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Letter to the Editor

Randomized controlled trial of an adjunctive sulforaphane nutraceutical in schizophrenia

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Dear Editor,

We report here on a randomized double blind placebo-control trial of an adjunctive sulforaphane nutraceutical to reduce symptoms and improve cognitive functioning in individuals with schizophrenia.

By way of background, it is widely recognized that high consumption of plant-based diets reduces the risk of cancer and many other chronic diseases (Hardman, 2014; Vanamala, 2015). Evidence for the special protective role of cruciferous plants has been ascribed largely to their high content of glucosinolates. A widely studied example is the presence in broccoli sprouts of the glucosinolate, glucoraphanin, which is converted by myrosinase to the isothiocyanate, sulforaphane (Fahey et al., 1997, 2001). Myrosinase is present in plant cells, compartmentalized separately from the glucosinolates. Sulforaphane crosses the blood brain barrier and has cytoprotective antioxidant and anti-inflammatory activities (Bahadoran et al., 2013; Koo et al., 2013). Sulforaphane has been studied as a therapeutic agent for the treatment of several somatic health conditions including prostate cancer and diabetes with promising but as yet inconclusive findings (Yagishita et al., 2019; Mazarakis et al., 2020).

Several studies have been performed in neuropsychiatric populations. A randomized controlled trial of broccoli sprout extracts performed in 44 adolescent and adult males with autism spectrum disorders found that adjunctive sulforaphane supplement was associated with improved psychiatric symptoms (Singh et al., 2014; Lynch et al., 2017). A trial in 60 children with autism found that adjunctive sulforaphane was associated with a reduction in irritability (Momtazmanesh et al., 2020). Another small open label trial of a broccoli sprouts extract in 10 adults with schizophrenia, 7 of whom completed the trial (Shiina et al., 2015), found no change in psychiatric symptoms.

Participants in the current trial were enrolled during the period February 24, 2017 – June 24, 2019 and were: age 18–65, with a primary Axis I diagnosis DSM5 of schizophrenia or schizoaffective disorder confirmed with the Structured Clinical Interview for Diagnosis (SCID; First et al., 1996); currently an outpatient; residual psychotic symptoms of at least moderate severity as evidenced by a total Positive and Negative Syndrome Scale (PANSS) score of ≥60 and one or more PANSS positive symptom score ≥4 or three PANSS positive or negative symptom scores of ≥3; receiving antipsychotic medication for ≥8 weeks prior to starting the study with no changes within the previous 21 days. Exclusion criteria included a diagnosis of intellectual disability; any clinically significant or unstable medical disorder; primary diagnosis within the last 3 months of substance use disorder, moderate or severe, except caffeine or nicotine; current use of a broccoli supplement; pregnant or planning to become pregnant during the study period. All participants signed an informed consent. The study was approved by the Sheppard Pratt IRB and registered on clinicaltrials.gov #NCT02810964

The active study compound and identical appearing placebo were prepared and provided by Nutramax Laboratories, Edgewood, MD, USA, the company that makes Avmacol® a commercially-available over the counter supplement (http://www.nutramaxstore.com/avmacolreg-60-tablets-p430.aspx). The active ingredient in Avmacol® is produced by extracting the biologically inactive glucosinolate, glucoraphanin, from broccoli seeds, and compressing it in tablets with active myrosinase from broccoli sprouts. The ingestion of this compound leads to the hydrolysis of glucoraphanin and the generation of sulforaphane within the gastrointestinal tract and the subsequent systemic absorption of the sulforaphane.

The dose was 16 mg of glucoraphanin or 37 μmol per tablet; 6 tablets per day are estimated to yield about 100 μmol of sulforaphane. The nutraceutical was provided as a 0.375 punch size, round concave tablet, about the size of a regular (325 mg) enteric-coated aspirin. The placebo was identical appearing but contained no active ingredients.

The study tablets were stored at −20 °C prior to distribution to the participants. Each participant received two weeks supply of the medication at each study visit that was to be stored at room temperature.

After a physical and psychiatric evaluation and complete blood count to establish eligibility, each participant was assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein et al., 2008). Participants then started a two-week single-blind placebo phase in which they received inactive compound. At week 2, participants were randomized to receive either the sulforaphane nutraceutical or placebo tablets for the 16 weeks of the double-blind phase. Block randomization, based on initial PANSS total scores, was used to assign participants to the two treatment groups. Participants were evaluated bi-weekly from week 2–18 for adverse events and for psychiatric symptom severity with the PANSS. The MCCB was administered again at week 18.

