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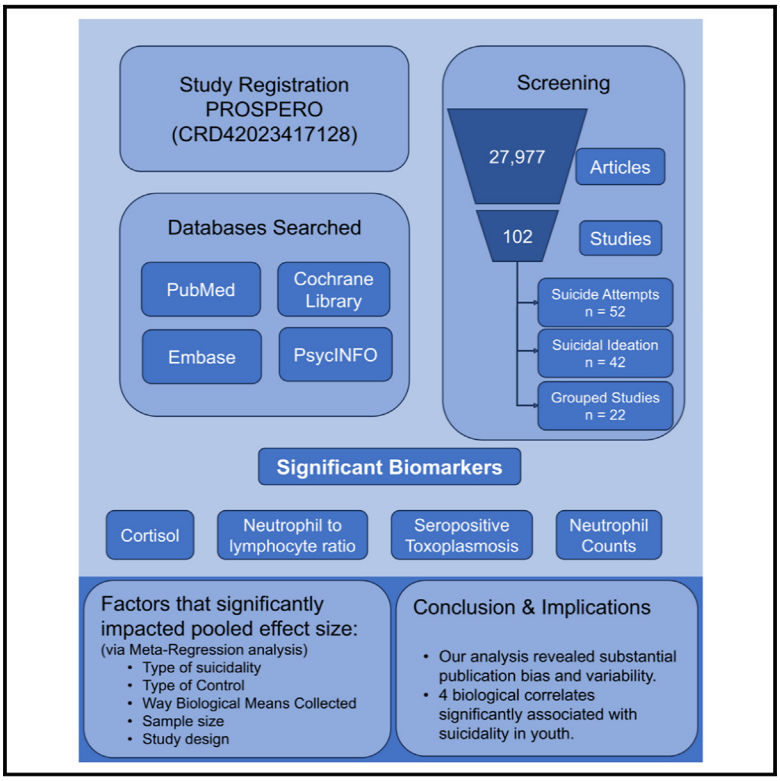
Peripheral biological correlates of suicidality in children and adolescents: A systematic review and meta-analysis

Graphical abstract



Highlights

- We sought to determine peripheral biological correlates of suicidality in children
- Cortisol and neutrophil were significantly associated with suicidality
- The type of suicidality and type of control affected the strength of the association
- The studies had significant publication bias and heterogeneity

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In brief

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Peripheral biological correlates of suicidality in children and adolescents: A systematic review and meta-analysis

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SUMMARY

A systematic review and meta-analysis were conducted to identify peripheral biological correlates of suicidality in children and adolescents. The review was pre-registered through PROSPERO (CRD42023417128) and included four databases (PubMed, Cochrane Library, Embase, and PsycINFO). From 27,977 non-duplicated articles, 102 full-text studies were selected. Studies investigated suicide attempts (n = 52), suicidal ideation (n = 42), or individuals with suicidal ideation or attempts grouped together (n = 22). Seropositive toxoplasmosis, cortisol, neutrophil, and neutrophil to lymphocyte ratio (NLR) exhibited significant effect size after Bonferroni correction. Effect sizes for biological correlates of suicidality were pooled using Cohen's d (effect size = −0.04, 95% confidence interval [CI]: −1.36 to 1.27) and odds ratio (effect size = −0.31, 95% CI: −1.06 to 0.42). Meta-regression analysis revealed that type of suicidality, type of control, means collected, and sample size significantly impacted the pooled effect size. Analysis showed significant publication bias and heterogeneity, as well as notable moderators and potential biomarkers for future research.

INTRODUCTION

Suicide is the third leading cause of death among children and adolescents in the United States.[1] The impact of youth suicide on public health, healthcare costs, and society is substantial.[2] Early identification and prevention of suicidal behaviors in youth are critical, offering the potential to save lives through timely intervention. Identifying suicide risk remains a challenge in clinical practice, predominantly relying on clinical interviews and associated clinical risk factors. Integrating biomarkers into this process has the potential to enhance risk prediction and subsequently prevent suicidal behaviors and attempts.[3] For the development of clinically useful biomarkers, identifying valid and reliable biological correlates is essential.[4]

Despite an increased number of research studies on suicidal ideation and behavior (suicidality) in adults,[5,6] there is a noticeable gap in research on biological correlates of suicidality in children and adolescents.[7] Research in children and adolescents is critical as there are developmental differences in children and adolescents that can affect the expression and detection of biomarkers.[8,9] Thus, this manuscript aims to expand the current research on suicidality in children and adolescents by identifying biological correlates associated with suicidality, and moderators for biological correlates associated with suicidality.

Previous reviews on suicidality in youth focused on clinical correlates,[7] peripheral correlates,[10,11] and neural correlates.[10,12] A scoping review by Sparrow-Downes et al. provided information on peripheral and neural correlates of self-harm in children and adolescents ages 3 to 19 years and identified both limited replication of studies and a predominance of female sex in study samples in the literature.[10] Two other systematic reviews in youth looked at biological correlates of suicidality, but each review only noted two studies that examined biological correlates of suicidality.[11,13] Other non-systematic reviews focused on genetic correlates of suicidality in children and adolescents.[14–16] Adult literature is more robust, with systematic reviews and meta-analyses of suicidality and a variety of biological correlates, including genes,[17] Brain-derived neurotrophic factor (BDNF),[18,19] Electroencephalography (EEG),[20] cortisol levels,[21] leptin,[22] cerebrospinal fluid (CSF) monoamines,[23] lipid,[24] and inflammation.[25–27] Some of these meta-analyses included patients younger than 18 years but did not conduct subgroup analyses for children and adolescents. Given the growing body of research on suicidality in this age group,[7] there is a critical

need for a systematic review examining biological correlates in these populations.

To address this gap in the literature, the authors conducted a systematic review of suicidality in children and adolescents and a meta-analysis of biological correlates associated with suicidality. This study is structured around three key objectives: First, descriptive characteristics of the literature focusing on suicidality in children and adolescents were reviewed, considering demographics, sample size, study design, type of suicidality, and type of biological correlates. Next, a meta-analysis for each biological correlate with results from at least three studies was conducted. Finally, a meta-regression was conducted to identify study characteristics that are moderators of effect size.

RESULTS

Systematic review

The systematic review yielded 27,977 non-duplicated articles, of which 591 were included based on titles and abstracts. After a full-text review, 102 articles were included for systematic review.[28–50,51–80,81–128] The PRISMA flow diagram depicts the search and selection process (Figure 1). Sixty-nine studies had data for meta-analysis, and 19 biological correlates had enough studies for individual meta-analysis.[129]

Table 1 presents the descriptive characteristics of each study, while Table 2 shows the summary characteristics of the studies. The extracted research articles are from 1985 to 2023, with a large number published in the last nine years (n = 56, 50%).

Most studies included male and female subjects (n = 91, 89%). In addition, 53 articles (52%) included the age range of children (6–12 years old) and adolescents (13–18 years old). The race/ethnicity reported in most articles is White/Caucasian (n = 42, 41.2%), followed by Black/African American (n = 26, 25.5%). Forty-seven articles (46.1%) did not report race or ethnicity. The sample sizes varied widely, from 14 subjects to 11,878 subjects. Many of the larger studies came from national health registries. In terms of the research setting, 67 articles (65.7%) recruited patients from the community setting, 49 articles (48.0%) recruited patients from the outpatient clinics, and 44 articles (43.1%) recruited patients from the inpatient or Emergency Department. One of the articles did not specify the setting.

The majority of the extracted research articles were case controls (n = 67, 65.7%), followed by prospective cohort studies (n = 23, 22.5%), and then cross-sectional studies (n = 11, 10.8%). Regarding the biological correlate categories, the genes category was the largest of the twelve categories (n = 25, 24.5%), followed by the stress response system (n = 21, 20.6). For types of suicidality, the largest category was suicide attempt (n = 52, 51%), followed by suicidal ideation (n = 42, 41.2%), and grouped suicide attempt and suicidal ideation (n = 22, 21.6%).

Quality assessment of the studies

The quality assessment of the studies, using the Joanna Briggs Institute (JBI) Risk of Bias tool (Table 1), showed that most articles were of good quality (scored 70%–99% of the checklist), totaling 81 articles (79.4% of the research articles), and 10 articles (9.8% of research articles) were rated as excellent (scored 100% of the checklist). This reflects the general robustness of the studies extracted. Eleven articles were categorized as fair (scored 50%–70% of the checklist), and none of the studies fell into the poor category (scored 0%–50%).

Meta-analysis and meta-regression results

Sixty-nine studies, comprising 333 total effects, provided the data to run a meta-analysis and meta-regression using Cohen's d or odds ratio. Nineteen individual biomarkers of suicidality met the criteria for individual meta-analysis (values from at least three individual studies[129]) and are shown in Table S1. Eight biological correlates were significantly associated with suicidality, displayed as forest and funnel plots (Figures 2 and 3), and 11 biological correlates were not significantly associated with suicidality, which are displayed as forest and funnel plots (Figures S1 and S2).

