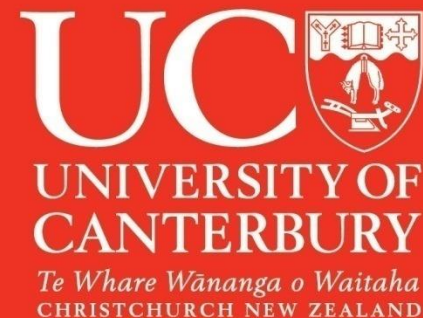




# ***Micronutrients as a treatment for psychiatric disorders: The evidence to date***

**Julia Rucklidge, PhD**  
**Professor of Psychology, University of  
Canterbury**  
**INTEGRATIVE MENTAL HEALTH, Jan 8<sup>th</sup>**  
**2015**

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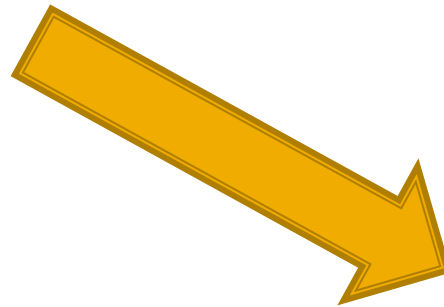
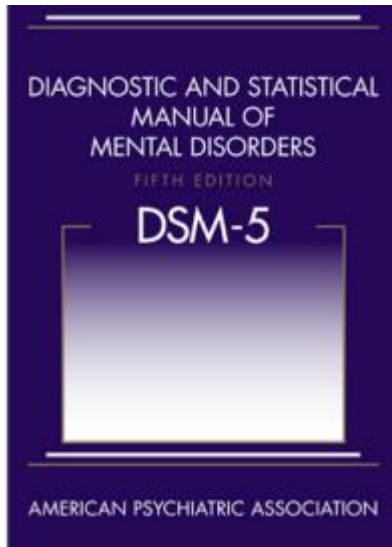
# Disclosure

- **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 spectrum* 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
- Side effects ongoing concern for many

# What's the evidence for broad spectrum micronutrients?



# Progression of Evidence on Micronutrients & Psychiatric Symptoms

- Case studies

- Case series

- Case controls

- RCTs

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

**Evidence-based medicine**

# Progression of Evidence on Micronutrients & Psychiatric Symptoms

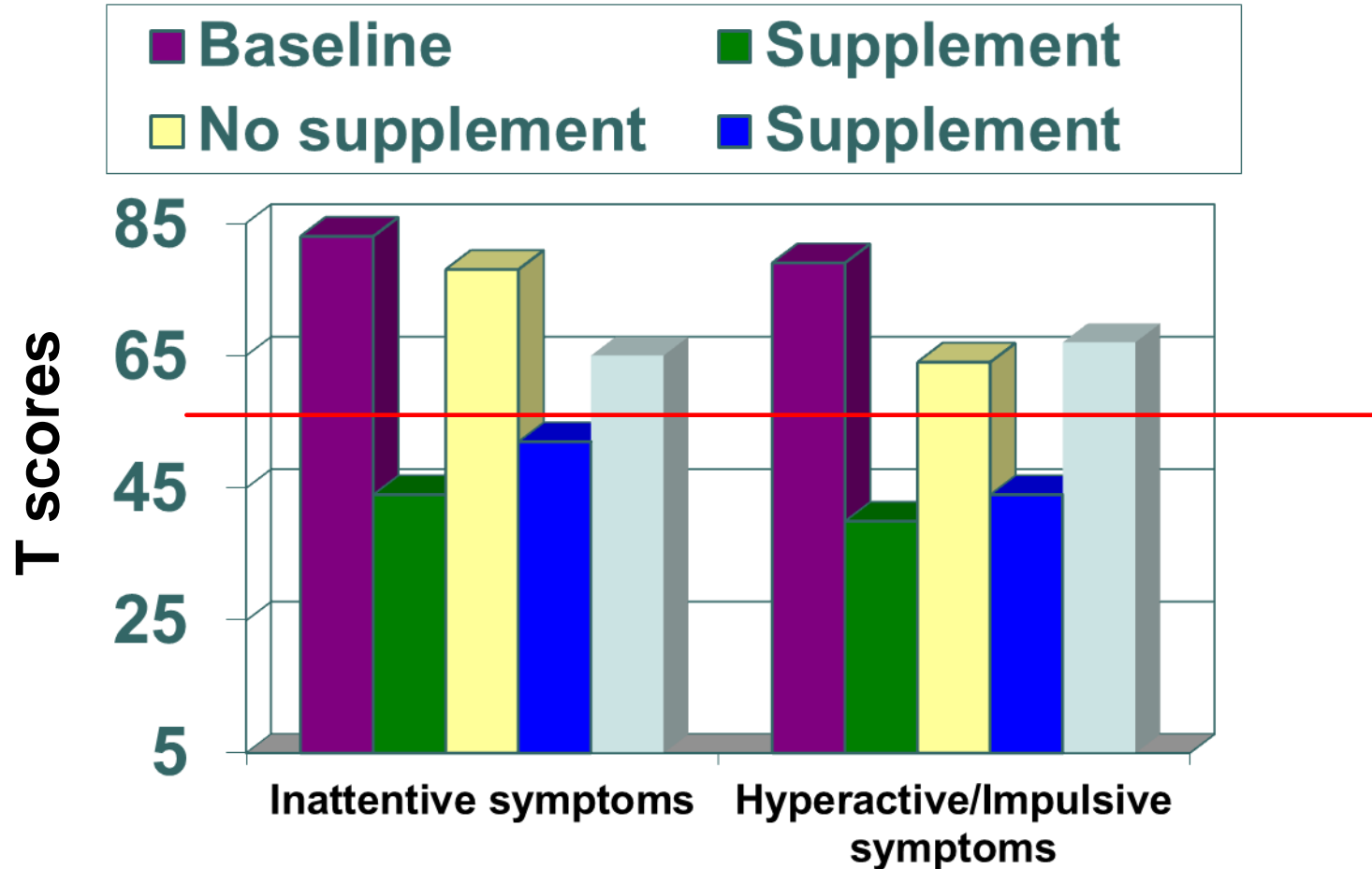
- **Case studies**
- Case series
- Case controls
- RCTs
- Roll out into clinical practice

# “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
- On (8 weeks)-off (8 weeks)-on (4 months)-“natural” off (5 months) using vitamin-minerals



# On-off control of ADHD symptoms



# Progression of Evidence on Micronutrients & Psychiatric Symptoms

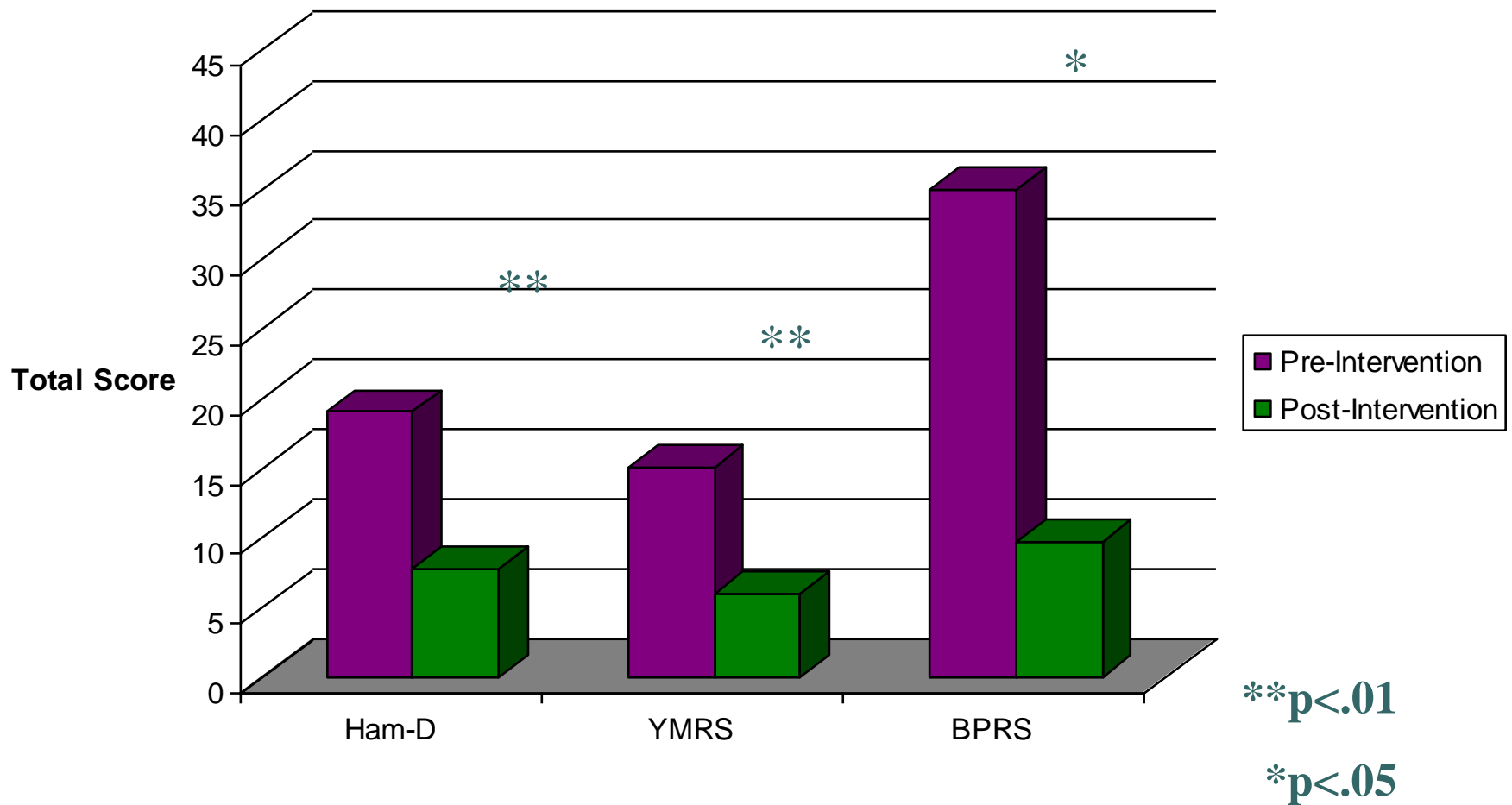
- Case studies
- **Case series**
- Case controls
- RCTs
- Roll out into clinical practice

