

Broad-spectrum micronutrient supplements as psychiatric disorder treatments: rationale, background, and safety



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Credits and Disclaimers

- Thank you to Charlie Popper MD, Julia Rucklidge PhD, and Bonnie Kaplan MD for allowing use of their slides
- Similar material is presented from the 2015 APA symposium “Mineral-vitamin Combinations as Primary Treatment of Psychiatric Disorders”, sponsored by the Caucus on Integrative Medicine
- No BSMN treatment has yet been approved by the U.S. FDA or by Health Canada

What is a micronutrient?

- an essential nutrient, as a trace mineral or vitamin, that is required by an organism in minute amounts, for the normal growth and development of living organisms.



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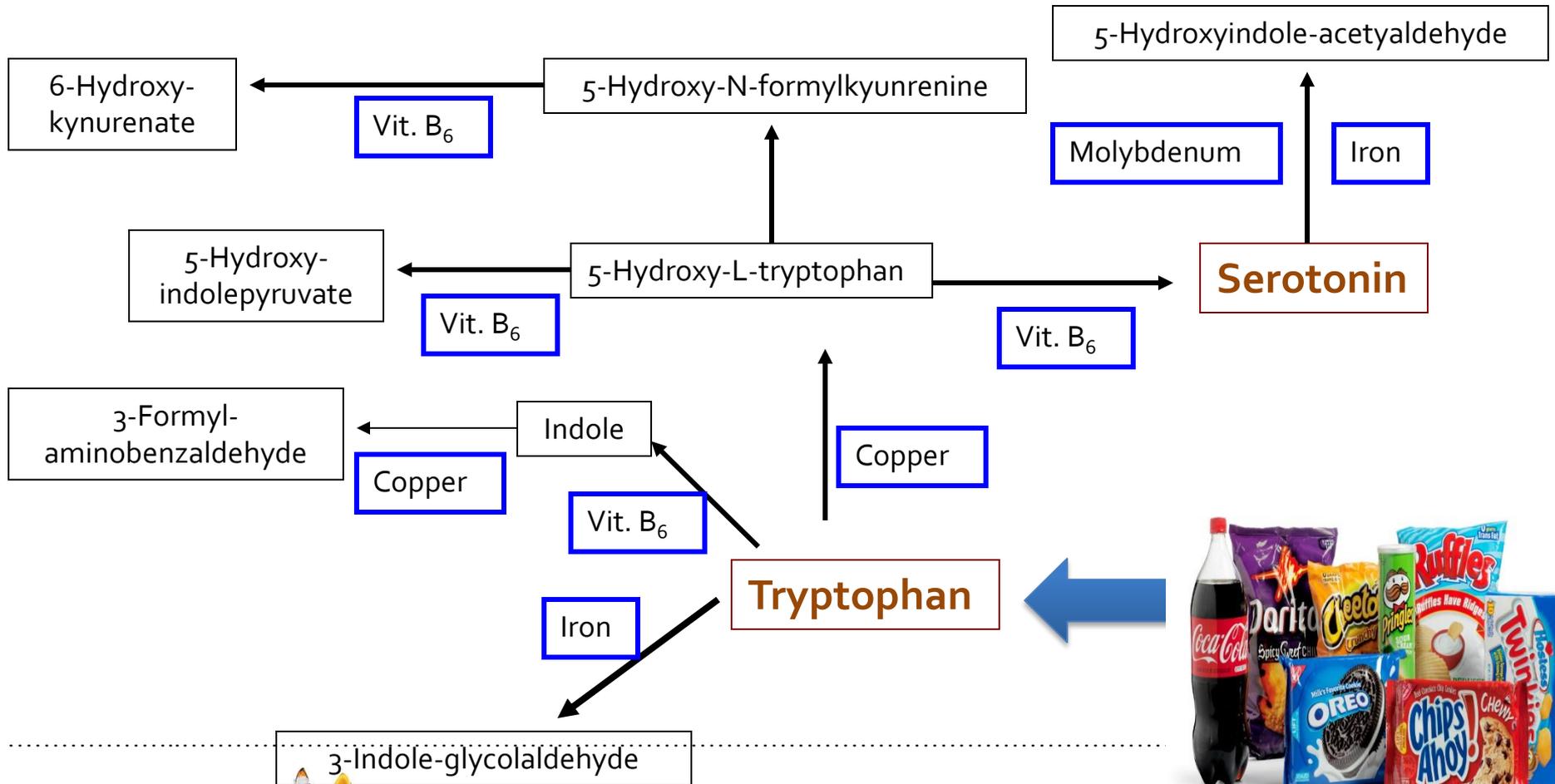
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- Scientific Rationale for BSMN treatments

1) The brain is a micronutrient-based organ

- Vitamins and minerals cross the blood brain barrier to:
 - operate as CNS cofactors of enzymatic reactions and transcription factor conversions
 - serve as structural components of enzymes involved in neurotransmitter synthesis and metabolism (minerals)
 - help with receptor transformation, transport systems, ion channels, and pump mechanisms;
 - alter membrane fluidity;
 - affect second and third messenger systems, leading to neuron growth and repair, preventing apoptosis

One small portion of serotonin pathway



2) Optimized micronutrients may reverse or prevent oxidative damage in the CNS

- Nutrient deficiencies and genetic variants in cofactors and enzymes can cause oxidative damage to nuclear DNA and mitochondria, leading to:
 - Inflammation
 - Endothelial dysfunction
 - Neuronal apoptosis
 - Accelerated aging

3) American diet quality is poor

- Modern agricultural and food supply practices have reduced micronutrient concentrations
- Naming just the top 4, 92% of Americans do not get enough potassium, 86% not enough vitamin E, 69% not enough calcium, and 57% not enough Mg++, as per the IOM estimated average dietary requirements



Population Health Studies: 12-15 nutritional epidemiology studies from Australia, Spain, UK, Japan, Canada

- People who eat ‘traditional’ ‘unprocessed’ ‘Mediterranean’ ‘prudent’ diets have *lower rates of mood and anxiety symptoms*
- People who eat ‘Western’ ‘processed’ diets have *higher rates of mood and anxiety symptoms*





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1 litre of blood enters your brain every minute

- That's 60 litres of blood every hour
- What is it carrying to your tissues?



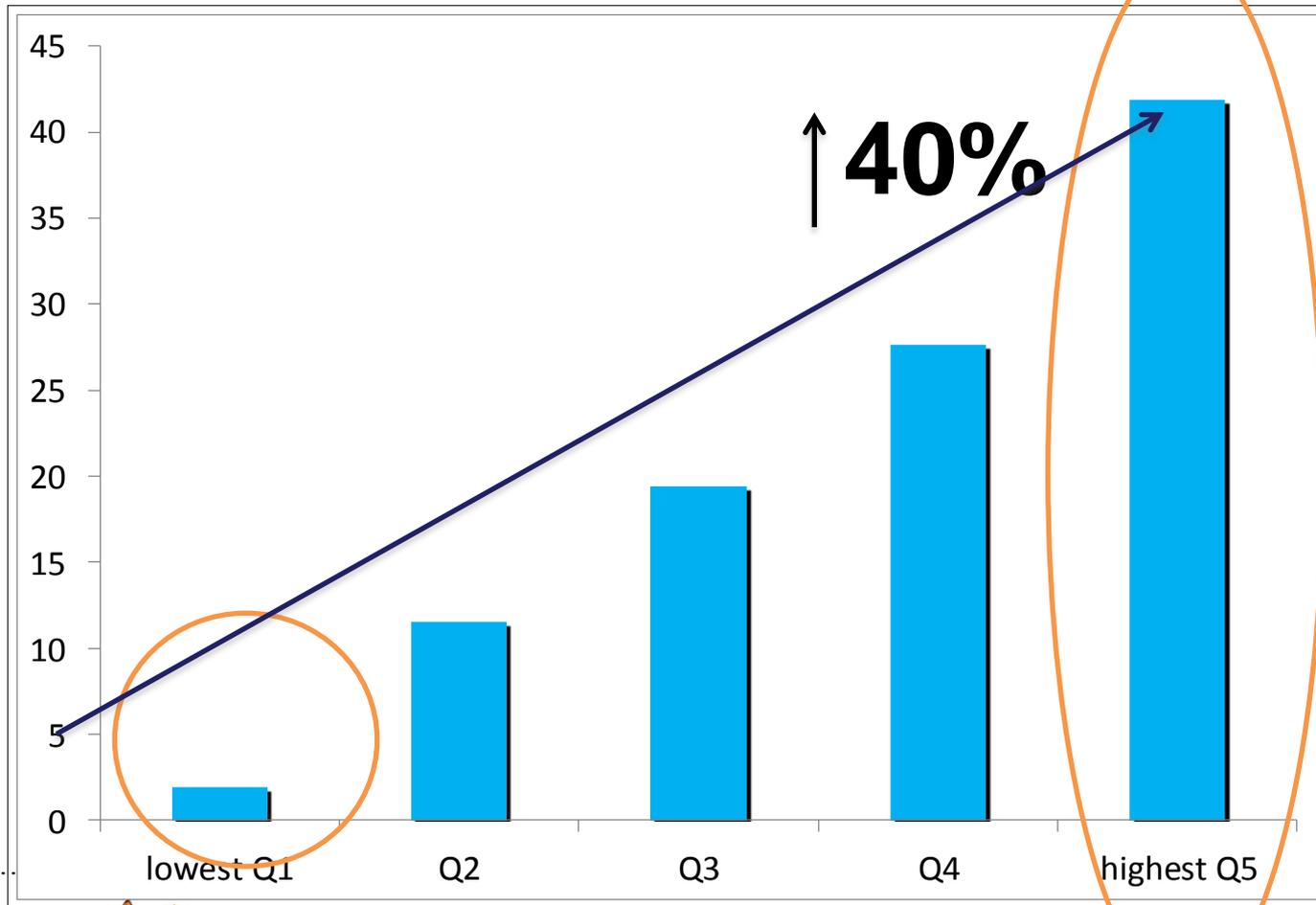
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Risk of depression within 6.2 years in ~9000 people

Based on fast food (hamburgers, pizza)



Sanchez-Villegas et al., *Public Health and Nutrition*, 2012



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Questions

- **1. How many of you are psychiatrists?..... clinicians of any type?**
- **3. How many of you have personal experience with mental disorders (you, close relative, friend).**
- ***Think about how hard it is to change someone's diet and exercise habits.....***



**Should we then consider
'supplementing' for some
and if so...**

- **Single or multiple nutrients?**



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4) Single nutrient effect sizes for mental disorders are generally small

- Nutrient insufficiencies, deficiencies, and nutrient-based pathway genetic variants are broad and ubiquitous across the population
- BSMNs are more likely to be more efficacious in more individuals than single nutrients

Nutrients work most effectively together

So treating with only ONE doesn't *usually* make physiological sense...



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- What evidence supports BSMN treatments for mental disorders?



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Safety and preliminary support for efficacy published since 2001

- Anxiety
- Aggression
- ADHD
- OCD
- Mood disorders/bipolar spectrum disorders (BPSD)
- behavioral symptoms associated with autism
- substance abuse
- acute stress following natural disasters



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Aggression and behavioral problems



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Aggression: Schoenthaler's studies

1997: 62 imprisoned juveniles using DBPCT over 3 months:

Supplement contained 11 minerals and 7 vitamins \geq RDA:

Active supplement  **28% less violence**

2000: 80 children (6-12) disciplined at least once:

DBPCT over 4 months of 13 vitamins and 10 minerals mostly below RDA:

Active supplement  **47% fewer rule infractions**
threats and fights, vandalism,
defiance, disrespect, obscenities



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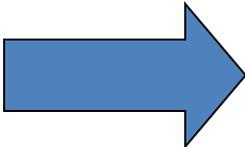


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BSMN supplementation in young adult prisoners Gesch et al., 2002, Brit J Psychiatry

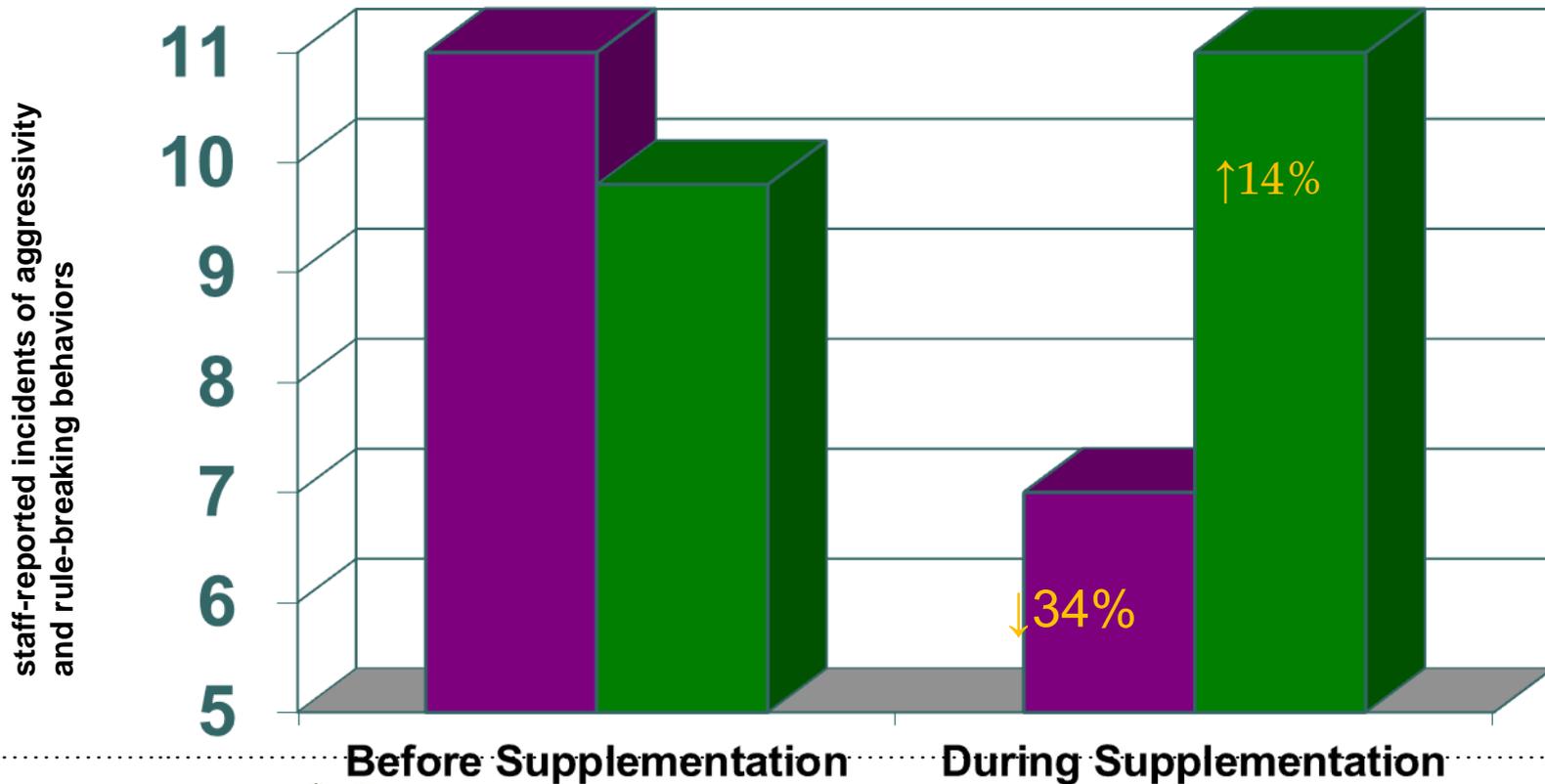
RCT in 231 young offenders:

