(My) Latest research on nutrition for mental health

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Australasian Integrative Medicine Association
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• No commercial interest in any company or sale of any product

and a Disclaimer

• There are many causes of mental disorders
What is new since 2018?

- Safety
- PMS
- Smoking cessation
- ADHD:
  - One year follow up
  - Methylation
  - Imaging
  - Microbiome
- Mosque shooting
Under what conditions might you need *more* nutrients than what you get out of food?
Vitamins like A, C, D, E, B₁-B₁₂
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
Therapeutic range?

How much?

- EAR
- RDA
- UL
- NOAEL
- LOAEL
- Risk of Inadequacy
- Risk of Adverse Effects
- Observed Level of Intake
- Low
- High
- Centrum ~ 25% RDA
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
Acute side effects/adverse effects? 
NONE (unless combined with meds)

Compliance? 
No difficulties with the regimen for those who stay on†

Impact on blood results? 
None to date…*

Long-term effects beyond a few years? 
Needs to be studied!

†one of most likely reasons to stop is number of pills & cost

*lack of difference in fasting glucose, lipids, white blood cell count, and neutrophils

Nutrients and Premenstrual Syndrome
Retallick-Brown et al., 2020, JACM

Percent in remission at 3 months

PMS (n=80)
PMDD (n=28)

Micronutrients  Vitamin B6
Smoking cessation
Reihana et al., 2018, Nicotine and Tobacco Research

Time

Baseline (1-2 weeks)

Pre-quit phase (4 weeks)

or

Quit phase (12 weeks)

Daily Diary

Quit Day
Smoking cessation

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

Full intervention (pills + quitline): n=77

- **4 wk quit**: Micronutrients 65% vs. Placebo 35%
- **12 wk quit (continuous abstinence)**: Micronutrients 40% vs. Placebo 20%
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*
Full intervention (pills + quitline): n=77

- NNT (nutrients) = 10
- NNT (Champix) = 11
- NNT (NRT) = 15

Per cent

<table>
<thead>
<tr>
<th></th>
<th>4 wk quit</th>
<th>12 wk quit (continuous abstinence)</th>
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<tbody>
<tr>
<td>Micronutrients</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>Placebo</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>NRT+Quit line</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>Varenicline (Champix) - Cochrane 2013</td>
<td>20</td>
<td>15</td>
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Smoking cessation
Reihana et al., 2018, *Nicotine and Tobacco Research*
Vitamin-mineral treatment improves aggression and emotional regulation in children with ADHD: a fully blinded, randomized, placebo-controlled trial

Julia J. Rucklidge, 1 Matthew J.F. Eggleston, 2 Jeanette M. Johnstone, 2 Kathryn Darling, 1 and Chris M. Frampton 1

1Department of Psychology, University of Canterbury, Christchurch; 2Canterbury District Health Board, Christchurch, New Zealand; 3Child and Adolescent Psychiatry, Oregon Health & Science University, Portland, OR, USA; 4Department of Psychological Medicine, University of Otago, Christchurch, New Zealand

Background: Evaluation of broad-spectrum micronutrient (vitamins and minerals) treatment for childhood ADHD has been limited to open-label studies that highlight beneficial effects across many aspects of psychological functioning.

Method: This is the first fully blinded randomized controlled trial of medication-free children (n = 93) with ADHD (7–13 years) assigned to either micronutrients (n = 47) or placebo (n = 46) in a 1:1 ratio, for 10 weeks. All children received standardized ADHD assessments. Data were collected from clinicians, parents, participants and teachers across a range of measures assessing ADHD symptoms, general functioning and impairment, mood, aggression and emotional regulation.

Results: Intent-to-treat analyses showed significant between-group differences favouring micronutrient treatment on the Clinical Global Impression–Improvement (ES = 0.46), with 47% of those on micronutrients identified as ‘much’ to ‘very much’ improved versus 28% on placebo. No group differences were identified on clinician, parent and teacher ratings of overall ADHD symptoms (ES ranged 0.03–0.17). However, according to clinicians, 33% of those on micronutrients versus 9% of those on placebo showed a clinically meaningful improvement on inattention (OR = 4.9, 95% CI: 1.5–16.3). Based on clinician, parent and teacher report, those on micronutrients showed greater improvements in emotional regulation, aggression and general functioning compared to placebo (ES ranged 0.35–0.66). There were two dropouts per group, no group differences in adverse events and no serious adverse events identified. Blinding was successful with guessing no better than chance.