We identified four promising biological correlates for suicidality: cortisol ($p < 0.0001$), neutrophil ($p < 0.0001$), neutrophil to lymphocyte ratio (NLR) ($p = 0.0023$), and seropositive toxoplasmosis ($p < 0.0001$). These four correlates remained significant after adjustment for multiple comparisons with Bonferroni correction. Our sensitivity analysis showed that only neutrophil ($p < 0.0001$) and NLR ($p = 0.0014$) remained significant after accounting for the type of suicidality and accounting for studies that had multiple results.

We highlight the certainty of our results for individual biological correlates using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) guideline (Table S1). While Egger's test identified a few correlates with potential publication bias, this was skewed by the small sample size. Therefore, the analysis relied more heavily on visually inspecting the funnel plots (Figure 3 and Table S1). Of the biological correlates associated with suicidality, most had a small to moderate effect size of Cohen's d, except for seropositive toxoplasmosis (effect size = 1.43, 95% confidence interval [CI]: 0.87 to 2.00, $p < 0.0001$). Cortisol levels had small confidence intervals and effect size of Cohen's d with suicidality (effect size = 0.33, 95% CI: 0.21 to 0.45, $p < 0.0001$). Multiple cell blood count measurements showed significant effect sizes of Cohen's d: neutrophil count (effect size = 0.47, 95% CI: 0.29 to 0.66, $p < 0.0001$), and NLR (effect size = 0.65, 95% CI: 0.23 to 1.07, $p = 0.0023$).

The overall pooled effect size (adjusted) for biological correlates and suicidality was not significant for Cohen's d meta-analysis (adjusted effect size = −0.045, 95% CI: −1.36 to 1.27, p = 0.94) or odds ratio (adjusted effect size = −0.31, 95% CI: −1.06 to 0.42, $p = 0.40$) (Table S2). Moderators significantly explained the variance in Cohen's d (QM = 69.7896, $p < 0.0001$) and odds ratio (QM = 191.318, $p < 0.0001$) meta-analyses. The meta-regression analysis identified which study characteristic categories moderated the effect size (Table S2). For Cohen's d meta-analysis, the type of control category and the biological means collected category significantly moderated the effect size. The psychiatric control category (adjusted effect size = −0.19, 95% CI: −0.34 to −0.03, $p = 0.016$) and the cerebrospinal fluid category (adjusted effect size = −1.371, 95% CI: −2.4

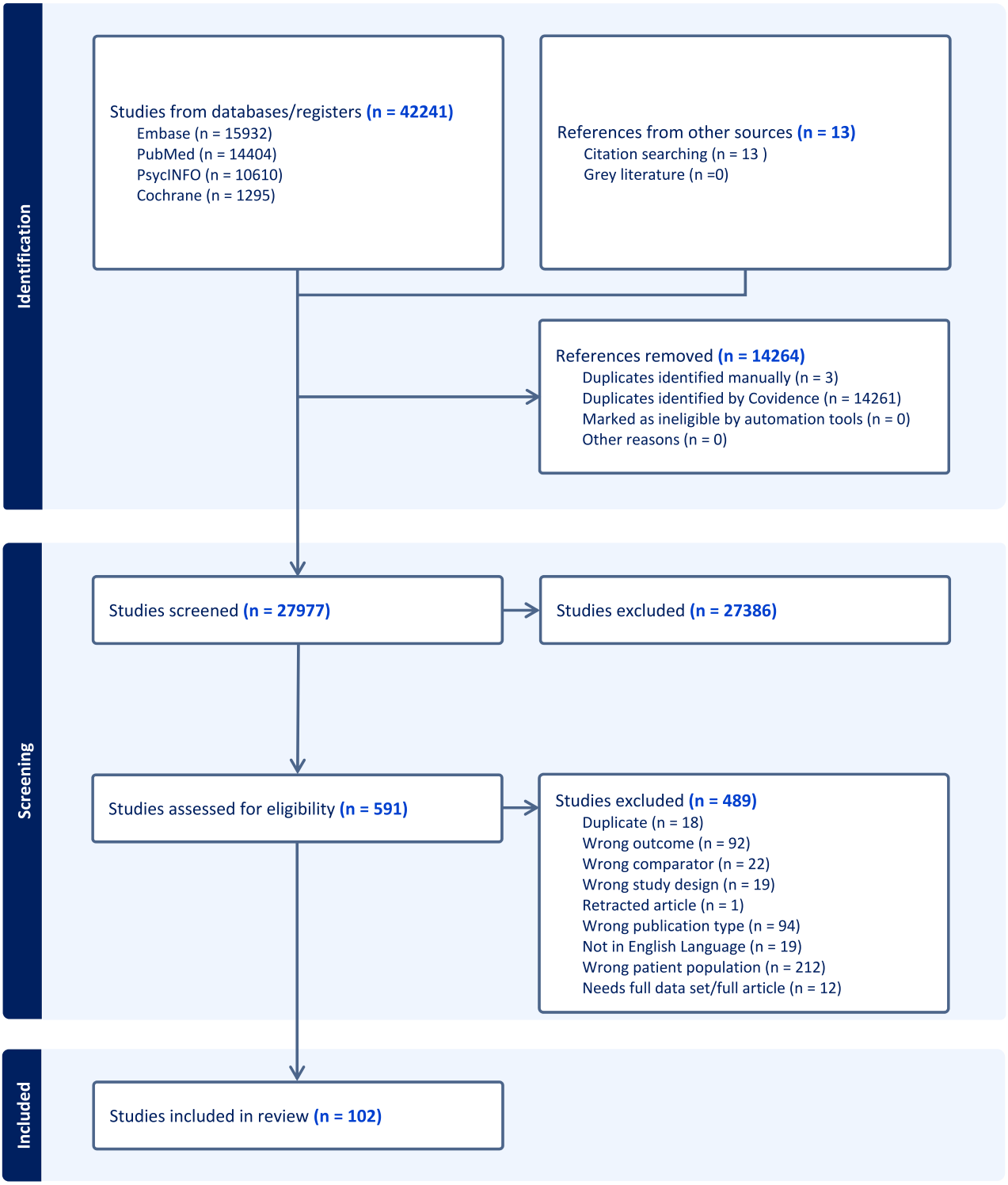

Figure 1. PRISMA flow diagram for systematic review

to −0.33, $p = 0.0093$). For odds ratio meta-analysis, these categories moderated the effect size including type of suicidality, study design, and sample size. Specifically, the following moderators were significant: suicidal ideation (adjusted effect size = −0.10, 95% CI: −0.17 to −0.02, $p = 0.0081$), retrospective cohort (adjusted effect size = 3.24, 95% CI: 2.08 to 4.54,

Table 1. Characteristics and quality of individual studies

First Author	Year	PMID or DOI	Study Number[a]	Race and Ethnicity	Sample Size (N)	Age Range	Mean Age[b]	Sex	% Female	Study Design	Specific Biological Correlate	JBI (%)
1. Cytokines												
Jha	2020	31756521	39	Black, White, and other	109	10-25 years	17.2	Both Sex	59	Case-control	Bio-Plex Pro Human Chemokine 40-plex assay: (chemokine, interleukin, MCP, TNF-a, Eotaxin, interferon)	80.0
Amitai	2020	31887416	48	Not reported	92	6-18 years	13.9	Both Sex	62	Prospective cohort	TNF-a, IL-6, IL-1β levels	81.8
Amitai	2020	32747326	6	Not reported	92	Not reported	13.9	Both Sex	62	Prospective cohort	IL-6, IL-1β, and TNF-α level	63.6
Clayton	2023	36853582	53	White, Black, Hispanic, and other	157	12-16 years	14.7	Female	100	Prospective cohort	Saliva IL-1β, IL-6, and TNF-α	81.8
Gabbay	2009	19702494	4	Not reported	45	12-19 years	16	Both Sex	60	Case-control	IFN-γ, TNF-α, IL-6, IL-1β, IL-4, IFN-γ	80.0
2. Endocrine System												
Dahl	1992	1644723	75	Black, White, and other	44	12-18 years	14.8	Both Sex	52	Case-control	Growth hormone	80.0
Garcia	1991	1905294	98	Black, White, and other	55	6-12 years	10.1	Both Sex	38	Case-control	Thyroid-stimulating hormone response to Thyroid releasing hormone (plasma)	80.0
Ryan	1988	2975304	43	Black, White, and other	48	12-17 years	15.3	Both Sex	41	Case-control	Mean GH response to desmethylimipramine	80.0
Sokolov	1994	8005899	18	Not reported	40	14-20 years	16.9	Both Sex	42	Case-control	Basal serum thyrotropin, T4, fT4, triiodothyronine (T3), reverse-T3, free thyroxine index (FTI), and T3 resin uptake	100.0
Lebowitz	2020	30699863	58	Not reported	168	7-16 years	11	Both Sex	51	Cross-sectional	Saliva oxytocin levels	87.5
Martin	1997	9359983	73	Not reported	160	15-19 years	16	Both Sex	50	Cross-sectional	Progesterone levels	87.5
Gokalp	2020	3965035	54	MENA and other	179	12-19 years	15.8	Female	100	Case-control	Serum thyroid-stimulating hormone and free T3 and free T4	80.0
3. Genes												
Cicchetti	2010	19779024	51	White, Black, Hispanic, and other	850	6-13 years	9.2	Both Sex	46	Case-control	Serotonin transporter gene-linked promoter region (5-HTTLPR) polymorphism	100.0

