A gluten- and casein- free (GFCF) diet as an intervention for autism spectrum conditions (ASC)

Paul Whiteley
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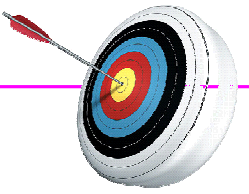

Presentation aims

- Overview of relationship between diet & health.
- Experimental trials of diet for ASC.
- "ScanBrit" randomised-controlled trial (RCT) of GFCF dietary intervention.

Note: not going to talk about dietary management in this presentation (other speakers will do that).

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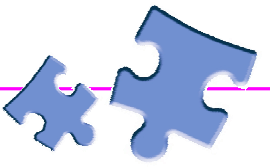
Clinical symptoms / diagnosis



- Diagnosed on the basis of behavioral ma… …on & scrutiny of developmental history.
- Current clinical definition co… …a triad of impairments:

Language & comm… …ion

Use of re… …social interaction

Pres… …of repetitive and/or stereotyped behaviours

Subject to change - DSM V ??

- With onset before 36 months of chronological age.

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Interventions for ASC

Any intervention for ASC should remember:

- ASC are **Pervasive**.
- ASC are **Heterogeneous** (not everyone is the same).
- ASC are **<u>often</u>** accompanied by **co-morbidities** (epilepsy, learning disability, DCD, sensory issues).
- People with ASC **differentially develop without intervention** (no such thing as failure to develop).

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Gluten and casein

What is gluten?

- Mixture of 2 proteins (gliadin & glutenin) giving elasticity.
- Present in wheat, barley, rye (↓ concentration in oats).

What is casein?

- Primary protein in mammalian dairy.
- Present in milk, cheese, yoghurts.
- Variants according to species (A1, A2, *etc*).

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History of GF-CF diets in Psychiatry

Schizophrenia & psychotic disorders.

- Improvement in psychiatric symptoms.
- Immune markers to gluten (not coeliac disease).

Dohan FC. *et al.* (1973) *Am J Psychiatry* 130: 685-688
Vlissides DN. *et al.* (1986) *Br J Psychiatry* 148: 447-452
Dickerson F. *et al* (2010) *Biol Psychiatry* (in press)

Extrapolation to autism and related ASDs.

- Improvement in core and peripheral symptoms.

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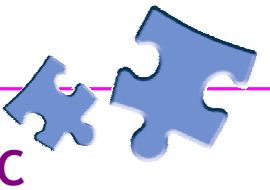

Effects of GF-CF diet on ASC

- Attention & concentration
- Communication & language use
- Social integration & interaction
- Motor co-ordination
- Self-injurious behaviour

Knivsberg A-M. *et al.* (1990) *Brain Dysfunct* 3: 315-327
Knivsberg A-M. *et al.* (1995) *Scand J Educ Res* 39: 223-236
Lucarelli S. *et al.* (1995) *Panminerva Medica* 37: 137-141
Whiteley P. *et al.* (1999) *Autism* 3: 45-65

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But..

- Indications of significant **group** changes but **not** a universally successful intervention.
- More detailed analysis suggested that *younger, more severely affected children were best responders*.

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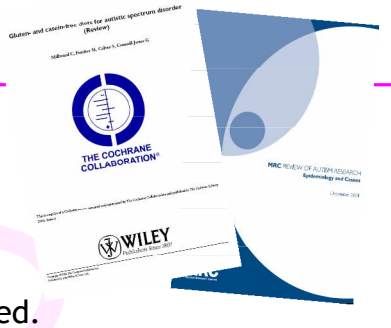
Methodological issues



- **Open-trials <u>not</u> RCTs.**
- Issues surrounding **confirmation of diagnosis & outcome measures** used.
- Clarity on why the diet/s were (not) working.
- Recommendations of Cochrane Reviews (2004; 2008) & MRC review of autism research (2001).

Reviewers' conclusions
This is an important area of investigation and large scale, good quality randomised controlled trials are needed.

Millward C. *et al.* (2004; 2008) *Cochrane Rev* CD003498

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RCTs of GF-CF diet for ASC

- 2 trials identified as RCTs*
- AMK = Single-blind (n=20) *vs.* JE = Double-blind (n=15).
- AMK: 1-year study *vs.* JE: 12 week crossover (6 weeks)
- AMK: sig^{n}. changes *vs.* JE: no sig^{n}. changes
- Various criticisms: time, subject numbers, outcomes.

(AMK) Knivsberg A-M. *et al.* (2002) *Nutr Neuro* 5: 251-261
(JE) Elder JH. *et al.* (2006) *JADD* 36: 413-420

* Trial by Hyman *et al* (IMFAR 2010) seemed to be testing response to <u>challenge</u> of GF-CF diet, not dietary efficacy (not published yet!)

