



The systemic immune-inflammation index (SII) as a biomarker for depression in a community sample of adolescents

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ABSTRACT

Background: Depression is associated with increased levels of pro-inflammatory biomarkers in children and adolescents. As research to date has primarily focused on inflammatory cytokines, the potential role of white blood cells (WBCs) and platelets in the inflammatory response is not well understood. This study examines the association of blood cell based inflammatory indices, including the systemic immune-inflammation index (SII), and depressive symptoms in participants in the Adolescent Brain Cognitive Development Study.

Methods: Adolescents were recruited from community settings and completed self-report measures of depression symptoms and semi-structured psychiatric interview to determine depression diagnosis. Participants provided blood samples to obtain absolute counts of neutrophil, lymphocyte, monocyte, and platelet levels for calculation of inflammatory indices. The association between depression and inflammatory markers was examined while accounting for participant age, sex, ethnicity, comorbid psychiatric disorder, parental education and annual household income.

Results: Of 858 participants (mean age: 12.4 ± 1.1 years; 45 % female), 101 received a diagnosis of a depressive disorder. Greater depressive symptoms were significantly associated with higher neutrophil and platelet levels ($\beta = 0.013$ and $\beta = 0.018$, respectively) and higher SII ($\beta = 0.012$), after adjusting for covariates. Diagnosis of depression was not associated with WBC levels or indices.

Conclusions: In this community-based sample of adolescents, greater depressive symptoms were associated with elevated SII and individual white blood cell levels. Future studies using larger, longitudinal clinical samples are needed to confirm the potential role of the SII in adolescent depression, and the involvement of inflammation in early-onset depression.

1. Introduction

Depression is one of the most common mental health disorders among children and adolescents globally, with higher incident rates among girls compared to boys [1,2]. Depression can have a significant impact on life quality, including reduced social connectedness and decreased school performance, and is a risk factor for poor physical health [3]. However, the diagnosis of depression in children can be challenging due to heterogeneous and developmental differences in presentations, compared with adults [4]. Childhood depression results from the interaction of multiple biological and psychosocial factors [5]. One biological pathway of interest is the immune system, as inflammation has been reported to be a pathophysiological mechanism of early

onset depression [6]. Indeed, previous research has shown that depressed children and adolescents exhibit altered cytokine levels, including increased interleukin 6, decreased tumor necrosis factor alpha, and decreased interferon gamma concentrations, compared with healthy controls [7,8].

While research to date has focused on inflammatory cytokines in investigating the potential role of inflammation in depression, the process of acquiring and analyzing inflammatory markers is expensive and labor-intensive. Assessment of white blood cell concentrations presents a less demanding alternative as it is part of routinely and commonly used complete blood counts. White blood cells are part of the innate and adaptive immune system, secreting inflammatory cytokines as a response to molecular cues [9,10]. The innate immune system is a

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non-specific defense system that initiates a rapid immune response, while the adaptive immune system is a memory-based defense mechanism that targets specific pathogenic intruders [10]. A recent meta-analysis of 27 studies examining levels of various white blood cells in depressed versus healthy adults found increased counts of neutrophils and monocytes and decreased counts of lymphocytes in participants with depression compared to controls [11]. In addition to examining individual concentrations of white blood cells, newer research has examined white blood cell ratios and indices to better understand the balance between the innate and the adaptive immune system. The neutrophil-to-lymphocyte ratio (NLR), the monocyte-to-lymphocyte ratio (MLR), and the systemic immune-inflammation index (SII) have been shown to act as more sensitive indicators of inflammation markers in adults with psychiatric disorders than individual white blood cell counts [12–14]. Elevated NLR and MLR indicate an overactive non-specific immune response due to increased levels of neutrophils and monocytes, respectively, which play a crucial role in the innate immune system, and a relative decrease in lymphocyte levels, which are part of the adaptive immune system [15,16]. The SII has similar characteristics, however, is thought to better reflect the balance between innate and adaptive immunity due its inclusion of platelet levels [17]. Platelets interact with cells of the innate and adaptive immune system, potentially escalating inflammatory processes and autoimmune responses [18].

Research findings regarding specific white blood cell markers present among adolescents with depression have been mixed, with individual studies reporting lymphocytes to be either elevated [19] or unchanged [20–23], reporting neutrophils to be either increased [20,21,23] or unchanged [22], platelets to be either increased [21,23] or unchanged [20,22], and NLR to be either increased [20–22] or unchanged [23] compared with healthy controls. Of white blood cell indices, research is more limited still, with only one study reporting an increase in SII among children and adolescents with depression who have attempted suicide, when compared with depressed youth without a history of suicide attempt [24]. Reasons for inconsistencies among previous research may include varying participant age range (i.e., depressed children 9–18 years old) and different diagnostic tools for assessment of a depressive disorder, decreasing comparability between studies. Moreover, while research in depressed adults has shown that the SII is a more sensitive index of immune system imbalance, the examination of this promising biomarker in depressed children and adolescents has received less attention. Thus, the primary objective of this study was to contribute new insights into the association between the SII and child and adolescent depression by investigating the association between depression and white blood cell levels in a community sample of children and adolescents. The secondary objective was to investigate potential moderating effects of sex on associations between depression and white blood cell levels, given the higher prevalence of depression among girls compared with boys in this age group.

