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RESEARCH ARTICLE OPEN ACCESS

Exploring serum neopterin and zonulin in children with attention-deficit/hyperactivity disorder: A case-control study of gut permeability and immune activation

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Abstract
Objective: Emerging evidence suggests gut-brain axis dysregulation and immune activation in ADHD. This study compared serum zonulin (intestinal permeability regulator) and neopterin (cell-mediated immunity marker) between children with ADHD and healthy controls, and explored associations with disease severity.
Methods: This case-control study enrolled 42 drug-naïve children with ADHD (combined presentation) and 42 age- and sex-matched healthy controls. Severity was categorised as mild, moderate, or severe using DSM-5-TR criteria. Serum zonulin and neopterin were measured by ELISA.
Results: Zonulin was significantly higher in ADHD versus controls (median: 16.30 vs. 12.36 ng/ml; p=0.033). Neopterin showed a non-significant elevation, but both biomarkers demonstrated a strong, statistically significant association with disease severity (p<0.001 for both). A significant positive correlation was observed between zonulin and neopterin (rho=0.941, p<0.001). Exploratory ROC analysis suggested good discriminatory ability for severe ADHD (AUC of neopterin: 0.873; zonulin: 0.847). Logistic regression identified zonulin as independently associated with ADHD case status (OR=1.206, p=0.019).
Conclusion: Elevated serum zonulin was independently associated with ADHD. Both biomarkers correlated strongly with symptom severity, and their interrelation suggests a potential link between increased gut permeability and systemic immune activation in more severe forms of ADHD. These molecules are promising exploratory biomarkers for disease staging, warranting further investigation in larger prospective studies.

Keywords: Attention Deficit Hyperactivity Disorder, Zonulin, Neopterin, Disease Severity, Gut-Brain Axis, Immune Activation

Plain English Summary

ADHD is a common condition that affects a child's ability to focus and control impulses. We still don't fully understand what causes it. Some recent ideas suggest that a child's gut health and their body's immune system might play a part. This study looked at two specific substances in the blood: one called 'zonulin', which can make the gut wall more 'leaky', and another called 'neopterin', which is a sign of the immune system being active.

We studied 42 children with ADHD who were not yet taking any medication for it, and compared them to 42 healthy children of the same age and sex. We found that children with ADHD had higher levels of zonulin in their blood. While neopterin levels weren't clearly higher in all children with ADHD, both zonulin and neopterin were much higher in the children whose ADHD symptoms were most severe. We also found a strong link between the levels of these two substances.

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These results suggest that for some children, especially those with more severe symptoms, a 'leaky gut' might be linked to a more active immune system, and this combination could influence ADHD symptoms. While this doesn't prove that gut problems cause ADHD, it opens the door for new ways of thinking about the disorder. In the future, doctors might be able to use these blood markers to understand better how severe a child's ADHD is or even explore new types of treatments that target gut health or inflammation.

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a prevalent neurodevelopmental condition characterised by persistent patterns of inattention, hyperactivity, and impulsivity that interfere with daily functioning and development (1, 2). Affecting approximately 5.9% of children and adolescents globally, it is a heterogeneous disorder with a complex aetiology involving genetic, environmental, and neurobiological factors (3). While traditionally viewed through a neurochemical lens, focusing on dopamine and norepinephrine pathways, there is a growing recognition that the pathophysiology of ADHD extends beyond the central nervous system alone (4).

A compelling new frontier in neuropsychiatric research is the role of the gut-brain axis—a bidirectional communication network linking the enteric nervous system, the gut microbiome, and the central nervous system (5, 6). Disruptions to the integrity of the intestinal barrier, often termed 'leaky gut', are increasingly implicated in various neurological and psychiatric conditions. Central to this process is zonulin, the only known physiological modulator of intercellular tight junctions in the gastrointestinal tract (7). Zonulin is a protein that reversibly regulates intestinal permeability. When its levels are chronically elevated, it can lead to increased passage of bacterial products and dietary antigens across the gut wall, potentially triggering systemic low-grade inflammation and affecting the blood-brain barrier (8, 9).

