each disorder a classification which best reflects the signs and symptoms and a set diagnostic code) as a 'severe and pervasive impairment in several areas of development: reciprocal social interaction skills, communication skills, or the presence of stereotyped behaviour, interests, and activities' (American Psychiatric Association, 2000: 69). Qualitative impairments are also observed and vary in type and degree according to the individual's developmental level and mental age (American Psychiatric Association, 2000: 69). It should,

however, be noted that ASD are categorized by both the DSM-IV-TR and the ICD-10 as pervasive developmental disorders. The term 'ASD' is nonetheless well accepted by both research and professional communities and now commonly replaces the term 'pervasive developmental disorders' (Lord, 2010: 815).

Five DSM-IV-TR subtypes of ASD can be distinguished. These five subtypes, briefly described below, are based upon the number and description of behavioural descriptors and the age of onset (Muhle *et al*., 2004: 473):

1. *Autistic disorder*: Also referred to as early infantile autism, childhood autism, classic autism or Kanner's autism (American Psychiatric Association, 2000: 70; Muhle *et al.,* 2004: 473), autistic disorder is characterized by a 'markedly abnormal or impaired development in social interaction and communication and a markedly restricted repertoire of activity and interests' (American Psychiatric Association, 2000: 70). Although commonly visible after the age of three years, some infants present with a lack of social interaction since birth, or shortly thereafter. The prognosis of this disorder is closely related to the overall intellectual level. Whereas some individuals present with developmental gains, for example an increased interest in social functioning during adolescence, others might present with further deterioration. Only about one-third of all children with autistic disorder grow up to be partially independent adults. Even then problems with social interaction, communication, and interests and activities remain present (American Psychiatric Association, 2000: 73).

2. *Rett's disorder:* Rett's disorder is a rather uncommon disorder and has distinctively only been reported in females. Likely to manifest before the age of four years (usually during the first or second year of life), this lifelong disorder is characterized by a persistent and progressive loss of skill (American Psychiatric Association, 2000: 76). Normal development is usually observed during the prenatal and perinatal period; including normal psychomotor development and head circumference. A decrease in the rate of head growth is typically noted after the age of five months (American Psychiatric Association, 2000: 76), resulting into microcephaly which is a prominent characteristic of Rett's disorder (Accardo,

2004: 135). A significant loss of previously acquired hand skill and problems with the coordination of the movements of the gait and trunk become prominent between the age of five and 30 months as well (American Psychiatric Association, 2000: 76). Rett's disorder has, however, been identified as a specific genetic disorder in the recent past, and will probably be removed from the PDD category in the next revision of the DSM system (Accardo, 2004: 135).

3. *Childhood disintegrative disorder:* Childhood disintegrative disorder is characterized by a distinctive 'regression in multiple areas of functioning following a period of at least two years of apparently normal development' (American Psychiatric Association, 2000: 77). The regression, usually before the age of 10 years, of previously acquired skills is clinically significant and includes at least two of the following areas: expressive or receptive language, social skills or adaptive behaviour, bowel or bladder control, play, or motor skills. Children with childhood disintegrative disorder often present with a loss of skill in all these areas of development (American Psychiatric Association, 2000: 77). Regardless of the presence of several autistic-like traits, childhood disintegrative disorder is now being conceptualized as a neurodegenerative disorder. Comprehensive neurological assessment, rather than educational and behavioural methods, is now being suggested as a method of intervention. It is most likely that childhood disintegrative disorders will also be excluded from the PDD category with the next DSM system revision (Accardo, 2004: 137). Though thought to be under-diagnosed, it is more common among men (American Psychiatric Association, 2000: 78).

4. *Asperger's disorder:* Asperger's disorder, as with other ASDs, is a continuous and lifelong disorder. Though closely related to autistic disorder, the absence of 'clinically significant delays or deviance in language acquisition' is a distinctive factor (American Psychiatric Association, 2000: 80). Asperger's disorder is thus characterized by 'severe and sustained impairment in social interaction and the development of restricted, repetitive patterns of behaviour, interests, and activities' with the absence of a delay in language skills (American Psychiatric Association, 2000: 80). Furthermore, other than in autistic disorder, mental retardation is not commonly observed; occasional cases of mild retardation have, however, been

reported in the past. Motor clumsiness, over-activity and inactivity are frequent, and most individuals with Asperger's disorder have a diagnosis of Attention-Deficit/ Hyperactivity Disorder (ADHD) prior to being diagnosed with ASD (American Psychiatric Association, 2000: 81). Although data is still limited, it does appear that there is an increase in frequency of Asperger's disorder in family members of persons with this disorder. An increased prevalence of other ASD and general social difficulties also appear to be present (American Association, 2000: 82).

5. *Pervasive developmental disorders not otherwise specified (PDD-NOS):* This category is used to describe ASD which do not meet the set criteria for the other ASD subtypes. Thus, severe and pervasive impairment of reciprocal social interaction, verbal and nonverbal communication skills, and stereotype behaviour, interests and activities are present, but not distinct to meet the criteria of ASD, schizophrenia, schizotypal personality disorder, or avoidance disorder. PDD-NOS are also referred to as 'atypical autism' (American Psychiatric Association, 2000: 84).

As mentioned, persons with ASD often present with mental retardation that varies between individuals from mild to profound. A diverse group of other medical condition, such as chromosomal abnormalities, congenital infections, and structural abnormalities of the central nervous system might also be present (American Psychiatric Association, 2000: 69 - 70). The methods of and diagnostic criteria for each of these ASD subtypes are described in section 6.

4. AETIOLOGY OF AUTISM SPECTRUM DISORDERS

Kanner paid little attention to the causes of ASD in his research paper published in 1943. He rather provided a short description of the families of the children first diagnosed with ASD. In the most cases he perceived both the mothers and fathers to be cold-hearted, and thus most

marriages to be 'rather cold' and some as a 'dismal failure'. Parents and grandparents were, furthermore, seen as 'strongly preoccupied' with other abstractions and with limited interest in other people (Kanner, 1943: 250). According to this observation he raised the question as to whether, and to what extent, the parent's 'cold-heartedness' had an influence on the condition of the children (Kanner, 1943: 250). Bruno Bettelheim further elaborated on this question in the 1950's as he assumed that ASD was caused by the way parents interacted with their children. This psychogenic theory was believed to be the cause of ASD until the late 1960's. Research on ASD during the 1970's, however, dismissed this theory as studies comparing the parenting skills of parents with children with ASD to that of parents with children with typical development, and autopsies and neuro-imaging of the brain of individual's with ASD did not support this theory (Manning-Courtney *et al*., 2003: 284).

Since those early days, extensive research on the aetiology of ASD has been conducted (Lord, 2010: 815); yet the exact causes of ASD remain unknown and ASD is now being classified as either idiopathic or secondary (Muhle *et al.,* 2004: e472). Up to 85% of all cases of ASD are attributed to idiopathic causes and without an identifiable risk factor. Only about 15% of all cases of ASD, therefore, do have an identifiable risk factor, but, found to be a heterogeneous disorder, no single factor can be identified (Gupta, 2004b: 55). Strong evidence towards a genetic component of ASD has recently been identified, while environmental and several other factors are also thought to contribute (Manning-Courtney *et al*., 2003: 284).

4.1 Genetic component

The first evidence of the genetic component of ASD came from a study conducted by Folstein and Rutter in the late 1970's. These authors found that 36% of monozygotic twins were concordant for ASD and none of the dizygotic twins (Manning-Courtney *et al*., 2003: 296). These findings were supported by studies in years to come with a review article by Mulhle *et al.* in 2004 stating a 60% - 92% and 0% - 10% concordance for ASD in monozygotic and dizygotic twins, respectively (Mulhle *et al.,* 2004: e475). These authors concluded that genetic inheritance was a 'predominant causative agent' of ASD (Mulhle *et al.,* 2004: e472). Thus, although Kanner wrongly attributed parents' 'cold-heartedness' to be

a possible cause of ASD, the possibility does exist that the parents did present with slight autistic traits such as aloofness, rigidity, hypersensitivity, and an anxious personality (Gupta, 2004b: 56).

ASD is a complex genetic disorder (Manning-Courtney *et al*., 2003: 296) with as many as 15 to 20 loci on different chromosomes likely to be causative factors (Gupta, 2004b: 59). These loci can either independently or in interaction with each other cause ASD. Environmental factors might also alter certain genes, causing ASD (Manning-Courtney *et al*., 2003: 296). Genetic anomalies, furthermore, include gene mutations, gene depletion and copy number variants (Landrigan, 2010: 219). Thus far chromosome 7q has been most strongly linked to ASD. This part of the chromosome is known to be a putative speech and language region and has been linked to language disorders. Other regions of the chromosome currently being investigated include, among others, 2q, 16p14, and 15q11-13; the latter is known to be associated with Angelman and Prader-Willi syndromes (Manning-Courtney *et al*., 2003: 296 - 297; Mulhe *et al.,* 2004: e442).

4.2 Environmental and other factors

Although various environmental factors are thought to be linked to ASD (Muhle *et al.,* 2004: e472), no single factor or specific exposures have been identified as a distinct causative factor (Grafodatskaya *et al.,* 2010: 759). Environmental factors include toxin exposure, teratogens, perinatal insults, and prenatal infections such as rubella and cytomegalovirus (Muhle *et al.,* 2004: e472). Obstetric complications were also once thought to be a causative factor, but research in this area could not identify a significant relationship between ASD and these complications (Muhle *et al.,* 2004: e472). Exposure of certain toxins and teratogens very early during the first trimester of pregnancy have, however, been identified to play a role in the aetiology of ASD. Examples of these intrauterine insults include the medications thalidomide, misoprostol and valproic acid, and the organophosphate insecticide chlorpyrifos (Grafodatskaya *et al.,* 2010: 759). During the late 1990's measles-mumps-rubella (MMR) vaccines were thought to be a causative factor of ASD. Due to the importance of this vaccine, about twenty epidemiological studies were conducted in the USA, the UK, Europe and Japan to address this issue. None of these studies found any credible evidence of a link

between the MMR vaccine and the aetiology of ASD (Landrigan, 2010: 222; Muhle *et al.,* 2004: e474). The MMR vaccines are thus now regarded as safe and a necessity in the childhood immunization programme.

Disorders such as epilepsy, tuberous sclerosis, fragile X syndrome, cerebral palsy and untreated phenylketonuria have also been studied for a possible link with ASD. Though not found to be a causative factor of ASD, children with these disorders commonly present with autistic traits. The opposite is also true, as children with ASD can present with other medical conditions (Muhle *et al.,* 2004: e472 – e474).

As no set factor has been identified as a causative factor for ASD, further interdisciplinary research on toxicology screening, neurobiology and epidemiological studies on the aetiology of ASD are recommended. According to Landrigan (2010: 224) the possibility of a breakthrough discovery in the near future is high.

5. SIGNS AND SYMPTOMS RELATED TO AUTISM SPECTRUM DISORDERS

As mentioned, no two children with ASD are the same as far as the combination of signs and symptoms and the severity of the impairments are concerned (Venter, 2011: 12). This variation is mostly due to the difference in the developmental level, mental age and intelligence quotient (IQ) of children (American Psychiatric Association, 2000: 69). Behavioural signs and symptoms related to ASD include impairments in social skills, motor coordination, communication and the response towards sensory stimuli. Bizarre or repetitive behaviours, self-injurious behaviour and gastro-intestinal related symptoms are also common. These signs and symptoms are briefly described in Table 1 (Erickson *et al.,* 2005: 713; Help Autism Now Society, 2006:7 – 27).

Table 1: Signs and symptoms related to autism spectrum disorders (adapted from Erickson *et al.*, 2005: 713; Help Autism Now Society, 2006:7 – 27)

Behavioural symptoms of ASD	Description
Social issues	• May show no interest in other children playing • May be vicious with siblings • May sit alone in crib screaming instead of calling out for mother • May not notice when parent leaves or returns from work • May show no interest in Peek-a-Boo or other interactive games • May strongly resist being held, hugged, or kissed by parents • May not raise arms to be picked up form crib when someone reaches out to pick him/ her up
Communication	• Unaware of environment and avoids eye-contact; do thus seem uninterested in communication • Hand-leading: will instead of communicating needs, place parent's hand on object he/ she desires
Bizarre/ Repetitive Behaviours	• Flapping • Staring at ceiling fan • Spinning • Lining up toy cars • May show no interest in toys but get attached to objects like a space-heater • Picking lint in the sunlight • May not play appropriately with toys and instead focuses only on one aspect, like spinning the wheels of a toy car • Rocking • Obsessively switching light on and off • Eats unusual objects like clothes, mattress or drapes • Flicks fingers in front of eyes • Finds ways to get deep-pressure applied to body (e.g. lie under the couch) • Smearing faeces • Finds ways to get heavy impact to body (e.g. jump of wardrobe)
Motor issues	• Fine motor deficits • Poor coordination • Toe-walking • Depth perception deficit • Exceptional balance (or) • Clumsy • Drooling • Unable to ride tricycle or trucks
Sensory overload	• Finds it extremely difficult to tolerate music, noise, texture, and new experiences or environments • Extremely difficult with haircuts • Unable to tolerate seat belts • May not like new experiences such as birthday candles or balloons • May be almost impossible to bath • Gags at common household smells • May have difficulty tolerating music

Table 1: Signs and symptoms related to autism spectrum disorders (adapted from Erickson *et al.,* 2005: 713; Help Autism Now Society, 2006:7 – 27) *(continued)*

Behavioural symptoms of ASD	Description
Sensory overload (continues from previous page)	• Spinning objects close to face • May appear deaf, not startle at loud noises, but at other times hearing seems normal • May have difficulty wearing outdoor clothing in winter • Resist having clothing changed • May rip at own clothes, labels and seams • During summer may insist on wearing winter clothing
Self injurious	• Head banging • Self-biting with no apparent pain • Ripping and scratching at skin • Pulling our handfuls of hair
Safety	• No sense of danger • Doesn't recognize situations where he/ she may get hurt • No fear of heights
Gastrointestinal	Although proven not to be a defining characteristic of ASD, children with ASD often present with, in comparison with children without ASD, a slightly higher prevalence of gastrointestinal related symptoms. Common gastrointestinal related problems include: • Esophagitis • Colitis • Gastritis • Lactose intolerance • Duodenitits • Diarrhoea • Constipation • Undigested food in stool • Severe self-limiting diet and/ or food sensitivity
Other	• Sleep disturbances • Seizures • Altered pain responses • Strong preference towards routine in everyday activities

Up to 71% of children with ASD present with self-injurous behaviour compared to four to 12% of children with intellectual disabilities (Richards *et al.,* 2012: 478). Self-injurious behaviour includes head-banging, self-biting, ripping and scratching of skin and pulling out of hair. In some instances this behaviour can be so severe that it becomes life-threatening (Erickson *et al.,* 2005: 713). Duerden *et al.* (2012: 2460) conducted a study to identify the possible risk factors associated with self-injurious behaviour. Atypical sensory processing, impaired cognitive ability, abnormal functional communication, abnormal social functioning,

age, the need for sameness (or resistance to change), and rituals and compulsions were the factors assessed. Although all these factors were found to contribute to self-injurious behaviour, abnormal sensory processing was found to be a major causative factor. According to Edelson ([n.d]:online) the sensation of pain or discomfort (for example middle ear infection, headaches, and gastrointestinal related symptoms) and certain sounds (such as a baby crying or a vacuum cleaner) might also contribute towards self-injurious behaviour (Edelson, [n.d]: online).

6. SCREENING AND DIAGNOSIS OF AUTISM SPECTRUM DISORDERS

Diagnosing ASD is not easy. Currently there is no medical marker (such as biochemical parameters) available and the diagnosis is made based on child's behaviour and development (Centres for Disease Control and Prevention, online). Early identification is crucial since early intervention is beneficial (National Research Council, 2001: 3) in changing the course of development (Venter, 2011: 12). In addition to an improved outcome, genetic counselling can be given to parents planning a family as the probability of having a second child with ASD is approximately 5% (Baird *et al.,* 2003: 490; Manning-Courtney *et al.*, 2003: 285). The diagnostic process is based upon developmental surveillance and screening with a comprehensive diagnostic evaluation recommended if abnormalities arise from the surveillance and screening (Centres for Disease Control and Prevention, online). The two levels of the diagnostic process, as well as the DSM-IV-TR criteria for the diagnosis of the ASD subtypes are discussed in the following section.

6.1 Developmental surveillance and screening

Developmental surveillance is a 'flexible, longitudinal, continuous and cumulative process' whereby health care professionals can identify developmental problems in children (Council on Children with Disabilities, 2006: 407). It entails evaluating a child's development by asking the parents about behavioural and developmental concerns, documenting and maintaining a detailed medical history (including a family history of ASD) and observing early signs of ASD (Carbone *et al.,* 2010: 453). The American Academy of Paediatrics

recommends this as part of every preventative visit to a health care professional during childhood (Council on Children with Disabilities, 2006: 419). As parents are most likely to first raise concerns about a child's development and behaviour to the general practitioner (GP) or the paediatrician, GP's and paediatricians play an integral role in the identification and diagnosis of ASD (Manning-Courtney *et al*., 2003: 285).

Developmental screening involves the use of a standardized and appropriate ASD screening tool to screen for ASD's in children in whom concerns of delayed or disordered development are raised (Council on Children with Disabilities, 2006: 419). The American Academy of Paediatrics, however, in addition to children with developmental concerns, recommends screening of all children at the age of 18 and 24 months (Johnson and Myers, 2007: 118). The CDC recommend that children be screened at the age of nine and thirty months of age as well. Screening of children with a high risk for developmental problems, for example children born preterm or with a low birth weight, or children presenting with other reasons which might alter the growth and development are also recommended (CDC, online).

Developmental screening tools which can be used to screen for ASD include: The Checklist for Autism in Toddlers (CHAT), The Modified Checklist for Autism in Toddlers (M-CHAT), The Pervasive Developmental Disorder Screening Test-Stage 1 (PDDST), and Screening Tool for Autism in Toddlers and Young Children (STAT); to list a few (Carbone *et al.,* 2010: 454; CDC, online; Manning-Courtney *et al.,* 2003: 287). Other primary care screening tools are listed on the CDC's website at www.cdc.gov. The CHAT was developed by Baron-Cohen and colleagues in England and is a 14-item checklist aimed at evaluating joint-attention, pretend play and imitation (Carbone *et al.,* 2010: 454). This is a very useful tool with a high specificity, but has been found to have a low sensitivity (Manning-Courtney *et al.,* 2003: 287). The M-CHAT is a modification of the CHAT, consisting of 23 parent-completed items. M-CHAT is promising in the early identification of ASD. The PDDST is also completed by parents and focuses on evaluating children aged birth to the age of three years (Manning-Courtney *et al.,* 2003: 287). The STAT is an interactive screening tool which takes about 20 minutes to administer. It is most commonly used in children in whom developmental concerns are present and consists of 12 activities to assess play, communication, and imitation skills (Centres for Disease Control and Prevention, online).

Tools for the screening of Asperger's disorder and high-functioning autism (mild form of ASD) are also available. These tools include: Autism Spectrum Screening Questionnaire (ASSQ), Australia Scale of Asperger's Syndrome (ASAS), Childhood Asperger's Syndrome Test (CAST), and Social Communication Questionnaire (SCQ) (Centres for Disease Control and Prevention, online).

The CDC and American Academy of Paediatrics both recommend an algorithm for the use of the screening tools. These algorithms indicate the steps to be taken in the case of either a negative or positive screen (Centres for Disease Control and Prevention, online). The algorithm is attached in appendix A.

6.2 Comprehensive diagnostic evaluation

As previously mentioned, there is no medical marker for the diagnosis of autism. Diagnosis is thus made by taking a detailed medical history, observation and an assessment tool specific for the diagnosis of ASD. Diagnosis is best made by a multidisciplinary team, preferably with experience in ASD, consisting, but not limited to, a physician (developmental paediatrician, child neurologist or psychiatrist), psychologist, speech language pathologist, and an occupational therapist (Manning-Courtney *et al.,* 2003: 287). Baird *et al.* (2003: 490) recommend that, as part of the medical assessment, the following be assessed as well: hearing and vision, lead toxicity in the case of pica being present, a full blood count when dietary habits are limited, and genetic tests to exclude and identify karyoptype, fragile X syndrome and Rett's disorder.