2. Methods

2.1. Participants

This study used de-identified, publicly available participant data from The Adolescent Brain Cognitive DevelopmentSM Study (ABCD Study®), a longitudinal study of children and adolescents followed from ages 9–10 years into early adulthood [25]. Participants were recruited through public and private schools from 21 sites across the United States, using probability sampling to ensure representation of demographic and socioeconomic characteristics of the general population [26]. Further information about design and characteristics of the ABCD study can be found elsewhere [27]. Participants with existing data on measures of mental health, inflammation, and demographics were retained. The current study was limited to cross-sectional data from 858 children and adolescents (11–16 years) that participated at one of the

three timepoints as mental health and blood count data were not available simultaneously during subsequent time points in the ABCD Study (data release 5.1). The ABCD Study was approved by the institutional review boards at all participating institutions. Children and adolescents provided informed written assent to participate in the study, while caregivers gave informed written consent.

2.2. Measures

2.2.1. Depression

Diagnosis of depression was determined using the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS), a semi-structured diagnostic interview designed to assess psychiatric disorders among children and adolescents (7–17 years old) [28]. KSADS assessments from adolescents and their caregivers were integrated to classify participants into two groups, defined as 1) depression group (participants or their caregivers reported a current or lifetime diagnosis of depressive disorder) and 2) control group (participants and their caregivers reported no current or lifetime diagnosis of depressive disorder), as is consistent with previous literature [29,30]. Caregivers of participants completed the Child Behavior Checklist (CBCL) to assess the severity of behavioral and emotional problems [31]. Using the CBCL depression subscale, depressive symptoms norm-referenced T-scores were obtained for the current analyses and used as continuous measures, with T-scores between 65 and 69 suggesting at-risk symptom levels and T-scores ≥ 70 indicative of clinical significance.

2.2.2. Inflammatory markers

Adolescents provided blood samples for a complete blood count, which included monocytes, neutrophils, lymphocytes, and platelets. The NLR (absolute neutrophil count / absolute lymphocyte count), MLR (absolute monocyte count / absolute lymphocyte count), and SII (NLR * absolute platelet count) were calculated for all participants.

2.2.3. Covariates

Participant age, sex, ethnicity, and comorbid psychiatric disorder (i.e., bipolar disorder, schizophrenia, anxiety disorder, obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, oppositional defiant disorder, conduct disorder, autism spectrum disorder, post-traumatic stress disorder) as well as parental education and annual household income were included as covariates. Ethnicity was examined as European and Non-European ancestry; comorbid psychiatric disorder was examined as present (any comorbid diagnosis) or absent; parental education was grouped into high school or less (low) and college or higher (high) for analyses; annual household income was considered as $< \$75,000$ USD (low) and $\geq \$75,000$ USD (high) to indicate participant socioeconomic status [32].

2.3. Statistical analysis

Data were cleaned and analyzed using R Statistical Software [33,34]. Data analysis was restricted to cross-sectional study design due to the limited availability of simultaneous mental health and blood count data at a single time point. Mental health assessments and blood draws were conducted at the same study visit, on one occasion. [25,27]. For monocyte levels, neutrophil levels, lymphocyte levels, platelet levels, NLR, MLR, SII, and depressive symptoms, Pearson's correlation was conducted to examine the association between the variables. Since depression diagnosis was dichotomous, a point-biserial correlation was calculated to investigate the association with the other continuous measures. Linear regressions were applied to examine relationships between depression severity, depression diagnosis, and inflammatory markers. Based on a meta-analysis showing that the direction of association from childhood depression to inflammation was stronger than the reverse direction [7], we used separate models to look at associations between depression severity (continuous) and depression diagnosis

(coded as 1 = depression diagnosis and 0 = no diagnosis) predicting inflammatory markers. In detail, model 1 examined the association between depressive symptoms (measured via CBCL) and inflammatory markers, while model 2 examined associations between depression diagnosis (measured via KSADS) and inflammatory markers. For both models, adjusted analyses were conducted to control for covariates (i.e., age, sex, ethnicity, comorbid psychiatric disorder, parental education, and annual household income). As the prevalence of depression in adolescence is increased in girls, as compared with boys, secondary data analyses examined whether the association between either depression symptom severity or diagnosis and inflammatory outcomes were moderated by sex.

3. Results

3.1. Participant characteristics

Details of demographic and mental health characteristics of the participants included in this study can be found in Table 1. The mean age of participants was 12.4 years (SD = 1.1, Range: 11–16 years), and 45 % were female. Of the 858 adolescents with complete blood count data, 101 had a clinical diagnosis of a depressive disorder and 757 had no depression diagnosis. Inflammatory markers, measured as white blood cell counts and ratios, exhibited normal distribution.

