

Micronutrients in mental illness: What is the evidence?

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Invited talk, April 13th 2014

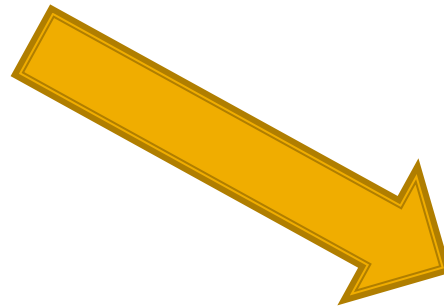
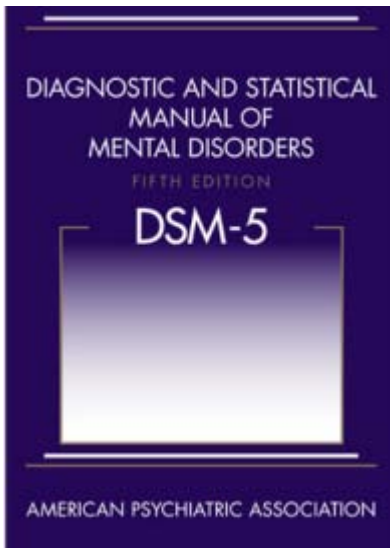
Disclosure

**No commercial interest in any
company or sale of any product**

Overview

- **Within framework of nutrients as being essential for optimal brain functioning**
 - Review evidence across a broad range of psychiatric conditions using micronutrients
 - Focus only on *broad based* supplementation
 - Select examples from mood, forensics, autism, stress, anxiety, trauma, ADHD

Our current approach to psychiatric problems



**Nonresponders can range from 20-50% with greater complexity of problems associated with worse outcomes
And side effects an ongoing concern for many**

What's the evidence for broad based micronutrients?



Progression of Evidence on Micronutrients & Psychiatric Symptoms

- Case studies

- Case series

- Case series of hundreds

- Case controls

Evidence-based medicine

- Roll out into clinical practice

**WHY IS THIS LEVEL OF
EVIDENCE IMPORTANT?**

Progression of Evidence on Micronutrients & Psychiatric Symptoms

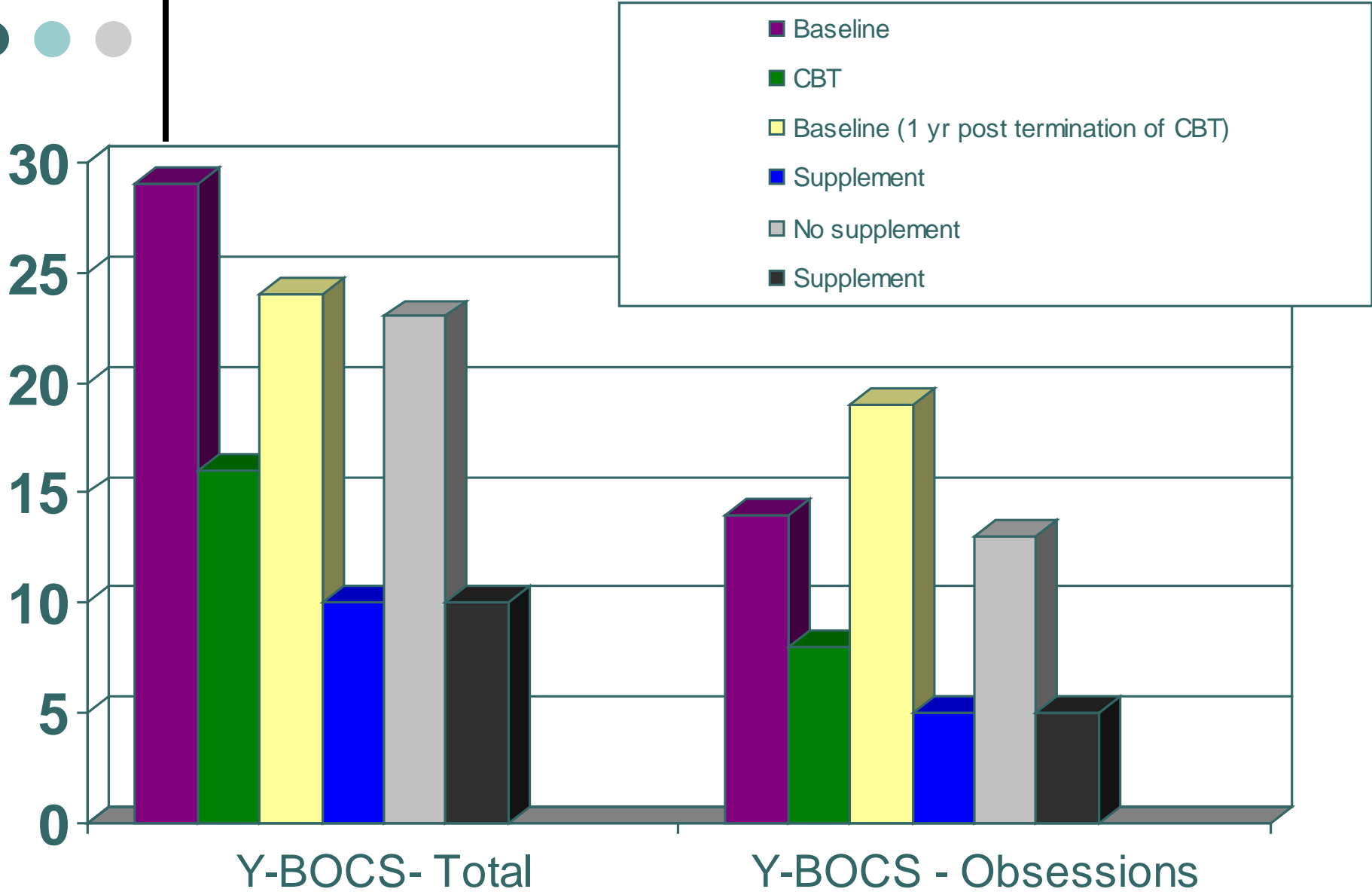
- **Case studies**
- Case series
- Case series of hundreds
- Case controls
- RCTs
- Roll out into clinical practice

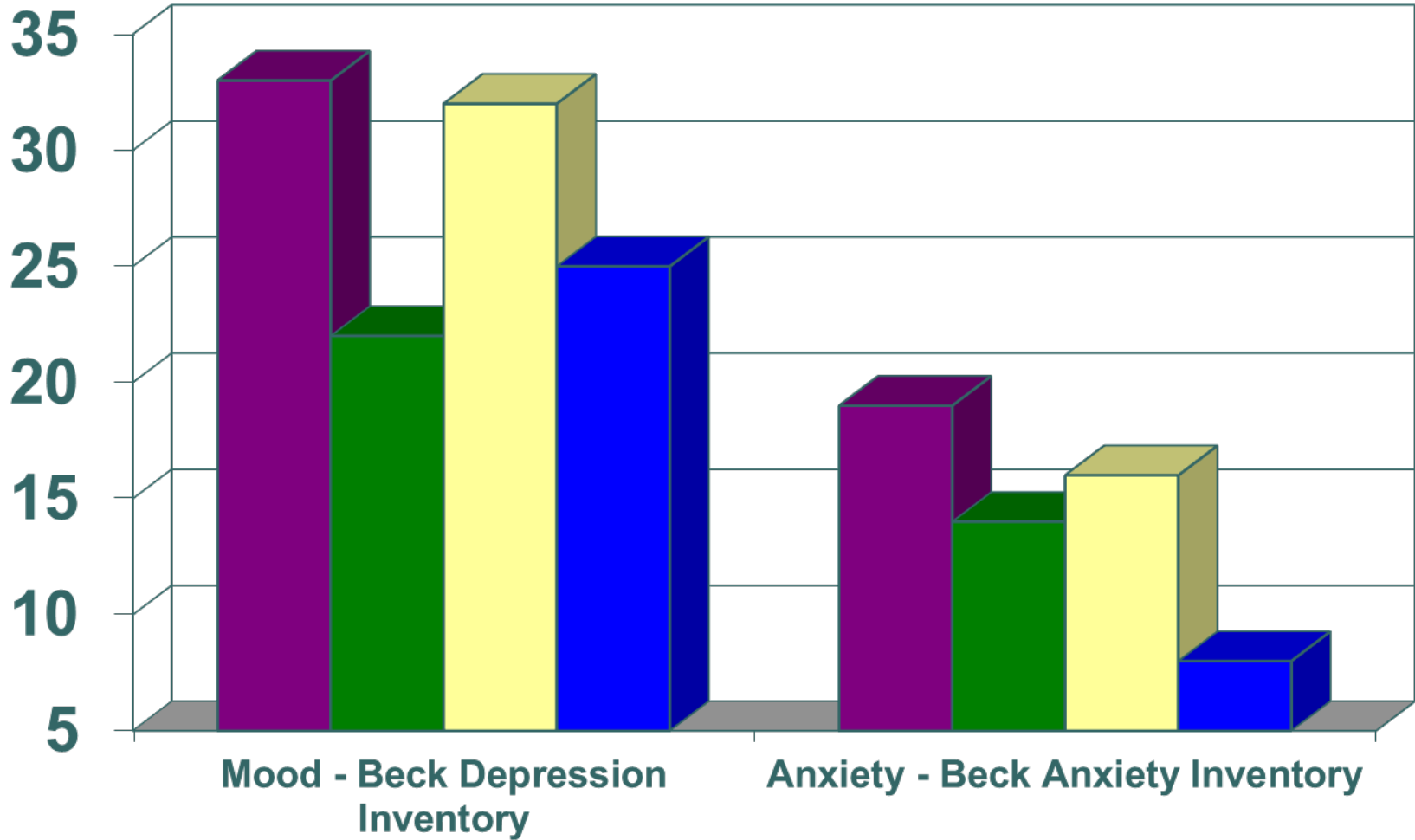
Case study: 18-yr-old boy with OCD

Rucklidge, 2009
Journal of Anxiety Disorders

- Hand washing, religiosity, etc.
- CBT for 1 yr with modest response
 - OCD had shifted from *severe* to *moderate*
- Within a year, anxiety deteriorated back to *severe* range and now had major *depression*
- Entered ABAB design trial using EMPowerplus
- After 8 wks on formula, his mood stabilized, anxiety reduced, and obsessions in remission
- Treatment discontinued for 8 wks, during which time obsessions and anxiety worsened and mood dropped. *{Note: he did not believe formula was responsible for improvement.}*
- Reintroduction of formula again improved the symptoms

