

# Gut Permeability and Relationship to Inflammation, Antigliadin Antibodies and Kynurenine Pathway Metabolites in People with Schizophrenia

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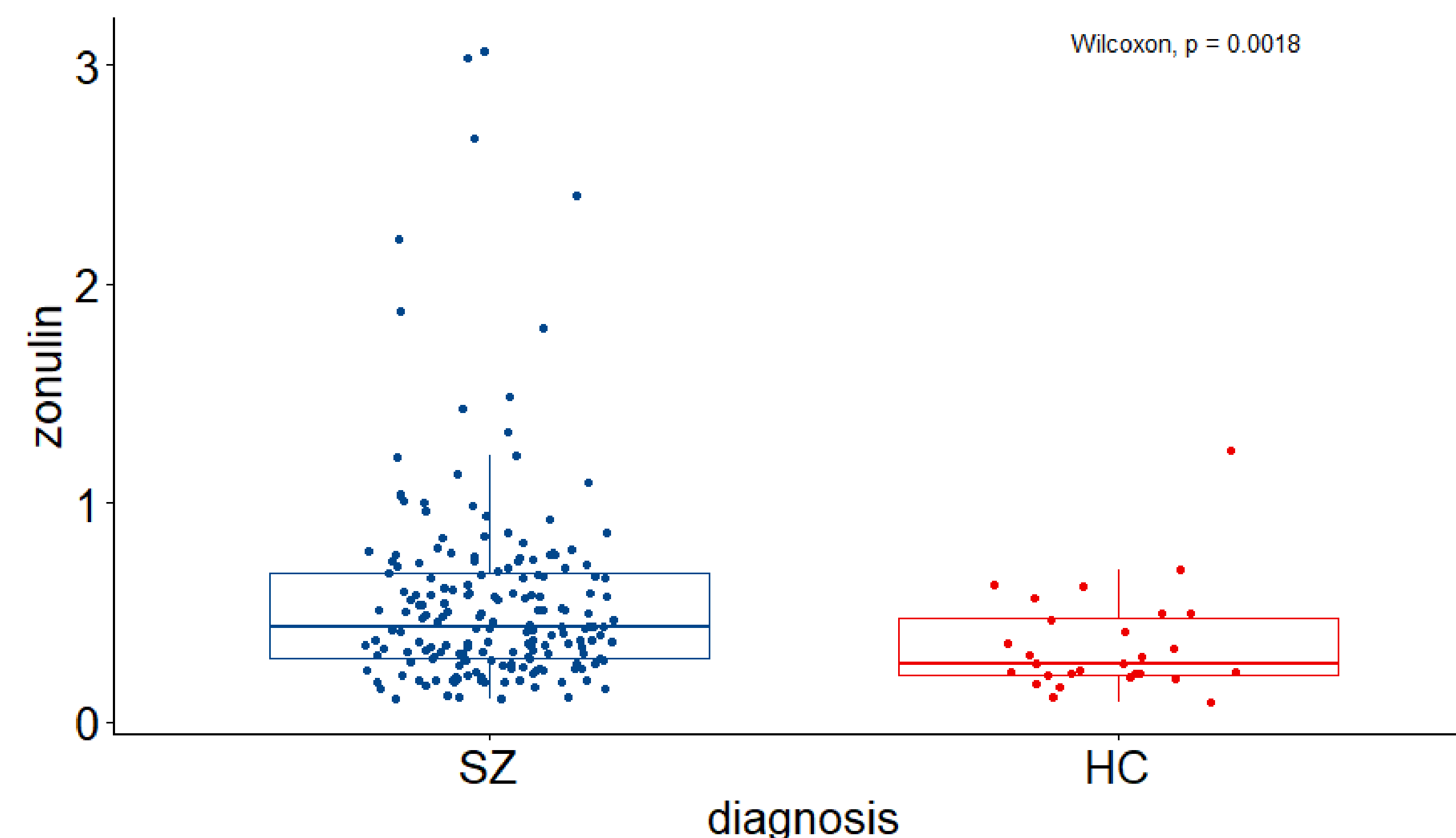
## Background