The DSM-IV-TR criteria for the diagnosis for ASD, as given in Table 2 (American Psychiatric Association, 2000: 69 – 84), provide clear guidelines as to features by which the ASD subtypes are characterized. These criteria are, however, insufficient in the diagnostic process and the use of diagnostic tools specifically designed for diagnosing ASD are crucial (Manning-Courtney *et al.,* 2003: 288). These diagnostic tools include: The Gilliam Autism Rating Scale – Second edition (GARS-2), The Parent Interview for Autism, The Pervasive Developmental Disorders Screening Test-Stage 3, the Autism Diagnostic Interview-Revised

(ADI-R), The Childhood Autism Rating Scale (CARS), The Screening Tool for Autism in Two-Year Olds and the Autism Diagnostic Observation Scale-Generic (ADOS-G) (CDC, online; Manning-Courtney *et al.,* 2003: 288). Of these the ADR-I and ADOS-G have been found to be the most reliable and are regarded as the gold standard in diagnosing ASD (Manning-Courtney *et al.,* 2003: 288; Venter, 2011: 14). The ADR-I has been found to be effective in making a diagnosis in children between the age of 20 and 42 months. The ADOS-G is currently being revised to serve as a diagnostic tool for children aged 15 months and older (Venter, 2011: 14).

The current DSM-IV-TR is, though, currently in the process of revision and the DSM-V is likely to be implemented in May 2013 (American Psychiatric Association DSM-5 Development, online). It is known that adjustments were made to the current diagnostic criteria for ASD. Although the exact adjustments are not yet known, some of the proposed changes are as follows (American Psychiatric Association DSM-5 Development, online):

- ASD to no longer be classified as pervasive developmental disorders by the DSM-IV-TR and ICD 10, but as ASD;
- To, whereas there were five ASD subtypes, decrease the subtypes to only four ASD subtypes, including: autistic disorder, Aperger's disorder, childhood disintegrative disorders, and pervasive developmental disorder not otherwise specified;
- The three domains, namely social interaction, communication and restricted, repetitive and stereotyped behaviours, by which ASD are currently characterized to be changed to only two domains: social/ communication deficits and fixated interest and repetitive behaviour. Deficits in social and communications skills are now regarded as inseparable and thus a single set of symptoms related to ASD. Furthermore, delays in language skill are now recognized to not be unique to ASD and can therefore not be classified as a defining characteristic of ASD;
- ASD to be regarded as a neurodevelopmental disorder which are present from infancy or early childhood, but which are generally not detected until later due to minimal social demands and interaction, and support from parents and caregivers;

Table 2: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text revision,* (DSM-IV-TR) criteria for the diagnosis of autism spectrum disorders (American Psychiatric Association, 2000: 69 – 84)

Autism spectrum disorders	DSM-IV-TR diagnostic criteria
Autistic disorder (299.00)	A. A total of six (or more) items from (1), (2), and (3), with at least two from (1), and one each from (2) and (3): 1. Qualitative impairment in social interaction, as manifested by at least two of the following: a. Marked impairment in the use of multiple nonverbal behaviours such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction; b. Failure to develop peer relationships appropriate to developmental level; c. A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g. by a lack of showing, bringing, or pointing out objects of interest); d. Lack of social or emotions reciprocity. 2. Qualitative impairments in communication as manifested by at least one of the following: a. Delay in, or total lack of, the development of spoken language (not accompanied by a attempt to compensate through alternative modes of communication such as gesture or mine); b. In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with other; c. Stereotyped and repetitive use of language or idiosyncratic language; d. Lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level; 3. Restricted repetitive and stereotyped patterns of behaviour, interest, and activities, as manifested by at least one of the following: a. Encompassing preoccupation with one or more stereotypes and restricted patterns of interest that is abnormal either in intensity or focus; b. Apparently inflexible adherence to specific, non-functional routines or rituals; c. Stereotyped and repetitive motor mannerisms (e.g. hand or finger flapping or twisting, or complex whole-body movements); d. Persistent preoccupation with parts of objects. B. Delays or abnormal functioning in at least one of the following areas, with onset prior to the age of three years: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play. C. The disturbance is not better accounted for by Rett's disorder or childhood disintegrative disorder.

Table 2: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text revision,* (DSM-IV-TR) criteria for the diagnosis of autism spectrum disorders (American Psychiatric Association, 2000: 69 – 84) *(continued)*

Autism spectrum disorders	DSM-IV-TR diagnostic criteria
Rett's Disorder (299.80)	A. All or the following: 1. Apparently normal prenatal and perinatal development; 2. Apparently normal psychomotor development through the first 5 months after birth; 3. Normal head circumference at birth. B. Onset of all of the following after the period of normal development: 1. Deceleration of head growth between the ages of 5 and 48 months; 2. Loss of previously acquired purposeful hand skills between ages 5 and 30 months with the subsequent development of stereotyped hand movements (e.g. hand-wringing or hand washing); 3. Loss of social engagement early in the course (although often social interaction develops later); 4. Appearance of poorly coordinated gait or trunk movements; 5. Severely impaired expressive and receptive language development with severe psychomotor retardation.
Childhood disintegrative disorder **(299.10)**	A. Apparently normal development for at least the first 2 years after birth as manifested by the presence of age-appropriate verbal and nonverbal communication, social relationships, plan, and adaptive behaviour. B. Clinically significant loss of previously acquired skills (before age 10 year) in at least two of the following areas: 1. Expressive or receptive language; 2. Social skills or adaptive behaviour; 3. Bowel or bladder control; 4. Play; 5. Motor skills. C. Abnormalities of functioning in at least two of the following areas: 1. Qualitative impairment in social interaction (e.g. impairment in nonverbal behaviours, failure to develop peer relationships, lack of social or emotional reciprocity); 2. Qualitative impairments in communication (e.g. delay or lack or spoken language, inability to initiate or sustain a conversation, stereotyped and repetitive use of language, lack of varied make-believe play); 3. Restricted, repetitive, and stereotype patterns of behaviour, interests, and activities, including motor stereotypies and mannerisms. D. The disturbance is not better accounted for by another specific pervasive developmental disorder or schizophrenia.

Table 2: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text revision,* (DSM-IV-TR) criteria for the diagnosis of autism spectrum disorders (American Psychiatric Association, 2000: 69 – 84) *(continued)*

Autism spectrum disorders	DSM-IV-TR diagnostic criteria
Aspergers' disorder **(299.80)**	A. Qualitative impairment in social interaction, as manifested by at least two of the following: 1. Marked impairment in the use of multiple nonverbal behaviours such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction; 2. Failure to develop peer relationships appropriate to developmental level; 3. A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g. by a lack of showing, bringing, or pointing out objects of interest to other people); 4. Lack of social or emotional reciprocity. B. Restricted repetitive and stereotyped patterns of behaviour, interest, and activities as manifested by at least one of the following: 1. Encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus; 2. Apparently inflexible adherence to specific, non-functional routines or rituals; 3. Stereotyped and repetitive motor mannerisms (e.g. hand or finger flapping or twisting, or complex whole-body movements); 4. Persistent preoccupation with parts of objects. C. The disturbances cause clinically significant impairment in social, occupational, or other important areas of functioning. D. There is no clinically significant general delay in language (e.g. single words used by the age of 2 years, communicative phrases used by age 3 years). E. There is no clinically significant delay in cognitive development or in the development of age-appropriate self-help skills, adaptive behaviour (other than in social interaction) and curiosity about the environment in childhood. F. Criteria are not met for another specific Pervasive Developmental Disorder or Schizophrenia.
Pervasive developmental disorder not otherwise specified (including atypical autism) (299.80)	This category should be used when there is a severe and pervasive impairment in the development of reciprocal social interaction associated with impairment in either verbal or nonverbal communication skills or with the presence of stereotyped behaviours, interests, and activities are noted, but the criteria are not met for a specific pervasive developmental disorder, schizophrenia, schizotypal personality disorder, or avoidance personality disorder.

- The severity of ASD to be classified into three levels of which level one refers to persons requiring support and level three persons whom are in need of very substantial support.

How these proposed changes will influence the diagnosis for ASD is not yet clear. It is hoped that these changes will streamline the diagnostic process of ASD, and, most importantly, improve the specificity of the diagnostic process without causing a decrease in the sensitivity of the current diagnostic method (American Psychiatric Association DSM-5 Development, online).

7. TREATMENT OF AUTISM SPECTRUM DISORDERS

ASD, similar to other neurodevelopmental disabilities, are not a curable group of disorders and thus require chronic management. Even though children with ASD grow up to become adults, most remain in the ASD spectrum and continue to experience problems with 'independent living, employment, social relationships and mental health' (Myers and Johnson, 2007: 1162). As ASD are a heterogeneous disorder of which the exact aetiology is unknown, there is no single best treatment for all. This has been proven time and again by various research studies stating a subgroup of participants whom either responded well to the intervention evaluated, or not at all (Centres for Disease Control and Prevention, online). Regardless, the primary goals of treatment, according to Myers and Johnson (2007: 1162) should be to 'maximize the child's ultimate functional independence and quality of life by minimizing the core ASD features. Facilitating development and learning, promoting socialization, reducing maladaptive behaviours, and education and support of families' should also motivate intervention (Manning-Courtney *et al.,* 2003: 289).

The importance of early intervention, as already mentioned, is crucial. Several research studies and case reports have indicated that more skills are learned if intervention takes place between birth and the age of three years. Parents are thus encouraged to speak to a GP or paediatrician as soon as behavioural and developmental problems are noticed. The CDC states that intervention, especially approaches focused on behaviour and speech, should be

put into practice as soon as possible, even if ASD have not yet been formally diagnosed (CDC, online).

Methods currently suggested for the treatment of ASD include behavioural and communication approaches, medical treatment, dietary intervention, and complementary and alternative methods of treatment. These treatment options are briefly discussed in the following section.

7.1 Behavioural and communication approaches

Behavioural and communication approaches (also referred to as educational intervention) are seen as the 'cornerstone' (Myers and Johnson, 2007: 1163) or as the 'primary management strategy' (Carbone *et al.,* 2010: 457) in ASD treatment. This is a life-long process (Manning-Courtney *et al.,* 2003: 291) which involves teaching the autistic child skills and knowledge to act independently and take personal responsibility (Myers and Johnson, 2007: 1163). There are several such methods and programmes and these can be administered at special schools or by therapists in public and private practice. Intensive behavioural therapy of at least 25 hours per week is recommended to ensure an optimal outcome (Carbone *et al.,* 2010: 457 - 458).

According to Myers and Johnson (2007: 1164 - 1167), examples of behavioural and communication approaches include, among others, the following:

- Applied behavioural analysis (ABA): Intervention method focused on encouraging positive behaviour and discouraging negative behaviour;
- Structured Teaching: This emphisizes on structure and thus the organization of the physical environment, activities, visual schedules, routines, work/ activity;
- Developmental models (for example the Denver Model): These models make use of designed approaches to address the deficits experienced by children with ASD;
- Speech and Language Therapy: Augmentative and alternative communication modalities, such as gestures, sign language and picture communication are implemented to improve communication skills;
- Sensory Integration Therapy: Enhance skills to deal with sensory information, for example sights, sounds and smells;

- Occupational Therapy: Entails the teaching and promoting of self-care- (for example dressing, using utensils, and personal hygiene), academic- (for example cutting with scissors and writing), and play skills, and modifying classroom activities, material and routines to enhance attention.

7.2 Medical treatment

Medical treatment is not a primary treatment as pharmacological intervention has not yet been proven to correct the core deficits of ASD (Myers and Johnson, 2007: 1163). Various medications have, however, been studied in the past, and the use of medication is now commonly recommended for the treatment of underlying etiological conditions and certain symptoms related to ASD. As mentioned, conditions such as fragile X syndrome, tuberous sclerosis, epilepsy, gastrointestinal problems and sleep disturbances are common in children with ASD. Symptoms known to respond well to medication include among others attention difficulties, impulsivity, anxiety, obsessive tendencies, self-injurious behaviour, mood lability, and hyperactivity (Manning-Courtney *et al.,* 2003: 289). The medications commonly used for the treatment of ASD related symptoms, as well as the symptoms thought to be alleviated due to this, are listed below (Manning-Courtney *et al.,* 2003: 289 – 290; Myers and Johnson, 2007: 1169):

- Selective serotonin reuptake inhibitors (SSRIs): repetitive behaviour, behavioural rigidity, obsessive-compulsive symptoms, aggression, explosive outburst, self-injury, anxiety, and depression related disorders;
- Atypical antipsychotics: repetitive behaviour, behavioural rigidity, obsessive-compulsive symptoms, hyperactivity, impulsivity, inattention, aggression, explosive outburst and self-injury;
- Stimulants and α-adrenergics: hyperactivity, impulsivity and inattention;
- Anticonvulsants/ antiepileptic drugs: aggression, explosive outburst, self-injury, and seizures;
- Melatonin: sleep dysfunction.

As the assessment on the efficacy of these medications is still ongoing, medication should be given for a trial period to assess individual response. Close observation by the GP or a

professional with more experience in this area is thus advised during medical intervention (Manning-Courtney *et al.,* 2003: 289).

7.3 Dietary interventions

Literature on various dietary interventions and their effect on child behaviour date back to as early as the 1920's, the most famous being Feingold's work on the role salicylates and food additives play in hyperactivity and learning disabilities. During the 1980's, the suspected adverse effects of sugar on hyperactive and aggressive behaviour also became apparent (Elder *et al.,* 2006: 414). Although much research has been done on the effect of dietary interventions on behaviour, Wolraich urged clinicians in the late 1990's to use caution when recommending dietary restrictions as evidence on the true impact was yet, as today, inconclusive (Wolraich, 1996: 29).

As the body of evidence on ASD has grown, anecdotal reports and parent surveys have indicated that dietary interventions might also be effective in the treatment of the signs and symptoms related to ASD (Srinivasan, 2009: 238). Today, as many desperate attempts have been made to find a cure for ASD, diet-related treatment options for ASD are endless. Although evidence on the efficacy of these interventions is limited, dietary interventions is one of the treatment options most commonly implemented for the treatment of ASD. In 2010 Christon *et al.* (2010: 249) stated that more than 70% of autistic children had followed at least one complementary or alternative method of treatment. Dietary interventions are commonly classified under complementary and alternative methods of treatment (CAM) in the case of ASD treatment. Of the CAM treatments appraised, dietary interventions scored the highest in terms of 'lifetime use' (Christon *et al.,* 2010: 249). In the following section the dietary intervention methods currently promoted in the lay media for the treatment of ASD are discussed in terms of hypothesis and related scientific evidence reported in peer-reviewed literature.

7.3.1 Gluten-free, casein-free (GFCF) diet

The GFCF diet is one of the most popular dietary intervention methods for the treatment of ASD (Elder, 2008: 583). Consisting of the exclusion of gluten (found in wheat, rye, barley

and oats) and casein (protein in milk and milk products), the GFCF diet is often the starting point in the journey of dietary interventions (Srinivasan, 2009: 243).

The effect of a GFCF diet on behaviour was first noted in patients with schizophrenia (Dohan, 1966: 152). Dohan noted fewer and less severe cases of schizophrenia in persons in the South Pacific Islands who followed a diet excluding products containing gluten and casein. This led him to believe that an excess of peptides from a diet containing gluten and casein were causative in the behavioural symptoms related to schizophrenia (Dohan, 1966: 152). Panksepp (1979: 174) was the first to propose this to be causative in ASD as well. In a research paper published in 1979 he proposed the 'opioid excess theory of autism', suggesting that the symptoms related to ASD were due to 'opioid peptides from an exogenous origin affecting the neurotransmission within the central nervous system' (Panksepp, 1979: 174). This theory is still commonly believed today. These peptides are thought to originate from the incomplete breakdown of gluten and casein, and are believed to cross the intestinal membrane due to an increased intestinal permeability (intestinal permeability, also referred to as 'leaky gut syndrome', is considered common in children with ASD). These peptides then enter the bloodstream from where they cross the blood-brain barrier, 'affecting the endogenous opiate system and neurotransmission within the central nervous system' (Elder, 2008: 584).

Much research has been undertaken on the effect of a GFCF diet on the signs and symptoms related to ASD. The majority of results available are, however, from preliminary studies (with small sample sizes) with only a few studies conducted as randomized controlled trials. The overall body of evidence on the effect of a GFCF diet are inconclusive, stating no to little statistically significant differences in behaviour post-intervention (Elder *et al.,* 2006: 413; Hyman *et al*., 2010: 3; Johnson *et al.,* 2010a: 213; Seung *et al.,* 2007: 337). Though small in effect, a better outcome has, however, been noted in studies with a longer intervention period (Knivsberg *et al.,* 2003: 248; Knivsberg *et al.,* 2002: 251 and Whiteley *et al.,* 2010: 45). Pennesi *et al.* (2012: 85 - 91) conducted an online survey to assess the implementation factors of a GFCF diet. From the 387 surveys assessed it was noted that the GFCF diet was most effective in children with gastrointestinal symptoms, allergies and food sensitivities. Strict implementation of the diet also resulted in a better overall outcome.

Parental report frequently serves as a means to evaluate post-intervention outcome. When considering this, the GFCF diet is believed to be successful in the treatment of ASD with some parents stating their children 'cured'. Since the very fact that an intervention is being implemented may impact on perceptions about the outcome of the intervention, the validity of such a report is questionable (Srinivasan, 2009: 243). Gillberg, however, stated in 1995 that mothers were reliable informants on child development in the case of both normal and deviant development (Knivsberg *et al.*, 2003: 248). Regardless, the following is commonly reported by parents whose children have followed a GFCF diet: improved language skills (Elder *et al.,* 2006: 418; Hsu *et al.,* 2009: 459, Whiteley *et al,* 1999: 45), improved eye contact (Hsu *et al.,* 2009: 245), improved social skills (Reichert *et al.,* 1990: 1), an improved sleep pattern (Reichert *et al.,* 1990: 1; Whiteley *et al,* 1999: 45), improved attention and concentration, improved coordination and motor skills (Whiteley *et al,* 1999: 45), decreased hyperactivity (Elder, *et al.,* 2006: 418), fewer tantrums (Elder, *et al.,* 2006: 418), decreased self-mutilation (Reichert *et al.,* 1990: 1), decreased aggressiveness (Whiteley *et al,* 1999: 45) and an improvement in overall autistic behaviour (Johnson *et al.,* 2010a: 213).

Lee *et al.* (2007: 423 - 430) have reported a limited availability and a higher cost of GFCF products. The economic burden of a GFCF diet might thus further lower the effectiveness of this dietary intervention (Lee *et al.,* 2007: 423), especially when considering that the GFCF diet should be implemented to precision for a long time period. Children with ASD, furthermore, commonly present with a restricted food repertoire, making the exclusion of gluten and casein containing products even more difficult (Elder, 2008: 586).

7.3.2 Multivitamin and mineral supplementation

Vitamins, minerals and essential amino acids are known to be essential for optimal health, primarily due to their critical function as coenzymes in numerous reactions in the body. These reactions include, among others, the production of neurotransmitters and fatty acids. Vitamin and mineral deficiencies are major contributing factors in many child health problems, including inadequate growth and development, anaemia, hypothyroidism, scurvy, rickets, abnormal brain wave patterns and convulsions (Adams *et al.,* 2011: 34). Recent studies state that children with ASD are likely to suffer from various vitamin and mineral deficiencies, probably due to chronic diarrhoea or constipation, gastrointestinal inflammation, and dietary restrictions (Adams and Holloway, 2004: 1034). Adams *et al.* (2003: conference

preceding) conducted a study in which they evaluated the vitamin and mineral status of over 150 children with ASD. In comparison with children without ASD, these children were found to have much lower levels of vitamins A, C, D, E, all the B vitamins, zinc, magnesium and selenium. According to Dosman *et al.* (2006: 103), children with ASD are likely to present with a compromised iron status.

As the benefits of an adequate vitamin and mineral status in the improvement of the intelligent quotient, scholastics test, early neurological development, and behavioural, cognitive, and academic gains in children with learning disabilities are well known (Adams and Holloway, 2004: 1033), the value of supplementation in the treatment of ASD related symptoms is being assessed. From research conducted to date, it is known that a more notable difference in behaviour is seen in children who receive a multivitamin- and mineral supplement compared to an individual vitamin or mineral (Adams and Holloway, 2004: 1033; Bertolgio *et al*., 2010: 555; Xia, 2011: 271). These differences in behaviour include improvements in sleep patterns, gastrointestinal related symptoms, communication, language skills, eye contact, temper, effectiveness and hyperactivity (Adams and Holloway, 2004: 1033; Xia, 2011: 271). Dosman *et al*. (2006: 152 - 158) evaluated the effect that iron supplementation had on the sleep patterns of children with ASD. Based on their research, Dosman *et al.* hypothesized that an iron deficiency affects the sleep pattern and thus has an impact on the central nervous system. Iron supplementation in children with ASD was found to result in a statistically significant improvement in restless sleep. Improvement in delayed sleep onset was, however, not noted (Dosman *et al.,* 2006: 152).

