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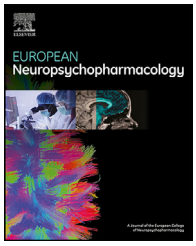

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REVIEW

Immune-related biomarkers and suicidal behaviors: A meta-analysis

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Abstract
Biomarkers that can differentiate between psychiatric disorders with and without suicidal behavior history from each other and from healthy volunteers may explain part of the pathogenesis of suicidal behavior. We conducted the hitherto largest meta-analysis comparing immune biomarkers between subjects with and without suicide attempt history or death by suicide. The study protocol was registered with PROSPERO, CRD42020212841. Standardized mean differences (SMD) were pooled with random-effects models. Heterogeneity between studies was assessed with the I^2-statistic and publication bias was evaluated by the Egger test and funnel plots. Data were based on 36 studies including 2679 persons with suicidal behaviors and 6839 comparison subjects, and four immune-related biomarkers (CRP, IL-6, TNF-α and IL-1β). Suicidal behavior was associated with higher CRP blood levels compared with: healthy controls (SMD [95%CI] = 1.42[0.85-1.98]); patients with depression alone (SMD [95%CI] = 1.23[0.20-2.26]); and patients with any psychiatric disorders (SMD [95%CI] = 0.39[0.22-0.55]). IL-6 blood level was higher in patients with suicidal behaviors compared with healthy controls (SMD [95%CI] = 1.13[0.45-1.82]) and when compared with psychiatric patients without suicidal behaviors (SMD [95%CI] = 0.22 [0.11-0.33]). Meta-regression and subgroup analyses revealed that increased CRP in suicidal behavior is primarily driven by recent suicidal behavior. These results implicate the immune system and inflammatory response in suicidal behavior independent of a relationship to major psychiatric disorders, and that these biological measures are predominantly state-dependent markers. Future studies are needed to determine the cause-and-effect relationship of these immune system biomarkers with suicidal behavior, and their potential predictive properties.

1. Introduction

Suicide accounted for about 700 000 deaths worldwide in 2019 (World Health Organization, 2021). For each suicide, there are more than 20 nonfatal suicide attempts (World Health Organization, 2019). Suicide attempters carry relatively higher burden of morbidity compared with psychiatric disorders (PD) not complicated by suicidal behavior, and an elevated risk of premature mortality due to suicide and other causes of death (Jokinen et al., 2018). A meta-analysis estimated a 10-year suicide rate of 7.4% among suicide attempters (Demesmaeker et al., 2022). Suicide and non-fatal suicidal behavior (SB) prevention are a priority, and prevention depends on better understanding of the causes (World Health Organization, 2019). Psychological autopsy studies from primarily high-income countries find that people attempting suicide or dying by suicide have (had) one or more psychiatric disorders, such as major depression, bipolar affective disorder, borderline personality disorder and substance use disorders at the time of the suicidal behavior (Cavanagh et al., 2003; Conwell et al., 1996; Dong et al., 2019; Hawton et al., 2013). Clinical prediction of imminent suicide risk has proven to be difficult, shifting interest to the detection of biological correlates of suicidal behavior that may inform us about pathogenesis, offer treatment and prevention targets, and have potential as predictors of risk (Mann and Rizk, 2020). It is critical that a study of the pathogenesis of suicidal behavior seek to separate the findings from the pathogenesis of the associated psychiatric disorder (Sudol and Mann, 2017).

Inflammation is involved in the pathophysiology of several major psychiatric disorders that are also linked to suicidal behavior, such as mood disorders, schizophrenia and substance use disorders (Dantzer, 2017; Köhler et al., 2017; Yuan et al., 2019). This observation raises the question of whether these indices of inflammation are also linked to the risk of suicidal behavior (SB) in these disorders. Previous systematic reviews and meta-analyses that have examined immune biomarkers in SB relative to patients without SB or relative to healthy volunteers, found differences in the levels of multiple immune markers including interleukin (IL)−1β, IL-2, IL-4, tumor necrosis factor (TNF)-α, transforming growth factor (TGF)−1, vascular endothelial growth factor (VEGF) and interferon (IFN)-γ (Black and Miller, 2015; Chang et al., 2016; Ducasse et al., 2015a; Ganança et al., 2016; Serafini et al., 2020). Unfortunately, the findings were not consistent, and the studies did not determine if inflammation in SB is independent of the associated psychiatric disorders. Therefore, we conducted a meta-analysis of immune and inflammatory biomarkers in SB in comparison with three distinct groups of individuals not attempting suicide or dying by suicide: healthy volunteers, major depressive disorder (MDD), and patients with other psychiatric disorders. This is the largest meta-analysis of inflammation and suicidal behavior reported to date and allowed for separation of effects due to depression or other psychiatric disorders from effects related to suicidal behavior. We also explored the impact of recency of suicidal behavior on the relationship to immune and inflammatory indices.

2. Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) reporting guidelines and is registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42020212841) (eAppendix 1 in the Supplement).

2.1. Eligibility criteria

We included original peer-reviewed studies conducted in humans of any age and sex that included:

1) General population-based or clinically-based observational studies with a quantitative design (cohort, cross-sectional, case-control or longitudinal).
2) Measurement of protein levels of at least one immune or inflammatory marker (including cytokines, chemokines or their receptors) in blood or cerebrospinal fluid (CSF) or postmortem brain.
3) SB systematically detected with a questionnaire or a structural interview or data from third party informants about suicide decedents. Studies of suicidal ideation and self-injury without intent to die were not included.
4) Biomarker levels reported from at least one comparitor group- psychiatric patients or nonpsychiatric non-suicide control or persons dying from other causes. Each biomarkers had to be reported by at least three studies in order to be included in the meta-analysis.

We defined nonfatal suicidal attempt (lifetime) or death by suicide as suicidal behavior. There was no timeline restriction for publications, and prospective studies were included. We excluded qualitative studies, case reports/series with <5 subjects, opinion articles, letters to the Editor, conference proceedings, reviews, or controlled trials. Studies were also excluded if they did not report on blood, CSF or brain biomarker levels at a group or individual levels, or did not provide the required data after contacting the corresponding author.

2.2. Data sources and search strategy

We searched MEDLINE, PsycINFO, Web of Science, Scopus, and Embase for records indexed from inception until March 17, 2023. Only articles published in English were considered. The search terms for biomarkers were inflammat*, immun*, cytokine, chemokine, interleukin, interferon, tumor necrosis factor, C-reactive protein, CRP, cellular immunity, lymphocytes, T cells, B cells, natural killer cell, macrophages or monocytes. For outcome measures, we used the search terms suicid*, non-suicidal self-injury, self-harm and parasuicide (eAppendix 2 in the Supplement). Cross-references were checked in published systematic reviews or meta-analyses.