3.2. Correlations between depression and inflammation

Bivariate correlations among depressive symptoms, depression diagnosis, and inflammatory markers are presented in Table 2. Levels of monocytes, lymphocytes, neutrophils, and platelets were positively correlated with one another, ranging from small to medium effects ($r = .13$ to $.41$). As expected, monocyte, neutrophil, and platelet levels were positively associated with their respective inflammatory ratios (NLR, MLR) and with the SII ($r = .13$ to $.78$), while lymphocyte levels were negatively correlated with NLR, MLR, and the SII ($r = -.30$ to $-.45$) indices. Depressive symptoms were positively correlated with

monocyte, neutrophil, and platelet levels as well as the SII ($r = .08$ to $.11$). Depression diagnosis was positively correlated with depressive symptoms ($r = .34$) and showed no significant associations with the inflammatory markers.

3.3. Associations between depressive symptoms and inflammatory markers

Associations between depressive symptoms and levels of inflammatory markers, after controlling for covariates, are presented in Table 3. Unadjusted analyses are shown in Supplementary Table 1, and model fit indices of adjusted and unadjusted models are shown in Supplementary Table 2. Depressive symptoms were significantly and positively associated with levels of neutrophils ($\beta = 0.013$, $p = .03$) and platelets ($\beta = 0.018$, $p = .004$), after adjusting for covariates. Depressive symptoms were significantly associated with the SII ($\beta = 0.012$, $p = .04$), with greater depressive symptoms associated with higher SII values, after adjusting for covariates. There were no significant associations between depressive symptoms and levels of monocytes and lymphocytes as well as the NLR or MLR, after adjusting for covariates. Sex was not observed to moderate the association between depressive symptoms and levels of monocytes ($\beta = -0.011$, $p = .32$), neutrophils ($\beta = -0.010$, $p = .36$), lymphocytes ($\beta = -0.0003$, $p = .98$), platelets ($\beta = 0.007$, $p = .53$), NLR ($\beta = -0.007$, $p = .56$), MLR ($\beta = -0.009$, $p = .41$), or SII ($\beta = -0.003$, $p = .75$).

3.4. Associations between depression diagnosis and inflammatory markers

Associations between depression diagnosis and levels of inflammatory markers, after controlling for covariates, are presented in Table 3. Unadjusted analyses are shown in Supplementary Table 1, and model fit indices of adjusted and unadjusted models are shown in Supplementary Table 2. Diagnosis of depression was not associated with monocytes, neutrophils, lymphocytes, or platelets levels, and was not associated with any of the inflammatory ratios (MLR, NLR or SII). Two-way interactions did not reveal moderating effects of sex on the associations between depressive diagnosis and levels of monocytes ($\beta = 0.001$, $p = .99$), neutrophils ($\beta = -0.197$, $p = .35$), lymphocytes ($\beta = 0.054$, $p = .80$), platelets ($\beta = 0.177$, $p = .40$), NLR ($\beta = -0.201$, $p = .34$), MLR ($\beta = -0.007$, $p = .98$), or the SII ($\beta = -0.093$, $p = .66$).

4. Discussion

This study examined the associations between depression, white blood cell markers and related inflammatory indices in a community sample of adolescents, and sought to investigate potential moderating effects of sex on associations between depression and inflammation. The results demonstrated a positive association between depressive symptoms and the SII as well as individual white blood cell levels. However, sex did not moderate these relationships. These associations were observed only at the symptom, and not the diagnostic, level.

In this study, depressive symptoms were positively associated with the SII in a community sample of adolescents. Cui and colleagues also found a positive association between the SII and depressive symptoms among depressed children who had attempted suicide [24]. However, the potential moderating effects of suicidality on the association were not accounted for, such that whether elevated depressive symptoms were associated with greater SII values in the absence of suicidal behavior was unable to be determined. Findings of the current study are also consistent with those reported in adult samples. For example, in a cross-sectional study of 29,001 adults in the community, Li and colleagues reported positive associations between the SII and depressive symptoms as well as depression risk [35]. In another study of 1312 adults with a diagnosis of a depressive disorder, individuals with moderate to severe major depression symptoms demonstrated increased SII

Table 1
Participant characteristics by study group.

