

# Using Metabolomics to Classify the Underlying Effects of Multi-Nutrient Supplementation in ADHD Youth

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## INTRODUCTION

### What is Attention Deficit Hyperactivity Disorder (ADHD)?

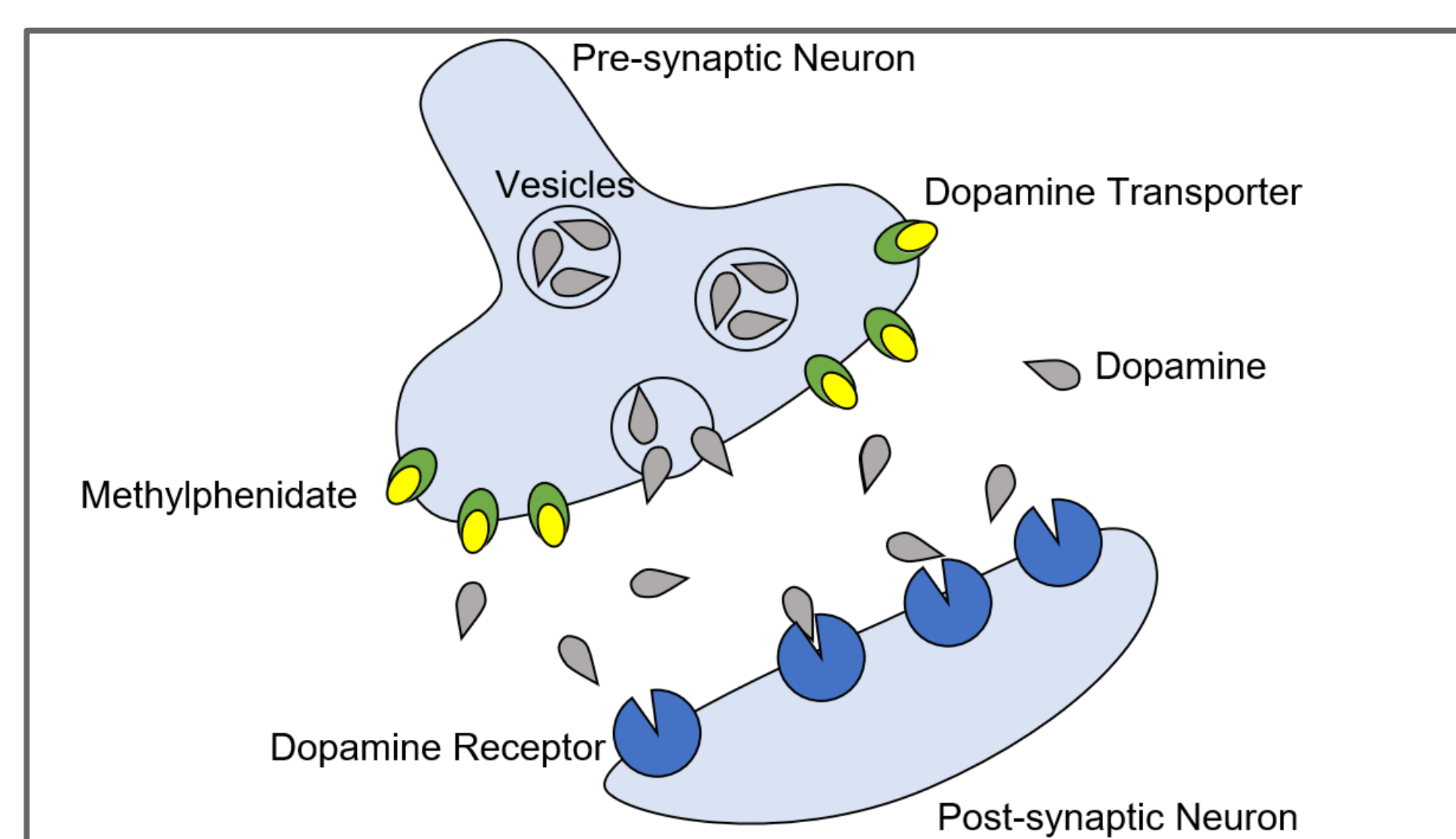
- ADHD is a neuropsychiatric disorder with high heritability (80%) and global prevalence (7.8% in children <18 years old) (1)
- ADHD is often diagnosed in childhood and includes symptoms of Inattention, hyperactivity, impulsivity, causing impairment in functioning