2.3. Study selection and data extraction

An expert librarian did the systematic search of relevant literature within the databases using the predefined keywords (see eAppendix 2a. and 2b.). Database search was first conducted in Nov 2020 and was updated in Mar 2023. Documents were managed using EndNote. Initial screening was conducted using a web-based screening solution *Rayyan (Ouzzani et al., 2016); full text search, extraction and quality assessment of each study was performed in the Covidence systematic review software (Covidence, 2023).* Records were reviewed independently by two reviewers at each step. An article was included if both reviewers selected it independently, or reached a consensus. In case of disagreement, selection of a paper was decided by a third reviewer (GZ or JJM). Data items were then extracted in duplicate by the same reviewer pairs, and these data included sample demographics and clinical characteristics, comparison groups with sample sizes, outcome measures, biomarker source (blood, CSF, brain tissue) and levels, and type of suicidal behavior (SB). Comparisons included: healthy controls (HC) vs. MDD-SB to assess effect of MDD and SB, MDD vs. MDD-SB to assess effect of SB controlling for MDD, and other psychiatric disorders vs. other psychiatric disorders with SB to assess SB while controlling for other psychiatric disorders. The primary outcome was biomarker concentration at group level. Exploratory analyses examined the effect of recency of SB in studies where the data were available.

2.4. Determination of methodologic quality

The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the National Heart, Lung, and Blood Institute was used to assess the methodological quality of the papers. This tool contains 14 criteria assessing potential selection, information and measurement biases or confounding factors, rated as yes (scored 1) or no/not reported/ cannot determine/ not applicable (scored 0). Based on this investigation, the overall quality rating of each study was then determined to be "good" (total score $\geq$10), "fair," (total score 6–9), or "poor" (total score $<$ 6), as recommended (Tawfik et al., 2019). Groups of two reviewers graded the studies independently and then reached a consensus for each study regarding the criteria and overall study quality.

2.5. Statistical analysis

We extracted mean and standard deviation or converted the reported quartile levels of each biomarker at the group level as previously described (Wan et al., 2014). Meta-analyses were initially performed using standardized mean differences and the 95% CIs from Review Manager 5 (The Cochrane Collaboration, Oxford, United Kingdom). Pooled effect sizes were calculated for each biomarker in each of the three comparisons. Due to anticipated heterogeneity, a random-effects meta-analysis was employed. Heterogeneity between studies was assessed with the I^2 test. To control for potential publication bias, funnel plots were visually analyzed (eAppendix 3). To determine if the meta-analysis was unduly influenced by a single study that was an outlier in terms of effect size estimate or sample size, sensitivity analyses were performed by recomputing pooled standard

mean difference after deleting these individual studies serially.

The meta-analysis was then conducted using the random effect model as implemented in the "metacont" function in the "meta" library in R (Balduzzi et al., 2019), compatible with the RevMan computer program used in the rest of the study. Group means, standard deviations and group sizes were entered as arguments as extracted from the papers. The effect size calculated and displayed for each study was the Standardized Mean Difference (SMD) as measured by Hedges' "g", which uses the pooled and weighted standard deviation. Prediction intervals were also calculated. The random effect variation of the inverse variance method was used for weighting studies' SMDs. When means or standard deviations were not available from the papers, the Cochrane meta-analysis suggestions were followed as to the conversion of statistics provided into means and SD estimates.

The heterogeneity was measured by a restricted maximum-likelihood estimator for tau statistic, by the l statistic, and by the H statistic. The test of heterogeneity used the Q (chi-square) test. For comparisons with substantial or large heterogeneity, (I^2 >40%), if study number was at least 10, meta-regression was performed, using the metareg function in R (Viechtbauer, 2010) to test for moderating effect of average age, sex composition, recency of SB as defined in study inclusion criteria (categorized as recent vs. lifetime), by source of participants : inpatient/outpatient/community sample, and by source of biological sample: serum or plasma. We also performed subgroup analyses in studies based on recent SB as inclusion criteria for cases, for all comparisons with at least 2 such studies.

The Egger test (Egger et al., 1997) for publication bias was performed for all comparisons with at least 7 studies using the "metabias" function in the "meta" library. Given the low power of the test, conclusions of non-significant Egger tests for fewer than 10 studies should be considered with caution; nevertheless, we are presenting them in the above cases for reference as the number of studies is generally lower in this research area. Visual inspection of the funnel plots, provided in the Supplement (eAppendix 3), should also be performed, although with caution as there can be different reasons for funnel plot asymmetry.

3. Results

The PRISMA flow diagram for the current study is shown in Fig. 1. The initial search returned 9754 unique records of which 9385 records were excluded after title and abstract review. Following full-text review of the remaining 369 articles, 36 articles were included in the meta-analysis comprising 73 unique comparisons. Studies that were fulltext, reviewed but not included, are listed with reasons for exclusion in the Supplement (eAppendix 6).

Characteristics of the studies included in the meta-analysis are presented in Table 1. Most studies had a cross-sectional design (n = 23) and mostly examined inflammatory biomarker in the context of a recent suicidal attempt (n = 20). Over half of the studies (n = 19) recruited inpatients.

3.1. Quality assessment

Most studies (n = 29) were rated as being "fair" quality, six studies were rated as "poor" quality and one study was rated as being "good" quality (eAppendix 5). Missing information regarding methods was common: only 8 studies reported participation rate of eligible persons; whereas three studies reported blindness of assessors to status of participants, and 13 studies either did not measure or statistically control for confounding variables.

3.2. Main analyses

3.2.1. Comparison of inflammatory biomarkers in patients with psychiatric disorders (PD) with and without SB

Fourteen studies comprising 21 unique comparisons of inflammatory biomarkers in PD patients with and without SB were included. Studies included mixed psychiatric populations or MDD samples with other diagnoses such as anxiety disorders, bipolar disorder, substance use disorders or psychotic disorders (Table 1). Eleven studies (Aguglia et al., 2019; Courtet et al., 2015; da Graça Cantarelli et al., 2015; Dolsen et al., 2021; Ducasse et al., 2015b; Gibbs et al., 2016; Huang et al., 2022; Loas et al., 2016; Melhem et al., 2017; Ventorp et al., 2015; Wiebenga et al., 2022) compared peripheral CRP concentrations in patients with PDs with and without SB. CRP levels were higher in the PD and SB group compared with PD without SB, with a moderate effect size for pooled difference (k = 11, SMD =0.39, 95% CI = 0.22 and 0.55, p < 0.0001, I^2 = 73%, Fig. 2A). Five studies (Conejero et al., 2019; Dolsen et al., 2021; Fernandez-Sevillano et al., 2022; Jiang et al., 2022; Wiebenga et al., 2022) investigated peripheral IL-6 in PDs with and without SB. Overall, IL-6 was higher in the PD with SB group compared with PD without SB (SMD = 0.22, 95% CI = 0.11 and 0.33, p < 0.0001, I^2 = 2%, a small effect size, Fig. 2B). Those same five studies assessed TNF-α and found no difference in PD with and without SB (SMD = −0.09, 95% CI = −0.36 and 0.19, p = 0.48, I^2 = 61%, Fig. 2C).