- ❖ **Supplement with a broad array of minerals, vitamins, and some EFAs (26 ingredients at RDA levels)**

Active supplement  **26.3% fewer rule infractions**
35.1% fewer violent acts

Replication in Dutch prisoners (n=221) 1-3 months; Zaalberg et al., 2010, Aggressive Behavior

■ Active ■ Placebo



*no significant reductions in rating scales of self- or staff-reported aggressivity or psychiatric symptoms, trend toward improved subjective sense of well-being



ADHD and micronutrients

- **Two (-) early studies (Arnold et al., 1978; Haslam et al., 1984)**
 - used megadoses and short trials
- **Evidence in last decade growing**
 - **Two RCTs**
 - **one negative: used low dose micronutrients (< RDA)**
-not compared directly to placebo
 - **one positive with BSMNs; ES range 0.33-2.2**

Rucklidge et al., 2010, 2011, 2014; Harding et al, 2003; Rucklidge & Harrison, 2010; Sinn & Bryan, 2010; Gordon et al., in prep



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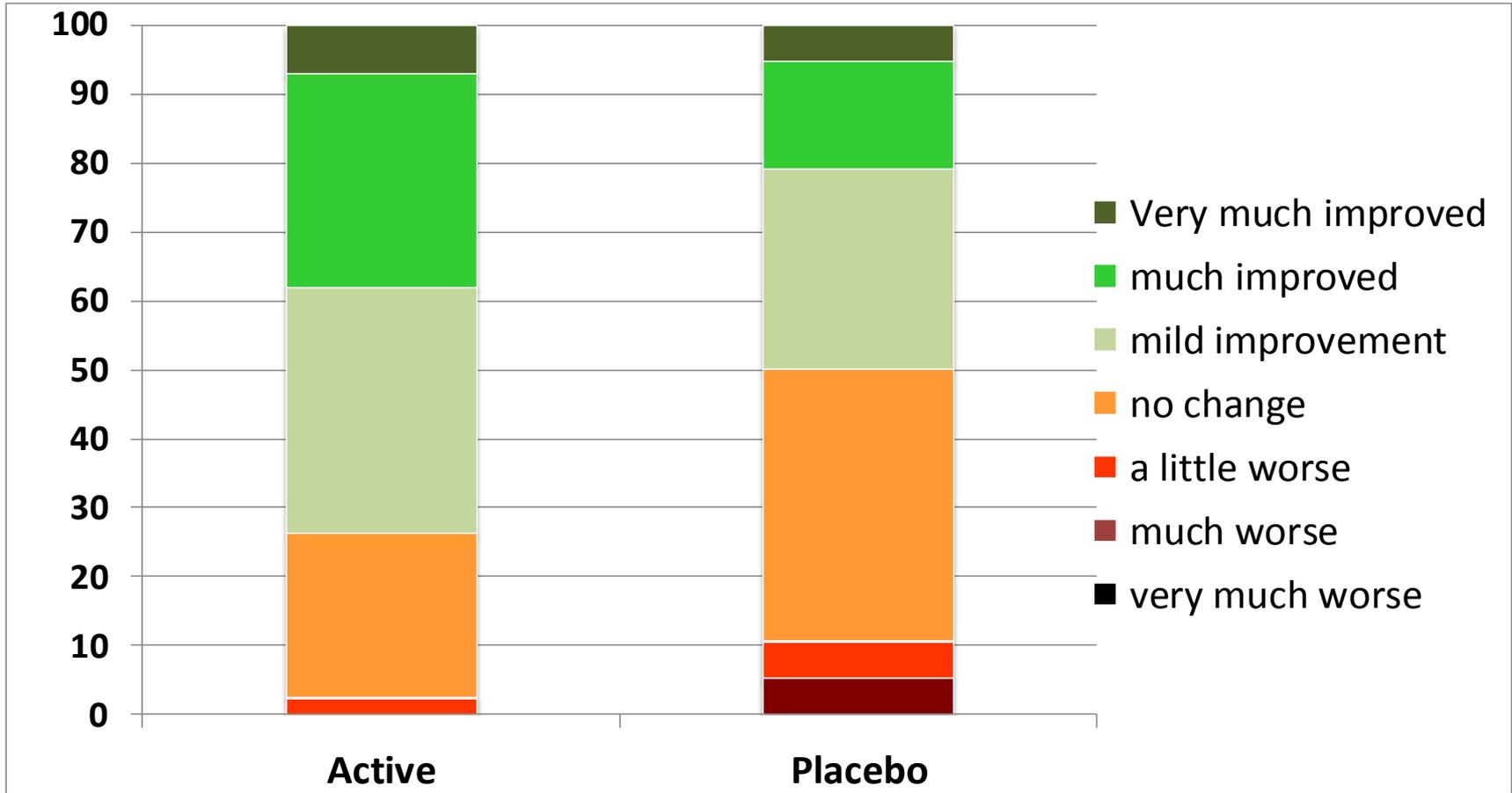
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Rucklidge et al. RCT: Micronutrients for Adults with ADHD (2014, Br J Psychiatry):

- **80 participants with ADHD (med free)**
 - Mean age: 35 years
 - Diagnosis: SCID-I , CAADID, *and* >70 on a CAARS scale (self/observer)
- **35% ADHD Inattentive type; 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
- **8 week RCT: 42 micronutrients (n=42) vs. placebo (n=38)**



End of study CGI-I-ADHD; % in each category



$p < .02, ES = 0.53$

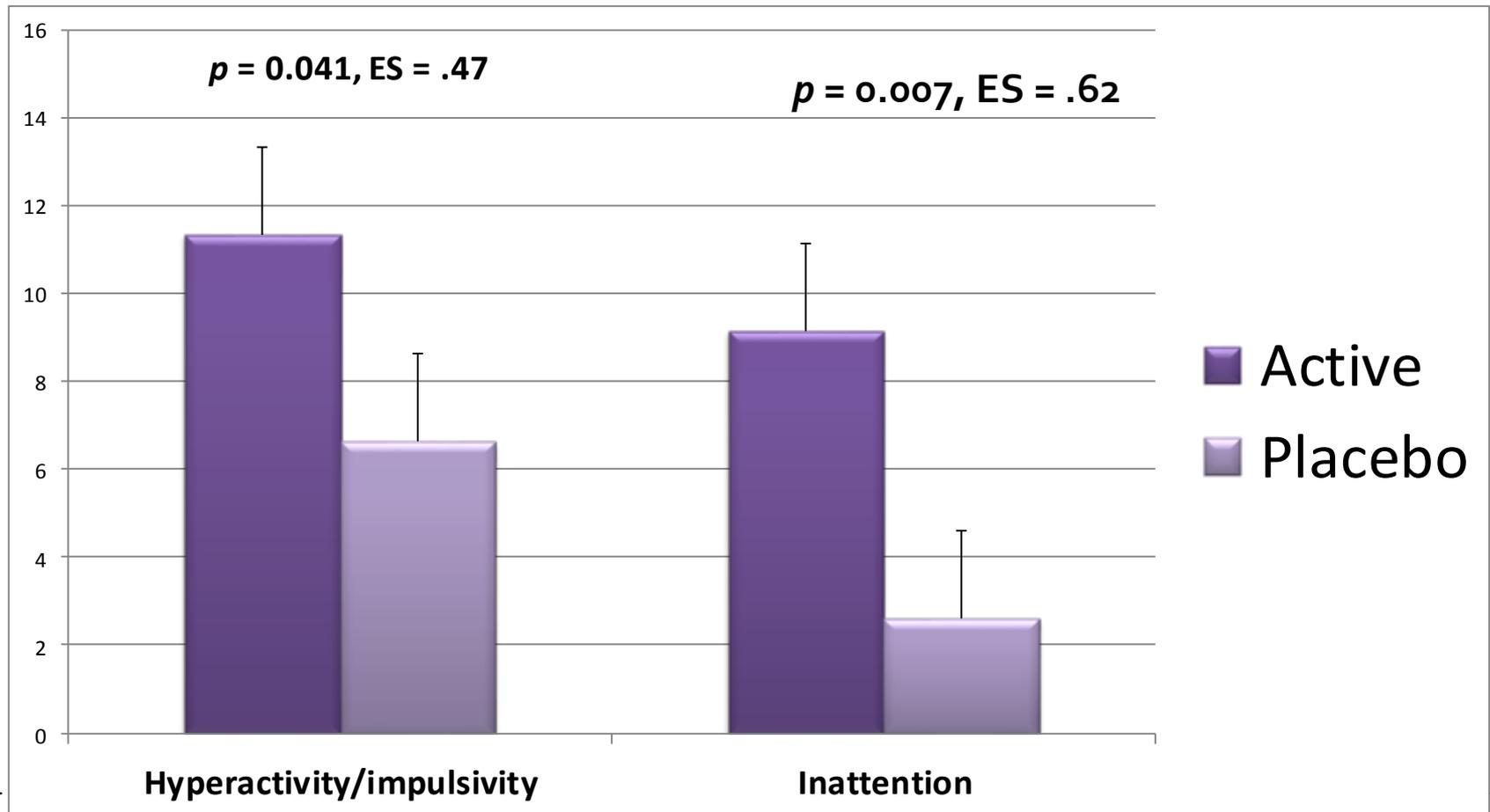


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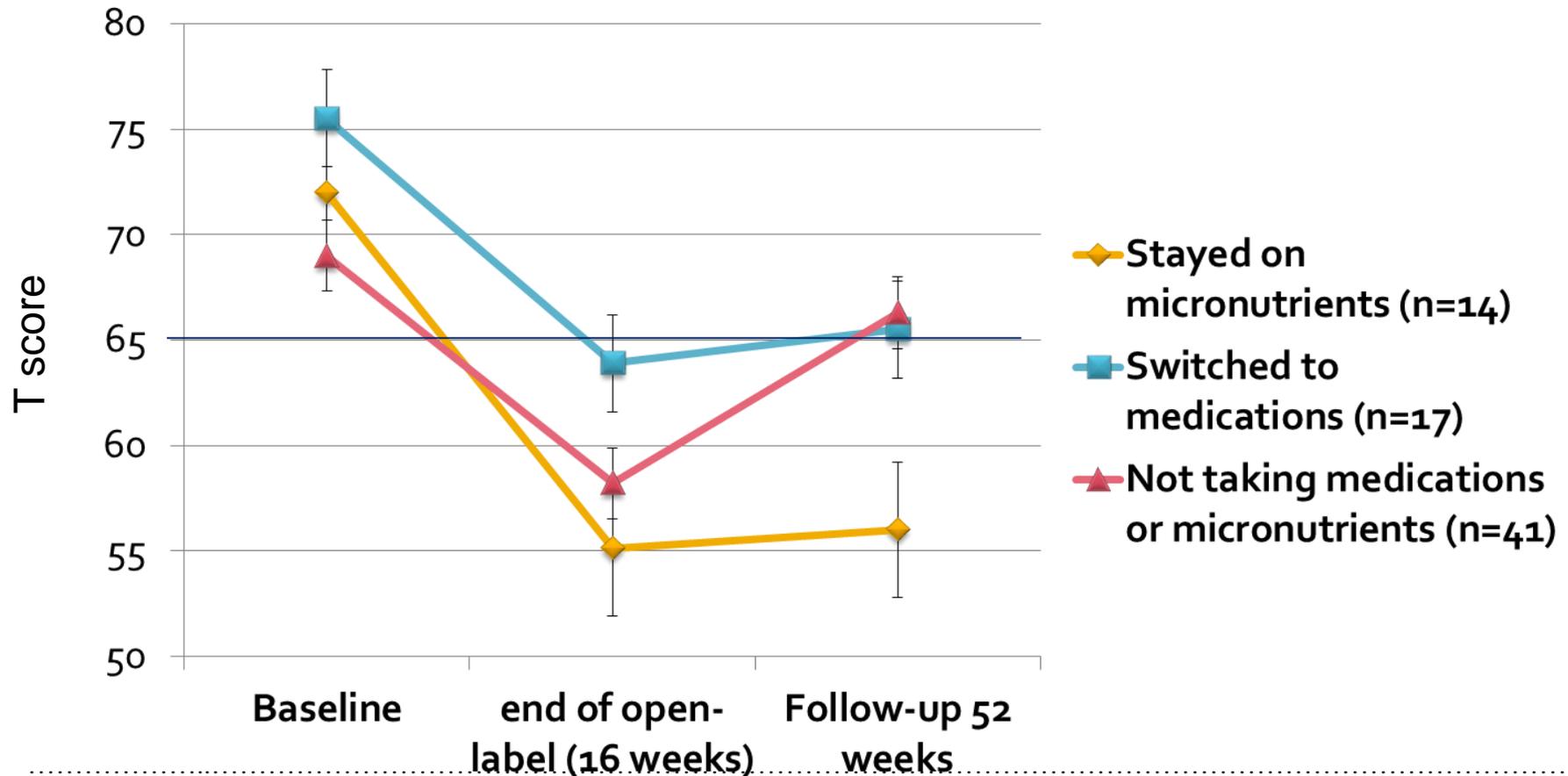
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Improvement in self rated ADHD symptoms; Rucklidge et al., 2014, BJP