Total: N = 858	Depressed	Control
Sample (n)	101	757
Age - M (SD)	12.7 (1.1)	12.3 (1.1)
CBCL Dep Score - M (SD)	59.3 (9.1)	53.0 (5.0)
Sex at birth		
Female - % (n)	49.5 % (50)	43.9 % (332)
Male - % (n)	50.5 % (51)	56.1 % (425)
Ethnicity		
European Ancestry - % (n)	51.5 % (52)	64.3 % (487)
Non- European Ancestry - % (n)	48.5 % (49)	35.7 % (270)
Annual Household Income		
High (≥ 75k) - % (n)	37.6 % (38)	59.3 % (449)
Low (<75k) - % (n)	62.4 % (63)	40.7 % (308)
Parent Education		
High (≥ College) - % (n)	60.4 % (61)	71.3 % (540)
Low (<College) - % (n)	39.6 % (40)	28.7 % (217)
Comorbid Psychiatric Disorder		
Bipolar Disorder	10.9 % (11)	7.3 (55)
Schizophrenia	5.0 % (5)	1.3 % (10)
Anxiety Disorder	61.4 % (62)	23.4 % (177)
Obsessive-Compulsive Disorder	17.8 % (18)	5.2 % (39)
Attention-Deficit/Hyperactivity Disorder	25.7 % (26)	11.5 % (87)
Oppositional Defiant Disorder	25.7 % (26)	10.3 % (78)
Conduct Disorder	14.9 % (15)	2.8 % (21)
Autism Spectrum Disorder	27.7 % (28)	14.9 % (113)
Post-Traumatic Stress Disorder	12.9 % (13)	3.4 % (26)

Note. CBCL Dep Score: Child Behavior Checklist depression subscale norm-referenced T-score (T-score <65 = normal range, T-score 65–69 = at-risk, T-score ≥70 = clinical significance). High Annual Household Income: ≥ \$75,000 USD. High Parent Education: ≥ College.

Table 2

Bivariate correlations among depression diagnosis, depressive symptoms, and inflammatory markers.

Variable	<i>M (SD)</i>	1	2	3	4	5	6	7	8
1. Monocytes	0.50 (0.19)								
2. Neutrophils	3.26 (1.39)	0.41**							
3. Lymphocytes	2.39 (0.67)	0.26**	0.13**						
4. Platelets	320.60 (81.55)	0.18**	0.29**	.17**					
5. NLR	1.46 (0.76)	0.20**	0.78**	−0.45**	0.13**				
6. MLR	0.22 (0.10)	0.71**	0.29**	−0.42**	0.05	0.54**			
7. SII	476.14 (303.74)	0.24**	0.76**	−0.30**	0.54**	0.87**	.45**		
8. Depressive Symptoms	53.73 (5.98)	0.08*	0.09*	.05	0.11**	0.06	0.04	0.10**	
9. Depression Diagnosis	0.12 (0.32)	0.01	0.01	0.02	0.06	0.03	0.02	.04	0.34**

Note. *M* and *SD* are used to represent mean and standard deviation, respectively. * indicates $p < .05$. ** indicates $p < .01$.

Table 3

Associations between a) depressive symptoms and levels of inflammatory markers and b) depression diagnosis and levels of inflammatory markers, after controlling for covariates.

Inflammatory Markers	a) Depressive Symptoms			b) Depression Diagnosis		
	β	95 % CI	<i>p</i>	β	95 % CI	<i>p</i>
Monocytes	0.010	−0.001; 0.022	.08	−0.018	−0.235; 0.200	.87
Neutrophils	0.013	0.001; 0.025	.03	−0.078	−0.293; 0.137	.48
Lymphocytes	0.010	−0.002; 0.022	.09	0.094	−0.122; 0.310	.39
Platelets	0.018	0.006; 0.029	.004	0.102	−0.115; 0.318	.36
NLR	0.005	−0.007; 0.017	.39	−0.032	−0.248; 0.183	.77
MLR	0.002	−0.010; 0.014	.73	−0.026	−0.244; 0.192	.81
SII	0.012	0.001; 0.024	.04	−0.030	−0.244; 0.184	.79

Note. Adjusted models controlled for participant age, sex, ethnicity, comorbid psychiatric disorder, parental education, and annual household income.

values when compared with those with mild depression symptoms [36].

The observation of an elevated SII in adolescents with increased depressive symptoms suggests an alteration in the immune system. Given the composition of the SII, an elevated level of the index indicates an overactive innate immune system via increased neutrophil and platelet levels. The significant association between depressive symptoms and the SII is consistent with previous studies in adult samples reporting the SII to be a sensitive index of inflammation and a reliable prognostic factor in several physical health conditions [17,37]. The identification of a positive association between depression symptoms and SII levels in the non-clinical sample of adolescents in this study suggests that pro-inflammatory processes may occur early in the course of depressive disorders, and possibly prior to making a diagnosis of depression. Thus, longitudinal research is needed to examine the potential prognostic value of the SII, and whether this index, measured using routine blood tests, could aid physicians in predicting onset or course of depression early in life in the future.