## Serum Zonulin by Diagnosis and Gluten Sensitivity

## Demographic Information

- Zonulin, an endothelial growth factor receptor stimulator, has previously been shown to regulate tight junction permeability of the gut and the blood brain barrier, but its role in the pathogenesis of schizophrenia (SZ) has only recently been investigated.
- Elevated zonulin has previously been implicated in a loss of barrier function of the gastrointestinal tract, allowing the passage of macromolecules, including endotoxins, into the body and possibly resulting in an immune response. process may lead to the establishment of chronic inflammation as suggested by many other chronic inflammatory diseases, including Celiac disease.
- A model of higher zonulin and higher IL-1 $\beta$  and TNF- $\alpha$  was associated with higher BPRS (Brief Psychiatric Rating Scale), anxiety/depression scores, and ratings of hostility, hinting that the combination of gut permeability and chronic inflammation may have some relationship to brain function.
- Here we examine the relationship of zonulin to peripheral inflammation, anti gliadin antibodies (AGA IgG) and kynurenine pathway metabolites, which are modulated by inflammation, in individuals with schizophrenia (SZ) and healthy controls (HC).

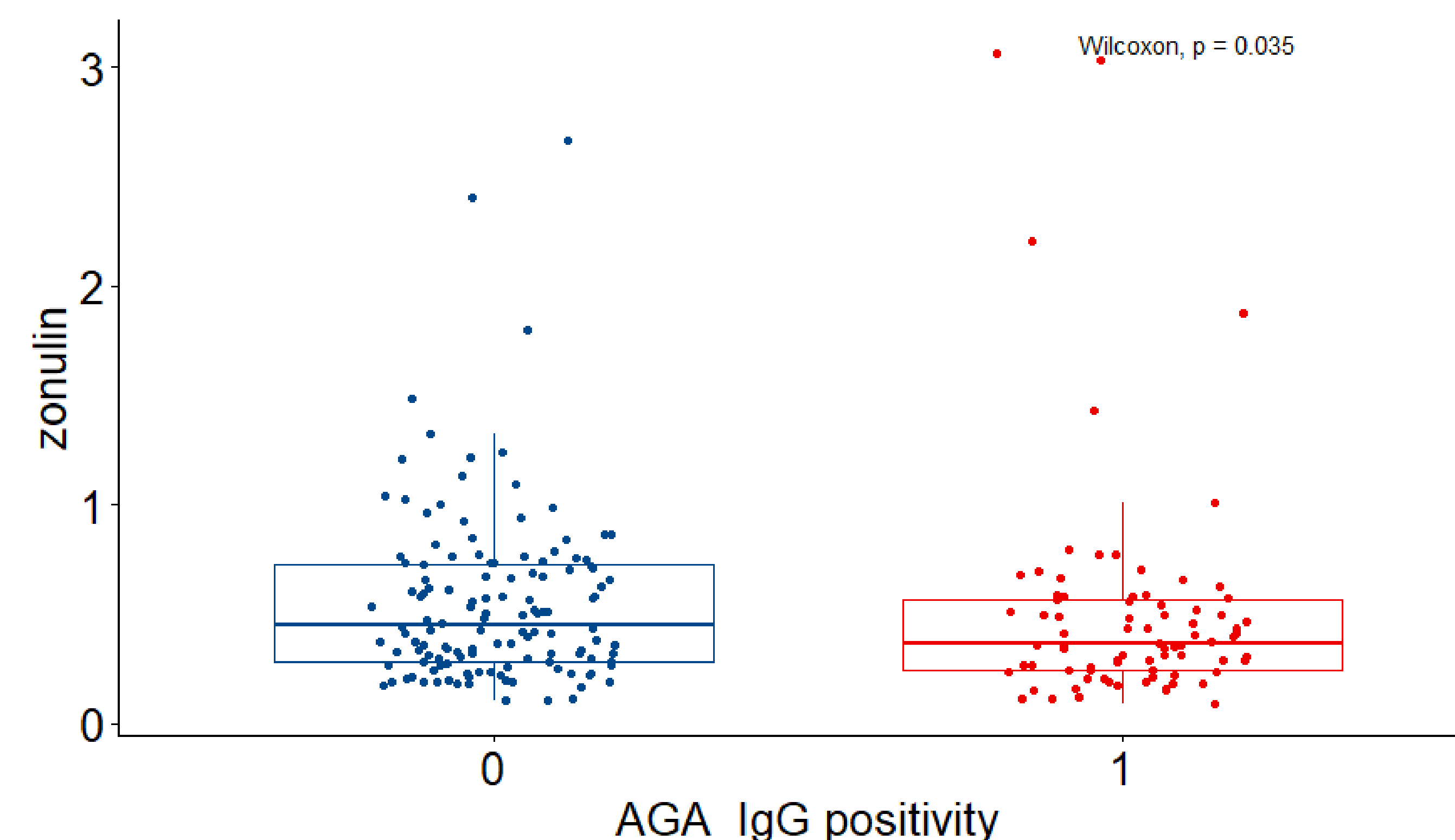
- Mean serum zonulin was elevated in the SZ group ( $\mu = 0.56$  ng/mL; SD = 0.47) in relation to the HC group ( $\mu = 0.36$  ng/mL; SD = 0.24) ( $p = 0.0018$ ).



