

# Randomized Double Blind Inpatient Study of a Gluten-Free Diet in People with Schizophrenia

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## Introduction

- There are no FDA-approved treatments for negative symptoms of schizophrenia spectrum disorders (SRD), the chief determinants of dysfunction and predictors of long-term functional outcomes<sup>1</sup>.
- We previously identified a subgroup of people with SRD, who have immune response to gliadin in gluten (AGA IgG+).
- Our open-label<sup>2</sup> and randomized double-blind study<sup>3</sup> found that the AGA IgG+ subgroup had predominant negative symptomatology which improved after receiving a gluten free diet (GFD).
- Abnormalities in tryptophan metabolism, seen in elevated kynurenic acid (KYNA), may be related to SRD etiology<sup>4</sup>.

## Aims

Primary: To confirm the efficacy of a GFD for improving negative symptoms in persons with SRD who are AGA IgG+.

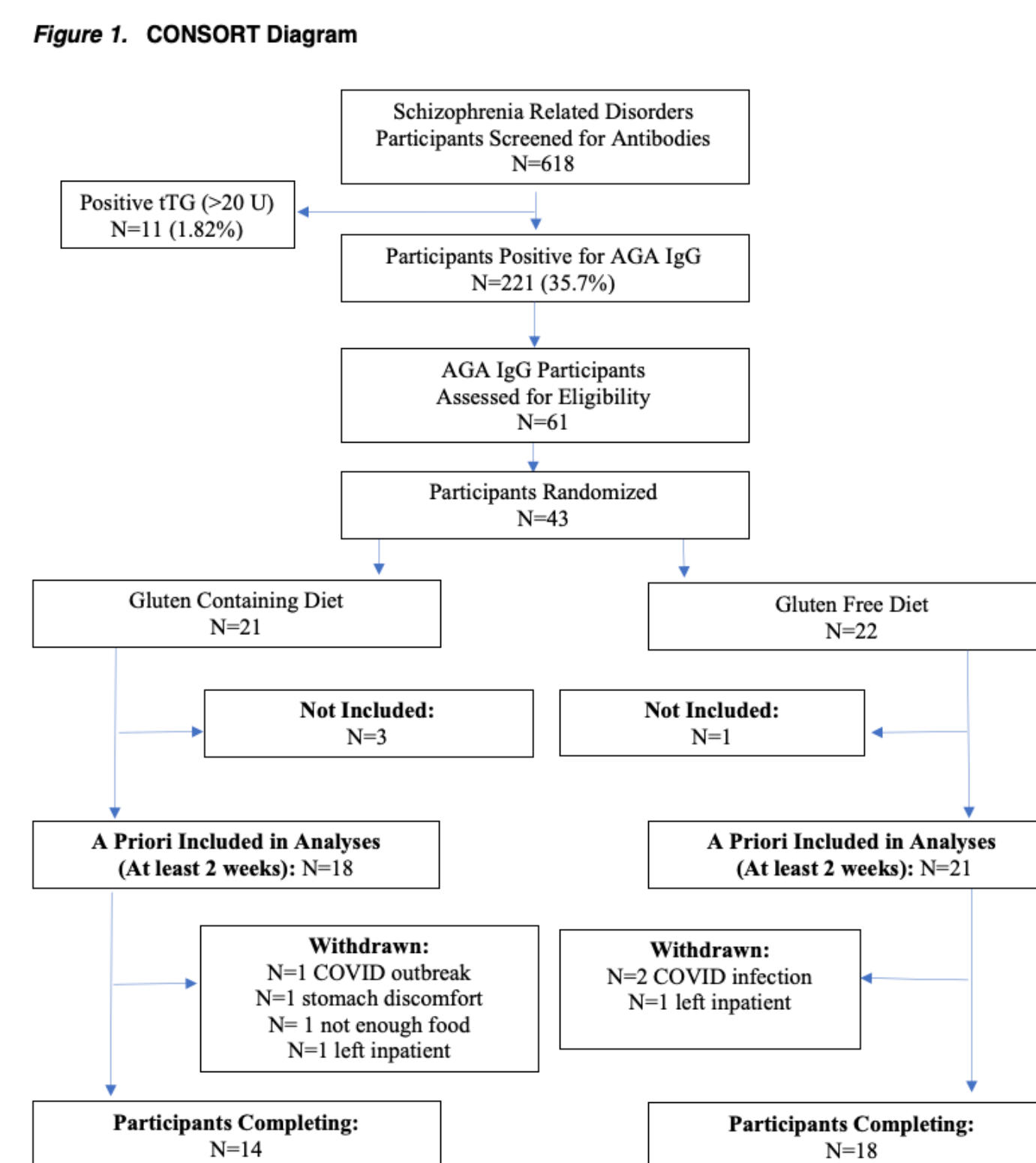
Secondary: To explore the effects of a GFD on biologic markers