This study did not observe an association between depression diagnosis and SII, nor between depression diagnosis and specific white blood

cell levels or other ratios, possibly due to the small number of participants with a diagnosis of depression in this community sample. Depression symptoms, based on parent-report using the CBCL, were generally within the normal range (i.e., T-score <65) for both the depressed and control group, suggesting that youth in the depressed group may have had sub-clinical symptoms, or that the range of symptom severity within the clinical subgroup was limited (i.e., the majority of youth had symptom severity in the mild range relative to a moderate/severe range), or representing partial response to treatment. As youth with depression have been shown to endorse greater symptom severity than parents detect [38], parent-informants may have under-reported depressive symptoms on the CBCL which were detected on semi-structured diagnostic interview [39]. Furthermore, although the prevalence rate of depression in the current sample is comparable to rates observed in the general population [40], the relatively small number of adolescents diagnosed with a depressive disorder in the study sample may have limited the statistical power needed to detect the associations examined. The pattern of results observed in the current study is supported by meta-analytic evidence that continuous measures of psychopathology (e.g., CBCL) are generally more reliable and valid than discrete measurement tools (e.g., KSADS), and reduce the sample size required to obtain statistical power [41]. There is also some evidence to suggest that the KSADS provides limited information about depressive symptoms in children, particularly in non-clinical samples [42]. Finally, the lack of association between depression diagnosis and inflammation markers may be due to different time periods captured by the measures. Diagnostic categorization was based on youth- and parent-report of their most severe depressive episode, which may not have coincided with the time point at which blood samples were collected. In comparison, symptom severity reported on the CBCL reflected functioning at the time of assessment, and occurred simultaneously with blood sample collection. Future studies in clinical settings are needed to further examine whether the SII is contemporaneously associated with depression severity in adolescents with clinically significant depression symptoms (38).

This study did not observe any moderating effects of sex on the associations between depression and inflammatory markers. These findings may have been due, in part, to the relatively young age of 12 years of the participants. In two separate meta-analyses including community-based cohorts, sex differences in depression began to emerge around 12 years of age, and peaked at 13–15 years of age [43]. It is therefore possible that the participants in this study did not exhibit sex differences

in these pathways due to their young age. Prospective studies that follow early adolescents into adulthood are needed to further examine the potential moderating effect of sex on the association between depression and white blood cell markers.

4.1. Strengths and limitations

This study has several strengths, including a robust sample size (858 participants) and a study cohort that represents the general population. Furthermore, only children and adolescents ≤ 18 years were included in this study to ensure investigation of a pediatric population. However, there are also limitations to consider. First, this study is cross-sectional due to the limitations of the ABCD Study® cohort (i.e., mental health and blood count data were only available simultaneously during a single time point), and was therefore not able to examine potential directional relationships between depressive symptoms or diagnosis and specific white blood cell levels or indices, including the SII. As such, longitudinal research is needed to address the potential direction of the associations observed. Second, participants were part of the population-based ABCD Study® cohort, which represents a community sample rather than a clinical population. Future studies are encouraged to include clinical samples of children and adolescents diagnosed with a depressive disorder to fully understand the relationship between depression and white blood cells/inflammatory indices across the full spectrum of depression severity. Third, the analysis model examining associations between depressive symptoms and white blood cell markers had greater analytical power (858 participants) than for depression diagnosis (101 participants with a diagnosis), which increased the likelihood of being able to detect an association between depressive symptoms and the SII as well as white blood cell levels. Thus, although associations between depression diagnosis and white blood cell markers may exist, larger clinical samples are needed to confirm or refute the findings of this study with respect to depressive illness in children and adolescents. And lastly, underlying medical conditions that may influence the observed inflammatory marker levels and ratios were not included. Given the relatively low global prevalence of chronic inflammatory diseases among children and adolescents (0.03–4 % for the five most common conditions) [44–49], it is unlikely that the observed effects in this study were impacted by immune-related conditions. However, future studies are encouraged to include both mental and physical health diagnoses to control for possible indirect effects.

4.2. Conclusion

Increased depressive symptoms were associated with a higher SII, indicating an elevated innate immune system in a cross-sectional community sample of adolescents. Depression diagnosis was not significantly associated with inflammatory markers. Future studies with larger clinical samples as well as longitudinal design are needed to confirm the potential role of the SII in children and adolescents with depressive disorders, and the involvement of inflammation in early-onset depression.

CRediT authorship contribution statement

Anett Schumacher: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Eric Tu:** Writing – review & editing, Investigation, Formal analysis. **Carly Albaum:** Writing – review & editing, Methodology, Conceptualization. **Daphne J. Korczak:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Conceptualization.

Availability of data and code

Access request for all data used in this study must be submitted to the

ABCD Study®. Reasonable requests for analytic codes can be made to Daphne J. Korczak, 1145 Burton Wing, Department of Psychiatry, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada M5G 1 × 8; Tel 416 813–6936; Fax 416-813-5236; email daphne.korczak@sickkids.ca

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cpnc.2025.100302>.

References

- [1] United Nations Children's Fund, *The State of the World's Children 2021: on My Mind – Promoting, Protecting and Caring for Children's Mental Health*, 2021. New York.
- [2] S. Li, X. Zhang, Y. Cai, L. Zheng, H. Pang, L. Lou, Sex difference in incidence of major depressive disorder: an analysis from the Global Burden of Disease Study 2019, *Ann. Gen. Psychiatr.* 22 (2023) 53, <https://doi.org/10.1186/s12991-023-00486-7>.