### Psychopathology of ADHD

- ADHD symptoms are believed to be the result of **dysfunctional levels of dopamine and norepinephrine** in the central nervous system, causing alterations in reward-feedback, attention and alertness responses, see Figure 1 (4).

### Current treatment options have drawbacks:

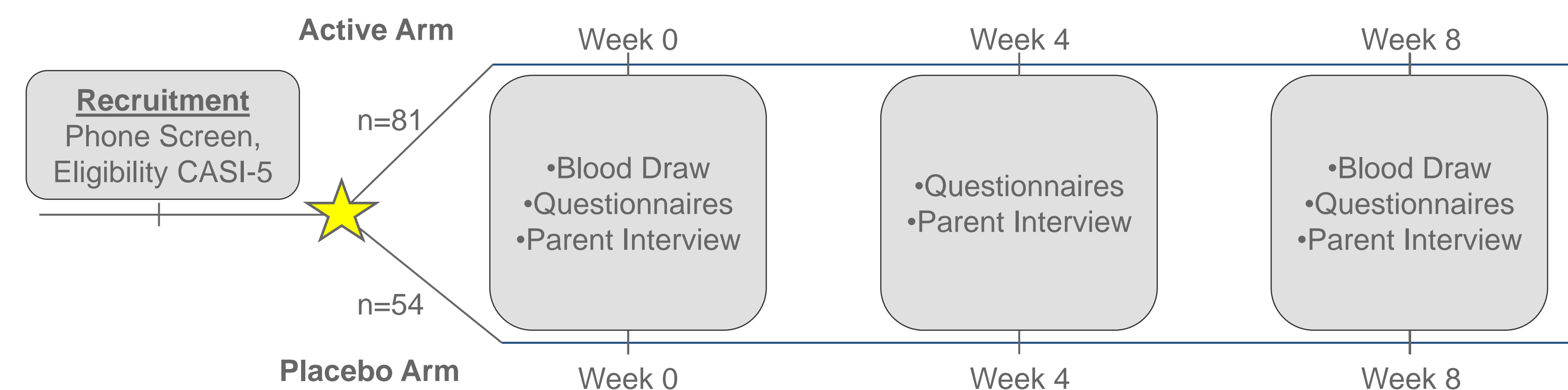
- Prescription psychostimulants – limited knowledge of long-term effects, poor side effects, concern over addiction
- Cognitive behavioral therapy – expensive and unavailable to many families
- A broad-spectrum multi-nutrient formula for ADHD has shown promise in children, but its effects on nutrient status and the underlying nutrient-metabolome interactions have not been characterized, see Figure 2.