Case study: Natural ABAB

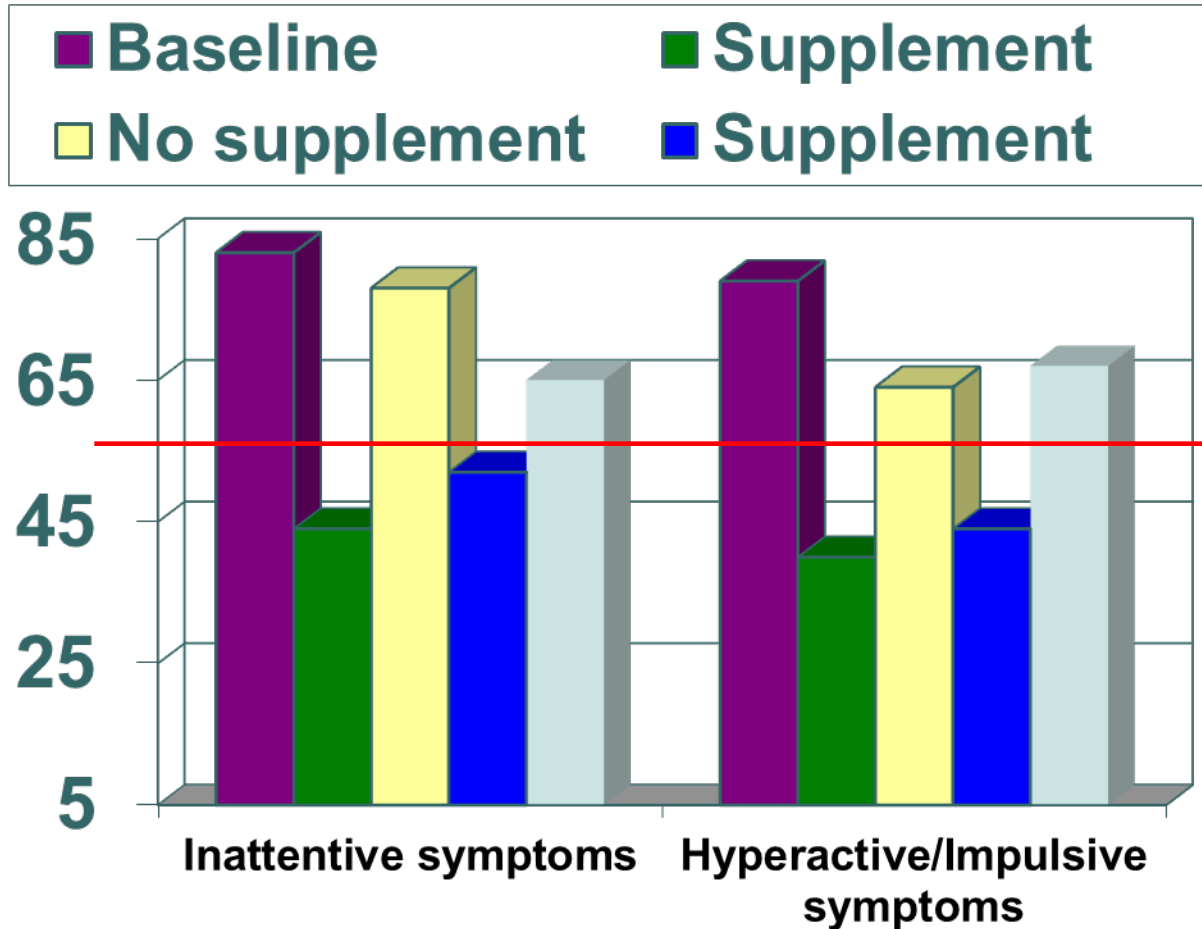




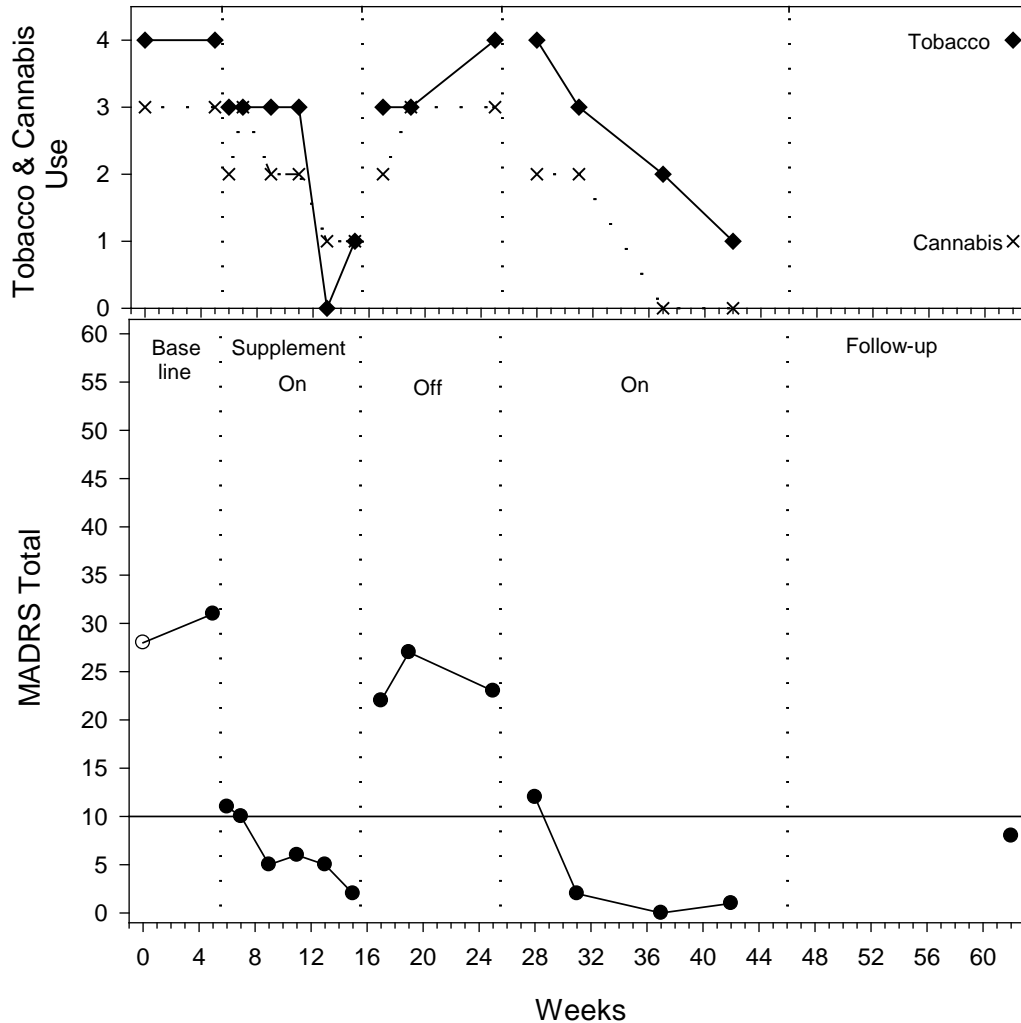
“Brian”

- 20 year old male
- ADHD, MDD, Panic Disorder, Substance Abuse (cannabis and nicotine)
- Past hx of tx with methylphenidate, imipramine, fluoxetine, clonidine, amitriptyline, lorazepam and clonazepam
- Monitored with CGI, Conners, MADRS, YMRS, GAF
- On (8 weeks)-off (8 weeks)-on (4 months)-“natural” off (5 months) using EMP

On-off control of ADHD symptoms



Can micronutrients help with reducing substance abuse?



Progression of Evidence on Micronutrients & Psychiatric Symptoms

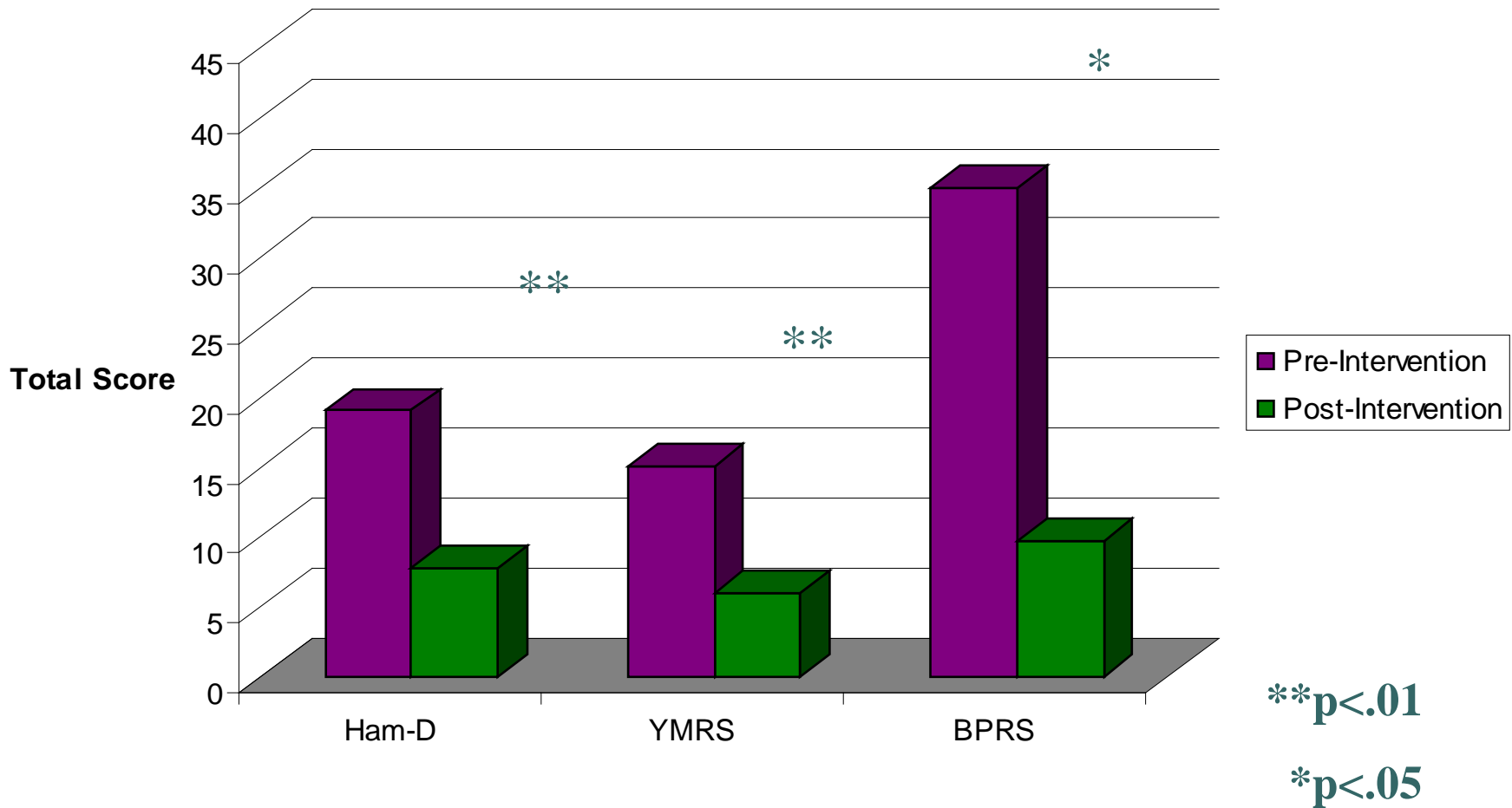
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Tx of Bipolar Disorder with nutrients

- All studies to date on one formula, EMP
- 3 case studies with reversals
 - Kaplan et al., 2002; Rucklidge & Harrison, 2010
- 5 open label trials
 - Significant reductions in all psychiatric symptoms
 - Significant reduction in medications
 - Response rates approx 80%
 - Simmons, 2003; JCP; Kaplan et al., 2001; JCP, Kaplan et al., 2004, JCAP; Popper, 2001, JCP; Frazier et al., 2012, JACM

Case series (open label), 11 adults

Kaplan, B. J., Simpson, J. S. A., Ferre, R. C., Gorman, C., McMullen, D., & Crawford, S. G. (2001). *J Clin Psychiatry*, 62, 936-944.

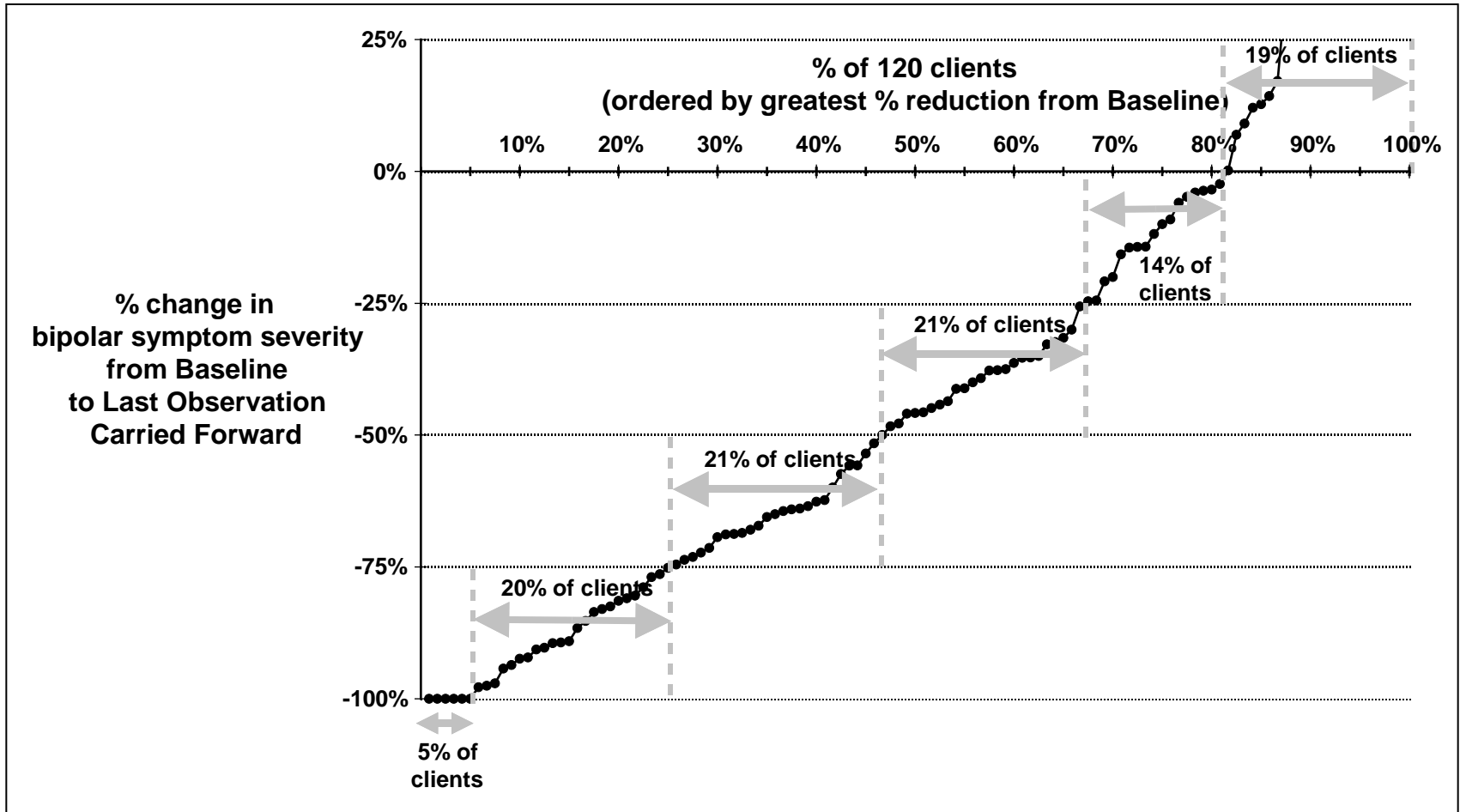


Progression of Evidence on Micronutrients & Psychiatric Symptoms

- Case studies
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Database analysis of 120 children with bipolar: percent improving using EMP

Rucklidge et al., 2009, BMC Psychiatry



Progression of Evidence on Micronutrients & Psychiatric Symptoms

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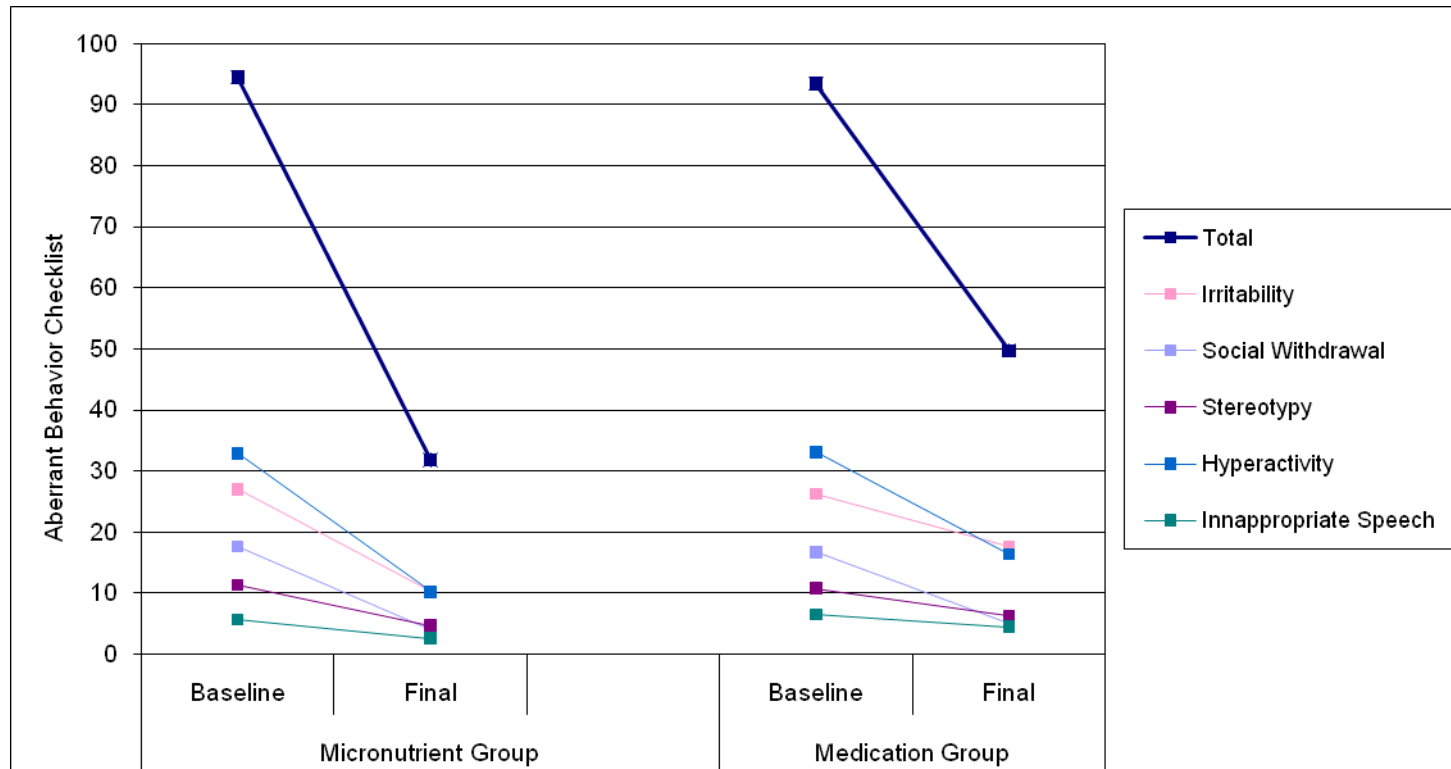
Micronutrients and autism