Concurrently, there is mounting evidence for immune system dysregulation in ADHD. Studies have reported elevated levels of pro-inflammatory cytokines, such as interleukin-6 and tumour necrosis factor-alpha, in individuals with ADHD (10, 11). Neopterin, a pteridine derivative synthesised by activated macrophages and dendritic cells upon stimulation by interferon-gamma, serves as a sensitive and stable marker of cell-mediated (Th1-type) immune activation and oxidative stress (12, 13). The synthesis pathway of neopterin is illustrated in Figure 1.

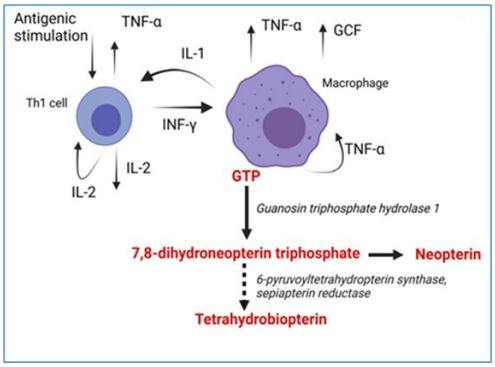


Figure 1: The synthesis of neopterin

Neopterin is produced from GTP via cyclohydrolase-I following IFN-γ stimulation. In human macrophages, 7,8-dihydroneopterin accumulates and is oxidised to neopterin

Elevated neopterin levels have been documented in several neuroinflammatory and neuropsychiatric disorders, making it a relevant molecule to study in ADHD (14).

Zonulin is an endogenous protein derived from the haptoglobin-2 precursor. It is regarded as the only modulator of physiologic intestinal permeability, belonging to the zonula occludens protein family. Upon activation, it binds its receptor PAR2, leading to reversible tight junction openings. This mechanism is summarised in Figure 2.

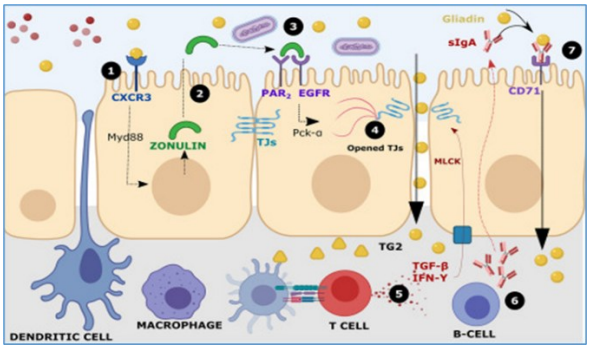


Figure 2: Zonulin role

Zonulin temporarily dissociates intestinal tight junctions via PAR2 activation, increasing epithelial permeability. Abbreviations: CXCR3, PAR2, PKC-α, TJs

While individual studies have explored either zonulin or neopterin in ADHD, few have investigated them simultaneously to understand the interplay between gut permeability and immune activation. We hypothesised that children with ADHD would exhibit altered serum levels of zonulin and neopterin compared to healthy peers, and that these levels would correlate with the clinical severity of the disorder. Therefore, the primary objective of this case-control study was to measure and compare serum concentrations of zonulin and neopterin in a cohort of drug-naïve children with ADHD and age- and sex-matched healthy controls. A secondary objective was to evaluate the association of these biomarkers with disease severity and to explore their potential as exploratory tools for disease staging.

Materials and Methods

Study Design and Participants

This was a case-control study conducted at the Babylon Teaching Hospital for Maternity and Children and affiliated private clinics in Babylon Province, Iraq, from September 2025 to February 2026. The study protocol was approved by the relevant ethics committees (see Declaration section). Verbal informed consent was obtained from the parents or legal guardians of all participants.

A total of 100 children (aged 4-18 years) were initially enrolled. Of these, 10 were excluded due to prior ADHD medication use or haemolysed serum samples. Following a statistical analysis for outlier detection (values exceeding ±3 standard deviations from the group mean), a further 6 participants (3 from each group) were excluded to meet the assumptions of parametric statistical tests, resulting in a final analytic sample of 84 participants: 42 in the ADHD group and 42 in the healthy control group. The study design is summarised in Figure 3.

