Eat2beNICE

Effects of Nutrition and Lifestyle on Impulsive, Compulsive, and Externalizing Behaviours

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D 2.4 – Manuscript: Effects of supplements on symptoms of impulsivity, compulsivity and aggression

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Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
ARI	Affective Reactivity Index
CGAS	Children's Global Assessment Scale
CGI-I	Clinical Global Impression scale of Improvement
CIMH	Central Institute of Mental Health
IP	Investigational product

1. Deliverable report

Vitamin and micronutrient supplementation in children and adolescents with irritability, impulsivity and compulsivity (VANTASTIC Study)

Background: Irritability is a cross-disorder trait that affects a significant proportion of adolescents with psychiatric disorders, predominately those with attention deficit hyperactivity disorder (ADHD). It puts serious burden on youth, families, and society while treatment options are limited. The consumption of micronutrients as food supplements to alleviate mental health issues has steadily increased in Europe over the recent decades, even though their efficacy and tolerability have not been sufficiently investigated. Previous studies that investigated micronutrient supplementation for the treatment of irritability and ADHD have reported inconsistent benefits, yet very good tolerability. However, no placebo-controlled studies examined the effect of micronutrients on irritability in medicated and unmedicated adolescents with and without ADHD so far.

Methods: The aim of this study was to investigate the effects of broad-spectrum micronutrients and vitamins on irritability in n=180 children and adolescents (50% medicated) between 11 and 17;6 years of age with a high level of irritability with ADHD (67%) or with other mental conditions. In addition, in order to capture sex differences, we aimed to include at least 30% female participants. The investigational product included NADH, Folic Acid, Vitamin B6, B12, and D3, Magnesium, Zinc, Iron, Selenium, Phospholipids and L-carnitine. The study consisted of a 10-week double blind, placebo-controlled supplement treatment phase, followed by a 10-week open-label treatment phase and concluded by a two-week follow-up. The primary outcome was response at the end of the placebo-controlled phase; defined as a clinical global impression scale of improvement (CGI–I) score with a focus on irritability of 1 or 2 [=very much improved or much improved] plus a reduction in the Affective Reactivity Index (ARI, parent-rated) total score of at least 30% compared to baseline. A broad range of secondary measures (behavioral, cognitive, biological) were also assessed during five study visits at intervals of five weeks. Participants were recruited from two centers: the Department of Child and Adolescent Psychiatry, Central Institute of Mental Health (CIMH) in Mannheim, Germany and the Accare Child Study Center in Groningen, the Netherlands.

Trial registration: The trial is registered with ClinicalTrials.gov: NCT03898336.

Results: In total n=120 participants were recruited and enrolled, of these n=83 in Groningen and n=37 in Mannheim. Of these, n=5 participants were screenfailures and n=115 were randomized while n=76 (66.1%) were male and n=38 (33.0%) were female. N=80 (69.6%) had a diagnosis of ADHD. Age ranged from 11 to 17 years, with a mean age of 13.2 years. N=72 (62.6%) were treated with medication at time of enrolment. For an overview see table 1.

Randomization - performed by an external pharmacy - was unfortunately and unexpectedly inadequate. In violation of the clearly communicated conditions and requirements of this particular study, the external pharmacy allocated investigational product and placebo to large blocks of participants. Due to the double blind nature of this study, the inadequate randomization could not be noticed any earlier than at the end of the study (after having received the randomization list by the external pharmacy). It resulted in an unbalanced allocation of subjects with n=85 of the participants having received IP (including all participants in Mannheim), and n=30 having received placebo during the double blind phase of the study.

Overall, 19.1% of the participants were classified as responders at the end of the placebo-controlled study phase based on the definition described above. The proportion of responders in the placebo group was higher (26.7%) than in the active group (16.5%) (see table 2 and figure 1). Moreover, a statistically significant improvement of irritability measured by the Affective Reactivity Index after 10 weeks (T2) and after 20 weeks (T4) was found in both groups, as well as improvements in the overall functioning of the participants (see figure 2 and 3). When considering the subgroups of participants with and without ADHD, significant differences emerge, with response rates of 12.5% in the ADHD group (15.2% in the active group and 0% in the control group) and 34.3% in the non-ADHD group (21.1% in the active group and 50.0% in the control group; for details see table 3 and 4). Further statistical analyses, including evaluations of secondary outcomes, will be performed as next steps .

The overall tolerability of the investigational product was very good. Overall and, of particular interest, including all participants who were treated with concomitant medication, no serious adverse events or side effects that could give rise to safety concerns were recorded.

Conclusion: Although limited by several aspects, including inadequate randomization, the findings of this study do not indicate support of the hypothesis that broad-spectrum micronutrients significantly improve irritability in adolescents in general. Although tolerability was very good, the findings of this study do not allow for the conclusion to recommend treating highly irritable adolescent patients with micronutrient supplements. As subgroup differences emerged, further studies focusing on patients with ADHD should be considered.