The primary outcome measurement was change in scores on the PANSS from the beginning to the end of the double-blind treatment phase, weeks 2–18. The secondary outcome was change in scores on the MCCB.

A total of 64 patients were enrolled, completed the baseline visit, and were randomized. A total of 58 participants, 91% of those randomized, completed the full 18 weeks of the study, 29 in the active and 29

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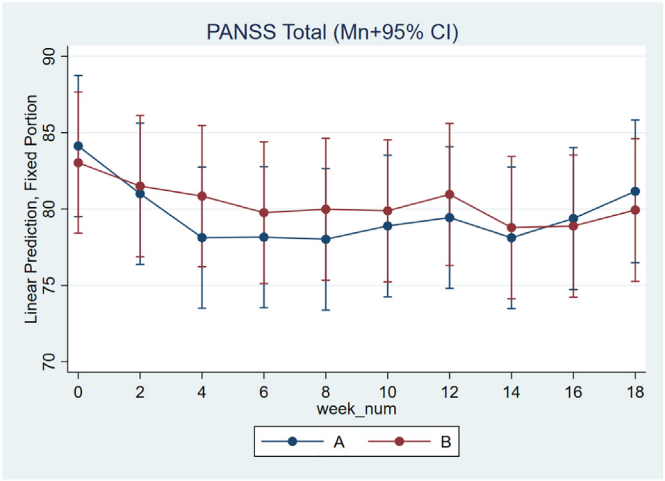

Fig. 1. PANSS total score by treatment group by week of the trial, means and 95% confidence intervals; A = Sulforaphane group, B = Placebo group; mixed effects model treatment group by week; coefficient −0.0543049 (95% CI −0.2054685, 0.0968586, $p = 0.481$).

in the placebo group (see Supplemental Fig. 1 and Supplemental Table 1). Mixed effects models of PANSS Total score (see Fig. 1) and also, Positive, Negative, and General scores (see Supplemental Figs. 2–4) by treatment group show no significant difference between groups during the double blind phase week 2–18 (all $p > 0.05$) and no significant associations between treatment group and study week. Mixed effects models of cognitive functioning as measured by the MCCB total (see Supplemental Fig. 5) and domain cognitive scores also showed no significant difference between groups at the beginning or the end of the study.

The sulforaphane study medication was well-tolerated. Adverse events did not differ appreciably by study group. There were a total of 8 Serious Adverse Events (SAEs) involving 7 participants during the course of the study, 2 SAEs in the sulforaphane group involving 2 participants, and 6 SAEs in the placebo group involving 5 patients.

Future trials in schizohrenia may consider a higher dose of the sulforphane preparation. More specialized populations may also be considered for future trials such as those closer to illness onset.

Declaration of competing interest

Author JF serves as a scientific advisor to Brassica Protection Products LLC (Baltimore, MD, USA). The other authors declare no conflicts of interest.

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Contributors

Authors Dickerson, Fahey, Goga, Katsafanas, Khushalani, Stallings, Origoni, and Yolken contributed to the study design. Authors Katsafanas, Squire, Newman, and Stallings contributed to subject recruitment and assessment. Authors Katsafanas and Origoni prepared and oversaw the dataset. Author Khushalani supervised the diagnostic assessment of participants and author Goga supervised the pharmacy. Authors Yolken and Xiao performed the laboratory tests. Author Yolken performed the statistical analyses. Author Dickerson wrote the first draft of the manuscript and all authors contributed to and have approved the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2021.03.018.