Conclusions: Micronutrients improved overall functioning, reduced severity and improved emotion regulation and aggression, but not hyperactive/impulsive symptoms, in this sample of children with ADHD. Although direct benefit for core ADHD symptoms was modest, with mixed findings across raters, the low rate of adverse effects and the benefits reported across multiple areas of functioning indicate micronutrients may be a favourable option for some children, particularly those with both ADHD and emotional dysregulation. Trial registered with the Australian New Zealand Clinical Trials Registry ACTRN12613000896774. Keywords: ADHD; micronutrient; vitamin; mineral; Treatment; Mood; aggression.
Responders across 2 studies
Rucklidge et al., 2014, *BJP* (n=80); Rucklidge et al., 2018, *JCPP* (n=93)

- Adults - CGI-I
  - OR = 3.4; 95% CI 1.3-9.2

- Children - CGI-I
  - OR = 2.2; 95% CI 0.9-5.3

![Bar chart showing response rates for adults and children, with OR and 95% CI values provided.](chart.png)
90% (n=84) of original sample of 93 children with ADHD followed 52 weeks post-baseline

Outcome considered based on dominant therapy at 52 weeks
- trial micronutrients (n=19)
- medications (n=21)
- no treatment (n=35)
- Nine children not categorized due to inconsistent therapies
Parent-rated ADHD

Those who continued to take micronutrients were rated as doing:
1. As well or better than those who switched to medications:
   ADHD Total, $d = 0.4\text{-}0.7$
2. Better than those who stopped treatment:
   ADHD Total, $d = 1.2\text{-}0.9$. 

<table>
<thead>
<tr>
<th></th>
<th>Stayed on Micronutrients (n=19)</th>
<th>Switched to Medication (n=21)</th>
<th>Stopped Treatment (n=35)</th>
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</thead>
<tbody>
<tr>
<td>INATTENTION</td>
<td></td>
<td></td>
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<tr>
<td>HYPERACTIVITY/IMPULSIVITY</td>
<td></td>
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<tr>
<td>TOTAL ADHD SYMPTOMS</td>
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Anxiety and mood

**Parent-rated Anxiety**

- Stayed on Micronutrients (n=19)
- Switched to Medication (n=21)
- Stopped Treatment

**Child Depression Rating Scale**

- Stayed on Micronutrients (n=19)
- Switched to Medication (n=21)
- Stopped Treatment
Responder/remitter by dominant treatment at follow up

Responder = 30% ↓ in ADHD symptoms

Remitter = Dropped below T score 65
Resting-state networks in children with ADHD after micronutrient supplementation: results from a randomized, placebo-controlled trial

Nadia Borlase, Tracy R. Melzer, Matthew J. F. Eggleston

Published online: 01 Mar 2019

Human gut microbiome changes during a 10 week Randomised Control Trial for micronutrient supplementation in children with attention deficit hyperactivity disorder

Aaron J. Stevens, Rachel V. Purcell, Kathryn A. Darling, Matthew J. F. Eggleston, Martin A. Kennedy & Julia J. Ruckledge

Exposure times and dosage required largely unknown. Aim: This exploratory research represents the first human study using observational measures to investigate relationships between micronutrient supplementation and resting-state networks in children with ADHD.
Effect on genes?
Diet and DNA methylation

Micronutrients are important cofactors to DNA methylation

\[
\text{e.g.} \text{ SAM (s-adenosyl methionine) donates methyl groups to DNA}
\]
Will micronutrient supplementation influence DNA methylation?

Stevens et al., 2018, *Epigenomics*

**Diagram:**
- **Baseline DNA methylation levels measured**
- **Population is split into 2 groups by random lot**
- **Dietary Supplements**
- **Placebo**
- Outcomes for both groups are measured

(RCT layout)
Methods for measuring $\text{CH}_3$

Use an array based technology that detects methylation at 850,000 CpGs across the genome.