Mehl-Madrona et al., 2010, JCAP

- 88 children in private practice – 44 taking micronutrients and 44 matched children taking medications
 - Micronutrient Group improved as much as Medication Group on both the Childhood Autism Rating Scale and the Childhood Psychiatric Rating Scale
 - Both groups exhibited significant decreases in total Aberrant Behavior Checklist scores, but the Micronutrient Group's improvement was greater, $p < 0.0001$.
 - Improvements in Micronutrient Group were also greater for Self Injurious Behaviour Intensity ($p = 0.005$), Clinical Global Impressions ($p = 0.0029$)
 - Adverse events and average weight gain were less in the Micronutrient Group

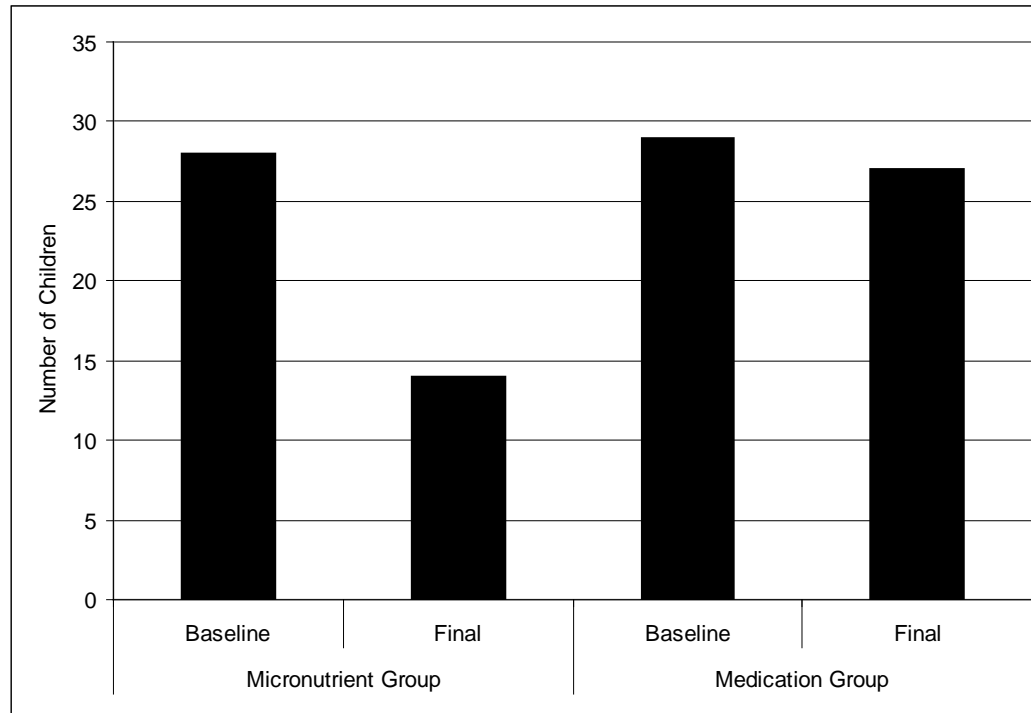
Case-control study of 88 children with autism

--Mehl-Madrona, Leung, Kennedy, Paul, Kaplan (2010, Journal of Child and Adolescent Psychopharmacology)



No grp differences on the Childhood Autism Rating Scale and the Childhood Psychiatric Rating Scale

Yale-Paris Self-injurious Behaviour



CGI Ratings also sig better in micronutrient group

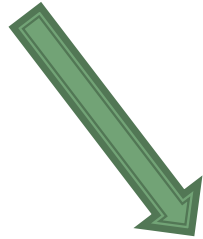
Progression of Evidence on Micronutrients & Psychiatric Symptoms

- Case studies
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- Case controls
- **Randomized controlled trials (RCTs)**
- Roll out into clinical practice

Natural disasters and nutrients

Micronutrients for stress

- ▶ **5 RCTs have shown that over-the-counter micronutrients (Berocca or Blackmore's):**
 - ▶ **decrease stress/anxiety, improve energy and mood in both stressed and nonstressed populations**
 - Carroll et al., 2000; Gruenwald et al., 2002; Schlebusch et al., 2000; Kennedy et al., 2010, 2011; Stough et al., 2011
- **Can this effect generalize to stress following an earthquake?**



**Poor food choices
after a disaster**

+

**growing research showing
micronutrients can have a
positive effect on a wealth
of psychological symptoms**



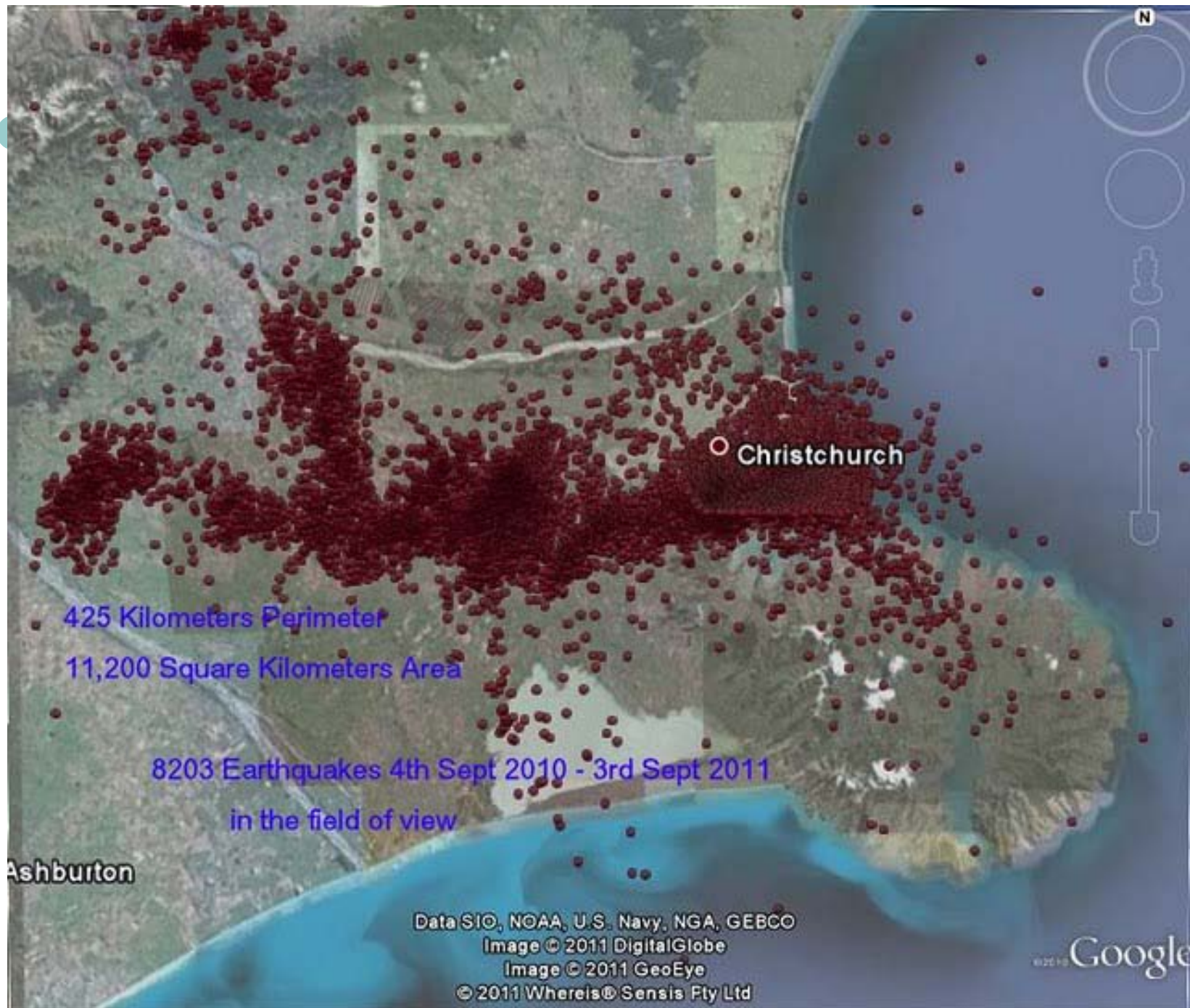
**suggests supplementation
following a natural disaster
could be beneficial**





185 people died, 6659 injured, 30,000 homes destroyed, cost to NZ: 12.9 billion dollars





Micronutrients on PTSD symptoms in general population experiencing stress following earthquake

Rucklidge et al., 2012, Human Psychopharmacology

▶ Recruited on-line

- ▶ 201 completed survey: 127 eligible

▶ 91 randomized

- 30 to Berocca (29 completed)
- 31 to EMP4 (30 completed)
- 30 to EMP8 (27 completed)

▶ 4 week trial with 1 month natural follow up – data collection May to July 2011

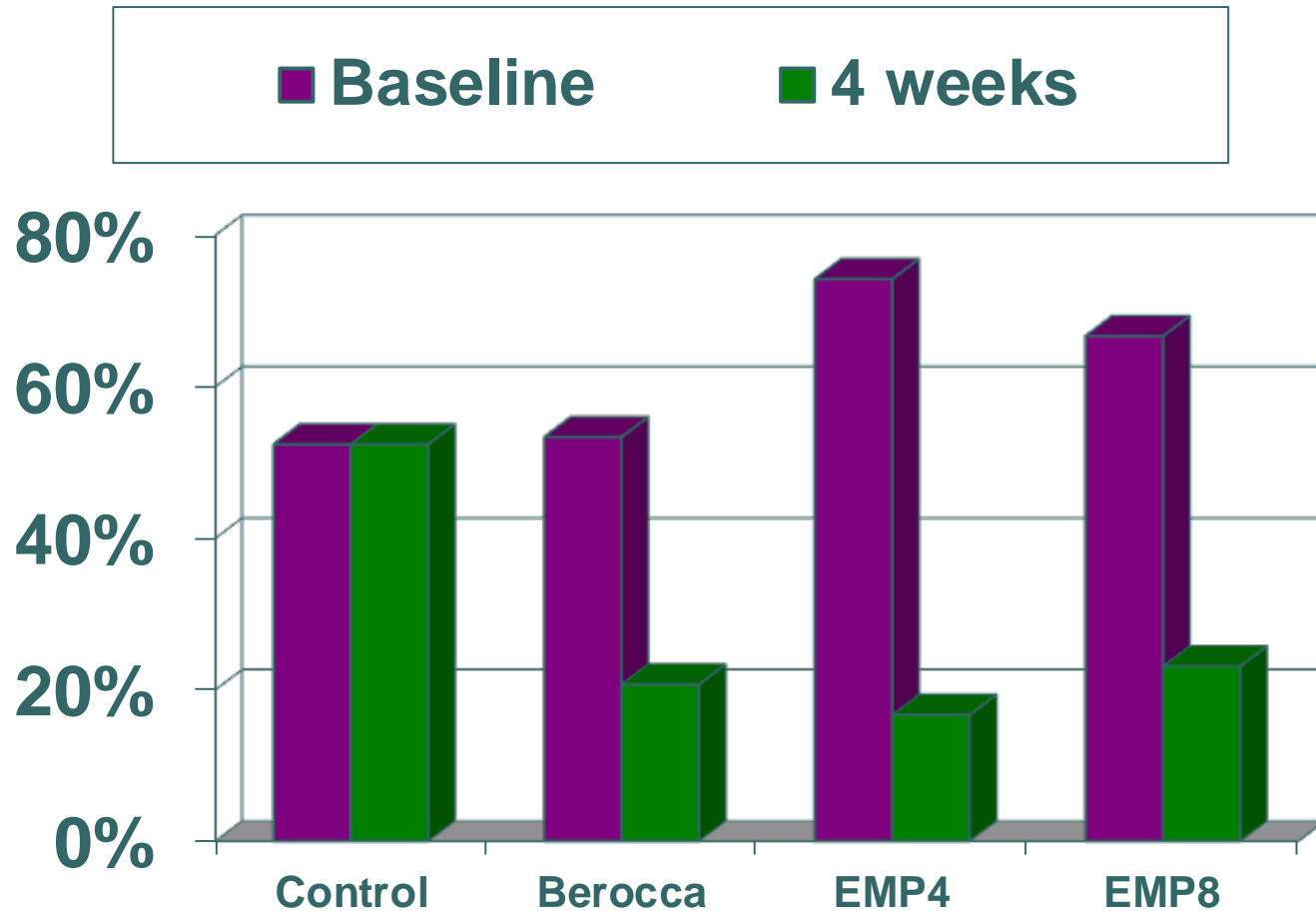
▶ Monitored weekly with on-line Q assessing stress, mood, anxiety and PTSD symptoms