# Tx of Bipolar Disorder with nutrients

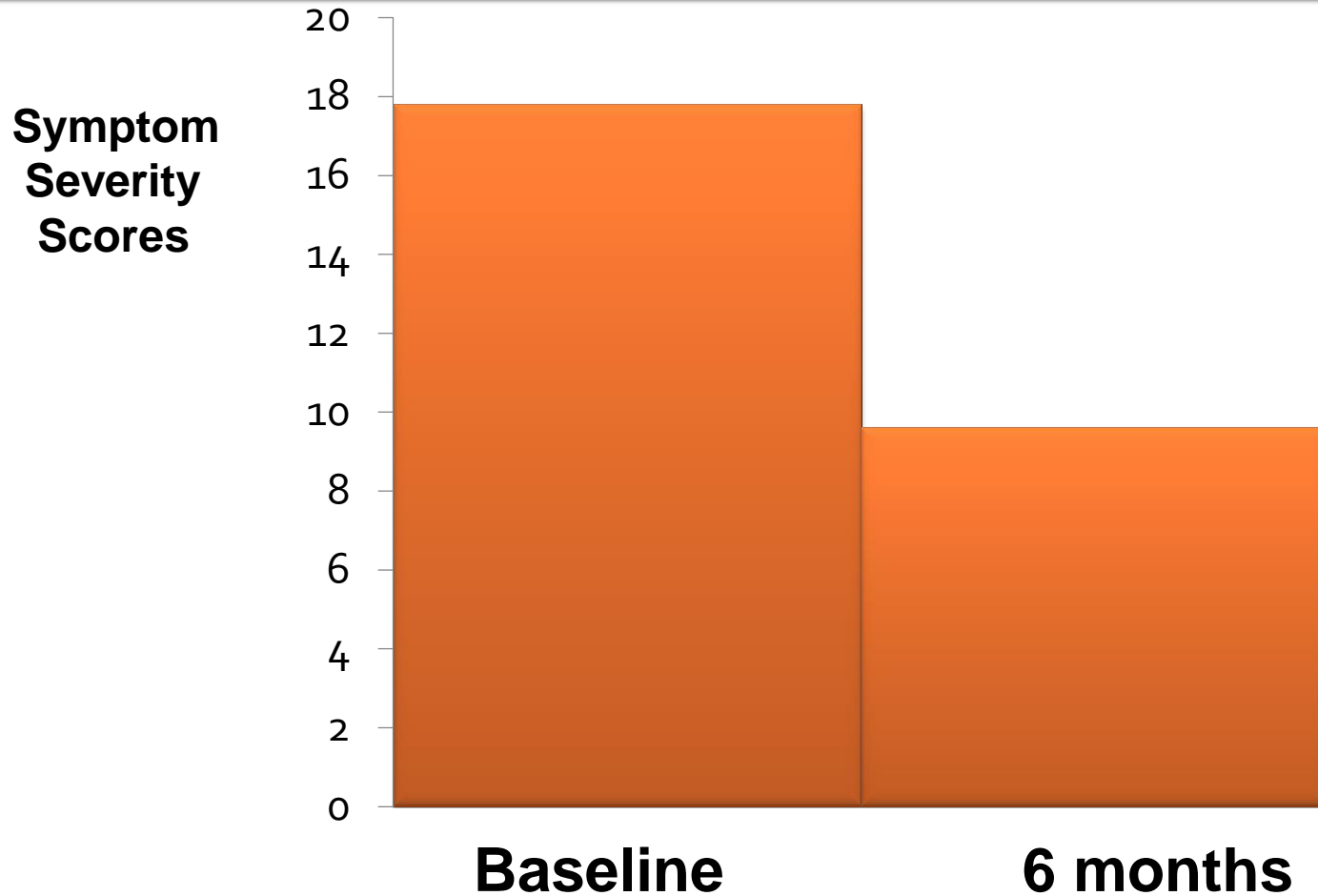
- All studies to date on one formula, EMPowerplus
- 5 open label trials; 2 database analyses
  - Significant reductions in all psychiatric symptoms
  - Significant reduction in medications
  - Response rates range from 50-80%
    - Simmons, 2003, JCP; Kaplan et al., 2001, JCP, Kaplan et al., 2004, JCAP; Popper, 2001, JCP; Frazier et al., 2012, JACM; Rucklidge et al., 2010, BMC Psychiatry; Gately & Kaplan, 2009, Clin Med

# 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.



# Improvement in Bipolar Disorder in 120 children over a 6-month period



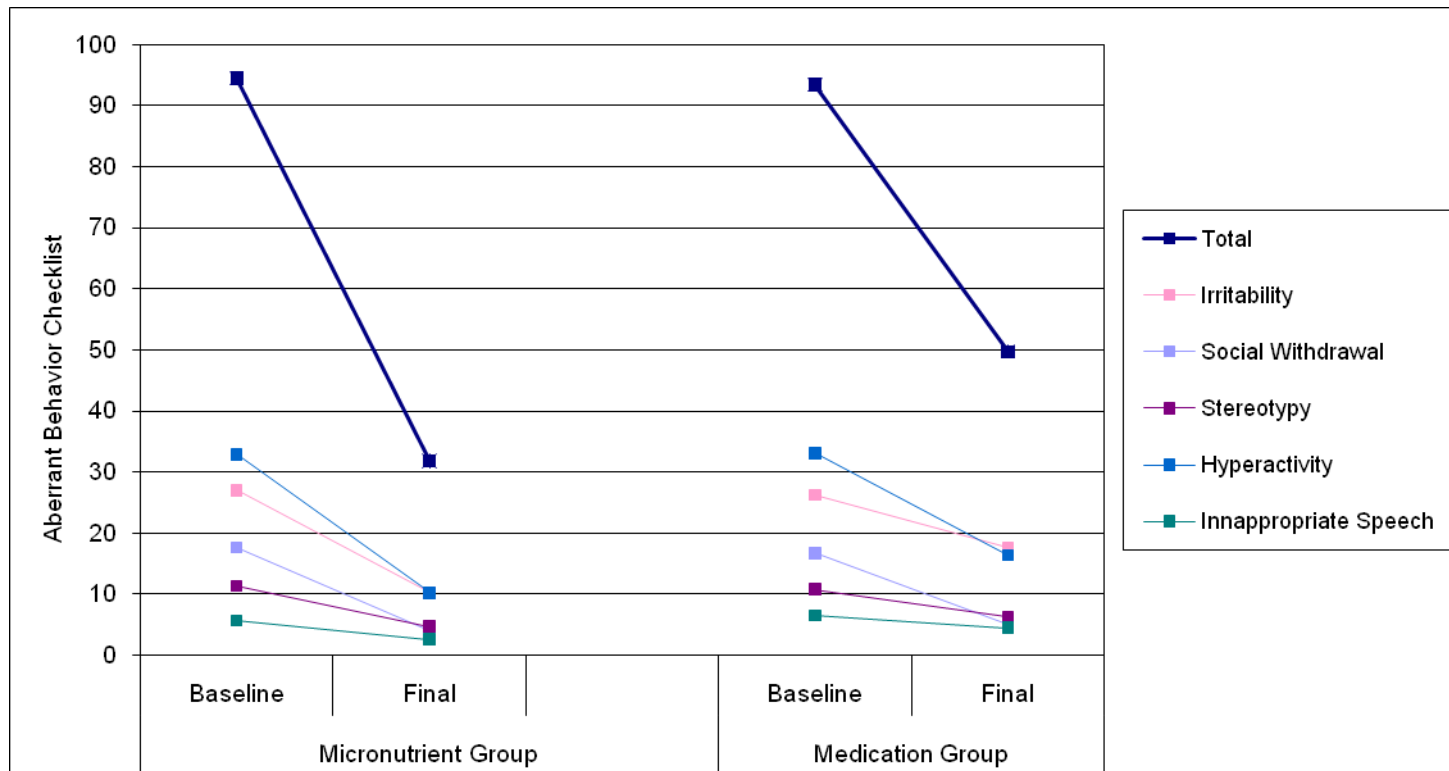
Rucklidge JJ, Gately D, Kaplan BJ; BMC Psychiatry 2010

# Progression of Evidence on Micronutrients & Psychiatric Symptoms

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

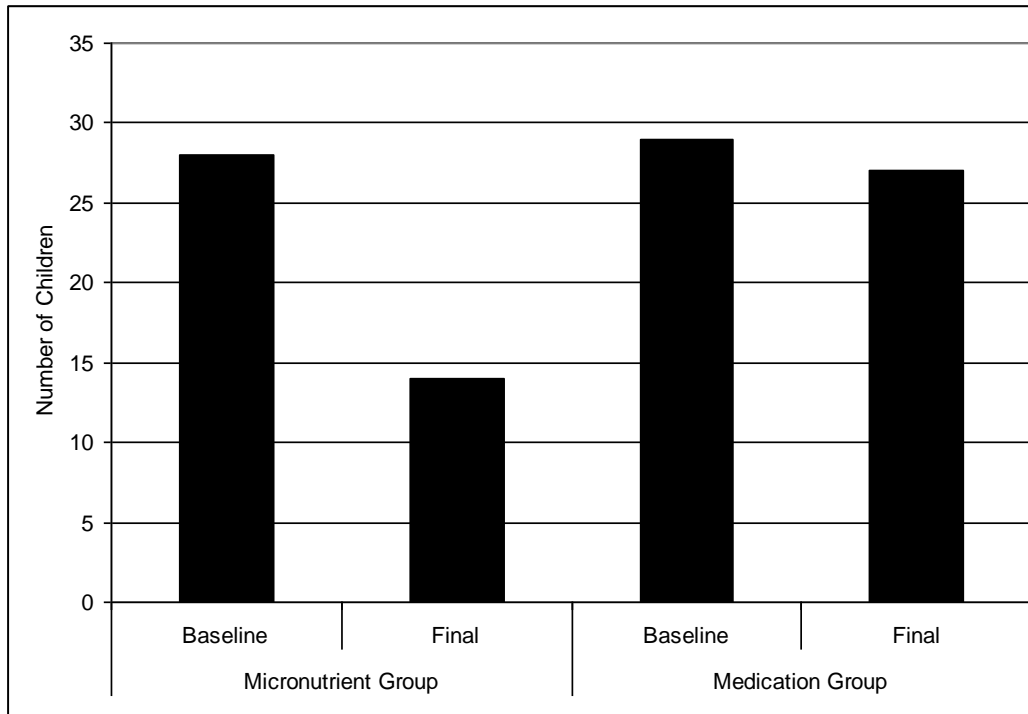
# Case-control study of 88 children with autism

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

# Broad-spectrum micronutrient formulas for the treatment of psychiatric symptoms: a systematic review

Expert Rev. Neurother. 13(1), 49–73 (2013)

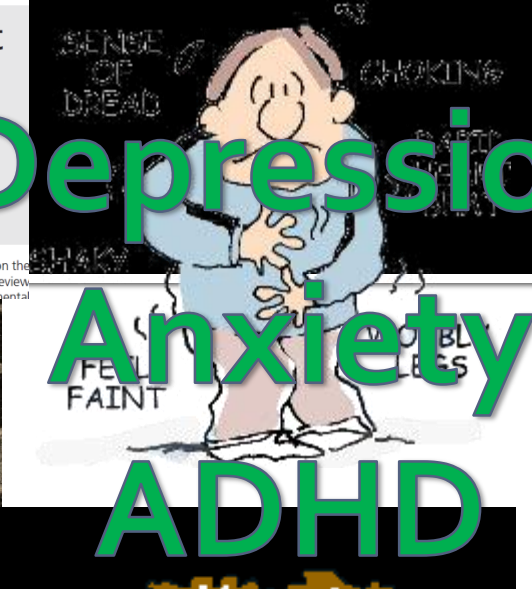
Julia J Rucklidge\*<sup>1</sup> and Bonnie J Kaplan<sup>2</sup>

Ingesting minerals and vitamins in combination makes physiological sense, and research on the use of broad-spectrum formulations for psychiatric symptoms is increasing rapidly. This review covers formulas consisting of at least four vitamins and/or minerals and includes four experimental

# Depression

# Anxiety

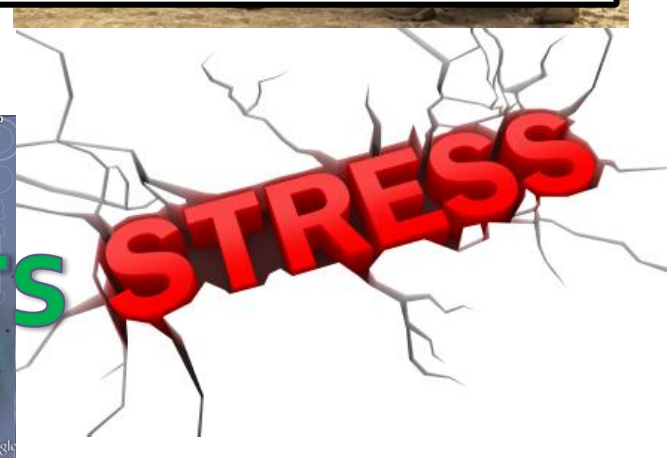
# ADHD



Over 20 positive RCTs to date  
All negative trials (6) done on people  
**WITHOUT** psychiatric symptoms