Naturalistic 1-year follow-up: ADHD symptoms

Rucklidge et al., 2014; J Attention Disorders

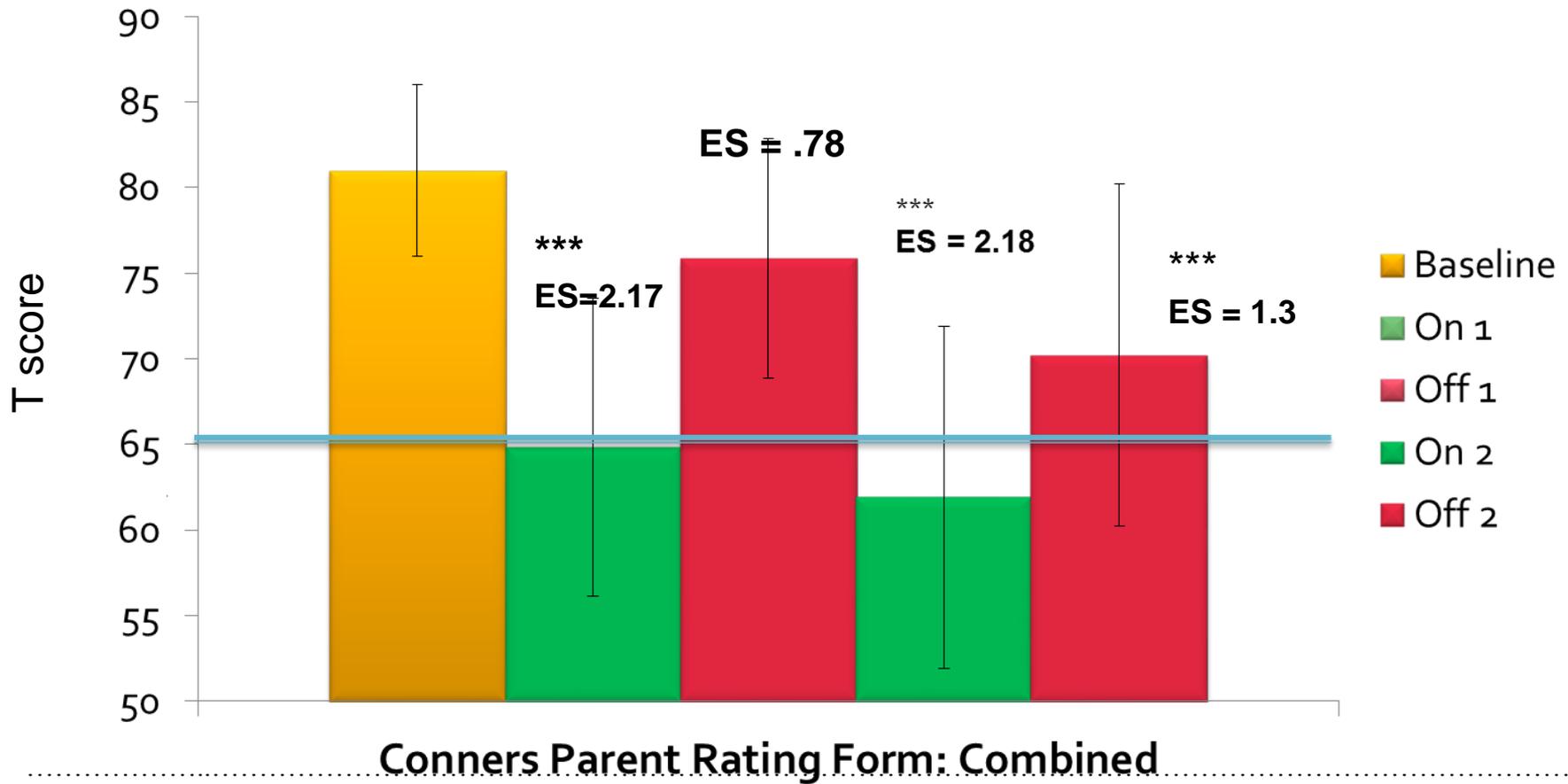


BSMNs for children with ADHD

- 14 Participants (14% Female) aged 8-12 years old (mean age 10.18) medication free
 - 6 Inattentive type, 8 Combined type
 - Co-occurring disorders (reflect usual population)
 - 14% Mood disorder
 - 21% Elimination disorder
 - 42% Oppositional defiant disorder
 - 14% Dyspraxia
 - 7% Autism spectrum disorder
 - 64% previously tried medication
- Reversal design, weeks: *8 on/4 off/8 on/4 off*



Combined ADHD symptoms; Gordon et al., under revision



Evidence to date for BSMNs in mood disorders



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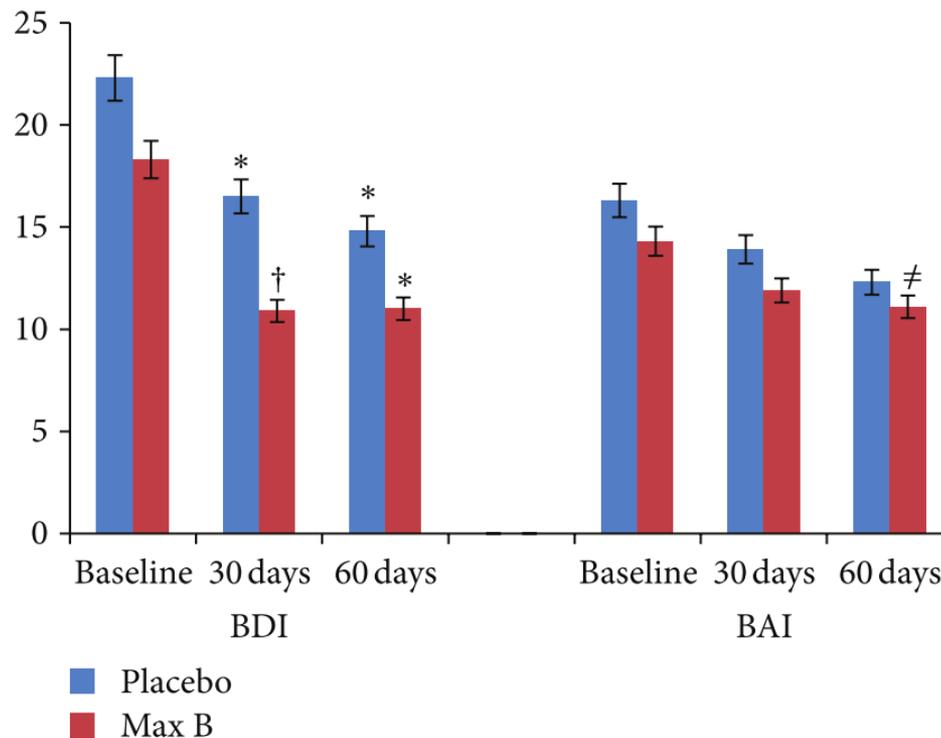
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Depression and depressive symptoms

- ***Very few good* trials on samples specifically recruited for depression –**
 - RCTs with normal populations:
 - 5 positive, 5 negative
 - A few other RCTs for those with other health conditions (3 positive, 1 negative)
 - **Only two RCTs have studied participants with depression**
-

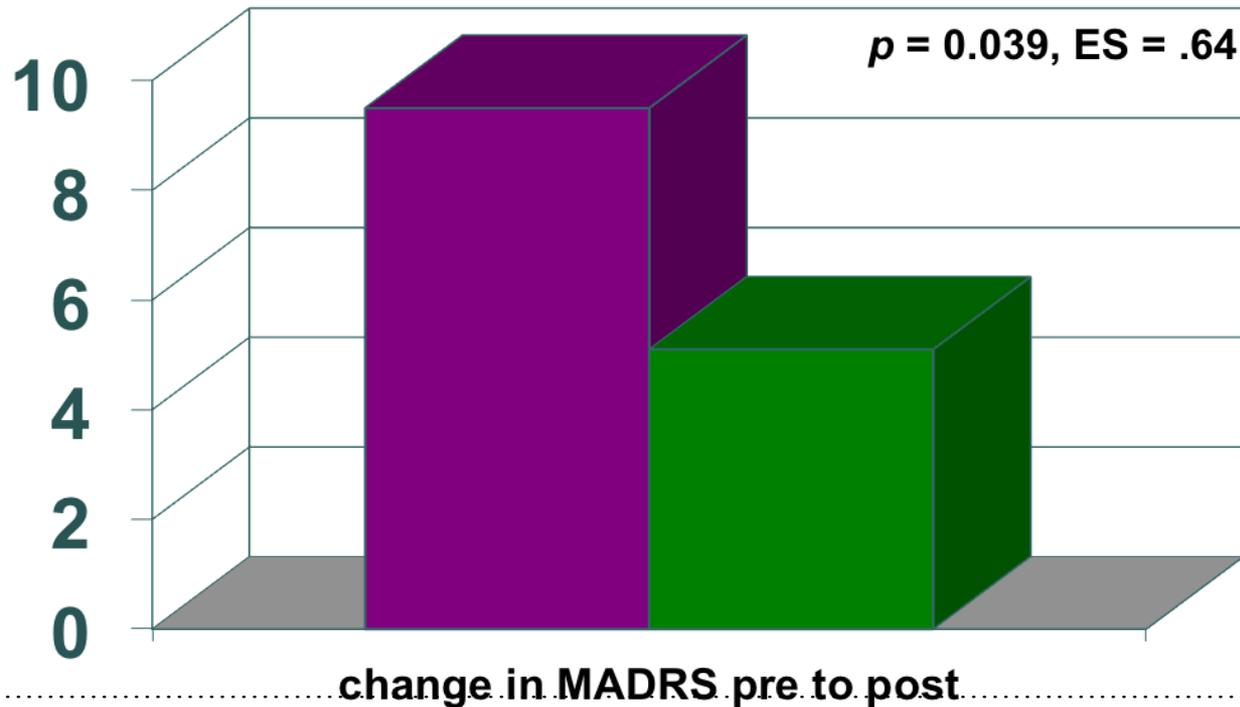
Methylated Vitamin B complex for depression & anxiety in depressed adults; Lewis et al., 2013, *ISRN Psychiatry*

- 2-month DB-RCT vit B complex vs. placebo
- 60 adults with MDD; 30 and 60 day follow up
- Modest improvement with group differences; unable to verify ES with statistics

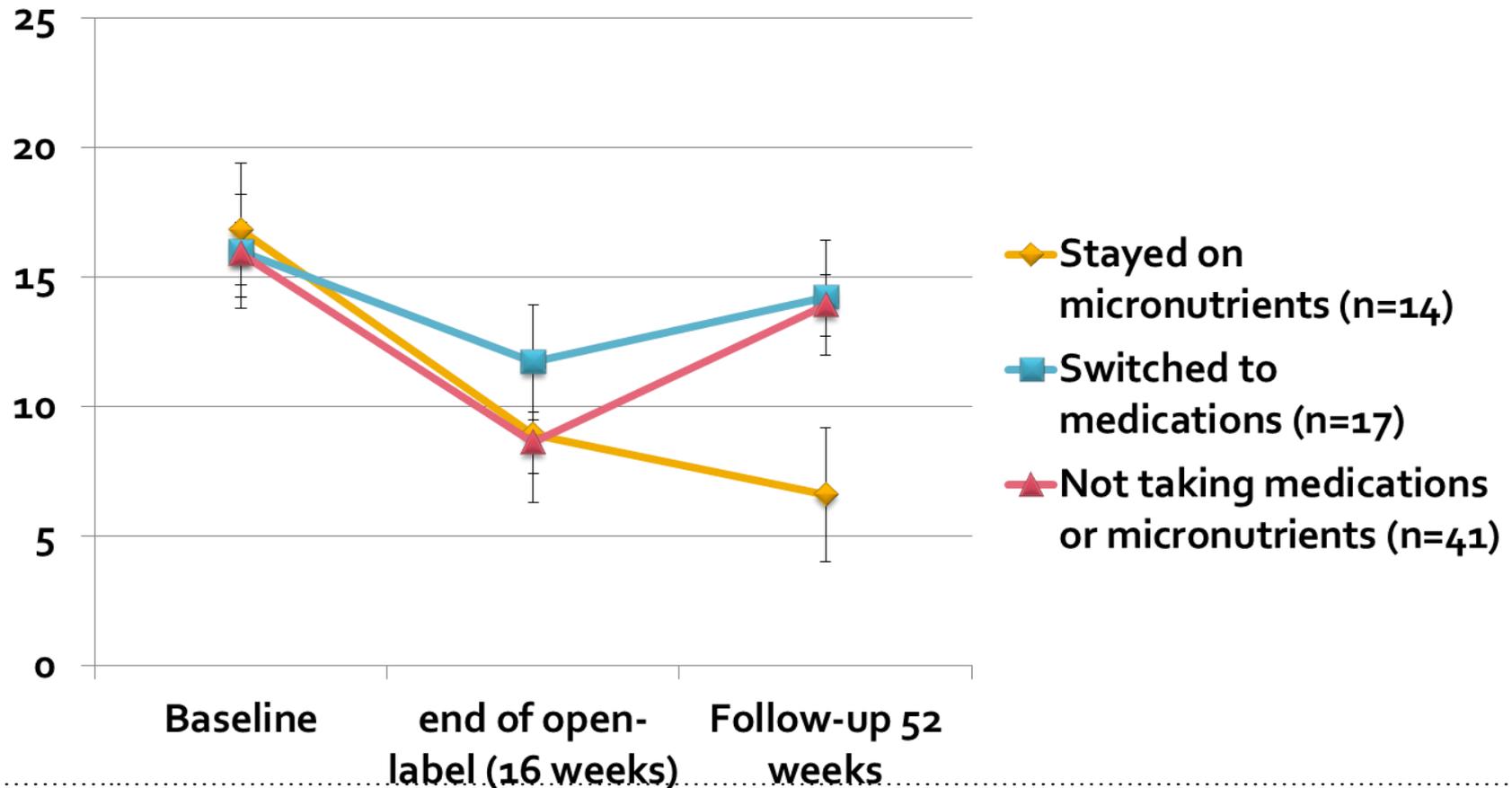


Change in depression in ADHD adults: for those *clinically depressed* at baseline;
Rucklidge et al., 2014, BJP

■ Active (n=11) ■ Placebo (n=10)



Naturalistic follow-up one year post-baseline: Mood symptoms (MADRS) Rucklidge et al., 2014; J Attention Disorders