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The ScanBrit trial

Nutritional Neuroscience 2010; 13 (2) 87-100

The ScanBrit randomised, controlled, single-blind study of a gluten- and casein-free dietary intervention for children with autism spectrum disorders

Paul Whiteley[1], Demetrious Haracopos[2], Ann-Mari Knivsberg[3], Karl Ludvig Reichelt[4], Sarah Parlar[4], Judith Jacobsen[5], Anders Seim[6], Lennart Pedersen[2], Maja Schondel[2], Paul Shattock[1]

[1]*Dept of Pharmacy, Health & Well-being, Faculty of Applied Sciences, University of Sunderland, UK*
[2]*Center for Autisme, Herlev Hovedgade, Herlev, Denmark*
[3]*National Centre for Reading Education & Research, University of Stavanger, Norway*
[4]*Department of Pediatric Research, University of Oslo, Rikshospitalet Medical Centre, Norway*
[5]*Statcon ApS, Kokkedal, Denmark*
[6]*Fjellstrand, Norway*

There is increasing interest in the use of gluten- and casein-free diets for children with autism spectrum disorders (ASDs). We report results from a two-stage, 24-month, randomised, controlled trial incorporating an adaptive 'catch-up' design and interim analysis. Stage 1 of the trial saw 72 Danish children (aged 4 years to 10 years 11 months) assigned to diet (A) or non-diet (B) groups by stratified randomisation. Autism Diagnostic Observation Schedule (ADOS) and the Gilliam Autism Rating Scale (GARS) were used to assess core autism behaviours, Vineland Adaptive Behaviour Scales (VABS) to ascertain developmental level, and Attention-Deficit Hyperactivity Disorder – IV scale (ADHD-IV) to determine inattention and hyperactivity. Participants were tested at baseline, 8, and 12 months. Based on per protocol repeated measures analysis, data for 26 diet children and 29 controls were available at 12 months. At this point, there was a significant improvement to mean diet group scores (time–treatment interaction) on sub-domains of ADOS, GARS and ADHD-IV measures. Surpassing of predefined statistical thresholds as evidence of improvement in group A at 12 months sanctioned the re-assignment of group B participants to active dietary treatment. Stage 2 data for 18 group A and 17 group B participants were available at 24 months. Multiple scenario analysis based on inter- and intra-group comparisons showed some evidence of sustained clinical group improvements although possibly indicative of a plateau effect for intervention. Our results suggest that dietary intervention may positively affect developmental outcome for some children diagnosed with ASD. In the absence of a placebo condition to the current investigation, we are, however, unable to disqualify potential effects derived from intervention outside of dietary changes. Further studies are required to ascertain potential best- and non-responders to intervention. The study was registered with ClinicalTrials.gov, number NCT00614198.

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The ScanBrit trial

- Scandinavian – British collaboration.
- Center for Autisme already part of the IMGSAC (International Molecular Genetics Study of Autism Consortium)
- Trained assessors of autism.
- Experience in dietary trials.
- External involvement (statistician & nutritionist/s).

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ScanBrit protocol

- Trial registered: ClinicalTrials.gov NCT00614198.
- 72 Danish children started (4 - 10y11m).
- Eligibility / ineligibility criteria (ICD: F84 & co-morbidity).
- Adaptive design with interim analysis
  (pre-determined statistical thresholds of improvement).
- Stratified randomisation (age / development).
- At start: Diet (A) (n=38) *vs.* non-diet (B) (n=34).
- Baseline, 8m, 12m & 24m testing protocol.

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ScanBrit protocol

- ADOS (Autism Diagnostic Observation Schedule)
  (@ Baseline, 8m, 24m to preclude practice effects)
- GARS (Gilliam Autism Rating Scale)
- VABS (Vineland Adaptive Behaviour Scales)
- ADHD-IV (Attention-Deficit Hyperactivity-Disorder DSM-IV)
- Urine screen (for potential "biomarker" studies)

Lord C. *et al.* (1989) *JADD* 19: 185-212
Gilliam JE. (1995) Pro-Ed
Sparrow S.S. *et al.* (1984) American Guidance Service
DuPaul G.J. *et al.* (1998) Guilford Press

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ScanBrit protocol (stage 1: 12m)

- Stage 1: Adaptive design*
  (stopping rule » "*drop-the-loser*" design).
- 8 month threshold (p<0.01).
- 12 month threshold (p<0.05).
- Attrition rate = 21% (A:29% *vs*. B:12%).
- Per-protocol statistical analysis.
- 12m – A (n=26) *vs*. B (n=29).

* Chow S-C. *et al*. (2008) *Orphanet J Rare Dis*. 3: 11

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ScanBrit results (stage 1: first 12 m)

- Sig^{n}. group changes on sub-domains of ADOS, GARS, ADHD-IV at 8 and 12 months.
- ADOS: communication sub-domain (n = 2 changed from module 2 to module 3: not verbally fluent to fluent).
- ADHD-IV: inattention & hyperactivity scores ↓.
- GARS: social interaction scores ↓.
- No adverse events reported.