215 participants total	Schizophrenia N=187	Healthy Control N=28	P-value
<b>Age, median</b>	42	29	0.0003
<b>Gender</b>			0.0002
Male	143 (76.5)	12 (42.9)	
Female	44 (23.5)	16 (57.1)	
<b>Race</b>			0.0226
White	80 (42.8)	15 (53.6)	
Black	91 (48.7)	7 (25.0)	
Other	16 (8.6)	6 (21.4)	

## Methods

- Mean serum zonulin level was lower in the AGA IgG positive group ( $\mu = 0.51$  ng/mL; SD = 0.53) compared to the AGA IgG negative group ( $\mu = 0.55$  ng/mL; SD = 0.39) ( $p = 0.0350$ ).



## Zonulin and Inflammatory Cytokines

- In the SZ group elevated zonulin was associated with lower IL-17A ( $r_s = -0.16$ ,  $p=0.03$ ), IL-1 $\beta$  ( $r_s = -0.25$ ,  $p=0.0008$ ), IL-6 ( $r_s = -0.25$ ,  $p=0.0007$ ), GM-CSF ( $r_s = -0.22$ ,  $p=0.0028$ ), IFN- $\gamma$  ( $r_s = -0.21$ ,  $p=0.004$ ) and a trend for IL-23 ( $r_s = -0.13$ ,  $p=0.08$ ).
- In the HC group elevated zonulin was associated with lower IL-23 ( $r_s = -0.54$ ,  $p=0.03$ ) only.
- No relationship was noted between KYNA or KYN and zonulin levels in either SZ or HC.

## Prediction of Zonulin Serum Concentration

- In a multivariable model controlling for age, race, diagnosis, and sex, we found that TNF- $\alpha$  is independently associated with higher serum zonulin ( $\beta = 0.24$ ,  $p = 0.0462$ ) and IL-6 with lower serum zonulin ( $\beta = -0.16$ ,  $p = 0.0002$ ).

## Discussion

- We replicate our earlier finding that serum zonulin levels are higher in SZ compared to HC. We found that zonulin levels were lower in SZ patients and HC with AGA IgG positivity compared to those without gluten sensitivity.
- Finding concluded in SZ that high zonulin levels are correlated to lower levels of many inflammatory markers.
- Finding demonstrates that in patients with high inflammation and a high immune response to AGA IgG, zonulin levels are lowest, suggesting a dysregulation of zonulin or a negative feedback mechanism of gut permeability. This negative correlation is of interest in understanding the unique role of zonulin in SZ.