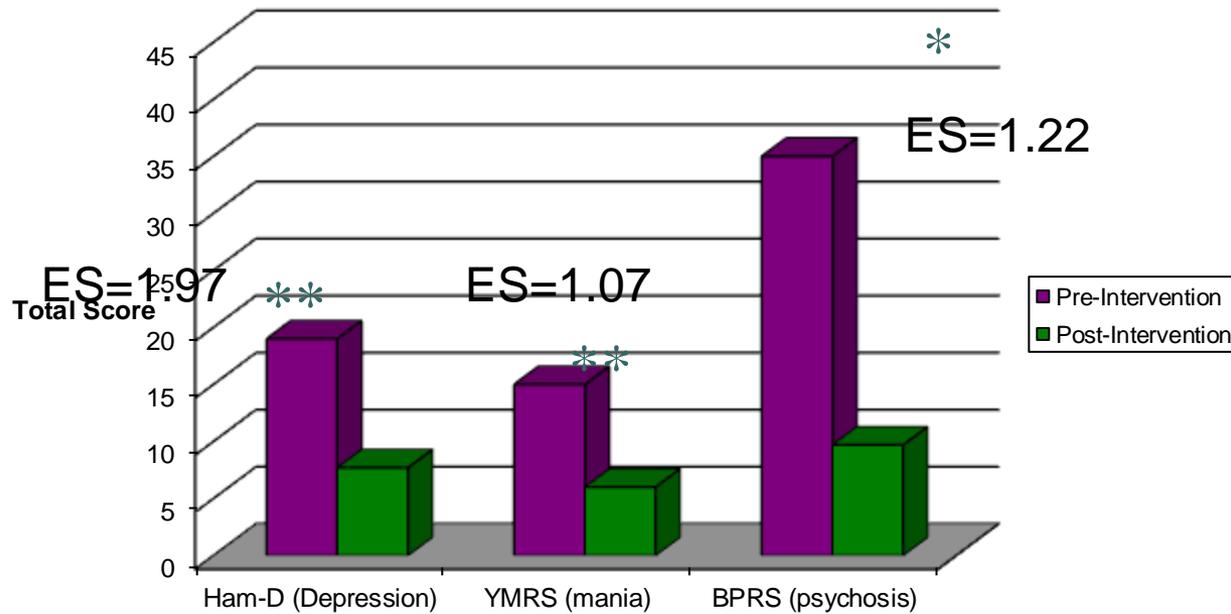
Bipolar Disorder treatment with BSMNs

- **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 et al., 2001, J Clin Psychiatry



Database analysis of 358 adults with Bipolar Disorder

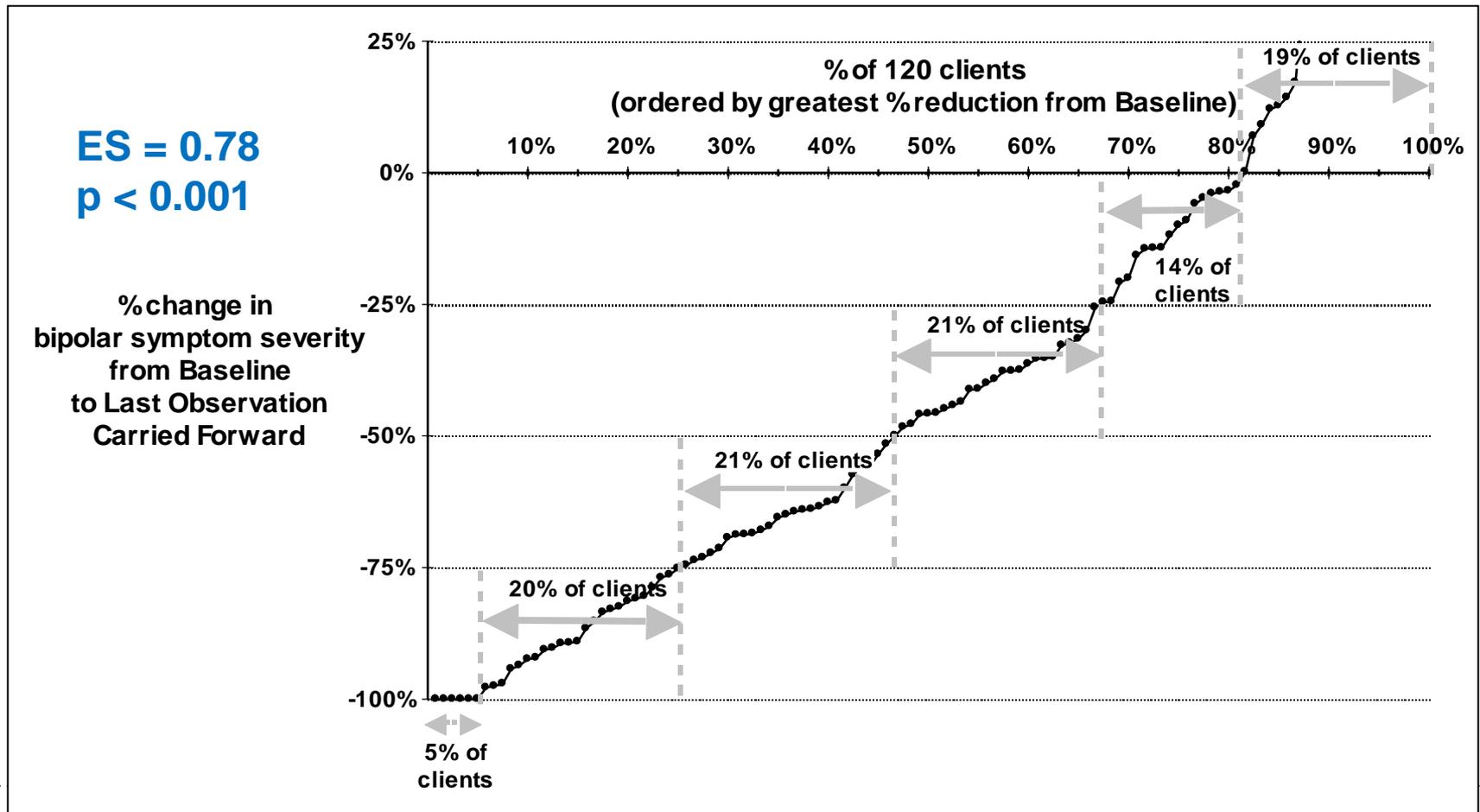
Gately and Kaplan, 2009; Clinical Medicine: Psychiatry

- Symptom severity
 - ↓ 41% after 3 months (ES = 0.78)
 - ↓ 45% after 6 months (ES = 0.76) ($p < 0.001$)
- Responder status:
 - 53% showed \geq 50% improvement at 6 months
- Regressions: ↓ symptom severity over 6 m sig associated with
 - ↑ micronutrient dosage
 - ↓ medication
- Symptom improvements sustained at 6 months, *suggesting not due to placebo/expectancy effects*



Database analysis (6 months) of 120 Youth with Parent-Reported Bipolar Disorder: % improving using BSMNs

Rucklidge et al., 2009, BMC Psychiatry



Evidence to date for BSMNs for addictions



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Application to addictions...

- Alcohol and other drugs affect the gut lining:
 - Decrease uptake of nutrients consumed, and of gut flora
- Blum and colleagues developed “neuro-adaptogens”
 - Mix of amino acids, minerals, vitamins
 - One RCT, 3 Open-label studies
 - Decrease drug hunger and withdrawal (alcohol, cocaine)
 - Reduce relapse rates
 - Improve psychological functioning
 - Research quite old and no stats provided
 - Poulos, 1981; Guenther, 1983; Blum et al., 1988; Brown et al., 1990



20 year old male;

Harrison et al., 2013, J Psychoactive Drugs

- **ADHD, MDD, Panic Disorder, Substance Abuse (cannabis and nicotine)**
- **Past history of treatment 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**



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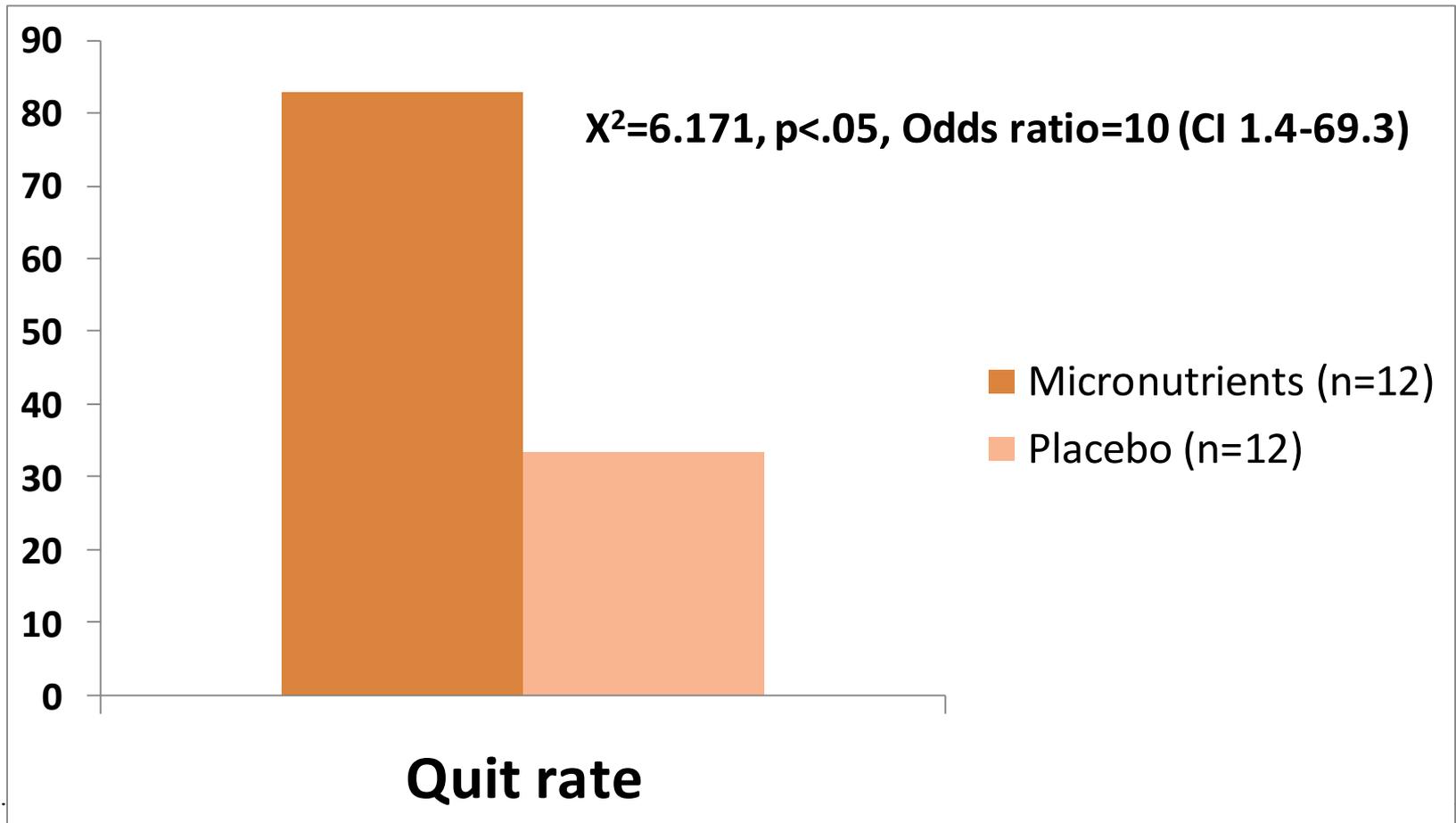
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Pilot RCT: Micronutrients for smoking cessation; Newton et al., under review

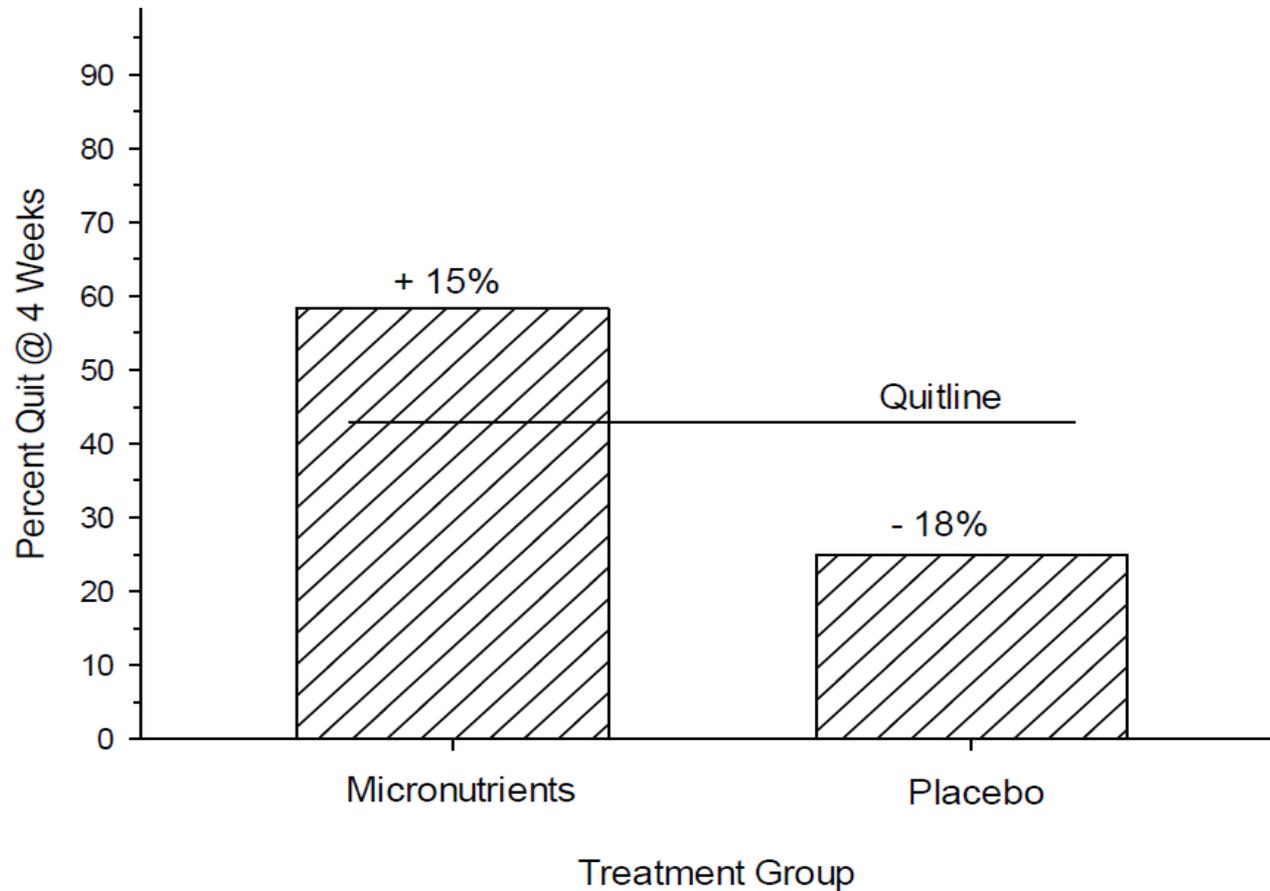
- 24 current smokers (>2 cigarettes/day for 12 months) randomized 1:1 placebo or micronutrients
 - 3 weeks multiple baseline
 - 4 weeks capsules
 - NZ Quitline plus 3 months capsules
 - Exit study if resume smoking
 - Monthly check in, daily diaries
 - Categorical outcome: quit/not quit
-