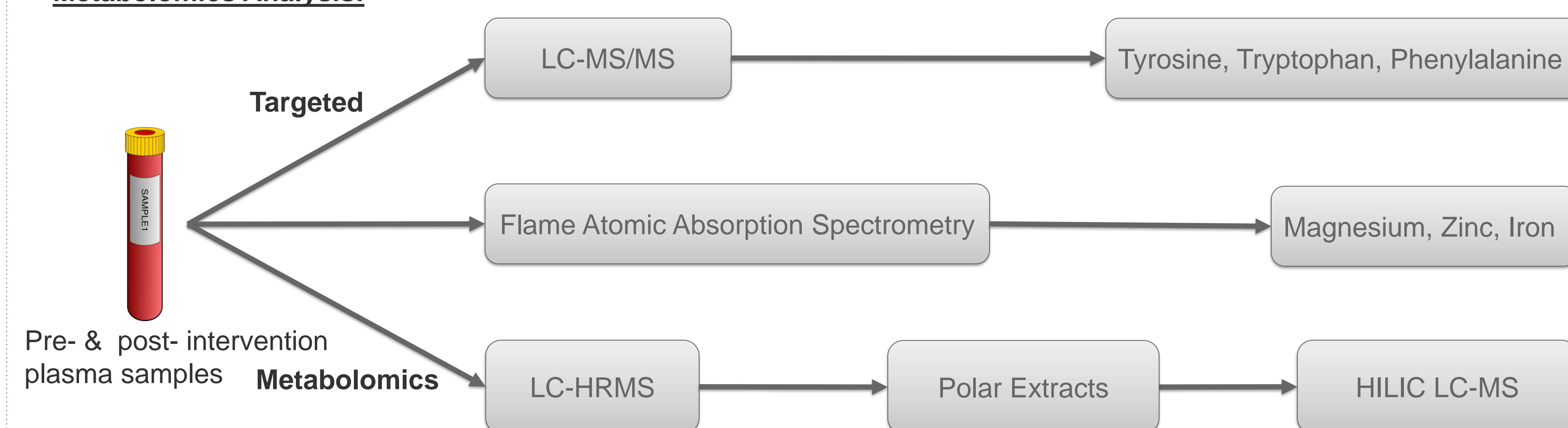
**Figure 1.** Mechanism of methylphenidate on dopamine receptors in the brain.

## METHODS

### Clinical Trial Timeline:



### Metabolomics Analysis:



### Linear Modeling:

$$\text{Metabolite Intensity} \sim \text{Treatment Group} + \text{CASI Score} + \text{Visit} + \text{Treatment Group} * \text{CASI Score} * \text{Visit}$$

#### Main Factors

- Treatment Group (placebo or multi-nutrient)
- CASI Score (inattention, hyperactivity, ODD, DMDD)
- Visit (baseline or week 8)

## RESULTS TO DATE

Table 1. Preliminary open label changes in ADHD and mood dysregulation symptom severity, N=74.

CASI 5 Category	Week 8 Median (min,max)	End of Study Median (min,max)	Change score	P-Value	Possible Score Range
Inattention	16 (7,27)	14 (3,26)	2	0.0435	0-27
Hyperactivity	15 (2,29)	12 (1,28)	3	0.0068	0-30
ODD	9.5 (0,24)	8 (0,20)	1.5	0.0108	0-24
DMDD	2 (0,6)	1 (0,5)	1	0.0119	0-6

