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Correspondence

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Magic bullet thinking – why do we continue to perpetuate this fallacy?

We write in response to the editorial on dietary supplementation for the treatment of attention-deficit hyperactivity disorder (ADHD). Although Rajyaguru & Cooper adequately reviewed some of the literature,[1] they missed an opportunity to challenge current methodologies and they simultaneously perpetuated an outdated model of disease pathophysiology.

These authors promote the idea that one single nutrient can effect a consistent change in ADHD symptoms. However, such magic bullet thinking is at odds with human physiology (which requires the ingestion of many nutrients in balance) and largely explains why the single-nutrient strategy has yielded only modest benefits.[2] Supplementing with broad-spectrum formulations ensures the patient's safety as the combination prevents imbalances, such as one nutrient causing a deficiency in another (e.g. taking zinc alone may cause copper deficiency). Recommending that researchers first understand how one nutrient functions on its own, in isolation, ignores the inevitable changes and potential for harm occurring in other nutrient levels.

In the authors' brief review of nutrients as part of a complex formula, they failed to highlight that this multi-ingredient method has the potential to be more beneficial for treating mental health symptoms than any one nutrient.[3] The concept underlying the use of micronutrients for the amelioration of mental health symptoms is that mental illness may be a manifestation of suboptimal nutrition, relative to genetically determined needs for optimal brain metabolic activity.[4] Neurotransmitters go through many metabolic steps to ensure synthesis, uptake and breakdown. Each step requires enzymes, and every enzyme is dependent on multiple co-enzymes (cofactors). A variety of vitamins and minerals are required as cofactors in most, if not all, of those steps. Some people may inherit an in-born error of metabolism that results in less-than-optimal use of nutrients that are present.[4] Flooding the system with high doses of nutrients ensures that the body receives what it requires for optimal brain functioning.

We also challenge the article's focus on serum nutrient levels, as the authors often fail to identity individual nutrient requirements unless a frank nutritional deficiency is present. Serum levels are simply too crude to provide a complete picture of the metabolic needs of the brain. How accurately can peripheral metabolites and biomarkers predict change in a complex, multifactorial disorder such as ADHD and reflect what might be going on at a subcellular level in a metabolically active brain?[5] To date, no single biomarker for ADHD has achieved clinical utility as a diagnostic tool or a predictor of treatment outcome.[6] We are not convinced that a single biological marker exists.

The one-disease, one-nutrient solution to mental disorders is outdated and needs to be replaced by a model that is responsive to the broad spectrum of human nutritional needs. Perhaps the perpetuation of single-nutrient studies continues because this methodology fits comfortably within the pharmaceutical paradigm and traditional scientific methodology where drugs are typically single ingredient and independent variables are manipulated one at a time. However, shifting psychiatric research towards a consideration of multi-ingredient formulations requires rethinking the scientific paradigm that has thus far shaped this field.

1 Rajyaguru P, Cooper M. Role of dietary supplementation in attention-deficit hyperactivity disorder. *Br J Psychiatry* 2013; **202**: 398–9.

2 Rucklidge JJ, Johnstone J, Kaplan BJ. Nutrient supplementation approaches in the treatment of ADHD. *Expert Rev Neurother* 2009; **9**: 461–76.

3 Rucklidge JJ, Kaplan BJ. Broad-spectrum micronutrient formulas for the treatment of psychiatric symptoms: a systematic review. *Expert Rev Neurother* 2013; **13**: 49–73.

4 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.

5 Benton D. To establish the parameters of optimal nutrition do we need to consider psychological in addition to physiological parameters? *Mol Nutr Food Res* 2013; **57**: 6–19.

6 Scassellati C, Bonvicini C, Faraone SV, Gennarelli M. Biomarkers and attention-deficit/hyperactivity disorder: a systematic review and meta-analyses. *J Am Acad Child Adolesc Psychiatry* 2012; **51**: 1003–19.

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Authors' reply: We thank the authors for their comments but would contest the view that our editorial actively promotes the premise that a single nutrient could consistently ameliorate attention-deficit hyperactivity disorder (ADHD) symptoms. We have summarised the literature to date and highlight that the single-nutrient literature is complicated by methodological heterogeneity and inadequately rigorous study designs, making overall interpretation difficult. But before dismissing the potential contribution of single agents in isolation it should be borne in mind that such methodological factors, as well as a potential genuine lack of effect, may also go some way to explaining why single-nutrient approaches have not yielded notable benefits.

Attention-deficit hyperactivity disorder is a complex, multi-factorial disorder and we agree with Rucklidge *et al* that serum levels may not reflect the complex metabolic requirements of the brain. Indeed, we emphasise in our article that it is unclear whether serum levels considered most favourable for general health would be optimal for improving brain function in ADHD, and that it needs to be further understood how we would determine such levels. However, caution should be exercised in dismissing the importance of serum levels, as this lack of clarity and the interlinked action between nutrients that Rucklidge *et al* highlight, whereby supplementing with one alone may lead to decreases in another, make it even more important to measure a range of serum levels when investigating supplements in the absence of baseline levels below standard reference ranges. Whatever the optimal levels of nutrients are for brain functioning in ADHD, 'flooding the system with high doses of nutrients' has the potential to confer risk to physical health. Potentially serious adverse outcomes of nutrient excess are documented[1,2] and, although nutritional interventions can be perceived as safer than stimulants, we should first ensure we are doing no harm. There

is no conclusive evidence to date that suboptimal nutrition is an aetiological factor in mental illness in general; however, dietary factors are biologically plausible agents and as such the field would certainly benefit from carefully designed trials, be that of single nutrients or of nutrient complexes.

1 Rutkowski M, Grzegorczyk K. Adverse effects of antioxidative vitamins. *Int J Occup Med Environ Health* 2012; **25**: 105–21.

2 Miller 3rd ER, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med* 2005; **142**: 37–46.

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