% successful quit defined as 3 days no smoking



Per cent quit at 4 weeks



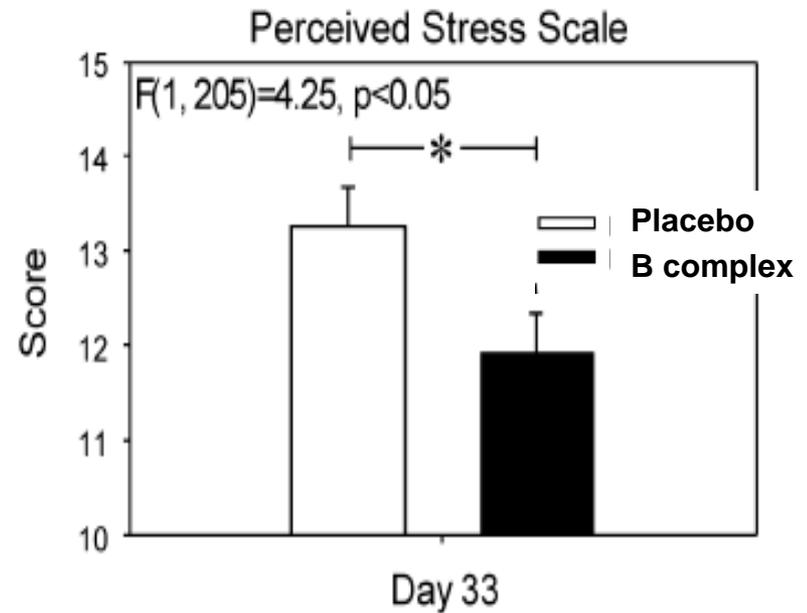
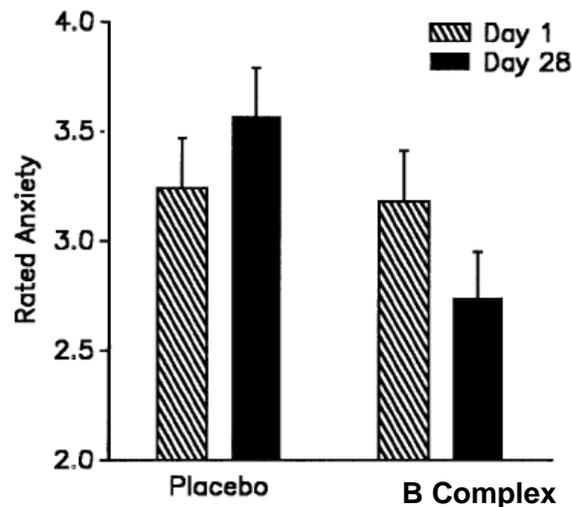
Evidence to date for BSMNs for stress and natural disasters

Natural disasters

- **~20-30%** of those in a natural disaster develop symptoms of psychological stress including PTSD, depression, and anxiety
- **Hard to implement efficacious tx (e.g. CBT, medications)**
- **4 RCTs of MNs (mostly B complex formulas) decrease stress/anxiety in both acutely stressed & acutely nonstressed populations**
 - Carroll et al., 2000; Schlebusch et al., 2000; Kennedy et al., 2010; Stough et al., 2011



RCT: Oral MVI effects on well-being in healthy young males



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

Douglas Carroll · Christopher Ring · Martin Suter
Gonneke Willemsen

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

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

September 4, 2010 4:35 am:

**A 7.1 earthquake occurred in
Christchurch, NZ during active
trials of multinutrient treatment**

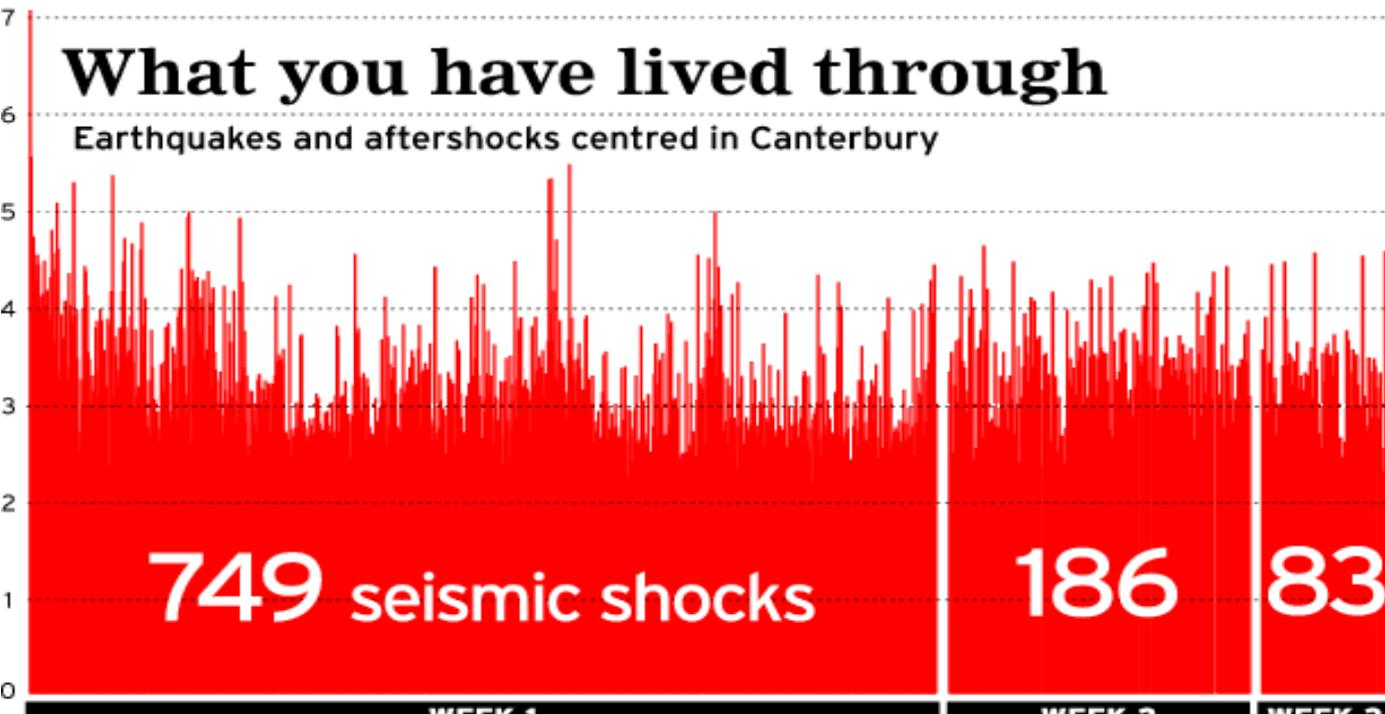


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**In the three weeks following
the earthquake there were
about 1000 aftershocks**

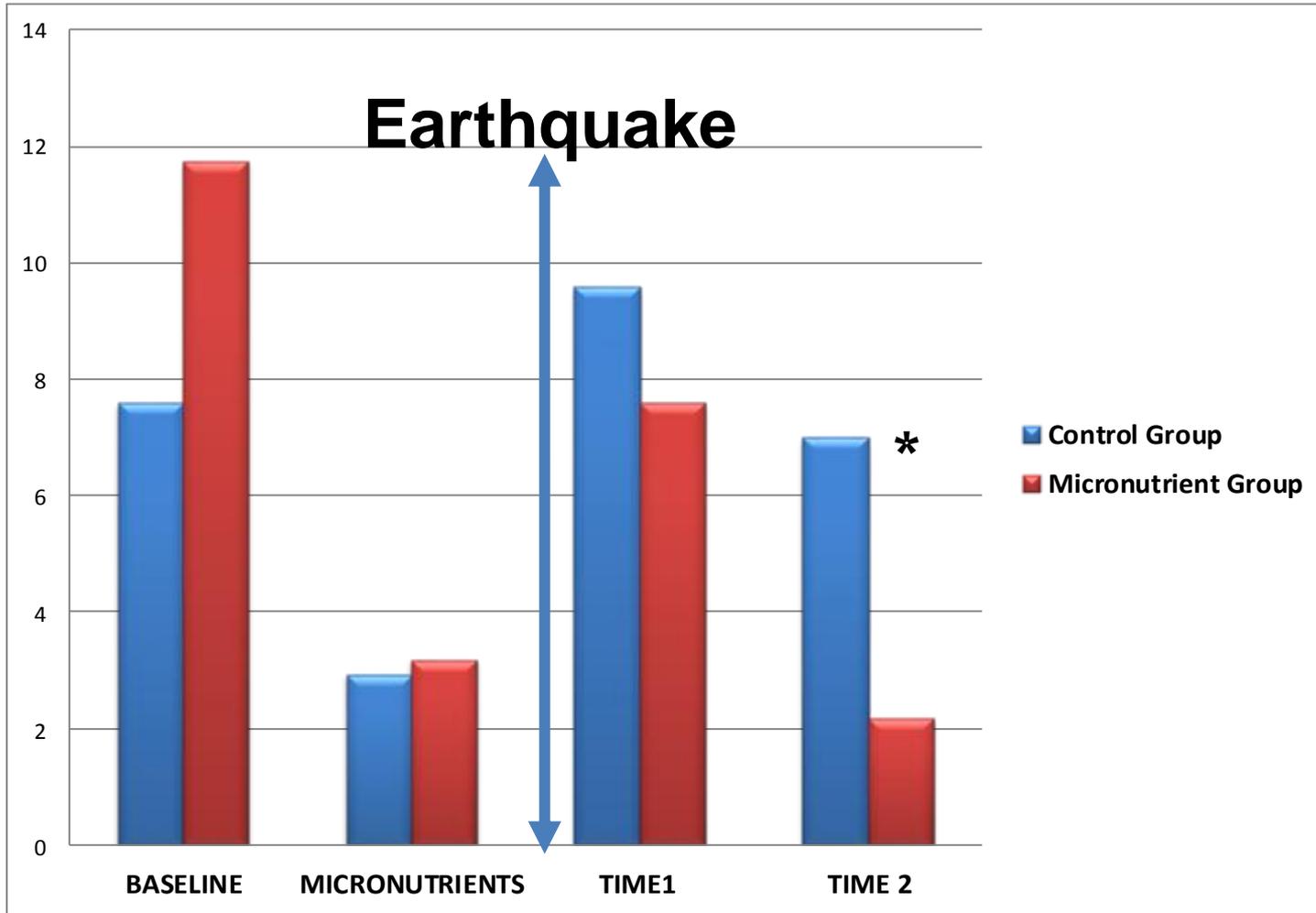


A “natural experiment”:

Sept 2010: The ADHD Diagnostic Assessment & Research Group at UC conducting trials on ADHD using a broad-spectrum formula (OL and RCT)

- **T0: participants assessed prior to the quake**
- **Some taking the formula, some not**
- **T1, T2: Surveyed by phone 1 and 2 weeks post-quake**
- **Used Depression, Anxiety, Stress Scale (DASS, + EQ impact questions**

Outcomes for BSMNs vs. controls



Rucklidge et al., *Psychiatry Res* 2011;

Rucklidge and Blampied, 2011, *NZ J Psychology*



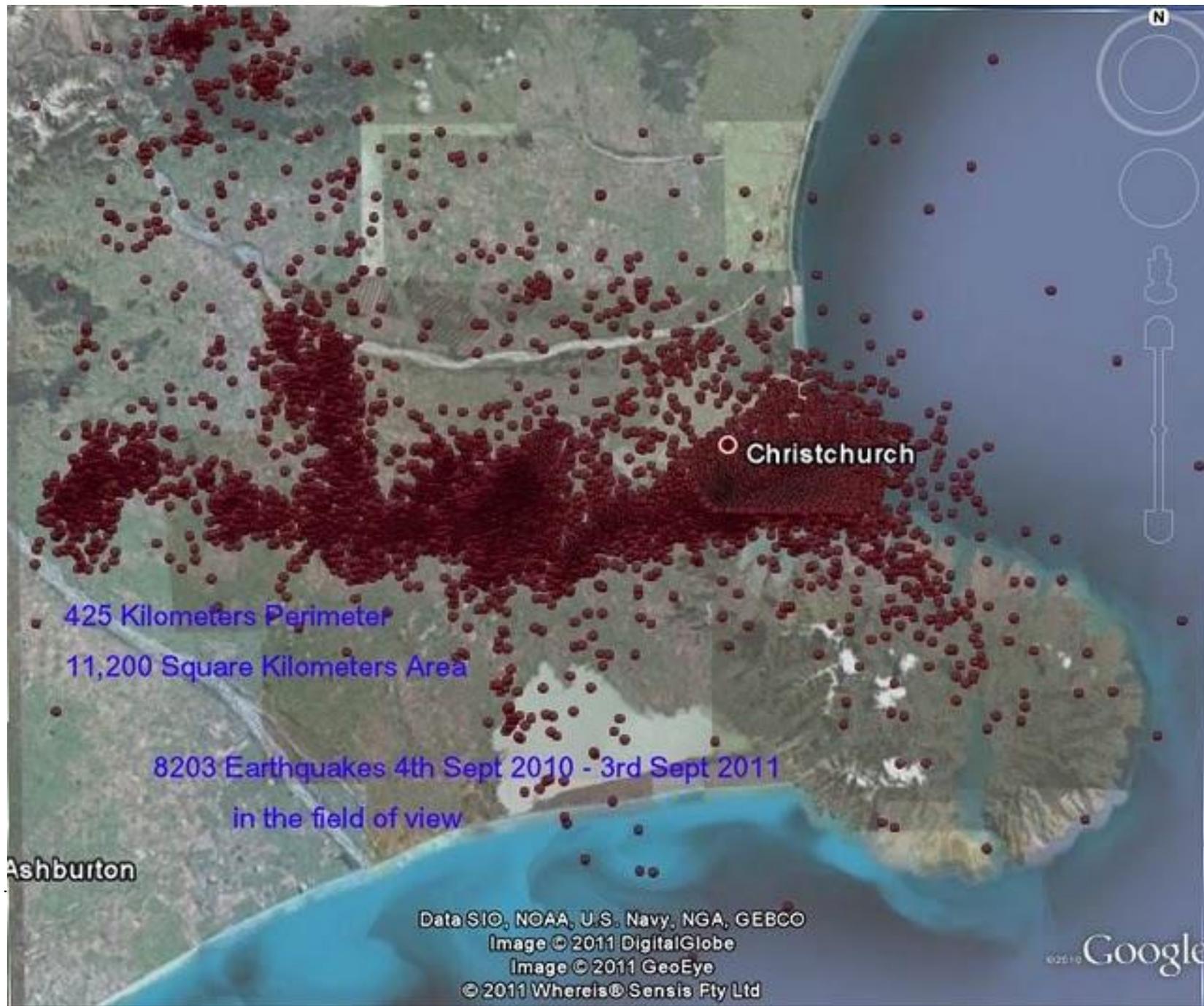
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Implications for disaster intervention

- Could these positive changes generalize to the wider “nonclinical” population?
- In a *randomized* trial?



