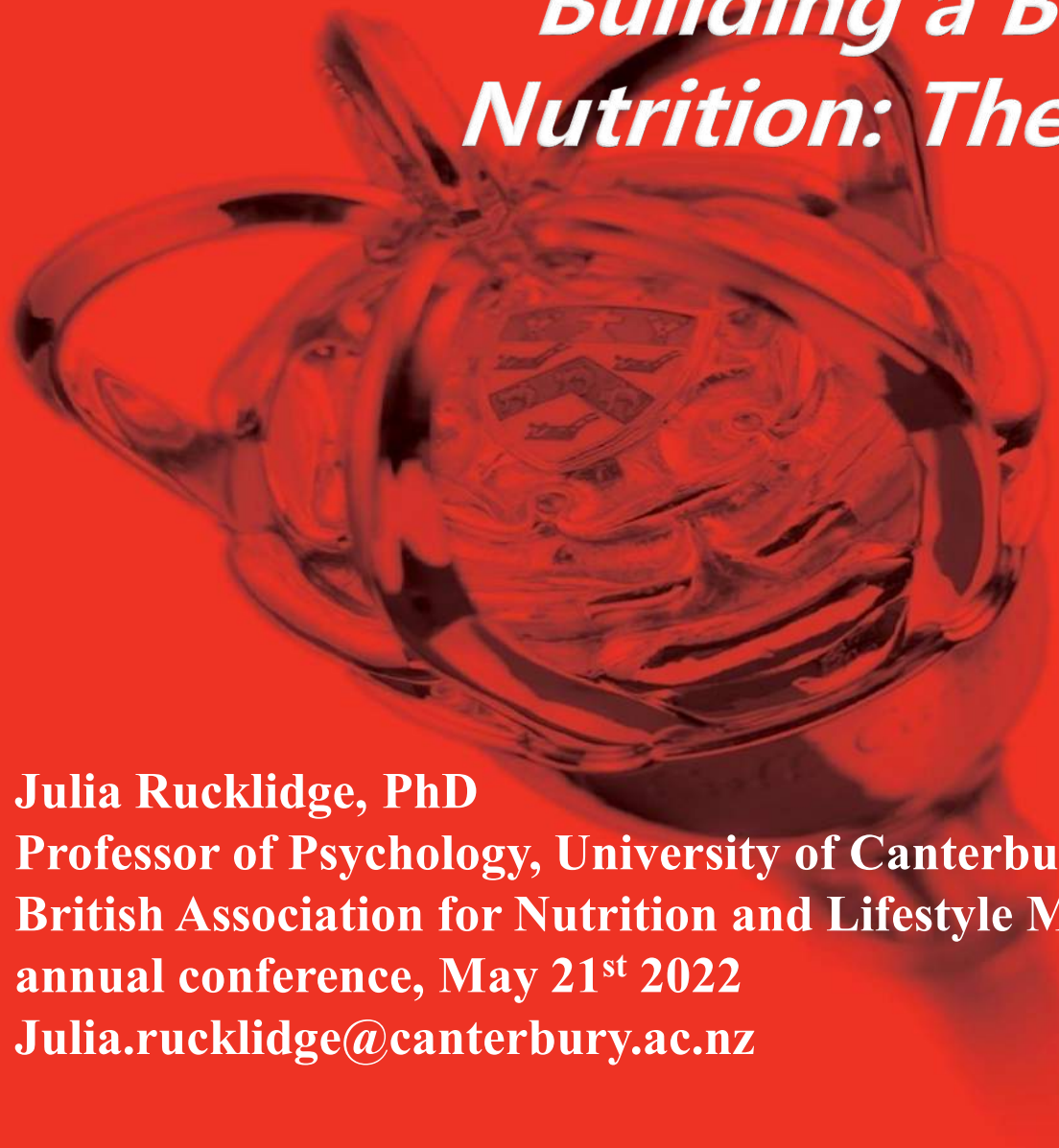
Building a Better Brain with Nutrition: The evidence to date



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British Association for Nutrition and Lifestyle Medicine annual conference, May 21st 2022
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CHRISTCHURCH NEW ZEALAND

Affiliations and Declarations of Interest

- Received or have received research funding from:
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  - Waterloo Foundation
  - Vic Davis Memorial Trust
  - University of Canterbury Foundation
  - Canterbury Medical Research Foundation
  - GAMA Foundation
  - Foundation for Excellence in Mental Health Care
- Royalties from Harper Collins for sales of The Better Brain
- No current or past funding from the companies that make products researched

The broader context

1. **Increasing prevalence of mental problems**
2. **There is a danger of (mental) health care bankrupting our society**
3. **Our current ‘gold standards’ are turning out to be less effective than hoped**

Then what are we to do?

Photo image credit: istockphoto.com

Dietary patterns and mental health in the 21st century

Mental illness

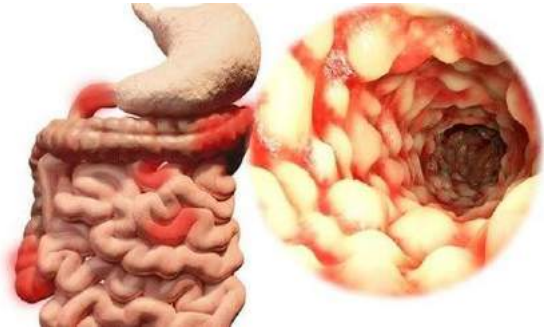
Mental illness

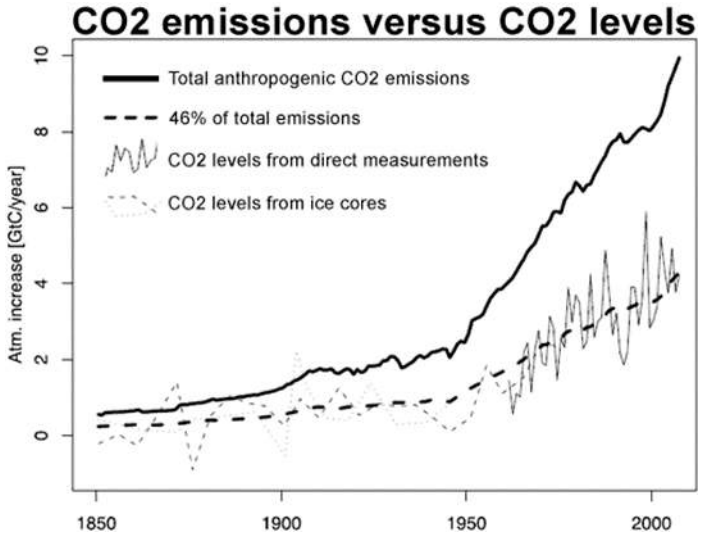
Photo credits: Elana Amsterdam, Sandy Austin, Christian Cable on Flickr

The obvious solution?

Tell everyone to eat better

Eating better is a good thing....
BUT





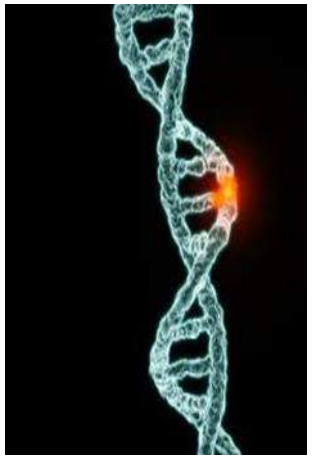
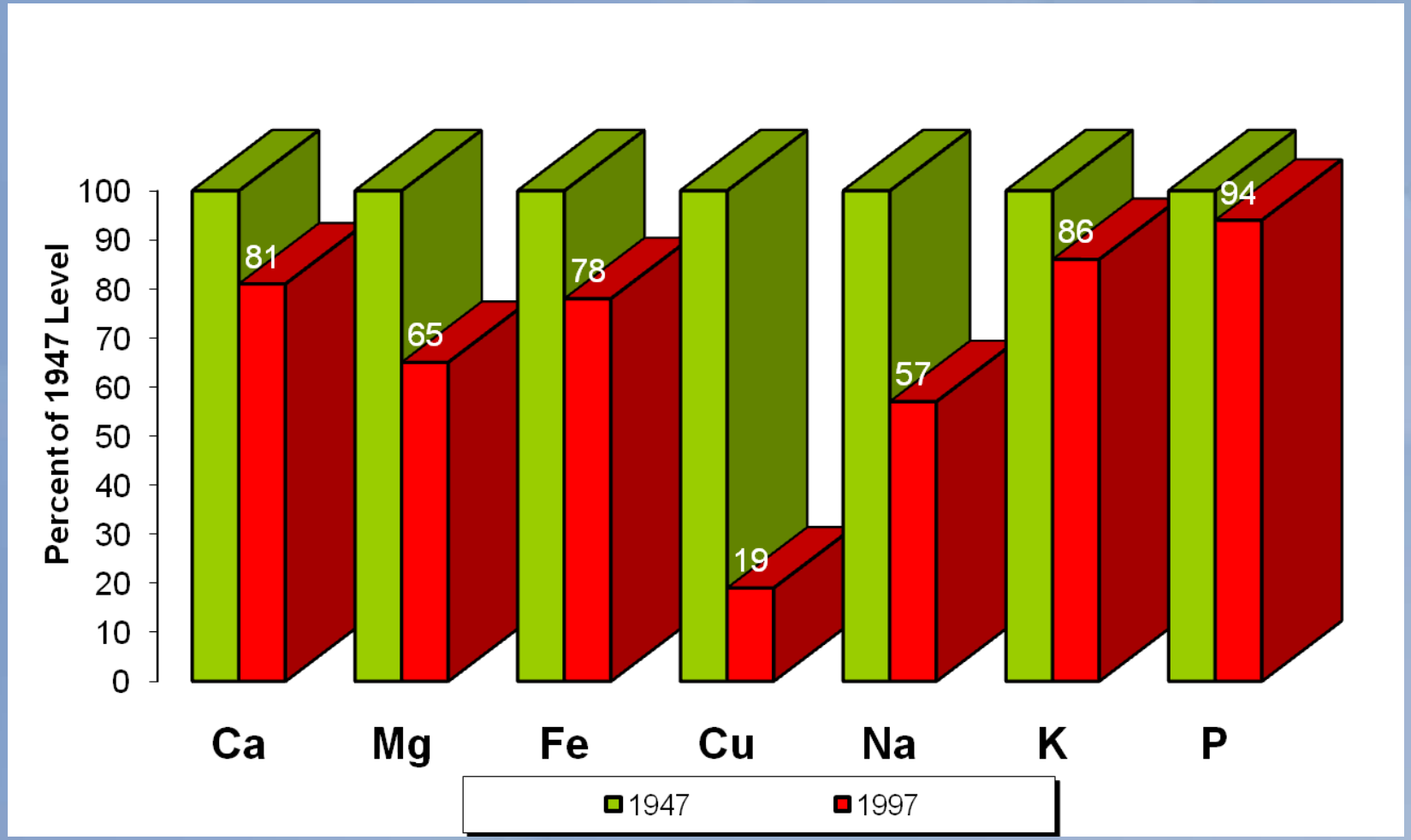


Image credits: GHS hazard pictograms, VectorStock, unsplash.com

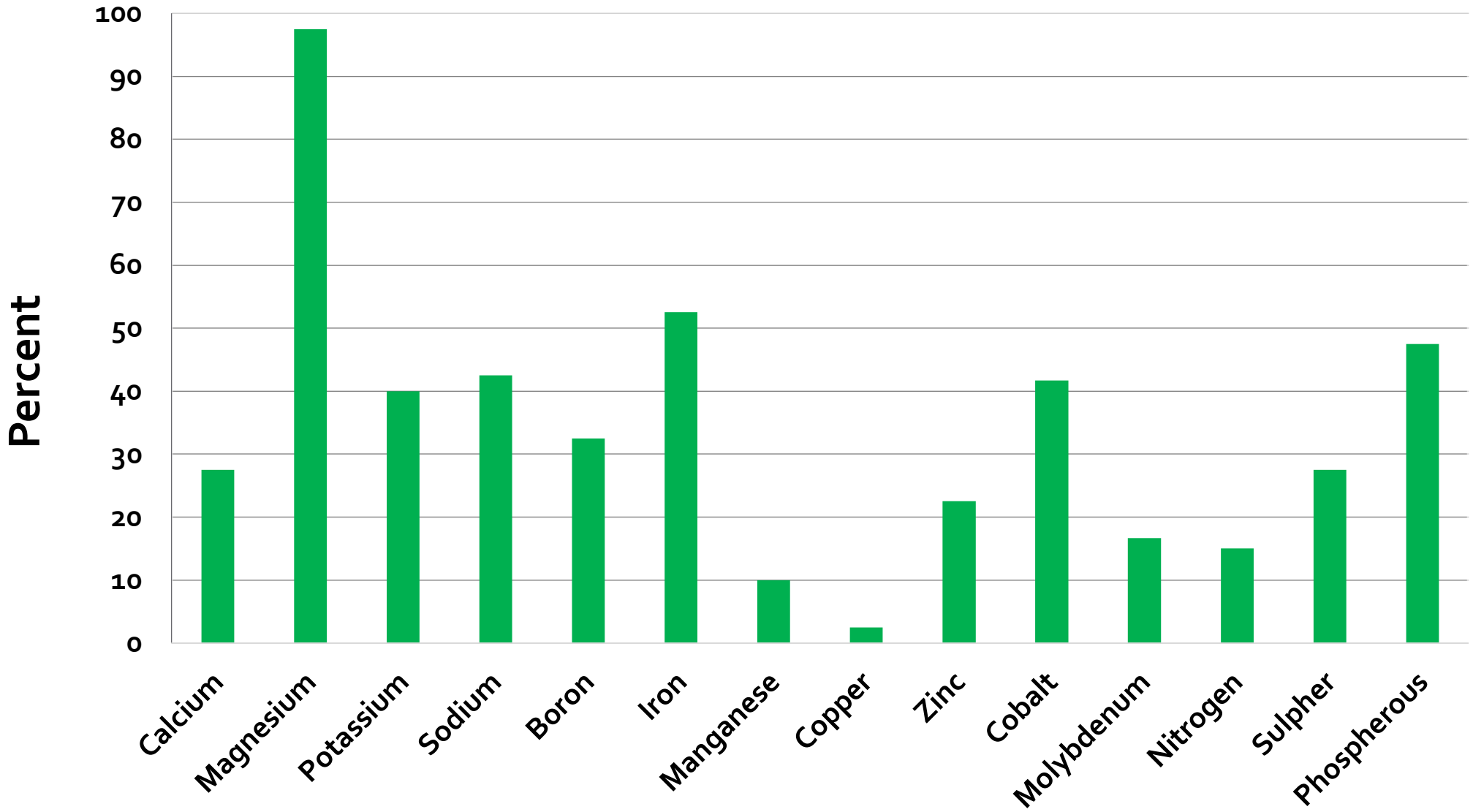
All of these factors could result in fewer nutrients available for brain health

Decrease in Mineral Content In Vegetables Over a 50 Year Period in the U.K.