- \* circulating kynurenic and KYNA levels
- \* circulating inflammatory markers
- \* imaging measures of cerebral blood flow
- \* imaging measures of neurochemistry in relevant brain area

## Methods

- Inpatient psychiatric setting (MPRC) from July 2017 to March 2024
- Women and men (18-64 y.o.) with AGA IgG >20 and Schizophrenia or Schizoaffective disorder, on consistent antipsychotic for > 4 weeks prior.
- Double-blind randomization, *a priori* analyses of intention to treat
- 5-week treatment: GFD (< 15mg/day) vs. gluten-containing diet (GCD)

- CAINS-MAP (1<sup>o</sup> outcome)
- CAINS-EXP
- SANS
- BPRS (positive symptoms)
- CDS (depression)
- CGI (global severity of illness)
- MCCB (cognitive function)
- ToL (executive function)
- Other medical: scales for pain, neuro symptoms, GI symptoms, akathisia, EPS, side effects, vitals, CBC, CMP.
- KYNA, kynurenic, 3-HK, 3-HK:KYNA ratio, cytokines
- Imaging cohort (N=20): Arterial Spin Labeling (ASL), Magnetic Resonance Spectroscopy (MRS)



## Results

Table 1: Demographic and Clinical Characteristics of Participants

|                                       | GCD (n=18) | GFD (n=21)  |
|---------------------------------------|------------|-------------|
| Age, years                            | 39.7 (8.6) | 36.8 (11.2) |
| Sex                                   |            |             |
| Male                                  | 13 (72.2%) | 16 (76.2%)  |
| Female                                | 5 (27.8%)  | 5 (23.8%)   |
| Race                                  |            |             |
| White                                 | 3 (16.7)   | 7 (33.3)    |
| Black                                 | 14 (77.8)  | 12 (57.1)   |
| American Indian                       | 1 (5.6)    | 0 (0)       |
| Asian                                 | 0 (0)      | 1 (4.8)     |
| Ethnicity                             |            |             |
| "Yes" to Hispanic or Latino           | 0 (0%)     | 1 (4.8%)    |
| "No" to Hispanic or Latino            | 18 (100%)  | 19 (90.5%)  |
| Level of education, years             | 11.7 (1.6) | 11.7 (2.2)  |
| Age at symptom onset, years           | 17.1 (5.4) | 15.9 (5.5)  |
| Gastrointestinal symptoms at baseline |            |             |
| "Yes"                                 | 6 (33.3%)  | 7 (33.3%)   |
| "No"                                  | 12 (66.7%) | 14 (66.7%)  |

Table 3: Cytokine levels

|                 | No. | GCD         | No. | GFD          | F    | df   | p value |
|-----------------|-----|-------------|-----|--------------|------|------|---------|
| IL-2, mean (SD) |     |             |     |              |      |      |         |
| Baseline        | 17  | 3.78 (10.8) | 19  | 33.01 (81.9) | 3.50 | 27.9 | 0.019   |
| 5 weeks         | 13  | 2.55 (7.1)  | 17  | 7.22 (18.6)  |      |      |         |

No significant treatment effects on circulating levels of IL-1β, IL-1ra, IL-4, IL-6, IL-10, IL-12, IL-13, IL-15, IL-17A, IL-18, IL-21, IL-23, IL-35, TNF-α, IFN-γ, TGF-β1, and GM-CSF.