(There are 28 million CpG sites in the human genome)

Detecting DNA methylation is technically difficult and requires extensive Chemical modifications of the DNA.
Magnitude of methylation changes at most significant sites

A) Expressed in the brain, neural development

B) Not within a gene region

C) Not within a gene region

D) Broad expression in the brain required for development of the central nervous system

Stevens et al., 2018, *Epigenetics*
Results

• General trend towards increased methylation with nutrients

• 84% of top changes demonstrated increase in methylation; however, changes not significant after adjusting for multiple testing (850,000 tests)

• Magnitude of changes small and randomly distributed among unrelated genes
Effect on neural processing?
The study
Borlase et al., 2019, NNS

- Scanned 27 children before and after 10 week exposure to nutrients (n=13) or placebo (n=14)
- Changes in ratios of neurometabolites, volume and resting state networks between two time points compared between groups
Results

- No significant alterations between groups on any brain metrics
- In treatment group, trend for:
  - decreased choline in the striatum
  - decreased glutamate in the prefrontal cortex
  - increased grey matter in the anterior thalamus
  - increased white matter in the fornix
  - improved network integrity of default mode network, dorsal attention network and frontal executive network
- Results did not survive correction for multiple comparisons
  - suggesting while potential association between micronutrient treatment and neurological changes, requires larger sample size and replication
Effect on microbiome?
Compared faecal microbiome content, using 16S rDNA sequencing

17 children with ADHD (7-12): 7 placebo, 10 micronutrients, 10 week trial

we investigated effects of micronutrient administration on faecal microbiome content using 16S rRNA gene sequencing

Fresh stool samples collected at baseline and post treatment using OmniporeGut faecal collection system
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

- magnitude of change significantly larger than compared with placebo group, which showed no mean change
- Suggests micronutrient treatment may support a more diverse microbiome?
Comparisons of community richness

Community richness post-RCT higher for micronutrient group
Changes in bacteria based on exposure to nutrients: Summary Stevens et al., 2019, Scientific Reports

- significant greater decrease observed in abundance of genus *Bifidobacterium* from phylum *Actinobacteria* in active versus placebo
  - Don’t know significance of changes observed – research is contradictory although its importance keeps replicating

- Also observed significant positive correlation between *Actinobacterium* abundance and Clinician ADHD IV-RS rating scale
  - Replicates Aarts et al 2017
Mechanism of action?

- Evidence nutrients increase methylation but not specific to any gene – *weak signal*
- *MTHFR* status *not* related to outcome
- Some *subtle* and possible broad effects on resting-state networks and neurometabolites (especially glutamate) – *don’t survive correction*
- *Possible* intriguing effects of nutrients on microbiome as possible mechanism of action
  - Micronutrient treatment may support a more diverse microbiome?
Translation of research to practice

Christchurch Mosque shootings, March 15th 2019
We all stand together.

Kia Kaha Aotearoa
The people behind our work at *Te Puna Toiora*

**Current graduate students**
- Hayley Bradley
- Meredith Blampied
- Ben Warren
- Siobhan Campbell
- Taryn Hale
- Sophie Waretini
- Jess Heaton
- Nurina Katta

**Graduates of the lab**
- Dr Heather Gordon
- Dr Amy Romijn
- Dr Hahna Retallick-Brown
- Dr Pip Raihana
- Dr Kathryn Darling

**Collaborators**
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- Prof Ian Shaw
- Prof Neville Blampied
- Prof Chris Frampton
- Prof Martin Kennedy
- Prof Dermot Gately
- Prof Rob Hughes
- Prof Roger Mulder
- Dr Aaron Stevens
- Dr Jeni Johnstone
- Dr Anna Boggis
- Dr Matt Eggleston
- Dr David Ritchie
- Dr Katharine Shaw
- Dr Joe Boden

- Dr Tracy Melzer
- Dr Nadia Borlese

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- Truehope/Hardy Nutritionals for providing formula/placebo for trials
- Participants and families for carefully monitoring symptoms over time

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