7.3.3 Polyunsaturated fatty acids (PUFAs)

Polyunsaturated fatty acid (PUFA) supplementation is also a common diet related intervention for the treatment of ASD with as many as 28% of families reporting PUFA supplementation in a survey conducted in 2006 (Green *et al.,* 2006: 70). PUFAs are fatty acids deemed essential for, among others, normal brain development and function, and, as they cannot be synthesized *de novo* in the human body, they should be provided by dietary sources (Richardson, 2004: 383). PUFAs are incorporated into phospholipids which make up a large portion of the neuronal cell membranes. Phospholipids form part of many important neural functions, including synaptic growth, cell signalling, neurotransmission and second messaging. Eicosopentanoic acid (EPA) and docohexanoic acid (DHA) are the primary

omega-3 fatty acids in the brain, and arachadonic acid (AA) the primary omega-6 fatty acid (Johnson *et al.,* 2010b: 1).

As an increased amount of evidence suggests functional deficiency or imbalance of these fatty acids in childhood developmental disorders (including ADHD, dyslexia, dyspraxia and ASD) (Richardson, 2004: 383), the impact of fatty acid supplementation in the treatment of ASD is an important consideration. The amount of research is, however, still limited and further investigation is required (Bent *et al.,* 2009: 1145). Currently, available data indicates no statistically significant improvement in autistic behaviour after omega-3 fatty acid supplementation (Amminger *et al*., 2007: 551; Bent *et al.,* 2011: 545; Johnson *et al*., 2010b: 1). In contrast, improvement in overall autistic behaviour was noted by Meguid *et al.* (2008: 1044 - 1048) after supplementing both omega-3 and omega-6 fatty acids. All studies were implemented for a short time period (about 12 weeks) and most studies had a relatively small sample size. Further investigation should thus consider longer intervention periods and a greater sample size, as, as seen in the case of the GFCF diet, a longer intervention period might yield a better outcome.

7.3.4 Probiotics

Probiotics are defined by the Food and Agricultural Organization of the United Nations and World Health Organization (FAO/WHO) Expert Consultation Report (2001: 1) as 'live microorganisms that, when administered in adequate amounts, have a beneficial effect on the health of the host'. Probiotics have shown efficacy in a wide array of healthy problems, including antibiotic-induced and acute infectious diarrhoea, inflammatory bowel disease, and irritable bowel syndrome. These microorganisms also contribute to improved immunity (Crithchfield *et al.,* 2011: 2).

When compared with typically developing children, children with ASD generally present with a higher prevalence of gastrointestinal symptoms. After conducting a study measuring the relationship between gastrointestinal symptoms and the severity of ASD, Adams *et al,* (2011: 22) reported the prevalence of gastrointestinal symptoms to increase as the severity of autism increased. As the importance of probiotics in optimal gastrointestinal tract health is being recognized, it is hypothesized that probiotic treatment might improve ASD related symptoms. Research in this field is, however, limited and Crithchfield *et al.* (2011:8)

recommend that well designed studies should be conducted to evaluate the effect of probiotics in ASD. Kaluzna-Czaplinska and Blaszczyk (2010: 124 - 126), conducted a study to evaluate the effect of probiotic treatment, but the effect of this on the signs and symptoms related to ASD were assessed secondary to the difference in the D-arabinitol (DA) level and D-/L-arabinitol (DA/LA) ratio post intervention. A significant decrease in the DA level and DA/LA ratio was noted after supplementing *Lactobacillus Acidophilus* for a period of 8 weeks. The decrease in the DA level and DA/LA ratio resulted in a significant improvement in the ability to concentrate and carry out orders. No improvements in social skills were, however noted.

As probiotics are known to alleviate gastrointestinal symptoms, further research on the role that probiotic supplementation plays in the treatment of gastrointestinal related symptoms in children with ASD (and secondary to this the improvement in behavioural symptoms), is recommended.

7.3.5 Ketogenic diet

The ketogenic diet is a dietary intervention commonly prescribed for the treatment of 'all types of seizures in children in whom drug therapy has failed' (Remig, 2008:1088). This approach was first introduced by Wilder in the 1920's. Based on an observation that fasting is beneficial in the control of seizures, this dietary method was developed and adjusted until it was implemented in the 1970's as a standard method of treatment for persons with seizures (Evangeliou *et al.,* 2003: 113). Children with drug refractory epilepsy on the ketogenic diet have been found to have a reduced prevalence of seizures and a decreased dependence upon medication (Remig, 2008: 1090). As the body of research on this dietary approach has grown, the potential benefit of this approach in the treatment of cancer, mental behaviour, hyperactivity, aging, Alzheimer's diseases, Parkinson's disease, Amyotrophic Lateral Sclerosis, strokes, brain injuries and ASD has became apparent as well. Much of the evidence is yet inconclusive, but research is ongoing (Stafstrom and Rho, 2012: 59).

The ketogenic diet aims to create and maintain a state of ketosis in the body. Although the mechanism of action is not yet understood, the ketogenic diet is known to influence the neuronal metabolism whereby the ketone bodies act as inhibitory neurotransmitters, producing an anticonvulsant effect (Remig, 2008: 1088). The traditional- and the medium-

chain triglyceride (MCT-) based approaches have been distinguished. With the traditional approach as much as 75% of the daily energy requirement should be met by dietary fat intake. The daily protein intake should be sufficient to meet the daily requirements for age, while carbohydrate intake is limited to the remaining portion of daily energy requirement (Remig, 2008: 1088). The MCT-approach is easier to implement since long-chain fatty acids are replaced by MCT oil which is more ketogenic. For this reason, more non-ketogenic foods such as fruits, vegetables, and small amounts of starches can be included in the diet (Remig, 2008: 1088).

Evangeliou *et al*. (2003: 113 - 118) conducted a pilot study to evaluate the worth of the ketogenic diet in the treatment of ASD. The study included an intervention period of 12 months. Participants (thirty children aged four to ten years) received a John Radcliffe diet (energy distributed: 30% from MCT, 30% from fresh cream, 11% from saturated fat, 19% of from carbohydrates and 10% of from protein), a variation of the MCT diet, during the first six months of the intervention period. Intervention during this time was not continuous as four weeks of strict adherence to the ketogenic diet was interrupted by two weeks of no dietary intervention. Participants received no dietary intervention during the second six month intervention period, but were followed-up for psychiatric examinations on regular intervals.

Significant improvements in social behaviour, interaction, speech, coordination, hyperactivity and learning ability were noted. These improvements were eminent during the diet-free intervals as well, and lasted well into the second six month intervention period. Improvements were, however, greater in children with mild ASD compared to children with severe ASD. Evangelio *et al*. (2003: 113 - 118) also found the ketogenic diet to be well tolerated by children with ASD.

7.3.6 Inositol

Inostiol, classified as a vitamin-like substance and thus a dietary supplement (WebMD, online), is a simple glucose isomer and a key metabolic precursor of serotonin (Levine *et al.*, 1997: 147). Although manufactured in laboratories for supplementation, inositol is found in many foods, in particular fruit (melon and oranges are especially good sources) (WebMD, online). Inositol has been reported to be effective in the treatment of psychological disorders

such as depression, panic disorder and obsessive-compulsive disorder (Levine *et al.*, 1997: 147-150). This led to research evaluating the effect of inositol on the signs and symptoms related to ASD. Levine *et al.* (1997: 147 - 155) undertook a study with a rather small sample size (10 study participants) during which they supplemented inositol for a period of only eight weeks. No statistically significant difference in the signs and symptoms of the children were noted post intervention. Based on these findings, methodologically sound research studies are required before inositol can be considered an option in the treatment of ASD.

7.3.7 Digestive enzymes

The use of digestive enzymes is closely related to the 'opioid excess theory' which motivated the development and implementation of the GFCF diet. Gluten and casein are thought to be insufficiently digested by the pancreatic and small intestine peptidases, resulting in short chain peptide molecules similarly structured as endogenous opioid substances. It is believed by some that the influence these opioid substances has on human brain functions is responsible for the ASD related signs and symptoms (Munasinghe *et al.,* 2010: 1131 - 1132).

Other than the exclusion of foods containing gluten and casein, dietary supplementation of peptidase enzymes is hypothesized to lower the effect of the endogenous opioid. The enzymes are believed to break down the exorphins into smaller particles which do not have an opioid activity (Munasinghe *et al.,* 2010: 1132). Munashinghe, *et al.* (2010: 1131 - 1138) tested this hypothesis by conducting a double-blind, randomized controlled trial on 43 study participants with ASD. Peptizyde, a digestive enzyme supplement, was supplemented for a period of six months. No statistically significant differences in overall autistic behaviour and other ASD related symptoms were, however, noted. As research participants did not follow a GFCF diet, the outcome of combined therapy remains unknown. Further research in this field is thus recommended.

7.3.8 Detoxification diet and therapies

As previously mentioned, the aetiology of ASD is largely unknown. One of the possible causative factors that has received considerable attention in the past is heavy metal exposure (such as mercury, lead and other toxic metals) (Adams *et al.,* 2009: 18). It is hypothesized that chelation and other detoxification methods may result in increased heavy metal

excretion, and thus an improvement in ASD related signs and symptoms (Soden *et al.,* 2007: 476).

This theory was tested by Adams *et al*. in 2009. They conducted a randomized, double-blind placebo controlled/ comparison trial, supplementing oral dimercapto succinic acid (DMSA) for one round in 65 participants, and for an additional six rounds in 49 participants. A statistically significant improvement in overall autistic behaviour was noted in 77% of the participants; 11%, however, presented with a deterioration in their condition (Adams *et al.,* 2009:17 - 26). These findings seem to highlight the fact that there is often a subgroup of individuals who do not respond in the same manner as others or even respond negatively to the treatment given.

7.3.9 Other dietary interventions

In addition to the mentioned interventions, the lay media claims that L-carnosine supplementation, the avoidance of food colorants, yeast-free-, specific carbohydrate- and low oxolate diets have a positive outcome in the treatment of ASD (Autism Nutrition, online; Treating Autism, online; Wikipedia, online). Scientific evidence on this is, however, limited and further research is therefore required before the effectiveness of these methods can be determined.

7.4 Complementary and alternative methods of treatments

Parents are likely to search for complementary and alternative methods of treatment when conventional and empirical treatment is ineffective or not satisfactory (Christon *et al.,* 2010: 249). Christon *et al.* (2010: 249) have reported that as many as seventy percent of the parents of children diagnosed with ASD have tried at least one complementary and alternative treatment. 'Complementary' refers to therapies or treatments which are used in addition to traditionally prescribed interventions and 'alternative' therapies and treatments refer to those treatments used in the place of such interventions (Christon *et al.,* 2010: 249). The use of complementary and alternative methods of treatment was found to be higher in children whose parents were well educated, from a medium to high socio-economic status and using complementary therapy themselves. The use of such therapies was also found to be more

common in children with more severe cases of ASD. When considering the reasons for using alternative therapies, it is probably due to the fact that parents are desperate to initiate early intervention and are unlikely to wait for research to prove effectiveness of treatment (Christon *et al.,* 2010: 249 - 250).

Complementary and alternative treatment is categorized as either non-biologic or biologic. Non-biologic treatments include treatments which 'use behavioural or sensory experiences to alter the psychological processes which in turn alter the symptoms of ASD' (Christon *et al.,* 2010: 249-250), and include auditory integration training, behavioural optometry, craniosacral manipulation, dolphin-assisted therapy, music therapy, and facilitated communication (Myers and Johnson, 2007: 1173). Biological treatment options, conversely, alter the physiology or change the underlying mechanisms that are related to the symptoms (Christon *et al.,* 2010: 249 – 250) and include the diet-related treatment options that have previously been mentioned (Myers and Johnson, 2007: 1173).

8. Conclusion

ASD are ever increasing, complex neurodevelopmental disorders which do not only affect every aspect of the affected individual, but influence every aspect of the loved-ones and caregivers lives as well. With ongoing, but yet inclusive research, the aetiology of this group of disorders remains unknown. Indirect to this, treatment options proven effective in the treatment of ASD related signs and symptoms are limited.

The worth of early intervention is becoming more apparent and is regarded crucial in the treatment of ASD. This, although it has contributed to a better overall outcome in some ASD cases, has also contributed to the implementation of CAM treatment. Parents, usually well-educated and from a medium or high socio-economic background, tend to implement various treatments usually promoted by the lay media to 'cure' ASD, with most of these treatment options never being previously scientifically appraised.

Health care professionals should thus attempt to find a cure for ASD, be well informed about the signs and symptoms related to ASD, the diagnostic criteria for these disorders and the treatment options consideredsafe and effective for the treatment of such individuals. As stated by Myers and Johnson (2007: 1162) the primary goal of treatment should be and remain to 'maximize the child's ultimate functional independence and quality of life by minimizing the core ASD features' without, in the light of the Hypocritical Oath, doing any harm.

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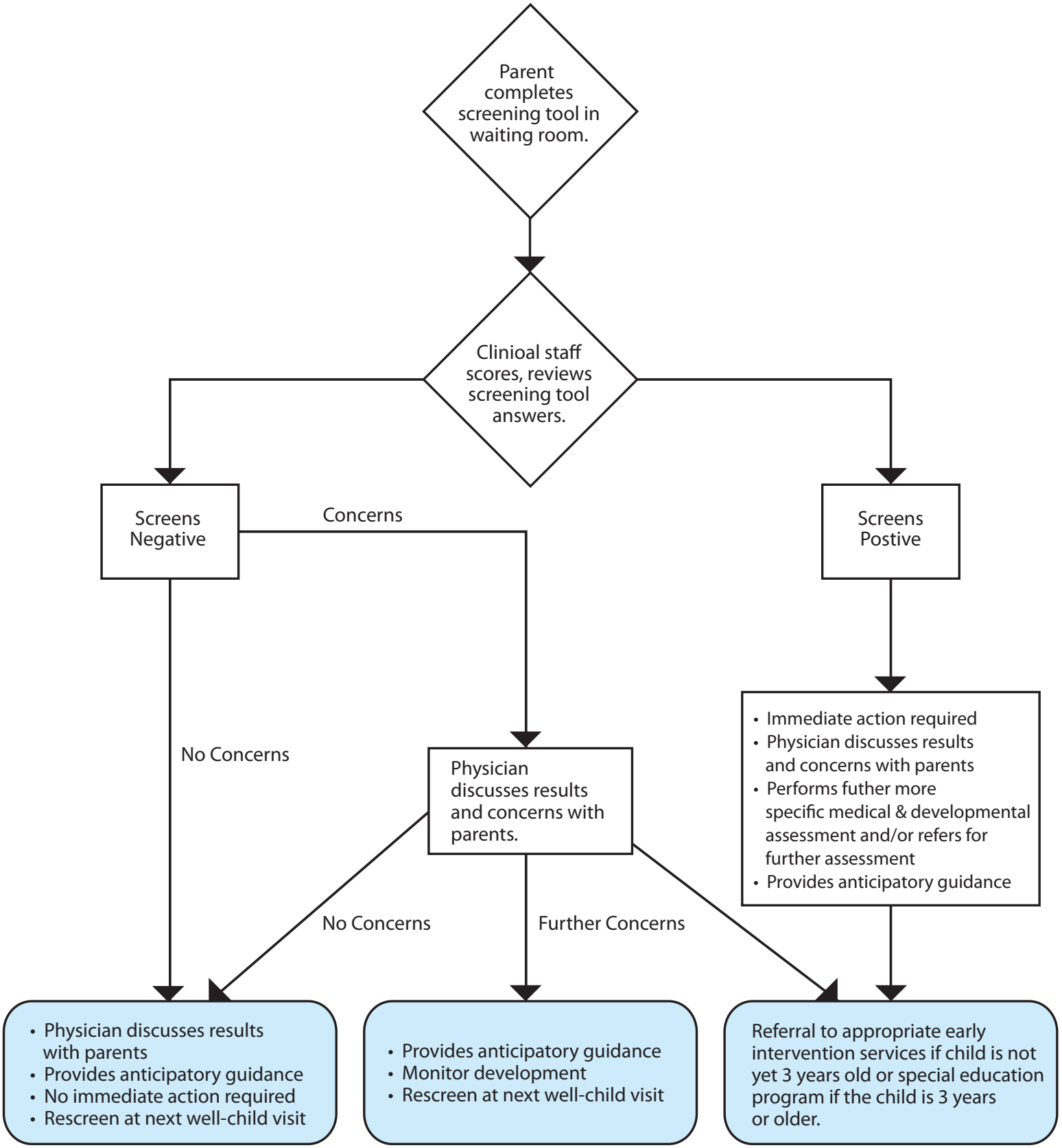
APPENDIX A

ASD screening algorithm

(Centres for Disease Control and Prevention, online)

Pediatric Developmental Screening Flowchart



Part C

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1. INTRODUCTION

Autism spectrum disorders (ASD) are a group of complex neurodevelopmental disorders characterized by and diagnosed according to its behavioural presentation (Elder, 2008: 583; Martins *et al.*, 2008: 1878). Generally perceived before the age of three years (NICHD, 2005: 2), this group of disorders remain evident throughout the lifespan of the affected individual (Elder, 2008: 583). ASD (also referred to as pervasive developmental disorders) are defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text revision* (DSM-IV-TR) as 'a severe and pervasive impairment in several areas of development: reciprocal, social interaction skills, communication skills, or the presence of stereotyped behaviour, interest and activities' (American Psychiatric Association, 2000: 69). No two individuals are, however, the same as evidenced by the wide array of abilities and disabilities reported. These abilities and disabilities vary from being severely impaired to being gifted; being socially aloof and passive to active, but odd; and from being non-verbal to verbal. Some individuals might present with hyposensitivity towards sensory stimuli, with others presenting with hypersensitivity. Motor-coordination might also vary from being clumsy to being well co-ordinated, and behaviour between intensely abnormal to mildly so (Venter, 2011: 12).

The prevalence of this group of disorders is thought to be increasing. Based upon data collected in 2008, ASD are now thought to affect one in 88 children in the United States of America (CDC, 2012: 1); this compared to a reported one in 150 children in 2007 (based upon data gathered in 2002) (CDC, 2009:1). A 78% increase in the prevalence of ASD has thus been noted during the six year time period between 2002 and 2008 (CDC, 2012: 13 - 14). An increase in the prevalence of ASD has also been noted in Denmark (one in 188 children) (Ellefsen *et al.*, 2007: 437), the United Kingdom (one in 86 children) (Baron-Cohen *et al*., 2009: 500), Canada (one in 126 children) (Lazoff *et al*. 2010: 715), Korea (one in 38 children) (Young *et al.*, 2011: 904) and Australia (varying for the different states and territories between one in every 280 children to one in every 1014 children) (Williams *et al.*, 2008: 504). To date no epidemiological study related to ASD has been conducted in South Africa (Bakare and Munir, 2010: 208) and the prevalence is thus, as in many countries

around the globe, still unknown in South Africa. Regardless, what was once thought to be a rare disability is now becoming one of the 'most frequent childhood neurodevelopmental disorders' diagnosed (Fombonne, 2009: 591).

ASD occur in all racial/ ethnic groups with only a slightly higher prevalence in non-Hispanic white children than in other racial/ ethnic groups (CDC, 2012: 16 – 17). The Autism and Developmental Disabilities Monitoring (ADDM) network has, as was indicated by the same group in 2009 (CDC, 2009: 1), confirmed the significantly higher prevalence of ASD in males in the USA: one in 54 boys compared to one in 252 girls (CDC, 2012: 16). Males are thus four to five times more likely than females to be autistic (CDC, 2012: 16).

Behavioural symptoms known to ASD can be divided into the following categories: communication issues, social issues, bizarre or repetitive behaviour, motor issues, sensory overload, sensory issues, and self-injurious behaviour (Venter, 2011: 12). As mentioned, the combination of signs and symptoms, and the severity of impairments vary between individuals. This is mainly due to the differences in developmental level, mental age and the intelligence quotient (IQ) (American Psychiatric Association, 2000: 69). Examples of these behavioural traits include lack of imaginative play, inability to initiate social interaction and thus no or little interest in playing with other children, avoidance of affection, flapping of hands, rocking from side to side, head-banging, self-biting, and an unwillingness towards change in daily activities and routine (Help Autism Now Society, 2011: 7 - 28). Impairments in language skills are also common as up to 40% of autistic children are unable to talk (Johnson, 2004: 115).