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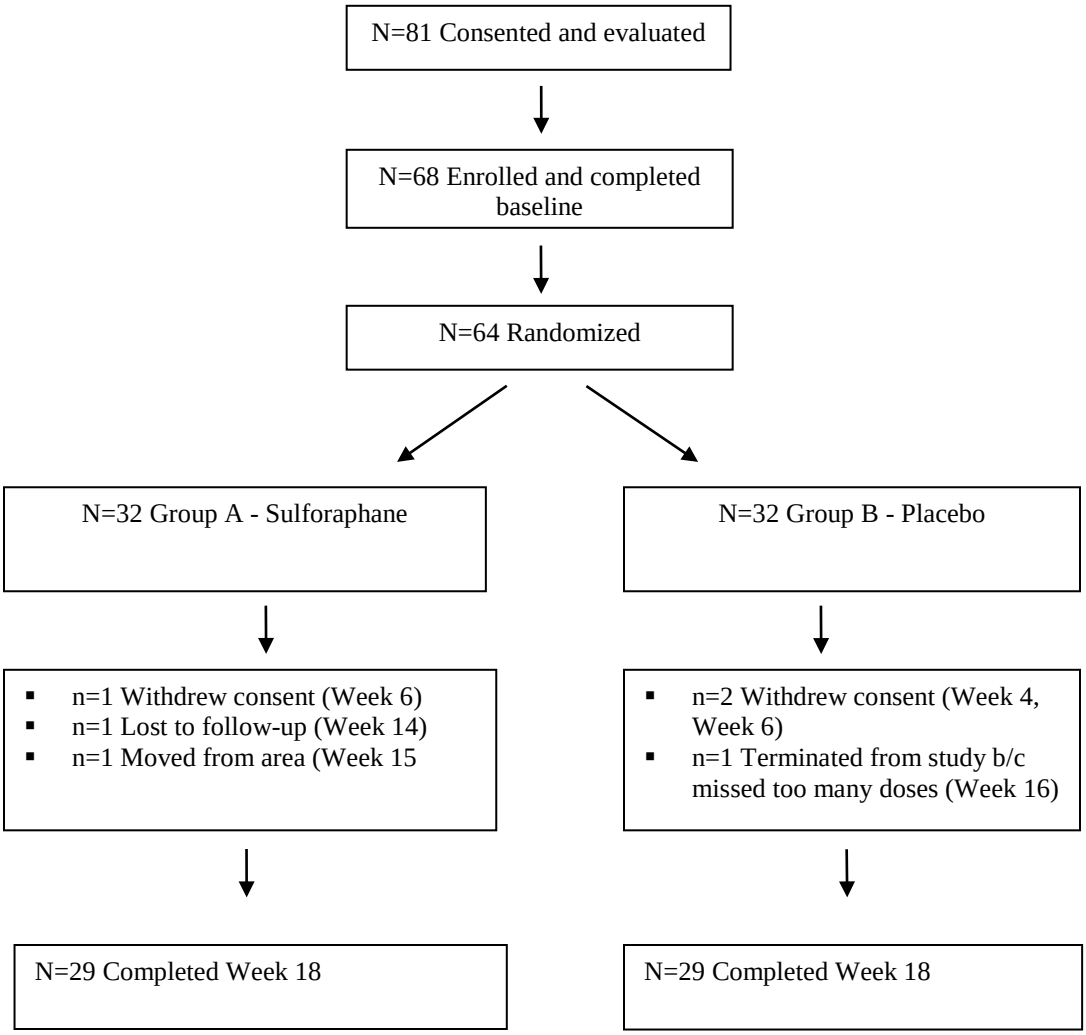
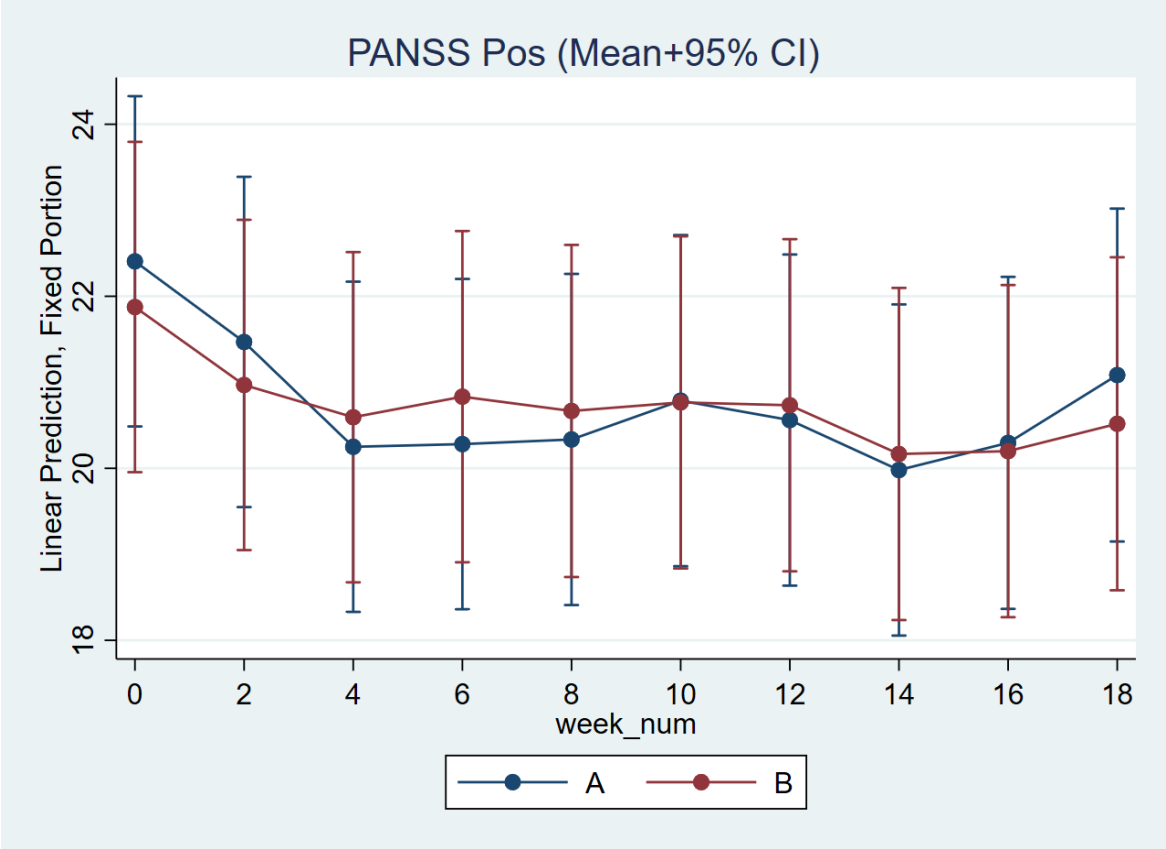