▶ 25 of original pool served as controls (7 medicated)

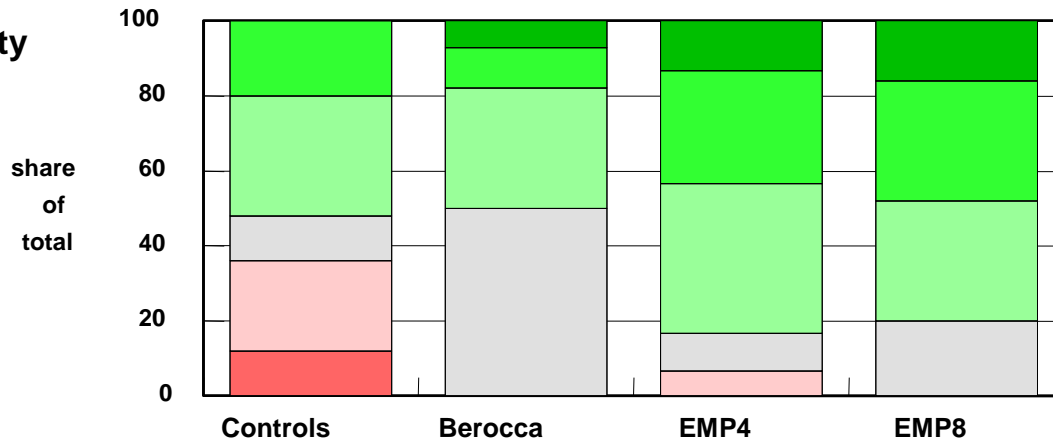
Results

- No grp diff in exercise, hx of mental illness, zoning, counselling, SES, age, sex, leaving town, diet
- All 3 tx groups showed large (Berocca) or very large (EMP both doses) changes from baseline
 - ▶ All 3 significantly better than controls
- EMP (both doses) showed superiority to Berocca for intrusions, and higher dose for CGIs of stress, anxiety, energy, mood
 - ▶ no tx differences on other measures
- 1 mnth follow up:
 - ▶ those who stayed on continued to improve, those who didn't, stayed same
 - ▶ preference for higher dose of EMP: 5x more of these participants stayed on EMP micronutrients compared with those in the Berocca™ group

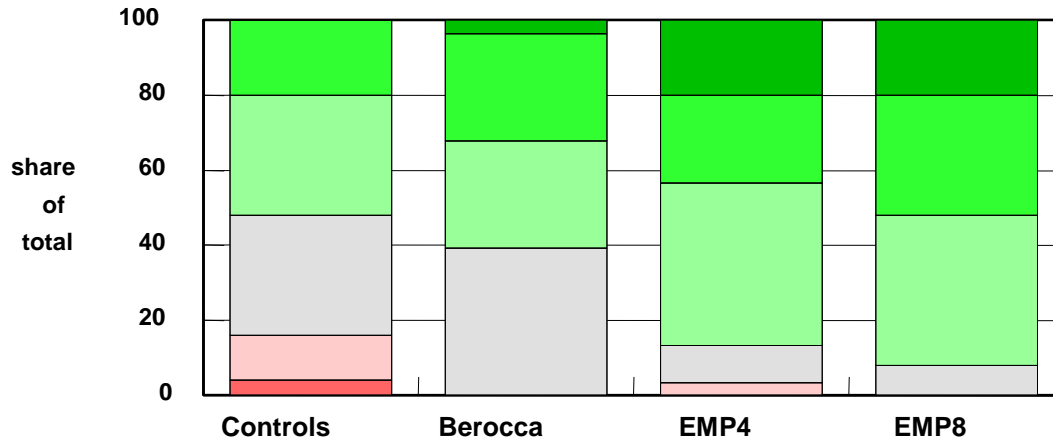
% with significant PTSD symptoms baseline and 4 weeks



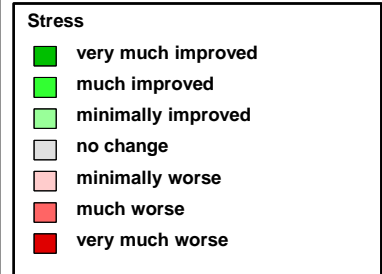
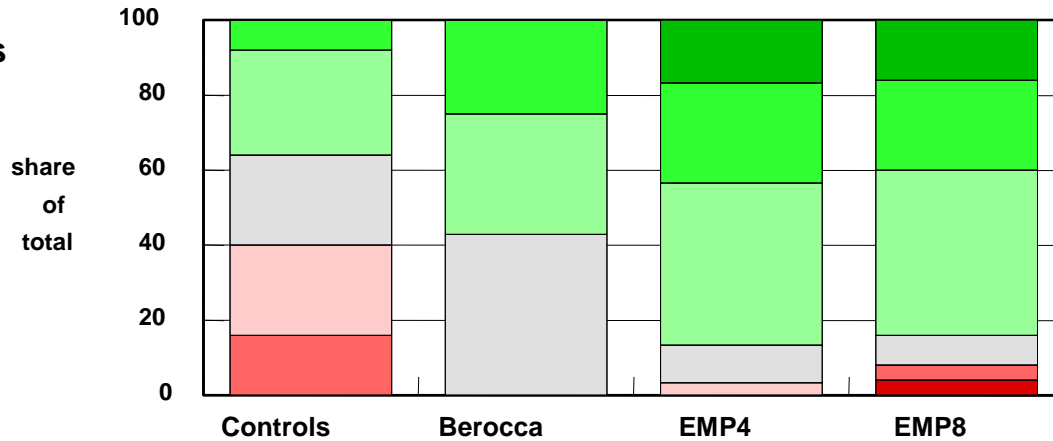
Anxiety



Mood



Stress



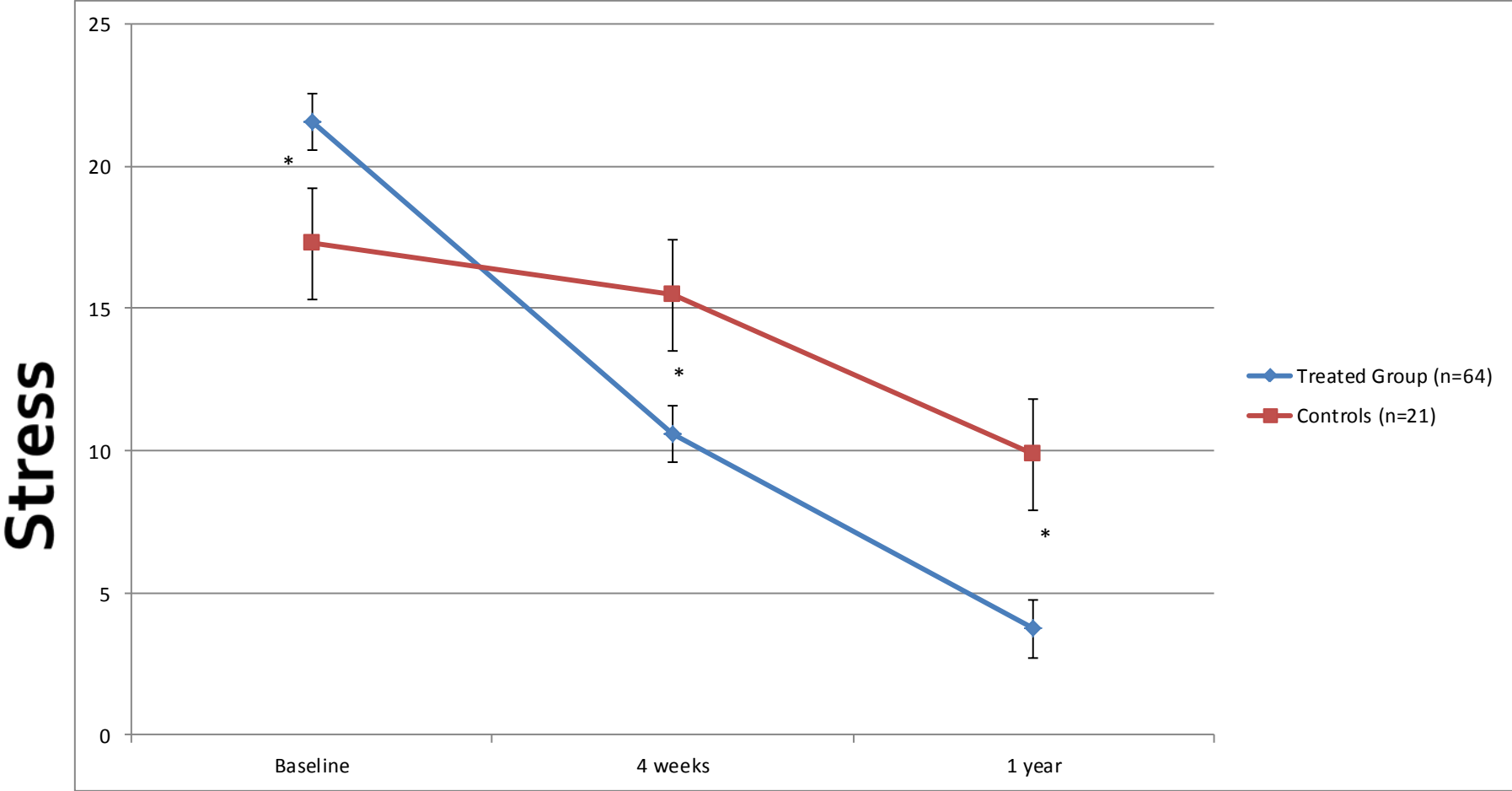
Maybe nutrients feed the brain and replete the system under chronic stress

“The triage theory posits that when the availability of a micronutrient is inadequate, nature ensures that micro-nutrient-dependent functions required for short-term survival are protected *at the expense* of functions whose lack has only longer-term consequences...”

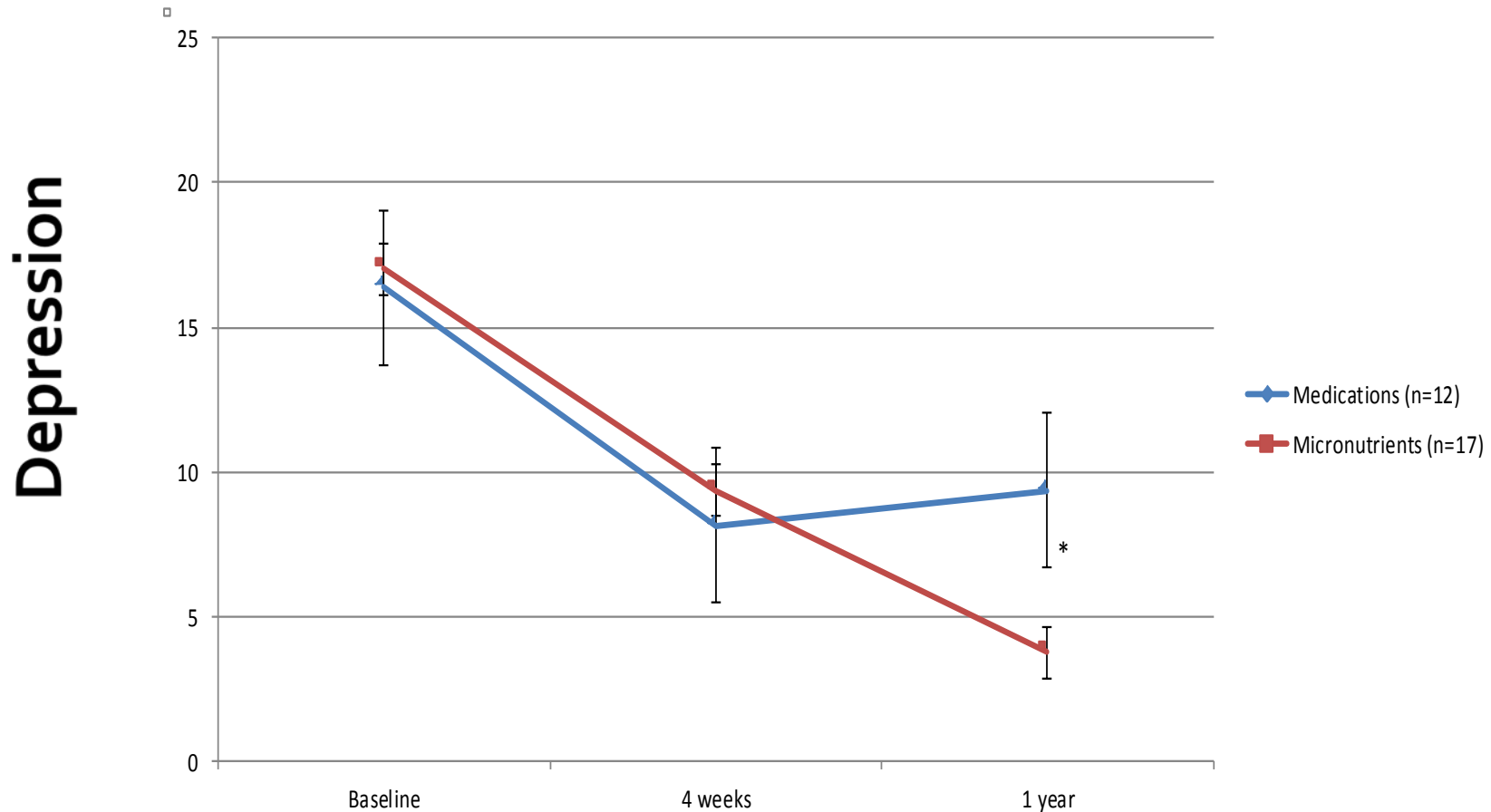
- McCann and Ames 2009



Change in stress over time between treated acutely with micronutrients and control group