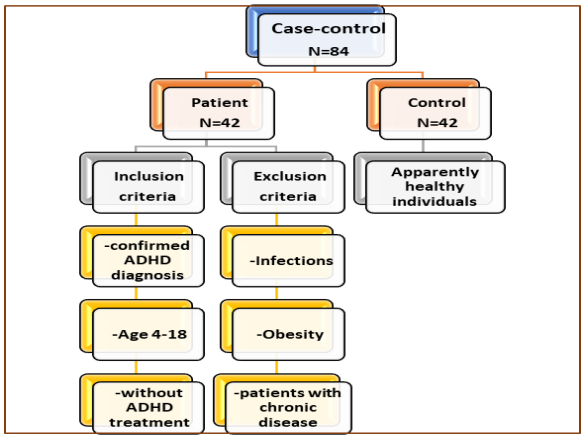


Figure 3: Study design, inclusion and exclusion criteria

Initial enrolment (N=100) → exclusions (treatment/haemolysis, n=10; outliers ±3 SD, n=6) → final analytic sample (N=84: 42 ADHD, 42 controls)

Participants in the ADHD group were diagnosed by a consultant paediatrician based on the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision (DSM-5-TR) criteria. All included patients had the combined presentation of ADHD (ADHD-C) and were treatment-naïve. Disease severity was categorised by the same clinician, based on the number and impact of symptoms as per DSM-5-TR guidelines: mild (few symptoms beyond

required for diagnosis, minor functional impairment), moderate (symptoms or functional impairment between 'mild' and 'severe'), and severe (many symptoms beyond required for diagnosis, or several particularly severe symptoms, or marked functional impairment). The severity distribution in the patient group was: mild (n=14), moderate (n=11), and severe (n=17).

Age- and sex-matched healthy controls were recruited from the same community and had no personal or family history of ADHD or any other neurodevelopmental or major psychiatric disorder.

Exclusion criteria for all participants were: autoimmune diseases (e.g., inflammatory bowel disease, type 1 diabetes, coeliac disease), acute or chronic infections, obesity (BMI ≥ 95th percentile for age and sex), and any other chronic medical condition.

Sample Collection and Biochemical Analysis

Venous blood samples (5 mL) were collected from all participants in a non-fasting state into plain gel tubes. The samples were centrifuged at 2000 x g for 20 minutes at room temperature to separate the serum. The serum was then aliquoted and stored at -20°C until analysis.

Serum concentrations of neopterin and zonulin were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits from the Bioassay Technology Laboratory Company (Shanghai, China) according to the manufacturer's instructions. The Human Neopterin ELISA kit (catalogue number E3155Hu) had a standard curve range of 0.1-38 nmol/L and a sensitivity of 0.061 nmol/L. The Human Zonulin ELISA kit (catalogue number E3704Hu) had a standard curve range of 0.3-90 ng/mL and a sensitivity of 0.13 ng/mL. All assays were performed in a single batch to minimise inter-assay variability. Due to sample volume limitations, duplicate measurements were not performed; however, the manufacturer-reported intra-assay coefficient of variation (CV) was <8% for both kits. Laboratory staff were blinded to the participants' clinical status.

Statistical Analysis

Data were analysed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, N.Y., USA) and Jamovi software (Version 2.3). The Shapiro-Wilk test was used to assess the normality of continuous variables. As most variables were non-normally distributed, data are presented as median and interquartile range (IQR). Group comparisons were performed using the Mann-Whitney U test. Comparisons across the three severity groups (mild, moderate, severe) were performed using the Kruskal-Wallis test, followed by Dunn's post-hoc test with Holm-Bonferroni correction for multiple comparisons. The strength of associations between biomarkers and other continuous variables was assessed using Spearman's rank correlation coefficient (rho). Binary logistic regression was employed to identify variables independently associated with ADHD case status. The diagnostic performance of neopterin and zonulin for differentiating severe ADHD from mild/moderate ADHD was explored using receiver operating characteristic (ROC) curve analysis, with the area under the curve (AUC) reported. A two-tailed p-value < 0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics

The ADHD and control groups were well-matched for age (ADHD: 7.61 ± 3.36 years; Control: 8.79 ± 4.01 years; p=0.214) and body mass index (BMI) (ADHD: 19.91 ± 4.71 kg/m²; Control: 20.55 ± 5.19 kg/m²; p=0.495). The ADHD group had a higher proportion of boys (52.5%) than girls (43.5%), as shown in Figures 4A and 4B.