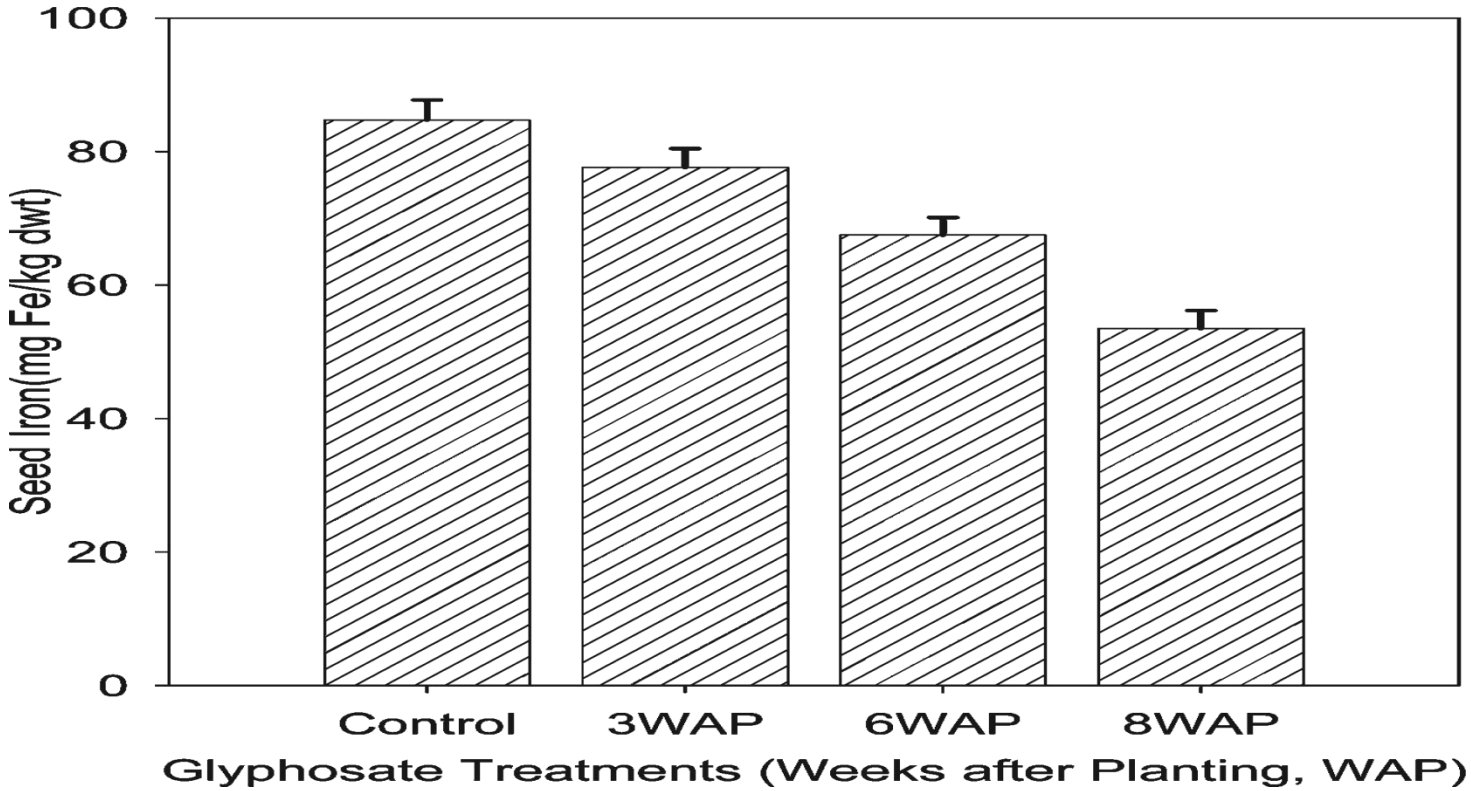
Mayer AB. Historical changes in the mineral content of fruits and vegetables. British Journal of Food 1997;**99:207-11.**

Percentage of 40 fields in which the nutrient was <u>above</u> the lowest level of the ideal range



Rucklidge JJ, Kaplan BJ. *The Better Brain. London, UK: Penguin Random House, 2021.*

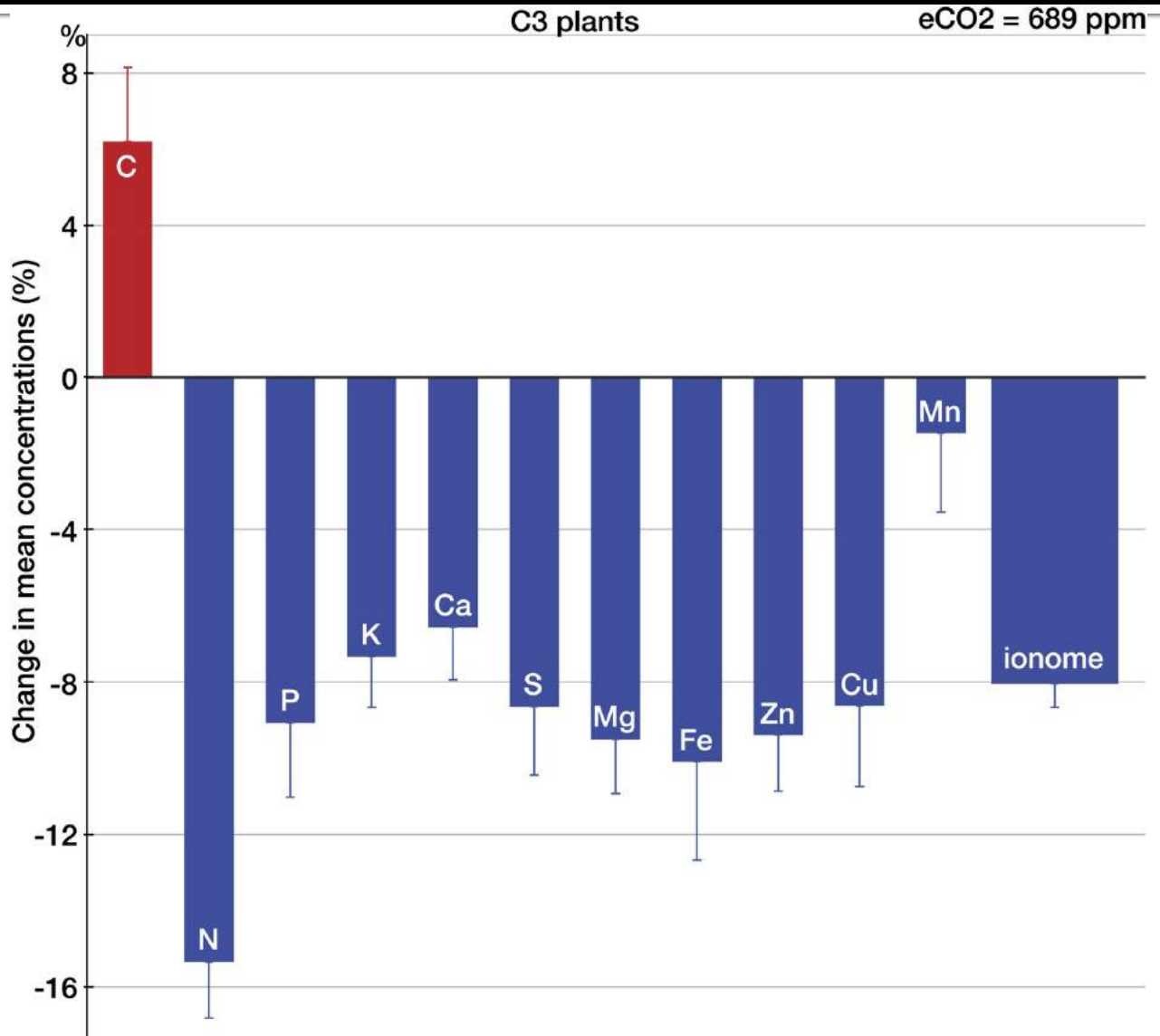
Effects of Gly treatment on soybean seed iron concentrations (mg of Fe/kg of dwt). The control did not receive any Gly treatment.

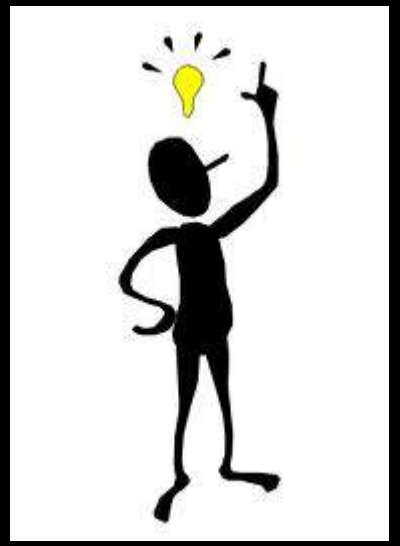


Bellaloui N, Reddy KN, Zablotowicz RM, et al. Effects of glyphosate application on seed iron and root ferric (III) reductase in soybean cultivars. J Agric Food Chem 2009;**57(20):9569-74.**

Does rising CO_2 levels affect nutrient content?

Loladze I. Hidden shift of the ionome of plants exposed to elevated CO(2) depletes minerals at the base of human nutrition. eLife 2014;**3:e02245.**

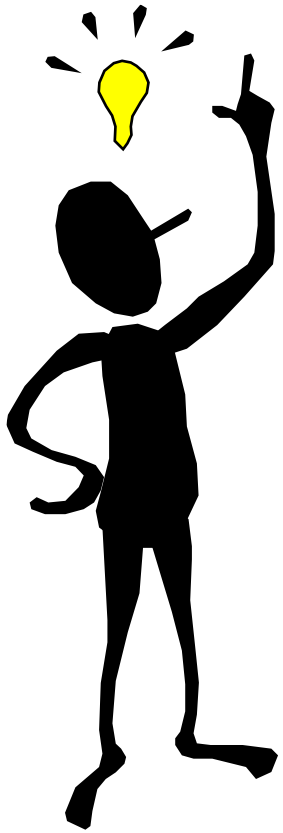




And what about individual variability and genetic mutations? Could some forms of mental illness reflect metabolic reactions going wrong?

AKA Inborn errors of metabolism

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



- Perhaps people inherit a *genetic polymorphism* 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 BN, Elson-Schwab I, Silver E. High-dose vitamin therapy stimulates variant enzymes with decreased coenzyme binding affinity (increased Km): relevance to genetic disease and polymorphisms. Am J Clin Nutr 2002;75:616-58; Kaplan BJ, Crawford SG, Field CJ, et al. Vitamins, minerals, and mood. Psychol Bull 2007;133(5):747-60.