425 Kilometers Perimeter

11,200 Square Kilometers Area

8203 Earthquakes 4th Sept 2010 - 3rd Sept 2011
in the field of view

Ashburton

Christchurch

Data SIO, NOAA, U.S. Navy, NGA, GEBCO
Image © 2011 DigitalGlobe
Image © 2011 GeoEye
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Impact of micronutrients on stress, anxiety and PTSD symptoms in general population

- ▶ Recruited on-line via Trade Me, Facebook, Community Websites
- ▶ 91 randomized
 - 30 to B complex (29 completed)
 - 31 to multinutrient low dose (30 completed)
 - 30 to multinutrient high dose (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



RCT Results

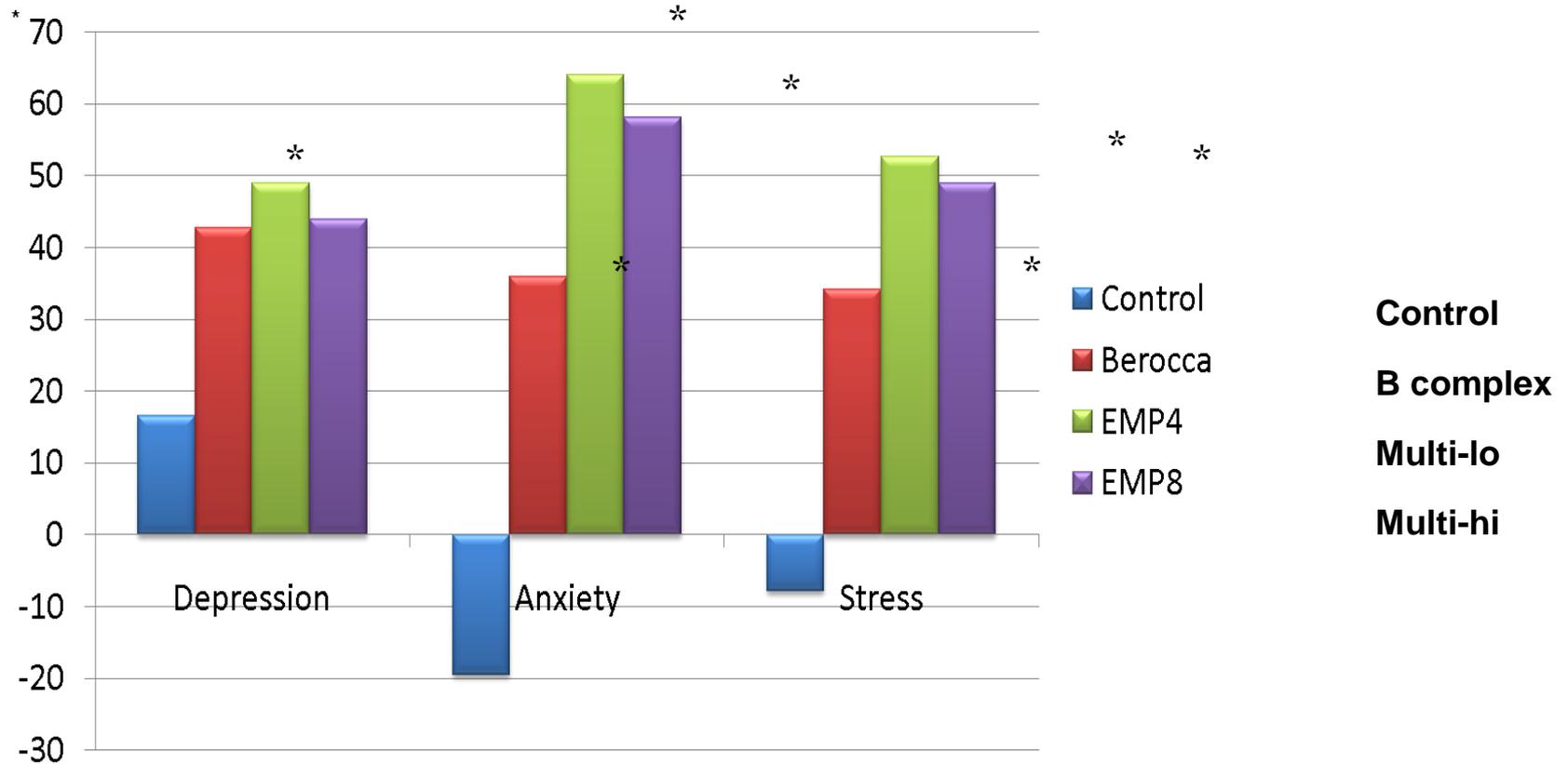
- No grp diff in exercise, hx of mental illness, zoning, counselling, SES, age, sex, leaving town, diet
- All 3 tx groups **showed large (B complex) or very large (multinutrient both doses) changes** from baseline ---- all better than controls
- **Multinutrient gps (both doses) showed superiority to B complex for intrusions, and higher dose gp on CGI (clinical global impressions) for stress, anxiety, energy, mood**

At one month follow-up

- Those who stayed on nutrients continued to improve
- Those who didn't, remained the same
- Clear preference: **five times** more of the 'high multivitamin dose' participants stayed on micronutrients compared with those in the B complex group



% change from baseline to 4 weeks

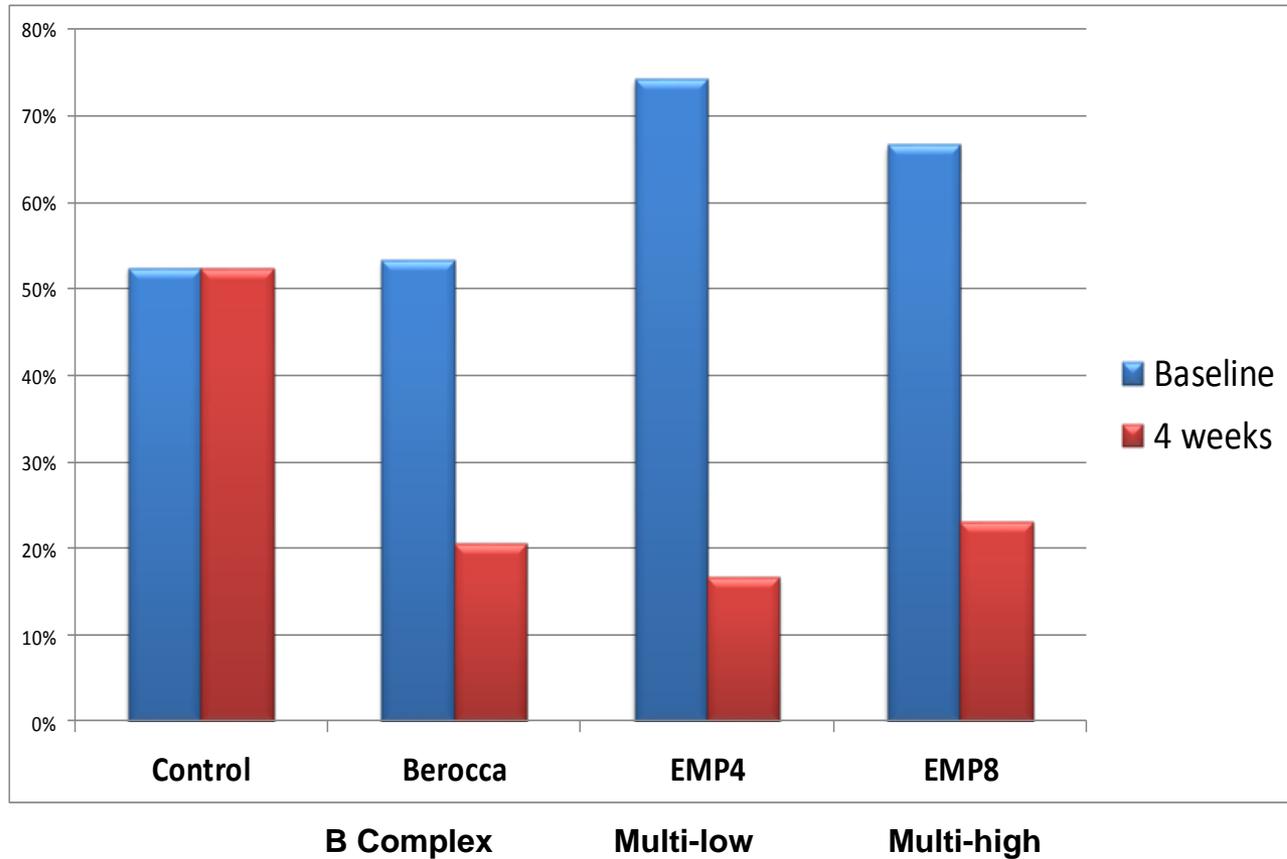


***sig different from control**
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% with significant PTSD symptoms baseline and 4 weeks