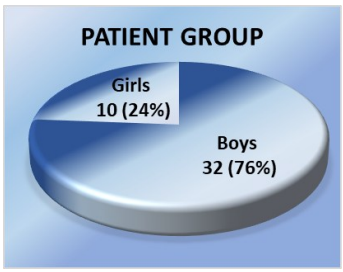


Figure 4A: Sex distribution in the patient group

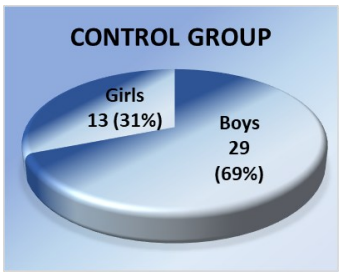


Figure 4B: Sex distribution in the control group

A substantial proportion of the ADHD group had a positive family history for the disorder (76%) and a history of speech delay (76%), highlighting potential genetic and developmental comorbidities. These findings are presented in Figures 5 and 6.

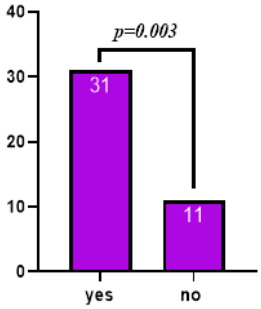


Figure 5: Family history distribution in the patient group
Positive family history = 76%

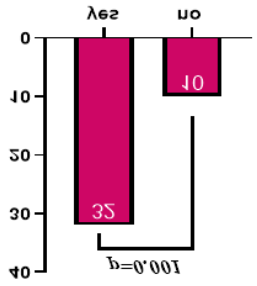


Figure 6: Speech delay in the patient group
Speech delay prevalence = 76%

Comparison of Biomarkers Between Groups
As shown in Table 1, serum zonulin levels were significantly higher in the ADHD group (median: 16.30 ng/ml, IQR: 12.23) compared to the control group (median: 12.36 ng/ml, IQR: 8.79), p = 0.033. While the median serum neopterin level was slightly elevated in the ADHD group (5.32 nmol/L, IQR: 4.43) compared to controls (4.28 nmol/L, IQR: 4.39), this difference did not reach statistical significance (p = 0.207). These comparisons are visualised in Figure 7.

Table 1: Comparison of Biochemical Parameters between ADHD Patients and Healthy Controls

Parameter	Group	Median (IQR)	p-value (Mann-Whitney U)	Effect Size (Rank biserial)
Zonulin (ng/mL)	ADHD (n=42)	16.30 (12.23)	0.033	0.271
	Control (n=42)	12.36 (8.79)		
Neopterin (nmol/L)	ADHD (n=42)	5.32 (4.43)	0.207	0.16
	Control (n=42)	4.28 (4.39)		

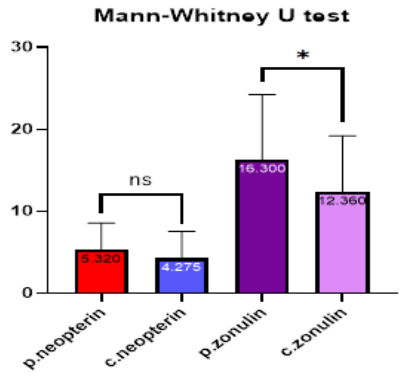


Figure 7: Comparison of zonulin and neopterin between patients and controls
Zonulin: p=0.033; neopterin: p=0.207

Association of Biomarkers with Disease Severity
A strong, statistically significant association was found between disease severity and both biomarkers (Kruskal-Wallis test, p < 0.001 for both neopterin and zonulin). Post-hoc analysis revealed that children with severe ADHD had significantly higher levels of both neopterin and zonulin compared to those with mild or moderate ADHD (p < 0.05). No significant differences were observed between the mild and moderate groups for either biomarker (Table 2). These results are displayed in Figures 8A (neopterin) and 8B (zonulin).