Change in depression over time based on treatment at 52 weeks



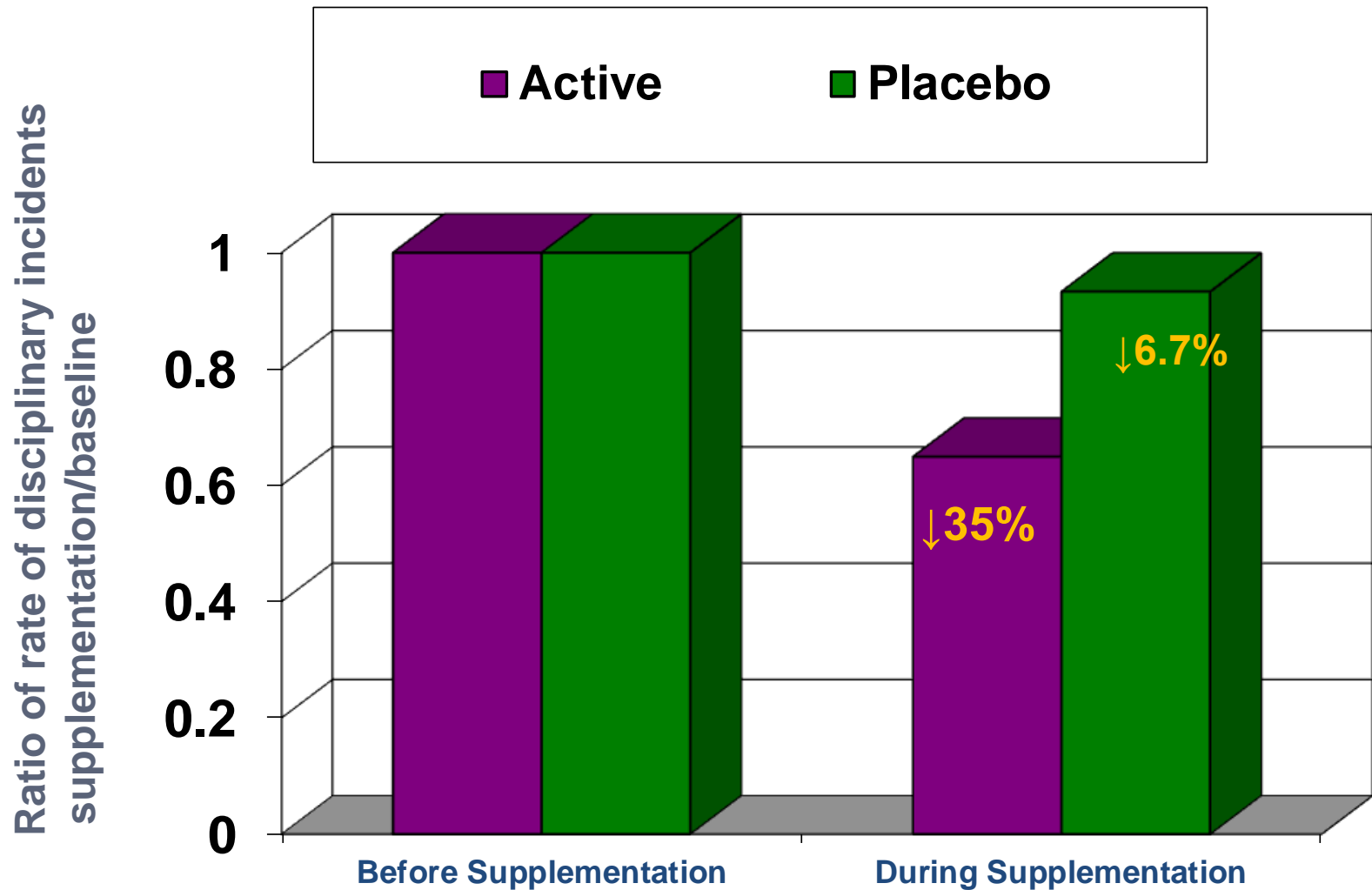
Forensics: 4 RCTs

All four studies show benefit for reducing violence acts and rule infractions

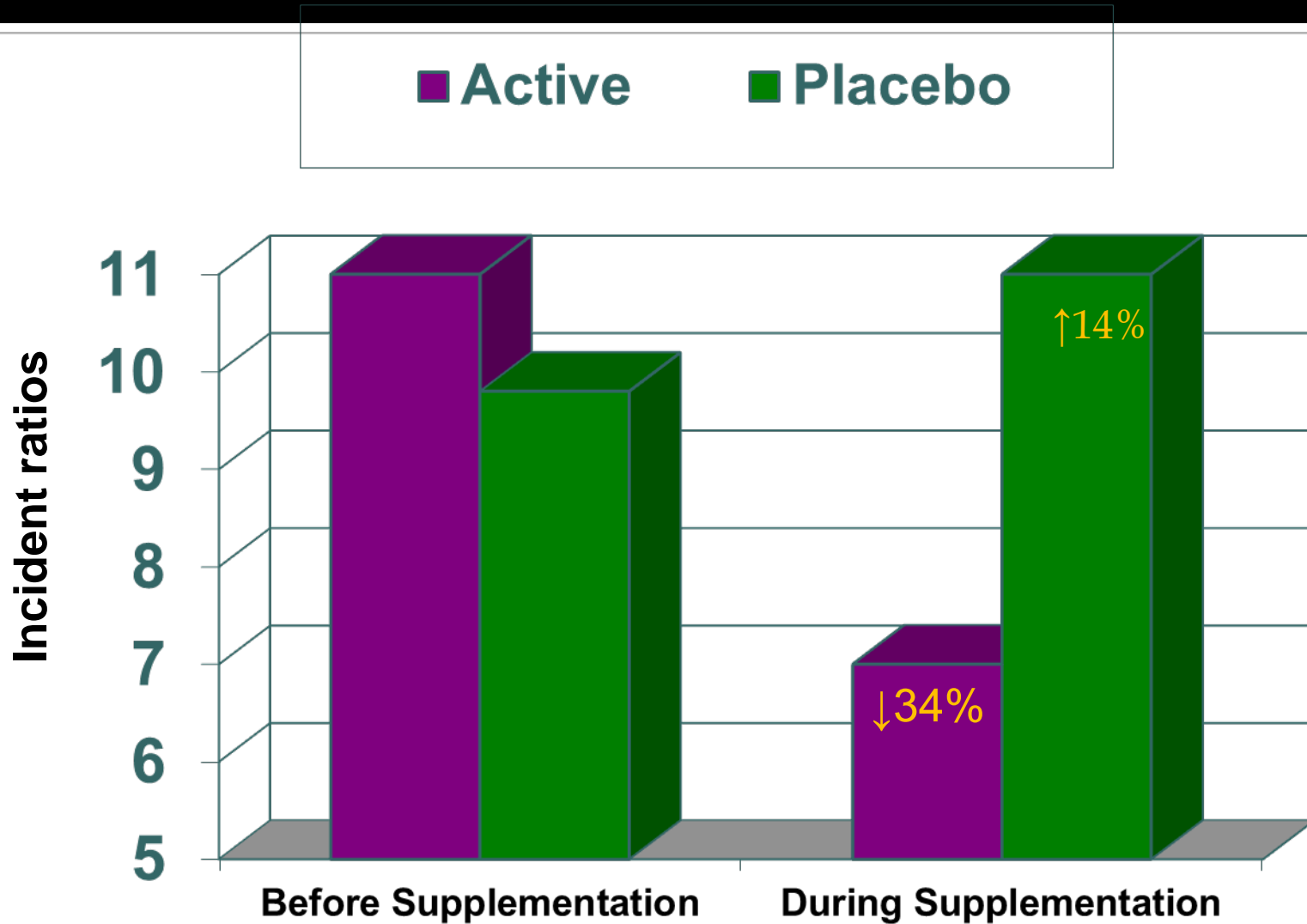
Schoenthaler et al., 1997, 2000; Gesch et al., 2002; Zaalberg et al., 2010



Micronutrient supplementation (Forceval) in 231 young adult prisoners, Gesch et al. 2002, *Brit J Psychiatry*



Replication in a Dutch sample, Zaalberg et al., 2010, Aggressive Behavior

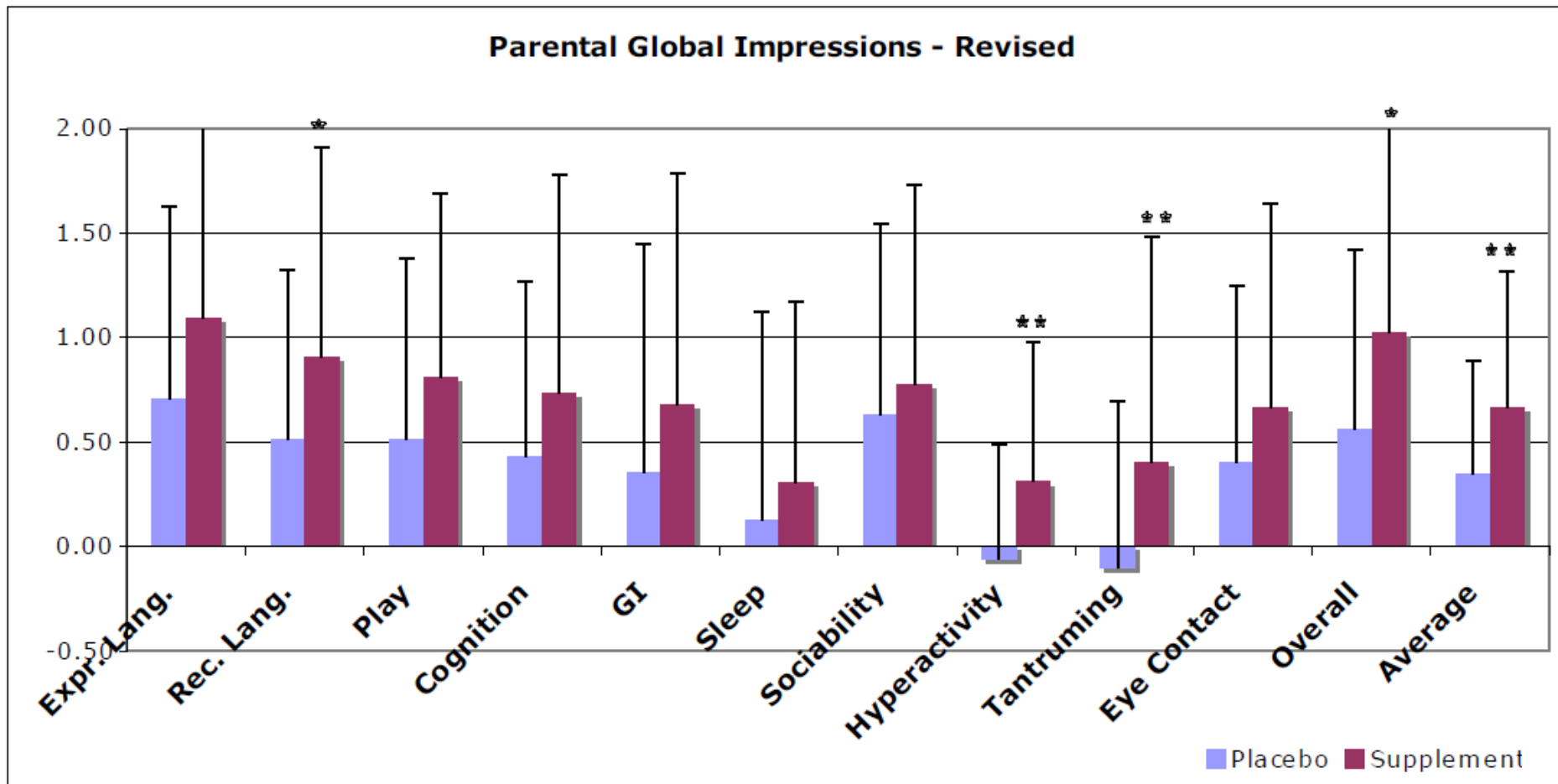


Autism

Micronutrients and autism: 2 RCTs; Adams et al., 2004, 2011

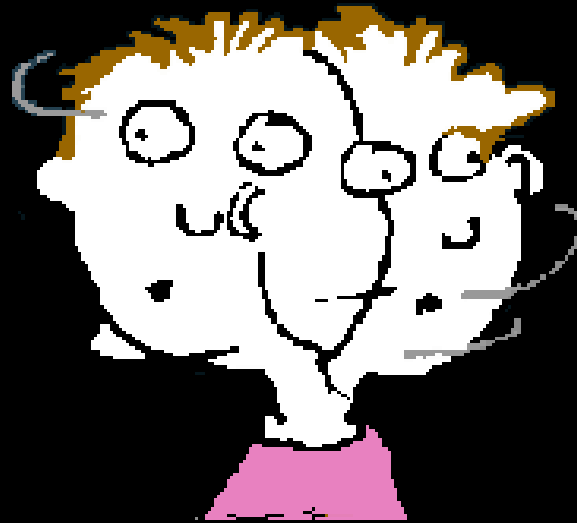
- First pilot trial = 20 children – 10 micronutrients (Spectrum Support) and 10 placebo
 - Improved sleep and GI problems
- Second trial: 141 children and adults with ASD treated with micronutrients (29 ingredients) – 3 month treatment
 - Vitamins/minerals used adjunctively (Syndion)
 - Those taking micronutrients showed improved sleep, reductions of tantrums, hyperactivity, and improved verbal language as well as GI problems compared with placebo