In meta-regressions, no significant moderating effect was found for average age of sample (QM(df = 1) = 0.27, p = 0.602), proportion of females (QM(df = 1) = 0.18, p = 0.669), and whether the cytokine was measured in serum vs. plasma (QM(df = 1) = 0.98, p = 0.321). The test of moderation was significant for recency of attempt (recent vs. lifetime: QM(df = 1) = 24.46, p< 0.001, amount of heterogeneity accounted for R^2 =97%) and type of participants (outpatients/community samples vs. inpatients: QM(df = 1) = 7.62, p = 0.006). When entered into a metaregression together, only the moderation by recency of SB was significant (estimate 0.39, SE= 0.14, p = 0.004), sample type was not (estimate=−0.08, SE=0.13, p = 0.543). The conclusion is that the recency of suicidal behavior is most likely to be the primary moderator of effect size in this case. When the meta-analyses for CRP was rerun with studies with recent SB only, the effect size was significant (SMD=0.65, 95%CI=[0.48; 0.82], z = 7.48, p< 0.001) with a significant and narrow prediction interval of 0.32 to 0.99; heterogeneity was very small (tau^2 = 0.01, 95%CI [0.00;

Table 1 Characteristics of the studies included in the meta-analysis.

First author, year	Country/ Territory	Sample characteristics	Study design	Sample type	Suicidal behavior	Biomarkers	Source
Agugglia, 2019	Italy	200 w/psychopathology (MDD, BD, schizophrenia or other) (145 females): age $M = 50.89$ (SD=16.11); 133 w/psychopathology (MDD, BD, schizophrenia or other)+SB with high lethality (82 females): age $M = 49.62$ (SD=20.69)	Cross-sectional	Inpatient	Recent SB (admitted after SB)	CRP	Serum
Al-Amarei, 2019	Iraq	38 w/MDD (14 females): age 30.8 (SD14.1); 22 w/MDD+SB (6 females): age 36.9 (SD10.3); 30 HC (17 females): age 31.1 (SD 15.4)	Cross-sectional	Inpatient + outpatient	Recent SB (admitted after SB)	CRP	plasma
Bastos, 2017	Brazil	20 w/psychopathology (diagnoses NA)+SB (15 females): age $M = 26$ (SD=4.71); 136 HC (68 females): age $M = 26.1$ (SD=4.9)	Cross-sectional	Community	Lifetime SB	IL-1β	Serum
Castilo-Avila, 2022	Mexico	18 w/psychopathology (diagnoses NA)+SB (14 females): age $M = 36.63$ (SD=11.64); 66 HC (21 females): age $M = 43.71$ (SD=11.83)	Cross-sectional	ER Patients	Lifetime SB	IL-6	Serum
Conejero, 2019	France	40 w/psychopathology all with MDD but also BD in 35% sample (females only): age $M = 35.48$ (SD=7.69); 42 w/psychopathology all with MDD but also BD in 60% sample+SB (females only): age $M = 38.82$ (SD=9.67); 19 HC (19 females): age $M = 39.14$ (SD=7.95)	Cross-sectional	Outpatient	Lifetime SB	IL-1β; IL-6; TNF-α	Serum
Coryell, 2018	USA	123 w/MDD or BD (87 females): age $M = 38.5$(SD=15.8); 79 w/MDD or BD+SB (54 females): age $M = 30.7$ (SD=15.9)	Cross-sectional	Inpatient and outpatient	Lifetime SB$\geq$2 with at least one in the last year	IL-6; TNF-α; IL-1β; CRP	Plasma
Coryell, 2020	USA	128 w/MDD or BD (91 females): age $M = 38.2$ (SD=15.4); 96 w/MDD or BD+SB (63 females): age $M = 32.6$ (SD=13.1)	Cross-sectional	Inpatient and outpatient	Lifetime SB$\geq$2 with at least one in the last year	IL-1β	Plasma
Courtet, 2015	France	80 w/psychopathology (MDD, BD, anxiety disorder, substance use disorder and chronic diseases) (48 females): age $M = 44$ (SD=15.03); 520 w/psychopathology (MDD, BD, anxiety disorder, substance use disorder and chronic diseases)+SB (325 females): age $M = 39.14$ (SD=13.08)	Cross-sectional	Inpatient	Lifetime SB	hs-CRP	Plasma
da Graça Cantarelli, 2015	Brazil	36 w/MDD or BD (24 females): age $M = 32.28$ (SD=13.91) 50 w/MDD or BD+SB (39 females): age $M = 27.83$ (SD=12.21)	Cross-sectional	Inpatient	Recent suicide attempt (last 15 days)	CRP	Serum
Dolsen, 2020	The Netherlands	1982 w/psychopathology (anxiety or depressive disorder or both) (1341 females): age $M = 42$ (SD=12.7); 338 w/psychopathology (anxiety or depressive disorder or both)+SB (234 females): age $M = 42.6$ (SD=12.1)	Cross-sectional	Community and Outpatient	Lifetime SB	CRP; IL-6; TNF-α	Plasma
Ducasse, 2015	France	274 w/BD (140 females): age $M = 42.49$ (SD=13.52); 179 w/BD+SB (114 females): age $M = 41.94$ (SD=12.35)	Cross-sectional	Outpatient	Lifetime SB	hs-CRP	serum

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Table 1 (*continued*)