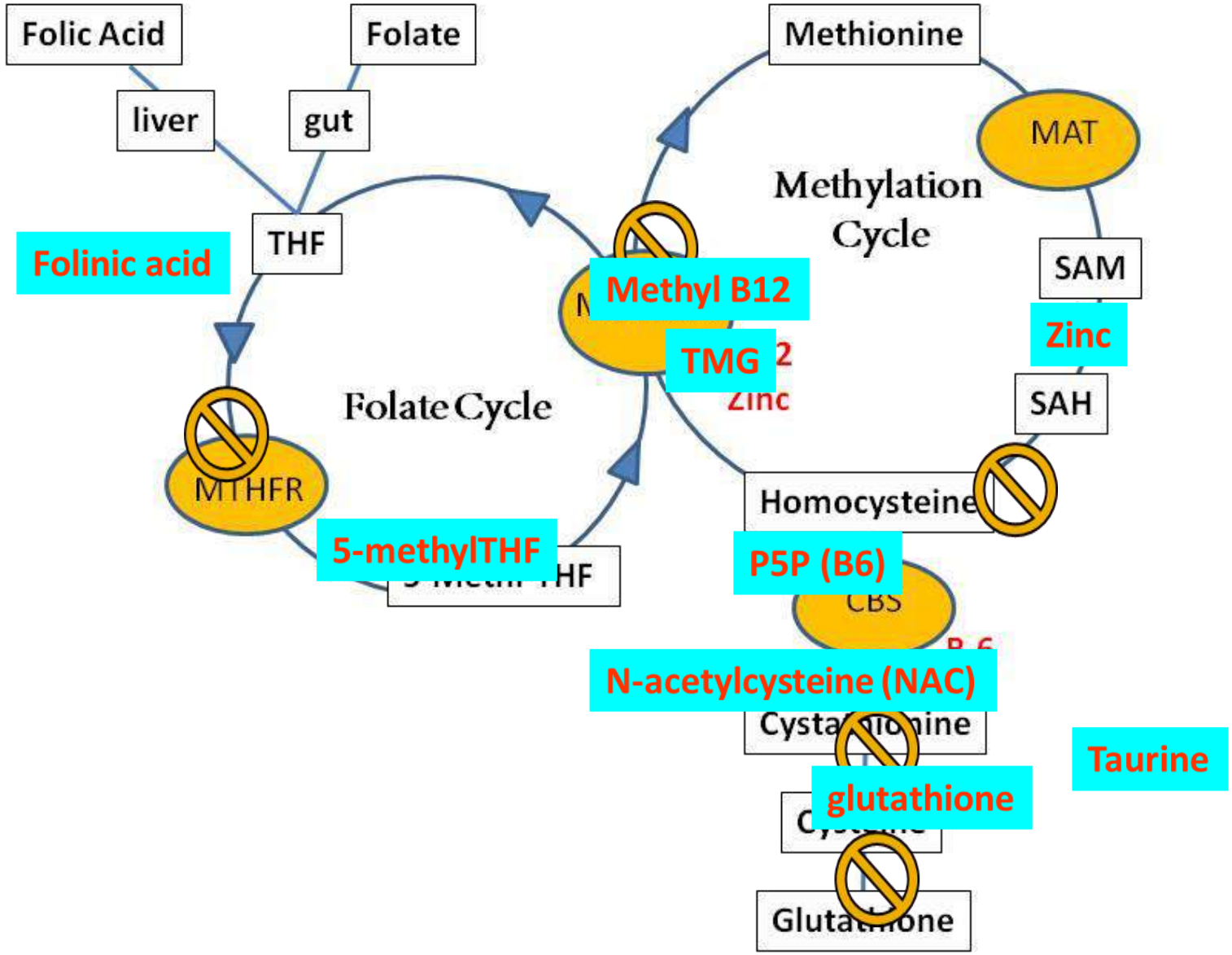
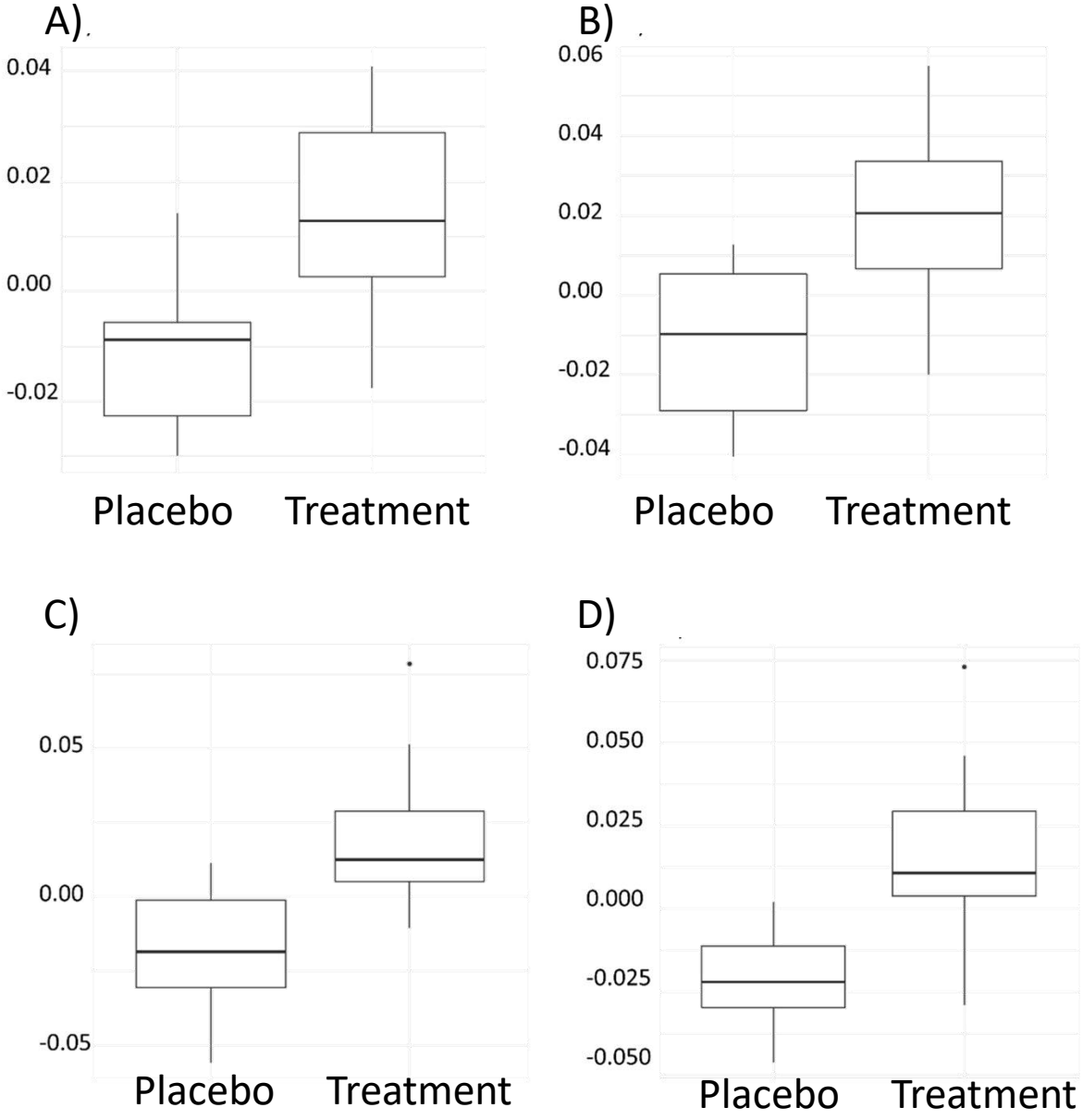


Image thanks to Natural Healing House

Methyl group can either activate or repress genes

Source: www.publicdomainpictures.net



Magnitude of methylation changes at most significant sites

<u>General trend</u> towards *increased* methylation with nutrients

84% of top changes demonstrated increase in methylation

Stevens AJ, Rucklidge JJ, Darling KA, et al. Methylomic changes in response to micronutrient supplementation and MTHFR genotype. Epigenomics 2018;**10(9):1201-14.**

The microbiome: its health affects mental health

Image credit: thinkstockphotos.com

Dysbiosis

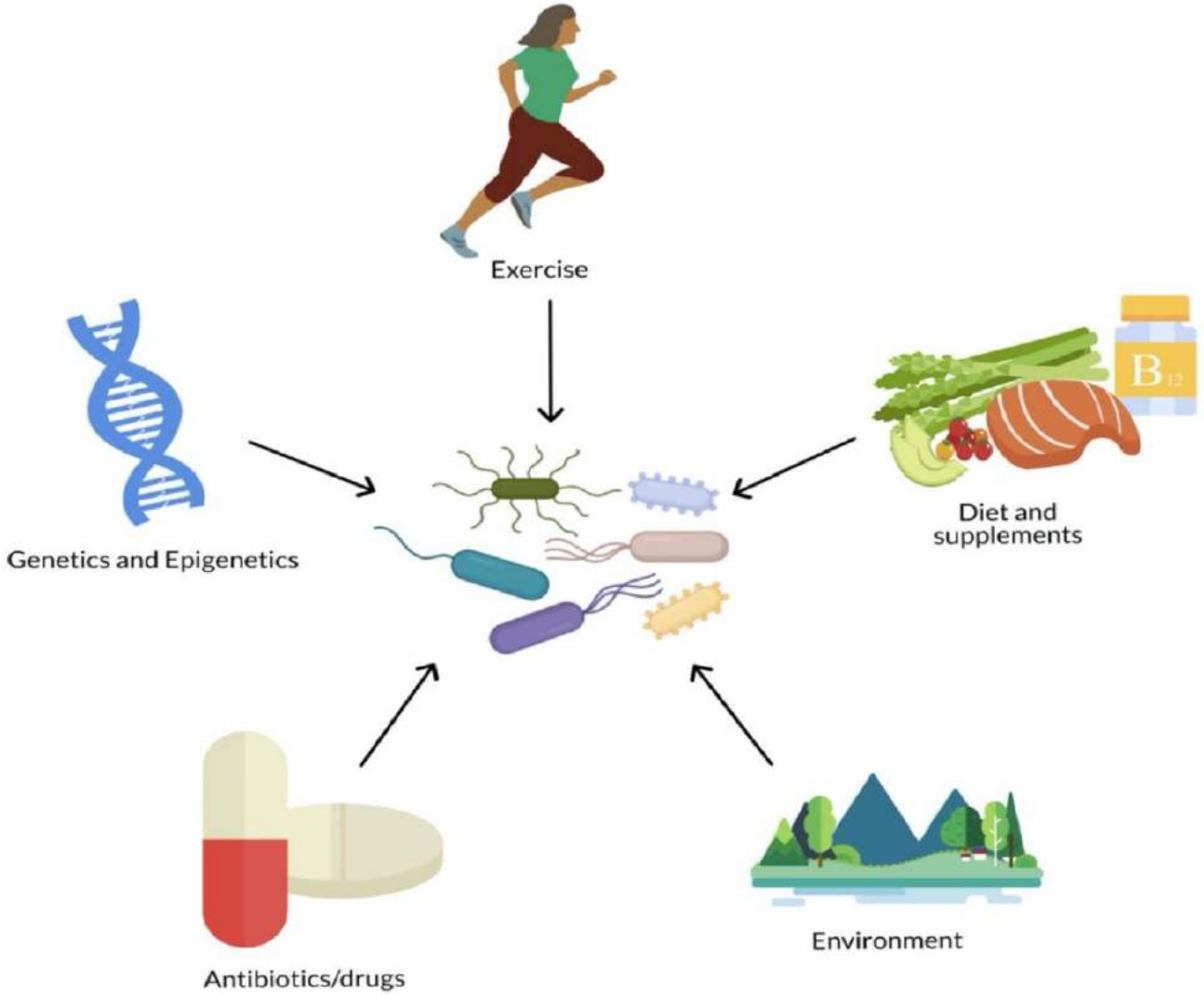


Image: Hughes RL. A Review of the Role of the Gut Microbiome in Personalized Sports Nutrition. Frontiers in Nutrition 2020;**6.**

Effects of Dysbiosis

- *Decreased nutrient synthesis*
- Altered production/ synthesis of neurotransmitters
- Chronic infections
- Increased permeability of the gut wall
- Increased production of endotoxins
- Increased inflammatory/immune activation
- Diversity of diet affects diversity of bugs

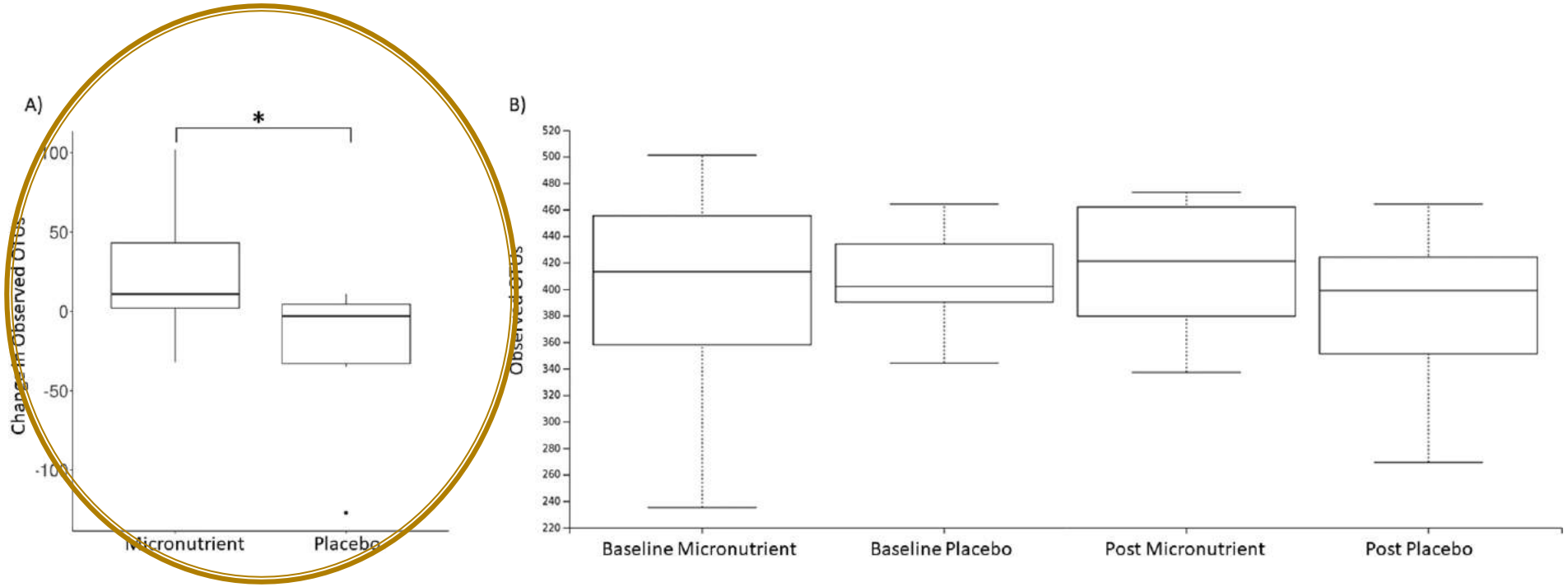
The microbiome subsample

- **17** children with ADHD (7-12): **7** placebo, **10** micronutrients, 10 week trial
- Investigated effects of micronutrient administration on faecal microbiome content using 16S rRNA gene sequencing
- Fresh stool samples collected at baseline and post treatment using OmnigeneGut faecal collection system