Although not seen as a distinct symptom and thus not part of the set diagnostic criteria of ASD (Erickson *et al.,* 2005: 713; Buie *et al.,* 2010: S3), gastrointestinal related symptoms are common. The prevalence of gastrointestinal related symptoms is slightly higher than in unaffected children, varying between one and 20 percent for the different gastrointestinal symptoms (Kushak *et al.,* 2005: 493). The gastrointestinal related symptoms most commonly seen in autistic children are constipation, encopresis due to constipation, abdominal pain,

diarrhoea, gastro-oesophageal reflux disease (GERD), abdominal bloating, and pathologic problems such as inflammation of the gastrointestinal tract and abnormalities of the enteric nervous system (Buie *et al.*, 2010: S3).

Neurodevelopmental disabilities such as ASD are not a curable group of disorders and thus require chronic management. Even though children with ASD grow up to become adults, most remain in the ASD spectrum and continue to experience problems with 'independent living, employment, social relationships and mental health' (Myers and Johnson, 2007: 1162). As ASD are a heterogeneous disorder of which the exact aetiology is unknown, there is no single best treatment for all (CDC, online). Methods currently implemented for the management and treatment of ASD include educational interventions (such as applied behavioural analysis, structured teaching programmes, speech and language therapy and occupational therapy), medical treatment (which involves the treatment of certain symptoms, such as irritability, hyperactivity and impulsivity with medication), complementary and alternative methods, and dietary interventions (Myers and Johnson, 2007: 1163 - 1174).

Literature on various dietary interventions and their effect on child behaviour date back to as early as the 1920's, the most famous being Feingold's work on the role that salicylates and food additives play in hyperactivity and learning disabilities. The possible adverse effect of sugar on hyperactivity and aggressiveness was also investigated during the 1980's (Elder *et al.*, 2006: 414). As the body of evidence regarding ASD has grown, anecdotal reports and parent surveys have suggested that dietary interventions may be effective in the treatment of ASD related symptoms (Srinivasan, 2009: 238). Today, as many desperate attempts have been made to find a cure for ASD, diet-related treatment options are almost endless. According to a survey conducted by Christon et al., in 2010, more that 70% of the autistic children evaluated at their centre had previously followed at least one dietary intervention (Christon *et al.*, 2010: 249), making dietary interventions (most often the gluten-free casein-free (GFCF) diet (Srinivasan, 2009: 243)), one of the treatment options most commonly implemented for the treatment of ASD.

Previous systematic reviews conducted on dietary interventions for the treatment of ASD either focused on critically appraising only one dietary intervention (Christison and Ivany, 2006; Elder, 2008; James *et al.*, 2011; Main *et al.*, 2010; Nye and Brice, 2005; Richardson, 2004), or simply state an overview of different dietary treatment options without critically appraising and comparing these dietary interventions (Cormier and Elder, 2007; Johnson, 2006; Srinivasan, 2009). As there is yet no set guidelines for the dietary treatment of ASD, the need for a thorough evaluation and comparison of dietary interventions currently suggested for the treatment of ASD, was noted. Such guidelines are a necessity to ensure the optimal treatment of children with ASD. The primary goals of treatment should, according to Myers and Johnson (2007:1162), be to 'maximize the child's ultimate functional independence and quality of life by minimizing the core ASD features. Facilitating development and learning, promoting socialization, reducing maladaptive behaviours, and education and support of families' should also motive intervention. The main objective of this systematic review was thus to critically appraise dietary intervention methods currently suggested for the treatment of ASD with reference to peer-reviewed scientific studies in order to recommend evidence based dietary guidelines for the treatment of ASD.

2. METHODS

Figure 1 depicts a schematic representation of the procedure followed to search, screen and select studies.

2.1 Study design

A systematic review of peer-reviewed scientific studies was performed to determine the efficiency of dietary interventions in the treatment of children with ASD.

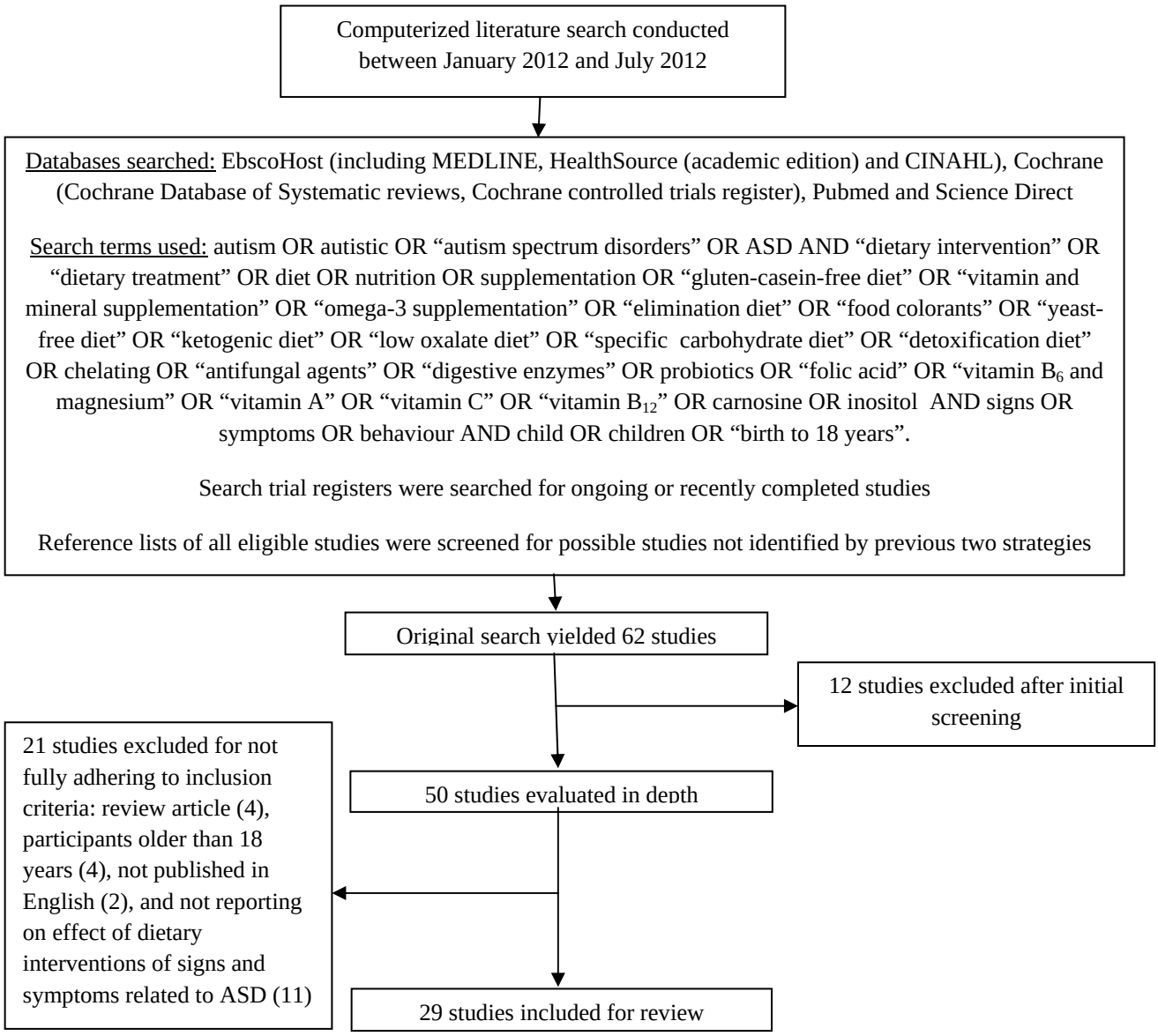

Figure 1: Schematic representation of the procedure followed to search, screen and select studies

2.2 Literature search strategy

Eligible studies were identified using the following three-part search strategy: firstly, electronic biographic databases were searched for relevant published articles. Secondly, search trial registers were searched for ongoing and recently completed trials, and finally the reference lists of all eligible studies were screened for possible studies not identified by the previous two strategies. The electronic biographic databases used to screen for eligible

studies as well as the search terms used to seek the eligible studies from the mentioned databases are listed in Figure 1.

Studies were included in this review if the following criteria were met:

- Studies (all study designs were included) with primary data on the overall impact of the dietary interventions on the signs and symptoms related to ASD;
- Studies which evaluated, as a secondary outcome, the effect of the dietary intervention on the growth, development and general well-being of the participant;
- Study population comprising infants, children and adolescents (up to the age of 18 years);
- Studies published between January 1990 and July 2012;
- Studies published in English.

Studies were excluded if the study population included persons with medical conditions not related to ASD.

Relevant studies were first screened according to their title after which abstracts were obtained. Two other researchers, namely Professor C. Walsh and Doctor L. van den Berg, both registered dietitians affiliated to the University of the Free State, also conducted the three part search strategy to ensure that no studies were overlooked. Full-text articles were obtained for all studies which met the inclusion criteria. All eligible studies were evaluated and discussed by the three researchers to confirm relevance and inclusion.

2.3 Quality assessment of studies

The quality of each included study was assessed using an evaluation tool designed by Reichow *et al.* (2008: 1311-1319): Evaluative Method for Evaluating and Determining Evidence-based practices in Autism. This tool was designed with the aim of aiding researchers and practitioners in determining evidence-based practices (EBP) for the treatment of ASD. The tool consists of three instruments: 1) Rubrics for the evaluation of research report rigor, (2) guidelines for the evaluation of research report strength, and (3) criteria for the determination of EBP (Reichow *et al.*, 2008: 1312).

2.4 Data extraction

Each of the included studies were evaluated according to study design, setting, study population, inclusion and exclusion criteria, dietary intervention used, additional interventions and outcome. Data were summarized in table format using an Excel spread sheet. Table 3 through to Table 12 illustrates a synopsis of all 29 studies included for review. Due to a large number of different dietary interventions implemented, homogeneity among studies was limited; the outcomes of each dietary intervention were thus assessed and interpreted individually.

2.5 Ethical considerations

The study was approved by the Ethics Committee of the Faculty of Health Sciences, University of the Free State (South Africa) on July 27th, 2012 (ECUFS NR 115/2012; Appendix A).

2.6 Statistical analysis

The results from the included studies were heterogeneous and varied in terms of the inclusion criteria, interventions, outcomes measured and the means by which the outcomes were measured, making the pooling of data almost impossible. A meta-analysis could thus not be conducted and a narrative systematic review was undertaken.

3. RESULTS

3.1 Literature search/ study selection

The initial literature search yielded a possible 62 studies. Abstracts and full-text articles were screened according to the inclusion and exclusion criteria. Twelve articles were excluded after initial screening for not being relevant to the specific purpose of this review. A further 21 articles were excluded for not fully adhering to the inclusion and exclusion criteria. Of these, four articles were excluded for being review articles, four with a study population older

than age of 18 years, two for not being published in English, and 11 on the grounds that the effect of the dietary intervention on the signs or symptoms were either not reported, or not reported appropriately according to the inclusion and exclusion criteria (Figure 1). The excluded articles, as well as a short description of the grounds for exclusion are stated in Table 1.

After the screening process was completed, 29 articles remained. These 29 studies evaluated the efficacy of either one of the following dietary interventions in the treatment of the signs and symptoms related to ASD: Gluten-free, casein-free (GFCF) diet, specific carbohydrate diet, elimination diet, ketogenic diet, detoxification diet and therapies, supplementation of digestive enzymes, probiotics, polyunsaturated fatty acids, inositol, vitamin and minerals supplementation, yeast-free diet or other methods of dietary intervention. Studies related to the following dietary interventions (that have been suggested to be successful in the lay media) were either excluded during the screening process, or could not be found during the literature search: avoidance of food colourants, supplementing anti-fungal agents, and carnosine.

Table 1: List of excluded studies

Study	**Reasons for the exclusion**
Adams *et al*., 2008	Study evaluates the acceptability of GFCF free foods by children with ASD; the effect of GFCF foods on the signs and symptoms related to ASD was not an outcome.
Arnold *et al.*, 2003	Although the study evaluated the effect of a GFCF diet on children with ASD, the effect of this on the signs and symptoms related to ASD was not included in the results.
Adams *et al.*, 2006	Although the study evaluated the effect of multivitamin and mineral supplementation on children with ASD, the effect of this on the signs and symptoms related to ASD was not noted.
Bolman and Richmond, 1999	This study evaluated the effect of a dietary intervention in ASD, but the study population included adults (30 years of age).
Cass *et al.*, 2008	Although participants in the study were on a GFCF diet, the difference in opioid levels in children with ASD and typically developing children were evaluated; the effect on the signs and symptoms was not an outcome.
Christison and Ivany, 2006	Review article, and not a primary study.

Table 1: List of excluded studies, *continued*

Study	Reasons for the exclusion
Cornish, 2002	Study evaluated the difference in food choices between children on a GFCF diet and children on a normal diet; the effect on the signs and symptoms was not an outcome.
James *et al.*, 2011	Review article, and not a primary study.
James *et al.*, 2009	Although the study evaluated the effect of multivitamin and mineral supplementation on children with ASD, the effect of this on the signs and symptoms related to ASD was not included.
Jung and Lee, 2000	Although the study does evaluated the effect of a dietary intervention on the signs and symptoms related to ASD, this article was not published in English.
Kaluza-Czaplinska *et al.*, 2011	Although the study evaluated the effect of multivitamin and mineral supplementation on children with ASD, the effect of this on the signs and symptoms related to ASD was not noted.
Kaluzna-Czaplinska *et al.*, 2011	Although the study evaluated the effect of multivitamin and mineral supplementation on children with ASD, the effect of this on the signs and symptoms related to ASD was not noted.
Knivsberg *et al.*, 1995	Although the study evaluated the effect of a GFCF diet on the signs and symptoms related to ASD, the study participants were have an age of 19years and older.
Lee *et al.*, 2007	Study evaluated the economical burden of a GFCF diet; the effect on the signs and symptoms was not an outcome.
Montgomery, 2006	This study evaluated the effect of the nutritional supplement dimethylglycine on the signs and symptoms related to ASD, but the study participants were 19years and older.
Nye and Brice, 2005	Review article, and not a primary study.
Richardson, 2004	Review article, and not a primary study.
Schreck *et al.*, 2004	Study evaluated the difference in eating behaviours in children with ASD and children without ASD; the effect on the signs and symptoms was not an outcome.
Soden *et al.*, 2007	The study evaluated the effect of detoxification methods on children with ASD, but the effect of this on the signs and symptoms related to ASD was not included.
Souza *et al*., 2012	Study population included children aged 9 years to 23 years. Also, intestinal permeability and dietary status of children on a GFCF diet were evaluated and not the effect of this diet on the signs and symptoms related to ASD.
Sponheim, 1991	This study evaluated the effect of a dietary intervention on the signs and symptoms related to ASD, but were not published in English.

3.2 Quality assessment

The quality rating of each of the included studies, as determined by the Evaluative Method for Evaluating and Determining Evidence-based practices in Autism (Reichow *et al.,* 2008: 1312) are shown in Table 2. Studies were, according to the rigor of each study, categorized as having a strong, adequate or weak research report strength. The quality of the Hyman *et al.* (2010) and Levine (1997) studies could, however, not be assessed as the literature search yielded only the article abstract. Pennesi and Klein (2012) conducted an online survey and could thus also not be evaluated for report strength.

Table 2: Quality rating of included studies

Quality rating	Studies
Strong	Bent *et al.,* 2011 Bertoglio *et al*., 2010 Chan *et al.,* 2012 Johnson *et al.,* 2010 Munasinghe *et al.,* 2010
Adequate	Adams and Holloway, 2004 Amminger *et al.,* 2007 Dosman *et al.,* 2006 Elder *et al.,* 2006 Evangeliou *et al.,* 2003 Irvin, 2006 Johnson *et al.,* 2010 Knivsberg *et al.,* 2003 Knivsberg *et al.,* 2002 Meguid *et al.,* 2008 Reichert *et al.,* 1990 Seung *et al.,* 2007 Whiteley *et al.,* 2010 Whiteley *et al,* 1999
Weak	Adams *et al.,* 2009 Hsu *et al.,* 2009 Kaluzna-Czaplinska and Blaszcyk, 2010 Luiselli *et al.,* 1994 O'Hara and Szakacs, 2008 Patel and Curtis, 2007 Xia, 2011

3.3 Dietary intervention

The effectiveness of each dietary intervention in alleviating the signs and symptoms related to ASD was critically appraised independently as homogeneity among the dietary interventions was limited. Outcome was regarded as statistically significant if the results yielded a p value of less than 0.05.

3.3.1 GFCF diet

The GFCF diet is one of the most popular dietary interventions for the treatment of ASD (Elder, 2008: 583). The diet excludes gluten (found in wheat, rye, barley and oats) and casein (protein in milk and milk products), and is often the first dietary intervention implemented (Srinivasan, 2009: 243).

Gluten and casein are believed to contribute to the severity of ASD related symptoms (Dohan, 1966: 152). The 'opioid excess theory of autism', proposed by Panskepp in 1979 and upon which the GFCF diet is based, suggests that opioid peptides from an exogenous origin affect the neurotransmission within the central nervous system (Panskepp, 1979: 174). These peptides are thought to originate from the incomplete breakdown of gluten and casein, and are believed to cross the intestinal membrane due to increased intestinal permeability (intestinal permeability, also referred to as 'leaky gut syndrome', is considered common in children with ASD). The peptides then enter the bloodstream from where they cross the blood-brain barrier, affecting the endogenous opiate system and neurotransmission within the central nervous system (Elder, 2008: 584).

Twelve of the 29 included studies evaluated the effect of a GFCF diet on the signs and symptoms related to ASD. A brief summary of each is given in Table 3. Homogeneity of these studies was limited as the study sample included eight randomized controlled trials (Elder *et al.*, 2006; Hyman *et al.*, 2010; Johnson *et al.*, 2010; Knivsberg *et al.*, 2003; Knivsberg *et al.*, 2002; Seung *et al.*, 2007; Whiteley *et al.*, 2010; Whiteley *et al.*, 1999), two case reports (Hsu *et al.*, 2009; Irvin, 2006), and one online survey (Pennesi and Klein, 2012).

In Reichert *et al.* (1990) participants were assigned to one of three groups according to the DSM III diagnosis and gel chromatography. The number of participants included in the studies varied, ranging between one and 72. The ages of participants ranged from two to 17 years, and the studies included both male and female participants. Pennesi and Klein (2012) evaluated 387 parental reports obtained from an online survey.

The implementation of the GFCF diet was also different between the studies with some studies comparing the impact of the GFCF diet to that of a regular diet (Elder *et al.,* 2006; Knivsberg *et al.,* 2002; Knivsberg *et al.,* 2003; Whiteley *et al.,* 1999; Whiteley *et al.,* 2010) or a healthy, low sugar diet (Johnson *et al.,* 2010), while others followed a pattern of days of strict adherence, interrupted by days of not following a GFCF diet (Irvin, 2006), double-blind food challenges (Hyman *et al*., 2010) and cross-over methods (Seung *et al.,* 2007). Information on the different forms of implementation is given in Table 3.

The duration of intervention also varied among the studies with the shortest intervention period being 10 weeks (Hsu *et al.,* 2009), and the longest 24 months (Whiteley *et al.,* 2010). Only one study, Irvin (2006), was conducted at a 24-hour residential treatment facility; all other participants lived at home and were followed-up and evaluated on a regular basis during the intervention period. In the studies of Elder *et al.* (2006), Hsu *et al*. (2009), Seung *et al.* (2007) and Whitely *et al.* (1999) the meals and snacks were provided by the research group. Parents of the participants evaluated by Johnson *et al*. (2010), Knivsberg *et al.* (2003) and Knivsberg *et al*. (2002) were, however, responsible for all meals and received only a guideline on what foods were allowed.

Outcome was evaluated using standardized ASD evaluation tools or questionnaires, video-imagining and parental report. Table 3 states the methods used by each of the studies. Elder *et al.* (2006), Hyman *et al*. (2010), Johnson *et al.* (2010) and Seung *et al.* (2007) found no statistical significant difference in overall autistic behaviour (including attention, frequency or quality of stools, sleep behaviour, activity levels, language skills, and verbal and non-verbal communication) after intervention. Statistically significant improvements were,

however, noted by Knivsberg *et al*. (2003), Knivsberg *et al*. (2002) and Whiteley *et al.* (2010). This observation can possibly be attributed to variations in the length of the intervention periods: Elder *et al.* (2006), Hyman *et al.* (2010), Johnson *et al.* (2010) and Seung *et al.* (2007) had an intervention period of only 12 weeks, whereas the participants in Knivsberg *et al*. (2003), Knivsberg *et al*. (2002) and Whiteley *et al.* (2010) followed a GFCF diet for a period of 12 months. The differences in study design and methods of intervention should also be considered.

