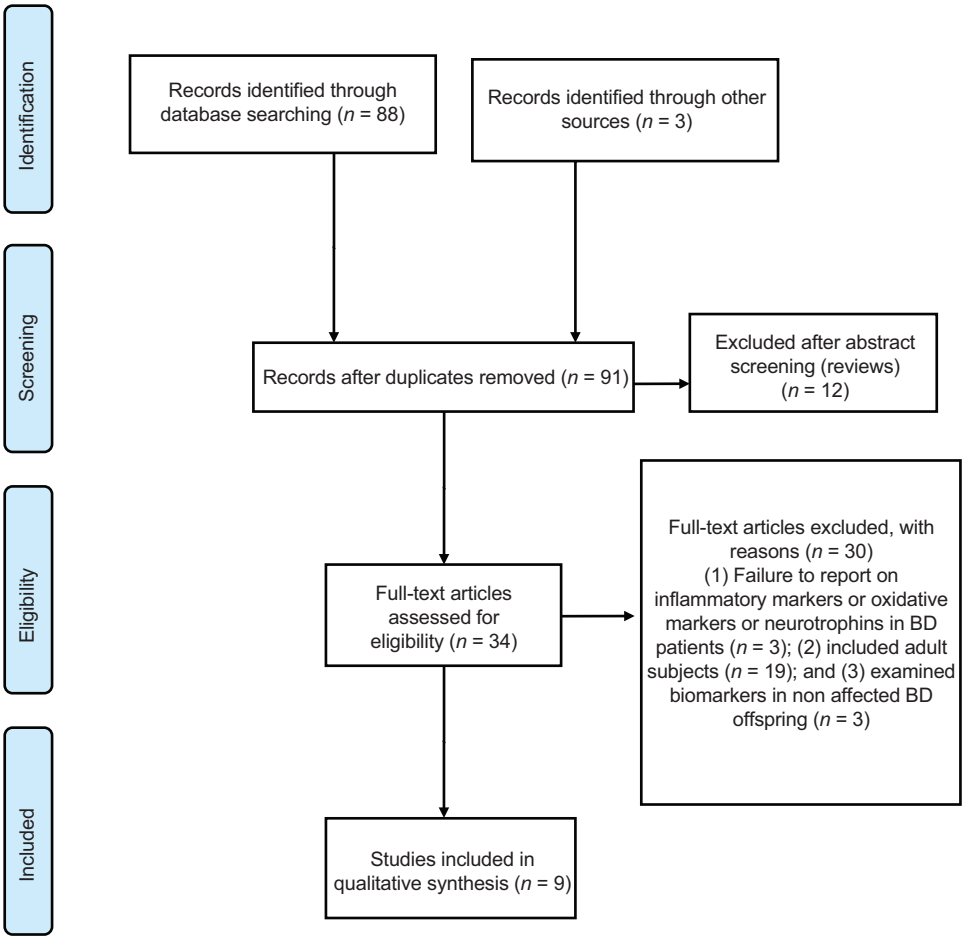

Figure 1: Flow diagram

Table 1: Summary of studies on biological markers in juvenile bipolar disorder

Study	Type of study	Subjects (Dx)	Age (years)	Psychiatric measures	Biological markers	Main findings
Barzman *et al.*[35]	Cross-sectional	*n* = 10 (BD-I)	12-17	WASH-U-KSADS; BRACHA	TNF gene	TNF gene expression correlates with both brain activations in amygdala, ACG, and OFC and aggression in adolescents with BD
Birmaher *et al.*[22]	Cross-sectional	*n* = 30 (18 BD-I; 1 BD-II; 11 BD-NOS)	12-19	K-SADS-PL; MRS; FHS	IL-6; hsCRP; BDNF	Manic symptom severity was significantly associated with hsCRP levels BDNF levels were not correlated with any illness phase
Pandey *et al.*[37]	Longitudinal (8 weeks)	*n* = 47 (26 BD; 21 HC)	7-17	YMRS; CDRS-R	BDNF	Lymphocyte BDNF mRNA and platelet BDNF levels in drug-free BD subjects were significantly lower than in HCs Lymphocyte BDNF mRNA was significantly increased in medicated BD subjects compared to drug-free BD subjects Lymphocyte BDNF mRNA levels in long-term treated BD subjects was similar to HCs
Chitty *et al.* [39]	Cross-sectional	*n* = 50 (24 BD-II; 9 BD-spectrum; 17 HC)	BD 18-30; HC 20-29	AUDIT; DASS; Kessler-10	GSH	Decreased GSH in the ACC of high risk drinkers BD subjects No differences in GSH concentration between BD subjects and HCs
Lagopoulos *et al.*[38]	Cross-sectional	*n* = 104 (13 BD-I; 25 BD-II; 15 BP-spectrum; 51 HC)	16-33	HDRS; BPRS; YMRS; SOFAS; K-10	GSH	No differences in GSH concentration between BD subjects and HCs No significant association between GSH and age of onset or duration of illness No significant correlations between GSH concentration and mania or depressive symptoms

Contd...