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Table 1. *Continued*

First Author	Year	PMID or DOI	Study Number[a]	Race and Ethnicity	Sample Size (N)	Age Range	Mean Age[b]	Sex	% Female	Study Design	Specific Biological Correlate	JBI (%)
Ran	2020	31629822	74	Asian	224	13-25 years	19	Both Sex	61	Case-control	Serotonin transporter gene SLC6A4	80.0
Zalsman	2004	15565493	38	MENA	236	15-24 years	Not reported	Both Sex	Not reported	Case-control	DRD4 receptor gene exon III polymorphism: greater/equal or lower than 7 repeats of DRD4	90.0
Kronenberg	2007	18315446	81	MENA	74	7-19 years	Not reported	Both Sex	59	Case-control	5-HTTLPR serotonin transporter polymorphism	80.0
Brezo	2009	19381154	34	White	1255	Not reported	Not reported	Both Sex	Not reported	Prospective cohort	Tag serotonergic SNPs	81.8
Brent	2010	20008943	11	White	155	12-18 years	15.7	Both Sex	70	Retrospective cohort	FKBP5 rs1360780TT and rs3800373GG genotypes	72.7
Zalsman	2011	20873971	13	White	211	13-22 years	15.9	Both Sex	58	Case-control	Polymorphisms of the serotonergic pathways (HTR2A, 5-HTTLPR, and MAOA)	60.0
Fiori	2020	21152090	12	White	1255	6 years	Not reported	Both Sex	59	Prospective cohort	Genotyped 63 polymorphisms	72.7
Doorley	2016	27267123	87	White and other	76	13-18 years	14.9	Both Sex	71	Case-control	Dopamine D4 receptor polymorphism. carrier of DRD4 or not	90.0
Blázquez	2016	27309038	60	White	46	10-17 years	15	Both Sex	78	Prospective cohort	Fluoxetine transportation (ABCB1) gene polymorphism. Dichotomous	63.6
Mirkovic	2017	28902619	3	Not reported	248	13-27 years	15.4	Both Sex	80	Case-control	22 SNPs in 12 genes	80.0
Sarmiento-Hernández	2019	30724325	8	Hispanic	435	11-18 years	14.3	Both Sex	64	Case-control	5-HTTLPR: genotype frequency	90.0
Brick	2019	30769295	61	White	3564	8-21 years	13.7	Both Sex	50	Cross-sectional	Manhattan plot of GWAS, SNPs	87.5
Koyama	2020	31870620	72	Not reported	158	9-17 years	13.9	Both Sex	50	Case-control	Impulsive aggression gene panel (CRH, CRHR2, MC2R, OXTR, BDNF)	90.0
Acikel	2020	31916884	92	Not reported	203	12-18 years	15.2	Both Sex	75	Case-control	Leptin receptor polymorphism - rs1171276. homo/het vs. control	90.0
Hill	2020	32745832	89	Not reported	330	8-18 years	11.57	Both Sex	49	Prospective cohort	Genetic variation (ANKK1, DRD2, COMT, SLC6A4, HTR2C)	72.7
Russel	2021	33892675	102	Not reported	8237	16-24 years	Not reported	Both Sex	Not reported	Prospective cohort	SNP-based heritability and Polygenic Risk Score	72.7
Sanabrais-Jiménez	2022	34342556	16	Hispanic	197	12-17 years	15	Both Sex	64	Case-control	SLC6A4, DRD2, COMT and MAOA genes	90.0

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Table 1. *Continued*

First Author	Year	PMID or DOI	Study Number[a]	Race and Ethnicity	Sample Size (N)	Age Range	Mean Age[b]	Sex	% Female	Study Design	Specific Biological Correlate	JBI (%)
Lee	2022	35216811	42	White, Black, Asian, Hispanic, and other	11878	9-10 years	9.91	Both Sex	47	Prospective cohort	Polygenic risk score for psychiatric conditions	72.7
Li	2013	24229544	35	White	659	Not reported	15.5	Both Sex	44	Prospective cohort	Polymorphism in the serotonin transporter linked promoter region gene (5-HTTLPR)	63.6
Laas	2014	24331455	52	White	1176	9-25 years	18	Both Sex	55	Prospective cohort	Neuropeptide S receptor gene polymorphism	81.8
Lvovs	2022	34924075	25	White	10000	15 years	15	Both Sex	Not reported	Prospective cohort	Cholecystokinin B receptor gene polymorphism	63.6
Haeffel	2008	18181793	9	White	176	Not reported	16.2	Male	0	Cross-sectional	Polymorphisms in the dopamine transporter gene	87.5
4. Gene expression												
Kong	2021	33971247	19	Not reported	200	11-18 years	15	Both Sex	87	Case-control	BDNF gene expression	80.0
El Gayed	2021	34568691	56	MENA	160	12-24 years	17.6	Both Sex	51	Case-control	CSMD1 gene's mRNA and protein expression	80.0
Perret	2023	36712964	17	Not reported	149	Not reported	10.47	Both Sex	Not reported	Prospective cohort	Epigenome-wide DNA methylation	81.8
5. Immune System												
Ambrosini	1992	1314256	69	Not reported	32	Not reported	13.9	Both Sex	56	Case-control	Platelet imipramine binding	70.0
Carstens	1988	2834765	20	Not reported	48	Not reported	15.4	Both Sex	62	Case-control	Equilibrium dissociation constant (Kd), and total number of binding sites (Bmax): 3H-p-aminoclonidine binding to platelets. 3H-p-aminoclonidine, 3H-imipramine binding, 3H-DHA binding to lymphocyte membranes.	100.0
Pine	1995	7755125	80	Not reported	121	12-18 years	15.7	Both Sex	85	Case-control	Density of platelet [3H] imipramine binding sites	80.0
Soreni	1999	10459397	31	Not reported	19	13-20 years	16.6	Both Sex	47	Case-control	[3H] PK 11195 binding to platelet membrane	100.0
Ragolsky	2013	23410141	90	Not reported	821	12.5–18 years	15.3	Both Sex	51	Case-control	Platelet counts	90.0
Ucuz	2020	32650198	24	Not reported	302	11-18 years	15.6	Both Sex	78	Case-control	Hemogram parameters - white blood cell, red blood cell, hemoglobin, neutrophil lymphocyte ratio	90.0
Amitai	2022	35470013	59	Not reported	160	6-18 years	13.9	Both Sex	62	Prospective cohort	Neutrophil/lymphocyte ratio (NLR), Platelet/lymphocyte ratio (PLR)	72.7