In addition to the standardized ASD evaluation tools and questionnaires, and video-imagining used to evaluate outcome, Elder *et al*. (2006), Hyman *et al*. (2010), Johnson *et al.* (2010), Knivsberg *et al*. (2002), Reichert *et al.* (1990) and Whiteley *et al*. (1999) also used parental and anecdotal reports. Since the very fact that an intervention is being implemented may impact on perceptions about the outcome of the intervention, the validity of such a report is questionable (Srinivasan, 2009: 243). Gillberg (1995), however, noted that mothers were reliable informants on child development (both normal and deviant development) and that such a report can thus serve as a means of evaluation (Knivsberg, 2003: 248). Regardless, the above mentioned studies reported a considerable improvement in autistic behaviour.

When comparing the case reports of Hsu *et al*. (2009) and Irvin (2009), the outcomes were contradicting, as an improvement in behaviour was observed after only two and a half months by Hsu *et al*. (2009). In contrast, no improvement was noted by Irvin (2009) after a 14 month observation period. It should, however, be noted that the boy evaluated by Hsu *et al.* (2009) aged 3 years and 6 months, while the boy evaluated by Irvin (2009) was 12 years old. The age of the participant at intervention is thus, according to this data, likely to influence the overall outcome.

Data from the online survey conducted by Pennesi and Klein (2012) stated a significant improvement in overall autistic behaviour (it should, however, be noted that this improvement was based on parental report). Improvement in autistic behaviour was found to be greater in children with gastrointestinal symptoms, food allergies and food sensitivities.

Strict implementation of the GFCF diet for a period of more than six months also yielded a greater improvement in overall autistic traits. This might, however, be difficult to achieve as Johnson *et al*. (2010) reported poor adherence to the GFCF diet.

When evaluating the GFCF diet according to the Evaluative Method for Evaluating and Determining Evidence-based practices in Autism, the GFCF diet was found to be an established evidenced based practice. This dietary intervention therefore may have merit in the treatment of ASD related signs and symptoms in some patients, but due to the heterogeneous nature of the included studies and insufficient evidence, a conclusive conclusion can not yet be made.

3.3.2 Vitamin and mineral supplementation

Vitamins and minerals are known to be essential for optimal health (Adams *et al.,* 2003: conference preceding). Deficiencies in nutrients are major contributing factors to many health problems experienced in childhood, including inadequate growth and development, anaemia, hypothyroidism, scurvy, rickets, abnormal brain wave pattern and convulsions (Adams *et al.,* 2003: conference preceding; Rolfes, *et al.*, 2005: 321 – 344). According to a recent study, children with ASD are prone to vitamin and mineral deficiencies. This is thought to be due to chronic diarrhoea, constipation, gastrointestinal inflammation, and dietary restrictions which are commonly seen in children with ASD (Adams and Holloway, 2004: 1034). Adams *et al.* (2003) conducted a study in which they evaluated the vitamin and mineral status of over 150 children with ASD. In comparison with children without ASD, these children were found to have, much lower levels of vitamins A, C, D, E, all the B vitamins, zinc, magnesium and selenium (Adams *et al.,* 2003: conference preceding). According to Dosman *et al*. (2006) children with ASD are likely to present with a compromised iron status as well.

As the benefit of an adequate vitamin and mineral status in the improvement of intelligent quotient, scholastics tests, early neurological development, and behavioural, cognitive, and academic gains in children with learning disabilities are well known (Adams *et al.,* 2003: conference preceding).

Table 3: Summary of included studies: Gluten-free, casein-free diet (12 studies)

1	**Author reference**	**Type of study**	**Diagnostic criteria/ method use**	**Study population**	**Exclusion criteria**	**Intervention**		**Addition/ other treatment**
	Elder *et al.*, 2006					**Dietary intervention**	**Intervention period**	
		Randomized, double blind repeated measures crossover study Pilot study	DSM-IV ADI-R	2 – 16 yrs, male and female	Significant medical problems Physical and sensory impairment	Cross-over study Total n = 15 Intervention: GFCF diet Control group: no dietary intervention/ regular diet	12 week intervention period (Crossover study or 6 weeks on GFCF diet, and 6 week on normal diet)	Not mentioned
		Outcome(s) measured		**Means by which outcome was measured**		**Follow-up/ Compliance**		**Outcome of intervention**
		Effect of GFCF diet on the severity of ASD related symptoms Effect of GFCF diet on urinary peptide levels To evaluate parent behaviour in dietary treatment of child with ASD		Childhood Autism Rating Scale (CARS) Ecological Communication Orientation Scale (ECOS) Direct behavioural observation at home (video recordings) Urinary Peptide Levels (UPL)		Evaluation at baseline, 6 weeks and 12 weeks 13 children complete trial period (86.7% compliance rate)		No statistical significant difference in found in behavioural presentation No statistical significant difference found in UPL No statistical significant difference in parental behavioural influence and/ or confound Anecdotal reports varied from statistical data: parents of 7 children noted improvement in language, and decreased hyperactivity and tantrums
2	**Author reference**	**Type of study**	**Diagnostic criteria/ method use**	**Study population**	**Exclusion criteria**	**Intervention**		**Addition/ other treatment**
	Hsu *et al.*, 2009					**Dietary intervention**	**Intervention period**	
		Case report	Unknown	3yrs 6mo old boy		n = 1 Intervention: GFCF diet	Improvement/ behavioural changes noted after 2 ½ months (Case report reflects 11 months on GFCF diet)	Physiotherapy Occupational therapy Speech therapy Sensory integration
		Outcome(s) measured		**Means by which outcome was measured**		**Follow-up/ Compliance**		**Outcome of intervention**
		(case report)		Chinese Child Developmental Inventory (CCDI) Bayley Scale of Infant Development, second edition				After 2 ½ months on GFCF diet interpersonal relations, e.g. eye to eye contact and verbal communication improved, and kept on improving Postprandial vomiting decreased Improvements noticed in weight, height and vitality

Table 3: Summary of included studies: Gluten-casein free diet, *continued*

3	Author reference	Type of study	Diagnostic criteria/ method use	Study population	Exclusion criteria	Intervention		Addition/ other treatment
						Dietary intervention	**Intervention period**	
	Hyman *et al*., 2010	Randomized, double blind study (abstract)	Not mentioned	2 ½ - 5 ½ yrs; male and female	Children with milk/ wheat allergy Children with celiac disease	Total n = 22 Intervention: 12 weeks on strict GFCF diet Weekly randomized, double-blind challenges of snacks containing either 20g of wheat flour, 23g of non-fat milk, both, or neither Each type of snack were given three times	12 weeks	At least 10 hours of EIBI per week

	Outcome(s) measured	**Means by which outcome was measured**	**Follow-up/ Compliance**	**Outcome of intervention**
	Effect of GFCF diet on symptoms related to ASD	Ritvo Freeman Real Life Rating Scale Direct observation, making use of parent kept diary of child's food intake, sleep habits and bowel habits Videotaped play sessions with researcher	Evaluation at baseline, 6, 18, and 30 months Measures were also taken before each snack challenge, and again 2 and 24 hours after the snack 14 children completed the 12 week trial period (63% compliance rate)	No statistical significant difference noted in parent/ teacher/ researcher score on attention or activity, frequency or quality of stools, sleep behaviour, or activity levels during the 12 week intervention period Slight statistical significant difference were however noted in 2h post-prandial test in social interaction

4	Author reference	Type of study	Diagnostic criteria/ method use	Study population	Exclusion criteria	Intervention		Addition/ other treatment
						Dietary intervention	**Intervention period**	
	Irvin, 2006 *(continues on the following page)*	Case report	Not mentioned	12 yrs old boy		n = 1 Initial phase: 1 yr: GFCF diet Followed by 12 days on regular diet Second phase: 10 days: GFCF diet Followed by 21 day on regular diet Follow-up: 30 months following regular diet (Study conducted in 24-hour residential treatment facility; all foods prescribed by dietician)	~ 14 months	Not mentioned

Table 3: Summary of included studies: Gluten-casein free diet, *continued*

	Irvin, 2006 *(continues from previous page)*	**Outcome(s) measured**	**Means by which outcome was measured**	**Follow-up/ Compliance**	**Outcome of intervention**
		Effect of GFCF diet on behavioural symptoms related to ASD	Self-injurious behaviour, property destruction and aggression were assessed using videotaped sessions	Analog assessment were conducted: Final 5 days of initial GFCF phase; Twice during initial regular dietary phase; Twice during second GFCF phase, and Twice during second regular diet phase And again 30 months after completion of trial period	No difference in behaviour were noted (Initial behaviour included self-injury, physical aggression, property destruction, and self-restain)

5	**Author reference**	**Type of study**	**Diagnostic criteria/ method use**	**Study population**	**Exclusion criteria**	**Intervention**	**Addition/ other treatment**
	Johnson *et al.*, 2010					**Dietary intervention** / **Intervention period**	
		Open label, randomized, parallel groups design Pilot study	DSM-IV Autism Diagnostic Observation Schedule (ADOS)	3-5 yrs; male and female	Not mentioned	Total n = 22 Intervention: GFCF diet (n = 8) Control: Healthy, low sugar diet (n = 14) Parents met with nutritionist whom explained and provided material regarding assigned diet / 12 weeks	Not mentioned

	Outcome(s) measured	**Means by which outcome was measured**	**Follow-up/ Compliance**	**Outcome of intervention**
	Effect of GFCF diet, compared to healthy, low sugar diet, on the signs and symptoms related to ASD Adherence of GFCF diet Nutritional status	Mullen Scales of Early Learning AGS Edition Child behaviour checklist Direct behaviour observation measure (video recordings) Side effect checklist 24h diet recall	Evaluation done at baseline, and at 3 month follow-up	Improvement noticed in behaviour, language and rating in the core features of ASD; there were however no statistical significant difference noted between the intervention and control group No nutritional deficiencies noted on GFCF diet No side effects noted on GFCF diet Poor adherence of GFCF diet however noted after 12 week intervention period

Table 3: Summary of included studies: Gluten-casein free diet, *continued*

6	**Author reference**	**Type of study**	**Diagnostic criteria/ method use**	**Study population**	**Exclusion criteria**	**Intervention**		**Addition/ other treatment**
						Dietary intervention	**Intervention period**	
	Knivsberg *et al*., 2003	Single-blind, controlled study	Not mentioned	~ 7 years; male and female	Not mentioned *(However known that all participant had urinary peptide abnormalities*)	Total n = 20 Intervention: GFCF diet (n=10) Control: no dietary intervention (n=10) Oral and written information regarding GFCF diet given by dietitian	12 months	Not mentioned
		Outcome(s) measured		**Means by which outcome was measured**		**Follow-up/ Compliance**		**Outcome of intervention**
		Effect of GFCF diet on signs and symptoms related to ASD and urinary peptide abnormalities Effect of GFCF diet on urinary peptide abnormalities in children with ASD		Diagnosis of Psychotic Behaviour in Children (DIPAB) Structured interviews Parental reports		Data collected at baseline and after the 12 month intervention period Compliance not mentioned		Statistical significant improvement noted in overall autistic behaviour, communication, social interaction, isolation, and unusual or bizarre behaviour in children on the GFCF diet; no difference noted in control group Better development noted for children on GFCF diet than in children receiving no dietary intervention
7	**Author reference**	**Type of study**	**Diagnostic criteria/ method use**	**Study population**	**Exclusion criteria**	**Intervention**		**Addition/ other treatment**
						Dietary intervention	**Intervention period**	
	Knivsberg *et al*., 2002	Single-blind controlled study	Not mentioned	5 – 10 yrs; male and female	Not mentioned *(However known that all participant had urinary peptide abnormalities*)	Total n = 20 Intervention: GFCF diet (n=10) Control: no dietary intervention (n=10) Oral and written information regarding GFCF diet given by dietitian	12 months	Not mentioned
		Outcome(s) measured		**Means by which outcome was measured**		**Follow-up/ Compliance**		**Outcome of intervention**
		Effect of GFCF diet on signs and symptoms related to ASD and urinary peptide abnormailities		Diagnosis of Psychotic Behaviour in Children (DIPAB) Structured interviews Parental reports		Data collected at baseline and after the 12 month intervention period Compliance not mentioned		Although changes were noted in both groups of children, the changes were more significant in children on the GFCF diet Better development seen in children on the GFCF diet Statistical significant improvement noted in all autistic traits in children on GFCF diet; this was not noted in children in control group

Table 3: Summary of included studies: Gluten-casein free diet, *continued*

	Author reference	Type of study	Diagnostic criteria/ method use	Study population	Exclusion criteria	Intervention		Addition/ other treatment
8	Pennesi and Klein, 2012					**Dietary intervention**	**Intervention period**	
		Parental report (online survey)		Not mentioned/ caregivers/ parents completed survey		Total surveys (n) = 387 Dietary intervention: GFCF diet	Data collected over a 5 month period of time	Not mentioned
		Outcome(s) measured		**Means by which outcome was measured**		**Follow-up/ Compliance**		**Outcome of intervention**
		Effect of GFCF diet on signs and symptoms related to ASD Extent to which compliance effect the signs and symptoms related to ASD		90-item online questionnaire evaluating GI symptoms, food allergy, suspected food sensitivities, and degree and length of diet implementation				Statistical significant improvement of ASD related signs and symptoms noted in children with GI symptoms, food allergies and food sensitivities Strict diet implementation also resulted in statistical significant improvements in ASD related signs and symptoms Statistical significant improvement noticed when diet were implement for a time period of longer than 6 months compared to a time period shorter than 6 months

	Author reference	Type of study	Diagnostic criteria/ method use	Study population	Exclusion criteria	Intervention		Addition/ other treatment
9	Reichert *et al.*, 1990					**Dietary intervention**	**Intervention period**	
		Not mentioned/ participants divided into 3 groups (A, B2 and B 1)according to DSM III criteria	DSM-III	3 – 17 yrs; male and female	Not mentioned	Total n = 15 Type A: Strict gluten-free diet (n =8) Type B2: Strict milk-free diet (gluten were also excluded to a certain extent by using gluten-free bread) (n=7) Type B1: Strict milk-and gluten-free diet (n=4)	12 months	Not mentioned
		Outcome(s) measured		**Means by which outcome was measured**		**Follow-up/ Compliance**		**Outcome of intervention**
		Diagnosis of ASD subtypes (using DSM-III criteria) Effect of dietary intervention on the effect of signs and symptoms related to ASD		Antibodies to dietary antigens Behavioural and educational evaluation (parent and teacher reports)		Continues evaluation during the 12 months, but only data from the 12 month post-intervention was used		Dominant changes noted after 12 months period: increased social contact, decreased stereotypy, an end to self-mutilation, a decrease in 'dreamy state' periods, and improved sleep patterns Decrease in epileptic periods noticed

Table 3: Summary of included studies: Gluten-casein free diet, *continued*

	Author reference	Type of study	Diagnostic criteria/ method use	Study population	Exclusion criteria	Intervention		Addition/ other treatment
10						**Dietary intervention**	**Intervention period**	
	Seung *et al.*, 2007	Randomized, double-blind repeated measures crossover design	DSM-IV ADI-R	2 – 16year; male and female	Children with sensory-, physical- or significant medical problems were excluded	Total n = 15 Cross-over study Intervention period: GFCF diet Control period: regular diet/ no dietary intervention Participants were on one diet for 6 weeks, and on the alternate the next 6 weeks	12week	Vitamin/ mineral supplementation Participants continued with speech-, language- and occupational therapy

Outcome(s) measured	Means by which outcome was measured	Follow-up/ Compliance	Outcome of intervention
Effect of GFCF diet on verbal/ nonverbal communication in children with ASD	Video recordings Systematic Analysis of Language Transcripts (SALT)	Recordings were made at baseline, after 6 weeks on one diet, and after another 6 week on the alternate diet 2 of the participants did not complete the trail period (87% compliance rate)	No statistical significant difference noted in verbal and non-verbal communication between GFCF diet and regular diet

	Author reference	Type of study	Diagnostic criteria/ method use	Study population	Exclusion criteria	Intervention		Addition/ other treatment
11						**Dietary intervention**	**Intervention period**	
	Whiteley *et al.*, 2010 *(continues on the following page)*	Randomized controlled trial	ICD-10 code F84 ADR-I ADOS	4 – 11yrs; male and female	Children with epilepsy, fragile X syndrome, tuberous sclerosis or a developmental age below 24 months	Total n = 72 Stage 1: Intervention group: GFCF diet (n = 38) Control group: no dietary intervention (n = 18) Stage 2: After 8 months the control group were divided into an intervention group (n = 34) and control group (n = 17). Again the intervention group received a GFCF diet, and control group no dietary intervention Nutritionists monitored participants to ensure strict compliance and nutritional intake	Stage 1: 12 months Stage 2: 12 months (Total intervention period: 24 months)	Multivitamin and mineral supplement (only intervention group)

Table 3: Summary of included studies: Gluten-casein free diet, *continued*

	Whiteley *et al.*, 2010 *(continues from the previous page)*	**Outcome(s) measured**	**Means by which outcome was measured**	**Follow-up/ Compliance**	**Outcome of intervention**
		Effect of dietary intervention by comparing GFCF diet with no dietary intervention	ADOS Gilliam Autism Rating Scale (GARS) Vineland Adaptive Behavioural Scale (VABS) Attention-Deficit Hyperactivity Disorders – IV Rating Scale (ADAH-IV)	Stage 1: Evaluated at baseline, 8 and 12 months Stage 2: Evaluated at 12 months 15 children dropped-out in stage 1 (79% compliance rate) 100% compliance in stage 2	Dietary intervention has positive effect on development of children with ASD At 12 months significant improvement were noted in social interaction, inattention, and hyperactivity in the intervention group Control group showed a deterioration in condition in the same time period Statistical significant effect of diet only noted after 8 months in the intervention group

12	**Author reference**	**Type of study**	**Diagnostic criteria/ method use**	**Study population**	**Exclusion criteria**	**Intervention**		**Addition/ other treatment**
	Whiteley *et al.*, 1999					**Dietary intervention**	**Intervention period**	
		Randomized controlled trial	DSM-IV	~ 4 years; male and female	Not mentioned	Total n = 31 Intervention: GFCF diet (n=22) Control: no dietary intervention (n=6)	5 months	Not mentioned
		Outcome(s) measured		**Means by which outcome was measured**		**Follow-up/ Compliance**		**Outcome of intervention**
		Evaluate the short-term effect of a GFCF diet on the signs and symptoms related to ASD		Parental Satisfaction Questionnaire (PASS) Behaviour Summarized Evaluation (BSE) Kaufmann Assessment Battery for Children (K-ABC) Urinary analysis		Parental and teacher observations conducted weekly Other evaluation took place pre- and post intervention 22 completed study (71% compliance rate)		Parental interviews, and parental and teacher observations stated an improvement in vocal and non-vocal communication, attention and concentration, coordination and motor skills, awareness of self and environment, sleep patterns and aggressiveness.