- [3] World Health Organization, Mental health of adolescents. <https://www.who.int/news-room/fact-sheets/detail/adolescent-mental-health>, 2021. (Accessed 10 April 2023).
- [4] D. Neavin, J. Joyce, C. Swintak, Treatment of major depressive disorder in pediatric populations, *Diseases* 6 (2018) 48, <https://doi.org/10.3390/diseases6020048>.
- [5] E. Bernaras, J. Jaureguizar, M. Garaigordobil, Child and adolescent depression: a review of theories, evaluation instruments, prevention programs, and Treatments, *Front. Psychol.* 10 (2019), <https://doi.org/10.3389/fpsyg.2019.00543>.
- [6] G. Zwołńska, M. Dmitrak-Węglarz, A. Słopeń, Biomarkers in child and adolescent depression, *Child Psychiatr. Hum. Dev.* (2021), <https://doi.org/10.1007/s10578-021-01246-y>.
- [7] M. Colasanto, S. Madigan, D.J. Korczak, Depression and inflammation among children and adolescents: a meta-analysis, *J. Affect. Disord.* 277 (2020) 940–948, <https://doi.org/10.1016/j.jad.2020.09.025>.
- [8] H. Lee, M. Song, J. Lee, J.B. Kim, M.S. Lee, Prospective study on cytokine levels in medication-naïve adolescents with first-episode major depressive disorder, *J. Affect. Disord.* 266 (2020) 57–62, <https://doi.org/10.1016/j.jad.2020.01.125>.
- [9] G. Altan-Bonnet, R. Mukherjee, Cytokine-mediated communication: a quantitative appraisal of immune complexity, *Nat. Rev. Immunol.* 19 (2019) 205–217, <https://doi.org/10.1038/s41577-019-0131-x>.
- [10] J.S. Marshall, R. Warrington, W. Watson, H.L. Kim, An introduction to immunology and immunopathology, *Allergy, Asthma & Clinical Immunology* 14 (2018) 49, <https://doi.org/10.1186/s13223-018-0278-1>.
- [11] É.M. Foley, J.T. Parkinson, R.E. Mitchell, L. Turner, G.M. Khandaker, Peripheral blood cellular immunophenotype in depression: a systematic review and meta-analysis, *Mol. Psychiatr.* 28 (2023) 1004–1019, <https://doi.org/10.1038/s41380-022-01919-7>.
- [12] V. Dionisie, G.A. Filip, M.C. Manea, R.C. Movileanu, E. Moisa, M. Manea, S. Riga, A.M. Ciobanu, Neutrophil-to-Lymphocyte ratio, a Novel inflammatory marker, as a predictor of bipolar type in depressed patients: a quest for biological markers, *J. Clin. Med.* 10 (2021) 1924, <https://doi.org/10.3390/jcm10091924>.
- [13] M.G. Mazza, S. Lucchi, A.G.M. Tringali, A. Rossetti, E.R. Botti, M. Clerici, Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in mood disorders: a meta-analysis, *Prog. Neuropsychopharmacol. Biol. Psychiatry* 84 (2018) 229–236, <https://doi.org/10.1016/j.pnpbp.2018.03.012>.
- [14] L. Zhou, X. Ma, W. Wang, Inflammation and Coronary Heart disease risk in patients with depression in China Mainland: a cross-sectional study, *Neuropsychiatric Dis. Treat.* 16 (2020) 81–86, <https://doi.org/10.2147/NDT.S216389>.
- [15] R. Zahorec, Ratio of neutrophil to lymphocyte counts—rapid and simple parameter of systemic inflammation and stress in critically ill, *Bratisl. Lek. Listy* 102 (2001) 5–14. <http://www.ncbi.nlm.nih.gov/pubmed/11723675>.
- [16] A.V. Muresan, E. Russu, E.M. Arbănași, R. Kaller, I. Hosu, E.M. Arbănași, S. T. Voidăzan, The predictive Value of NLR, MLR, and PLR in the outcome of End-Stage Kidney disease patients, *Biomedicine* 10 (2022) 1272, <https://doi.org/10.3390/biomedicine10061272>.
- [17] B. Hu, X.-R. Yang, Y. Xu, Y.-F. Sun, C. Sun, W. Guo, X. Zhang, W.-M. Wang, S.-J. Qiu, J. Zhou, J. Fan, Systemic immune-inflammation index Predicts Prognosis of patients after Curative Resection for Hepatocellular Carcinoma, *Clin. Cancer Res.* 20 (2014) 6212–6222, <https://doi.org/10.1158/1078-0432.CCR-14-0442>.
- [18] M. Scherlinger, C. Richez, G.C. Tsokos, E. Boilard, P. Blanco, The role of platelets in immune-mediated inflammatory diseases, *Nat. Rev. Immunol.* 23 (2023) 495–510, <https://doi.org/10.1038/s41577-023-00834-4>.
- [19] S.J. Schleifer, J.A. Bartlett, S.E. Keller, H.M. Eckholdt, S.C. Shiflett, B.R. Delaney, Immunity in adolescents With Major depression, *J. Am. Acad. Child Adolesc. Psychiatry* 41 (2002) 1054–1060, <https://doi.org/10.1097/00004583-200209000-00005>.