Stevens AJ, Purcell RV, Darling KA, et al. Human gut microbiome changes during a 10 week Randomised Control Trial for micronutrient supplementation in children with attention deficit hyperactivity disorder. Sci Rep 2019;**9(1):10128.**

Comparisons of community richness in ADHD children

Stevens et al., 2019, *Scientific Reports*



Community richness post-RCT higher for micronutrient group (n=10) than placebo (n=7)
OTU=Operational Taxonomic Unit

Changes in bacteria based on exposure to nutrients: Summary Stevens et al., *2019, Scientific Reports*

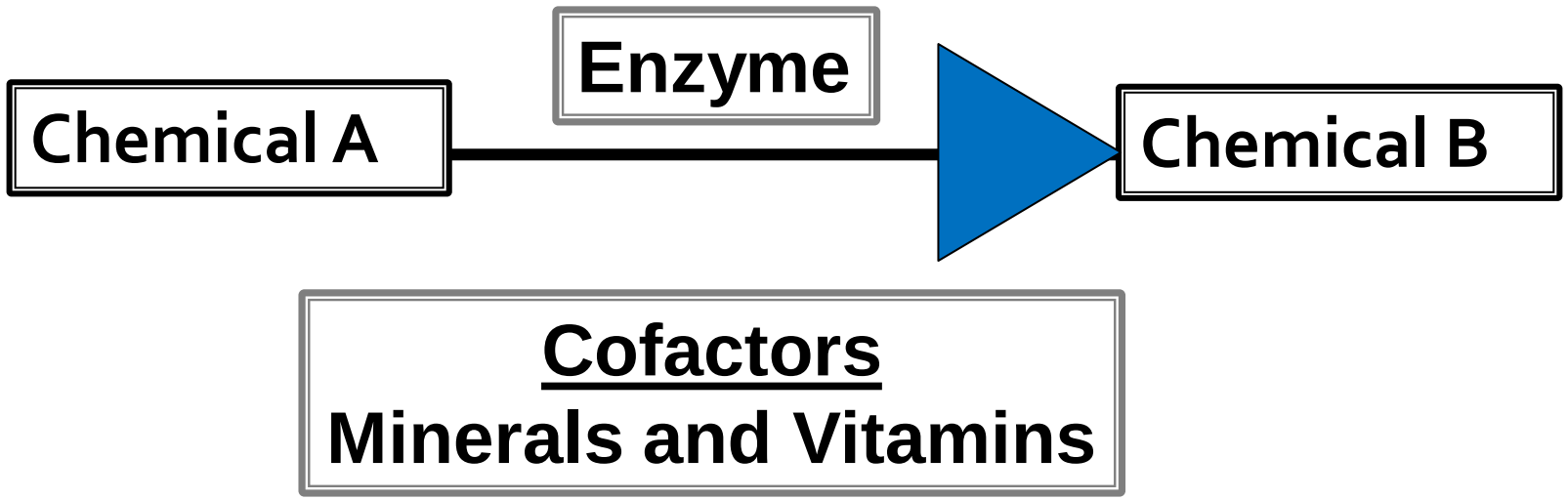
- Micronutrient treatment did *not* drive large scale changes in composition or structure of microbiome
- Observed taxonomic units (OTU), measure of community richness, significantly increased in treatment group but not in placebo group
  - Suggests micronutrient treatment may support a more diverse microbiome?

Should we then consider supplementing with micronutrients in *some* cases (vitamins and minerals) for some and if so…

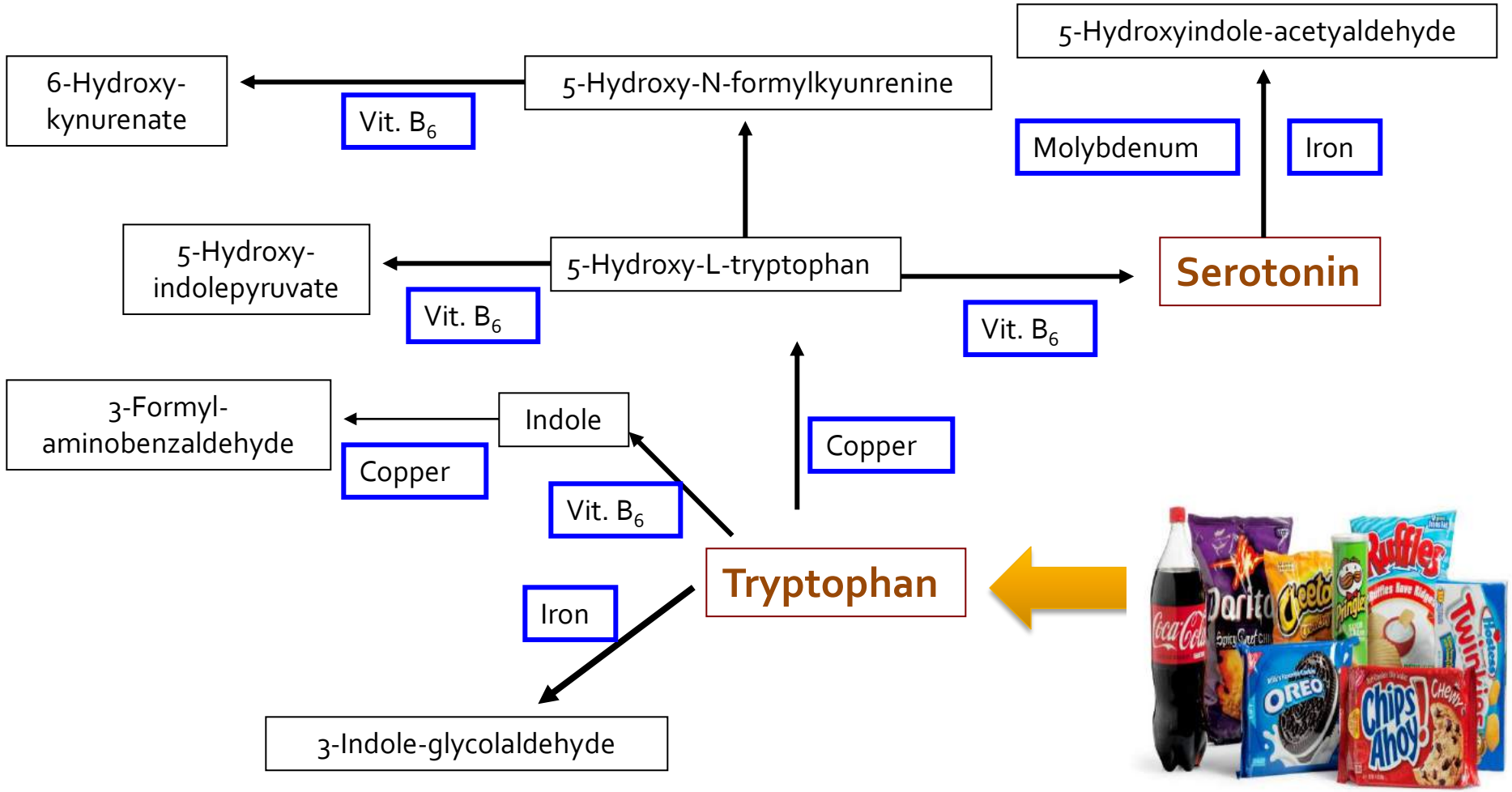
Single or multiple?

BRAIN METABOLISM.....

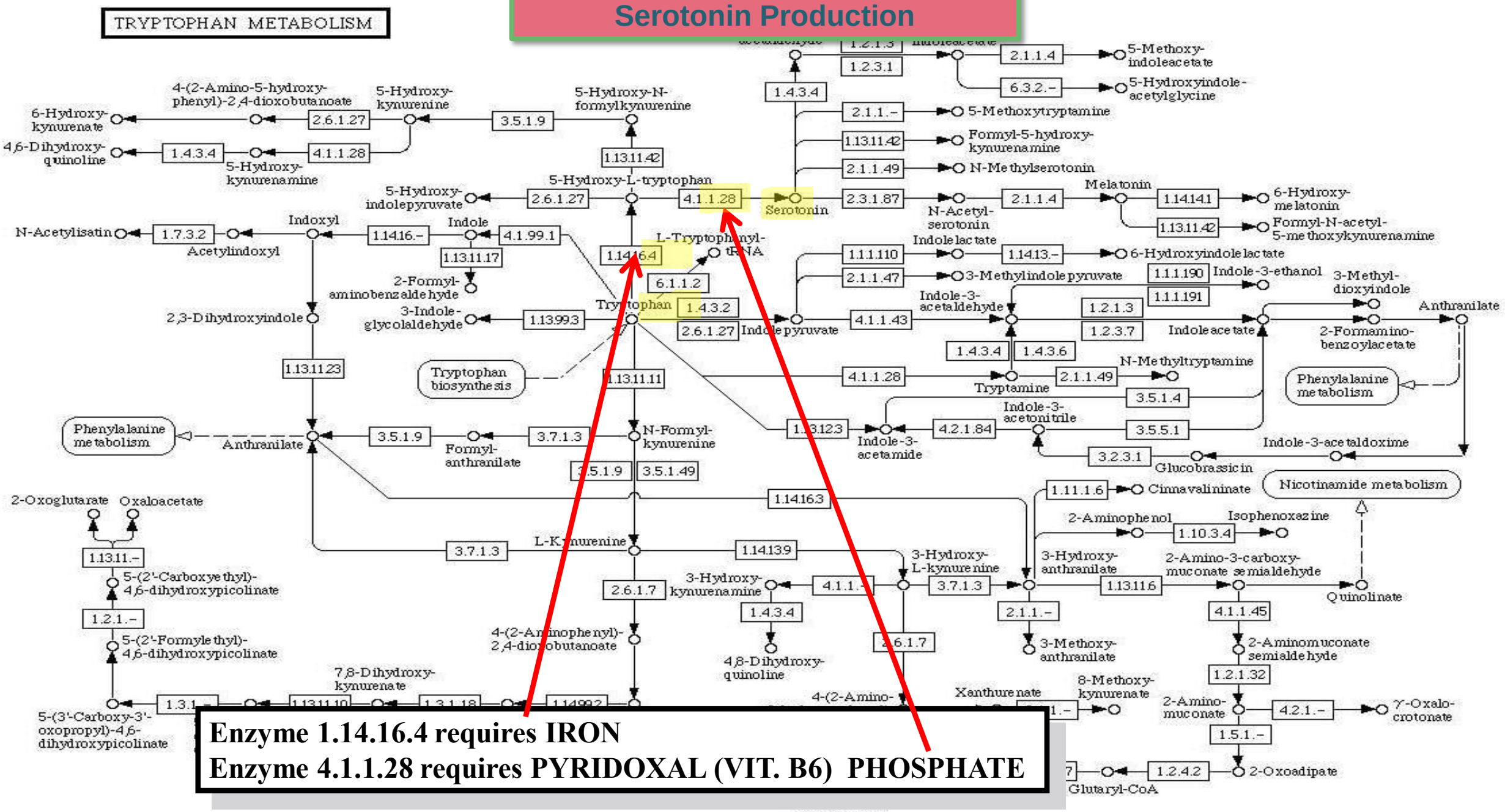
the transformation of one compound to another



One small portion of serotonin pathway



Serotonin Production



Enzyme 1.14.16.4 requires IRON
Enzyme 4.1.1.28 requires PYRIDOXAL (VIT. B6) PHOSPHATE

What does our body do to combat inflammation, oxidative stress?