First author, year	Country/ Territory	Sample characteristics	Study design	Sample type	Suicidal behavior	Biomarkers	Source
Eidan, 2019	Iraq	38 w/MDD (14 females): age $M = 30.76$ (SD=14.01); 22 w/MDD+SB (6 females): age $M = 36.91$ (SD=10.3); 30 HC (17 females): age $M = 31.1$ (SD=15.4)	Case-control	Inpatients and Patients at ED	Recent SB (index visit)	IL-6	Plasma
Ekinci, 2017	Turkey	102 w/MDD (75 females): age $M = 41.88$ (SD=11.49); 37 w/MDD+SB (22 females): age $M = 43$ (SD=14.15); 50 HC (37 females): age $M = 44.12$ (SD=4.23)	Case-control	Inpatient	SB in the last 15 days	CRP	Serum
Fernandez-Sevillano, 2022	Spain	23 w/MDD or BD (18 females): age $M = 50.57$ (SD=9.93); 20 w/MDD or BD+*w*/SB (13 females): age $M = 44.70$ (SD=8.78); 20 HC (14 females), age $M = 44.58$ (SD=9.22)	Cross-sectional	Inpatient	SB in the last 30 days	IL-2; IL-2R; IL-4; IL-6; TNF- α	Serum
Gambi, 2005	Italy	23 w/MDD (female NA): age *M*=NA (SD=NA); 14 w/MDD+SB (females NA): age *M*=NA (SD=NA)	Cross-sectional	Outpatient	Lifetime SB	CRP	Serum
Ganaca, 2021	USA	20 w/MDD+SB (10 females): age $M = 32.70$ (SD=13.44); 24 HC (9 females): age $M = 33.67$ (SD=9.84)	Cross-sectional	Patients	SB in the last five years	TNF-α; IL-6; IL-1β	Plasma
Gibbs, 2016	USA	55 w/psychopathology (w/affective or/and psychotic disorder or/and substance abuse) (22 female): age $M = 39.5$ (SD=15.6); 22 w/psychopathology (w/affective or/and psychotic disorder or/and substance abuse)+SB (14 females): age $M = 37.8$ (SD=11.7)	Cross-sectional	Inpatient	Recent SB (73% two days prior to hospitalization)	hS-CRP	Serum
Gökalp, 2021	Turkey	108 w/psychopathology (MDD, impulse control disorder, generalized anxiety disorder, and other)+SB (102 females): Age $M = 15.1$ (SD=2); 131 HC (121 females): Age $M = 15.7$ (SD=1.3)	Cross-sectional	Patients at ED	Recent SB (index visit)	CRP	Serum
Huang, 2007	Taiwan	31 w/MDD: age $M = 39.6$; 11 w/MDD+SB: age $M = 33.3$; overall 30 females	Case-control	Inpatient	Recent SB (before admission)	IL-1β; TNF- α; IL-10; IL-1b/IL-10 ratio; TNF-α/IL-10 ratio	Serum
Huang, 2022	Taiwan	48 w/BD (27 females): age $M = 34.9$ (SD=12.2); 29 w/BD+SB (20 females): age $M = 37.7$ (SD=12.9); 61 HC (38 females): age $M = 32.4$ (SD=9.7)	Cross-sectional	Outpatient	Lifetime SB	CRP; sIL-6R; TNF-αR1	Serum
Jiang, 2022	China	24 w/BD (12 females): age $M = 26.13$ (SD=1.91); 14 w/ BD+SB (8 females): age $M = 26.79$ (SD=7.68); 26 HC (16 females): age $M = 28.23$ (SD=7.69)	Cross-sectional	Inpatient	Lifetime SB	IL-1β; IL-6; TNF- α	Plasma
Kumar, 2021	India	40 w/psychopatology (diagnoses NA)+SB (27 females): age $M = 28.28$; 40 HC (11 females): age $M = 28.98$	Case-control	Patients at ED	Recent SB (index visit)	hs-CRP	Serum
Loas, 2016	France	81 w/psychopatology diagnoses mood or anxiety disorder) 41 w/psychopatology (diagnoses mood or anxiety disorder)+SB Total sample: 89 females, 33 males; age: $M = 44.64$ (SD=13.48)	Cross-sectional	Inpatient	Recent SB (past 15 days)	CRP	Serum
Lu, 2019	China	22 w/schizophrenia, MDD, or unknown+SB (11 females): age $M = 38.86$ (SD=13.97); 22 HC (11 females): age $M = 38.73$ (SD=16.38)	Case-control	Suicide descendants	Suicide death	IL-1β	Plasma

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Table 1 (*continued*)

First author, year	Country/ Territory	Sample characteristics	Study design	Sample type	Suicidal behavior	Biomarkers	Source
Melhem, 2017	USA	37 w/psychopathology (17 females): age $M = 23.6$ (SD=3.9); 40 w/psychopathology+SB (11 females): age $M = 22.8$ (SD=3.8); 38 HC (20 females): age $M = 22.1$ (SD=2.2)	Cross-sectional	Inpatient	Recent SB (admitted after SB)	hs-CRP	Plasma
Nowak, 2019	Argentina	33 w/MDD+SB (25 females): age $M = 36.36$; 20 HC (15 females): age $M = 34.5$	Case-control	Inpatient	SB 48-h before admission	IL-6	Plasma
Oh, 2019	USA	1158 w/MDD (764 female): age $M = 47.3$; 172 w/MDD+SB (100 females): age $M = 49.2$	Case-control	Primary care	Lifetime SB	CRP	Plasma
Ohlsson, 2019	Sweden	13 w/any diagnosis (7 female): age $M = 34.5$; 54 w/MDD+SB (30 females): age $M = 38.5$	Case-control	Inpatient	Recent SB	IL-6	Plasma
Priya, 2016	India	42 w/unknown diagnosis+SB (20 females): age $M = 28.07$; 42 HC (20 females): age $M = 28.38$	Case-control	Outpatient	Recent SB	IL-6	Serum
Rasheed, 2019	Iraq	38 w/MDD (14 female): age $M = 30.76$ (SD= 14.1); 22 w/MDD+SB (6 females): age $M = 36.91$ (SD= 10.3); 30 HC (17 females): age $M = 31.1$ (SD= 15.4)	Case-control	Patients at ED	Recent SB (index visit)	TNF-α; IL-1β	Plasma
Strumila, 2023	Lithuania	52 w/MDD (39 females): age $M = 39.75$ (SD=13.24); 51 w/MDD+SB (34 females): age $M = 41.63$ (SD=19.80); 53 HC (35 females): age $M = 33.49$ (SD=12.77)	Cross-sectional	Patients in ICU and inpatients	SB in the last 48 h	CRP	Serum
Toffol, 2022	Italy	27 w/psychopathology (mood disorder, personality disorder, substance abuse/dependent or other)+SB (males only): age M NA; 27 controls (males only): age M NA	Case-control	Inpatient	Recent SB (admitted after SB)	hs-CRP	Serum
Vai, 2021	Italy	28 w/MDD (18 females): age $M = 54.3$ (SD=7.4); 28 w/MDD+SB (18 females): age $M = 51.4$ (SD=9.1); 28 HC (20 females): age $M = 44.5$ (SD=8.4)	Case-control	Inpatient	Lifetime SB	A panel of 27 cytokines including IL-1β; IL-6; IFN-γ; TNF-α	Plasma
Ventorp, 2015	Sweden	19 w/depression (10 females): age $M = 34$ (SD=10.3); 52 w/psychopathology (any)+SB (30 females): age $M = 38.5$ (SD=14.5); 19 HC (10 females): age $M = 34.7$ (SD=10.8)	Cross-sectional	Outpatient and emergency room	Recent SB (index visit)	CRP	Plasma
Wiebenga, 2022	Netherlands	1231 w/psychopathology (depression or/and anxiety) (842 females): age $M = 41.2$ (SD=12.6); 195 w/psychopathology (depression or/and anxiety)+SB (136 females): age $M = 43.1$ (SD=11.9)	Cross-sectional	Community, primary care, and outpatient	Lifetime SB	CRP; IL-6; TNF-α	Plasma
Yagci, 2021	Turkey	46 patients w/psychopathology (diagnoses NA) (33 females); 45 HC (24 females) Age of all sample $M = 32.53$ (SD=10.39)	Case-control	Patients at ED	Recent SB (index visit)	CRP	Serum

Notes: MDD: major depressive disorder; BD: bipolar disorder; HC: healthy controls; SB: suicidal behavior; NA: not available.