- [20] H.N. Uçar, Ş. Eray, D. Murat, Simple peripheral markers for inflammation in adolescents with major depressive disorder, *Psychiatry and Clinical Psychopharmacology* 28 (2018) 254–260, <https://doi.org/10.1080/24750573.2018.1423769>.
- [21] G. Özyurt, N.C. Binici, Increased neutrophil-lymphocyte ratios in depressive adolescents is correlated with the severity of depression, *Psychiatry Res.* 268 (2018) 426–431, <https://doi.org/10.1016/j.psychres.2018.08.007>.
- [22] M. Öztürk, Y. Ozkan, Ş. Yalın Sapmaz, H. Kandemir, Neutrophil-to-lymphocyte ratio and platelet distribution width: a potential new peripheral biomarker in adolescent depression (eng), *J. Clin. Psychiatr.* 25 (2022) 244–251, <https://doi.org/10.5505/kpd.2022.48091>.
- [23] Ö. Önen, H.Ö. Erkuran, Ö. Bağ, F. Abacıgil, Blood count Parameters as inflammation indicators in children and adolescents diagnosed with depressive disorder, *Psychiatry and Clinical Psychopharmacology* 31 (2021) 425–433, <https://doi.org/10.5152/pcp.2021.21137>.
- [24] S. Cui, Z. Liu, Y. Liu, G. Yao, Y. Wu, J. Li, F. Sun, L. Sun, L. Sun, Correlation between systemic immune-inflammation index and suicide attempts in children and adolescents with first-episode, Drug-naïve major depressive disorder during the COVID-19 Pandemic, *J. Inflamm. Res.* 16 (2023) 4451–4460, <https://doi.org/10.2147/JIR.S433397>.
- [25] N.R. Karcher, D.M. Barch, The ABCD study: understanding the development of risk for mental and physical health outcomes, *Neuropsychopharmacology* 46 (2021) 131–142, <https://doi.org/10.1038/s41386-020-0736-6>.
- [26] H. Garavan, H. Bartsch, K. Conway, A. Decastro, R.Z. Goldstein, S. Heeringa, T. Jernigan, A. Potter, W. Thompson, D. Zahs, Recruiting the ABCD sample: design considerations and procedures, *Dev Cogn Neurosci* 32 (2018) 16–22, <https://doi.org/10.1016/j.dcn.2018.04.004>.
- [27] N.M. Saragosa-Harris, N. Chaku, N. MacSweeney, V. Guazzelli Williamson, M. Scheuplein, B. Feola, C. Cardenas-Iniguez, E. Demir-Lira, E.A. McNeilly, L. G. Huffman, L. Whitmore, K.J. Michalska, K.S. Damme, D. Rakesh, K.L. Mills, A practical guide for researchers and reviewers using the ABCD Study and other large longitudinal datasets, *Dev Cogn Neurosci* 55 (2022) 101115, <https://doi.org/10.1016/j.dcn.2022.101115>.
- [28] J. Kaufman, B. Birmaher, D. Brent, U. Rao, C. Flynn, P. Moreci, D. Williamson, N. Ryan, Schedule for Affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): Initial reliability and validity data, *J. Am. Acad. Child Adolesc. Psychiatry* 36 (1997) 980–988, <https://doi.org/10.1097/00004583-199707000-00021>.
- [29] M. Olsson, M.M. Wall, S. Wang, C. Blanco, Prevalence and Correlates of mental disorders in children aged 9 and 10 Years: results from the ABCD study, *J. Am. Acad. Child Adolesc. Psychiatry* 62 (2023) 908–919, <https://doi.org/10.1016/j.jaac.2023.04.005>.
- [30] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders: DSM-5, fifth ed., American Psychiatric Association, 2013 <https://doi.org/10.1176/appi.books.9780890425596>.
- [31] T.M. Achenbach, Achenbach system of Empirically based assessment (ASEBA), in: Encyclopedia of Clinical Neuropsychology, Springer International Publishing, Cham, 2018, pp. 1–7, https://doi.org/10.1007/978-3-319-56782-2_1529-3.
- [32] I.Y. Shao, A.A.A. Al-shoabi, A. Testa, K.T. Ganson, F.C. Baker, J.M. Nagata, The association between Family environment and subsequent risk of Cyberbullying Victimization in adolescents, *Acad Pediatr* (2023), <https://doi.org/10.1016/j.acap.2023.11.019>.
- [33] Posit team, RStudio: integrated development environment for R. <http://www.posit.co/>, 2022. (Accessed 22 April 2024).
- [34] R Core Team, R: a language and environment for statistical computing. <https://www.R-project.org/>, 2023. (Accessed 22 April 2024).