# Autism Offenders



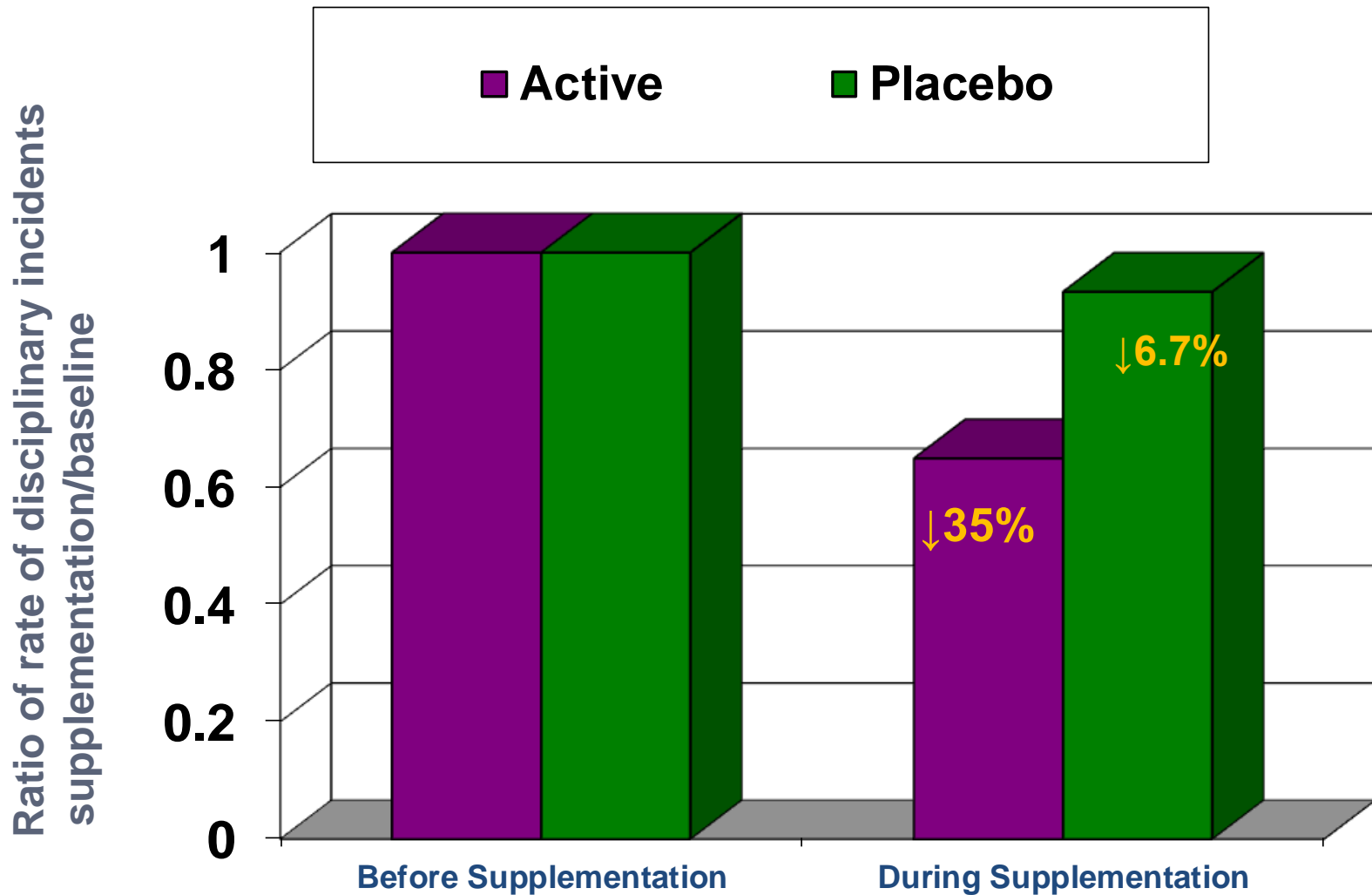
# Forensics: 4 RCTs

**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

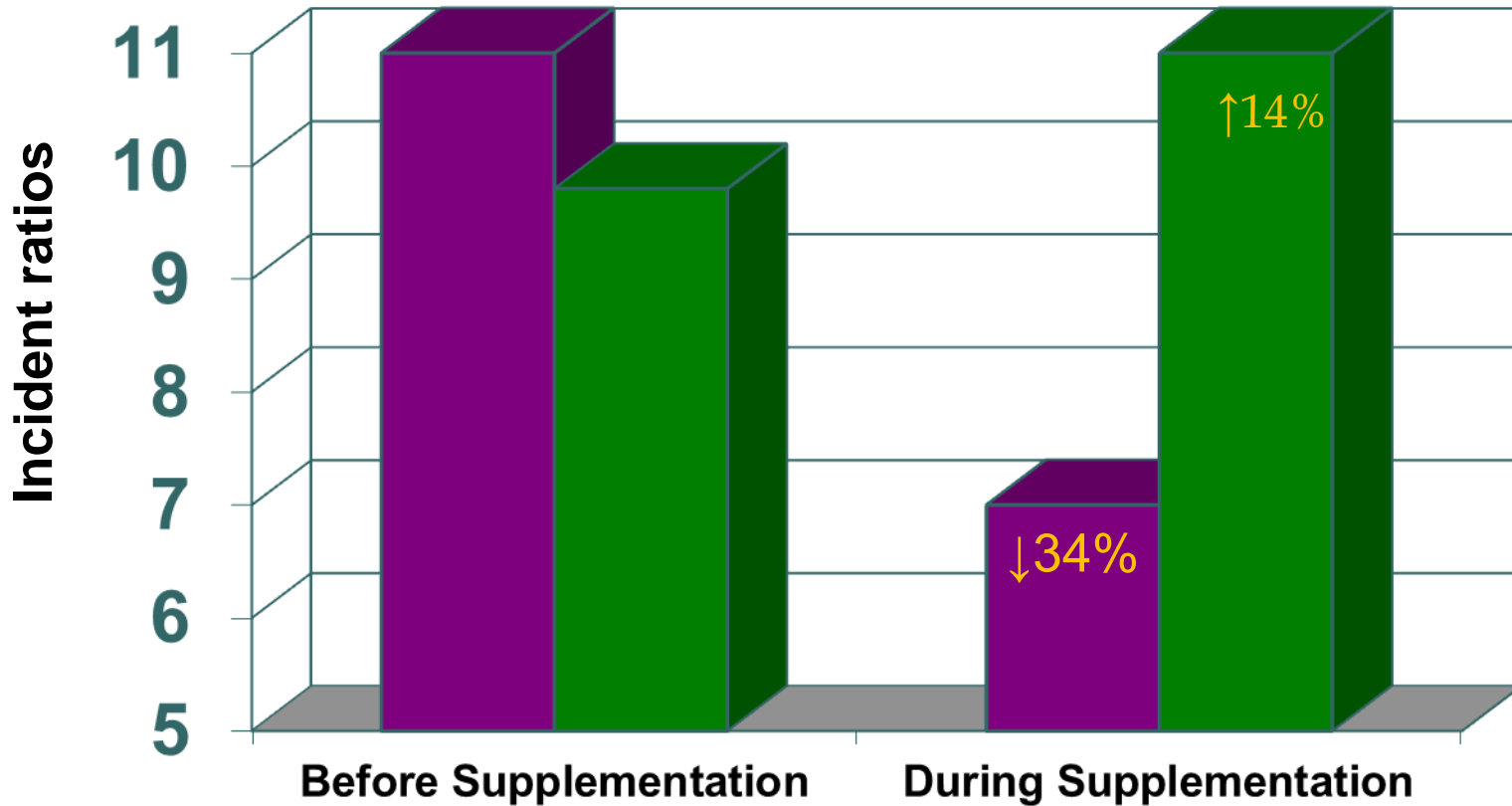


# Micronutrient supplementation (Forceval) in 231 young adult prisoners, Gesch et al. 2002, *Brit J Psychiatry*



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

■ Active    ■ Placebo

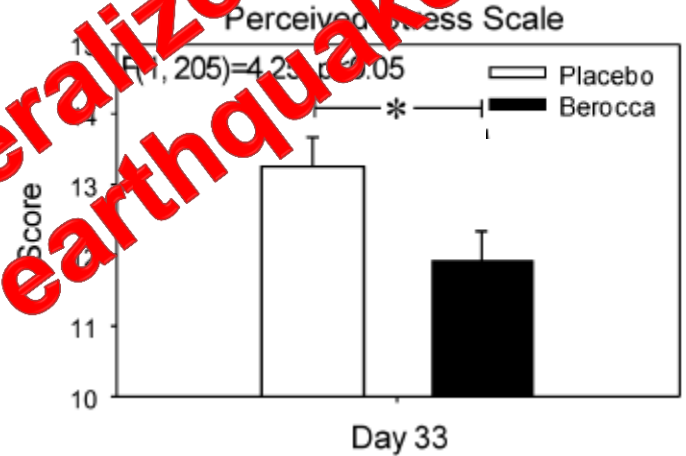
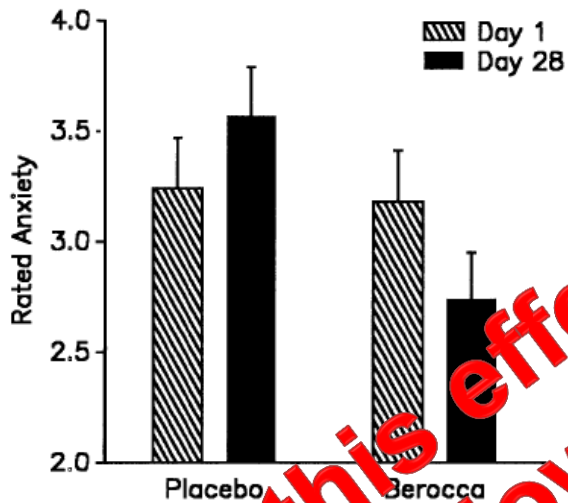


# Stress, Natural disasters and nutrients

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# 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



Effects of high-dose B vitamin complex with vitamin C and minerals on subjective mood and performance in healthy males

David O. Kennedy · Rachel Veasey · Anthony Watson ·  
 Fiona Dodd · Emma Jones · Silvia Maggini ·  
 Crystal F. Haskell

Douglas Carroll · Christopher King · Martin Suter ·  
 Gonneke Willemsen

The effects of an oral multivitamin combination with calcium, magnesium, and zinc on psychological well-being in healthy young male volunteers: a double-blind placebo-controlled trial

Can this effect generalize to stress following an earthquake?





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

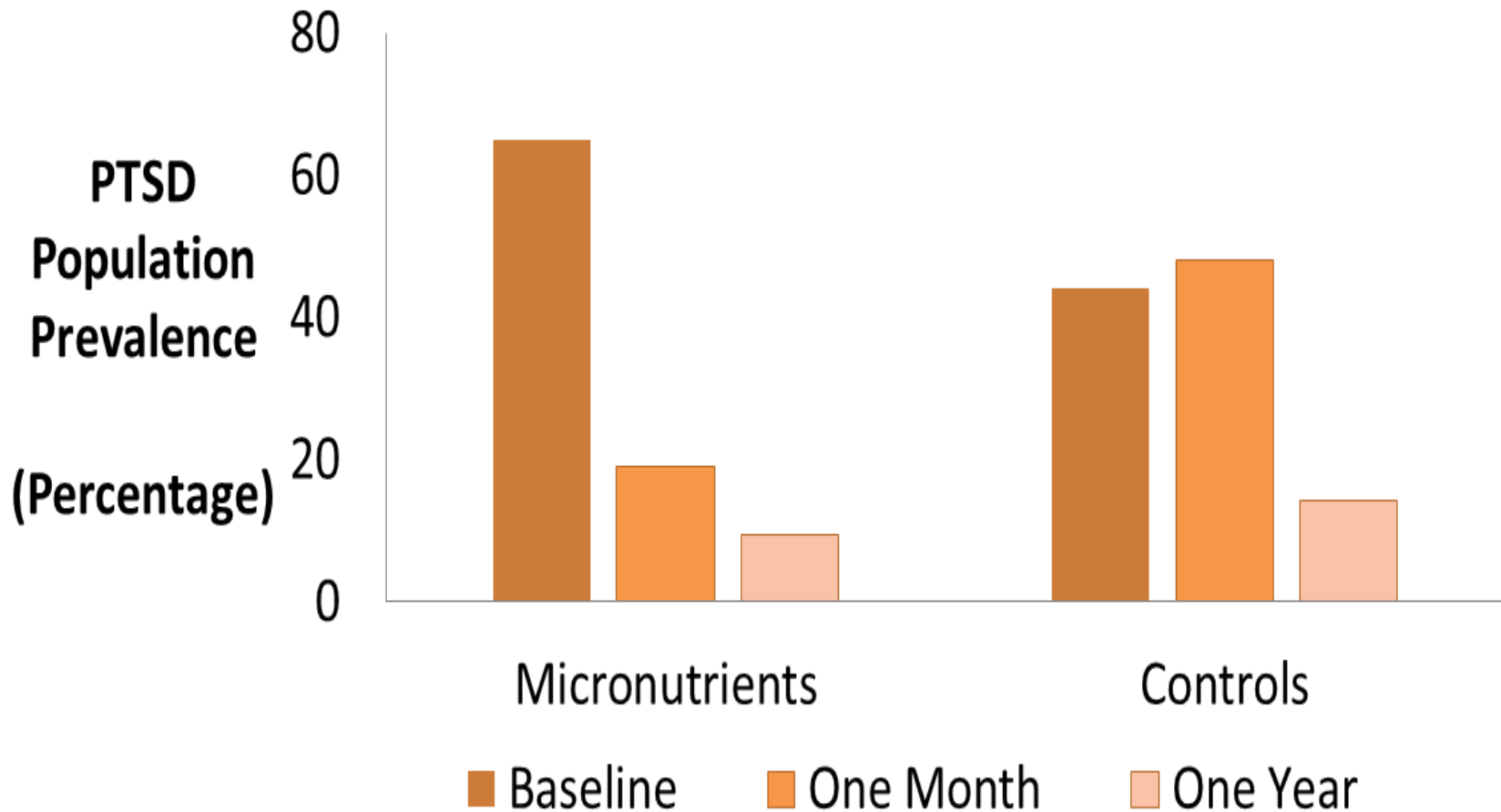
- 30 to Berocca (29 completed)
- 31 to EMP4 (30 completed)
- 30 to EMP8 (27 completed)