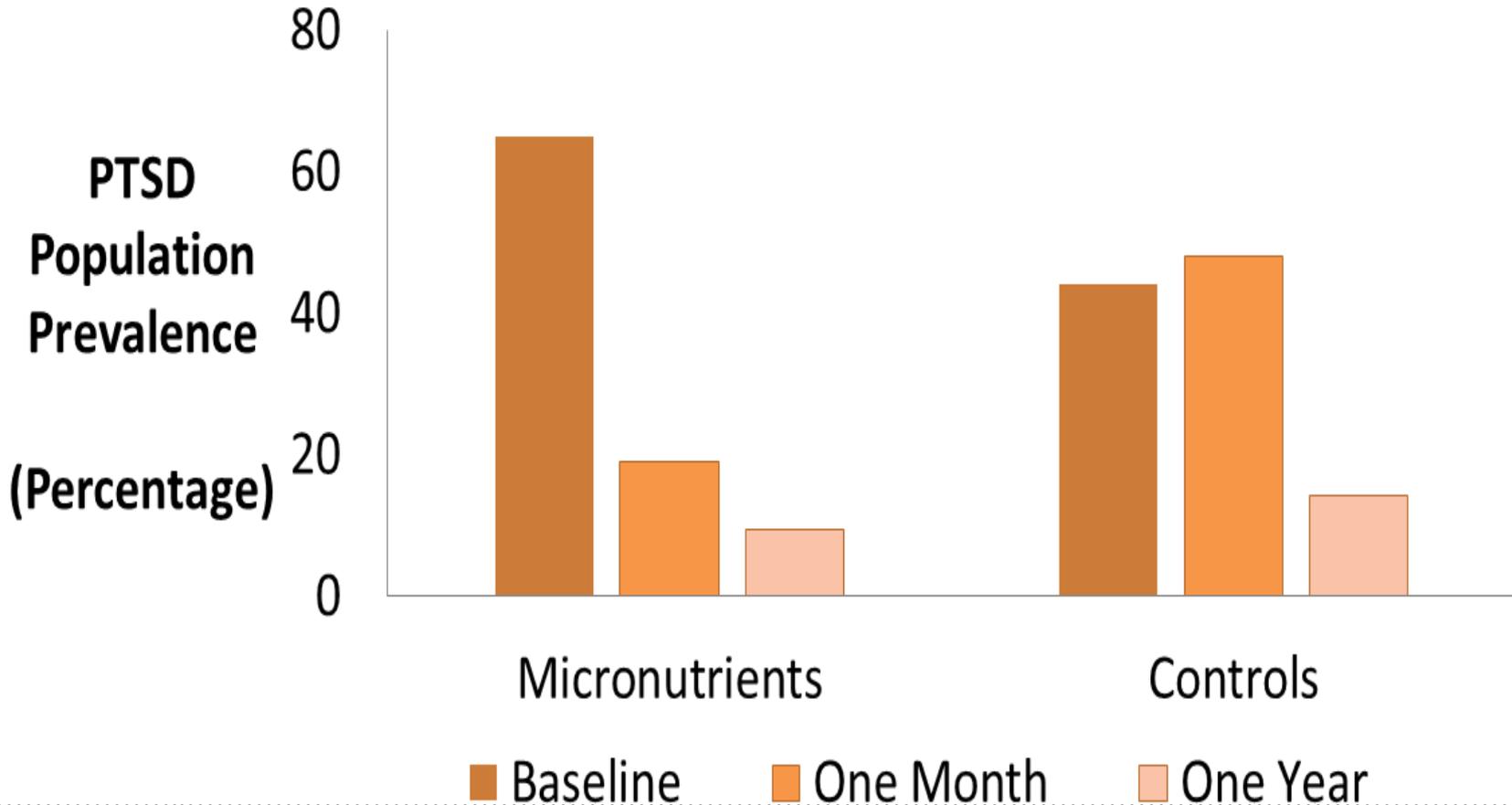


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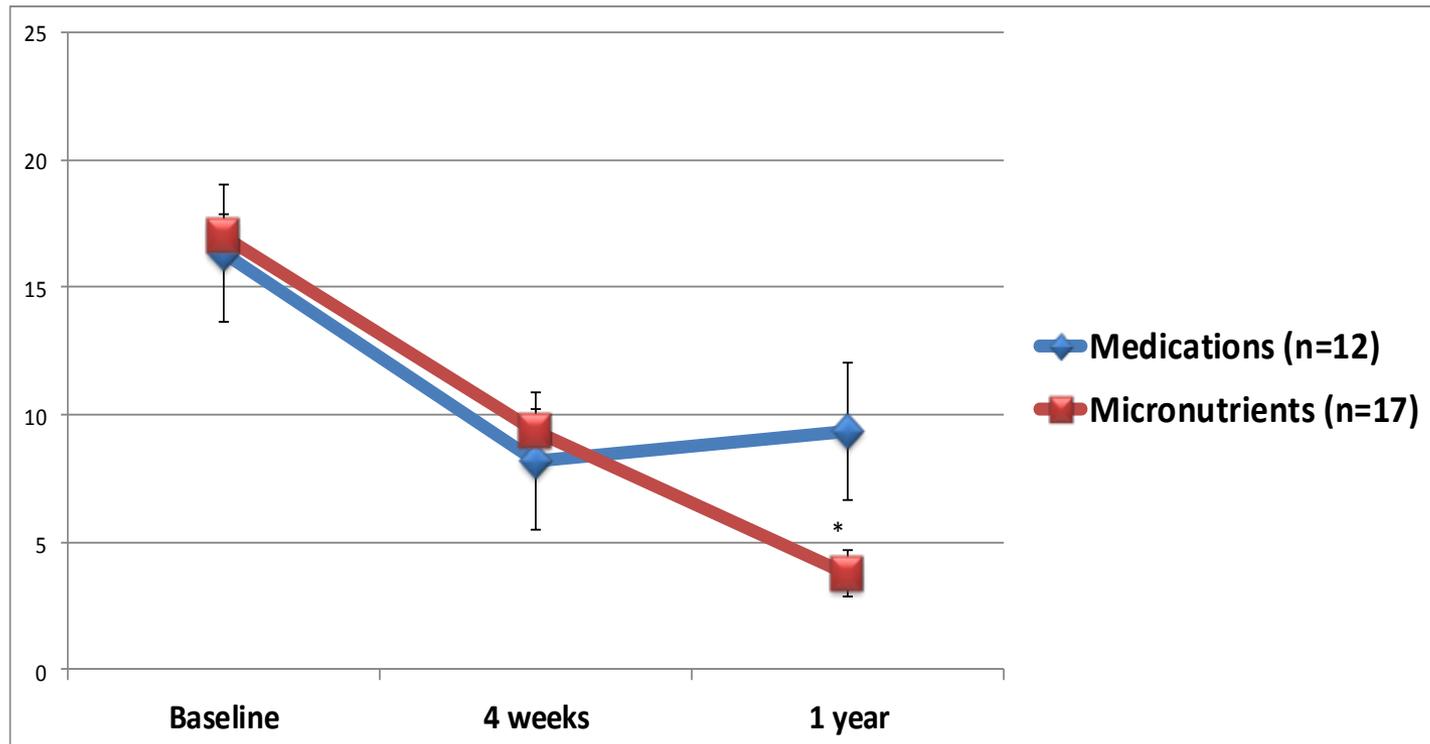


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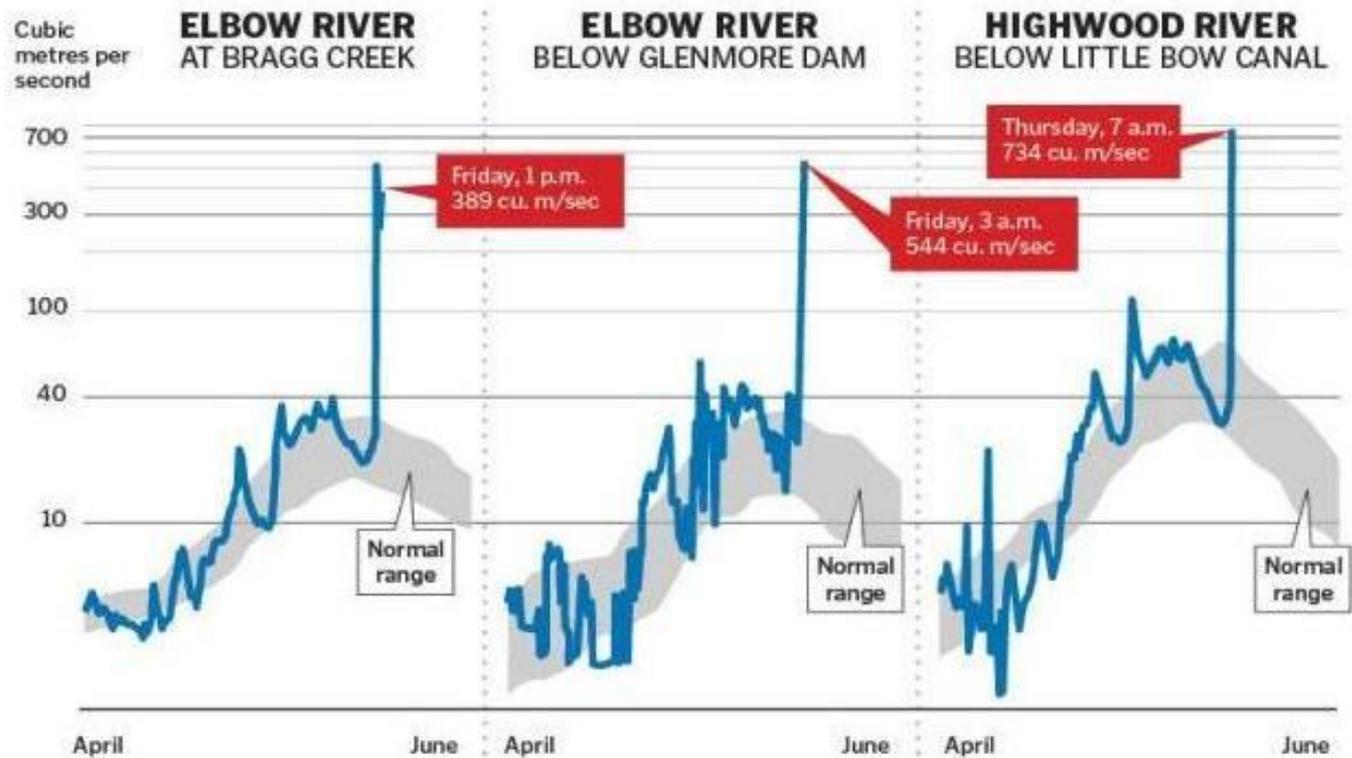
Reduction in trauma after earthquakes



Change in depression over time based on treatment at 52 weeks



Replication: The 2013 Southern Alberta flood



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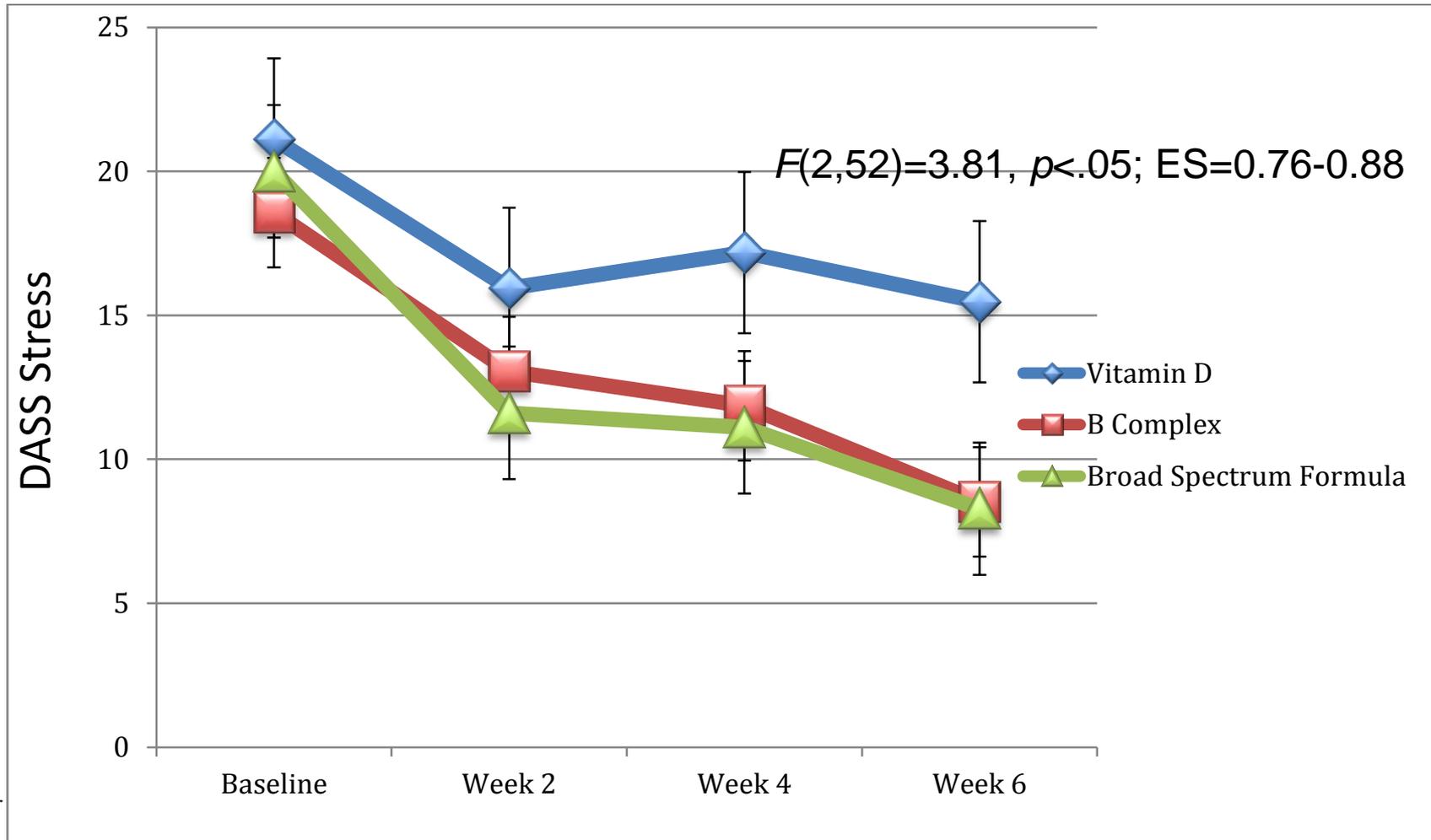
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Alberta Flood Study

- **Sample: 56 adults aged 23 – 66**
- **Med-free, evidence of moderate depression and/or anxiety on the Depression, Anxiety and Stress Scale (DASS)**
- **Placebo: *unethical***
- **Randomized to 3 groups – 6 week blinded RCT:**
 - **Single nutrient (vitamin D 1000 IU): n=17**
 - **Few nutrients (B complex): n=21**
 - **Broad spectrum (~30 minerals and vitamins): n=18**

AB-NZ collaboration

Kaplan et al., Psychiatry Res. 2015 Jun 27 epub first



Societal implications of multinutrient treatments

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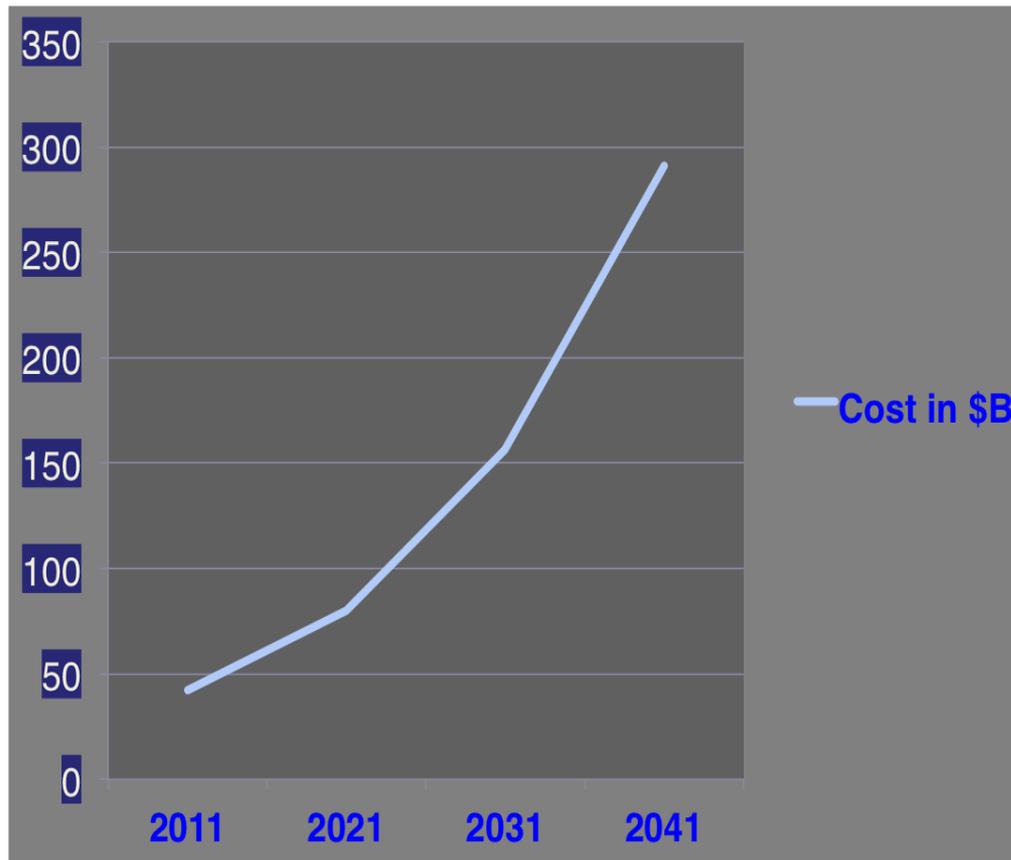


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An Example of Cost Projections: Canadian Costs for Mental Disorders



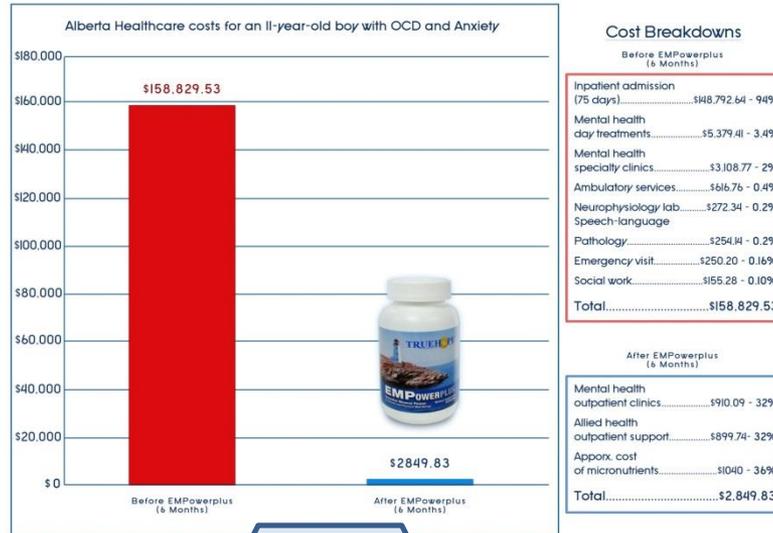
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Comparison of costs for one 10 y/o boy with severe OCD, hallucinations