Supplemental Figure 1. Flow chart of patient participation

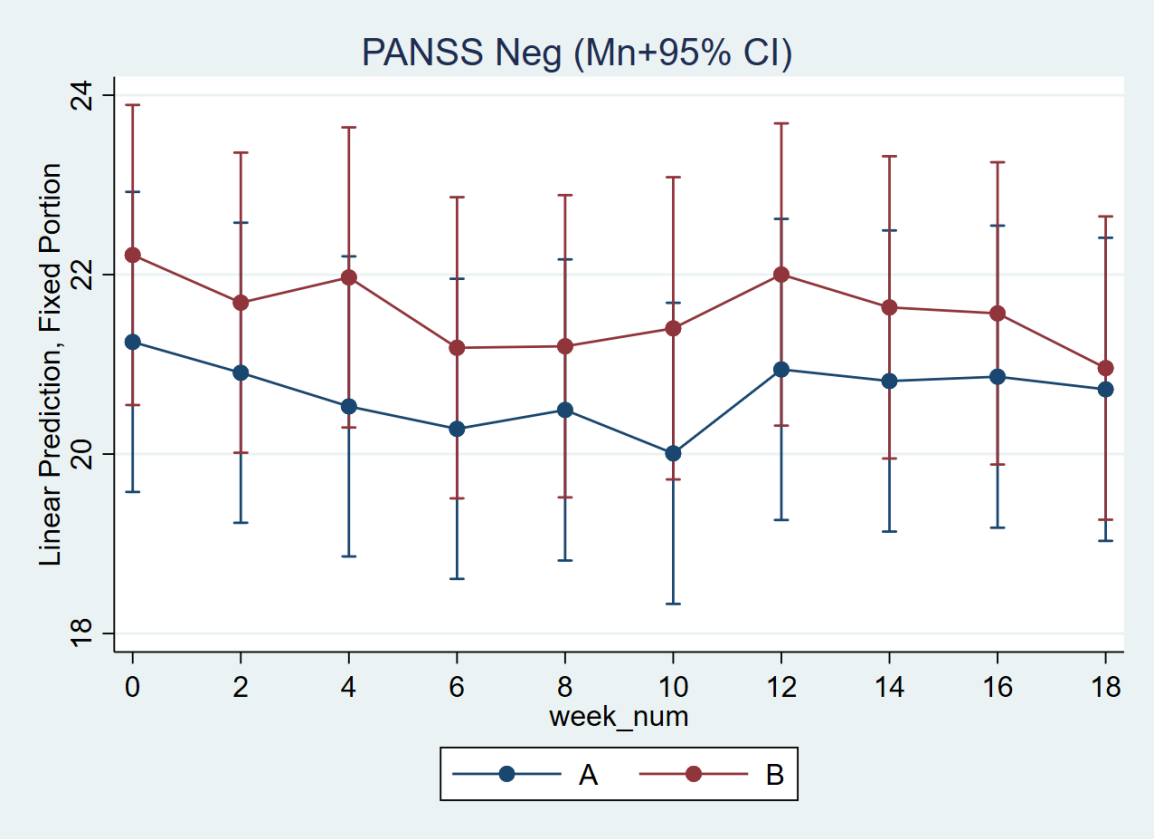
Supplemental Table 1. Clinical characteristics of trial participants at baseline