Table 1: Contd...

Study	Type of study	Subjects (Dx)	Age (years)	Psychiatric measures	Biological markers	Main findings
Kauer-Sant'Anna, *et al.*[10]	Cross-sectional	*n* = 120 (30 BD-I early-stage; 30 BD-I late-stage; 60 HC)	Early-stage BD 15-35; late-stage BD 18-65	YMRS; HAMD-21; GAF	BDNF; TNF-α; IL-6; IL-10	Decreased BDNF levels in late-stage BD patients compared to HCs Higher TNF-α and IL-6 levels in BD subjects than in HCs during both early and late stage BD Significant negative correlation between length of illness and decreased BDNF levels Positive correlation between TNF-α levels and length of illness
Magalhaes *et al.*[40]	Cross-sectional	*n* = 231 (33 BD-I; 22 BD-II; 82 MDD; 94 HC)	18-24	SCID	PCC; TBARS	Higher PCC levels BD subjects than in HCs No change in TBARS levels between BD subjects and HCs MDD were not different from control subjects in either PCC or TBARS levels PCC or TBARS levels could not differentiate MDD from BD subjects MDD and BD duration of illness did not correlate with either TBARS or PCC Serum PCC levels were associated with a current manic episode Serum TBARS levels were not associated with mania or depression
Su *et al.*[36]	Cross-sectional	*n* = 62 (10 bipolar depression; 13 reactive depression; 18 major depression; 21 HC)	18-30	BPRS; HAM-D	BDNF; adiponectin; hsCRP; TNF-α; IL-6	All depressed groups had serum BDNF levels lower than HCs No differences in BDNF levels between depressive subtypes Plasma adiponectin was lower in BD subjects than in HCs TNF-α was significantly higher in depressed patients than in HCs No differences in TNF-α levels between depressive subtypes No differences in IL-6 and hsCRP concentrations were found between depressed and healthy subjects or between depressive subtypes
Wiener *et al.*[41]	Cross-sectional	*n* = 231 (82 MDD; 33 BD-I; 22 BD-II; 94 HC)	18-24	HDRS; YMRS; ASSIST	Uric acid; PCC; TBARS	No association between oxidative stress parameters and clinical diagnosis of MDD and BD for women and men

BD: bipolar disorder; NOS: not otherwise specified; HC: healthy control; MDD: major depressive disorder; TNF: tumor necrosis factor; TBARS: thiobarbituric acid reactive substances; PCC: protein carbonyl content; IL: interleukin; hsCRP: high-sensitivity C-reactive protein; BDNF: brain-derived neurotrophic factor; GSH: glutathione; TBARS: thiobarbituric acid reactive substances; ACC: anterior cingulate cortex; mRNA: messenger RNA; ACG: anterior cingulate gyrus; OFC: orbitofrontal cortex

inclusion and exclusion criteria and were included in this review.

Table 1 provides the characteristics of each study, number of included subjects, diagnosis at baseline, age range of the subject sample, considered inflammatory/oxidative stress markers or neurotrophins, and main findings of the considered study.

Pro-inflammatory markers

One study examined serum pro-inflammatory markers IL-6 and hsCRP and serum BDNF among 30 adolescents diagnosed with BD [18 bipolar type I disorder (BD-I), 1 bipolar type II disorder (BD-II) and 11 BD not otherwise specified] from the Course and Outcome Bipolar Youth study.[29] They found a positive association between manic and hypomanic symptom severity and hsCRP levels. Manic symptom severity was associated with high levels of hsCRP, but not with IL-6 serum levels. Notably all three subjects with hsCRP levels > 10 μg/mL had a very high manic symptom score (Mania Rating Scale > 20). Depressive symptom severity was not significantly associated with hsCRP or IL-6 serum levels. Forty percent of participants had levels of hsCRP that are considered at risk for cardiovascular diseases among adults.

Barzman *et al.*[35] examined the associations between TNF gene expressions, functional brain activation under a frustrative nonreward task and aggression in a sample of 10 adolescents affected by BD-I. They found that gene expression of protein in the TNF pathways correlates with both activation in amygdala, anterior cingulate cortex (ACC) and orbito-frontal cortex and aggression in adolescents with BD suggesting that TNF-related inflammatory genes may play a role in neural activity associated with frustrative nonreward and aggressive behaviors in pediatric BD.

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