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Table 1. *Continued*

First Author	Year	PMID or DOI	Study Number[a]	Race and Ethnicity	Sample Size (N)	Age Range	Mean Age[b]	Sex	% Female	Study Design	Specific Biological Correlate	JBI (%)
Önen	2021	38765642	22	Not reported	148	9-16 years	14	Both Sex	70	Case-control	Neutrophil to lymphocyte ratio; mean platelet volume; platelet to lymphocyte ratio; hemoglobin; hematocrit; white blood cell; red cell distribution width	80.0
6. Infection Serology												
Coryell	2016	27045220	100	Not reported	110	15-20 years	18.7	Both Sex	71	Case-control	Serum toxoplasmosis titers or presence	72.7
Sapmaz	2019	31238296	76	Not reported	73	11-18 years	15	Both Sex	75	Case-control	Seropositivity for Toxoplasma gondii	90.0
Sari	2019	31688493	14	Not reported	100	12-18 years	Not reported	Both Sex	86	Case-control	Toxoplasma gondii IgM and IgG antibodies	90.0
Yucel	2020	33378287	7	Not reported	53	12-18 years	15.9	Both Sex	63	Case-control	Toxoplasma gondii serology. (specific with IgG)	90.0
Bayturan	2022	35821494	77	Not reported	76	11-18 years	15.1	Both Sex	83	Case-control	HSV1, CMV, EBV, HHV6 seropositivity and serum antibodies	90.0
7. Inflammatory Marker												
Falcone	2010	20559426	85	Not reported	84	12-18 years	14.3	Both Sex	42	Case-control	Serum S100B levels	90.0
Falcone	2015	25669696	79	White, Hispanic, Asian, and Black	115	7-18 years	15	Both Sex	46	Case-control	Serum S100B levels	90.0
Liu	2020	33381770	27	Black, White, and other	64	12-20 years	15.1	Both Sex	68	Cross-sectional	C-reactive protein	100.0
Liu	2021	34166062	55	Black, White, and other	127	12-20 years	15.2	Both Sex	61	Case-control	C-reactive protein	100.0
8. Metabolism												
Glueck	1994	8065845	45	Black, White, and other	1268	5-18 years	12.3	Both Sex	38	Case-control	Total cholesterol and triglyceride levels	90.0
Plana	2010	20047063	99	Not reported	120	8-18 years	15.3	Both Sex	73	Case-control	Total serum cholesterol	90.0
Gokalp	2020	32384132	93	Not reported	415	7-18 years	15	Both Sex	95	Case-control	Serum vitamin D, calcium, and phosphorus levels	90.0
Wu	2023	36493942	21	Not reported	90	13-18 years	15	Both Sex	68	Case-control	Intestinal permeability (plasma levels of zonulin, I-FABP, LPS and claudin-5)	80.0
Apter	1999	10459404	83	MENA and other	152	12-21 years	16.1	Both Sex	52	Case-control	Serum cholesterol levels	80.0
Kong	2022	35899094	10	Not reported	533	13-25 years	17.6	Both Sex	73	Case-control	Uric acid - serum	90.0

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Table 1. ***Continued***

First Author	Year	PMID or DOI	Study Number[a]	Race and Ethnicity	Sample Size (N)	Age Range	Mean Age[b]	Sex	% Female	Study Design	Specific Biological Correlate	JBI (%)
9. Neuromodulators												
Gulec	2010	DOI[c]	66	Not reported	55	15-18 years	16.5	Both Sex	37	Case-control	Neuropeptide Y (NPY) levels - plasma	80.0
Venne	2021	32961416	63	Not reported	129	12-17 years	14.9	Female	100	Case-control	Plasma beta endorphin levels	100.0
10. Neurotrophin												
Kavurma	2017	29017139	37	Not reported	105	12-18 years	15.1	Both Sex	72	Case-control	Serum BDNF levels	90.0
Bilgiç	2020	32027188	41	Not reported	110	11-19 years	15.6	Both Sex	76	Case-control	Serum BDNF, GDNF, NGF, and NTF3 levels	90.0
Lee	2020	32090756	40	Not reported	135	12-17 years	14.8	Both Sex	62	Prospective cohort	BDNF levels	72.7
11. Serotonin System												
Sallee	1998	9666634	70	Black, White, and other	46	9-17 years	14.2	Both Sex	47	Case-control	Platelet 5-HTPR kinetic analysis in reduced binding capacity	90.0
Pfeffer	1998	9787881	64	White, Black, and Hispanic	110	6-12 years	8.93	Both Sex	34	Case-control	Whole blood tryptophan	90.0
Clark	2003	12914891	86	White and Black	54	Not reported	16.2	Both Sex	60	Prospective cohort	Tryptophan ratio to other amino acids in the serum (index of serotonin precursor available to the brain), along with serum tryptophan	63.6
Tyano	2006	16076550	67	MENA and other	211	Not reported	15.9	Both Sex	58	Case-control	Plasma serotonin levels	90.0
Bradley	2015	25865484	97	Black, White, and other	30	12-18 years	15.8	Both Sex	67	Case-control	Tryptophan, kynurenine, 3-hydroxyanthranilic acid (plasma)	90.0
Zhou	2006	16828946	68	Not reported	100	15-19 years	17.2	Male	0	Case-control	Plasma serotonin levels	90.0
Modai	1989	2812295	82	Not reported	34	Not reported	Not reported	Not reported	Not reported	Case-control	Serotonin uptake of platelets	80.0
12. Stress Response System												
Dahl	1992	1420629	95	Black, White, and other	61	11-17 years	15	Both Sex	61	Case-control	Cortisol levels (serum), dexamethasone suppression test	100.0
Birmaher	1992	1636803	94	Black, White, and other	82	11-18 years	15.1	Both Sex	42	Case-control	Dexamethasone-induced cortisol levels	80.0
Dahl	1991	1892959	1	Black, White, and other	59	12-18 years	15.03	Both Sex	61	Case-control	Cortisol levels	80.0
Pfeffer	1991	2049489	88	White, Black, Hispanic, and other	49	6-12 years	10.6	Both Sex	29	Case-control	Cortisol levels (plasma) and dexamethasone suppression test	90.0
Weller	1990	2136395	33	White	18	7-18 years	13	Both Sex	22	Cross-sectional	Dexamethasone suppression test	70.0

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Table 1. *Continued*

First Author	Year	PMID or DOI	Study Number[a]	Race and Ethnicity	Sample Size (N)	Age Range	Mean Age[b]	Sex	% Female	Study Design	Specific Biological Correlate	JBI (%)
Puig-Antich	1989	2673131	30	White, Black, and Hispanic	45	6-12 years	9.2	Both Sex	39	Cross-sectional	Plasma cortisol	70.0
Dahl	1989	2763857	29	Not reported	88	12-18 years	15.2	Both Sex	45	Case-control	Cortisol secretion (plasma)	90.0
Rao	1996	8879467	96	White and other	63	12-18 years	63	Both Sex	61	Prospective cohort	Plasma cortisol levels	81.8
Mathew	2003	12784120	36	Not reported	77	Not reported	25.52	Both Sex	Not reported	Prospective cohort	24-h cortisol secretion	72.7
Klimes-Dougan	2019	30590339	46	White, Black, Asian, and other	162	12-19 years	16.4	Both Sex	67	Case-control	Salivary cortisol levels in context of Trier social stress test	90.0
Shalev	2019	31299399	28	White and other	223	6-25 years	12.3	Both Sex	Not reported	Case-control	Cortisol response	100.0
Denton	2021	33876491	26	Black and other	50	8-17 years	14	Both Sex	66	Cross-sectional	Cortisol levels (saliva)	87.5
Robbins	1985	DOI[d]	91	Not reported	45	13-18 years	Not reported	Both Sex	Not reported	Case-control	Dexamethasone suppression test	90.0
Young	2010	20419739	101	Not reported	501	Not reported	15.3	Both Sex	42	Cross-sectional	Morning cortisol levels (saliva)	87.5
Ghaziuddin	2014	24524706	32	White and other	44	13-17 years	15.5	Both Sex	66	Case-control	Cortisol response	100.0
Giletta	2014	24958308	57	White, Black, Asian, Hispanic, and other	138	12-16 years	14.3	Female	100	Prospective cohort	Salivary cortisol levels to Trier social stress test	63.6
Beauchaine	2015	25208812	71	Not reported	57	13-17 years	16	Female	100	Case-control	Dexamethasone suppression test	90.0
Eisenlohr-Moul	2018	30267013	44	White, Black, Asian, Hispanic, and other	220	12-16 years	14.6	Female	100	Prospective cohort	Salivary cortisol to Trier social stress test	63.6
Bendezú	2021	33762041	5	White, Black, Asian, Hispanic, and other	241	12-17 years	14.7	Female	100	Prospective cohort	Salivary cortisol	72.7
13. Multiple Biological Categories												
Melhem	2018	28135675	23	White and other	115	15-30 years	23	Both Sex	43	Case-control	Stress Response System: hair cortisol concentration, cellular measures of glucocorticoid receptor sensitivity Inflammatory Markers: plasma C-reactive protein. Cytokines: stimulated production of IL-6	90.0
Zakowicz	2023	37041682	65	Not reported	79	Not reported	15	Both Sex	55	Case-control	Neurotrophins: BDNF, proBDNF, p75NTR Inflammatory Marker: S100B plasma levels	90.0
Zhang	2022	36733417	15	Asian	179	13-18 years	15.4	Both Sex	71	Cross-sectional	Endocrine: thyroid-stimulating hormone Metabolism: lipids	87.5

(*Continued on next page*)