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

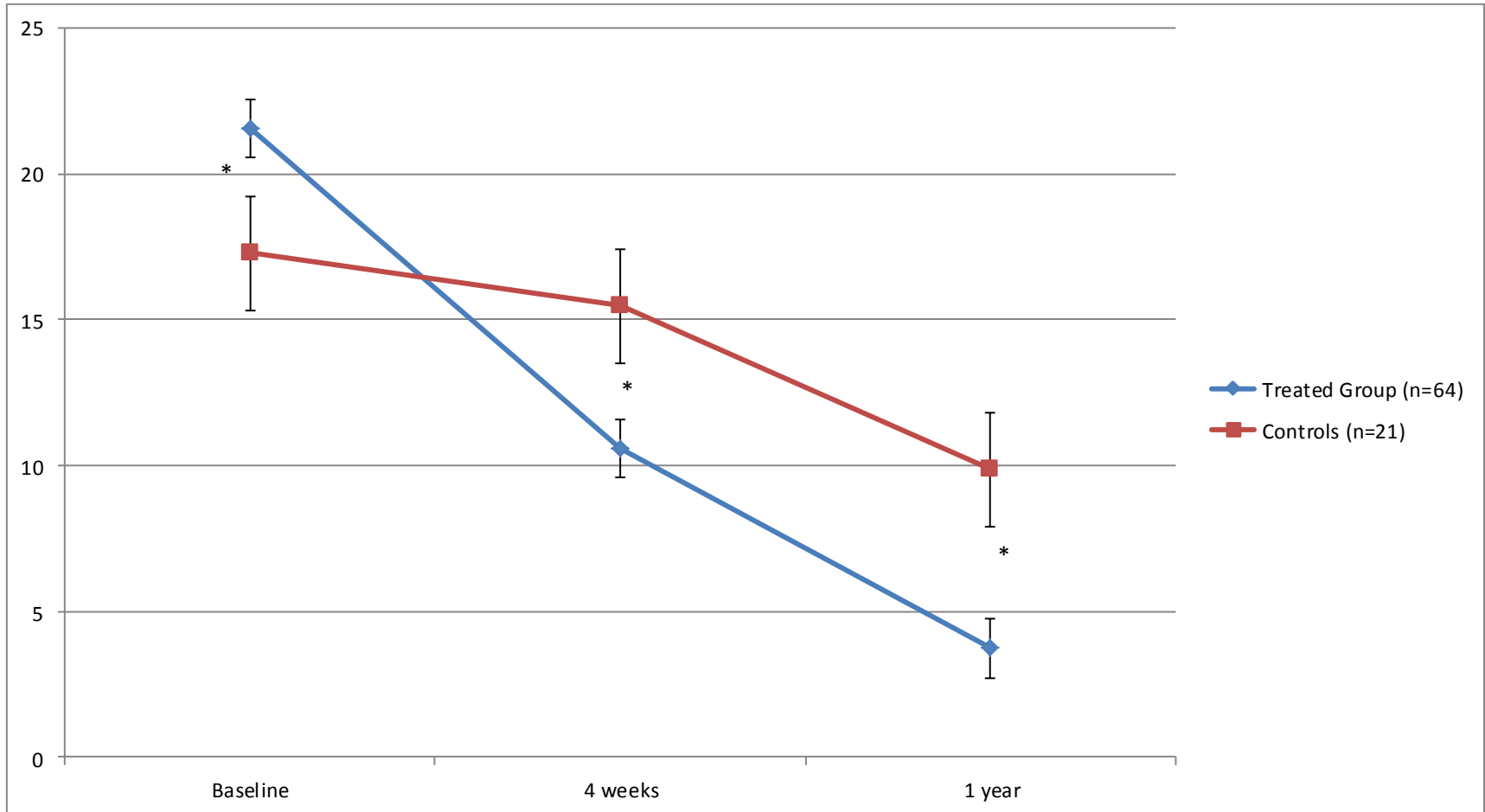
## ▶ Monitored weekly with on-line Q assessing stress, mood, anxiety and PTSD symptoms

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

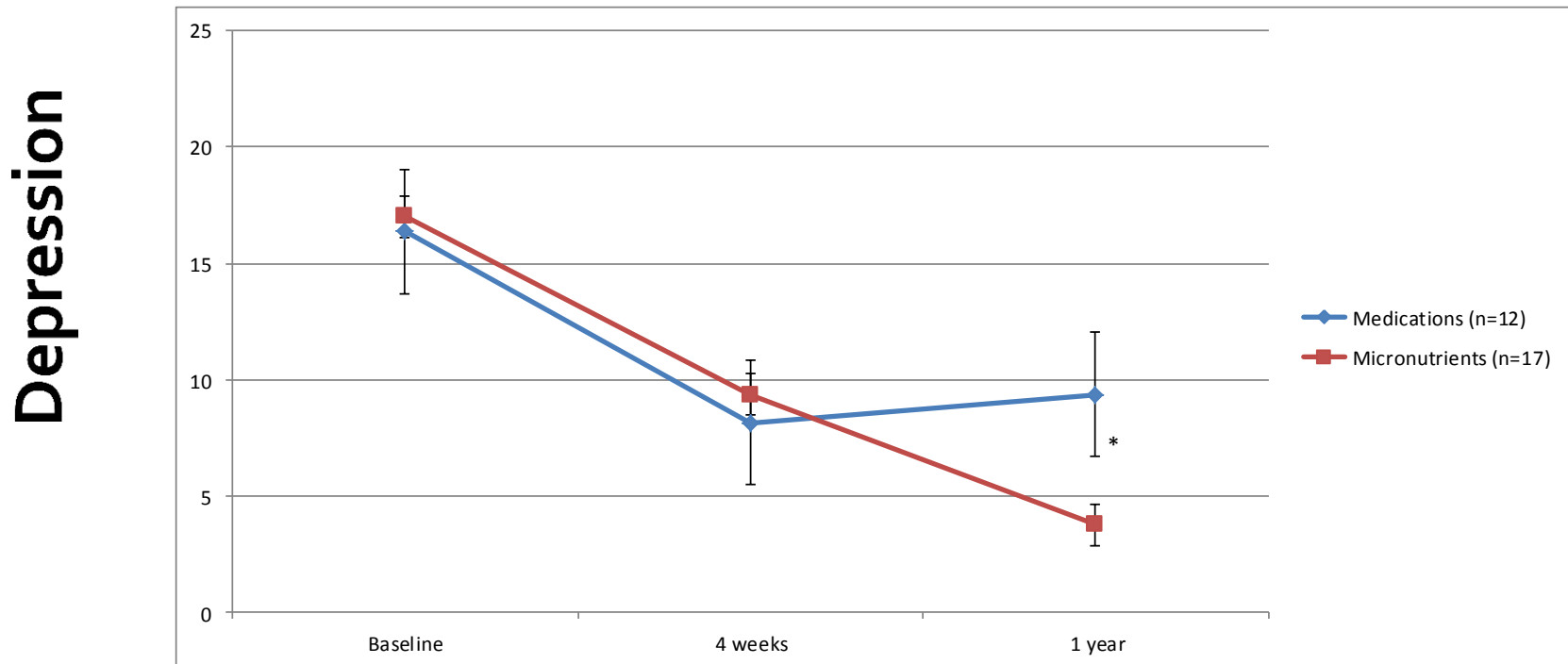
# Reduction in trauma after earthquakes



# Protective in the Long term? Change in stress over time between those treated acutely with micronutrients and control group



# Change in depression over time based on treatment at 52 weeks



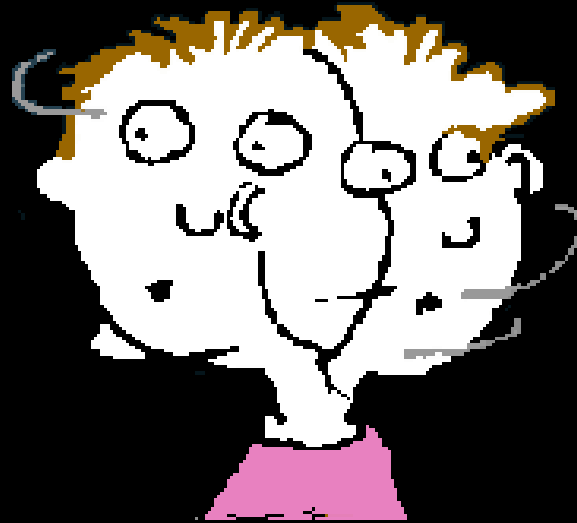
# Maybe nutrients feed the brain and replete the system under chronic stress

“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



ADHD





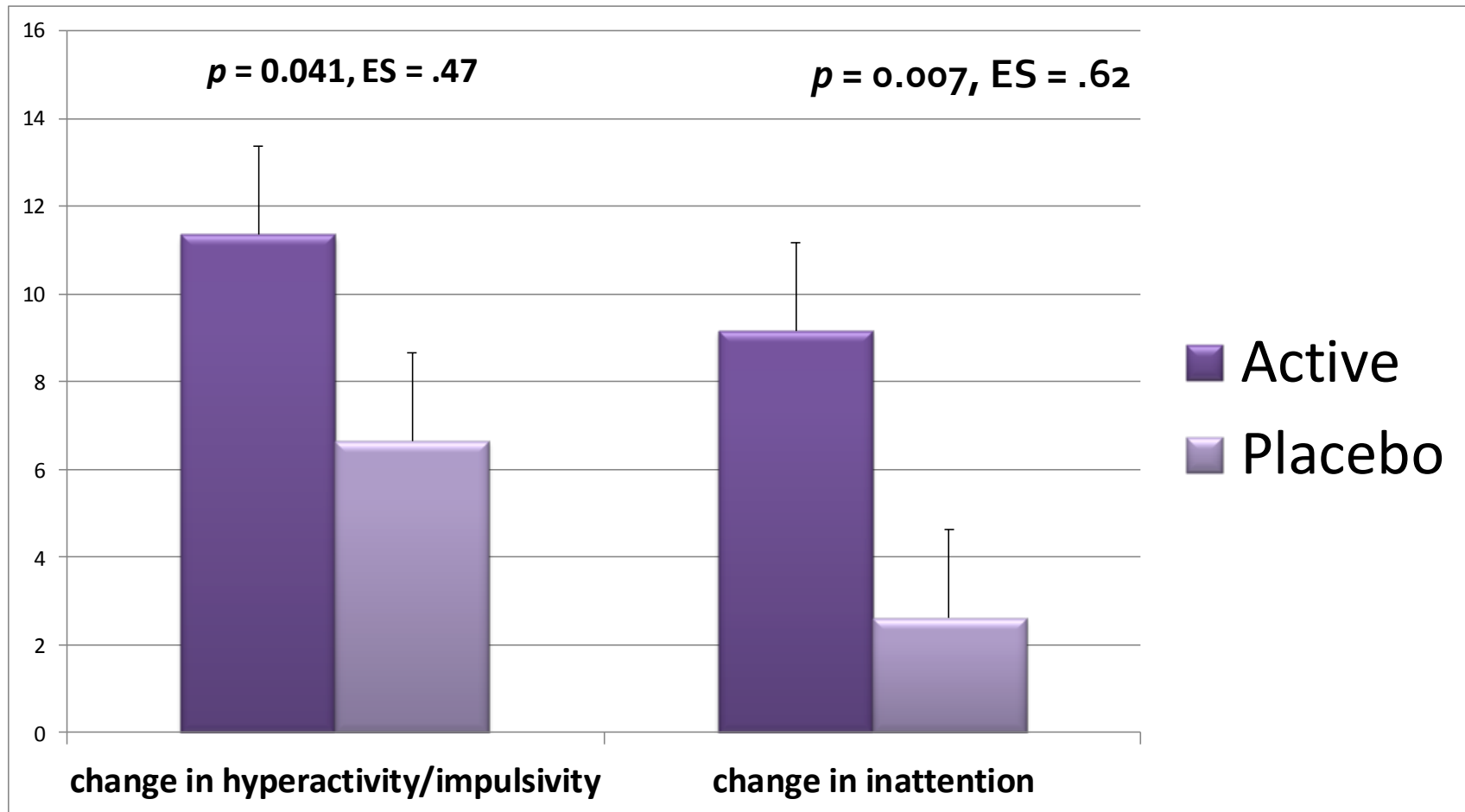
# Micronutrients with adults with ADHD: RCT evidence