Table 2: Pairwise Comparison of Biomarkers According to ADHD Severity (Dunn's Post-hoc Test)

Biomarker	Comparison	Median (IQR)	p-value	p_{holm}
Neopterin	Mild vs. Moderate	3.03 (2.60) vs. 5.31 (1.21)	0.137	0.137

	Mild vs. Severe	3.03 (2.60) vs. 10.22 (14.38)	<0.001	<0.001
	Moderate vs. Severe	5.31 (1.21) vs. 10.22 (14.38)	0.015	0.03
Zonulin	Mild vs. Moderate	12.83 (8.23) vs. 13.51 (3.21)	0.684	0.684
	Mild vs. Severe	12.83 (8.23) vs. 27.65 (37.35)	<0.001	0.001
	Moderate vs. Severe	13.51 (3.21) vs. 27.65 (37.35)	0.005	0.009

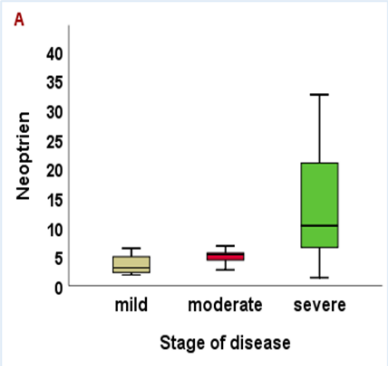


Figure 8A: Neopterin levels by ADHD severity
Significant difference (p<0.001), severe > mild/moderate

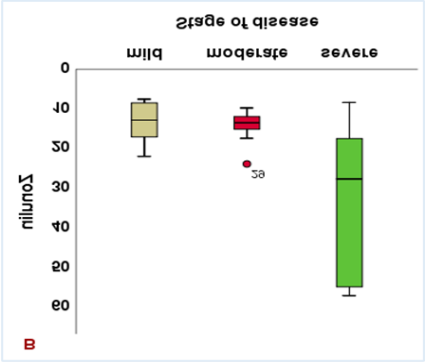


Figure 8B: Zonulin levels by ADHD severity
Significant difference (p<0.001), severe > mild/moderate

Correlations and Regression Analysis
A very strong, significant positive correlation was observed between serum zonulin and neopterin levels (Spearman's rho = 0.941, p < 0.001), as illustrated in Figure 9. Both biomarkers also showed a significant positive correlation with the stage of disease (severity) (p < 0.001 for both). No significant correlations were found between either biomarker and age or BMI (Table 3).

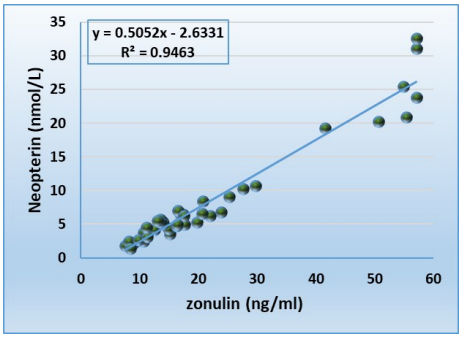


Figure 9: Correlation between zonulin and neopterin
Spearman's rho = 0.941, p<0.001

Table 3: Spearman's Rank Correlation Coefficients (rho) Among Study Parameters

Variable	Zonulin	Neopterin	Age	BMI	Stage of Disease
Zonulin	---	0.941 (<0.001)	-0.072 (0.652)	0.166 (0.294)	0.562 (<0.001)
Neopterin	0.941 (<0.001)	---	0.003 (0.984)	0.220 (0.161)	0.673 (<0.001)

Note: Values are rho (p-value). Statistically significant correlations (p<0.001) are bolded.