Table 4: Summary of included studies: Vitamin and mineral supplementation (4 studies)

	Author reference	Type of study	Diagnostic criteria/ method use	Study population	Exclusion criteria	Intervention		Addition/ other treatment
						Dietary intervention	Intervention period	
1	Adams and Holloway, 2004	Randomized, double-blind, placebo-controlled trial	Not mentioned	3 – 8 yrs, both male and female	Multivitamin/ mineral supplementation prior to trial period other that a standard multivitamin/ mineral supplement	Total n = 25 Intervention: Spectrum Support: contains broad range of most vitamins and minerals, no copper and has moderate amount of vitamin B_6. Dose was gradually increased until a full dose of 3ml/5 pounds (2.25kg) Control group: Placebo	3 months	

Outcome(s) measured	Means by which outcome was measured	Follow-up/ Compliance	Outcome of intervention
Determine the levels of vitamin B_6, Vitamin C and alpha lipioc acid in children with ASD To determine the effect of multivitamin/ mineral supplement on the signs and symptoms related to ASD	Urine sample Biochemical tests Global impressions parental questionnaire	Baseline and post-intervention 20 children completed trail period (80% compliance)	Statistically significant improvements in sleep and gastrointestinal problems noted in intervention group, compared to control group Compared to typically developed children, autistic children has elevated levels of vitamin B_6 Although vitamin C levels increased during supplementation, it was still significantly below average for typical developing children

	Author reference	Type of study	Diagnostic criteria/ method use	Study population	Exclusion criteria	Intervention		Addition/ other treatment
						Dietary intervention	Intervention period	
2	Bertoglio *et al.*, 2010 *(continues on following page)*	Double-blind, placebo-controlled, cross-over clinical trial	DSM-IV-TR ADOS ADI-R	3 – 8 yrs, both male and female	Children who were already on methyl B_{12} supplementation, and participants not willing to change or add treatment for a 12 week period	Total n during 12 week trail period: 30 Total n during 6 month voluntary intervention period: 22 Cross-over design Intervention for 6 weeks: methyl B_{12}; 64.5µg/kg – administered in buttocks Control for 6 weeks: Placebo of saline	12 week intervention period 6 month voluntary extended intervention period	

Table 4: Summary of included studies: Vitamin and mineral supplementation, *continued*

	Bertoglio *et al.*, 2010 *(continues from previous page)*	**Outcome(s) measured**	**Means by which outcome was measured**	**Follow-up/ Compliance**	**Outcome of intervention**
		Assess whether methyl B_{12} treatment improved behavioural signs and symptoms related to ASD Assess whether methyl B_{12} supplementation were associated with increased plasma concentrations of glutathione (GSH) and an increased redox ratio	Parental Interview for Autism - Clinical Version (PIA-CV) Clinical Global Impression Scale of Improvement (CGI-I) CARS Peabody Picture Vocabulary Test – Third Edition (PPVT-III) Stanford Binet Fifth Edition Routing Subsets Aberrant Behaviour Checklist (ABC) Child Behaviour Checklist (CBCL) MacArthur Communication Developmental Inventory (MCDI)	Blood for GSH and behavioural assessment took place at: baseline, 6 weeks and 12 weeks	No statistically significant difference were noted in the behavioural presentation of children with ASD But a subgroup of participants did respond to the intervention: 9 subjects showed statistically significant improvement in some of the behavioural signs and symptoms

3	**Author reference**	**Type of study**	**Diagnostic criteria/ method use**	**Study population**	**Exclusion criteria**	**Intervention**		**Addition/ other treatment**
	Dosman,*et al*., 2006					**Dietary intervention**	**Intervention period**	
		Open-label treatment trial Pilot study	ADI-R ADOS Clinical observation	~ 6 yrs 6 mo, both male and female	Children already on iron supplements	Total n = 43 Oral iron supplementation (6 mg elemental iron/ kg/ day) (Each participant served as his/ her own control)	8 weeks	Not mentioned

Table 4: Summary of included studies: Vitamin and mineral supplementation, *continued*

	Dosman *et al*., 2006 (continued)	**Outcome(s) measured**	**Means by which outcome was measured**	**Follow-up/ Compliance**	**Outcome of intervention**
		Determine relationship between low serum ferritin and sleep disturbances Evaluate relationship between low ferritin and dietary iron intake	Sleep Disturbance Scale for Children Food Record Clinical Global Impression Scale Blood samples Growth measurements	Information obtained at baseline and 8 weeks 33 completed trail period (77% compliance rate)	A significant improvement in restless was sleep noted; 29% showed improvement No difference however seen in delayed sleep onset No difference found in dietary iron intake during trial period: 8% of children followed a GFCG diet and no difference in iron intake was noted compared to other/ no special diet. (Significant improvement noticed in ferritin levels noted in all participants)

4	**Author reference**	**Type of study**	**Diagnostic criteria/ method use**	**Study population**	**Exclusion criteria**	**Intervention**		**Addition/ other treatment**
	Xia, 2011					**Dietary intervention**	**Intervention period**	
		Case Report	Not mentioned	9 yr old boy		Total n = 1 Were on vitamin B_6 (pyridoxine HCl; 12.5mg per capsule) and magnesium (citrate-glycinate-oxide; 60mg per capsule) supplementation daily; received 3 capsules of each per day 4 months later he started on DMG (dimethylglycine; 125mg per capsule) while continuing on vitamin B_6 and magnesium. He received 3 capsules of DMG per day	Post-intervention: after 5 months Report given after 2 years on nutritional supplements	
		Outcome(s) measured		**Means by which outcome was measured**		**Follow-up/ Compliance**	**Outcome of intervention**	
		(case report)		Autism Treatment Evaluation Checklist (ATEC)		Evaluation done pre-intervention period, and at 5 months post-intervention	ATEC score improved by 47.6% and 53.1% , respectively (2 independent assessors) Improvements were noted in the following areas: communication, eye contact, sleep pattern, temper, attentiveness and hyperactivity, daily routine Improvements were also noted by teacher; better academic performance	

Methods of intervention varied among the studies with Adams and Holloway (2004) evaluating multivitamin and mineral supplementation, Bertoglio *et al*. (2010) evaluating vitamin B_{12} supplementation, Dosman *et al.* (2006) iron supplementation and Xia (2011) evaluating vitamin B_6, magnesium and dimethylglycine (DMG) supplementation (the method of implementation used by each study is briefly described in Table 4). As supplementation was evaluated, supplements were, together with an indication of the required daily dosage and means of administration, provided by the research group. The shortest intervention period was that of Dosman *et al.* (2006) (a period of eight weeks). Bertoglio *et al*. (2010) had an initial intervention period of 12 weeks with a voluntary extended intervention period of six months. Adams and Holloway (2004) and Xia (2011) had an intervention period of three and five months, respectively.

The primary outcome evaluated by all studies was the effect of vitamin and mineral supplementation on the signs and symptoms related to ASD. Dosman *et al.* (2006) evaluated the relationship between low ferritin levels and dietary intake as well. Outcome was evaluated using standardized ASD evaluation tools and questionnaires, urine samples, biochemical tests, food record and anthropometric measurements to assess growth. A significant improvement in autistic behaviour was noted by Dosman *et al*. (2006), Adams and Holloway (2004) and Xia (2011).

Dosman *et al.* (2006) reported a 29% improvement in restless sleep; no difference in delayed sleep onset was, however, observed. When comparing the diversity in food patterns and dietary intake during the intervention period (8% of participants also followed a GFCF diet), no difference in the dietary iron intake was noted. Adams and Holloway (2004) found multivitamin and mineral supplementation to improve (statistically significant outcome) the overall autistic behaviour; the greatest outcome was noted in sleep patterns and gastrointestinal related symptoms. Xia (2011) reported that vitamin B_6, magnesium and DMG improved communication, eye contact, sleep patterns, temper, attentiveness and hyperactivity. Although Bertoglio *et al.* (2010) found no statistically significant difference 1033), determining the value of supplementation in the treatment of ASD is necessary. Four of the 29 included studies evaluated the effect of vitamin and mineral supplementation on the

signs and symptoms related to ASD. Of these studies, briefly summarized in Table 4, two were conducted as randomized controlled trials (Adams and Holloway, 2004; Bertoglio *et al*., 2010), one as an open-label treatment trail (Dosman *et al.,* 2006) and one as a case study (Xia, 2011). The number of participants included in the studies varied between one and 43 participants, and the ages between three and nine years. The study population of these four studies included both male and female participants.

Although four studies on vitamin and mineral supplementation in ASD were identified by the literature search, the heterogeneity was such that this dietary intervention could not be evaluated in terms of evidence-based practice. The quality rating of the individual articles evaluated were as follows: one article (Bertoglio *et al.,* 2010) was classified as having a strong report quality, two articles (Adams and Holloway, 2004; Dosman *et al.,* 2006) had an adequate report quality, and one article (Xia, 2011) was of poor quality. As multivitamin- and mineral supplementation w be effective in the treatment of ASD in some studies, further research on supplementing this at levels adequate for optimal health and according to the recommended daily intake (as determined by the Food and Nutrition Board, Institute of Medicine in 2002) for age is recommended. Correcting vitamin and mineral deficiencies might be more effective and safer, than supplementing mega-dosages.

3.3.3 Polyunsaturated fatty acid supplementation

Polyunsaturated fatty acid supplementation is also a common diet related intervention for the treatment of ASD with as many as 28 % of families reporting PUFA supplementation in a survey conducted in 2006 (Green, *et al.,* 2006: 70). PUFAs are fatty acids deemed essential for, among others, normal brain development and function, and, as it cannot be synthesized by *de novo* in the human body, it should be provided by dietary sources (Richardson, 2004: 383). PUFAs are incorporated into phospholipids which make up a large portion of the neuronal cell membranes. Phospholipids are part of many important neural functions, including synaptic growth, cell signalling, neurotransmission and second messaging. Eicosopentanoic acid (EPA) and docohexanoic acid (DHA) are the primary omega-3 fatty

acid in the brain, and arachadonic acid (AA) the primary omega-6 fatty acid (Johnson *et al.,* 2010: 1).

As an increased amount of evidence suggests functional deficiency or imbalance of these fatty acids in childhood developmental disorders (including ADHD, dyslexia, dyspraxia and ASD) (Richardson, 2004: 383), the effect of fatty acid supplementation in the treatment of ASD is an important consideration. Four of the 29 included studies assessed this; a summary of each is given in Table 5. Homogeneity was once again limited. Although all studies were conducted as randomized controlled trials, two studies evaluated the effect of omega-3 fatty acid supplementation (Bent *et al.,* 2011; Johnson *et al.,* 2010), one the effect of omega-3 fatty acid- together with vitamin E supplementation (Amminger *et al*., 2007) and one (Meguid *et al.,* 2008) omega-3 and -6 supplementation. Table 5 provides a brief summary on the interventions and the dosage of omega-3 and/ or omega-6 fatty acids received by each of the participants. All studies, except for Bent *et al.* (2011), used omega-3 and -6 capsules for supplementation. Bent *et al.* (2011) used orange-flavoured pudding packets to administer the omega-3 fatty acids. The supplements were provided by the research group, and all participants lived at home during the time of intervention; regular follow-up consultations were scheduled with caregivers during this time. Children participating in the Amminger *et al.* (2007) study, however, attended the same specialized day care centre for the long-term treatment of ASD and assessment took place on a regular basis at the school.

The number of participants included in the studies varied between 13 and 60 and all studies included both male and female participants. Ages of the participants ranged between three to 17 years. Bent *et al*. (2011), Johnson *et al.* (2010) and Mequid *et al.* (2008) had an intervention period of 12 weeks and Amminger *et al.* (2007) had an intervention period of only 6 week.

Outcome was assessed using standardized ASD assessment tools and questionnaires, and video recordings. Bent *et al*. (2011) and Johnson *et al.* (2010) reported that omega-3 fatty acid supplementation did not yield a statistically significant change in autistic behaviour. Omega-3 fatty acid supplementation together with vitamin E supplementation was, however, found by Amminger *et al.* (2007) to yield a statistically significant improvement in

hyperactivity in children with ASD. A slight improvement in speech and stereotypic behaviour was also noted. Meguid *et al.* (2008), who supplemented both omega-3 and omega-6 fatty acids for a period of 12 weeks, found a statistically significant improvement in the overall autistic behaviour in 20 of the 30 study participants.

As with vitamin and mineral supplementation, PUFA supplementation could not be evaluated on terms of being an evidence-based practice as the heterogeneity among the four included studies was too big. When evaluating the four articles according to the research report rigor, Bent *et al.* (2011) and Johnson *et al. (*2010) were identified as having a strong report quality, and Amminger *et al.* (2007) and Meguid *et al.* (2008) to have an adequate quality. Further research related to the effect of correcting fatty acid deficiencies and imbalances and supplementing both omega-3 and -6 fatty acids according to the recommended daily intake levels for age, is recommended.

3.3.4 Probiotic supplementation

Probiotics are defined by the Food and Agricultural Organization of the United Nations and World Health Organization (FAO/WHO) Expert Consultation Report (2001:1) as 'live microorganisms that, when administered in adequate amounts, have a beneficial effect on the health of the host'. Probiotics have shown efficacy in a wide array of health problems, including antibiotic-induced and acute infectious diarrhoea, inflammatory bowel disease, and irritable bowel syndrome. These microorganisms also contribute to improved immunity (Crithchfield *et al.,* 2011: 2).

When compared with typically developing children, children with ASD generally present with a higher prevalence of gastrointestinal symptoms. After conducting a study to measure the relationship between gastrointestinal symptoms and the severity of ASD, Adams *et al.*, (2011: 22) reported an increased prevalence of gastrointestinal symptoms with increased severity of autism. As the importance of probiotics in optimal gastrointestinal tract health is being recognized, it is hypothesized that probiotic treatment might play a role in alleviating

Table 5: Summary of included studies: Polyunsaturated fatty acid supplementation (4 studies)

	Author reference	Type of study	Diagnostic criteria/ method use	Study population	Exclusion criteria	Intervention		Addition/ other treatment
1	Amminger *et al.*, 2007					**Dietary intervention**	**Intervention period**	
		Randomized, double-blind, placebo-controlled trial Pilot study	DSM-IV ADI-R ADOS	5 -17 yrs, male and female	Children who had other serious medical conditions as well; And children on psychotropic drugs	Total n = 13 Intervention group: 1.5g Omega-3 fatty acid per day (0.84g EPA and 0.7g DHA), plus 1 mg vitamin E (n = 7) Control group: placebo (n = 6)	6 weeks	
		Outcome(s) measured		**Means by which outcome was measured**		**Follow-up/ Compliance**		**Outcome of intervention**
		Effect of omega-3 fatty acid supplementation on signs and symptoms related to ASD		ABC		Assessment done at baseline, and at 6 week follow-up (post intervention)		Statistical significant improvement in hyperactivity noticed in intervention group Slight difference also noted in inappropriate speech and stereotypy as well
2	**Author reference**	**Type of study**	**Diagnostic criteria/ method use**	**Study population**	**Exclusion criteria**	**Intervention**		**Addition/ other treatment**
	Bent *et al.*, 2011					**Dietary intervention**	**Intervention period**	
		Randomized, controlled trial Pilot study	DSM-IV TR ADOS Social Communication Questionnaire (SCQ)	3-8 yrs, male and female	Children with allergy for fish or nuts, diabetes, a bleeding disorder, seizure disorder, cancer, perinatal brain injury, other mental illness, or prior use of omega-3 fatty acids	Total n = 27 Intervention group: omega-3 fatty acids (provided as orange-flavoured pudding packets containing 650mg omega-3 (0.35g EPA and 0.23g DHA); given twice per day to provide a dose of 1.3g per day (n = 14) Control group: placebo (also provided as orange-flavoured pudding packets, but omega-3 fatty acids were replaced by safflower oil) (n = 13)	12 weeks	
		Outcome(s) measured		**Means by which outcome was measured**		**Follow-up/ Compliance**		**Outcome of intervention**
		Feasibility and initial safety of omega-3 fatty acid supplementation Effect of omega-3 fatty acid supplementation on hyperactivity in children with ASD		PPVT-III ABC Behaviour Assessment System for Children (BASC) Clinical Global Impression-Improvement scale (CGI-I)		Families were contacted telephonically at week 2 and 8 Brief clinical evaluation took place at 6 weeks Outcome assessment done at 12 weeks Compliance rate: 69% in intervention group, and 75% in control group		Improvement measured in hyperactivity; improvement were however not statistically significant Other behavioural signs and symptoms also showed an slight improvement, but once again none of the scores were statistically significant

Table 5: Summary of included studies: Polyunsaturated fatty acid supplementation, *continued*

3	Author reference	Type of study	Diagnostic criteria/ method use	Study population	Exclusion criteria	Intervention		Addition/ other treatment
	Johnson *et al*., 2010					**Dietary intervention**	**Intervention period**	
		Open label, randomized, parallel groups design Pilot study	DSM-IV ADOS	~ 3 yrs, male and female	On prescription medication, any identifiable genetic or metabolic conditions which might the reason for the ASD, low platelet count, or a bleeding disorder	Total n = 23 Intervention group: omega -3 supplementation (400mg DHA per day; took 2 capsules per day) (n =10) Control group: healthy, low sugar diet (n=13)	12 weeks	

Outcome(s) measured	Means by which outcome was measured	Follow-up/ Compliance	Outcome of intervention
Effect of omega-3 supplementation on the signs and symptoms related to ASD	Child Behaviour Checklist Direct observation (video recordings) Mullen scales of early learning AGS edition Side-effect checklist	Evaluation done at baseline and at 12 weeks post-treatment 85.3% adherence to treatment	No statistical significant difference experience in the signs and symptoms related to ASD No side effects noted for omega-3 supplementation

4	Author reference	Type of study	Diagnostic criteria/ method use	Study population	Exclusion criteria	Intervention		Addition/ other treatment
	Meguid *et al*, 2008					**Dietary intervention**	**Intervention period**	
		Not mentioned (controlled trial)	DSM-IV CARS	3 - 11yrs, male and female	Not mentioned	Total n = 60 Intervention group: 2 capsules Efalex twice per day (DHA fish oil and evening primrose oil supplement; thus containing both omega-3 and omega-6; each capsule contained 60mg DHA, 12mg gamma-linolenic acid, 13mg EPA and 5mg AA). (n=28) Control group: no intervention (n=30)	12 weeks	

Outcome(s) measured	Means by which outcome was measured	Follow-up/ Compliance	Outcome of intervention
Estimation of free PUFA in the blood of children with ASD Evaluation of effect of PUFA supplementation on signs and symptoms related to ASD	CARS	Evaluation done at baseline and after the 12 week intervention period	20 of 30 participants had a statistically significant improvement in the CARS score; Statistically significant improvement in ASD related behaviour were noted The other 10 children had no clinical improvement

Table 6: Summary of included studies: Probiotic supplementation (1 study)

1	Author reference	Type of study	Diagnostic criteria/ method use	Study population	Exclusion criteria	Intervention		Addition/ other treatment
						Dietary intervention	Intervention period	
	Kaluzna-Czaplinska and Blaszczyk, 2010	Preliminary study (not mentioned)	DSM-IV	4 – 10 yrs, male and female	Not mentioned *(though mentioned that all participant suffered from severe GI problems, e.g. abdominal pain, constipation and diarrhoea)*	Total n = 22 Probiotic supplementation: Lactobacillus acidophilus orally twice per day ($5x10^9$ CFU/g) Diet: all followed a sugar free diet, but 12 followed a varied diet and 10 a restricted diet (Each participant served as his/ her own control)	8 weeks	Vitamin and mineral supplementation varied between participants

Outcome(s) measured	Means by which outcome was measured	Follow-up/ Compliance	Outcome of intervention
Evaluate the difference between DA and DA/LA ratio in the urine of children with ASD before and after probiotic treatment Effect probiotics have on behavioural symptoms related to ASD	Urine samples Questionnaires (not specified)	Evaluation at baseline and post-treatment Post treatment (100% compliance)	Significant decrease in both DA and DA/LA noted post intervention Significant improvement also noted in the ability to concentrate and to carry out orders No difference noted in social skills

Table 7: Summary of included studies: Inositol (1 study)

1	Author reference	Type of study	Diagnostic criteria/ method use	Study population	Exclusion criteria	Intervention		Addition/ other treatment
						Dietary intervention	Intervention period	
	Levine.,1997	Controlled-double blind cross-over trial (abstract)	DSM-III-TR	~ 5.6 years	Not mentioned (abstract)	Total n = 10 Cross-over trial: Intervention group: Inositol (200mg/ kg twice per day) Control group: Placebo (dextrose) (200mg/ kg twice per day)	8 weeks	Not mentioned (abstract)

Outcome(s) measured	Means by which outcome was measured	Follow-up/ Compliance	Outcome of intervention
Effect of inositol on signs and symptoms related to ASD	CARS	Evaluation took place at baseline, 2, 4, 6 and 8 weeks	No statistical significant difference in the signs and symptoms related to ASD were found

ASD related symptoms (Crithchfield *et al.,* 2011: 2). Research in this field is, however, limited as only one study by Kaluzna-Czaplinska and Blaszczyk (2010) has evaluated probiotic supplementation in ASD. Table 6 provides a brief overview of this study. A total of 22 participants, aged four to 10 years, were included for evaluation. *Lactobacillus Acidophilus* was administered twice daily for a period of 8 weeks while participants followed a healthy, sugar-free diet.