Table 1. *Continued*

First Author	Year	PMID or DOI	Study Number[a]	Race and Ethnicity	Sample Size (N)	Age Range	Mean Age[b]	Sex	% Female	Study Design	Specific Biological Correlate	JBI (%)
Kruesi	1992	1376104	2	Black, White, and other	29	6-17 years	11.3	Both Sex	7	Prospective cohort	Serotonin system: cerebrospinal fluid 5-hydroxyindoleacetic acid, Metabolism: homovanillic acid	72.7
Karadeniz	2020	32496844	84	Not reported	50	12-18 years	14.7	Both Sex	67	Case-control	Neuromodulators: serum nesfatin-1, ghrelin, Metabolism: lipid levels	80.0
Bilginer	2021	34185736	62	Not reported	74	12-17 years	14.9	Both Sex	83	Case-control	Inflammatory marker: Serum S100B Stress response system: malondialdehyde (MDA), total oxidant status (TOS), and total antioxidant status (TAS)	80.0
Chin Fatt	2022	36120101	47	Not reported	14	12-18 years	14.4	Female	100	Case-control	Immune system and inflammatory markers: panel of 30 antibodies. Includes immune dysregulation markers (e.g., CCR2, CXCR5, chemokine receptors) and inflammatory markers (CD294)	90.0
Zalsman	2005	15657646	78	MENA	60	Not reported	17	Both Sex	50	Case-control	Genes: serotonin transporter promoter polymorphism (5-HTTLPR), Immune System: platelet serotonin transporter (SERT) binding, number of platelets	90.0
Si	2020	32559305	49	Asian	682	Not reported	16.9	Both Sex	56	Cross-sectional	Genes: TNF-RII gene variations on lipid levels Metabolism: Lipids	75.0
Goldstein	2016	26646032	50	White and other	123	13-28 years	20.4	Both Sex	38	Prospective cohort	Cytokines: serum levels of IL-6, TNF-α, Inflammatory marker: high-sensitivity C-reactive protein (hsCRP)	72.7

5-HTPR, Serotonin transporter; 5-HTTLPR, Serotonin transporter linked promoter region; ANKK1, Ankyrin repeat and kinase domain containing 1; BDNF, Brain-derived neurotrophic factor; CMV, Cytomegalovirus; COMT, Catechol-O-methyltransferase; CRH, Corticotropin-releasing hormone; CRHR2, CRH receptor 2; CSMD1, CUB and Sushi multiple domains 1; DNA, Deoxyribonucleic acid; DOI, Digital object identifier; DRD4, Dopamine Receptor D4 Gene; EBV, Epstein Barr virus; FKBP5, FK506-Binding Protein 5; fT4, Free Thyroxine; GDNF, Glial cell line-derived neurotrophic factor; GH, Growth Hormone; GWAS, Genome-Wide association study; HHV6, Human herpesvirus 6; HSV1, Herpes Simplex Virus 1; HTR2A, 5-hydroxytryptamine receptor 2A; HTR2C, 5-hydroxytryptamine receptor 2C; I-FABP, Intestinal fatty acid binding protein; IFN, Interferon; IgG, Immunoglobulin G; IgM, Immunoglobulin M; IL, Interleukin; JBI, Joanna Briggs Institute critical appraisal tool; LPS, Lipopolysaccharide; MAOA, Monoamine oxidase A; MC2R, Adrenocorticotropic hormone receptor; MCP, Monocyte chemoattractant protein; MENA, Middle Eastern and North African descent; mRNA, messenger RNA; NGF, Nerve growth factor; NTF3, Neurotrophin-3; OXTR, Oxytocin receptor; p75NTR, p75 Neurotrophin receptor; SNP, Single nucleotide polymorphism; T4, Thyroxine; TNF, Tumor Necrosis Factor.

[a]Each study was assigned a unique ID number for identification in Figure 2 and Supplementary Figures. These are not reference numbers.

[b]Studies grouped by corresponding biological category. Some studies have examined multiple biological categories.

[c]DOI: https://doi.org/10.1080/10177833.2010.11790647.

[d]DOI: https://doi.org/10.1016/0006-3223(85)90144-1.

Table 2. Summary characteristics of included studies

Study characteristics	N	%
Sex		
Male only	2	2.0
Female only	8	7.8
Both sexes	91	89.2
Not specified	1	1.0
Age		
Children (6–12 years)	5	4.9
Adolescents (13–18 years)	18	17.6
Children and adolescents (6–18 years)	53	52.0
Adolescents and young adults (13–30 years)	11	10.8
All three age groups (children, adolescents, young adults)	15	14.7
Race and ethnicity[a]		
White	42	41.2
Black	26	25.5
Hispanic	12	11.8
Asian	9	8.8
Middle Eastern and North African	7	6.9
Other (race or ethnicity not listed above)	31	30.4
Not specified	47	46.1
Sample size		
14-50 (small)	20	19.6
51-100 (medium)	25	24.5
101-250 (large)	39	38.2
251-1000+ (very large)	18	17.6
Sample source[a]		
Community	67	65.7
Outpatient	49	48.0
Inpatient/Emergency Department	44	43.1
Not specified	1	1.0
Study design		
Case-control	67	65.7
Prospective cohort	23	22.5
Cross-sectional	11	10.8
Retrospective cohort	1	1.0
Biological correlate category[a]		
Genes	25	24.5
Stress response system	21	20.6
Serotonin system	10	9.8
Immune system	10	9.8
Metabolism	10	9.8
Inflammatory markers	9	8.8
Endocrine system	8	7.8
Cytokines	7	6.9
Infection serology	5	4.9
Neuromodulators	3	2.9
Neurotrophin	4	3.9
Gene expression	3	2.9
Types of suicidality[a]		
Suicide attempt	52	51.0
Suicidal ideation	42	41.2
Suicide attempt and suicidal ideation grouped	22	21.6

[a]Individual articles may have included multiple categories of these study characteristics.

$p < 0.0001$), and small sample size (adjusted effect size = −2.69, 95% CI: −4.42 to −0.81, $p = 0.0044$).

DISCUSSION

Our systematic review summarized the results of 102 studies and identified biological correlates of suicidality in youth. Our meta-analysis identified promising biological correlates of suicidality in youth (NLR, neutrophil, cortisol, and seropositive toxoplasmosis). These results will encourage further research on these inflammation and endocrine correlates. In addition, our meta-regression results revealed specific moderators of correlates of suicidality: type of suicidality, control, sample size, means collected, and sample size. This is critical for future studies of correlates of youth suicidality as the design of the studies would need to factor these moderators.

This systematic review of children and adolescents is valuable since suicide is the third leading cause of death in this age group,[1] and this age group also undergoes significant physiological changes during development that differ from adults,[9] which may lead to differences in the biological correlates associated with suicidality. Furthermore, youth are at increased risk for medication non-adherence, which increases the risk for suicide.[130] Previous literature reviews linking biological correlates of suicidality in children and adolescents are limited, including two systematic reviews[11] and one scoping review.[10] Herein, 102 studies for peripheral biological correlates of suicidality were identified. The biological correlates were grouped into categories as noted in the STAR Methods section. Similar to other reviews,[10,14] studies investigating genes, stress response system, serotonin system, immune system, and inflammatory markers were the most common types of biomarkers that were encountered.

This systematic review revealed the need for better documentation of the demographics and the inclusion of more diverse demographics in the sample. Many of the studies ($n = 47$, 46.1%) did not report the race and/or ethnicity of their samples. White/Caucasian individuals were the most studied group ($n = 42$, 41.2%), followed by Black individuals ($n = 26$, 25.5%). Furthermore, many of the studies grouped male and female data together, which may mask the results for meta-analysis as there are sex differences in biological correlates of suicidality.[131,132] In addition, the systematic review found widespread use of the case-control ($n = 67$, 65.7%) study design. This raises concerns about selection and information biases, potentially confounding the findings.[133,134]