	All (N=64)	Sulforaphane (N=32)	Placebo (N=32)
Characteristic[1]			
Age, years	44.2 (±12.0)	42.7 (±12.3)	45.8 (±11.7)
Race Caucasian African American	 34 (53%) 30 (47%)	 18 (56%) 14 (44%)	 16 (50%) 16 (50%)
Gender, male	49 (77%)	24 (75%)	25 (78%)
Education	11.6 (±1.7)	11.8 (±1.5)	11.4 (±1.8)
Maternal education	12.6 (±2.4)	13.1 (±2.3) n=26	12.3 ± (2.4)
Diagnosis schizophrenia/ schizoaffective	46/18	24/8	22/10
PANSS[2] total symptom score	83.6 (±12.8)	84.1 (±13.5)	83.0 (±12.3)
PANSS positive score	22.1 (±5.3)	22.4 (±5.4)	21.9 (±5.3)
PANSS negative score	21.7 (±4.8)	21.3 (±4.8)	22.2 (±4.8)
PANSS general score	39.7 (±6.6)	40.5 (±6.8)	38.9 (±6.6)
MCCB[3] Working Memory	29.3 (±12.9)	30.6 (±12.7)	28.0 (±13.2)
MCCB Reasoning and Problem Solving	36.7 (±7.3)	37.8 (±7.5)	35.6 (±7.1)
MCCB Social Cognition	33.5 (±14.5)	34.6 (±13.0)	32.5 (±16.1)
MCCB Speed of Processing	29.4 (±11.7)	31.0 (±10.9)	27.8 (±12.4)
MCCB Attention/Vigilance	32.4 (±10.8) n=30	33.6 (±10.9) n=29	31.2 (±10.8)
MCCB Verbal Learning	36.7 (±7.9)	38.2 (±8.4) n=31	35.2 (±7.2)
MCCB Visual Learning	30.6 (±11.3)	32.7 (±10.9) n=31	28.6 (±11.5)
MCCB Overall Composite score	22.3 (±12.9) n=30	25.0 (±12.0) n=28	19.5 (±13.4)
Body Mass Index	33.2 (±7.3)	34.7 (8.8)	31.8 (±5.2)
Current tobacco smoker	44 (69%)	19 (59%)	25 (78%)