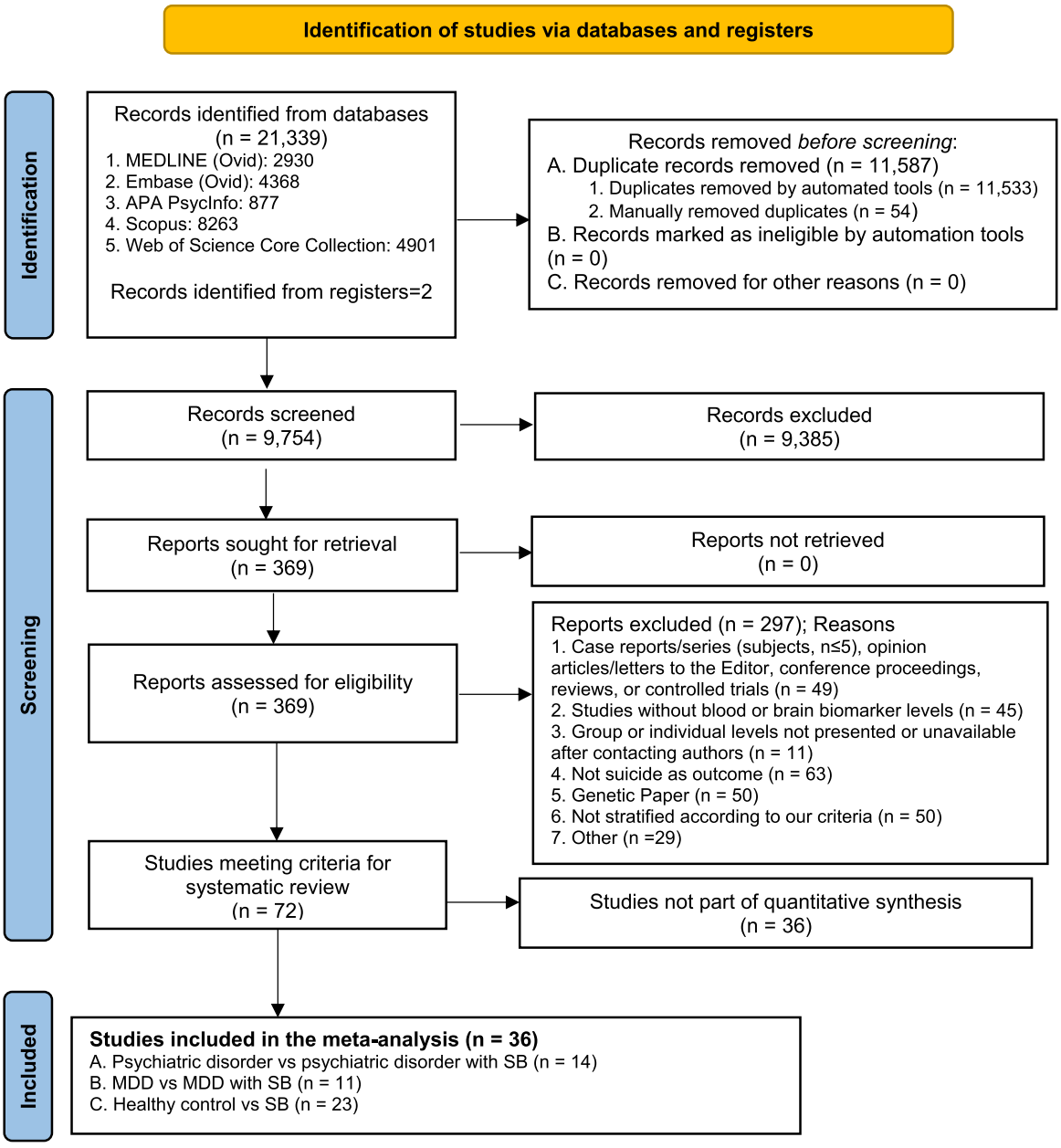


Fig. 1 PRISMA flow diagram for the current study.

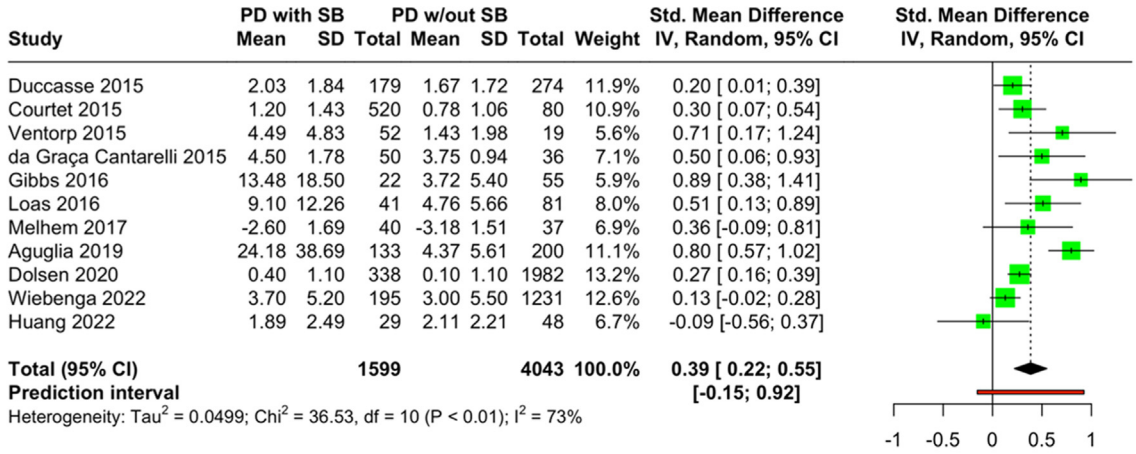
0.20], I^2 = 0.8%, 95%CI [0.0%; 74.8%], Q = 5.04, df=5, p = 0.411) (eAppendix 4).

3.2.2. Comparison of inflammatory biomarkers in MDD with and without SB

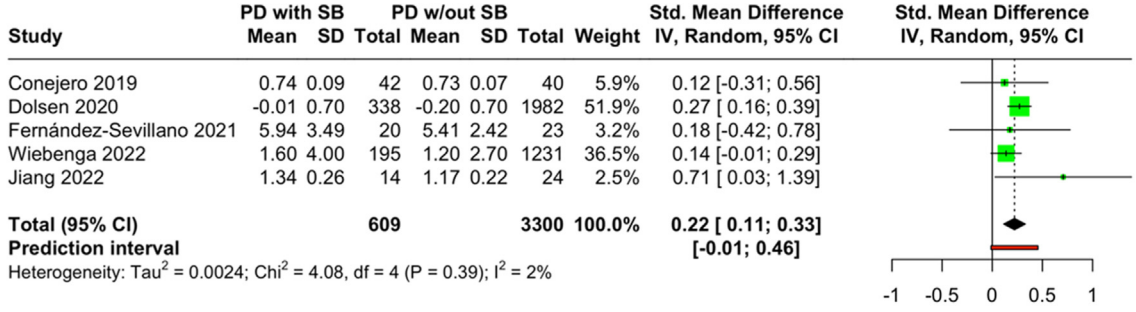
Eleven studies comprising 18 unique comparisons of inflammatory biomarkers in MDD with and without SB were included. Five studies (Al-Amarei et al., 2019; Coryell et al., 2018; Ekinci and Ekinci, 2017; Gambi et al., 2005; Oh et al., 2020) investigated CRP in MDD with and without SB. Overall, CRP was higher in MDD with SB versus MDD without SB (SMD = 1.23, 95% CI = 0.20 and 2.26, < 0.0001, I^2 = 97%, a large effect size, Fig. 3A).