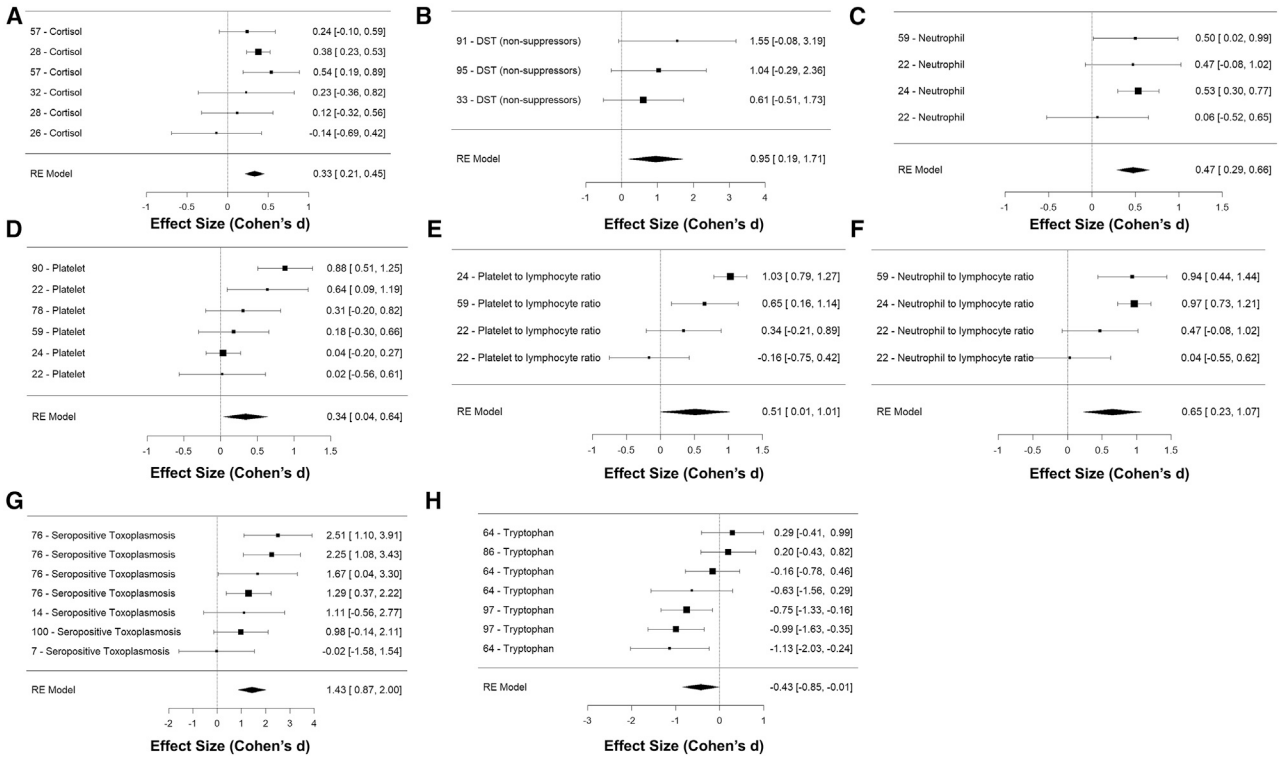

Figure 2. Forest plot of effect size (Cohen's d) of biological correlates of suicidality

(A) Forest plot for cortisol ($p < 0.0001$).

(B) Forest plot for dexamethasone suppression test (non-suppressors) ($p = 0.013$).

(C) Forest plot for neutrophil ($p < 0.0001$).

(D) Forest plot for platelet ($p = 0.025$).

(E) Forest plot for platelet to lymphocyte ratio ($p = 0.046$).

(F) Forest plot for neutrophil to lymphocyte ratio ($p = 0.0023$).

(G) Forest plot for seropositive toxoplasmosis ($p < 0.0001$).

(H) Forest plot for tryptophan ($p = 0.045$). The Black Diamond at the bottom is the pooled effect size. Each horizontal line represents a specific biomarker from a specific study. The study number and biomarker are listed on the left of the forest plot. The study numbers reflect the study numbers in Table 1 and are not reference numbers. The dots and whiskers at the center represent the effect size and 95% confidence interval. The right of the forest plot is the numerical data of the effect size and the 95% confidence interval. Cortisol, neutrophil, neutrophil to lymphocyte ratio, and seropositive toxoplasmosis remained significant after Bonferroni correction. Some study numbers are listed multiple times since different study characteristics were utilized for assessing biological correlates of suicidality (different types of suicidality and control). DST; dexamethasone suppression test. RE, random effect.

Although previous meta-analyses of biological correlates of suicidality have been conducted in the general population, these studies did not partition the meta-analyses for children and adolescents from adults.[19–21,26] The current meta-analysis identified multiple biological correlates for suicidality (Figure 2 and Table S1), in the immune system, stress response system, and the infection serology categories. The current observations will inform future studies on identifying and establishing biomarkers with analytical validity and clinical utility.[4]

For the immune system, we identified multiple biological correlates associated with suicidality (complete blood count markers [CBC]; neutrophil, and NLR). NLR as a correlate of suicidality aligns with adult studies, which also noted that NLR was a better correlate than platelet to lymphocyte ratio (PLR).[135,136] This could explain why PLR and platelet counts only trended significance in our analysis. Of note, for adults, the severity of suicide attempts was associated with PLR and platelet counts, which could not be factored into the results.[137] For adult studies, studies were inconsistent on neutrophil counts.[135,137] Additionally, we could not assess sex differences in the CBC and inflammatory ratio, which is a limitation as sex-based CBC differences in psychiatric disorders have been observed previously.[138]

The inflammation markers—tumor necrosis factor alpha (TNF-α) and cytokines (interleukin-6 [IL-6], IL-1β, interferon gamma [IFN-γ], IL-4), did not associate significantly with suicidality. In contrast, an adult meta-analysis of TNF-α, IL-6, and IL-1β observed a significant association of IL-6 with suicidality. This difference in IL-6 results between adults and youth could be due to the correlation of puberty and age with IL-6[139] or the limited number of studies in this meta-analysis. In adult psychiatric samples, inflammation markers emerge as promising biomarkers of suicidality in adults, given the growing evidence of a dysregulated immune system in the pathophysiology of suicidality.[140] Proposed

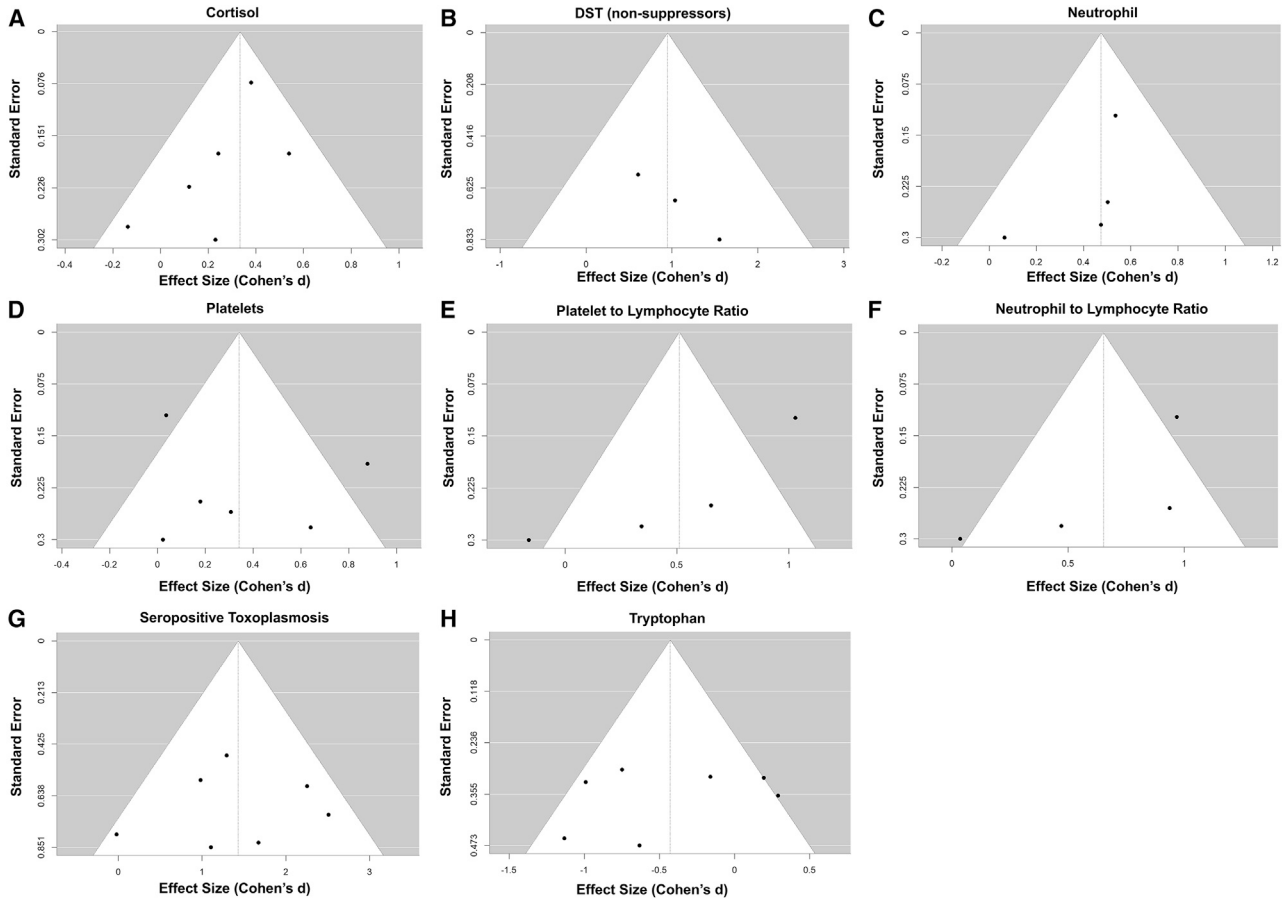

Figure 3. Funnel plot of effect size (Cohen's d) of biological correlates of suicidality

(A) Funnel plot for cortisol.