*Rucklidge et al., 2014, British Journal of Psychiatry*

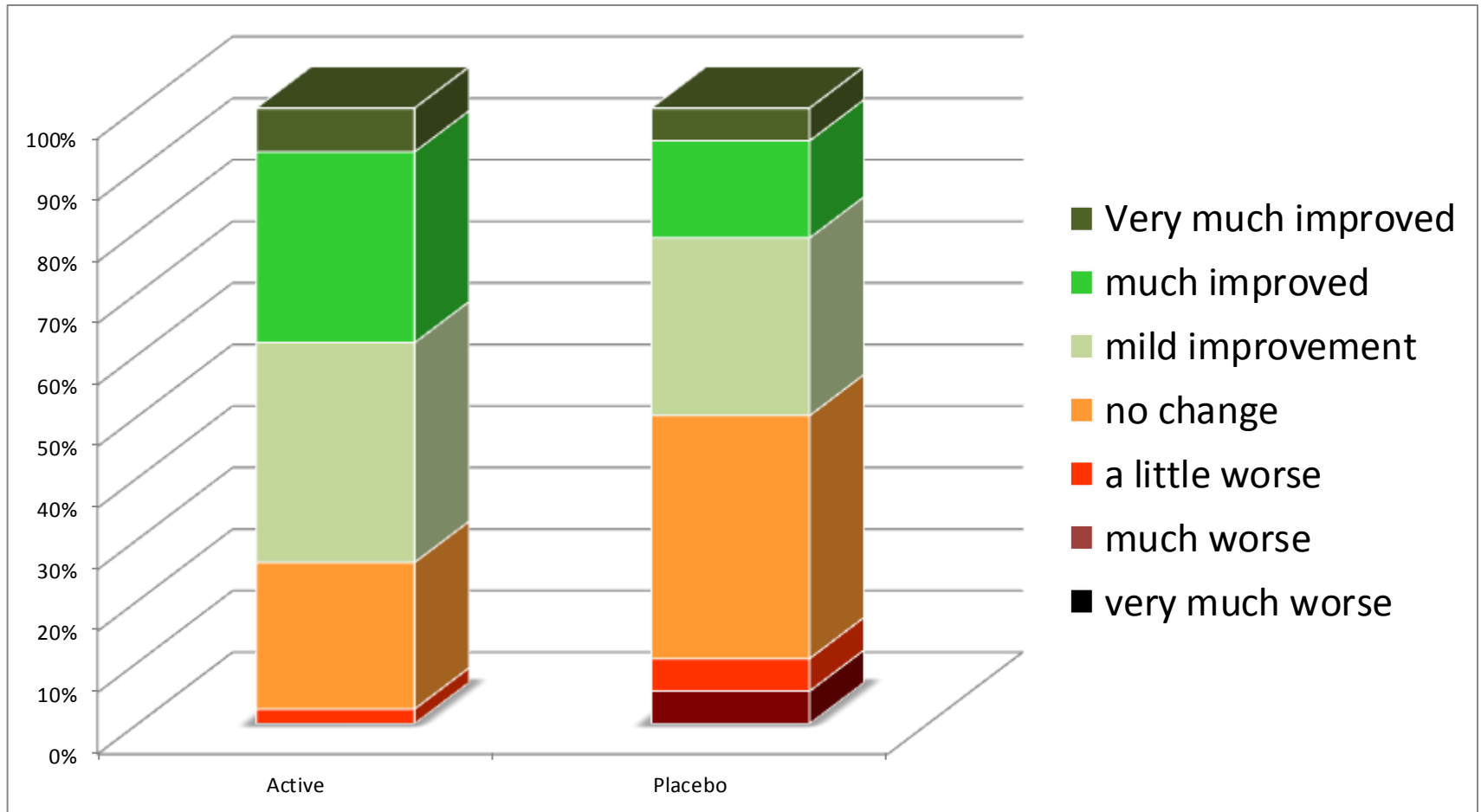
- 80 participants: 42 micronutrients, 38 placebo
- Mean age: 35 years
- Diagnosis:
  - SCID-I and CAADID *and*
  - >70 on one of the DSM based scales of CAARS (self/observer)
- 35% ADHD Pred Inatt; 57% ADHD combined
- Co-occurring current diagnoses:
  - 23% mood disorder; 35% an anxiety disorder; 14%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

# Change in self-rated ADHD symptoms

Rucklidge et al; *British Journal of Psychiatry*, 2014

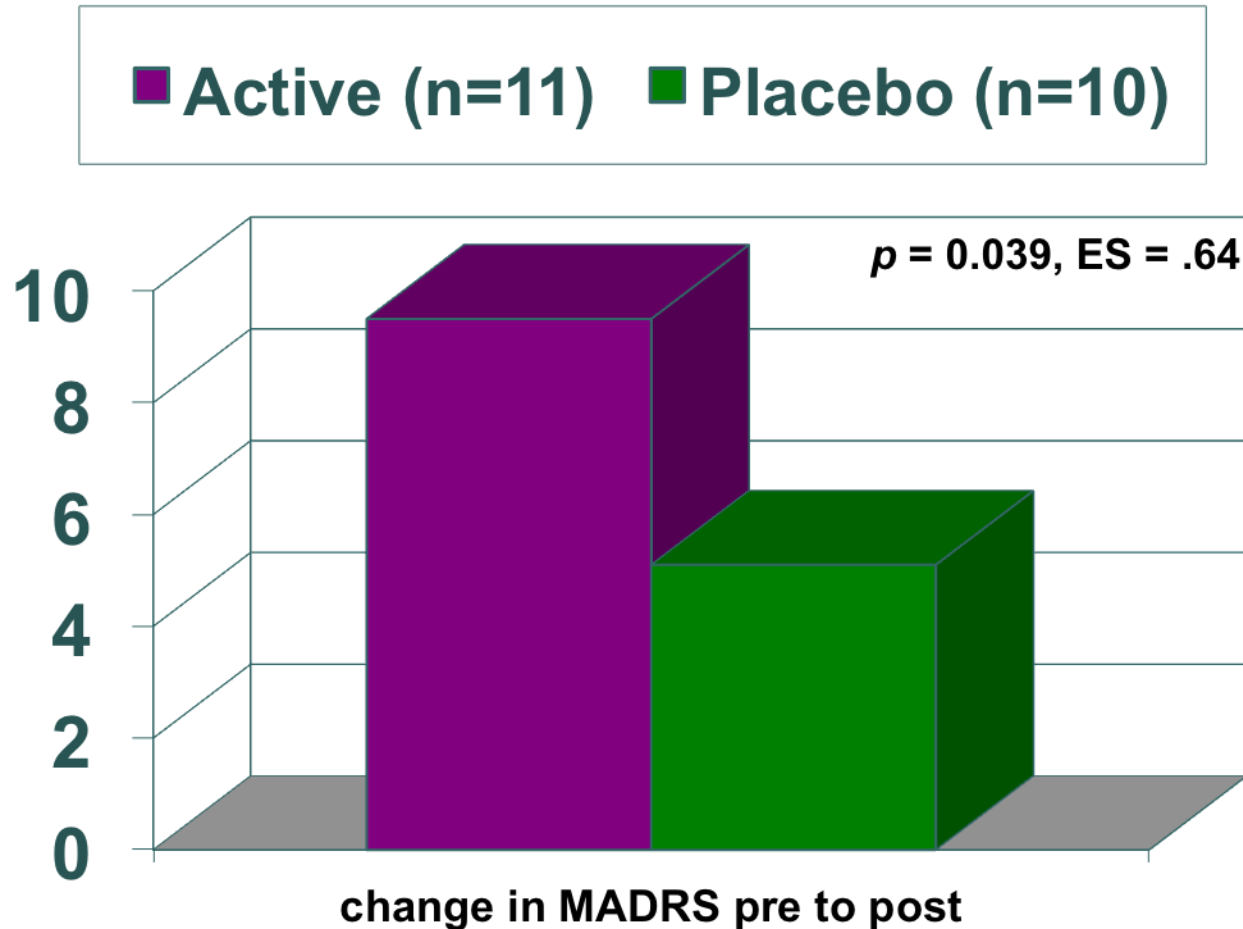


# CGI – I – ADHD post RCT



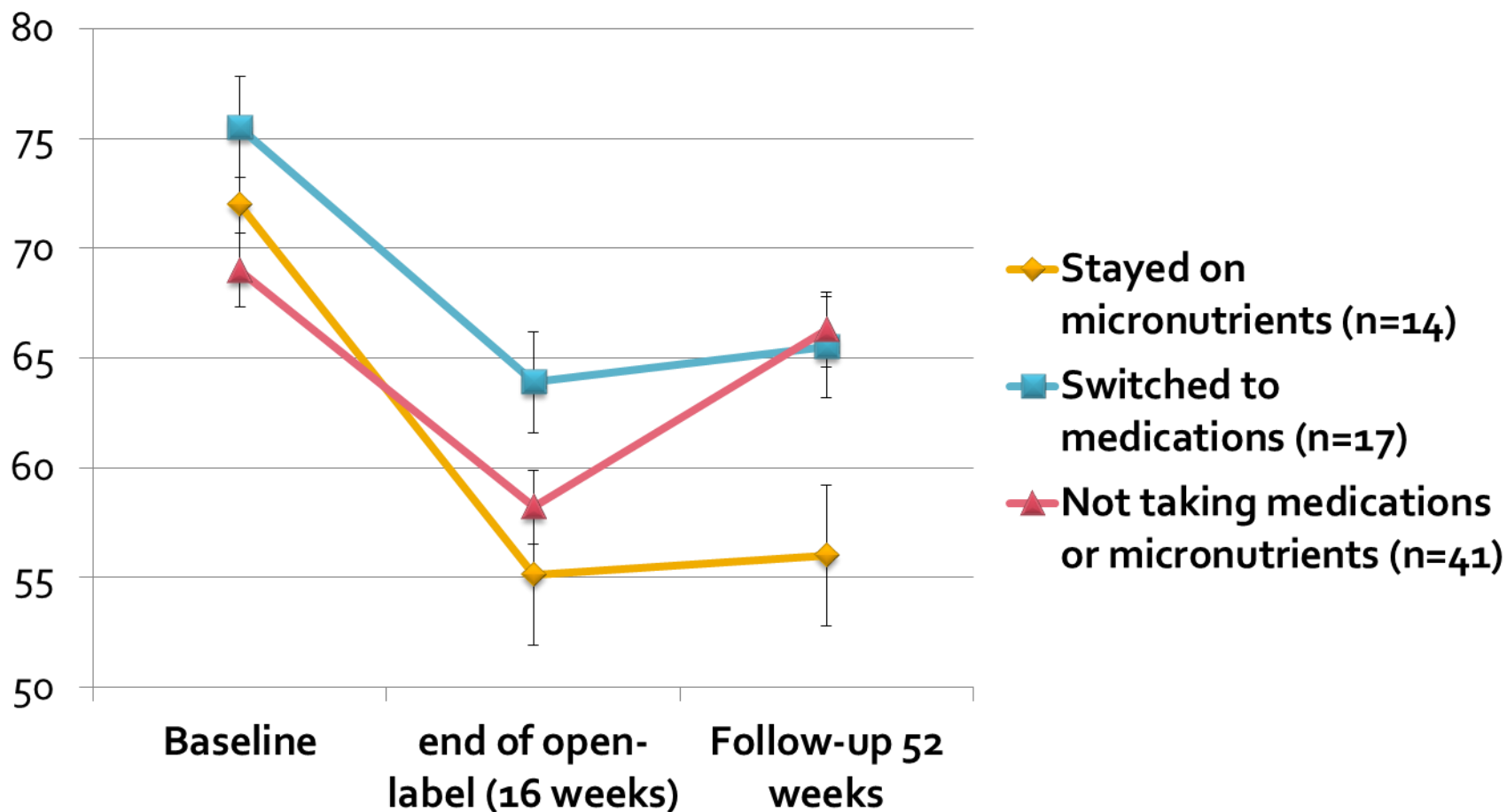
$p < .02, ES = 0.53$

# Change in depression: only those *clinically depressed* at baseline



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

Rucklidge et al., 2014; Journal of Attention Disorders





Contents lists available at ScienceDirect

## Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: [www.elsevier.com/locate/pnp](http://www.elsevier.com/locate/pnp)