Costs of 6 months of conventional inpatient treatment compared to 6 months of outpatient follow-up with micronutrient treatment



Vit/
min

6 months medication



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6 months micronutrients



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6 months of micronutrient treatment

<2% of the cost of his
previous 6 months
conventional treatment



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An overview of safety of BSMN treatments



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One example: suggested “therapeutic doses” vs. Tolerable Upper Intake Levels (ULs)

	Amount in a typical therapeutic dose, 15 capsules daily	UL for adult
Vitamin A	5,760 IU	10,000 IU
Vitamin C	600 mg	2,000 mg
Vitamin D	1,440 IU	2,000 IU
Vitamin E	360 IU	1,500 IU
Vitamin B1	18 mg	none set
Vitamin B2	13.5 mg	none set
^a Vitamin B3	90 mg	35 mg
Vitamin B5	21.6 mg	none set
Vitamin B6	36 mg	100 mg
^b Folate	1,440 mcg	1,000 mcg
Vitamin B-12	900 mcg	none set
Vitamin H	1,080 mcg	none set
Calcium	1,320 mg	2,500 mg
Phosphorous	840 mg	4,000 mg
^c Magnesium	600 mg	350 mg
Potassium	240 mg	none set
Iodine	204 mcg	1,100 mcg
^d Zinc	48 mg	40 mg
Selenium	204 mcg	400 mcg
Copper	7.2 mg	10 mg
Manganese	9.6 mg	11 mg
Chromium	624 mcg	none set
Molybdenum	144 mcg	2,000 mcg
Iron	13.74 mg	45 mg

Table 1, Simpson et al.
BMC Psychiatry, 2011

Another product example: suggested therapeutic dose vs. UL, LOAEL for 9-13 y/o

Amount in 15 capsules	% DV	RDA/AI		UL	LOAEL		
		Unit	M	F	M/F	Adult	
Vitamin A	5,760IU	114%	IU	2,000	2,000	5,666.7	46,667
Vitamin C	600 mg	999%	mg	45	45	1,200	3,000
Vitamin D	3,000 IU	750%	IU	600	600	4,000	3,800
Vitamin E	360 IU	1200%	IU	16.5	16.5	900	750
Vitamin K	120 mcg	150%	mcg	60	60	*	*
Thiamin	60 mg	3999%	mg	0.9	0.9	*	*
Riboflavin	18 mg	1059%	mg	0.9	0.9	*	*
Niacin	90mg	450%	mg	12	12	20	50
Vitamin B₆	69.9mg	3501%	mg	1	1	60	500
Folate	801mcg	201%	mcg	300	300	600	5,000
Vitamin B ₁₂	900 mcg	15000%	mcg	1.8	1.8	*	*
Biotin	1,080 mcg	360%	mcg	20	20	*	*
Pantothenic Acid	30 mg	300%	mg	4	4	*	*
Calcium	1,320 mg	132%	mg	700	1,300	3,000	4,000
Iron	13.8 mg	75%	mg	8	8	40	70
Phosphorus	840 mg	84%	mg	1,250	1,250	4,000	10,200
Iodine	204 mcg	135%	mcg	120	120	600	1,700
Magnesium	600mg	150%	mg	240	240	350	360
Zinc	48mg	321%	mg	8	8	23	60
Selenium	204 mcg	291%	mcg	40	40	280	913
Copper	7.2 mg	360%	mg	0.7	0.7	5	10
Manganese	9.6mg	480%	mg	1.9	1.6	6	15
Chromium	624 mcg	519%	mcg	25	21	*	*
Molybdenum	144 mcg	192%	mcg	34	34	1,100	1,500
Potassium	240 mg	6%	mg	4,500	4,500	*	*

Also consider proprietary blends when thinking about safety and tolerability

A variety of antioxidants/botanicals:

Ginkgo biloba (from leaf), grape seed (extract), citrus bioflavonoids

Differing amino acids:

Glutamine, DL-Phenylalanine, L-Methionine

Alpha-lipoic acid, N-acetyl cysteine,

Acetyl-L-carnitine

Choline and inositol

Other trace minerals

Organic lithium

Safety and tolerability data from clinical studies

Adverse effects- MCN vs. usual tx. in ASD

Case-control study: N=44 for each group

- retrospective chart review
 - Matched by age, sex, parental education, income, IQ category, CGI symptom severity.
- Family chose treatment; 3 differing MCN products
- Single prescriber, 2 sites
- Sample largely urban, Caucasian, male, young (<12 y/o)
- Over 65% on rx medications at referral; goal to use lowest minimum dose for traditional medications

Mehl-Madrona et al. J Child Adolesc Psychopharm 2010; 20(2):95-103.

Number of AEs: MCN 33, medication 214

<i>Adverse event</i>	<i>Micronutrient group (n)</i>	<i>Medication group (n)</i>	<i>Group difference p value^a</i>
Increased appetite	1	32	<0.0001 med>MCN
Fatigue	1	29	<0.0001 “
Drowsiness	1	31	<0.0001 “
Vomiting	1	9	0.015 “
Anxiety	6	19	0.004 “
Diarrhea	4	5	1.000
Constipation	0	6	0.026 “
Sleep problems	1	4	0.360
Droling	0	4	0.116
Headache	2	8	0.089
Stomach ache	9	9	1.000
Dry mouth	0	6	0.026 “
Increased thirst	0	5	0.055
Dizziness	0	5	0.055
Dyskinesia	0	7	0.012 “
Nausea	3	5	0.713
Decreased appetite	2	5	0.434
Tremor	2	8	0.089
Tachycardia	0	4	0.116
Muscle rigidity	0	4	0.116
Restlessness	0	3	0.241
Akathisia	0	6	0.026 “

^a*p* values obtained from Fisher exact test

Safety, tolerability, and serum micronutrient levels in children with BPSD

10 youth ages 6-12 took up to 15 capsules/day for 8 weeks
7 completed; 3 dropped out due to swallowing issues

All AEs were mild and transient

- GI upset, resolved with taking product with food
- Initial insomnia, resolved with taking product earlier

One child started a stimulant without difficulty

4/10 serum levels increased:

- Vitamin A (retinol), vit B6, vit E-alpha tocopherol, folate

Frazier et al. 2013 J Child Adolesc Psychopharmacol 2013;

23(8):558-567



Mean Serum Concentrations of Vitamins and Minerals Pre- and Supplementation

<u>Nutrient</u>	<u>Reference range</u>	<u>Average pre- level Mean (SD)</u>	<u>Average post-level Mean (SD)</u>	<u>Significance (p)</u>
sTfR	2.9–8.3 µg/mL	3.9 (0.82)	3.6 (0.46)	0.600
Ferritin	20.0–400.0 ng/mL	138.3 (104.31)	90.5 (69.97)	0.091
Mg	15.0–30.0 µg/mL	17.3 (1.02)	17.7 (0.49)	0.176
Zinc	>0.8 µg/mL	1.7 (0.42)	1.8 (0.47)	0.612
Vit A: Retinol	>0.70 µmol/L	3.3 (1.16)	5.0 (1.58)	0.018[*]
Vit B₆: PLP	20.0–120.0 nmol/L	54.3 (16.61)	104.0 (41.24)	0.028[*]
Vit D	>20.0 ng/L	26.3 (3.93)	38.7 (22.22)	0.063
Vit E: α-TC	6–12 µg/mL	6.6 (2.07)	10.6 (3.00)	0.043[*]
Vit E: γ-TC	—	1.3 (0.59)	0.92 (0.35)	0.063
Folate	3.8–23.2 µg/mL	3.9 (1.72)	5.9 (0.75)	0.028[*]

Rucklidge ADHD in adults study

Adverse effects: NSD between groups

	Micronutrient formula group (n = 42)	Placebo group (n = 38)	P
Headache	16	15	1.00
Dry mouth	13	15	0.49
Sleep disruptions	16	8	0.14
Gastrointestinal disturbances/diarr hoea	13	9	0.62
Nausea	12	8	0.61
Constipation	5	8	0.37
Agitation	8	5	0.55
Sedation	4	7	0.33
Anxiety	5	8	0.37
Abdominal pain	3	5	0.47
Weight gain	2	4	0.42
Blurred vision	2	3	0.66

Nutrient level changes, MCN vs. placebo

Nutrient levels	MCN Baseline mean, (s.e.)	MCN Change, mean, (s.e.)	Placebo Baseline mean, (s.e.)	Placebo Change, mean, (s.e.)	<i>p</i>
Vitamin D, nmol/l	62.4 (4.4)	15.6 (3.1)	68.5 (3.8)	0.4 (3.4)	0.002
Vitamin B₁₂, pmol/l	353.3 (18.3)	383.1 (30.2)	374.9 (22.7)	1.1 (31.3)	<0.001
Folate, nmol/l	21.1 (1.5)	24.3 (2.2)	22.4 (1.4)	-1.6 (31.3)	<0.001
Magnesium, mmol/l	0.89 (0.01)	-0.00 (0.01)	0.92 (0.01)	-0.01 (0.01)	0.724
Ferritin, µg/l	116.9 (13.1)	-2.44 (5.57)	105.6 (11.8)	-6.83 (5.49)	0.577
Iron, µmol/l	18.3 (0.9)	-0.4 (1.0)	19.3 (1.2)	0.4 (1.0)	0.568
Calcium, mmol/l	2.39 (0.02)	0.03 (0.02)	2.39 (0.02)	0.01 (0.02)	0.286
Zinc, µmol/l	12.1 (0.2)	0.4 (0.3)	12.5 (0.2)	0.1 (0.3)	0.423
Copper, µmol/l	15.4 (0.6)	0.4 (0.4)	13.5 (0.4)	-0.4 (0.4)	0.171



1-year naturalistic follow up, ADHD in adults

72/80 were followed up at a mean of 11 mo.

19% continued the broad-spectrum MCN after 10 weeks

24% switched to medications/stopped MCN

57% stopped MCN and were not taking medications

Reasons for cessation:

- 1) cost; 2) number of pills; 3) lack of benefit; 4) AEs.

No participant continuing MCN reported any ongoing AEs.

Rucklidge JJ et al. BJPsych 2014; 204:306-315.

Example of labeling information for clinicians

“Because interactions ... with psychiatric medications have not been systematically evaluated, caution is warranted. Any agent with CNS activity has the potential to interact with broad spectrum micronutrients and complicate the management of micronutrient treatments.”

“These include psychiatric medications, medical drugs with CNS actions (antihistamines, medications for ‘colds’, theophylline, etc.), recreational agents (alcohol, marijuana, heroin, etc.), other commonly used substances that are not necessarily thought of as recreational agents (caffeine, nicotine), and certain hormones (e.g., glucocorticoids).”

Common side effects of broad spectrum MCNs

Renal:

Common: “Neon” yellow urine (due to riboflavin excretion; not harmful)

GI:

Dyspepsia, nausea, or rarely vomiting, if not taken with food

Loose stools, flatulence, watery diarrhea

CNS:

Insomnia

Headache

Anxiety, agitation, or impulsivity if dose too high/sensitivity

Other important nutrient product-drug interactions

Antibiotics:

- Change gut flora, decrease breakdown and absorption
 - symptoms may worsen; can raise dose temporarily

Antacids (e.g. Zantac, Prilosec, Tagamet):

- neutralize or inhibit the production of stomach acid, reduce the breakdown and absorption of nutrients

Caffeine, chocolate, marijuana:

- decreased effectiveness

Patient selection factors

Strict contraindications:

Wilson's disease (copper overload)

-what about carriers?

Hemochromatosis and hemosiderosis

what about carriers/early expression?

Phenylketonuria

only for the supplement with phenylalanine?

Trimethylaminuria (risk of choline overload)

Immunosuppressed

Active or remitted cancer

Active infectious disease

Acute or chronic liver, renal disease

Summary I

There are no formal product development phase I, II, III bioavailability, pharmacokinetic or dosing safety trials

Therefore, check the MCN preparation to ensure doses under the LOAEL

- *Pay attention to individual patient factors as key to safe use*
- *Added proprietary blend ingredients are often without sufficient study and require screening for contraindications for any specific patient*

Products have government product licenses; manufacturing processes may be monitored and regulated for quality control, and several products have had FDA Investigational New Drug (IND) approvals for study

Short-term profile of side effects in clinical studies to date show adequate safety and tolerability

Only one RCT to date of short-term use

No prospective RCTs of long-term use

Summary II

Independent, foundation and/or federal funding is critically needed to provide research data on safety, tolerability, and confirm dosing for different populations and uses

Practitioners desiring to use MCN treatments should:

- educate themselves *sufficiently* about products, studies to date
- obtain experienced consultation around their use
- update regularly on nutritional safety data-
 - a constantly changing field!

Perhaps our ancestors had it right

- ▶ **1910 People's Home Library**
- ▶ **guided families; health care providers were not easily accessed**
- ▶ ***The number one cause of acquired insanity was:***

“imperfect nutrition”

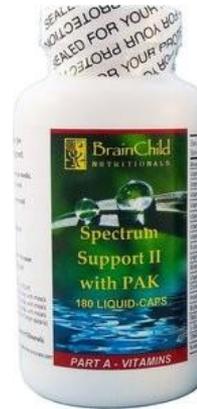


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Which BSMNs have evidence of benefit with mental symptoms?



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Summary

- **Offending**: Four RCTs showed superiority of nutrients over placebo in reducing offending behaviours (28-47% reduction) in incarcerated adults and antisocial youth
 - **ADHD**: most trials, including 1 RTC, showed benefits of micronutrients (ES=0.33-2.18)
 - **Depression**: Two RCTs showed superiority of nutrients over placebo for reducing clinical depression (ES=0.64)
 - Other RCTs examined mood changes in healthy or medically ill populations (8 positive, 6 negative), making generalization to psychiatric samples difficult
 - **Bipolar disorder**: 5 OL trials showed benefit with large effect sizes (>0.8)
-

Summary

- **Addictions**: very old studies documenting some benefit of nutrients in diminishing alcohol and opiate withdrawal symptoms
 - A pilot RCT showed benefits of multinutrients in assisting people with quitting smoking
 - Most consistent results obtained from formulas with broad range of nutrients higher than RDA
 - *Challenges*: doses, sample sizes, generalizability, variable nutrients used, lack of controlled studies, replication, *urgent research is required*
-



Useful References

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