The effect of probiotic supplementation on the level of D-arabinitol (DA) and the ratio of D-/L-arabinitol (DA/LA) were evaluated as the primary outcome of the study. A change in the ASD related signs and symptoms were evaluated secondary to this. Outcome was assessed using urine samples and questionnaires, and a decrease in the DA level and DA/LA ratio were noted. Improvements in the ability to concentrate and carry out orders were also observed, which could possibly be attributed to the change in the DA level and DA/LA ratio.

Probiotic supplementation could not be assessed in terms of being an evidence-based practice as the literature search yielded only one study on this. When evaluating the quality of the study according to research report rigor, the study is, however, classified to be of poor quality.

Further research on how probiotic supplementation affects the severity and prevalence of gastrointestinal related symptoms in children with ASD probiotic supplementation is thus required before this intervention method can be regarded as a distinct method of treatment for ASD related symptoms.

3.3.5 Inositol

Inostiol, classified as a vitamin-like substance and thus a dietary supplement (WebMD, online), is a simple glucose isomer and a key metabolic precursor of serotonin (Levine, 1997: 147). Although manufactured in laboratories for supplementation, inositol is found in many foods, in particular fruit (melon and oranges are especially good sources) (WebMD, online). Inositol has been reported to be effective in the treatment of psychological disorders such as depression, panic disorder and obsessive-compulsive disorder (Levine, 1997: 147 – 150).

This led to research evaluating the effect of inositol on the signs and symptoms related to ASD.

Of the 29 studies included, only Levine (1997) evaluated inositol supplementation in ASD. The study by Levine (1997), summarized in Table 7, consisted of a double-blind, controlled, cross-over trial for a period of eight weeks. The study population was relatively small as only 10 children, with a mean age of 5 ½ years, participated. As the literature search yielded only the abstract of the study, the gender of the participants and the facility where the study was conducted is not known. The quality of the study could also thus not be evaluated.

Outcome was assessed using the Childhood Autism Rating Scale (CARS). No statistically significant differences in the signs and symptoms related to ASD were noted after intervention. Based on these findings, further methodologically sound research is encouraged before inositol can be considered as a treatment option for ASD.

3.3.6 Ketogenic diet

The ketogenic diet is a dietary intervention commonly used for the treatment of 'all types of seizures in children in whom drug therapy has failed' (Remig, 2008:1088). Based upon an observation that fasting is beneficial in the control of seizures (Evangeliou *et al.,* 2003: 113), this dietary method aims to create and maintain a state of ketosis in the body (Remig, 2008: 1088). Children with drug refractory epilepsy on the ketogenic diet have been found to have a reduced prevalence of seizures and a decreased dependence upon medication (Remig, 2008:1090). The potential benefit of this dietary intervention has also been suggested in the treatment of cancer, mental behaviour, hyperactivity, aging, Alzheimer's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis, stroke, brain injuries and ASD (Stafstrom and Rho, 2012: 59). The mechanism of action is, however, not fully understood. It is, though, known that the ketogenic diet influences the neuronal metabolism by causing ketone bodies to act as inhibitory neurotransmitters. This produces an anticonvulsant effect (Remig, 2008: 1088).

The traditional- and the medium-chain triglyceride (MCT-) based approaches have been distinguished. With the traditional approach, as much as 75% of the daily energy requirement should be met by dietary fat intake. The daily protein intake should be sufficient to meet the daily requirement for age, while carbohydrate intake is limited to the remaining portion of daily energy requirements for age (Remig, 2008: 1088). The MCT-approach is easier to implement since long-chain fatty acids are replaced by MCT oil which is more ketogenic. For this reason more non-ketogenic foods such as fruits, vegetables, and small amounts of starches can be included in the diet (Remig, 2008: 1088).

Of the 29 included studies, only Evangeliou *et al*. (2003) studied the outcome of a ketogenic diet on ASD related symptoms. Table 8 provides a summary of this study. This study was conducted as a prospective, follow-up study for a period of 12 months. Participants followed a ketogenic diet during the first six months of the intervention period; four weeks of strict adherence to the ketogenic diet were interrupted by two weeks of no dietary intervention. The John Radcliffe diet, a variation of the MCT oil approach, was used. Daily energy intake was distributed as follows: 30% of energy as MCT oil, 30% as fresh cream, 11% as saturated fat, 19% as carbohydrates and 10% as protein. No dietary intervention was implemented during the second six months of the intervention period, but monthly psychiatric examinations were scheduled. A total of 30 children aged four to 10 years and including both males and females, participated in the study. Participants were admitted to the Paediatric Clinic of the University Hospital of Heraklion, Crete, for the entire 12 month intervention period.

CARS, biochemical tests, electrocardiogram and alert-phase electroencephalogram (EEG) were used to assess the outcome of the diet on ASD related symptoms. A significant improvement in learning ability was noted as 60% of participants presented with improvements in social behaviour, interaction, speech, cooperation, stereotypy and hyperactivity. This beneficial effect was eminent even during the diet-free intervals, and lasted well into the second six months after the intervention. These improvements were, however, more significant in children with mild ASD than in children with more severe autistic behaviour. The ketogenic diet was well tolerated by 76% of the participants.

This diet related treatment method could not be evaluated on terms of evidence-based practice as the literature search yielded only one study. The research report rigor was classified as adequate (it should be noted that the study was a pilot study). Although no firm conclusions can be drawn, the ketogenic diet can be regarded as a dietary intervention with a possible promising outcome and further research is required.

3.3.7 Digestive enzymes

The use of digestive enzymes is closely related to the 'opioid excess theory' which motivated the development and implementation of the GFCF diet. In children with ASD, gluten and casein are thought to be insufficiently digested by the pancreatic and small intestine peptidases, resulting in short chain peptide molecules similarly structured as endogenous opioid substances. It is believed by some that the influence of these opioid substances on the human brain function induces ASD related signs and symptoms (Munasinghe *et al.,* 2010: 1131-1132).

Other than the exclusion of foods containing gluten and casein, dietary supplementation of peptidase enzymes are hypothesized to lower the effect of the endogenous opioid. The enzymes are believed to break down the exorphins into smaller particles which do not have an opioid activity (Munasinghe *et al.*, 2010: 1132). The study by Munashinghe *et al.* (2010) was the only study found to test this hypothesis. This study, briefly summarized in Table 9, was conducted as a double-blind, randomized controlled, cross-over trial for a period of six months. Forty three male and female children aged three to eight years participated in the study. As a cross-over trial was conducted, participants were divided into two groups with one group initially being part of the intervention group and the other of the control group. The cross over took part after three months, and each participant served as his/ her own control. Peptizyde, a plant-derived proteolytic enzyme supplement, was provided by the research group. Participants lived at home during the time of intervention and were assessed on a monthly basis during the six month intervention period.

The Global Behaviour Rating Scale (GBRS), Additional Rating Scale (ARS), Language Development Survey and a therapist adapted version of the GBRS were used to assess the outcome of the digestive enzymes on ASD related symptoms. No statistically significant improvement in overall autistic behaviour (including gastrointestinal symptoms, sleep quality, social interaction and language skills) was noted after the intervention period. A slight increase in the variety of foods consumed was, however, seen. Data reporting was of high quality. As study participants did not follow a GFCF diet during the intervention period, the value of combined therapy has not been determined. Methodologically sound research is thus required before digestive enzyme supplementation can be regarded as an intervention method of merit in the treatment of ASD.

3.3.8 Detoxification

As previously mentioned, the aetiology of ASD is largely unknown. One of the possible causative factors that have received considerable attention in the past is heavy metal exposure (such as mercury, lead and other toxic metals) (Adams *et al.*, 2009: 18). It is hypothesized that chelation and other detoxification methods may result in increased heavy metal excretion, and thus an improvement in the ASD related signs and symptoms (Soden *et al.*, 2007: 476).

Only one of the included 29 studies tested this theory. In 2009, Adams *et al.* (briefly summarized in Table 10) conducted a randomized, double-blind, placebo controlled/ comparison trial, supplementing one round of oral dimercapto succinic acid (DMSA) in 65 participants, and an additional six rounds in 49 participants. Participants aged three to eight years. The Pervasive Developmental Disorder Behaviour Inventory (PDD-BI), Autism Treatment Evaluation Checklist (ATEC), Severity of Autism Scale (SAS) and the Autism Diagnostic Observation Schedule (ADOS) tools were used to assess outcomes. Seventy seven percent of the participants responded well to the treatment and showed a statistically significant improvement in overall autistic behaviour. Improvement was, however, similar for the participants who received one round of treatment and those who received seven

Table 8: Summary of included studies: Ketogenic diet (1 study)

1	Author reference	Type of study	Diagnostic criteria/ method use	Study population	Exclusion criteria	Intervention		Addition/ other treatment
						Dietary intervention	Intervention period	
	Evangeliou *et al.*, 2003	Prospective follow-up study (pilot study)	Not mentioned	4 -10 yrs, male and female	Not mentioned	n =30 Intervention: Ketogenic diet (John Radcliffe diet with an energy distribution of: 30% from MCT oil, 30% from fresh cream, 11% from saturated fat, 19% from carbohydrates and 10% from protein) (Each participant served as his/ her own control) Children were admitted to the Pediatric Clinic of University Hospital of Heraklion, Crete from May 1999 to May 2000	Total trail period: 12 months. Ketogenic diet was, however, only implemented for 6 months during which 4 weeks of strict diet adherence were interrupted by 2 week of no dietary intervention Participants were followed-up for the second 6 months on a monthly basis (no dietary intervention)	Multivitamin and mineral supplement to meet RDI's for age were also given

Outcome(s) measured	Means by which outcome was measured	Follow-up/ Compliance	Outcome of intervention
Effect of ketogenic diet on autistic behaviour	CARS Biochemical test Electrocardiogram Alert-phase electroencephalogram (EEG)	Evaluation, including laboratory examinations, was performed at the end of each 4-week diet phase, and at the end of each 2-week interval diet-free phase. Monthly psychiatric evaluation were performed during the 6 months follow-up period	60% of participants presented with improvements in social behaviour and interaction, speech, cooperation, stereotypy and hyperactivity. These improvements contributed significantly to learning ability. Improvements were more significant in patients with mild autistic behaviour, than in patients with severe autistic behaviour. The beneficial effect lasted during diet-free intervals; even during the post-treatment follow-up period the beneficial actions were maintained for relatively long period. Diet was tolerated well by 76.6% of participants.

Table 9: Summary of included studies: Supplementation of digestive enzymes (1 study)

1	Author reference	Type of study	Diagnostic criteria/ method use	Study population	Exclusion criteria	Intervention		Addition/ other treatment
						Dietary intervention	Intervention period	
	Munasinghe *et al.*, 2010	Double-blind randomized controlled trial	DSM-IV-TR	3 – 8yrs, male and female	Hearing or vision loss Co-morbid conditions such as tuberous sclerosis, neurofibromatosis, genetic abnormalities, allergies and GI related problems	Total n = 43 Intervention group: Peptizyde: initially ½ to 1 capsule with largest meal of the day, increasing gradually over several days to a dose of 2 capsules with each meal Cotrol group: Placebo Cross-over design (took place after 3 months): Sequence 1 Peptizyde: 21 Sequence 2 Placebo: 22	6 months	Participants whom were on complementary treatment before the intervention period continued with this during the study

Outcome(s) measured	Means by which outcome was measured	Follow-up/ Compliance	Outcome of intervention
Effect of digestive enzyme supplementation on improving expressive language, behaviour and other symptoms related to ASD	Global Behaviour Rating Scale (GBRS) Additional rating scale (ARS) Language Development Survey Therapist Rating Scale	Evaluation took place before enrolment and monthly thereafter during the 6 month intervention period 63% compliance rate	No clinically significant improvement were noted in behaviour, gastrointestinal symptoms, sleep quality, engagement with therapist, language and vocabulary Small statistically significant improvement was though noted in the variety of food consumed

Table 10: Summary of included studies: Detoxification (1 study)

1	Author reference	Type of study	Diagnostic criteria/ method use	Study population	Exclusion criteria	Intervention		Addition/ other treatment
						Dietary intervention	Intervention period	
	Adams *et al.*, 2009	Randomized, double-blind, placebo controlled/ comparison trial	Not mentioned	3-8 yrs	Not mentioned	Phase 1: one round of oral dimercapto succinic acid (DMSA) treatment (3 days) (n = 65) Phase 2: 6 additional rounds of DMSA treatment (n = 49)	Not mentioned	

Outcome(s) measured	Means by which outcome was measured	Follow-up/ Compliance	Outcome of intervention
Effect of detoxification therapy on the signs and symptoms related to ASD	PDD-BI ATEC SAS ADOS	ATEC conducted beginning phase 1 and end phase 2; other 3 instruments and the beginning and end of phase 2	77% op participants had an statistical significant improvement in the behaviour 11% of participant however presented with a deterioration in condition The difference noted between participants in phase 1 and phase 2 was the same, and therefore a difference between 1 round and 7 rounds of treatment is not much

rounds of treatment. Eleven percent of participants presented with a deterioration in their condition.

Even though reporting in this study was considered of poor quality, the findings have highlighted the fact that there is often a subgroup of participants whom will either not respond to treatment in the same manner as others, or will respond negatively to the treatment given. As with the diet-related treatment options previously discussed, further research is required.

3.3.9 Other dietary interventions

One of the included studies, Chan *et al. (*2012), evaluated a dietary intervention based upon a traditional Chinese concept of healing that has been practiced within the *Shaolin*-temple for over a thousand years. This method of treatment, also referred to as the *Shaolin* medical approach, is based upon the concept of 'food as medicine' and is commonly implemented for promoting both mental and physical health. *Chanyi,* the subcategory of the *Shaolin* medicine evaluated, is based upon the hypothesis that an 'excessive intake of hot and spicy foods (including all meats, seafood, eggs, ginger, garlic, spring onions, Chinese chives, and chilli) with a high fat and energy content generates excessive heat in the body and causes blood and *Qi* stagnation' (Chan *et al.,* 2012). This, in turn, is thought to result in both physical and mental illnesses, including ASD.

Chan *et al.* (2012) conducted a randomized, controlled trial to assess this hypothesis (Table 11). Twenty-four male and female children aged seven to 17 years, participated in the four week intervention. Participants were divided into an intervention group (dietary intervention according to *Chanyi* guidelines and beliefs*)* and a control group (no dietary intervention). The dietary intervention was as follows: the intake of ginger, garlic, green onion, spicy foods, eggs, meat, and fish were limited and thus the diet mainly consisted of foods from the grain (e.g. noodles, brown rice), vegetable (e.g. broccoli, tomatoes), fruit (e.g. grapes, apples), bean (e.g. soy, peas), mushroom (e.g. black fungus, straw mushrooms), nut (e.g.

walnuts, almonds) and root (e.g. potatoes, yams) categories. The type and amount of food was not specified, but children were asked to eat until they were about 80% full at each meal.

Outcome was evaluated using standardized tools and questionnaires (indicated in Table 11). This dietary intervention yielded no change in the attention ability of the children. Statistically significant differences in mental flexibility and inhibitory control were, however, perceived. Parents furthermore reported improvement in communication and in flexibility towards daily routine and schedules. The publication was considered to have a strong report quality.

As the dietary intervention included mainly whole wheat grains, fruits, vegetables, nuts, legumes and roots, it can be hypothesized that a diet limiting refined carbohydrates and foods with a high saturated fat content, and providing large amounts of vitamins, minerals and antioxidants might yield a positive outcome in the treatment of ASD related signs and symptoms. How strong spices and flavourings affect ASD related symptoms should, however, also be further investigated.

The remaining three included studies (Luiselli *et al.*, 1994; Patel and Curtis, 2007; O'Hara and Szakacs, 2008) represented data on the outcome two or more dietary interventions implemented simultaneously had on ASD related signs and symptoms (Table 11 provides a summary of these studies). Luiselli *et al.* (1994) reported on a 15 year old boy with a diagnosis of ASD and chronic lead poisoning accompanied with severe ruminative vomiting. The boy followed a restricted diet for a period of 16 months. He received chelation- and applied behavioural analysis (ABA) therapy and medical treatment (antacid for vomiting) during this time as well. The diet was restricted to only low-fat foods; tomato sauce, mixed vegetables, apples and all products containing lactose were excluded, and meat products were restricted. Outcome was determined by observation only. The ruminative vomiting decreased over time, subsiding after 16 weeks. Weight lost due the ruminative vomiting was also regained, this correcting malnutrition in the child.

O'Hara and Szakacs (2008) reported a case study related to the response of a three year old boy diagnosed with ASD to a special carbohydrate diet combined with anti-yeast therapy. ASD related sign and symptoms noted in the participant prior to intervention included chronic constipation, poor language skills, hyperflexia, repetitive speech, severe echolalia, pervasive behaviours, severe mood swings and obsessive behaviour. The article reflected a two year intervention and follow-up period. During this time the boy followed a specific carbohydrate diet and received anti-yeast therapy. The specific carbohydrate diet mainly consisted of simple sugars (glucose, fructose and galactose) which do not need further digestion. It is believed by some that these molecules are more easily absorbed and thus less likely to contribute to gut inflammation, maldigestion and malabsorption (O'Hara and Szakacs, 2008: 43). Dietary carbohydrates were thus restricted to fruits, honey and non-starchy vegetables (excluding rice, corn and potatoes). The anti-yeast therapy entailed vitamin C, magnesium, probiotics, oil of oregano, and bicarbonate supplementation. Outcome was also determined by observation only. According to the authors, the boy's medical condition improved to such an extent that he was no longer regarded as autistic.

Patel and Curtis (2007) reported an open-label, observational study. The study was conducted as a pre-pilot study, with only 10 children with a diagnosis of ASD or Asperger's together with Attention Deficit Hyperactivity Disorder (aging four to 10 years, and including both male and female) participating in the study. A multidimensional treatment protocol was implemented for a period of three to six months. During this time, participants were admitted to an environmental medicine clinic in New York. The multidimensional treatment protocol entailed the following: control and avoidance of environmental triggers (mite control, moisture/ mould control, avoidance of tobacco smoke and pesticides, the use of less toxic cosmetics and cleaners and the avoidance of paint containing lead), an organic diet (low in refined sugar and free from additives, salicylates, and artificial colouring), gastrointestinal support (supplementation with digestive enzymes, probiotics and Tricycline), antigen injection therapy, nutritional supplements (including vitamins, minerals, amino acids, peptides, omega-3 and -6 fatty acids, milk thistle, coenzyme Q_{10}, digestive enzymes and probiotics), chelation therapy, and glutathione and methylcobalamin (vitamin B_{12}) injections one to three times per week. Participants also continued with behaviour and educational therapy received prior to intervention.

Table 11: Summary of included studies: Other methods of intervention (4 studies)

1	Author reference	Type of study	Diagnostic criteria/ method use	Study population	Exclusion criteria	Intervention		Addition/ other treatment
						Dietary intervention	Intervention period	
	Chan *et al.*, 2012	Randomized, controlled trial	DSM-IV-TR ADI-R	7 – 17 yrs, male and female	Children with other neurodevelopmental, psychiatric or neurological co-morbidities or on psychiatric medication	Total n = 24 Intervention group: *Shaolin* medical approach (reduced intake of ginger, garlic, green onion, spicy foods, eggs, meat and fish) (n = 12) Control group: No dietary intervention (n = 12)	4 weeks	

Outcome(s) measured	Means by which outcome was measured	Follow-up/ Compliance	Outcome of intervention
Effect of the *Shaolin*-medicine-base dietary modification on the signs and symptoms related to ASD	D2 test of Concentration Go/ No-Go Task Child's Colour Trials Test (CCTT) The Five Point Test (FPT) The Tower of California Test (ToC) ATEC	Evaluation done at baseline and at 4 week post-intervention follow-up	No statistical significant difference seen in attention ability of children in intervention group Statistical significant difference thought noted in mental flexibility and inhibitory control Parents reported improvement in social communication and flexibility in daily behaviour/ routine

2	Author reference	Type of study	Diagnostic criteria/ method use	Study population	Exclusion criteria	Intervention		Addition/ other treatment
						Dietary intervention	Intervention period	
	Luiselli *et al.*, 1994	(Case report)	Not mentioned	15 year old boy		Total n = 1 Restricted diet: Tomato sauce, mixed vegetables and apples were excluded All products containing lactose (thus milk and milk products) were eliminated Only low-fat foods included Meat (beef, lamb and pork) were restricted Chelation therapy Other treatment given: ABA and medication	16 months (Boy had severe ruminative vomiting ; this subsided after 4 months)	

Table 11: Summary of included studies: Other methods of intervention, *continued*

	Luiselli *et al.*, 1994 (continued)	**Outcome(s) measured**		**Means by which outcome was measured**	**Follow-up/ Compliance**	**Outcome of intervention**
		The effect of a multi-component behavioural medicine programme on ruminative vomiting		Observation		Vomiting decreased over time, but subsided after 16 weeks of intervention Weight increased with 14 pounds (6.3 kg), correcting malnourished status

3	**Author reference**	**Type of study**	**Diagnostic criteria/ method use**	**Study population**	**Exclusion criteria**	**Intervention**		**Addition/ other treatment**
	O'Hara and Szakacs, 2008					**Dietary intervention**	**Intervention period**	
		Case report	Not mentioned	3 yrs old boy		Total n = 1 Special carbohydrate diet: restricting intake of carbohydrate fruit, honey and non-starchy vegetables Anti-yeast therapy: Vitamin C, magnesium, probiotics, bicarbonate, oil of oregano supplementation	Case report reflects a 2 year intervention period	
		Outcome(s) measured		**Means by which outcome was measured**		**Follow-up/ Compliance**	**Outcome of intervention**	
		Case report		None mentioned (Parental and therapist observation)			Special carbohydrate diet and anti-yeast intervention are claimed to have improved condition to such an extent that after one year the boy did not longer have ASD.	