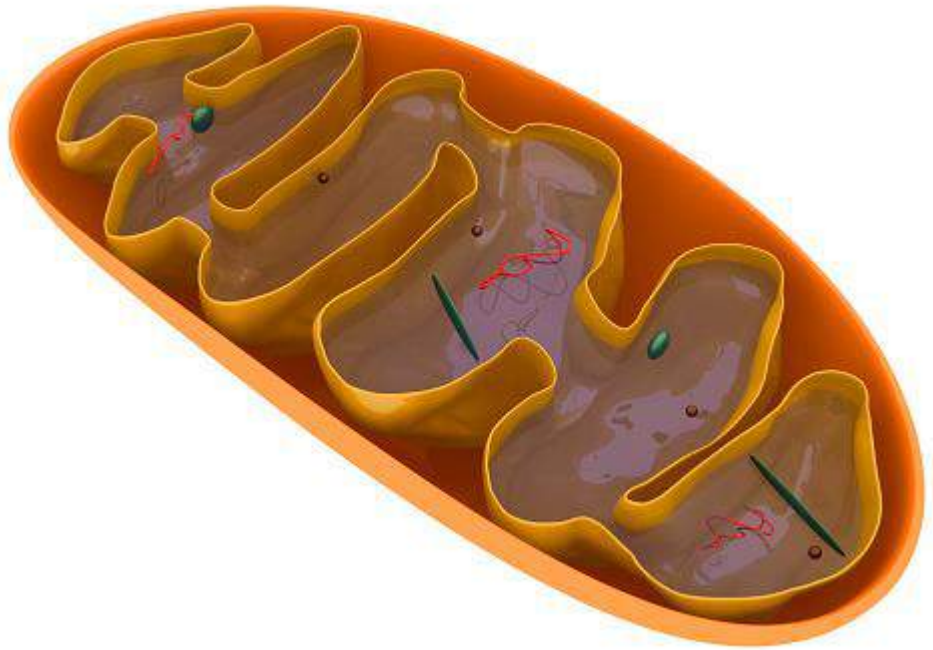


Image credit: unsplash.com

Mitochondria: What do they *do?*

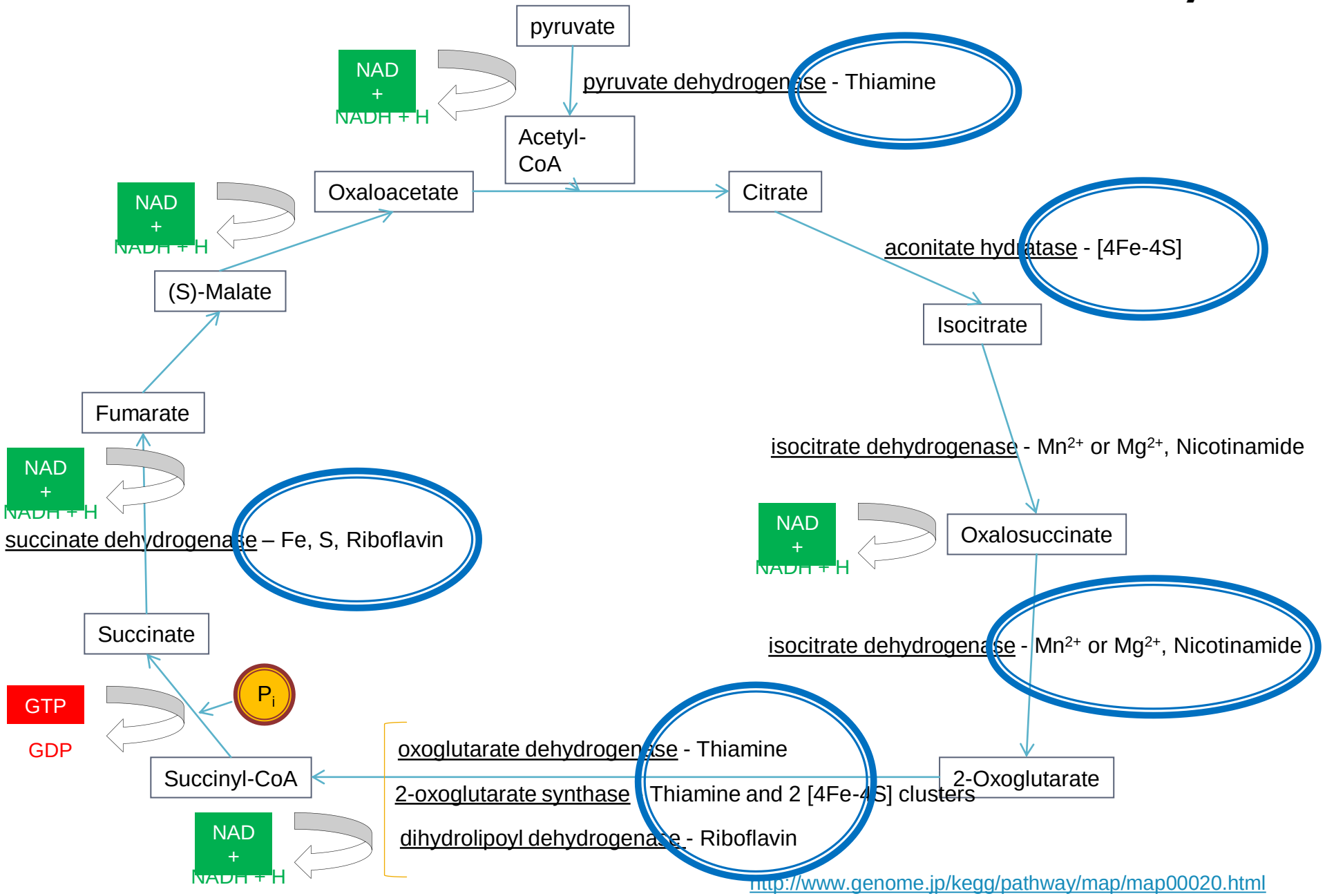
- **The ‘powerhouse’ of every cell, for their ability to form energy in the form of adenosine triphosphate (ATP)**

ALL mitochondrial function is

dependent on nutrients…. Possibly

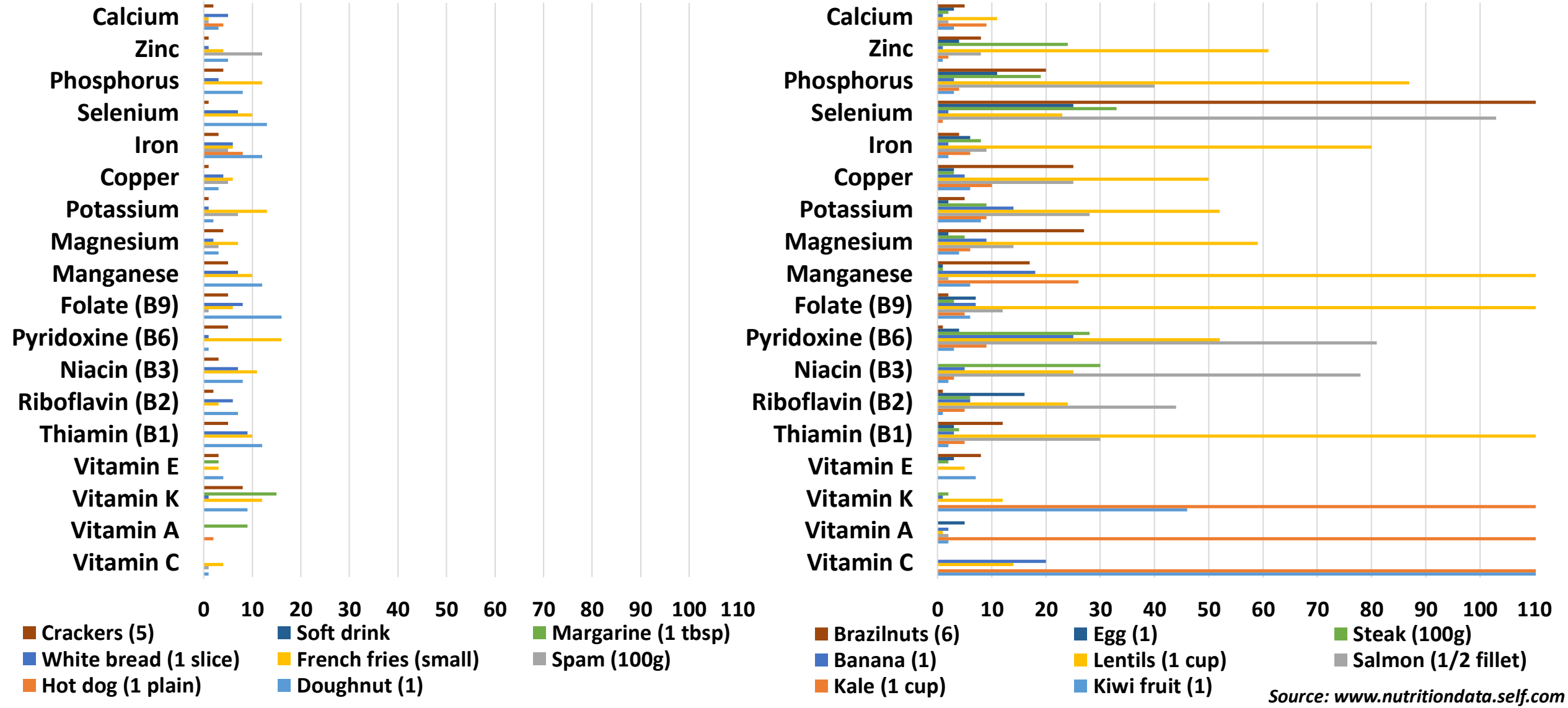
ALL nutrients

Krebs (TCA/Citric Acid) Cycle



http://www.genome.jp/kegg/pathway/map/map00020.html

Percentage of RDA of micronutrients across ultra-processed foods and whole foods



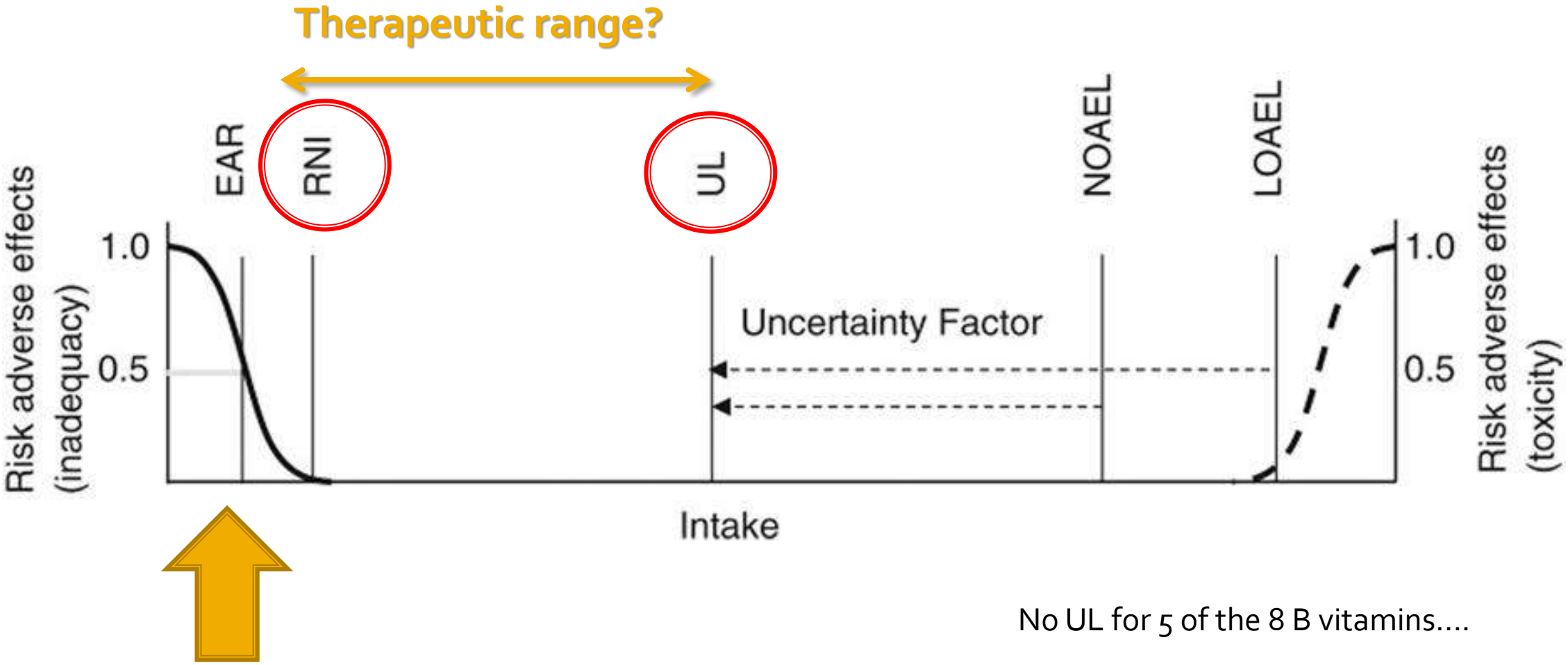
Source: www.nutritiondata.self.com

Perhaps multi-ingredients makes more sense?

What is in a broad-spectrum micronutrient formula?

- Vitamins like A, C, D, E, B_1-B_{12}
- Minerals like Calcium, Iron, Phosphorous, Iodine, Magnesium, Chromium, Molybdenum, Potassium, Zinc, Selenium, Copper, Manganese
- Amino acids like dl-Phenylalanine, alpha-lipoic acid, acetyl-L-carnitine, L-methionine, N-acetyl-cysteine, Glutamine
- *Often at doses higher than RDA but lower than UL*

How much?



No UL for 5 of the 8 B vitamins....