## FUTURE WORK AND ANTICIPATED RESULTS

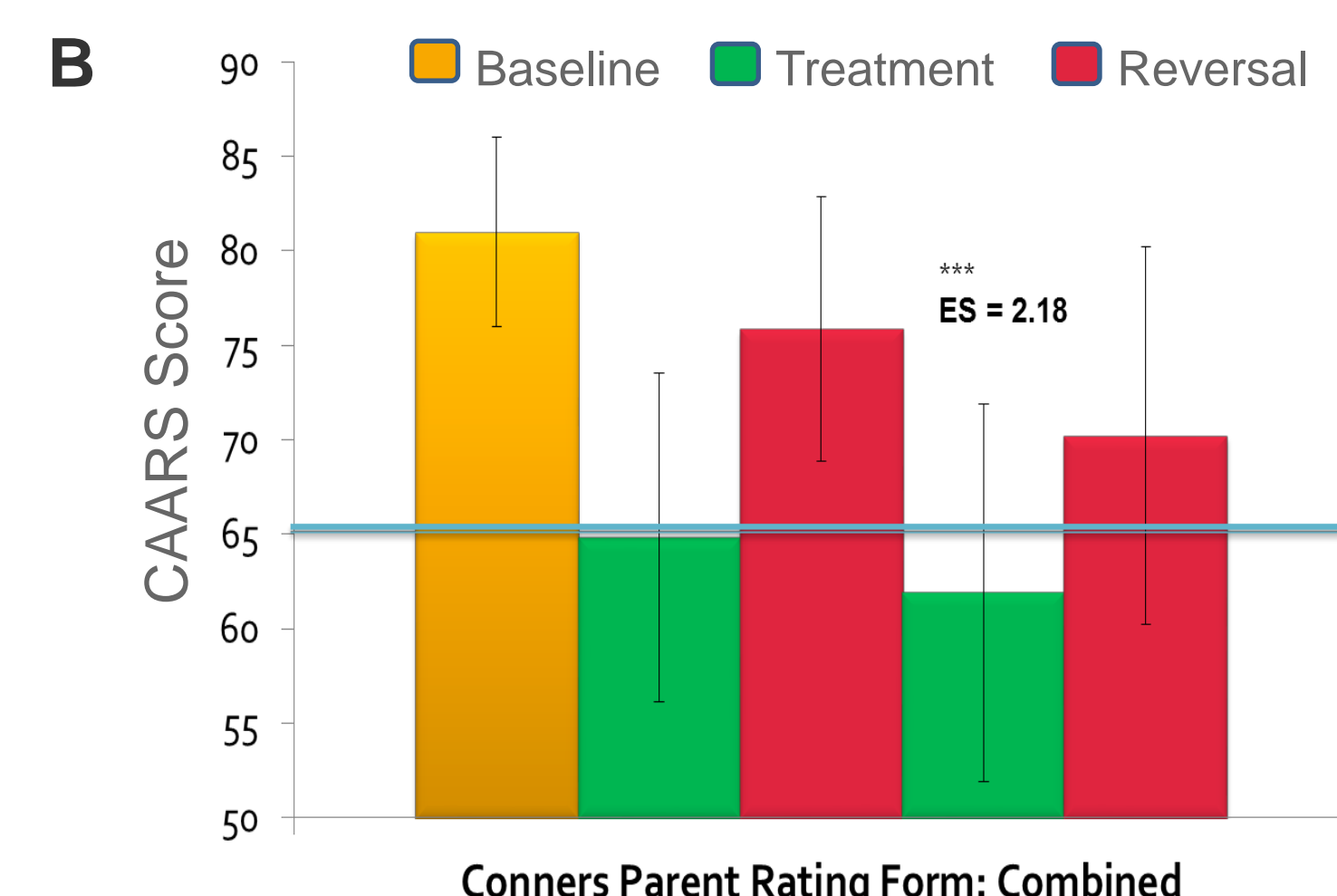
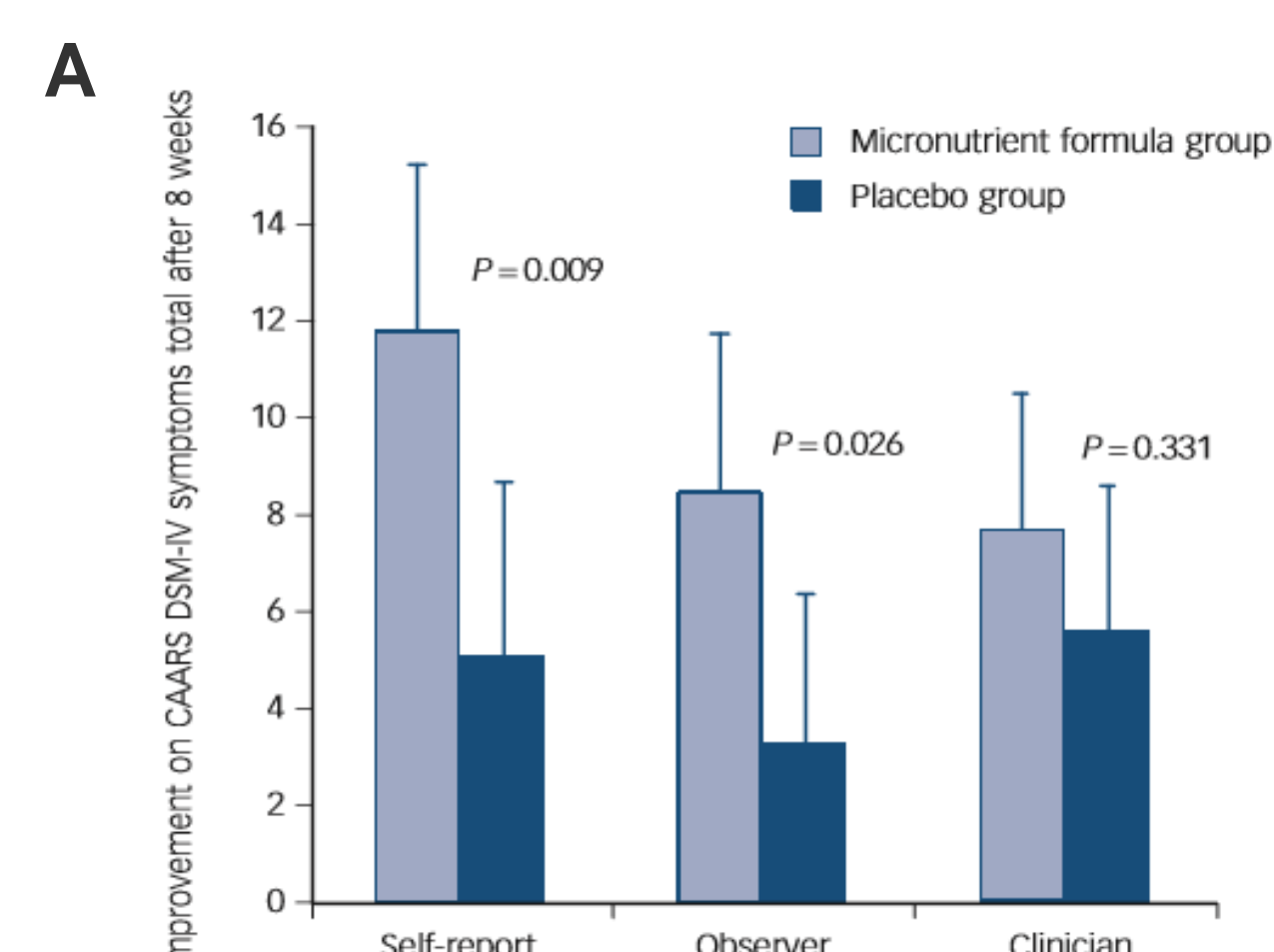
- Targeted metabolite quantitation, metabolomics analyses and data processing, linear modeling, metabolite Identification
- Metabolites associated with the cognitive changes in ADHD following essential nutrient supplementation in a pediatric population
- Insight into the biochemical pathways implicated in ADHD pathology