Table 2: Primary and Secondary Clinical Outcomes on Psychiatric Measures

|   | No. | GCD         | No. | GFD         | F    | df   | p value |
|---|-----|-------------|-----|-------------|------|------|---------|
| CAINS Motivational Deficit (MAP), mean (SD) |     |             |     |             |      |      |         |
| Baseline                                    | 18  | 15.9 (5.5)  | 21  | 15.6 (6.6)  | 2.78 | 30.1 | 0.045   |
| 5 weeks                                     | 13  | 13.8 (7.0)  | 18  | 12.3 (6.7)  |      |      |         |
| CAINS Expressive Deficit (EXP), mean (SD)   |     |             |     |             |      |      |         |
| Baseline                                    | 18  | 6.9 (3.2)   | 21  | 7.7 (3.9)   | 0.31 | 30.1 | 0.870   |
| 5 weeks                                     | 13  | 5.4 (4.1)   | 18  | 5.9 (3.8)   |      |      |         |
| SANS Total, mean (SD)                       |     |             |     |             |      |      |         |
| Baseline                                    | 18  | 36.2 (10.5) | 21  | 38.2 (10.6) | 0.74 | 28.0 | 0.570   |
| 5 weeks                                     | 13  | 34.4 (13.8) | 18  | 31.8 (8.2)  |      |      |         |
| SANS Anhedonia/Asociality, mean (SD)        |     |             |     |             |      |      |         |
| Baseline                                    | 18  | 2.4 (0.7)   | 21  | 2.5 (0.9)   | 1.84 | 29.5 | 0.150   |
| 5 weeks                                     | 13  | 2.3 (1.0)   | 18  | 2.1 (0.8)   |      |      |         |
| BPRS, mean (SD)                             |     |             |     |             |      |      |         |
| Baseline                                    | 18  | 38.2 (10.7) | 21  | 37.3 (10.2) | 1.67 | 28.6 | 0.180   |
| 5 weeks                                     | 13  | 37.3 (16.2) | 18  | 32.6 (9.1)  |      |      |         |
| CDS, mean (SD)                              |     |             |     |             |      |      |         |
| Baseline                                    | 17  | 4.0 (2.9)   | 21  | 2.3 (3.0)   | 0.67 | 30.7 | 0.620   |
| 5 weeks                                     | 13  | 2.7 (2.9)   | 18  | 2.1 (3.0)   |      |      |         |
| CGI-global, mean (SD)                       |     |             |     |             |      |      |         |
| Baseline                                    | 7   | 4.1 (0.4)   | 7   | 4.0 (0.0)   | 1.08 | 9.0  | 0.420   |
| 5 weeks                                     | 13  | 3.8 (0.4)   | 18  | 3.8 (0.9)   |      |      |         |

Group mean (SD) at baseline and 5 week timepoints for GFD and GCD groups; Stats from ANCOVA models (F, df, p) with treatment group as independent variable.

Figure 2. Cerebral blood flow: effect size differences (Cohen's d) between the GFD relative to the GCD.