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ScanBrit (stage 2: 12m-24 m)

- Stage 2: Open-trial (all participants on intervention).
- 24m – A (n=18) *vs*. B (n=17).
- Again, no adverse events reported.
- Less pronounced positive effect from results (plateau?).
- No sig^{n}. group effects from ADOS (revised algorithm*).
- Sig^{n}. group effect on sub-domains of GARS & ADHD-IV.
- ADHD-IV: Parallel improvement profiles across groups.

* Gotham K. *et al.* (2007) JADD 37: 613-627

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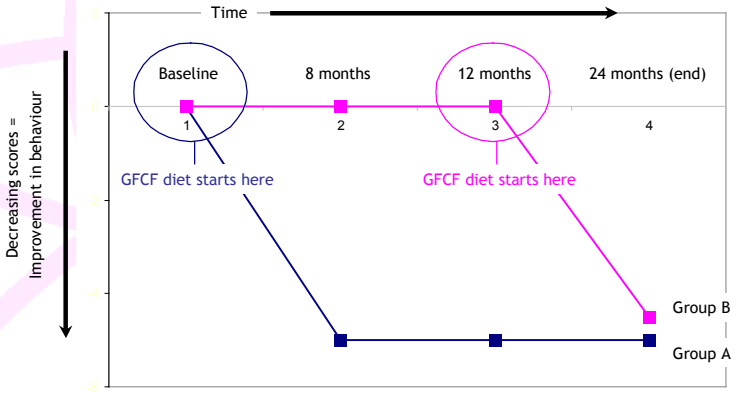
Most feasible "best scenario" results



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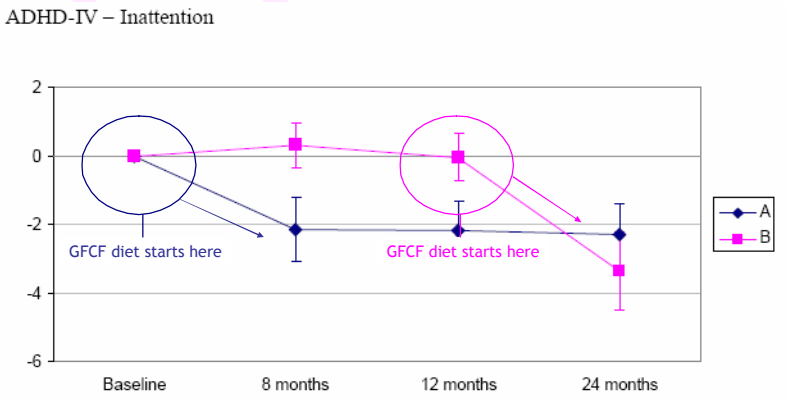
ScanBrit - ADHD-IV results



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ScanBrit summary

- Some significant positive effects noted for group results.
- Language, inattention & hyperactivity were key areas of response.
- Wide variation in individual responses to diet.

Conclusion:

- Strong probability that GFCF diet can affect symptoms and developmental outcome for some children with ASC.

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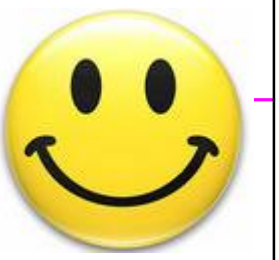

ScanBrit trial - positives

- RCT (stratified randomisation).
- Largest group studied to date.
- Chronological age included largely avoids diagnostic instability and/or pubertal effects.
- Co-morbidities / medication controlled for.
- Comprehensive assessments using standardised instruments.
- Long experimental period (avoiding any wash-out period).
- Ethical aspect to adaptive design.
- Smaller than expected attrition rate
- Reporting using CONSORT guidelines.

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ScanBrit trial - drawbacks

- Not a double-blind trial (single-blind) (although ADOS).
- No placebo arm.
- Bias based on surviving participant data (not ITT or LOCF).
- Socio-economic status not recorded.
- Results applicable to pre-pubescent only.
- Reporting based on group results not individuals.
- No screening for coeliac disease, *etc* (urinanlysis).

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Rationale for using GF-CF diet?

Several hypotheses put forward including:

1. Classical allergy /atopy to foods.
2. Underlying coeliac disease or casein-intolerance condition.
3. The "*opioid-excess*" & "*leaky gut*" models.

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To intervene or not to intervene?

- Some debate about whether it is ethical to try & "change" people with autism.
- Is autism a part of someone, or does it "affect" someone?
- Charter of Rights for Persons with Autism.
- Informed consent (*e.g.* Gillick competence – u16 consent).
- Quality of Life (pain relief, development).
- Who is intervention better for? Individual, family, society?

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The Norwegian Protein Intolerance Association
The Robert Luff Foundation

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