Change in functioning after 3 months micronutrients versus placebo



Small to medium effects in group differences

ADHD



ADHD and micronutrients

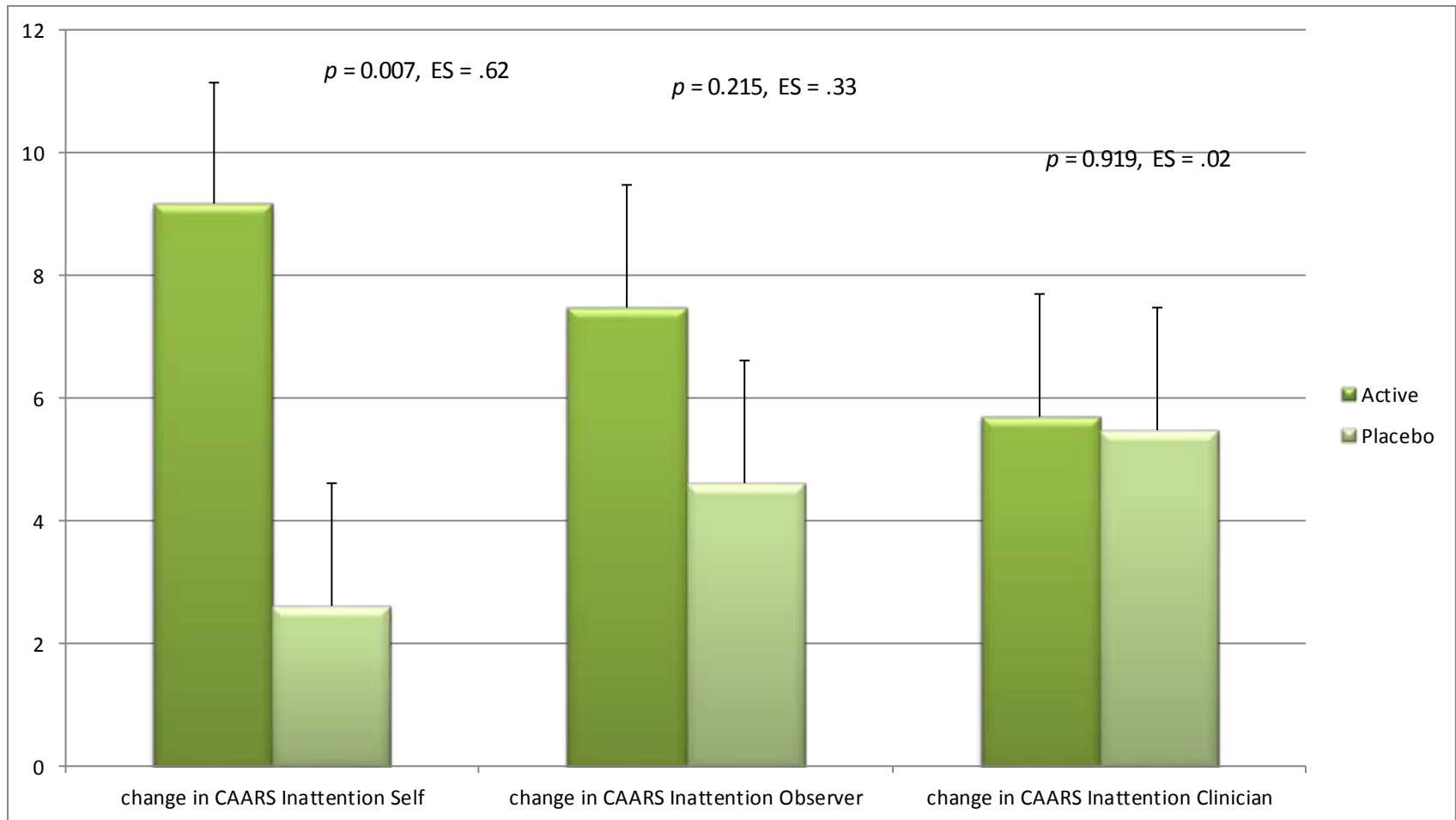
- **Early studies negative**
 - used megadoses and short trials
- **Evidence in last decade growing based on:**
 - open-label
 - retrospective database analyses
 - case reports
 - patient preference studies
 - **One RCT on micronutrients**
 - Rucklidge et al., 2010, 2011, 2014; Harding et al, 2003; Rucklidge & Harrison, 2010

Micronutrients with adults with ADHD: RCT evidence

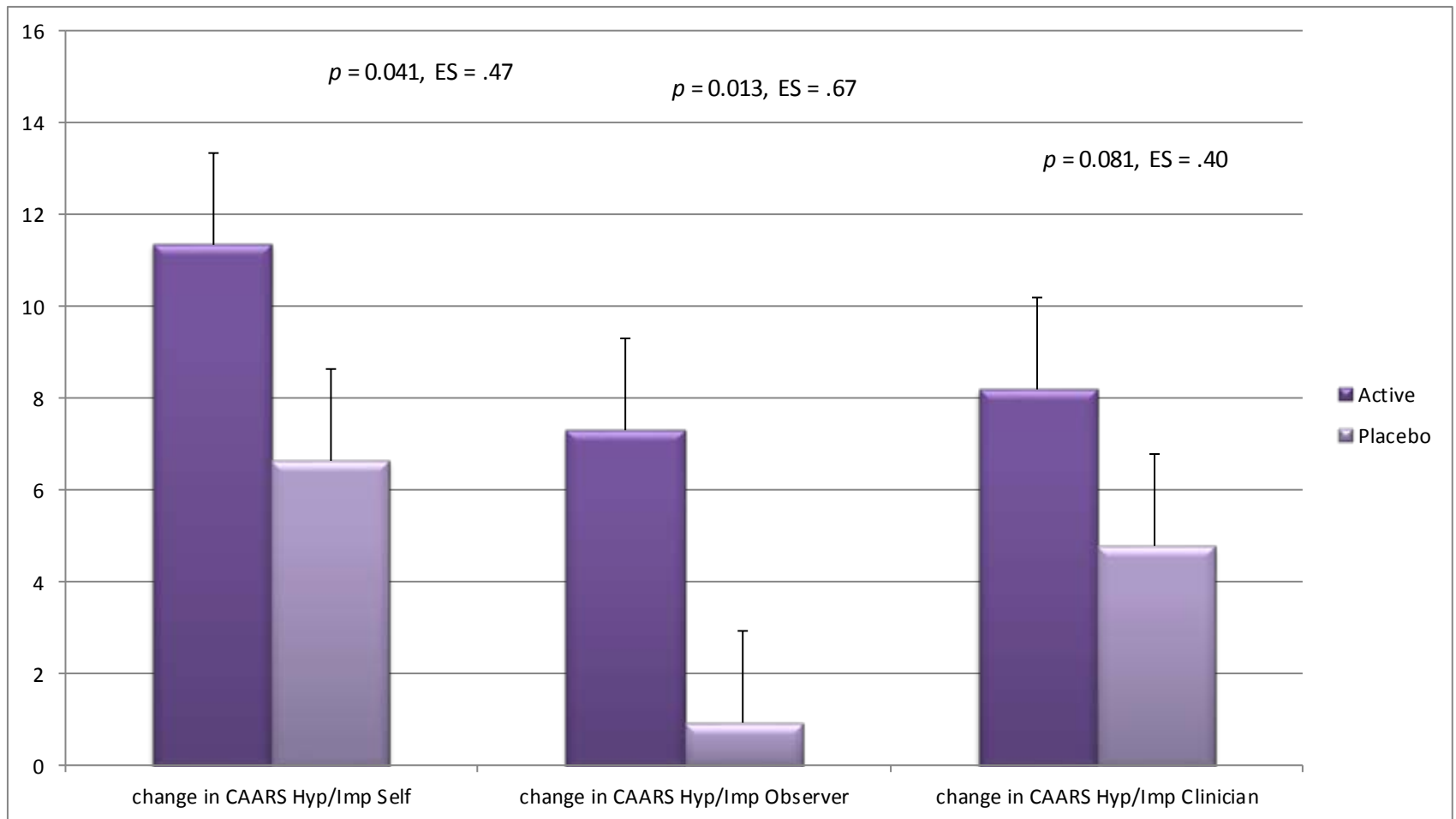
Rucklidge et al., 2014, British Journal of Psychiatry

- 80 participants: 42 micronutrients, 38 placebo
- Mean age: 35 years
- Diagnosis:
 - SCID-I and CAADID *and*
 - >70 on one of the DSM based scales of CAARS (self/observer)
- 35% ADHD Pred Inatt; 57% ADHD combined
- Co-occurring current diagnoses:
 - 23% mood disorder; 35% an anxiety disorder; 14% drug/alcohol abuse/dependency; 19% LD
 - Mean GAF at baseline = 59