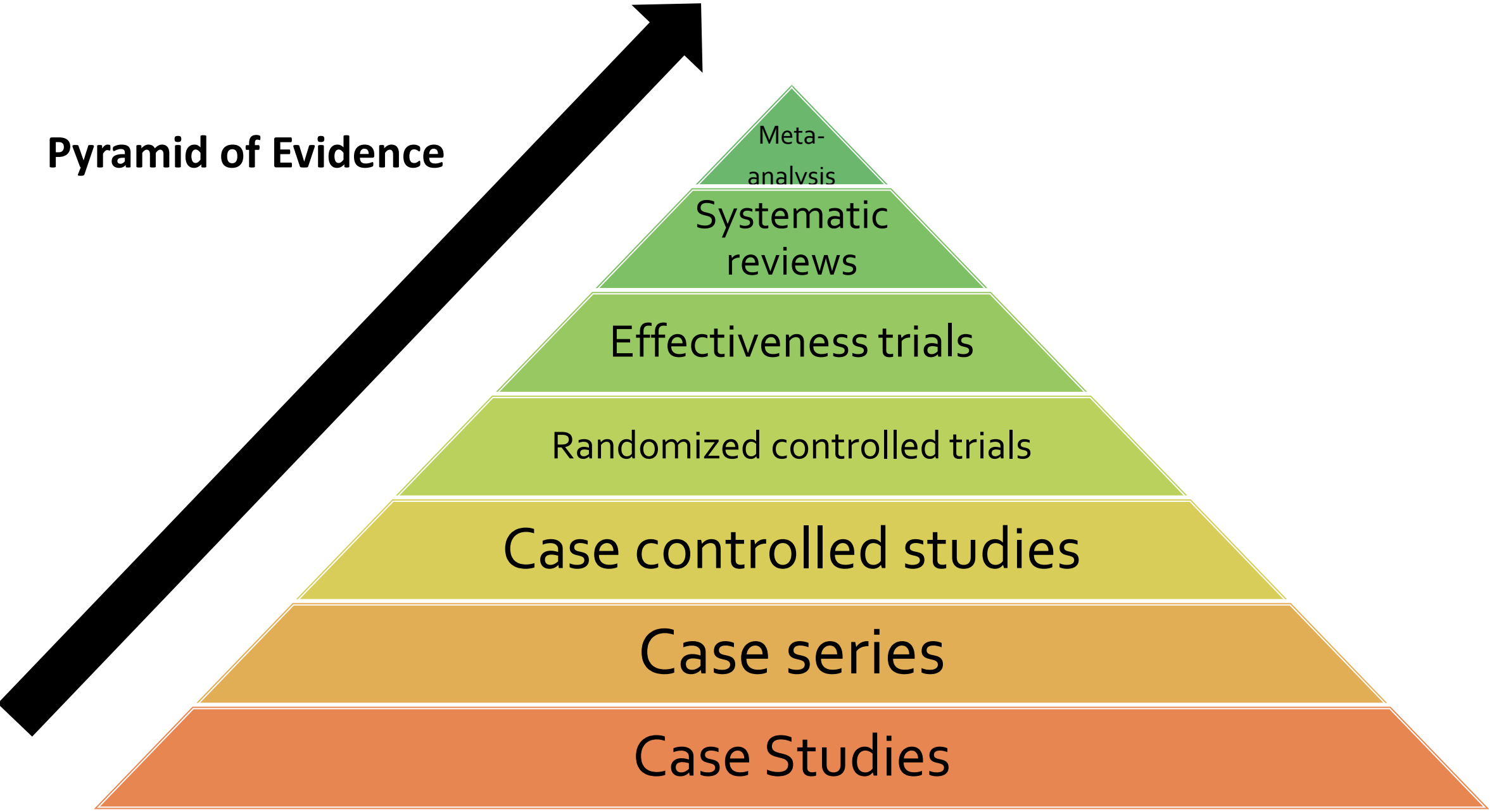
Centrum ~ 25% RDA

Pike V, Zlotkin S. Excess micronutrient intake: defining toxic effects and upper limits in vulnerable populations. Ann N Y Acad Sci 2019;**1446(1):21-43.**

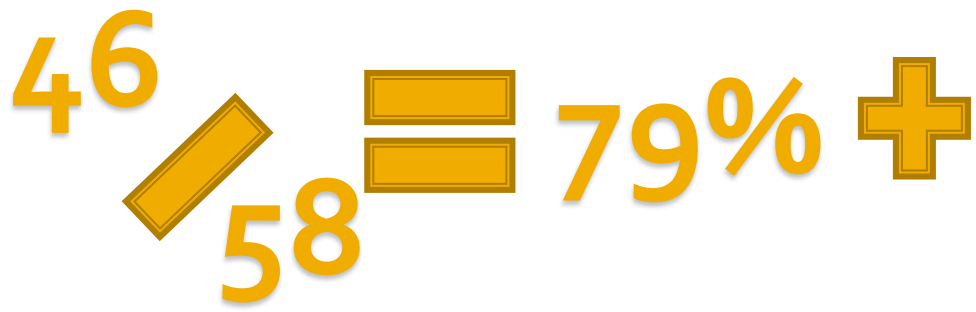
What's the evidence for broad spectrum micronutrients?

Image credit: iStock Getty Images

Pyramid of Evidence



Broad spectrum multinutrient placebo-controlled RCTs directed at improving psychological/psychiatric symptoms



- **Studies on <u>aggression</u> (6+RCTs, 1-RCT)**
- **Studies on <u>autism</u> (2+RCTs)**
- **Studies on <u>addiction</u> (2+RCTs)**
- **Studies on <u>mood/PMS</u> (19+RCTs, 7-RCTs)**
- **Studies on <u>stress</u> (many B Complex; 8+RCTs, 2-RCT)**
- **Studies on <u>attention/hyperactivity/cognition</u> (9+RCTs, 2-RCTs)**
- **COMMON THEME: emotion regulation, lowering irritability, managing anger**
- **Some *clinical*, some *nonclinical* populations**

See Rucklidge JJ, Kaplan BJ. Broad-spectrum micronutrient formulas for the treatment of psychiatric symptoms: a systematic review. Expert Rev Neurother 2013;13(1):49-73; Blampied M, Bell C, Gilbert C, et al. Broad spectrum micronutrient formulas for the treatment of symptoms of depression, stress, and/or anxiety: a systematic review. Expert Rev Neurother 2020;20(4):351-71. **Email me for a full list of RCT studies: julia.rucklidge@canterbury.ac.nz**

Nutrients 2020;12(11).

The Treatment we have been researching

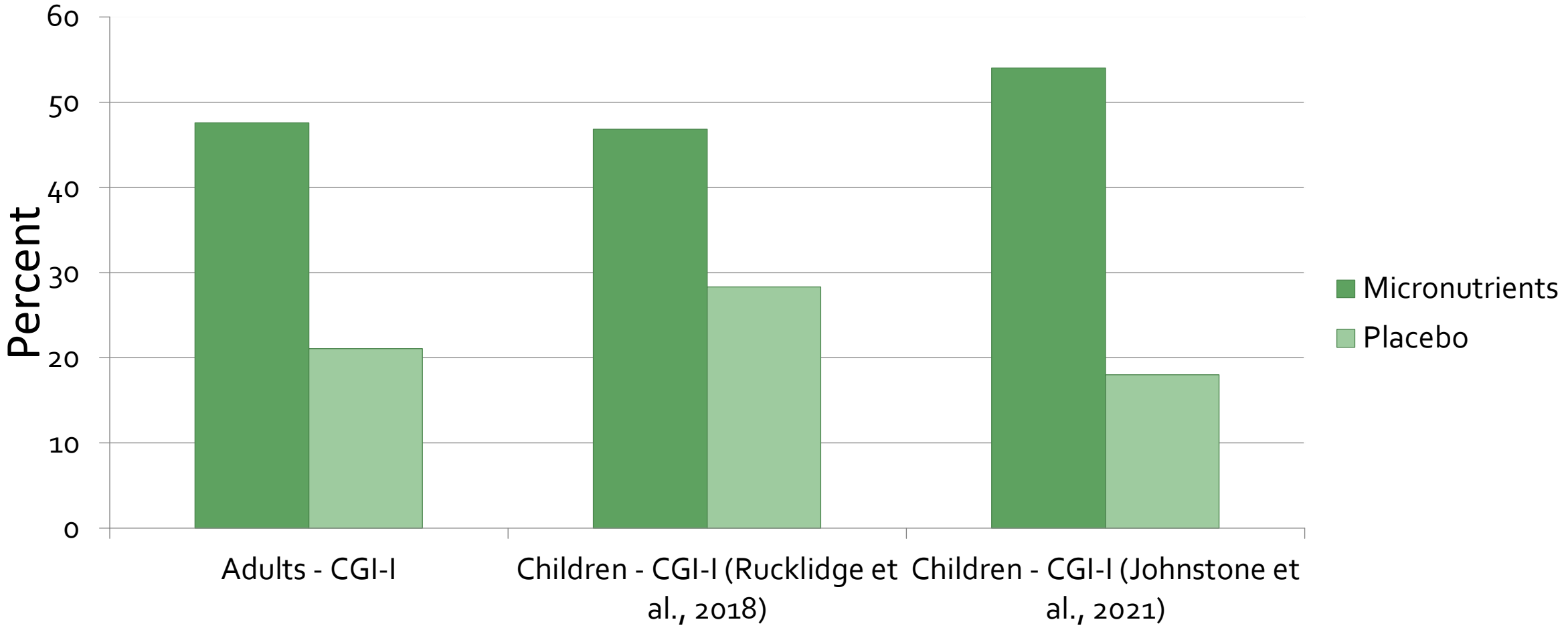
In divided doses, participants took:

- 1 capsule, 3x day for 3 days
- 2 capsules, 3x day for 3 days
- 3 capsules, 3x day for 3 days
- up to 12 capsules/day

http://research4kids.ucalgary.ca/pillswallowing
for a training video

ADHD: Responders across 3 RCTs

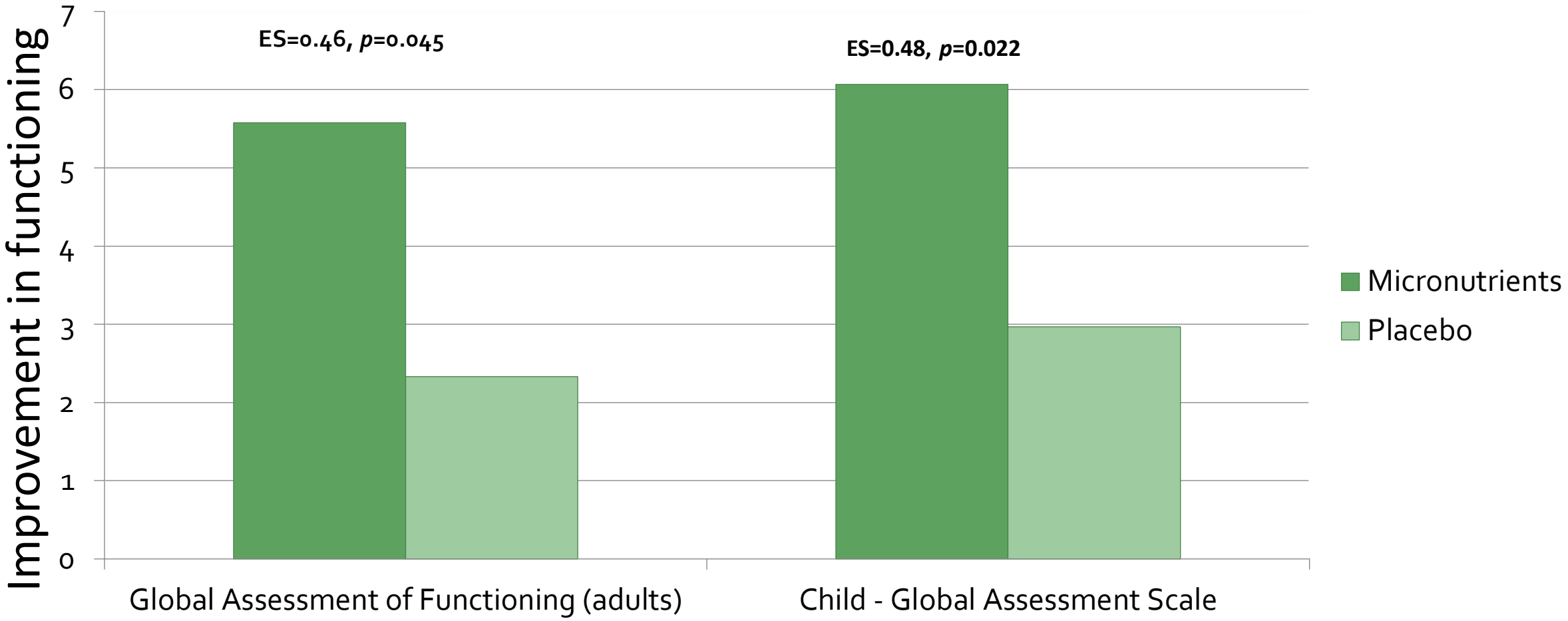
Rucklidge et al., 2014, *BJP* (n=80); Rucklidge et al., 2018, *JCPP* (n=93); Johnstone et al., 2021, *JAACAP* (n=126)