### Moderators of treatment response in adults with ADHD treated with a vitamin–mineral supplement<sup>☆</sup>



Julia J. Rucklidge<sup>a,\*</sup>, Jeanette Johnstone<sup>a</sup>, Brigette Gorman<sup>a</sup>, Anna Boggis<sup>b</sup>, Christopher M. Frampton<sup>c</sup>

<sup>a</sup> Department of Psychology, University of Canterbury, Christchurch, New Zealand

<sup>b</sup> Canterbury District Health Board, Christchurch, New Zealand

<sup>c</sup> Department of Psychological Medicine, University of Otago, Christchurch, New Zealand

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Micronutrients

Minerals

Predictors

#### ABSTRACT

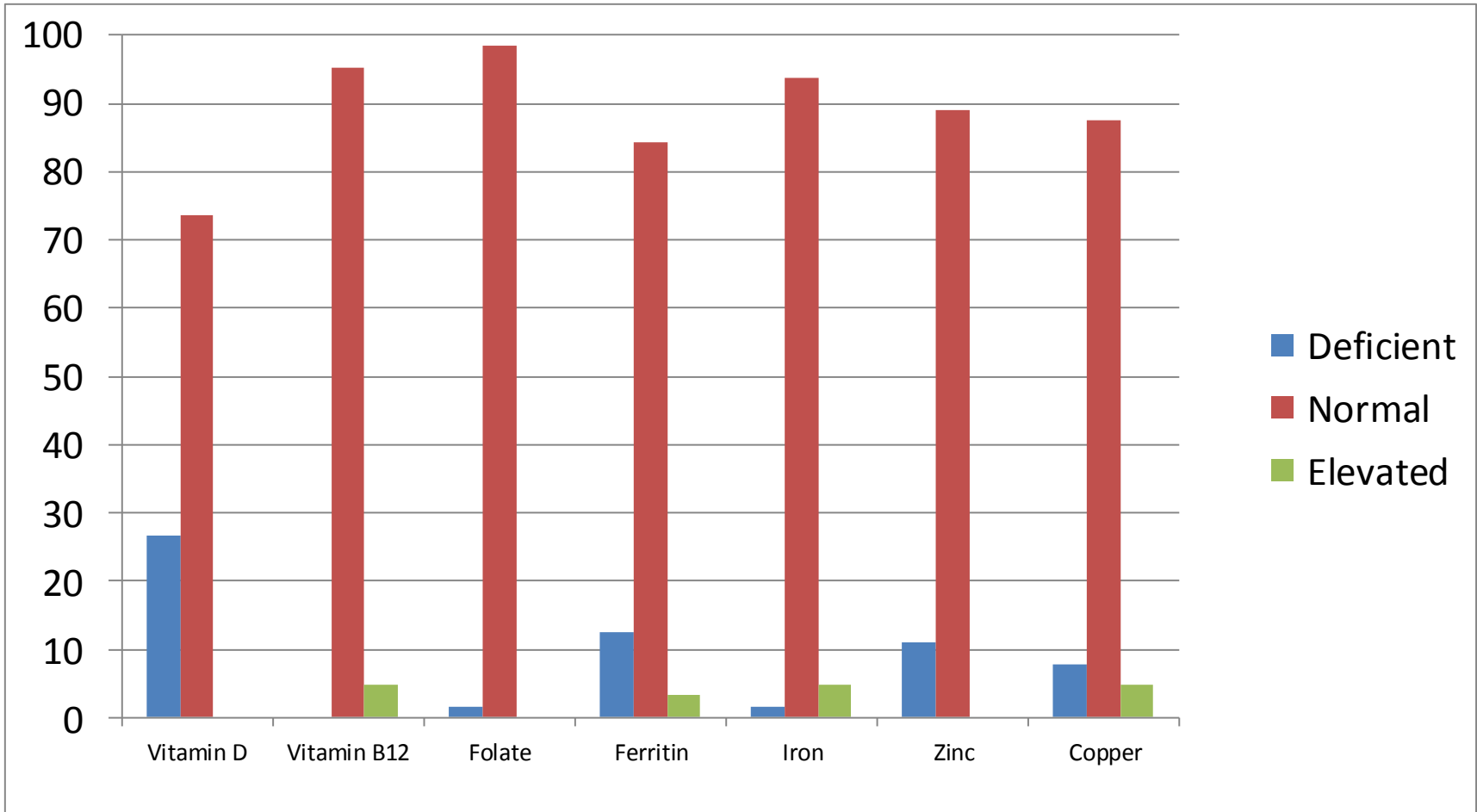
**Background:** To date there has been no research investigating moderators of response to micronutrient treatment of mental illness, specifically baseline nutrient levels.

**Method:** We conducted analyses of data from a randomized placebo-controlled trial (RCT) of 80 adults ( $\geq 16$  years) with Attention-Deficit/Hyperactivity Disorder (ADHD), whereby participants were treated acutely (8 weeks) with micronutrients or placebo followed by an open-label (OL) phase of 8 weeks whereby all participants received micronutrients. To ensure that all participants had been exposed to the micronutrients for 8 weeks, only those 64 who had adhered to the treatment protocol and completed 8 weeks on nutrients were included in the data analysis: 34 from the group that had been randomized to the micronutrient arm, and 30 from the group that had been randomized to the placebo group and hence had only received nutrients in the OL phase. Six outcomes were examined: change in ADHD symptoms (self/clinician), ADHD responder, Clinical

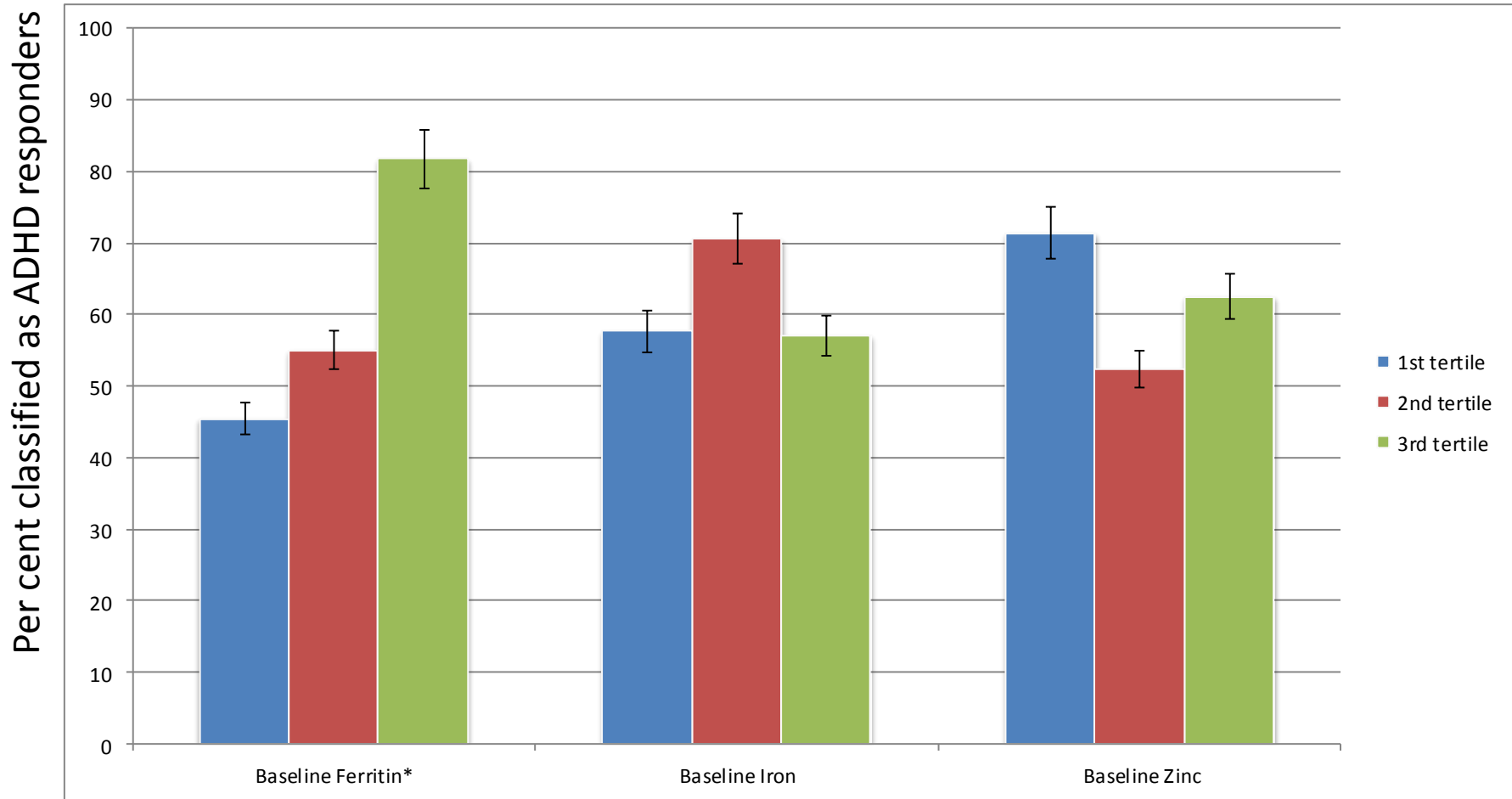
# Can we predict who will respond to micronutrients?