Binary logistic regression, with ADHD case status as the dependent variable, identified serum zonulin as the only factor independently associated with the risk of having ADHD (Odds Ratio = 1.206, 95% CI: 1.031-1.411, p = 0.019). Neopterin, age, and BMI were not significant predictors in this model.

Exploratory Diagnostic Performance for Severity

ROC curve analysis was performed to explore the ability of each biomarker to discriminate between participants with severe ADHD (n=17) and those with mild/moderate ADHD (n=25). Neopterin demonstrated excellent discriminatory ability with an AUC of 0.873 (95% CI: 0.740-1.000). A cut-off value of 6.4 nmol/L yielded 100% specificity and 77% sensitivity. Zonulin also showed good performance with an AUC of 0.847 (95% CI: 0.711-0.983). A cut-off value of

20.2 ng/mL gave a specificity of 93% and a sensitivity of 71% (Figure 10). These results, while promising, are exploratory and derived from a single sample without external validation.

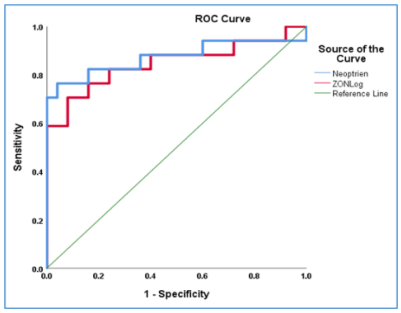


Figure 10: ROC curves for neopterin and zonulin
Neopterin AUC = 0.873, zonulin AUC = 0.847

Discussion

This study investigated the potential link between gut permeability and immune activation in children with ADHD by measuring serum levels of zonulin and neopterin. Our primary findings reveal that children with ADHD have significantly elevated zonulin levels compared to healthy controls, and that zonulin is independently associated with ADHD case status. While neopterin levels were not significantly elevated across the entire ADHD group, both zonulin and neopterin showed a powerful, graded association with the clinical severity of ADHD. Furthermore, the strong positive correlation between these two molecules suggests a functional interplay between intestinal barrier dysfunction and systemic cell-mediated immunity, particularly in more severe forms of the disorder.

Zonulin, Gut Permeability, and ADHD

Our finding of elevated zonulin in children with ADHD aligns with several previous studies (8, 15, 16), though some have reported non-significant trends (17, 18). This consistency lends weight to the hypothesis that increased intestinal permeability may be a feature of ADHD in a substantial subset of patients. Zonulin is the master regulator of paracellular permeability; its elevation leads to the opening of tight junctions between enterocytes, allowing the passage of bacterial products (e.g., lipopolysaccharides, LPS) and dietary antigens into the bloodstream (7). This process, often referred to as 'leaky gut', can trigger a systemic low-grade inflammatory state. In the context of ADHD, such systemic inflammation could have direct consequences for the brain. Circulating inflammatory mediators can compromise the integrity of the blood-brain barrier, activate microglia, and disrupt neurotransmitter systems, including dopamine and norepinephrine pathways, which are central to the pathophysiology of ADHD (9, 19). The fact that zonulin was a significant predictor of ADHD case status in our regression model further supports its potential relevance.

Neopterin, Immune Activation, and Disease Severity

Although neopterin did not distinguish the overall ADHD group from controls, its striking elevation in the severe ADHD subgroup is a key finding. This suggests that marked cell-mediated immune activation is not a universal feature of all ADHD cases but may characterise a more severe clinical phenotype. This aligns with the concept of 'sickness behaviour', where systemic inflammation leads to symptoms like fatigue, psychomotor slowing, reduced social engagement, and cognitive impairment—symptoms that can overlap with and exacerbate inattention and motivational deficits seen in severe ADHD (20). Mechanistically, neopterin, produced by macrophages upon IFN-γ stimulation, is a robust marker of Th1-type immune responses and oxidative stress (13). Elevated neopterin could signal the presence of chronic, low-grade inflammation that, via cytokines, can alter tryptophan metabolism along the kynurenine pathway. This diversion from serotonin synthesis towards the production of neuroactive metabolites like quinolinic acid could contribute to the neurochemical imbalances underlying severe ADHD symptoms (21).