2. Tables and other supporting documents where applicable and necessary

Table 1. Characteristics of the study sample

	Total	N=115	100 %
Gender	Male	76	66.1 %
	Female	38	33.0 %
	Missing	1	0.9 %
Intervention	IP	85	73.9 %
	Placebo	30	26.1 %
Group	ADHD	80	69.6 %
	Non-ADHD	35	30.4 %
Site	Groningen	83	72.2 %
	Mannheim	32	27.8 %
Medication	Current use	72	62.6 %
	No current use	42	36.5 %
	Missing	1	0.9 %

Table 2. Response based on Affective Reactivity Index (ARI) and Clinical Global Impression Improvement CGI-I with a focus on irritability

	CGI-I Irritability 1 or 2 at T2			ARI (parent) reduction ≥ 30% at T2			Responder (both yes)	
	n	%		n	%		n	%
All (N=115)								
Response	25	21,7		44	38,3		22	19,1
No response	74	64,3		50	43,5		77	62,6
Missing	16	13,9		21	18,3		21	18,3
IP (n=85)								
Response	17	20,0		31	36,5		14	16,5
No response	57	67,1		38	44,7		55	64,7
Missing	11	12,9		16	18,8		16	18,8
Placebo (n=30)								
Response	8	26,7		13	43,3		8	26,7
No response	17	56,7		12	40,0		17	56,7
Missing	5	16,7		5	16,7		5	16,7

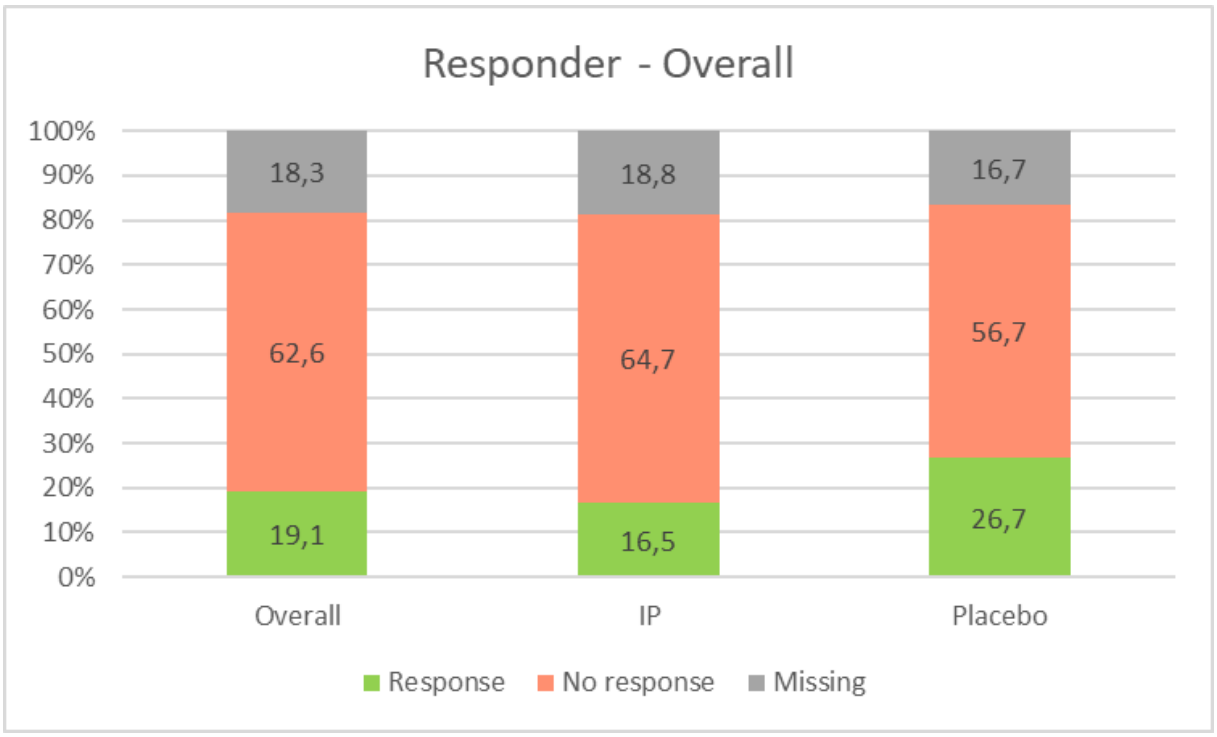

Figure 1. Responder based on Affective Reactivity Index (ARI) and Clinical Global Impression Improvement CGI-I in the full study sample.