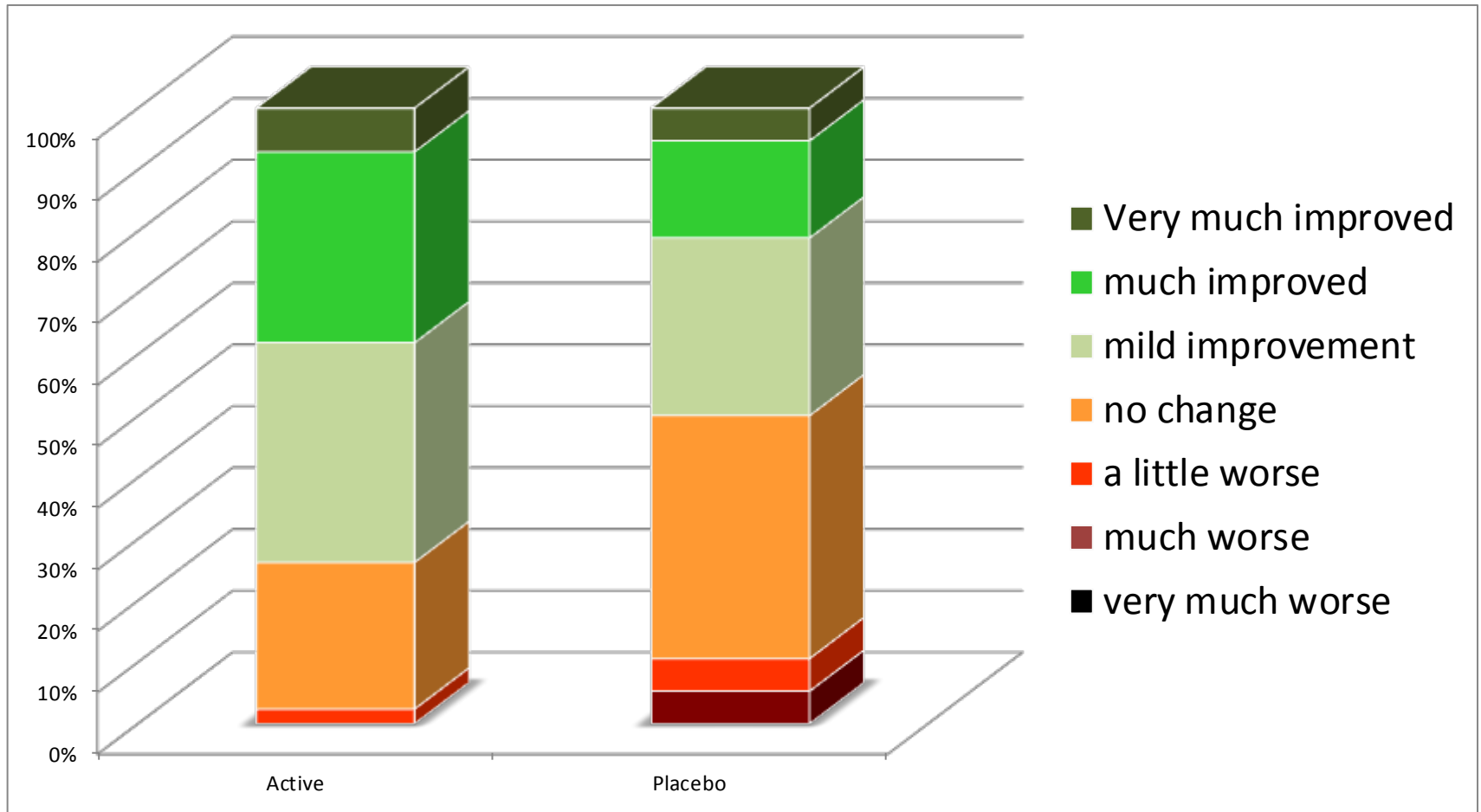
Change in Inattention across raters



Change in Hyperactivity/Impulsivity across raters

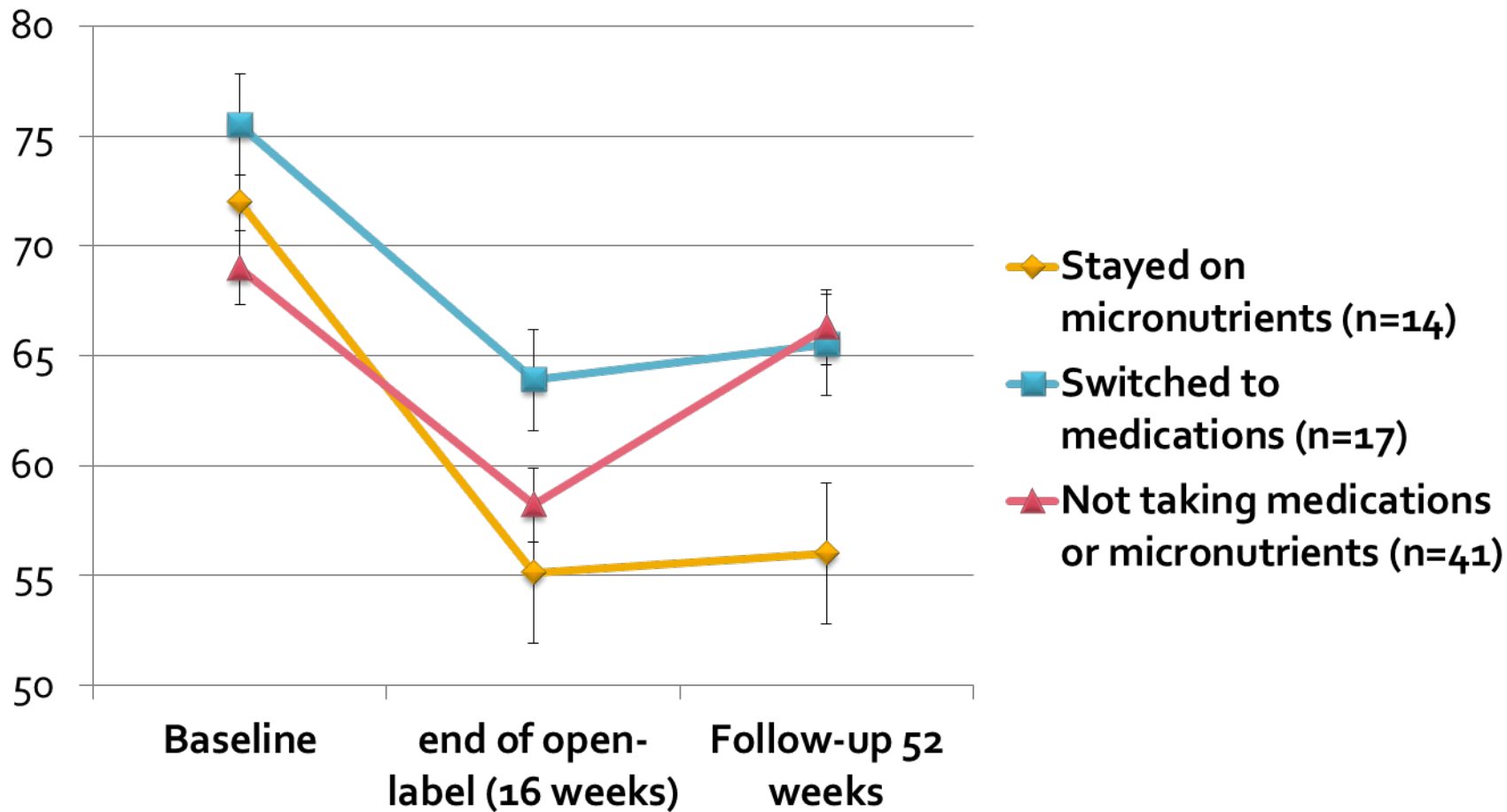


CGI – I – ADHD post RCT

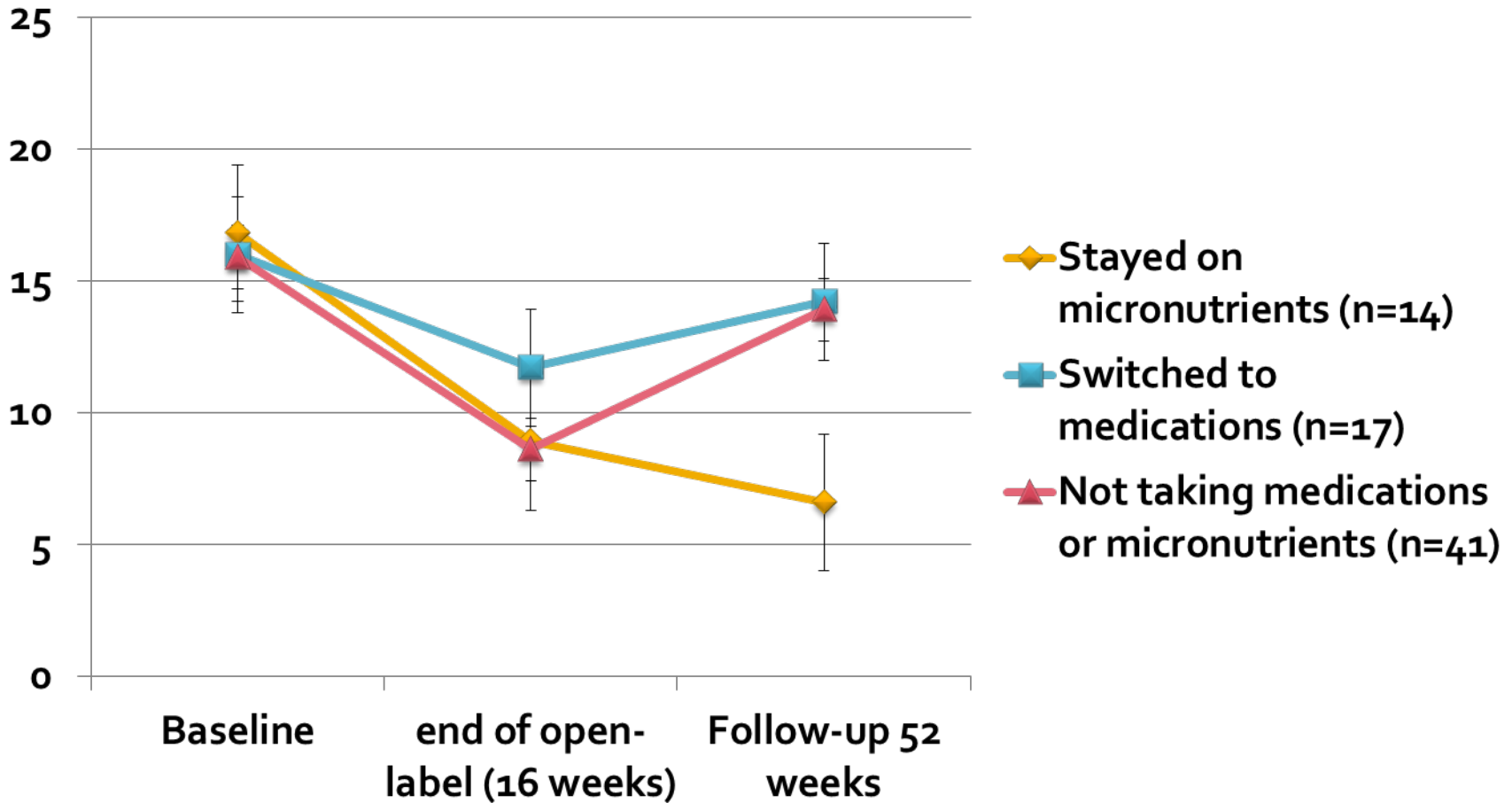


$p < .02, ES = 0.53$

Naturalistic follow-up one year post-baseline: ADHD symptoms



Naturalistic follow-up one year post-baseline: Mood symptoms

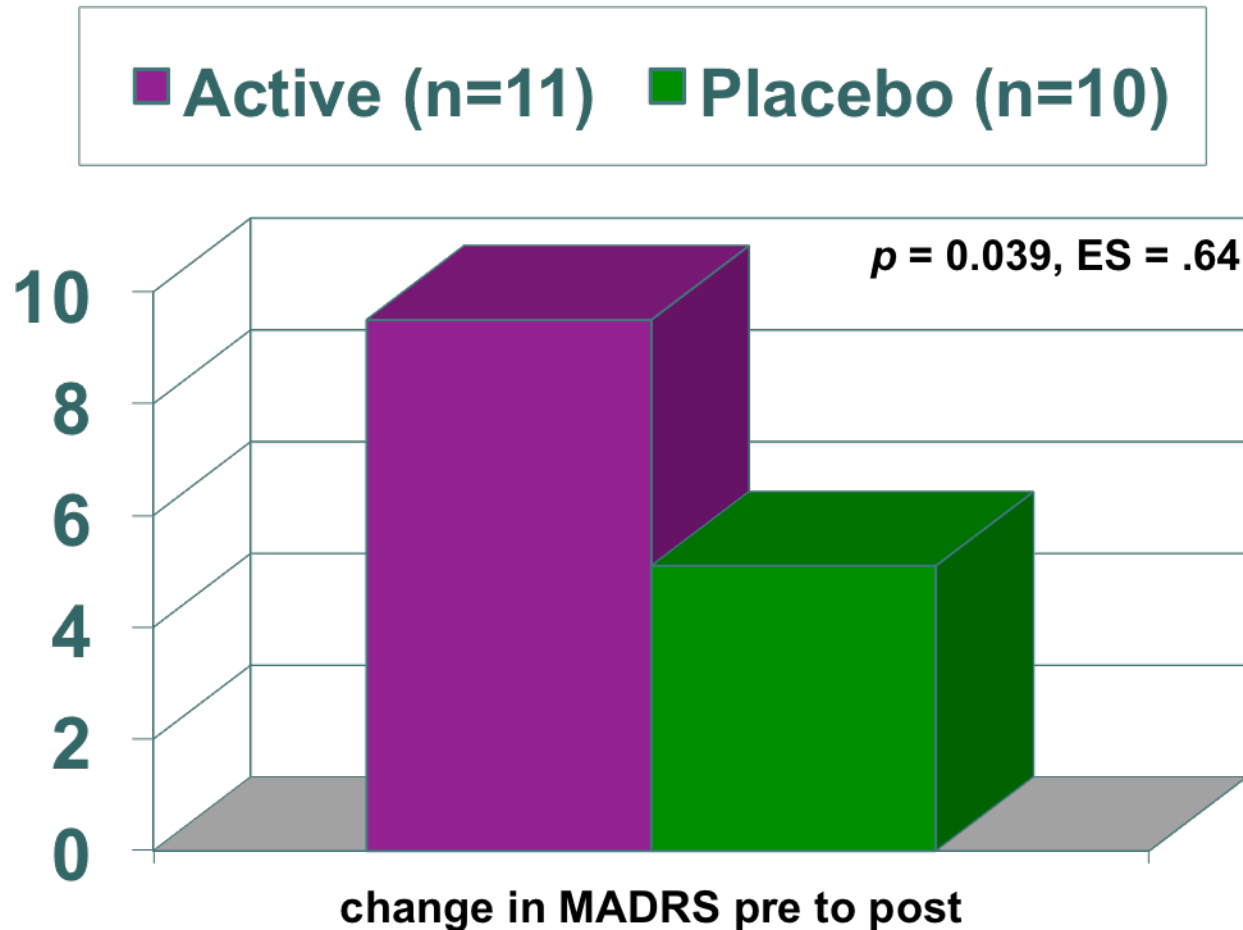


Mood

Depression

- **Depression: No good trials on samples specifically recruited for depression –**
 - lots of RCTs with normal populations (5 +ve RCT, 5 –ve RCTs) and others with health conditions (3 +ve RCTs, 1 –ve RCT)
 - Our RCT using EMP with ADHD showed benefit for a small subgroup who entered trial moderately to severely depressed

MADRS: only those clinically depressed at baseline



Does any of this amount to evidence?

- Depends how we conceptualize mental illness
 - DSM based categories suggest each category may have a separate etiology
 - But are they that separate? – can we lump all of the studies together?
- Bradford Hill, 1952: Created the basis for modern RCTs
- 1965: Recognized limitations – defined Bradford Hill criteria for establishing causation – *5 are relevant here*



➤ Biologic rationale



➤ Strength of association (clinical significance)



➤ Consistency of the evidence (across sites, studies)



➤ Temporal sequence (A must precede B)



➤ Experimental evidence (RCTs *and others* – *such as studies where the effect is manipulated like ABAB*)

But could vitamins
be... Killing you....?



Side effects?



minor and transitory

Compliance?



No difficulties with the regimen†

Impact on blood results?



None to date...*

Long-term effects?



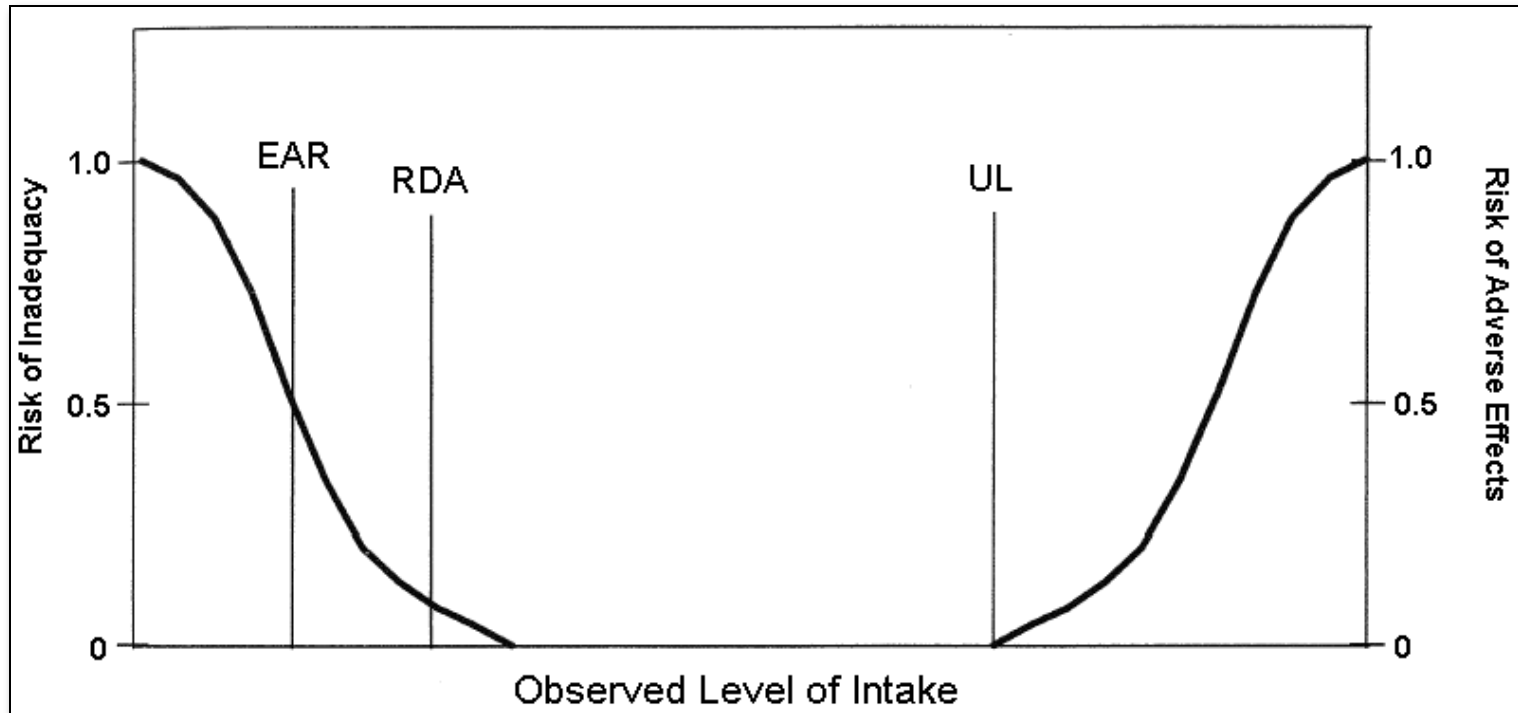
Needs to be studied *properly*

* *lack* of difference in fasting glucose, lipids, white blood cell count, and neutrophils, slight elevation on prolactin but still within normal range

† some find taking the pills tedious and stop for that reason

Simpson, JSA, Crawford, SG, Goldstein, ET, Field, C, Burgess, E, Kaplan, BJ (2011). Safety and tolerability of a complex micronutrient formula used in mental health: A compilation of eight datasets. *BMC Psychiatry*. 11:62.