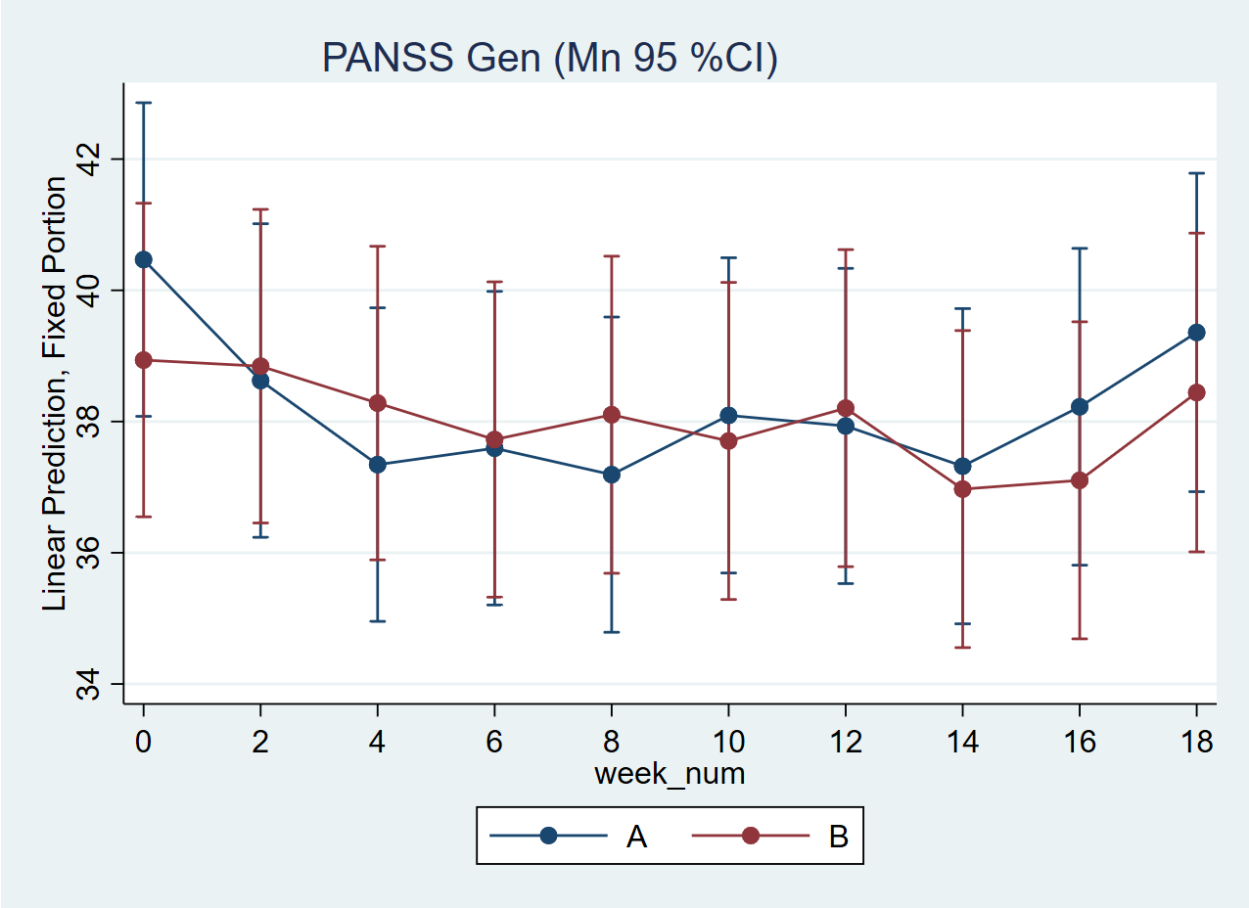
[1] Placebo vs. active all n.s. ($p>0.05$)
[2] PANSS, Positive and Negative Syndrome Scale
[3] MCCB, MATRICS Consensus Cognitive Battery; Note MCCB scores are domain scores expressed as t scores



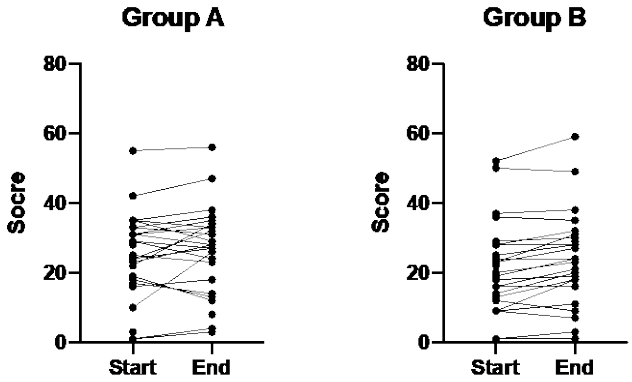
Supplemental Figure 2. PANSS Positive Subscale Scores by treatment group by week of the trial, means and 95% confidence intervals; A= Sulforaphane group, B= Placebo group; mixed effects model treatment group by week, coefficient = 0.0024075 (95% CI -0.0553682, 0.0601832, p=0.935).



Supplemental Figure 3. PANSS Negative Subscale Scores by treatment group by week of the trial, means and 95% confidence intervals; A= Sulforaphane group, B= Placebo group; mixed effects model treatment group by week coefficient = -0.0266361 (95% CI -0.0827351, 0.0294629, p= 0.352).



Supplemental Figure 4. PANSS General Subscale Scores by treatment group by week of the trial, means and 95% confidence intervals. A= Sulforaphane group, B= Placebo group; mixed effects model treatment group by week coefficient = -0.0311785 (95% CI -0.1320388, 0.0696817, p= 0.545).



Supplemental Figure 5. MATRICS Consensus Cognitive Battery (MCCB) total scores by group at start and end of the trial, n=26 in group A (Sulforaphane) and n=28 in group B (Placebo); mixed effects model treatment group by time coefficient = 0.8557823 (95% CI -1.575093, 3.286657, p=0.490)