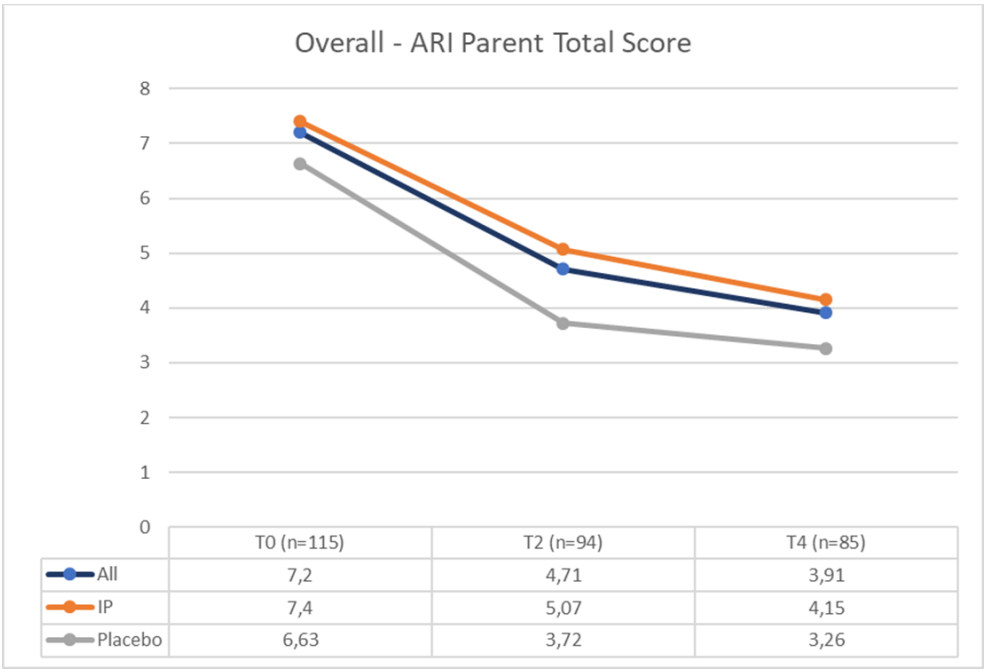

Figure 2. Irritability assessed by Affective Reactivity Index (ARI, parent-rated)

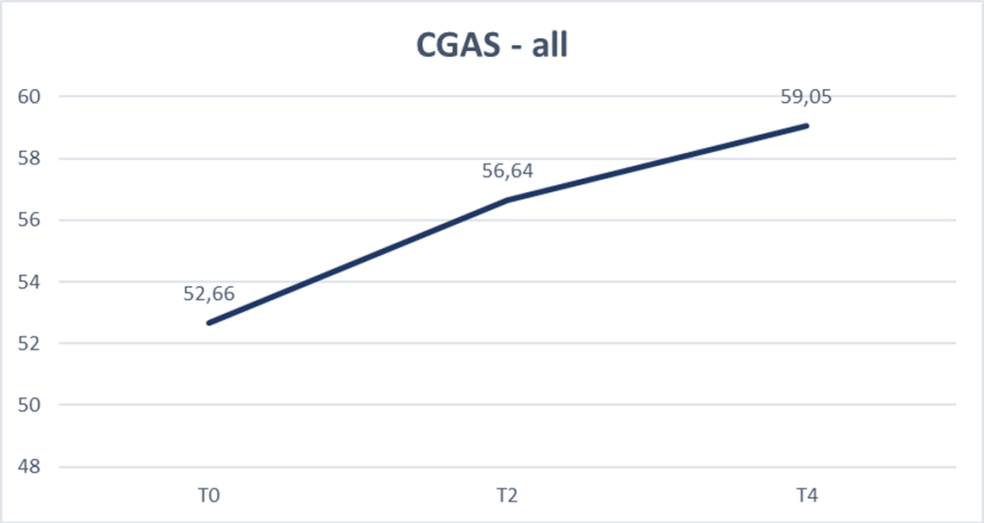

Figure 3. General functioning assessed by Children's global assessment scale (C-GAS).

Table 3. ADHD group – response based on Affective Reactivity Index (ARI) and Clinical Global Impression Improvement CGI-I with a focus on irritability

ADHD Group	CGI-I Irritability 1 or 2 at T2			ARI (parent) reduction ≥ 30% at T2			Responder (both yes)	
	n	%		n	%		n	%
All (N=80)								
Response	12	15,0		25	31,3		10	12,5
No response	55	68,8		39	48,8		54	67,5
Missing	13	16,3		16	20,0		16	20,0
IP (n=66)								
Response	12	18,2		22	33,3		10	15,2
No response	45	68,2		32	48,5		44	66,7
Missing	9	13,6		12	18,2		12	18,2
Placebo (n=14)								
Response	0	0,0		3	21,4		0	0,0
No response	10	71,4		7	50,0		10	71,4
Missing	4	28,6		4	28,6		4	28,6

Table 4. Non-ADHD group – response based on Affective Reactivity Index (ARI) and Clinical Global Impression Improvement CGI-I with a focus on irritability

Non-ADHD Group	CGI-I Irritability 1 or 2 at T2			ARI (parent) reduction ≥ 30% at T2			Responder (both yes)	
	n	%		n	%		n	%
All (N=35)								
Response	13	37,1		19	54,3		12	34,3
No response	19	54,3		11	31,4		18	51,4
Missing	3	8,6		5	14,3		5	14,3
IP (n=19)								
Response	5	26,3		9	47,4		4	21,1
No response	12	63,2		6	31,6		11	57,9
Missing	2	10,5		4	21,1		4	21,1
Placebo (n=16)								
Response	8	50,0		10	62,5		8	50,0
No response	7	43,8		5	31,3		7	43,8
Missing	1	6,3		1	6,3		1	6,3

3. Acknowledgement and Disclaimer

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