(B) Funnel plot for dexamethasone suppression test (non-suppressors).

(C) Funnel plot for neutrophil.

(D) Funnel plot for platelet.

(E) Funnel plot for platelet to lymphocyte ratio.

(F) Funnel plot for neutrophil to lymphocyte ratio.

(G) Funnel plot for seropositive toxoplasmosis.

(H) Funnel plot for tryptophan. Each dot represents an individual biological correlate from a study. The x axis is the effect Size (Cohen's d) and the y axis is the standard error. DST, dexamethasone suppression test.

mechanisms of behavioral changes from dysregulated immune systems include impairments of the kynurenine pathway of tryptophan catabolism, changes in monoamine metabolism, and increased activation of the HPA axis.[141] Further research is necessary to validate these findings in younger populations.

Lipid levels have previously been associated with suicidality, with a proposed mechanism of altering the neuronal membranes, which affect inflammation and serotonergic transmission.[142] While adult meta-analysis shows a link between lipid levels and suicidality,[143] this study found that high-density lipoprotein (HDL) and low-density lipoprotein (LDL) did not significantly associate with suicidality in youth. This difference could be due to changes in lipid levels during puberty.[144]

Cortisol was also identified as a promising correlate for suicidality, though sensitivity analyses did not reveal a significant association. The discrepancy in the results could be due to the differences in the collection methods of cortisol. Adult studies show that dysregulation of the stress response system is associated with suicidality,[6] with a meta-analysis showing a significant association of morning cortisol with suicidality.[21] One of the extracted studies did not show a correlation between baseline cortisol and suicide attempt,[56] but the salivary cortisol samples were collected from a time range of morning to afternoon. Toxoplasmosis seropositivity was significantly associated with suicidality in youth but was not significant in the sensitivity analysis. A meta-analysis of toxoplasmosis seropositivity was associated with suicidality in adult studies, but this was focused on suicidal behavior, and not suicidal ideation, which can explain the discrepancy in results.[145]

Meta-regression analysis identified study characteristics that affect the effect size of the biological correlates of suicidality (Table S2). We identified that the type of suicidality, type of

control, sample size, study design, and how the biological samples were collected serve as significant moderators. These results emphasize the importance of considering these study characteristics when designing future studies of biomarkers of suicidality in adolescents. Of note, the way suicidality is measured is quite variable which also affected the analysis. While suicide attempts were generally classified as a binary outcome, suicidal thoughts were reported either as categorical[77] by clinician assessment or via continuous data by validated scales such as the Beck Scale for Suicidal Ideation[102] and the Suicidal Ideation Questionnaire.[58]

Another study characteristic that serves as a moderator is the type of control group used. Some studies include healthy controls,[75] whereas others use psychiatric controls.[38,45] Meta-regression with Cohen's d effect size showed that psychiatric controls significantly decreased the overall effect size of biomarkers of suicidality. This finding emphasizes the inclusion of psychiatric controls when analyzing biological correlates. Although healthy controls provide important insights, using psychiatric controls may also provide a more precise assessment of the correlation between biomarkers and suicidality, as it helps distinguish the effects of suicidality from those of underlying psychiatric disorders, which are known to increase suicide risk.[146]

Another category that influences the relationship between biological correlates and suicidality is the method utilized for collecting the biological correlate. The meta-regression specifically noted that compared to collecting samples by blood, collecting samples by cerebrospinal fluid affects the relationship, which aligns with research in adult studies.[5] A meta-analysis of adult suicidality and BDNF[19] showed differences between BDNF collected from serum and plasma. Although the meta-regression did not find collection from serum or plasma to be a moderator, further investigation with specific correlates is warranted.

The methodological variability and limited number of studies underscore the need for more standardized research on biological correlates of suicidality. The meta-regression findings emphasized key moderators for biomarkers associated with suicidality, including the type of suicidality, type of control, means that the biological samples are collected, sample size, and study design. Improved documentation and standardization of demographics, study design, and sex-specific data are critical for enhancing the generalizability and consistency of suicide biomarker research in youth.

In conclusion, this systematic review and meta-analysis add valuable insights into the biological underpinnings of suicidality in children and adolescents. A comprehensive overview of 102 studies reveals how distinct biological correlates relate to suicidality in youth. Although we did not identify a biomarker of suicidality in youth, we identified promising biological correlates of suicidality, mainly related to immune function and the stress response system, warranting further research. This study identified peripheral markers with potential clinical utility in screening for suicidality in youth. Future studies should explore the temporal relationship of suicide-related variables with clinical features. As part of our ongoing efforts, our research group is currently conducting a longitudinal study to identify whether suicidality correlates with immune markers.[147]

Limitations of the study

A limitation is the exclusion of non-English language papers, which may have led to the omission of relevant studies. The publication bias also highlights the need for a more comprehensive search strategy, including expanded use of gray literature and unpublished studies. This paper was also narrow in the scope of looking at peripheral biological correlates and suicidality. Future research could investigate neural biological correlates and examine non-suicidal self-injury.

Another limitation is the limited number of studies, with individual biomarkers ranging from 3 to 9 results. Some of the meta-analyses may be underpowered to show the significance of biological correlates of suicide or publication bias, including funnel plot symmetry. Further replication studies are needed to establish these correlates as biomarkers of suicidality for adolescents. Some studies produced multiple results, but this effect is factored in the multi-level meta-analysis.

The multi-level meta-analysis accounts for variation across specific biomarkers, but a limitation is the effects of the moderators may be masked by biological correlates that indirectly relate to suicidality. Given that many biological correlates had both negative and positive effect sizes, the factor of biological correlates with indirect relation to suicidality could not be addressed in the framework. In addition, it would be ideal to conduct a meta-regression analysis of individual biomarkers, but due to the small number of studies for each individual biomarker, these meta-regression results would be limited and underpowered. In addition, we could not determine the time elapsed since the suicide attempt and the measurement of the biological correlate, which could impact the strength of the association.

RESOURCE AVAILABILITY

Lead contact

Requests for further information and resources should be directed to and will be fulfilled by the lead contact, Dr. Madhukar H. Trivedi (Madhukar.trivedi@utsouthwestern.edu).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- This study is a systematic review and meta-analysis. The data analyzed in this study were extracted from previously published studies and publicly available resources. Raw data used for meta-analysis is available upon request.
- The meta-analysis was conducted in R using the standard function available in the *metafor* package, and no custom code was developed. As a result, code sharing is not necessary for reproducing our results.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

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AUTHOR CONTRIBUTIONS

T.K.P., conceptualization, writing – original draft preparation, investigation, and data curation; E.R.A., conceptualization, project administration, writing – original draft preparation, and investigation; T.C., formal analysis and writing – review and editing; L.J., writing – review and editing, investigation, and data curation; Z.F., writing – review and editing, and investigation; A.N., writing – review and editing, and data curation; G.E., conceptualization, writing – review and editing; M.H.T., conceptualization, funding acquisition, project administration, resources, supervision, and writing – review and editing.

DECLARATION OF INTERESTS

T.K.P., E.R.A., D.C., L.J., Z.F., and A.N. report no conflicts of interest. G.E. is a consultant for Lundbeck and Neuronetics. G.E. receives research support from American Foundation for Suicide Prevention (AFSP), Janssen Pharmaceuticals, Janssen Research & Development, the National Institutes of Health, Patient-Centered Outcomes Research Institute (PCORI), and the State of Texas. M.H.T. has received research funding from NIMH, NIDA, NCATS, the American Foundation for Suicide Prevention, the Patient-Centered Outcomes Research Institute, and the Blue Cross Blue Shield of Texas. He has served as a consultant or advisor for ACADIA PHARMACEUTICALS INC., Akili Interactive, ALKERMES INC (Pub Steering Comm-ALKS5461), Allergan Sales LLC, Alto Neuroscience, Inc. , Applied Clinical Intelligence, LLC (ACI), Axome Therapeutics, Boehringer Ingelheim, Engage Health Media, Gh Research, GreenLight VitalSign6, Inc., Heading Health, Inc., Health Care Global Village, Janssen – Cilag.SA, Janssen Research and Development, LLC (Adv Committee Esketamine), Janssen Research and Development, LLC (panel for study design for MDD relapse), Janssen - ORBIT, Legion Health, Jazz Pharmaceuticals, LUNDBECK RESEARCH U.S.A, Medscape, LLC, Merck Sharp & Dohme Corp., Mind Medicine (MindMed) Inc., Myriad Neuroscience, Neurocrine Biosciences Inc, Navitor, Pharmaceuticals, Inc., Noema Pharma AG, Orexo US Inc., Otsuka Pharmaceutical Development & Commercialization, Inc. (PsychU, MDD Section Advisor), Otsuka America Pharmaceutical, Inc. (MDD expert), Pax Neuroscience, Perception Neuroscience Holdings, Inc., Pharmerit International, LP, Policy Analysis Inc., Sage, Therapeutics, Rexahn Pharmaceuticals, Inc., Sage Therapeutics, Signant Health, SK Life Science, Inc., Takeda Development Center Americas, Inc., The Baldwin Group, Inc., and Titan Pharmaceuticals, Inc. M.H.T. also received editorial compensation from Oxford University Press. Disclaimer: The Intellectual Property of VitalSign6 belongs to the University of Texas Southwestern Medical Center (Principal Investigator, M.H.T.) and is now licensed to GLVS6 for future distribution.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
Covidence		https://www.covidence.org/
R with metafor package		https://www.r-project.org/
Prospero		https://www.crd.york.ac.uk/prospero/
Microsoft Excel		https://www.microsoft.com/en-us/microsoft-365/excel
Other		
Data published/compiled from the literature	PubMed	https://www.ncbi.nlm.nih.gov/pubmed
Data published/compiled from the literature	the Cochrane Library	https://www.cochranelibrary.com/
Data published/compiled from the literature	Embase	https://www.embase.com
Data published/compiled from the literature	PsycINFO	https://www.apa.org/pubs/databases/psycinfo