- [35] X. Li, J. Huan, L. Lin, Y. Hu, Association of systemic inflammatory biomarkers with depression risk: results from national health and Nutrition examination Survey 2005–2018 analyses, *Front. Psychiatr.* 14 (2023), <https://doi.org/10.3389/fpsyg.2023.1097196>.
- [36] S. Cui, J. Li, Y. Liu, G. Yao, Y. Wu, Z. Liu, L. Sun, L. Sun, H. Liu, Correlation of systemic immune-inflammation index and moderate/major depression in patients with depressive disorders: a large sample cross-sectional study, *Front. Psychiatr.* 14 (2023), <https://doi.org/10.3389/fpsyg.2023.1159889>.
- [37] Y. Xia, C. Xia, L. Wu, Z. Li, H. Li, J. Zhang, Systemic immune inflammation index (SII), system inflammation response index (SIRI) and risk of all-Cause Mortality and Cardiovascular Mortality: a 20-Year follow-Up cohort study of 42,875 US adults, *J. Clin. Med.* 12 (2023) 1128, <https://doi.org/10.3390/jcm12031128>.
- [38] N. Baumgartner, I. Häberling, S. Emery, M. Strumberger, K. Nalani, S. Erb, S. Bachmann, L. Wöckel, U. Müller-Knapp, B. Rhiner, B. Contin-Waldvogel, K. Schmeck, S. Walitzka, G. Berger, When parents and children disagree: Informant discrepancies in reports of depressive symptoms in clinical interviews, *J. Affect. Disord.* 272 (2020) 223–230, <https://doi.org/10.1016/j.jad.2020.04.008>.
- [39] B.A. Makol, A.J. Polo, Parent-child Endorsement discrepancies among youth at chronic-risk for depression, *J. Abnorm. Child Psychol.* 46 (2018) 1077–1088, <https://doi.org/10.1007/s10802-017-0360-z>.
- [40] S. Shorey, E.D. Ng, C.H.J. Wong, Global prevalence of depression and elevated depressive symptoms among adolescents: a systematic review and meta-analysis, *Br. J. Clin. Psychol.* 61 (2022) 287–305, <https://doi.org/10.1111/bjc.12333>.
- [41] K.E. Markon, M. Chmielewski, C.J. Miller, The reliability and validity of discrete and continuous measures of psychopathology: a quantitative review, *Psychol. Bull.* 137 (2011) 856–879, <https://doi.org/10.1037/a0023678>.
- [42] T.M. Olino, L. Yu, D.N. Klein, P. Rohde, J.R. Seeley, P.A. Pilkonis, P.M. Lewinsohn, Measuring depression using item response theory: an examination of three measures of depressive symptomatology, *Int. J. Methods Psychiatr. Res.* 21 (2012) 76–85, <https://doi.org/10.1002/mp.1348>.
- [43] R.H. Salk, J.S. Hyde, L.Y. Abramson, Gender differences in depression in representative national samples: meta-analyses of diagnoses and symptoms, *Psychol. Bull.* 143 (2017) 783–822, <https://doi.org/10.1037/bul0000102>.
- [44] R. Li, X. Yuan, Y. Ou, Global burden of rheumatoid arthritis among adolescents and young adults aged 10–24 years: a trend analysis study from 1990 to 2019, *PLoS One* 19 (2024) e0302140, <https://doi.org/10.1371/journal.pone.0302140>.
- [45] B. Gong, W. Yang, Y. Xing, Y. Lai, Z. Shan, Global, regional, and national burden of type 1 diabetes in adolescents and young adults, *Pediatr. Res.* 97 (2025) 568–576, <https://doi.org/10.1038/s41390-024-03107-5>.
- [46] I.Y.K. Iskandar, R. Parisi, C.E.M. Griffiths, D.M. Ashcroft, Systematic review examining changes over time and variation in the incidence and prevalence of psoriasis by age and gender, *Br. J. Dermatol.* 184 (2021) 243–258, <https://doi.org/10.1111/bjd.19169>.
- [47] J. Tian, D. Zhang, Y. Yang, Y. Huang, L. Wang, X. Yao, Q. Lu, Global epidemiology of atopic dermatitis: a comprehensive systematic analysis and modelling study, *Br. J. Dermatol.* 190 (2023) 55–61, <https://doi.org/10.1093/bjd/bjad339>.
- [48] T.H. Kim, H. Kim, J. Oh, S. Kim, M. Miligkos, D.K. Yon, N.G. Papadopoulos, Global burden of asthma among children and adolescents with projections to 2050: a comprehensive review and forecasted modeling study, *Clin Exp Pediatr* 68 (2025) 329–343, <https://doi.org/10.3345/cep.2025.00423>.
- [49] H. Xu, X. Liang, K. Li, Y. Wang, Z. Zhang, Y. Deng, B. Yang, Trend analysis and cross-national inequity analysis of immune-mediated inflammatory diseases in children and adolescents aged 10–24 from 1990 to 2021, *World Allergy Organization Journal* 18 (2025) 101033, <https://doi.org/10.1016/j.waojou.2025.101033>.