Four studies (Coryell et al., 2018; Eidan et al., 2019; Ohlsson et al., 2019; Vai et al., 2021) assessed IL-6 and found no difference in MDD without SB compared with MDD and SB (SMD = 0.24, 95% CI = −0.05 and 0.53, p = 0.10, I^2 = 31%, Fig. 3B). TNF-α levels (Coryell et al., 2018; Huang and Lee, 2007; Rasheed et al., 2019; Vai et al., 2021) also did not differ in MDD without SB compared with SB (k = 4, SMD = 0.03, 95% CI = −0.24 and 0.29, p < 0.17, I^2 = 31%, Fig. 3C). Five studies(Coryell et al., 2018, 2020; Huang and Lee, 2007; Rasheed et al., 2019; Vai et al., 2021) examined IL-1β in MDD with and without SB and the levels did not differ between groups (SMD = −0.19 95% CI = −0.59 and 0.22, p = 0.31, I^2 = 76%, Fig. 3D). When the meta-analyses for CRP was rerun with studies with recent SB only, the effect size was significant (SMD=2.45, 95%CI=[1.96; 2.94], z = 9.76, p< 0.001) and heterogeneity was small (tau^2 = 0.04, I^2 = 32.7%, Q = 1.49, df=1, p = 0.23).

A) CRP



B) IL-6



C) TNF-α

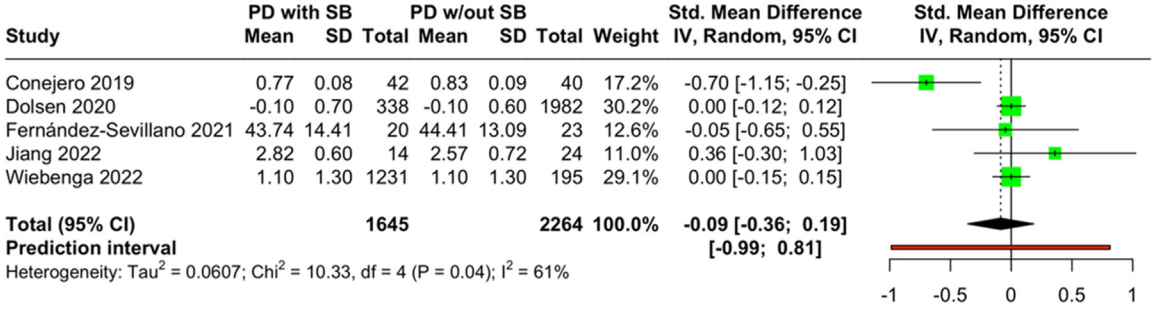


Fig. 2 Comparison of peripheral inflammatory biomarkers in patients with psychiatric disorders (PD) with and without suicidal behavior (SB). A) CRP B) IL-6 and C) TNF-α.

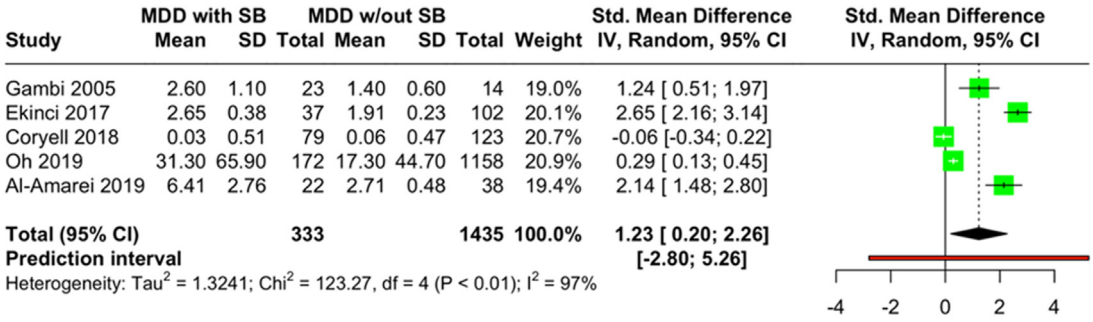
For IL-6, there was a strong trend-level effect for higher levels in MDD with SB and with a minimal heterogeneity (eAppendix 4).

3.2.3. Comparison of inflammatory biomarkers in HC and patients with SB

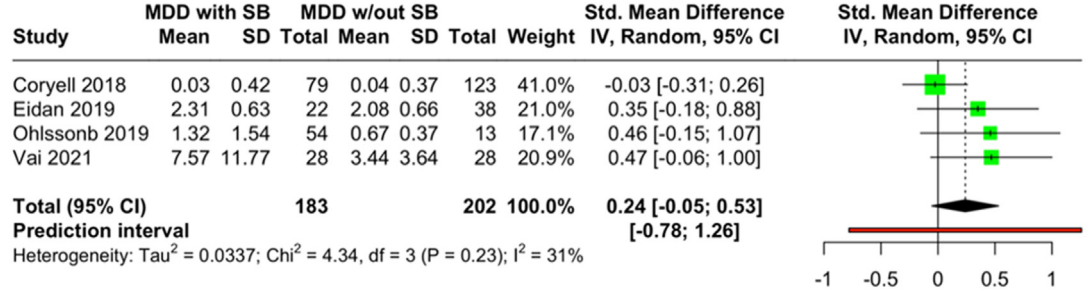
Twenty-three studies comprising 34 unique comparisons of inflammatory biomarkers in HC and patients with SB were included. CRP levels were higher in patients with SB versus HC across studies (Al-Amarei et al., 2019; Ekinci and Ekinci, 2017; Gökalp et al., 2021; Huang et al., 2022; Kumar et al., 2021; Melhem et al., 2017; Priya et al., 2016; Strumila et al., 2023; Toffol et al., 2022; Ventorp et al., 2015; Yagci and Avci, 2021) (k = 11, SMD = 1.42, 95% CI = 0.85 and 1.98, p < 0.0001, I^2 = 92%, very large effect size, Fig. 4A).