The Gut-Immune-Severity Axis: An Integrated View

The most compelling finding of our study is the exceptionally strong positive correlation between zonulin and neopterin, coupled with their independent association with disease severity. To our knowledge, this is the first report of such a direct correlation in a drug-naïve, combined-type ADHD cohort. This data provides plausible correlational evidence for a model where increased gut permeability (indexed by zonulin) leads to systemic immune activation (indexed by neopterin), which in turn may exacerbate ADHD

symptoms, particularly in severe cases. The 'threshold effect' observed—where levels of both markers are similar in mild and moderate cases but dramatically higher in severe cases—suggests that a critical level of gut barrier dysfunction and immune activation may need to be breached before they exert a clinically noticeable impact on symptom severity.

Study Limitations

This study has several important limitations. First, the cross-sectional design precludes any inference of causality. We cannot determine whether elevated zonulin and neopterin contribute to ADHD severity, are a consequence of severe ADHD (e.g., via stress-induced gut changes), or are both driven by a third, unmeasured variable. Second, the sample size, while comparable to similar studies, is relatively modest. The exclusion of 'extreme values' (defined as ±3 SD from the mean) was performed post-hoc, which, while improving the robustness of statistical tests, introduces a potential bias. Third, the lack of duplicate ELISA measurements, while mitigated by a low reported intra-assay CV, is a methodological weakness that could affect the precision of our absolute concentration estimates. Fourth, we did not perform direct assessments of gut permeability (e.g., lactulose/mannitol test) or detailed gut microbiome analysis, which would have strengthened our interpretation. Finally, our ROC analyses are exploratory, performed on the same dataset used to derive the associations, and thus their reported sensitivity and specificity are likely over-optimistic and require validation in an independent cohort.

Conclusion

This study demonstrates that in a cohort of children with drug-naïve, combined-type ADHD, elevated serum zonulin is independently associated with the disorder, while both zonulin and neopterin show a strong, graded association with clinical severity. The powerful correlation between these two markers provides novel, exploratory evidence linking increased gut permeability and systemic immune activation, particularly in severe ADHD. These findings suggest that zonulin and neopterin are promising exploratory biomarkers that warrant further investigation for disease staging and may point towards a subpopulation of patients with a distinct gut-immune pathophysiology. Future prospective, longitudinal studies with larger sample sizes, direct measures of gut permeability, and external validation of these biomarkers are essential to confirm these findings and to explore whether modulating gut barrier function or immune response could represent novel therapeutic avenues.

List of Abbreviations

ADHD: Attention-Deficit/Hyperactivity Disorder
AUC: Area Under the Curve
BMI: Body Mass Index
CI: Confidence Interval
CV: Coefficient of Variation
DSM-5-TR: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision
ELISA: Enzyme-Linked Immunosorbent Assay
IFN-γ: Interferon-gamma
IQR: Interquartile Range
LPS: Lipopolysaccharide
OR: Odds Ratio
ROC: Receiver Operating Characteristic
Th1: Type 1 T-helper cell

Declarations

Ethics Approval and Consent to Participate

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Approval was obtained from the scientific research ethics committee at the University of Babylon/College of Medicine (Approval Document No. 5.66, dated September 18, 2025) and the Health Department of Babylon. Verbal informed consent was obtained from the parents or legal guardians of all participating children. The consent process was reviewed and approved by the local ethics committee.

Consent for publication

The author gave consent for the publication of the work under the Creative Commons Attribution-Non-Commercial 4.0 license.

Data Availability

The datasets generated and/or analysed during the current study are not publicly available due to local institutional restrictions and the need to protect participant confidentiality, but are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Author Contributions

YMJ worked on the Conceptualisation, Methodology, Investigation, Formal Analysis,

Writing of the Original Draft, Writing of the Review & Editing and Visualisation.
ASA did the Conceptualisation, Methodology, Validation, Resources, Supervision, Writing of Review & Editing.
JN worked on the Methodology, Validation, Clinical Assessment (patient diagnosis and severity classification), Writing of Review & Editing.
All authors reviewed and approved the final version of the manuscript.

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