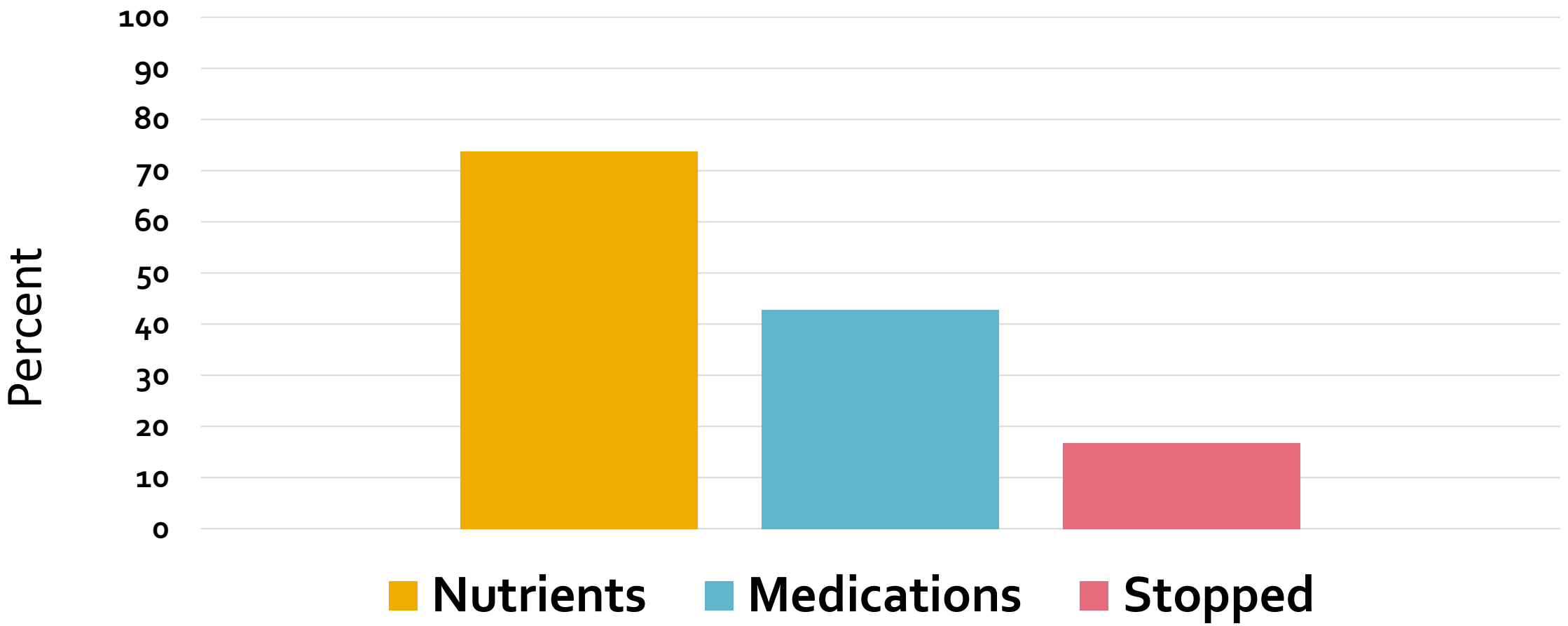
J Am Acad Child Adolesc Psychiatry 2021; J Child Psychol Psychiatry 2018;59(3):232-46; Br J Psychiatry 2014;204(4):306-15.

Functional impairment across 2 studies

Rucklidge et al., 2014, *BJP* (n=80); Rucklidge et al., 2018, *JCPP* (n=93)

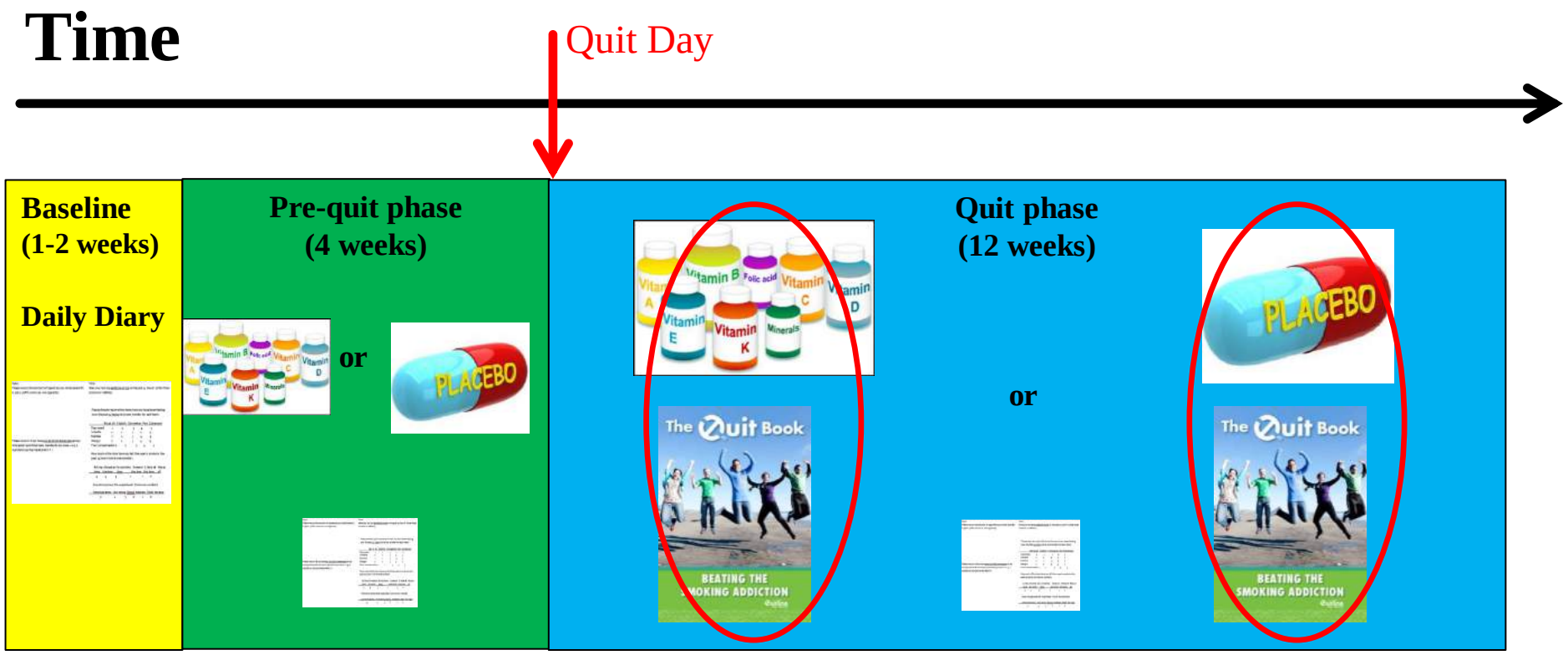


Long-term benefit of nutrients: % ADHD responders: 1 year follow up



Darling KA, Eggleston MJF, Retallick-Brown H, et al. Mineral-Vitamin Treatment Associated with Remission in Attention-Deficit/Hyperactivity Disorder Symptoms and Related Problems: 1-Year Naturalistic Outcomes of a 10-Week Randomized Placebo-Controlled Trial. J Child Adolesc Psychopharmacol 2019;29(9):688-704.

Smoking cessation

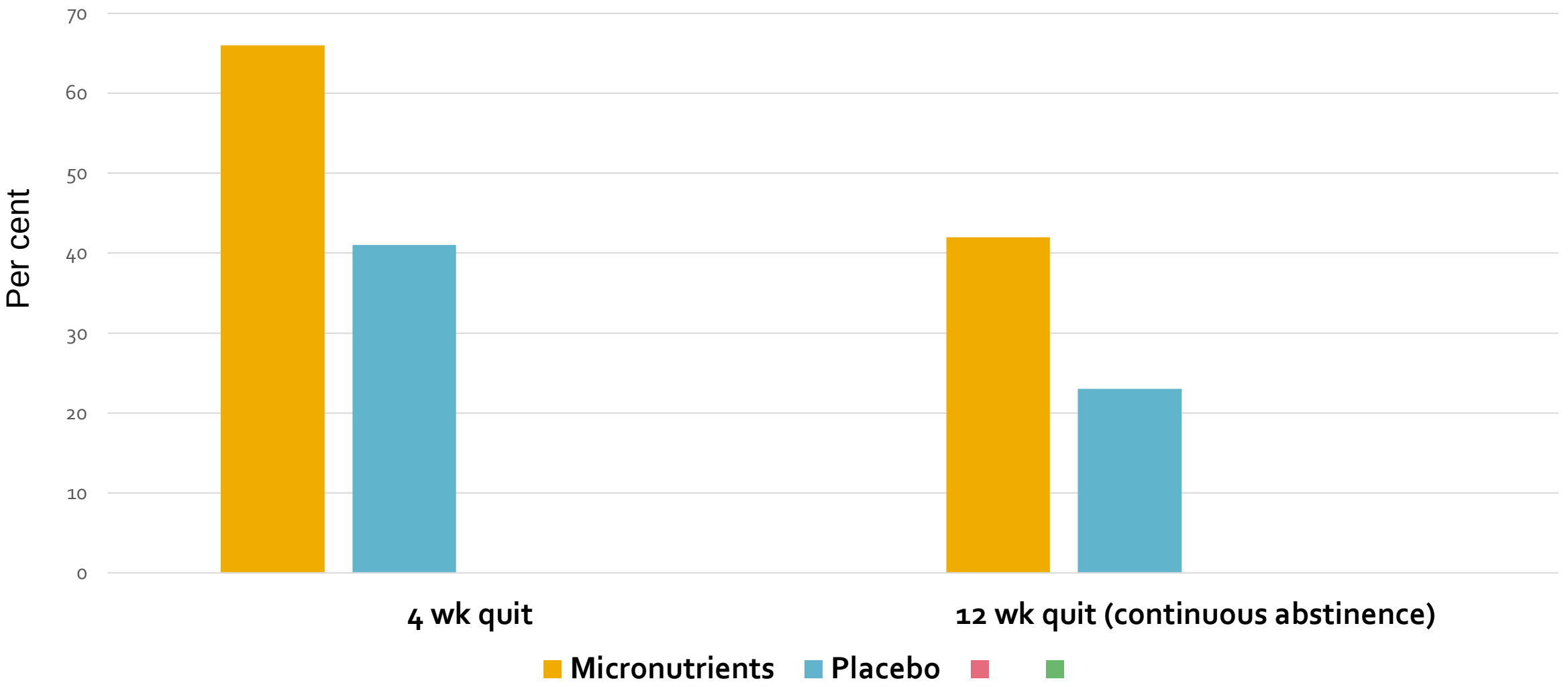


Reihana P, Blampied N, Rucklidge J. Novel Mineral–Vitamin Treatment for Reduction in Cigarette Smoking: A Fully Blinded Randomized Placebo-Controlled Trial. Nicotine & Tobacco Research 2018;21(11):1496-505.

Smoking cessation

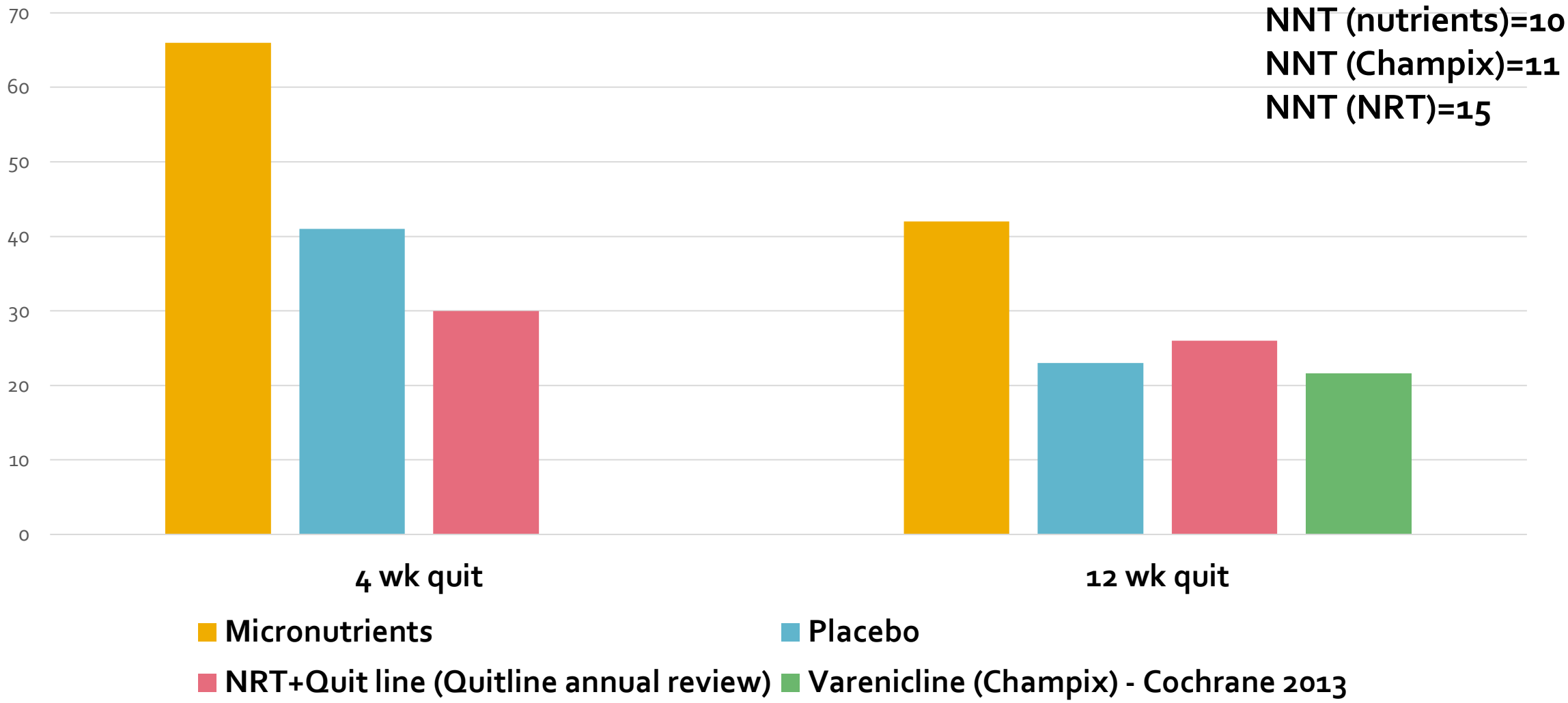
Reihana et al., 2018, *Nicotine and Tobacco Research*