IL-6 was higher in patients with SB versus HC (Castillo-Avila et al., 2022; Conejero et al., 2019; Eidan et al., 2019; Fernandez-Sevillano et al., 2022; Gananca et al., 2021; Jiang et al., 2022; Nowak et al., 2019; Priya et al., 2016; Vai et al., 2021) (k = 9, SMD = 1.13, 95% CI = 0.51

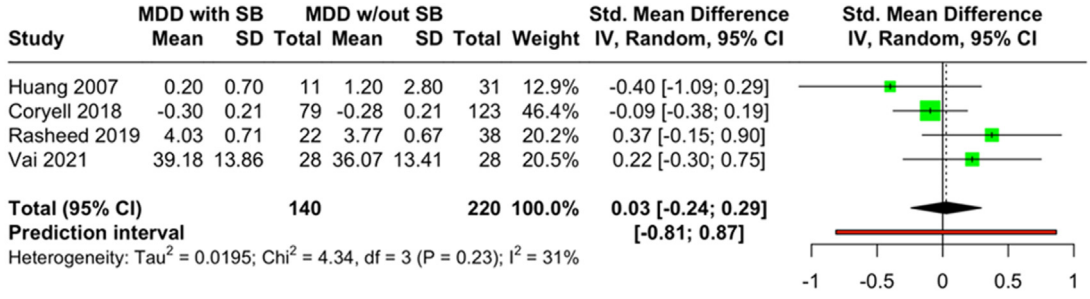
A) CRP



B) IL-6



C) TNF-α



D) IL-1β

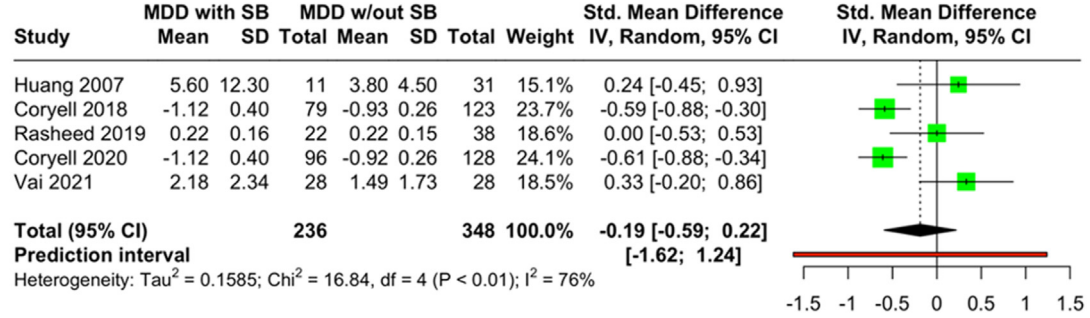
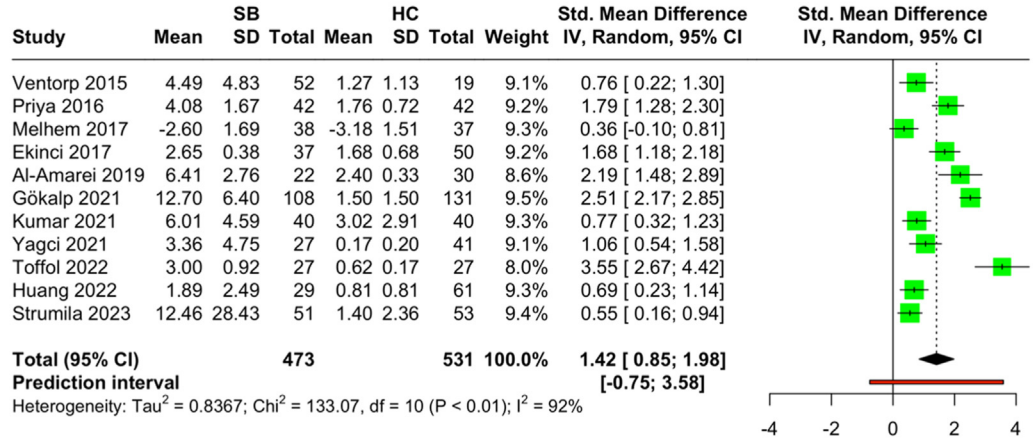
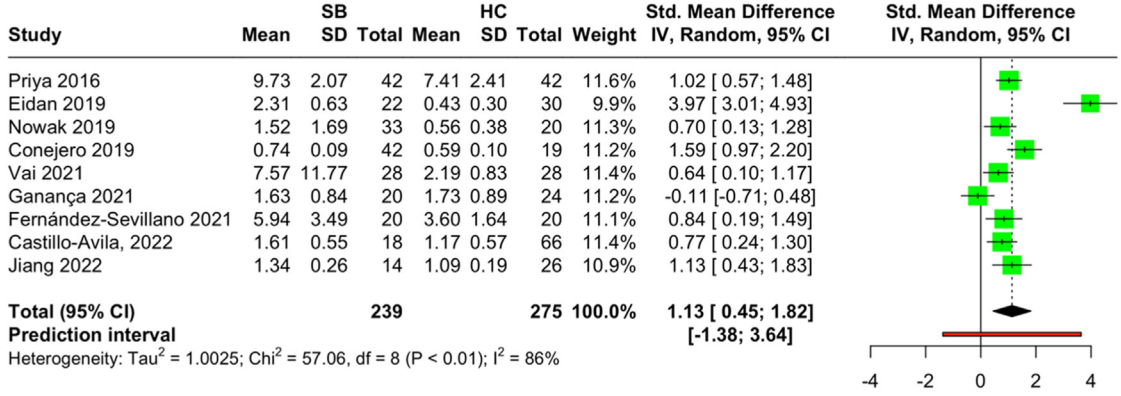


Fig. 3 Comparison of peripheral inflammatory biomarkers concentration in major depressive disorder (MDD) patients with and without suicidal behavior (SB). A) CRP B) IL-6 C) TNF-α and D) IL-1β.