Micronutrient safety

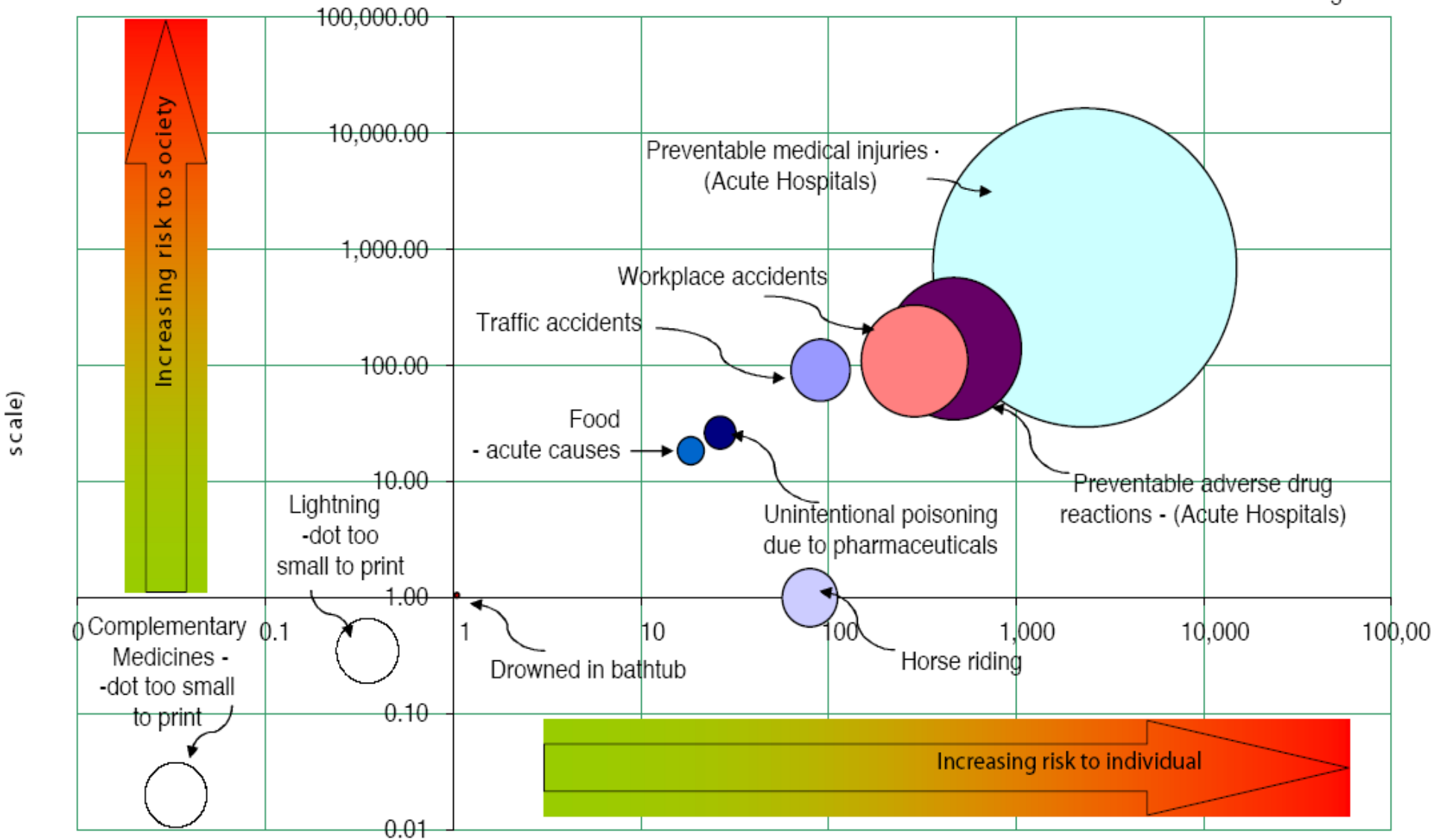


“The tolerable Upper Intake Level (UL) is the highest level of **daily nutrient intake** that is likely to pose **no risk of adverse health effects** for almost all individuals in the specified life stage group.”

- Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes*. National Academy Press, Washington, D.C., 2001.

Societal vs Individual Risk in Australia

Bubble size represents risk relative to 1: million individual risk or equivalent to the risk of a single flight on a Boeing 747 anywhere in the world.
 Note: Log scales



We need to do a cost-benefit analysis for each individual...*because there are some people who will not tolerate nutrients*



Progression of Evidence on Micronutrients & Psychiatric Symptoms

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- Case series of hundreds
- Case controls
- Randomized controlled trials (RCTs)
- **Roll out into clinical practice....**

Interestingly, risk factors associated with nutrition are typically *HIGHER* than any odds ratio ever reported for genetics

Why do we not give this more weight when explaining aetiology to patients?



vs



?

Kuntsi et al., 2006: genes and ADHD

Table 1: Average odds ratios and 95% confidence (CI) from the pooled analysis of genetic variants in more than one study (Faraone et al., 2005) [1]. Quantitative trait effects are estimated for these components 2 relative risk calculator <http://pngu.mgh.harvard.edu/~purcell/gpc/vc2rr.html>. This p assuming a standard normal trait distribution, such that the QTL variance for the discrete category be the same as the QTL variance for the continuous measure. Assuming an additive genetic mode variance explained by the associated genes is around 3.2%. The number of families needed to repli alpha of 0.05 and 80% is listed, in addition to the power from a sample of 200 families for the same

Gene	OR	95% CI	Allele frequency	QTL	Number of families to replicate with 80% power
DRD4	1.16	1.03 1.31	0.12	0.001	3196
DRD5	1.24	1.12 1.65	0.35	0.004	728
DAT1	1.13	1.03 1.24	0.73	0.001	2748
DBH	1.33	1.11 1.59	0.5	0.007	391
SNAP-25 (T1065G)	1.19	1.03 1.38	0.5	0.003	1043
SERT (HTTLPR)	1.31	1.09 1.59	0.6	0.006	466
HTR1B	1.44	1.14 1.83	0.71	0.010	315

ADHD Is Associated With a “Western” Dietary Pattern in Adolescents

Journal of Attention Disorders
15(5) 403–411
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DOI: 10.1177/1087054710365990
<http://jad.sagepub.com>



Amber L. Howard^{1,2}, Monique Robinson¹, Grant J. Smith¹,
Gina L. Ambrosini¹, Jan P. Piek², and Wendy H. Oddy¹

Abstract

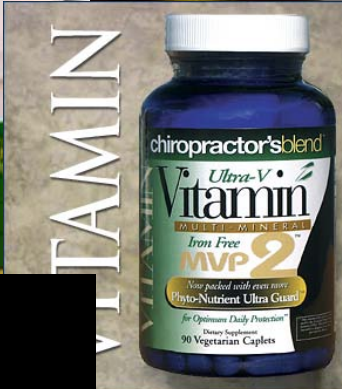
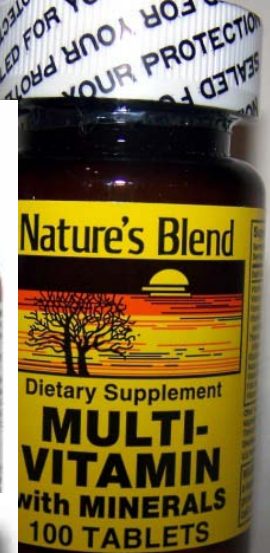
Objective: To examine the relationship between dietary patterns and ADHD in a population-based cohort of adolescents. **Method:** The Raine Study is a prospective study following 2,868 live births. At the 14-year follow-up, the authors collected detailed adolescent dietary data, allowing for the determination of major dietary patterns using factor analysis. ADHD diagnoses were recorded according to International Classification of Diseases, 9th Revision coding conventions. Logistic regression was used to assess the relationship between scores for major dietary pattern and ADHD diagnoses. **Results:** Data were available for 1,799 adolescents, and a total of 115 adolescents had an ADHD diagnosis. Two major dietary patterns were identified: “Western” and “Healthy.” A higher score for the Western dietary pattern was associated with ADHD diagnosis (odds ratio = 2.21, 95% confidence interval = 1.18–4.13) after adjusting for known confounding factors from pregnancy to 14 years. ADHD diagnosis was not associated with the “Healthy” dietary pattern. **Conclusion:** A Western-style diet may be associated with ADHD. (*J. of Att. Dis.* 2011; 15(5) 403-411)

Keywords

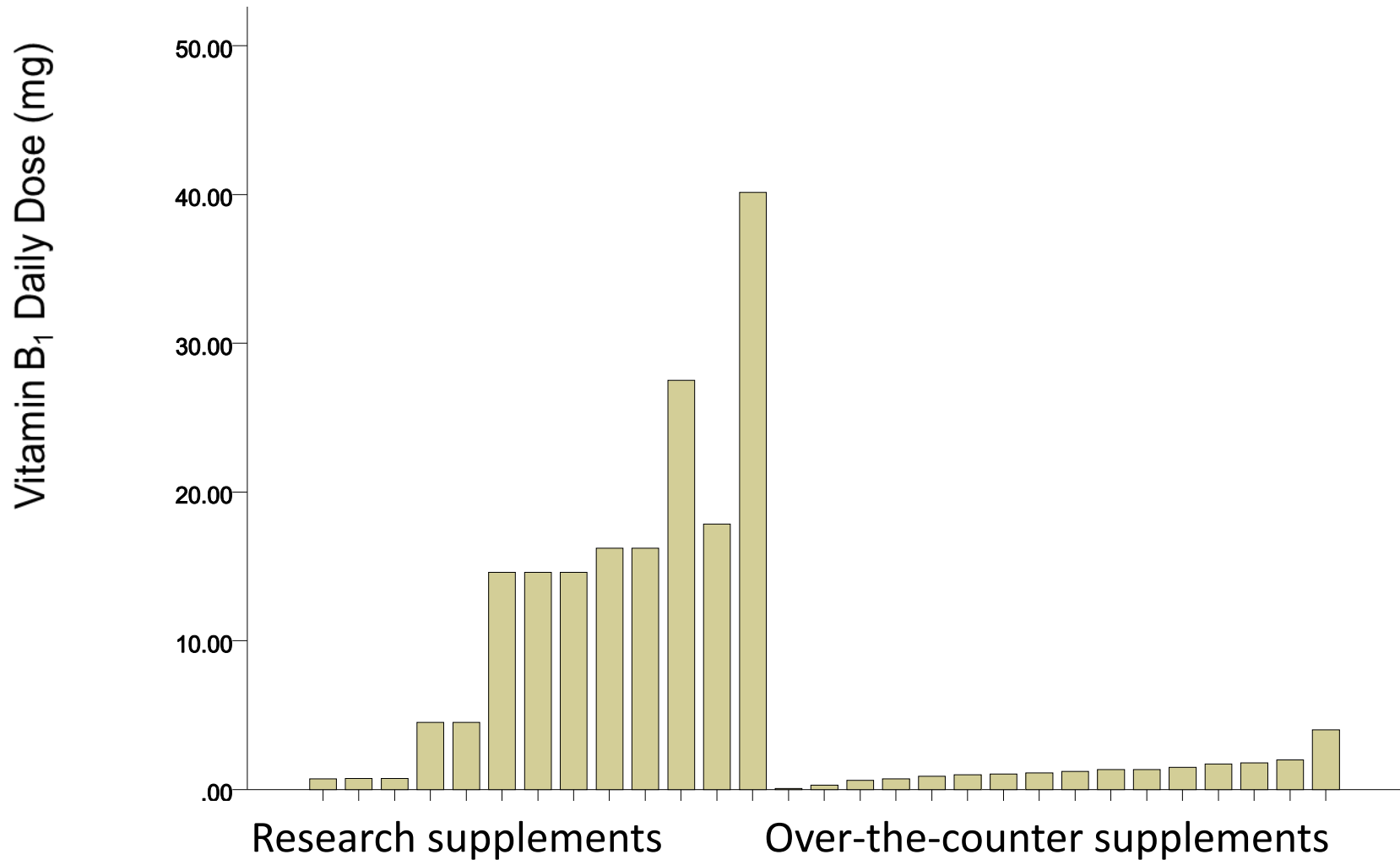
Adolescents with a high score for the “Western” dietary pattern more likely to have ADHD, OR=2.21 even after adjusting for potential confounding factors

WHICH FORMULA DOES ONE CHOOSE????

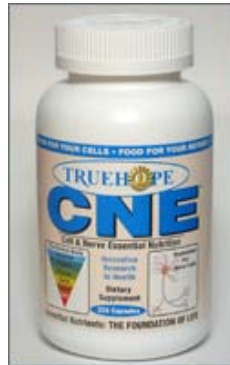
None of them have been developed specifically for mental health symptoms...



Commercial vs research products: are they the same? Rucklidge, Harris & Shaw, 2014, NZMJ



Which ones have any evidence to help with mental illness?



Other considerations

- Which nutrient(s) is necessary? Could we get away with a smaller set of key nutrients?
- Dietary changes versus supplementation?
- antibiotic use/inflammation/food allergies
- Other medications (particularly psychiatric ones)
- Short and long-term compliance – many people stop them, even if working...
- Yeast infections and illness – do they impact on response?
- Cost to patients
- *Not everyone improves* – one size doesn't fit all
 - An example – those with a mutation to the MTHFR gene affects metabolism of folic acid



Conclusions...

- Physiologically, makes sense to provide body/brain with a broad spectrum of nutrients to correct possible metabolic deficiencies/inflammation to optimize functioning
- After a decade of research, most studies positive across different countries, different formulas
 - ▶ And depending on how we conceptualize mental illness, the evidence is pretty strong
 - ▶ over 20 DBRCTs showing benefit for psychological/psychiatric symptoms
- ▶ *how long can we ignore these data?*

For further info on the formulas mentioned here today.....

- **EMPowerplus/CNE/Q96:** www.truehope.com
- **Daily Self Defense:** <http://optimusnutraceuticals.com/>
- **Daily Essential Nutrients:** <http://www.hardynutritionals.com/>
- **Brain Child Spectrum Support:**
<http://www.brainchildnutritionals.com/spectrum-support-vitamins.html/>
- **Forceval:** <http://www.forceval.co.uk/>
- **Blackmores Executive B:**
<http://www.blackmores.com.au/products/executive-b-stress-formula>
- **Max Stress B**
http://www.healthproductsusa.net/30_max_stress_b_health.htm
- **Swisse Ultivite:** <http://www.swisse.com/au/vitamins-and-supplements/mens-health/73/swisse-mens-ultivite-f1>
- **Bayer's Berocca:** <http://www.berocca.com/en/home.php>