## Not really, not yet

# Percentage falling within or outside normal reference ranges for serum nutrients



# Baseline nutrient levels converted to tertiles and compared with per cent ADHD responders



\* $p < 0.05$



**Side effects?**



minor and transitory

**Compliance?**



No difficulties with the regimen†

**Impact on blood results?**



None to date...\*

**Long-term effects?**



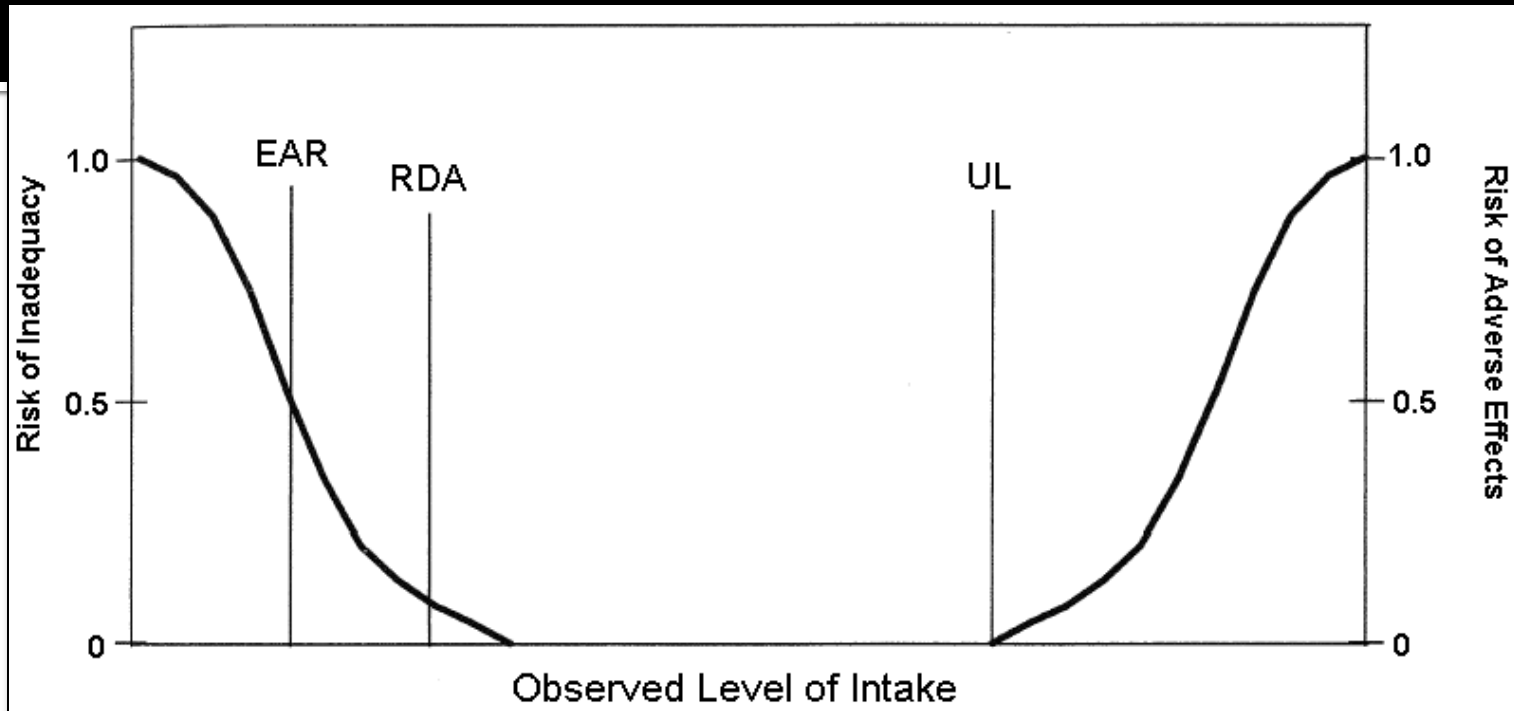
Needs to be studied *properly*

\* *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.

# Progression of Evidence on Micronutrients & Psychiatric Symptoms

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


# Rodway et al., BMJ Case Reports, 2012



Cost of conventional inpatient treatment



Cost of micronutrient outpatient treatment

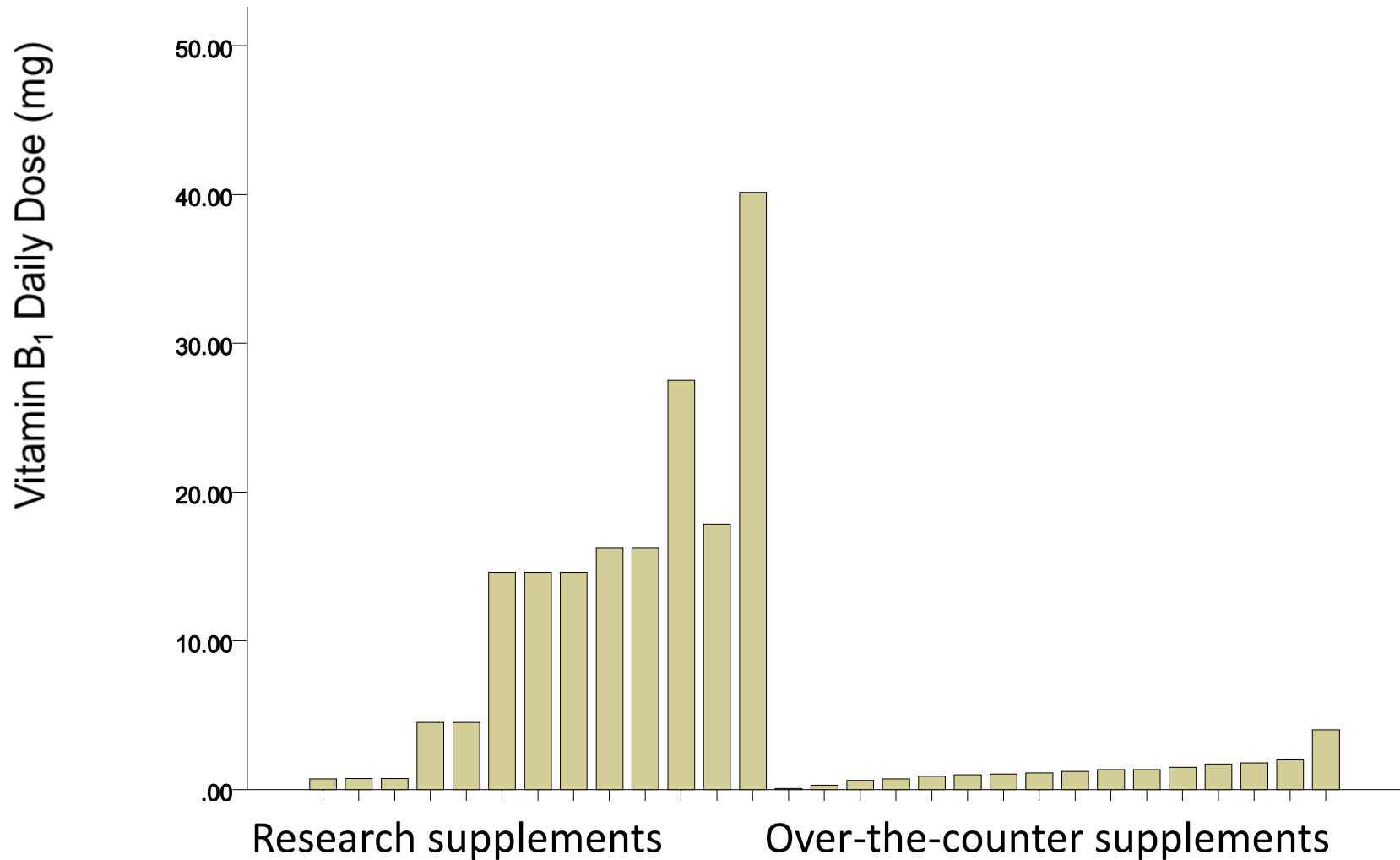


# WHICH FORMULA DOES ONE CHOOSE????

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

Family Value Pack

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

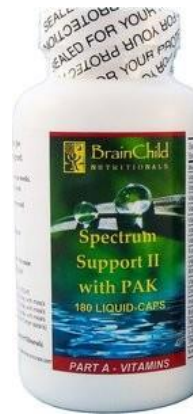








# Which ones have any evidence to help with mental illness?



**Do these data challenge our  
conceptualization of mental  
illness?**

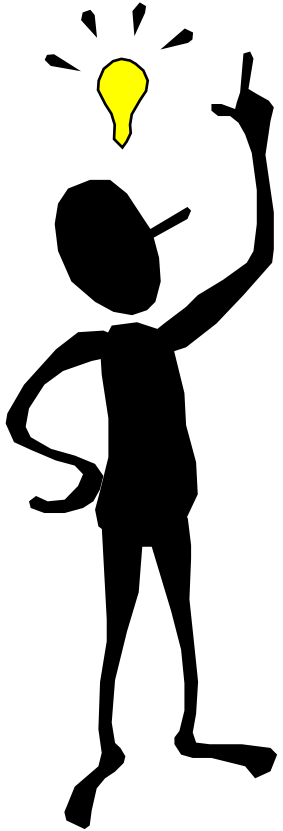
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Could some forms of  
mental illness reflect  
metabolic reactions going  
wrong?