Table 11: Summary of included studies: Other methods of intervention, *continued*

3	Author reference	Type of study	Diagnostic criteria/ method use	Study population	Exclusion criteria	Intervention		Addition/ other treatment
						Dietary intervention	**Intervention period**	
	Patel and Curtis, 2007	Open-label observational study Prepilot study	Criteria not mentioned, but children were diagnosed with both ASD and ADHD	4 – 10 yrs, including male and female	Patients on psychotropic medication	Total n = 10 Multidimensional treatment: • Environmental control and avoidance of triggers • Organic diet (low in refined sugar and free from additives, salicylates, and artificial colouring • Gastrointestinal support: digestive enzymes, probiotics and Tricycline • Antigen injection therapy • Nutritional supplements: vitamins, minerals, amino acids, peptides, omega 3 and 6 fatty acids, milk thistle, coenzyme Q10, digestive enzymes and probiotic bacteria • Chelation therapy • Glutathione and methylcohalamin injections weekly • Usual therapies: ABA	12 to 24 weeks	
		Outcome(s) measured		**Means by which outcome was measured**		**Follow-up/ Compliance**		**Outcome of intervention**
		Effect of multi dimensional treatment plan signs and symptoms related to ASD		Observations made by parents, teachers and the physician		Evaluation took place at baseline and post intervention		All participants had an improvement in behaviour-, social- and motor skills and GI symptoms Four of the participants could return to regular classes from special education Eight participants had improvement in verbal skills

Outcome was determined by parental, teacher and physician observation; the methods or tools used to make a detailed assessment of the motor, behavioural and educational capabilities post intervention were not mentioned in the article. An improvement in behavioural-, social- and motor skill and gastrointestinal symptoms were noted in all participants. Four of the participants improved to such extent that they could return to regular classes from special education and a further eight participants presented with an improvement in verbal skills.

As the three above mentioned studies did not evaluate similar methods of combined dietary treatment, implementation of two or more dietary interventions simultaneously could not be assessed in terms of being an evidence-based practice. Although the outcomes of these combined treatment on ASD related signs and symptoms were substantial, the degree of research report bias was found to be inadequate. Additional methodologically sound research (especially in terms of comparing participants to a control group, and evaluating outcome using standardized tools and questionnaires) is therefore recommended.

4. DISCUSSION

Research on diet-related interventions in the treatment of ASD is limited. Of the 62 studies identified by the literature search, only 29 studies reported on the effect of dietary modifications on the signs and symptoms related to ASD. These 29 studies represented a possible 11 diet-related methods used to treat ASD, including the gluten-free, casein-free (GFCF) diet, specific carbohydrate diet, elimination diet, ketogenic diet, detoxification diet and therapies, supplementation of digestive enzymes, probiotics, polyunsaturated fatty acids, inositol, vitamin and mineral supplementation and a yeast-free diet. Methods of combined treatment were also identified.

No firm conclusion about the efficacy of any of the interventions could be drawn. The GFCF diet was considered to be the one intervention that was based on a relatively comprehensive

body of evidence, but heterogeneity related to different methodological approaches and reporting made it difficult to confirm the efficacy of this approach. In many cases, the literature search yielded either only one study per dietary interventions evaluated, or the heterogeneity among the studies included per intervention method was such that the scale of evidence-based practice could not be determined. Research report rigor also varied among the individual studies with only four studies (Bent *et al.*, 2011; Bertoglio *et al.*, 2010; Johnson *et al.*, 2010; Munasinghe *et al.*, 2010) classified as having a strong quality rating. For these reasons, a meta-analysis could not be conducted

This review was limited by the small number and heterogeneity of published studies. Based on these observations, it can be concluded that research related to dietary interventions in ASD conducted to date is insufficient to make any firm conclusions about efficacy. Further research (based upon methodologically sound research methods and of good quality) is thus required before evidence-based guidelines for the dietary management of signs and symptoms in children with ASD can be compiled. This should be regarded as a necessity and of high priority as the number of children diagnosed with ASD is ever increasing.

In order to generate an evidence-based body of evidence and also to improve the quality of life of children affected by ASD, the following recommendations are, however, suggested:

- *Length of the intervention period:* A more substantial outcome was noted in studies with an intervention period longer than six months. Dietary modifications should thus be regarded as a long term intervention and should be adopted as a lifestyle in the household.

- *Adherence to the dietary intervention: S*trict adherence to the dietary intervention also yielded a better outcome. This is, however, not always feasible as children with ASD commonly present with fussy eating habits due to a restricted food pattern. A thorough medical and dietary evaluation is therefore essential when deciding upon realistic dietary modifications. To ensure a positive outcome, the dietary interventions chosen should be comprised of foods that are well tolerated by the autistic individual.

- *Age of the child when dietary modifications are made:* Behavioural-, medical- and dietary interventions were all found to yield a more substantial outcome the earlier the intervention was implemented. Guidelines recommend that interventions should be implemented before the age of three years if at all possible, or as soon as a diagnosis of ASD is made. The CDC (CDC, online) recommends that parents and health care professionals implement interventions as soon as problematic behaviour arises, even in the absence of a definite ASD diagnosis.

- *Signs and symptoms with which the child presents:* A thorough evaluation of the signs and symptoms of the autistic individual is important when considering dietary interventions. In children presenting with gastrointestinal related symptoms, the GFCF diet may be more effective than in children who do not experience these symptoms.

- *The severity of autism:* Interventions were found to yield a better outcome in children with a more severe case of ASD.

- *Overall health status of the child:* The detrimental effect of macro- and micronutrient and essential fatty acid deficiencies on health in the general population is well known. The diets of autistic children are often limited to certain foods and thus it is recommended that nutrient deficiencies should be corrected in autistic individuals. A thorough medical- and dietary evaluation should be routine before the implementation of any intervention. Treatment should always endeavour to better the overall health status of the child, while also maximising the child's functional ability and quality of life.

- *Sub-group of children which might not respond to the treatment given:* Several studies have indicated a subgroup of individuals whom either do not respond, or respond in a negative manner, to the treatment given. Comprehensive observation is therefore a necessity during the implementation of both medical- and dietary interventions.

- *Combined methods of treatment:* Some studies have indicated that combined treatments may yield a positive outcome in ASD. As long as none of these approaches are detrimental to overall health, a trial and error approach may be beneficial in

determining what approach or combination of approaches result in an improvement of signs and symptoms in a specific individual. These could include combinations of behavioural-, medical- and dietary interventions.

5. CONCLUSION

More and more children are being diagnosed with ASD. Signs and symptoms of this life-long disorder can have a significant influence on the quality of life of the autistic individual. In addition to the contribution of medical and behavioural therapy, the role of evidence-based dietary interventions needs to be considered. Evidence-base research is currently insufficient to make any firm conclusions about the efficacy of any of the dietary interventions that have been suggested to date. Further research of a sound methodological nature is thus recommended and encouraged.

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APPENDIX A

Confirmation of Ethical Approval

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
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UFS UV

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Ms H Strauss

2012-07-30

REC Reference nr 230408-011
IRB nr 00006240

MS C KING
BODENSTEIN STREET 18
BAILLIEPARK
POTCHEFSTROOM
2531

Dear Ms King

ECUFS NR 115/2012
PROJECT TITLE: A SYSTEMATIC REVIEW OF DIETARY INTERVENTIONS IN AUTISM SPECTRUM DISORDERS.

- You are hereby kindly informed that the Ethics Committee approved the above project at the meeting held on 24 July 2012.

  [Prof C Walsh did not take part in the discussion of this project]

- Committee guidance documents: Declaration of Helsinki, ICH, GCP and MRC Guidelines on Bio Medical Research. Clinical Trial Guidelines 2000 Department of Health RSA; Ethics in Health Research: Principles Structure and Processes Department of Health RSA 2004; Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa, Second Edition (2006); the Constitution of the Ethics Committee of the Faculty of Health Sciences and the Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines.

- Any amendment, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.

- The Committee must be informed of any serious adverse event and/or termination of the study.

- A progress report should be submitted within one year of approval of long term studies and a final report at completion of both short term and long term studies.

- Kindly refer to the ECUFS reference number in correspondence to the Ethics Committee secretariat.

Yours faithfully

.....
FOR CHAIR: ETHICS COMMITTEE

ETHICS COMMITTEE

OF THE FACULTY OF HEALTH SCIENCES

ATTENDANCE LIST OF THE MEETING HELD ON 24 JULY 2012

A. FACULTY MEMBERS

1. SCHOOL OF MEDICINE REPRESENTATIVES

Prof WH Kruger	Dept of Community Health (Chairperson) M.B. Ch.B (UFS) M.Med. (Community Health) (UFS) MBA (PU for CHE) Ph.D (Community Health) (UFS)	Present
Prof DK Stones	Dept of Paediatrics and Child Health M.B. CH.B (UCT) M.Med Paediatrics (UFS)	Present
Dr SM le Grange (Lady)	Dept of Surgery (Vice-chair) M.B. Ch.B (UFS) M.Med. (Surgery) (UFS) Cert. Paediatric Surgery (College of Surgeons of SA)	Present
Prof PJ Pretorius	Dept of Psychiatry M.B. Ch.B (UFS) M.Med (Psychiatry)	Absent
Prof BJS Diedericks	Dept of Anaesthesiology FFA (SA) M.Med (Anaesthesiology) (UFS) BA (Philosophy) UNISA M.B. Ch.B (UFS)	Present
Prof WJ Steinberg	Dept of Family Medicine M.B. Ch.B; DPH; DTM & H (Wits) M.Fam.Med (UFS) Dip. Obst (SA), FCFP	Present

Prof PH Wessels	Dept of Obstetrics and Gynaecology M.B. Ch.B; M. Med. (O. et G.) (UFS) L.K.O.G. (SA) MD (UFS)	Absent
Prof BW J van Rensburg	Dept of Internal Medicine M.B. Ch.B (UP) M. Med (Internal Medicine) (UP) FCP (SA)	Absent
Dr WJ Rabie	Dept of Family Medicine M.B. Ch.B (UFS) M.Fam.Med. (UFS) ATLS, Trauma Society ATLS instructor, Trauma Society	Present
Ms M Nel (Lady)	Dept of Biostatistics B.A. (Urbanology) B.A. Hons. (Statistics) M.Med.Sc (Biostatistics) (UFS) IRENSA Diploma in International Research Ethics 2006	Present

2. SCHOOL OF NURSING REPRESENTATIVES

Ms RM Mpeli (Lady)	School of Nursing Diploma in General Nursing Diploma in Midwifery Advance University Diploma in Clinical Nursing (Advanced Midwifery and Neonatology) B.Soc.Sc. (Nursing Education) M.Soc.Sc (Nursing)	Absent
Dr DE Botha (Lady)	School of Nursing M. Soc.Sc (Nursing) (UFS) Ph.D (Nursing) (UFS)	Present

3. SCHOOL OF ALLIED HEALTH PROFESSIONS REPRESENTATIVES

Prof CM Walsh (Lady)	Dept of Human Nutrition B.Sc Dietetics (UFS) M.Sc Dietetics (UFS) Ph.D (Dietetics) (UFS)	Present

Ms PA Hough (Lady)	Dept of Occupational Therapy B.Sc Occupational Therapy (UFS) M.Sc Occupational Therapy (UFS)	Present
Ms R Smith (Lady)	Dept of Physiotherapy B.Sc (Physiotherapy) (UFS)	Present

4. BIOSTATISTICIAN

Prof G Joubert (Lady)	Dept Biostatistics B.A. UCT, B.Sc. UCT B.Sc (Hons) (Mathematical Statistics) UCT M.Sc. (Mathematical Statistics) UCT	Present

B. NON-SCIENTIFIC MEMBERS

1. RELIGIOUS/LAY MEMBER

Religious member has to be appointed.

2. LEGAL MEMBER

Prof H Oosthuizen	Dept Criminal Law B.Iur., LL.B., LL.D. (UFS)	Present
Prof R-M Jansen (Secundus) (Lady)	Dept Private Law B.Soc.Sc. (Nursing) Hons. B.Iur., LL.B., LL.M. (UFS)	Absent

C. INDEPENDANT MEMBERS NOT AFFILIATED WITH INSTITUTION

1. LAY MEMBERS

Ms KM Jingosi (Lady)	Child and Family Welfare Society Social Auxiliary Work SA Council for Social Service Professions	Absent

Ms SS Seclave (Secundus) (Lady)	Retired Primary Lower Teacher's Certificate Teacher's Higher Bilingual Certificate Education Diploma for the Junior Primary Phase (UFS)	Present
Ms EF Makowa (Secundus) (Lady)	Admin Clerk Drakensberg Logistics Bloemfontein	Absent

Prof WMJ v d Heever Kriek (Lady)	Ph.D Clinical Technology School of Health Technology Central University of Technology, Free State Bloemfontein	Present

Dr NRJ van Zyl	Clinical Head: Universitas Hospital Bloemfontein M.Med. (UFS) Business MBL (UNISA)	Absent
Dr BM Masitha (Lady)	H.O.C.S. – Chief Medical officer Free State Psychiatric Complex Bloemfontein M.B. Ch.B. B.Sc Hons Health Sciences IFE - Nigeria B.Sc NBLS – ROMA	Absent

Dr RJ Khoali	Chief Executive Officer Pelonomi Hospital Bloemfontein	Absent
Dr BA Benganga	Head: Clinical Services Pelonomi Hospital Bloemfontein	Absent
Ms BJ Ramodula	Chief Executive Officer National District Hospital Bloemfontein	Absent

.....
for CHAIR: ETHICS COMMITTEE

Part D

SUMMARY

SUMMARY

Background: Autism spectrum disorders (ASD) are an ever-increasing group of neurobiological developmental disorders, affecting every aspect of the affected individual's life. As a heterogeneous disorder of which the aetiology is unknown, many desperate attempts have been made to find a cure for this group of disorders. Methods of treatment currently suggested for the treatment of ASD include educational interventions, medical treatment, complementary and alternative methods of treatment, and dietary interventions. The efficacy of dietary interventions currently suggested in the lay media for the treatment of the signs and symptoms related to ASD is largely unknown.

Objective: The aim of the study was to critically appraise dietary interventions suggested in peer-reviewed literature for the treatment of signs and symptoms related to ASD in children aged birth to 18 years.

Methods: A systematic literature strategy was undertaken. The initial literature search yielded a possible 62 studies of which 33 studies were excluded for not adhering to the inclusion and exclusion criteria. To be included, studies had to evaluate a dietary intervention in children with ASD aged birth to 18 years, and be published in English between January 1990 and July 2012. The 29 included articles reported on gluten-free, casein-free (GFCF) diet; specific carbohydrate diet; elimination diet; ketogenic diet; detoxification diet and therapies; supplementation of digestive enzymes; probiotics; polyunsaturated fatty acids; inositol; vitamin and minerals; yeast-free diet and implementation of two or more methods of treatment simultaneously.

Results: No firm conclusion about the efficacy of dietary interventions in the treatment of ASD could be made. The review was limited by the small number of scientific articles published on this topic, and the heterogeneous nature of the studies. A meta-analysis could thus not be conducted. Of the dietary interventions evaluated, the GFCF diet was most likely to yield a positive outcome. This could not be confirmed due to different

methodological approaches and reporting used by the different researchers. The following factors did, however, impact on the outcome of the dietary interventions and should be taken into account when implementing a dietary intervention to treat ASD: the length of intervention period, the degree of adherence to the dietary modification, age of individuals, sign and symptoms perceived prior to the intervention, severity of the ASD, and the combination of the treatment given.

Conclusion: Evidence-based research is yet insufficient to make any firm conclusion about the efficacy of the dietary interventions currently suggested for the treatment of ASD. Further research based upon methodologically sound research methods is thus recommended.

Key terms: autism, dietary interventions, dietary treatment, children

OPSOMMING

Agtergrond: Die voorkoms van outisme spektrum afwykings is geweldig aan die toeneem. Hierdie groep neurobiologiese ontwikkelingstoornisse affekteer nie net elke aspek van die outistiese individu nie, maar ook die van sy/ haar geliefdes. Weens die heterogene aard van hierdie groep stoornisse is die etologie nog onbekend. Vele pogings is al gemaak om ‘n kuur vir outisme te vind en die metodes wat tans voogestel word vir die behandeling van outisme is soos volg: opvoedkundige intervensies, mediese behandeling, aanvullende en alternatiewe metodes van behandeling en dieetintervensies. Die ware uitkoms van dieet behandeling op die simptome van outisme is grootliks onbekend.

Doel van die studie: Die doel van hierdie studie was om die dieetintervensies voorgestel vir die behandeling van die simptome in kinders (geboorte tot 18 jaar) met die breë spektrum van stoornisse krities te ondersoek en te vergelyk deur gebruik te maak van wetenskaplike joernale.

Metodes: ‘n Sistematiese literatuur-soek strategie was gebruik om die studie uit te voer. Die aanvanklike literatuur-soek het 62 studies opgelewer. Drie-en-dertig van hierdie studies is weggelaat op grond daarvan dat dit nie aan die insluitings- en uitsluitings kriteria voldoen het nie. Studies is slegs ingesluit indien die studie ‘n dieetintervensie in kinders met outisme (geboorte tot 18 jaar) ondersoek het, en tussen Januarie 1990 en Julie 2012 gepubliseer is. Die 29 artikels wat vir die doel van hierdie studie ingesluit is, het data verteenwoordig van die volgende dieetintervensies: gluten-vrye, kaseien-vrye dieet; spesifieke koolhidraat dieet; uitsluitings- en elimineringsdieet; ketogene dieet; ontgiftigings dieet en terapieë; aanvulling van verteringsensieme; probiotika; poli-onversadigdevetsure; inositol; vitamien- en mineralaanvulling; gis-vrye dieet en inplementering van twee of meer voedingsverwante metodes van behandeling ter gelyke tyd.

Resultate: Geen definitiewe gevolgtrekking kon oor die effek van dieetintervensies in die behandeling van die simptome wat verwant hou met outsime spektrum afwykings kon gemaak word nie. Hierdie studie was beperk ten opsigte van die klein hoeveelheid gepubliseerde artikels wat oor dieetintervensies in die behandeling van outisme beskikbaar is. Die heterogene aard van die data ook ook verder die studie beperk en ‘n meta-analise kon dus nie uitgevoer word nie. Van die dieetintervensies geëvalueer, het die gluten-vrye, kaseien-vryeedieet die grootste waarskynlikheid tot ‘n positiewe uitkoms getoon. Die omvang van hierdie positiewe uitkoms kon egter nie bevestig word nie weens die verskillende metodologiese benaderinge wat deur die verskillende navorsers gebruik is. Die volgende faktore is gesien om die uitkoms van ‘n dieetintervensie te beïnvloed en behoort daarom in ag geneem word met die beplanning van dieetintervensies vir die behandeling van die simptome wat verwant hou met outsime spektrum afwykings: die tydperk van die dieet geïmplementeer is, die graad waartoe die dieet nagekom word, die ouderdom van die individu, simptome waargeneem in die outistiese individu, die graad van die outsime en die verskillende tipes behandeling wat gelyk geimplementeer is.

Gevolgtrekking: Bewysgebaseerdenavorsing is nog onvoldoende en geen definitiewe gevolgtrekking kon oor die effek van dieetintervensies in die behandeling van outisme gemaak word nie. Verdere navorsing gebaseer op metiodiologies korrekte metodes word dus aanbeveel.