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Inclusion and exclusion criteria

Studies were eligible for inclusion if they were cohort, cross-sectional, case-series, or randomized controlled studies, and if they provided empirical data on peripheral biological correlates of suicidality in children and adolescents. The population of interest includes children (6-12 years of age) and adolescents (13-18 years of age) as defined by Medical Subject Headings (MESH) produced by the National Library of Medicine. Some studies did not include the age range but were included only if they explicitly noted they included children or adolescents. If a study had the age range of interest but included patients outside the age range, there were two conditions to keep them: 1) the study included a subgroup analysis for the age range of interest, or 2) the study's age range was a maximum of 30 years old and included adolescents. We used 30 years of age as a cut-off to include as many adolescent studies since adolescence can be defined as the onset of puberty to ending in the mid-20s.[9] To control the age-related variability, the age groups were categorized as children, adolescents, and young adults. Reviews, editorials, unpublished literature, book chapters, conference proceedings, abstracts (without an associated paper), studies not in English, animal studies, and *in vitro* studies were excluded.

METHOD DETAILS

Procedures

After consulting with a research librarian experienced in systematic reviews, a comprehensive search strategy was developed, and the study was registered in PROSPERO (CRD42023417128). Any deviations to the protocol are noted in the supplemental information (Document S1). We adhered to PRISMA guidelines (Table S3).

Four databases (PubMed, the Cochrane Library, Embase, and PsycINFO) were utilized to identify articles published from the earliest date of the respective database to April 2023. Search terms were chosen to identify peripheral biological correlates of suicidality and self-harm behavior in children and adolescents. The full details of the search strings are provided in (Table S4). In addition to database searches, manual searches of reference lists from relevant review articles were conducted to ensure comprehensive coverage.

The web-based systematic review software Covidence was utilized to assist with screening, including the removal of duplicate articles. Initial screening based on titles and abstracts was performed independently by two authors (TP, LJ), and full-text screenings were also performed independently by two authors (TP, LJ). Disagreements were resolved by a third author (EA). Data extraction was completed using a standardized template based on previous systematic reviews.[10,148] The following data were extracted into categories: date of publication, sex, age, race and ethnicity, sample size, population source recruited, study design, biological correlate category, and types of suicidality. For race and ethnicity, the categories were based on the NIH general guidance for race and national origin.[149] The biological correlate categories were determined from previous reviews[10,17,150] and discussion among the authors. We categorized the biomarkers (Table 1) using the twelve categories: Cytokines, the endocrine system, gene expression, genes, the immune system, inflammatory markers, metabolism, infection serology, neuromodulators, neurotrophins, the serotonin system, and the stress response system. The "endocrine system" consists of hormones, including growth hormone[28] and thyroid stimulating hormone.[151] The "immune system" is a wide category, which includes "inflammatory markers" and "cytokines." However, given their distinct roles in the immune system, we separated "inflammatory markers" and "cytokine" for an improved categorization framework of the biological correlates. Although these biomarkers work in concert during pathological processes and may have dependent or

independent functions, we categorized them based on their biological types/classifications (cells vs. cytokines vs. acute phase proteins). Similarly, the ''stress response system,'' which includes cortisol, was separated from the ''endocrine system,'' and we had separate categories for ''neuromodulators'' and ''serotonin system,'' aligning with previous reviews.[10,17] Table 1 includes the biological correlates and their corresponding biological categories. Table 1 also includes study numbers (not reference numbers) that we used to refer to specific studies in our figures. Types of suicidality were separated into three categories: suicide attempt, suicidal ideation, and individuals with suicidal ideation or attempts grouped together. The suicide attempt category included any self-harm attempt with any intent to die. The suicidal ideation category included any thoughts/plans to die by suicide. The third category was individuals with suicide attempt or suicidal ideation grouped into a single group. For example, one study grouped ''MDD [major depressive disorder] with recent suicide behavior/ideation'' into a single group.[29] Of note, some individual articles looked at multiple biomarker categories and multiple types of suicidality. For types of control, it was noted if the study compared suicidality with groups that are psychiatric controls (such as MDD with suicidality vs MDD without suicidality[29]), specific population controls (such as juvenile detainees with suicidal ideation vs juvenile detainees without suicidal ideation[50]), and healthy controls.[54]

The quality of the included studies was independently assessed by two authors (TP, ZF) using the Joanna Briggs Institute (JBI) Critical Appraisal tools evidence.[152] The JBI tool provides a checklist to evaluate the methodological quality based on the study design of the case series, case-control, and cohort studies. Articles were of excellent quality (scored 100%), good quality (scored 70%-99% of the checklist), fair quality (scored 50%-70% of the checklist), and poor quality (scored 0%-50% of the checklist). The cutoffs were determined from other research articles[153,154] using JBI tools. Deviations from the original registered PROSPERO protocol are noted in the supplemental information.

QUANTIFICATION AND STATISTICAL ANALYSIS

All statistical analyses were performed using ''R'' with the ''metafor'' package. Figures were created using ''R'' and tables were created using Microsoft Excel. The meta-analysis of peripheral biological correlates of suicidality was conducted using effect sizes for Cohen's d or effect sizes for the natural log of odds ratio. To improve the variance estimate, an estimation method of Restricted Maximum Likelihood was used.[155]

To calculate Cohen's d for meta-analysis, the studies used reported 1) mean and standard deviation of biological correlate levels, 2) median, minimum, and maximum of biological correlate and calculations based on Wan et al.,[156] 3) odds ratios derived from dichotomization of continuous biological correlate and converted to Cohen's d based on calculations from Chinn[157]; (we did not convert odds ratios that derived from non-continuous biological correlates), and 4) Pearson correlations of biological correlates converted to Cohen's d based on calculations from Mathur and VanderWeele.[158] With data that reported median and IQR, the 1st quartile and 3rd quartile range were approximated, assuming a normal distribution. For the interpretation of effect size (Cohen's d), a value of 0.2 was considered small, 0.5 was considered moderate, and 0.8 was considered large.

A single-level mixed-effect meta-analysis was conducted for individual biomarkers from at least three studies.[129] A separate meta-analysis based on the type of suicidality was not conducted as that would have limited the number of individual biomarkers. Instead, a sensitivity analysis was conducted that accounted for the type of suicidality, and multiple results were from the same study. This analysis was conducted on the four significant biological correlates after Bonferroni correction. Sensitivity analysis was conducted with a multi-level mixed-effects meta-analysis to account for multiple measurements per study and factored in the fixed effect of type of suicidality.[159] To assess the certainty of the meta-analysis of the individual biomarker, the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) guideline was used.[160] These results are shown in Table S1.

To examine study characteristics that moderate the strength of biological correlate to suicidality, a multi-level meta-analysis and meta-regression of all the studies with available effect sizes was conducted. The meta-analysis was conducted using effect sizes for Cohen's d or effect sizes for the natural log of odds ratio. The following moderators were studied: study design, sex, age category, sample size category, type of controls, means collected, and type of suicidality. Many studies did not specify the means the biological samples were collected. In addition, hematological measures were from whole blood samples, lipids were measured using serum samples, and cytokines were collected from whole blood samples or plasma.

An Egger's test was conducted to assess publication bias in the meta-analysis. The test measures asymmetry in a funnel plot, which indicates publication bias. The funnel plots were also visually inspected to assess for asymmetry.

ADDITIONAL RESOURCES

Amendments to protocol

The Supplementary Information documents the changes to the registered PROSPERO protocol (CRD42023417128).