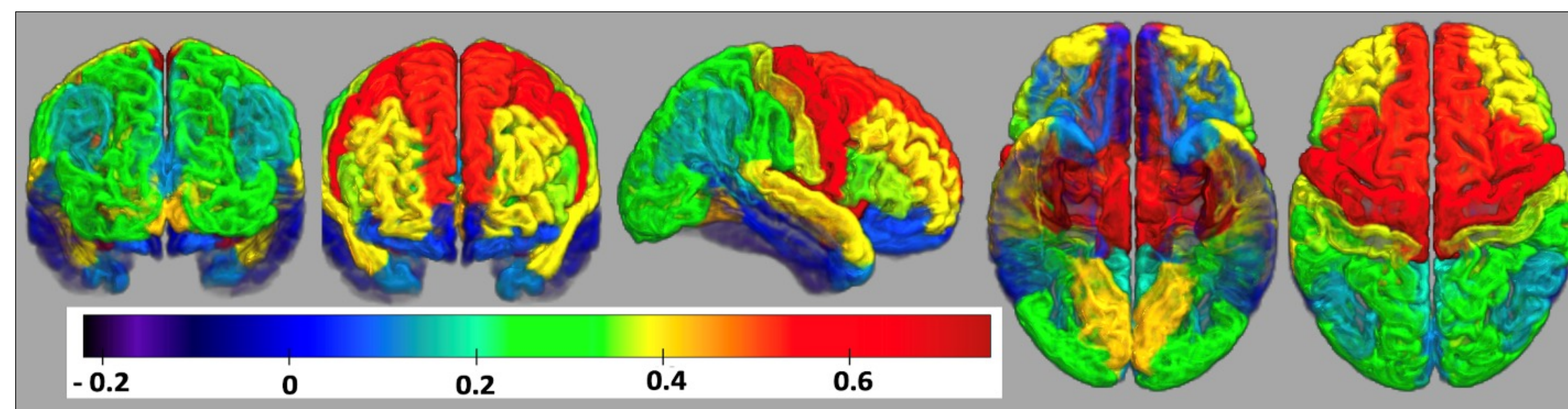
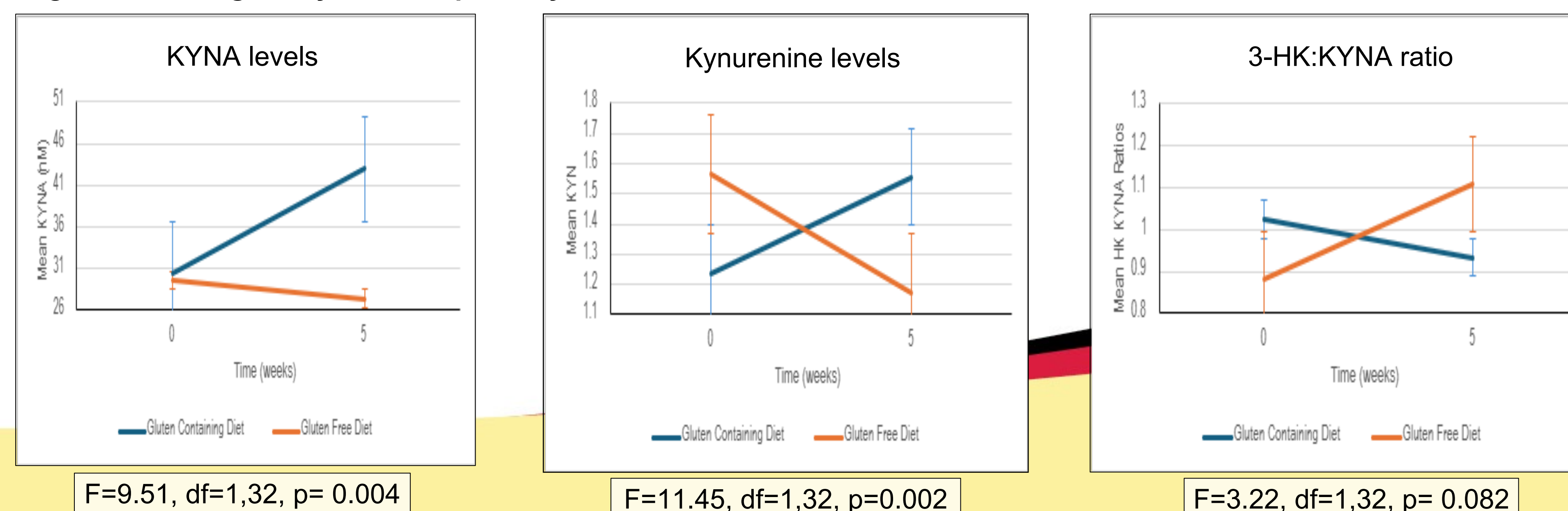


Figure 3. Change in kynurenic pathway metabolites over 5 weeks of a GFD; ANCOVA mixed model stats shown below.



(Figure 3 copied with permission from Kelly D, Eaton WW, et al. Under review, Lancet Psychiatry)

## Conclusions

**This is the first known double-blind RCT demonstrating that a GFD improves negative symptoms of SRD in AGA IgG+ persons (our third independent cohort w/ this finding).**

- Specifically, clinical improvement was found in the "experiential" domain (anhedonia, avolition), not in the "expressive" domain (blunted affect, alogia) or measures of depression or cognitive function. (Tab. 2)
- GFD decreased circulating levels of kynurenic pathway metabolites; and those decreased levels correlated with improved negative symptoms. (Fig. 3)
- GFD decreased circulating IL-2 (growth factor that regulates T cell function), agreeing with literature and suggesting mechanistic role of T cell function. (Tab. 3)
- GFD improved CBF and increased creatine in frontal and parietal regions, which are known to be associated with motivation and planning. (Fig. 2)

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## References

- Keefe RS, Poe M, Walker TM, Harvey PD. The relationship of the Brief Assessment of Cognition in Schizophrenia (BACS) to functional capacity and real-world functional outcome. J Clin Exp Neuropsychol. 2006;28(2):260-9.
- Jackson J, Eaton W, Cascella N, Fasano A, Warfel D, Feldman S, et al. A gluten-free diet in people with schizophrenia and anti-tissue transglutaminase or anti-gliadin antibodies. Schizophr Res. 2012;140(1-3):262-3.
- Kelly DL, Demyanovich HK, Rodriguez KM, Cihakova D, Talor MV, McMahon RP, et al. Randomized controlled trial of a gluten-free diet in patients with schizophrenia positive for antigliadin antibodies (AGA IgG): a pilot feasibility study. J Psychiatry Neurosci. 2019;44(4):269-76
- Pocivavsek A, Schwarcz R, Erhardt S. Neuroactive Kynurenic as Pharmacological Targets: New Experimental Tools and Exciting Therapeutic Opportunities. Pharmacol Rev. 2024;76(6):978-1008