Full intervention (pills + quitline): n=77



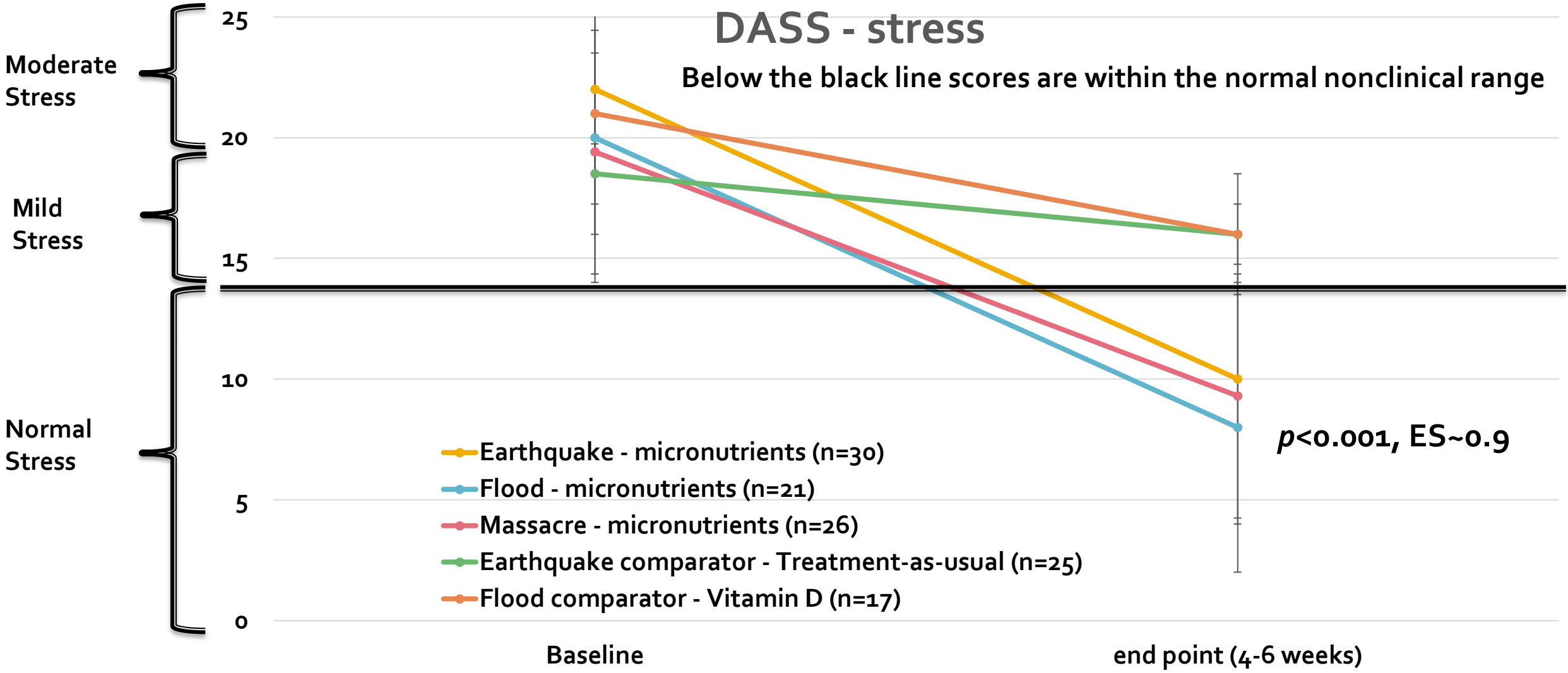
Smoking cessation

Reihana et al., 2018, Nicotine and Tobacco Research



Reduction in stress after earthquakes, flood, massacre with broad spectrum micronutrients

Rucklidge et al., 2012, 2014, 2021



International Perspectives in Psychology 2021;10(1):39-54.

How about side effects?

- No group differences in side effects across three RCTs
- No differences in chemistry and haematology safety screens
- Increase in prolactin in micronutrient group in adult ADHD trial but not outside reference range; not observed in child trials
- Blood pressure: no group differences
- Weight and height: growth velocity appears stronger on active

J Am Acad Child Adolesc Psychiatry 2021; J Child Psychol Psychiatry 2018;59(3):232-46; Br J Psychiatry 2014;204(4):306-15.

AE	Micronutr gp (n)	Med gp (n)	Group diff
Increased appetite	**1**	**32**	**<0.0001**
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
Drooling	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**
	33	**214**	

Mehl-Madrona L, Leung B, Kennedy C, et al. Micronutrients versus standard medication management in autism: a naturalistic case-control study. J Child Adolesc Psychopharmacol 2010;20(2):95-103.

Micronutrient "Side Effects"

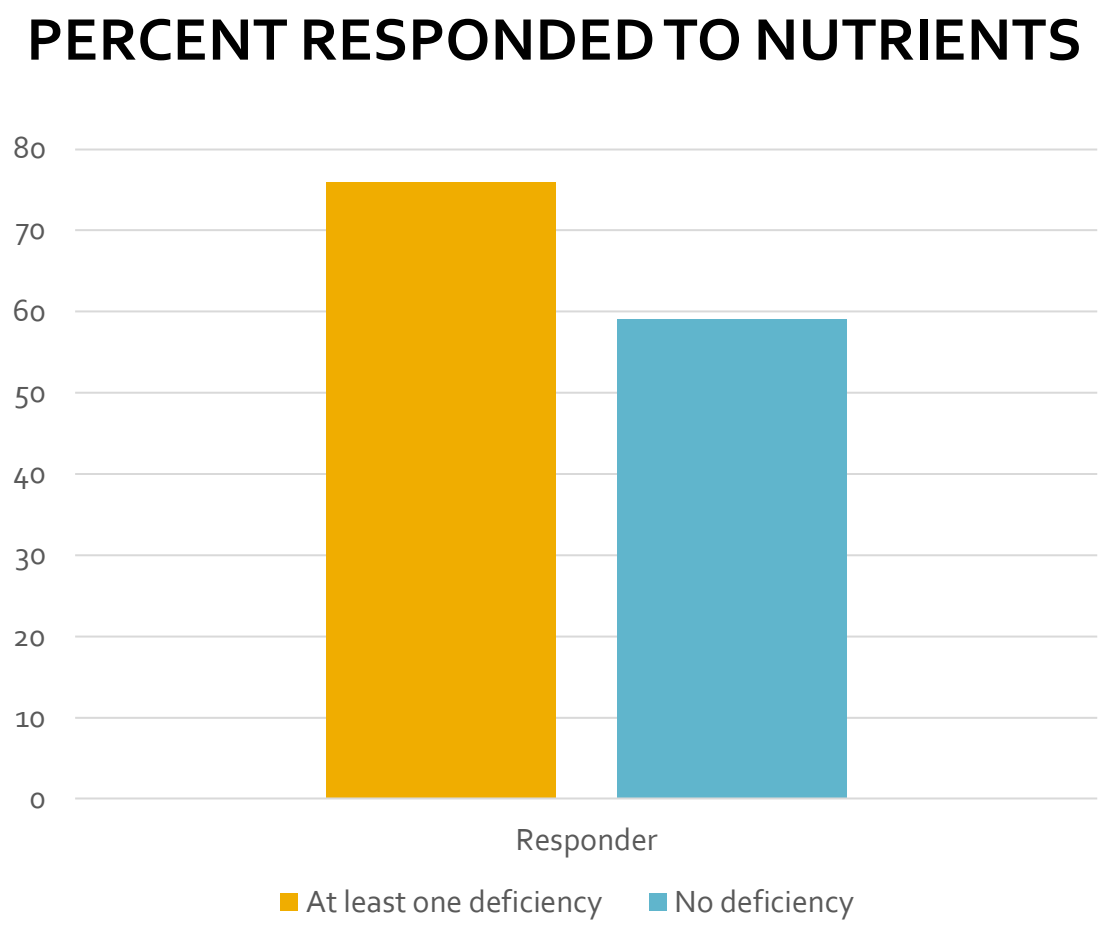
- ↓alcohol, cigarettes & cannabis use
- ↓ sickness
- ↑ ability to cope with stress
- ↑ energy; returning to work
- Between 50-80% of people respond to this intervention

Can we usefully use serum nutrient levels to predict who needs to take nutrients AND to track progress?

Consider those deficient at baseline…

- vit D, copper, zinc, iron, ferritin, potassium, sodium, folate
- 21/
  - C
  - ast
- 7
  - ident
  - end of OL
- BUT…59% of those with NO deficiencies also responders
  - $X^2 = 2.135$, ns

- By focusing on deficiency, ALL of these kids would miss the opportunity to benefit from treatment!



Prog Neuropsychopharmacol Biol Psychiatry 2019;89:181-92.

Nutrients poor predictors…

- Most participants had *normal* levels of nutrients at baseline and yet improved
- Perhaps…More apt to describe people with ADHD have *nutrient deficiency relative to their metabolic needs* rather than relative to general population
- (or could be reference ranges not sensitive to optimal functioning)

Does this matter? Do people use nutrient levels to guide on decisions?

- I think some do
  - Many companies use nutrient levels to design personalized protocol based on levels (and other things)
  - I get emailed on topic *all the time*
- BUT…we don't know if shot gun approach *less/more* effective than personalized
  - LOVE to research personalized vs shot gun

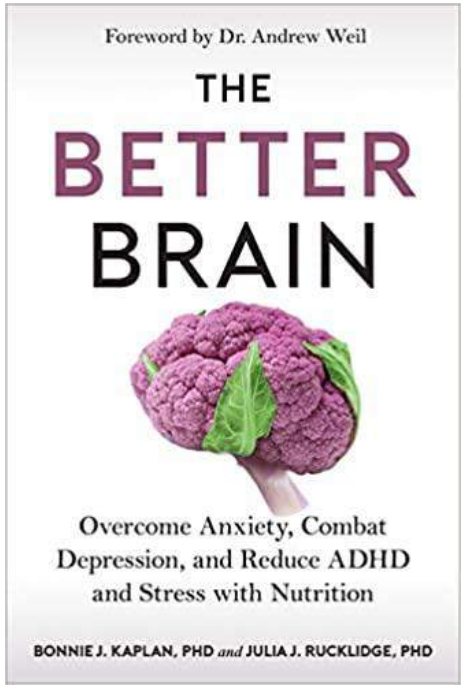
Test	Result	Target
CRP	4	<5
Homocysteine	8.6	0-15
Vit D	52	50-150
Folate	28	>7
EBV	IgM	Negative
	IgG	Positive
Copper serum	17.6	11-22
Zinc	12.1	9-19
Magnesium	2.41	1.4-2.25
Histamines WB	0.9	0.2-2
Pyrroles	61.3	<20
TSH	0.5	0.4-4
H Pylori	negative	
SAMe	158	86-145
SAH	35	10-22
SAMe/SAH	4.5	>4
Methionine	32.1	15-37
Adrenals morning	12.2	6-42
midday	11.4	2-11
afternoon	8.2	2-11
evening	4.2	0-5
total	36	11-76
DHEA morning	24.9	5-30
DHEA/Cortisol	2.04	0.2-0.6
Neurotransmitters urine		
Glycine	66	43-173
Serotonin	65.8	47.6-140.3
Gaba	219	167-463
Dopamine	146	103-282
Adrenaline	12.6	10-35.7
Glutamate	1311	1213-4246
DOPAC	0.76	0.65-1.53
HVA	0.34	0.0-6.8
VMA	2.3	1.09-4.7
5HIAA		2.4-13.5

Summary: take home messages

- Micronutrients exert *positive* effects on mental health problems
- Evidence nutrients may increase methylation but not specific to any gene
- *Possible* intriguing effects of nutrients on microbiome
  - Micronutrient treatment may support a more diverse microbiome?
- Pre-treatment nutrient levels **not great** predictors of clinical outcome – some *weak signals*, not replicated
  - Deficiency not a great predictor of outcome
  - Nutrients can increase serum levels over time – BUT, not always directly related to clinical outcomes

Two new resources

- BOOK! **The Better Brain**: Overcome Anxiety, Combat Depression, and Reduce ADHD and Stress with Nutrition
- www.thebetterbrainbook.com
- OUT now!



- MOOC!
- https://www.edx.org/course/mental-health-and-nutrition
- Free!
- ENROL NOW!

Want to keep up with the research?

bit.ly/UCNutritionresearch

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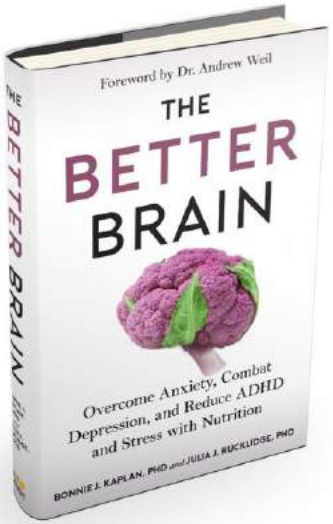

I am not here to sell products, just here to sell an idea…for information on all the research internationally, email: mentalhealthnutrition@canterbury.ac.nz

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