## BIBLIOGRAPHY

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**Figure 2.** (a) Improvement of ADHD symptoms following 8 weeks of vitamin-mineral treatment or placebo (taken from ref. 5). (b) ADHD symptom scores throughout an open label reversal design study (taken from ref. 6).

## AIMS

**Aim 1:** Determine the blood nutrient status of those nutrients whose levels are anticipated to correlate with ADHD symptom improvement using well accepted blood biomarkers of ADHD, using liquid-chromatography-tandem mass spectrometry (LC-MS/MS) and flame absorption spectrometry.

**We hypothesize** that after 8 weeks of supplementation, increases in amino acids including tyrosine and phenylalanine; magnesium, plasma zinc, omega-3 fatty acids, and ferritin for iron will be correlated with reduced ADHD symptom severity as assessed by the CASI-5 [20].

**Aim 2:** Observe changes in ADHD symptoms which correlate with changes in metabolite profiles pre-and post- supplement intervention using liquid-chromatography-high resolution mass spectrometry metabolomics (LC-HRMS).

**We hypothesize** that metabolomics profiles of subjects at baseline will be distinguishable from the subjects after 8 weeks of supplementation, and a subset of metabolites (e.g. those involved in neurotransmitter synthesis or branched chain amino acid metabolism) will be positively correlated with improvements in ADHD symptom measures following multinutrient supplementation.