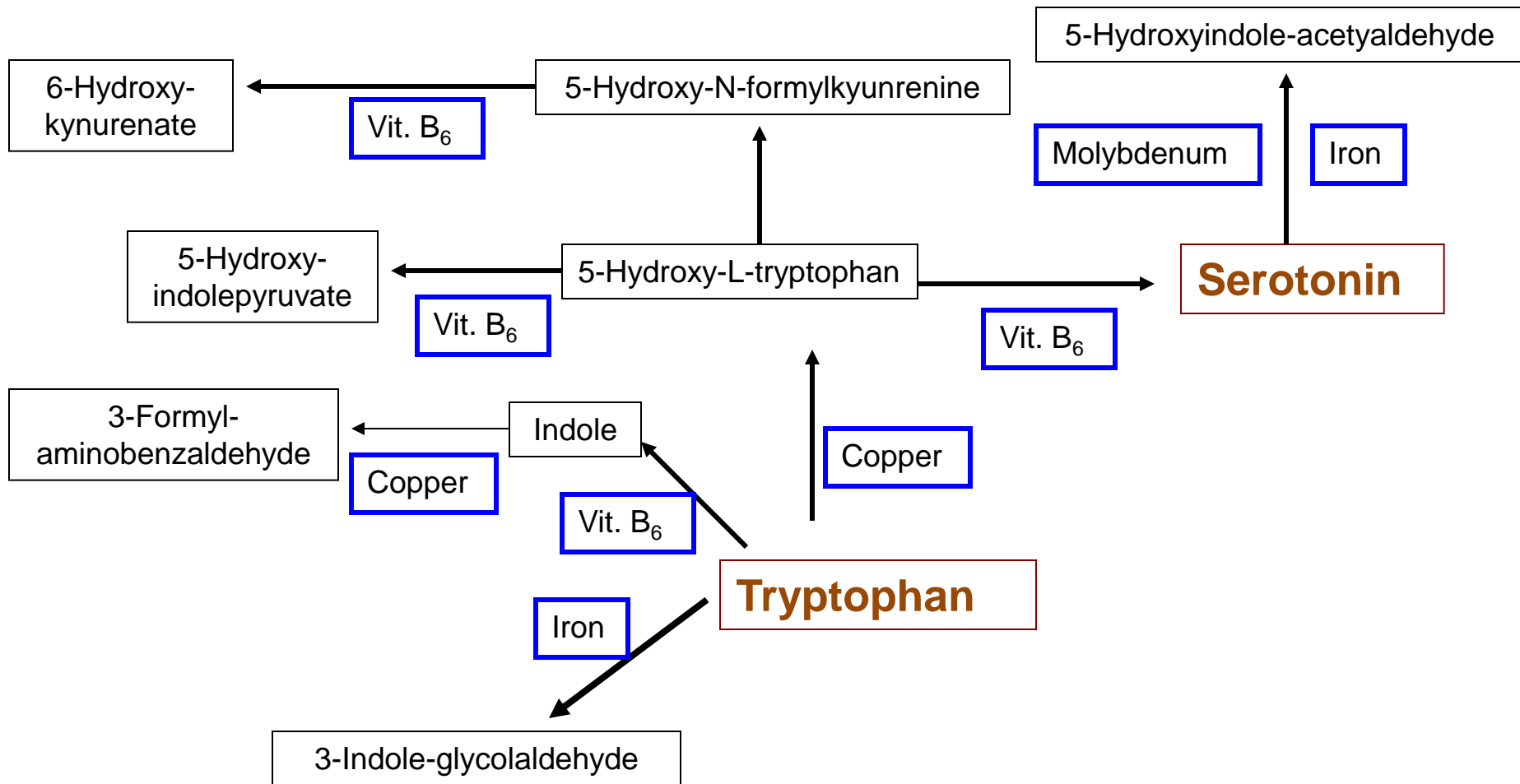
AKA Inborn errors of metabolism

# Could some cases of mental disorders reflect inborn errors of metabolism?

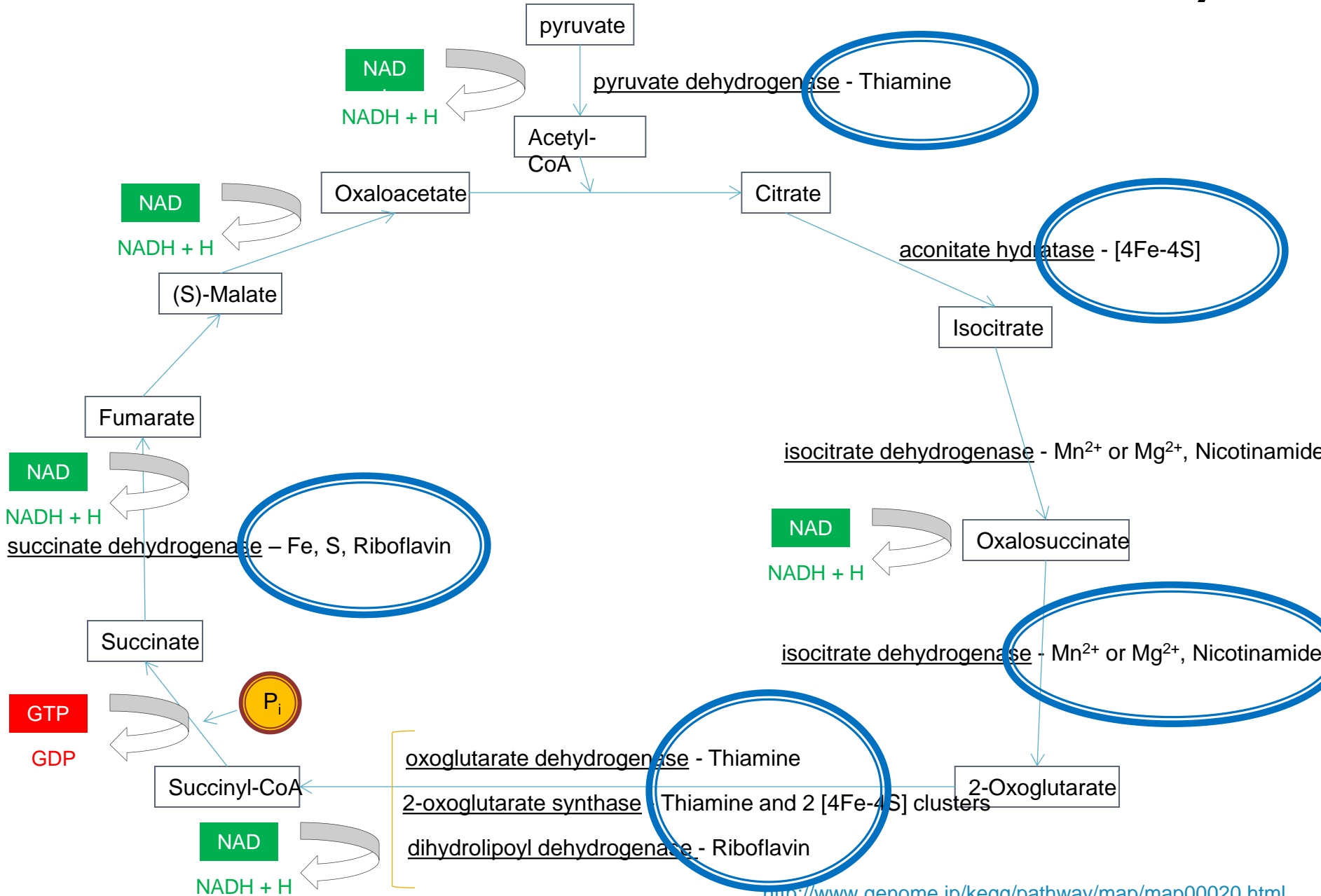


- People inherit a *genetic defect* that results in decreased binding ability of an enzyme(s)
- results in slowed metabolic reactions
- Less efficiency in making chemicals for optimal functioning
  - resulting in psychiatric symptoms
- Can be corrected at endpoint by:
  - administration of **high doses of the vitamin component** of corresponding coenzyme, restoring enzymatic activity
    - Ames et al., 2002; Kaplan et al., 2007

# One small portion of serotonin pathways



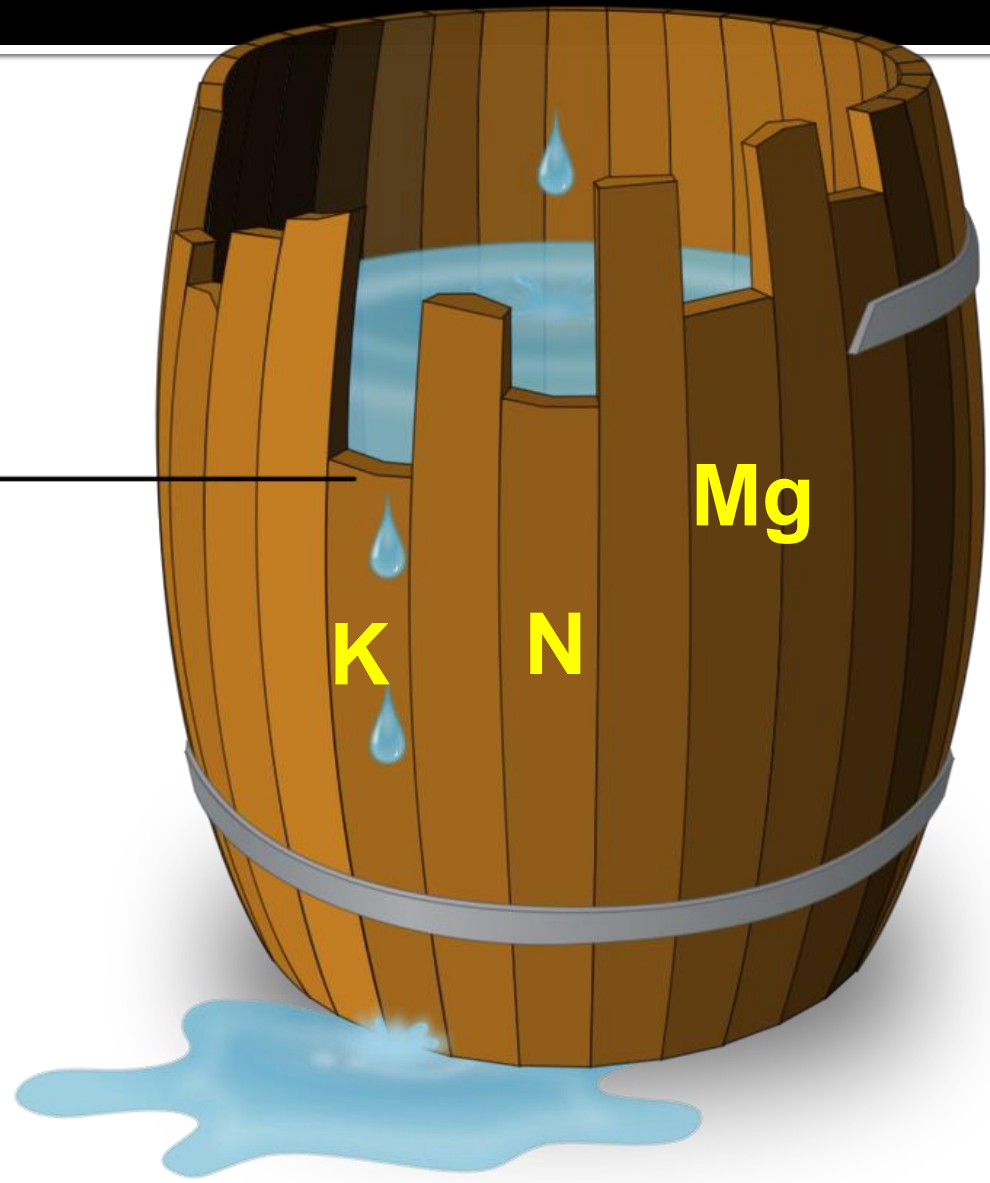
# Krebs (Citric Acid) Cycle



# Liebig's Law of the Minimum

Minimum

**Growth is controlled not by the total amount of resources available, but by the scarcest resource (limiting factor)**



# Future research

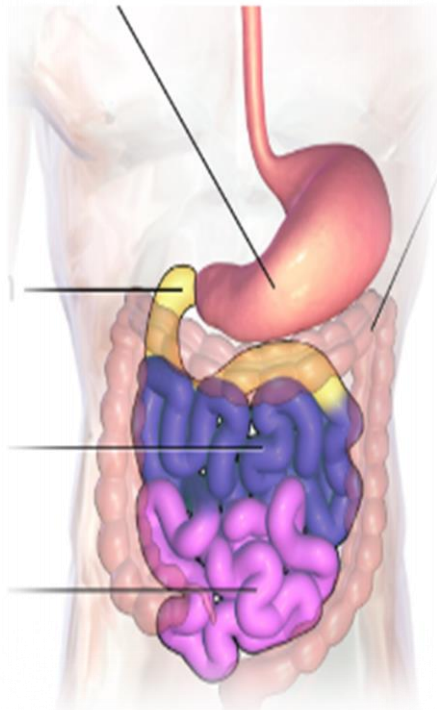
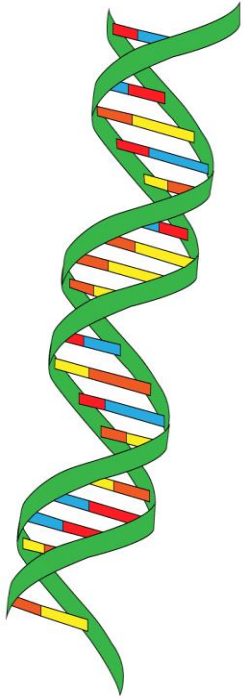


Photo credits: Greg Emmerich; [Blausen.com](https://www.blausen.com) staff. "[Blausen gallery 2014](https://www.blausen.com/gallery)".  
Wikiversity Journal of Medicine; Taki Steve



# Considerations and challenges

- Which nutrient(s) is necessary? Could we get away with a smaller set of key nutrients?
- Dietary changes versus supplementation?
- Other medications (particularly psychiatric ones)
- Short and long-term compliance – many people stop them, even if working...
- Cost to patients

# Conventional medicine



**other**

**therapy**

**medication**

# Integrative medicine



**lifestyle/diet/exercise/supplements**

**stress  
reduction/therapy**

**meds**

# Concluding messages...

- Physiologically, makes sense to provide body/brain with nutrients to optimize functioning for those with psychiatric symptoms
- If can't be achieved through diet or diet manipulation alone, then additional nutrients may be required
- After a decade of research, most studies on broad spectrum nutrients positive across different countries, different formulas, different conditions
  - But we need replication, consideration of the role of specific nutrients and optimal doses

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- ***Current Graduate students***

- Heather Gordon
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- Rachel Harrison
- Sarah Antich
- Kathryn Whitehead
- Dr Nicola Ward
- Dr Brigette Gorman
- Jeni Johnstone
- Dr Petra Hoggarth

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- Prof Dermot Gately
- Prof Rob Hughes
- Prof Bonnie Kaplan
- Prof Ian Shaw
- Prof Neville Blampied
- Assoc Prof Chris Frampton

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- Dr Matt Eggleston
- Dr. David Ritchie
- Dr. Katharine Shaw

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- Private Donation from Marie Lockie
- Summer studentships
- Truehope/Nutratak for providing formula for trials

## ***Thanks to:***

- participants and families for carefully monitoring symptoms over time

**julia.rucklidge@canterbury.ac.nz**

# *The most studied micronutrient formula: EMPowerplus*

- ❖ **Vitamins A, C, D, E, B<sub>1</sub>, B<sub>2</sub>, B<sub>3</sub>, B<sub>5</sub>, B<sub>6</sub>, B<sub>9</sub>, B<sub>12</sub>**
- ❖ **Biotin, Pantothenic acid, Calcium**
- ❖ **Iron, Phosphorous, Iodine, Magnesium**
- ❖ **Chromium, Molybdenum, Potassium**
- ❖ **Zinc, Selenium, Copper, Manganese**
- ❖ **dl-Phenylalanine, Glutamine, Citrus bioflavonoids, Grape seed, Ginkgo biloba**
- ❖ **Vanadium, Boron, Methionine, Germanium, Inositol, Nickel**

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

- EMPowerplus/CNE/Q96: [www.truehope.com](http://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](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>