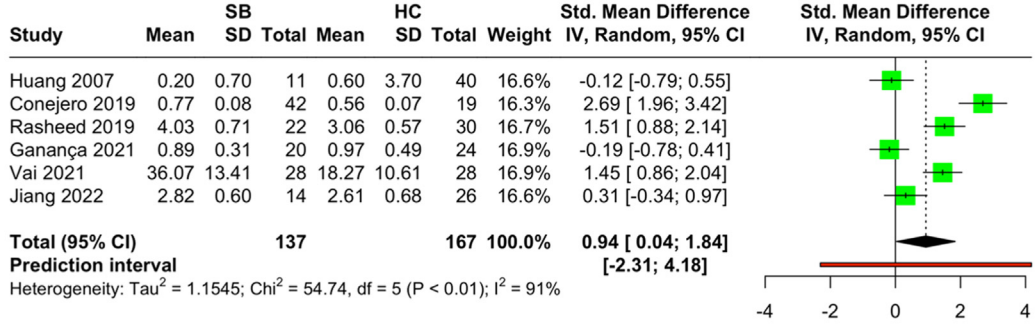
A) CRP



B) IL-6



C). TNF-α



D) IL-1β

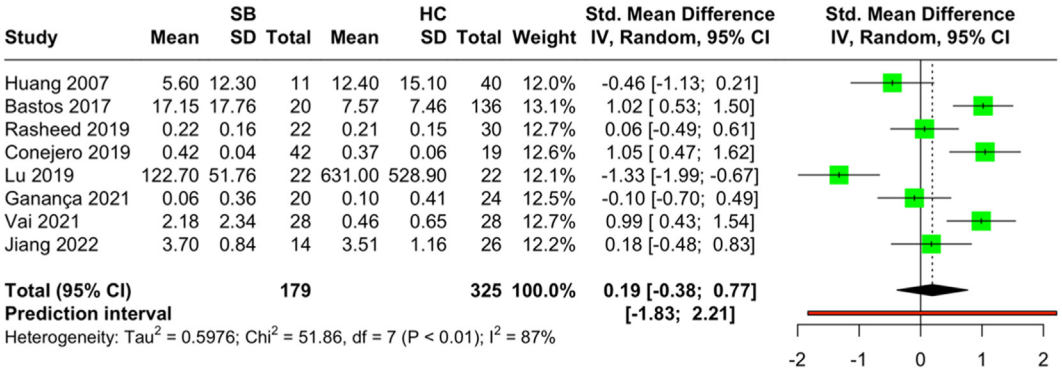


Fig. 4 Comparison of peripheral concentration of inflammatory biomarkers in Healthy Controls (HC) and patients with suicidal behavior (SB).

to 1.82, p < 0.0001, I^2 = 86%, very large effect size, Fig. 4B). TNF-α was higher in patients with SB versus HC (Conejero et al., 2019; Gananca et al., 2021; Huang and Lee, 2007; Jiang et al., 2022; Rasheed et al., 2019; Vai et al., 2021) (k = 6, SMD = 0.94, 95% CI = 0.04 to 1.84, p = 0.01, I^2 = 91%, Fig. 4C). IL-1β was not different in patients with SB versus HC (Bastos et al., 2017; Conejero et al., 2019; Gananca et al., 2021; Huang and Lee, 2007; Jiang et al., 2022; Lu et al., 2019; Rasheed et al., 2019; Vai et al., 2021) (k = 8, SMD = −0.19, 95% CI = −0.38 to 0.77, p = 0.50, I^2 = 87%, Fig. 4D). The sensitivity analysis shows that removing the outlier (Lu et al., 2019) did not change the statistical significance (SMD = 0.41, 95% CI = −0.04 to 0.86, p = 0.08, I^2 = 77%).

In meta-regressions, no significant moderating effect was found for average age of sample (QM(df = 1) = 0.6256, p-value = 0.4290), proportion of females (QM(df = 1) = 0.3741, p-value = 0.5408), whether the cytokine was measured in serum vs. plasma (QM(df = 1) = 0.4875, p-value = 0.4851), or type of participants (3 levels: outpatients vs. inpatients vs. ED patients: QM(df = 2) = 0.4841, p-value = 0.7850). All but one of the studies had recent, as opposed to lifetime, SB as their inclusion criterion for cases; after rerunning the meta-analysis without the study with lifetime SB the effect size remained significant (SMD=1.49, 95%CI= [0.88; 2.10], $z = 4.82$, $p < 0.001$), however heterogeneity was still large (tau^2 = 0.88, 95%CI= [0.38; 3.32]; I^2 = 92.8%, 95%CI= [88.8%; 95.4%]; $Q = 124.83$, df=9, $p < 0.001$).

Our review did not identify sufficient articles to consider brain or cerebrospinal fluid levels for similar meta-analytic comparisons.

Publication bias was not detected for the PD with SB vs. PD without SB comparison of CRP levels (bias estimate= 1.60, SE bias=1.13, intercept=0.15, SE intercept=0.13; t = 1.41, df = 9, p-value = 0.1918). Publication bias was not detected for the SB vs. HC comparison of CRP levels (bias estimate= 2.65, SE bias=5.14, intercept=0.69, SE intercept=1.26; t = 0.52, df = 9, p = 0.6188) or IL-6 levels (bias estimate= 8.95, SE bias=4.07, intercept=−1.71, SE intercept=1.23; t = 2.20, df = 7, p = 0.0638), but was detected for the IL-1β comparison (bias estimate= −17.80, SE bias=6.51, intercept=−5.56, SE intercept=1.94; $t = -2.74$, df = 6, p-value = 0.0340).

4. Discussion

We believe the present study is the hitherto most comprehensive meta-analysis examining the associations of immune and inflammatory biomarkers in SB. We performed analyses including three distinct sets of comparisons: mixed psychiatric populations with and without SB, major depressive disorder with and without SB, and patients with SB vs. healthy controls. Our main finding is that higher CRP blood levels are associated with SB, over and above an association with mood disorders. This indicates a two-hit model whereby inflammatory abnormalities are found in major depression, but additional abnormality is found in the subgroup attempting suicide or dying by suicide. The strength of this association was moderate when the comparison was within psychiatric patients, and larger when suicide attempters were compared with HC. CRP higher levels were associated with recent but not remote SB compared with patient samples and further confirmed by a narrow prediction interval within the subgroup analysis. This observation indicates that CRP level has potential as a predictor of imminent risk of SB.

IL-6 blood levels were higher in patients with SB compared with HC, and when SB with other psychiatric disorders were compared with psychiatric disorders and no SB. MDD with SB did not differ in IL-6 blood levels compared with MDD without SB. Therefore, meta-analysis did not detect a relationship of SB with higher IL-6 that was independent of MDD, but did find such a difference with other psychiatric disorders. TNF-α was not associated with SB, MDD or psychiatric disorders. IL-1β was also not found to be associated specifically with SB.

Higher CRP was reported in MDD with SB compared with MDD without SB (Köhler et al., 2017) and the same finding has been made in bipolar disorder (Solmi et al., 2021), and schizophrenia (Fraguas et al., 2019). If inflammation is also part of the pathophysiology of PDs, it is also possible that higher CRP levels in SB and PD could be due to greater severity of the underlying disease associated with SB. However, one study observed that the association between CRP levels and a history of SB in depression remained significant even after adjusting for severity of depression, suggesting that high CRP levels may be a marker of SB (Courtet et al., 2015).

CRP is an acute-phase reactant protein synthesized in the liver in response to IL-6 mediated increased transcription of the CRP gene during the acute phase of inflammation (Nehring et al., 2021). CRP may serve as a potential biomarker of fluctuating risk of SB. CRP has a longer half-life than cytokines and is more stable, indicating a rolling average of recent risk. CRP is a nonspecific biomarker, and longitudinal studies are needed to determine whether CRP blood concentrations vary with clinical state and risk for SB.

Elevated IL-6 level was found in association with specifically MDD (Ganança et al., 2016), but no independent association was found with SB. This may indicate that higher IL-6 is associated with MDD (Köhler et al., 2017) and not with SB. But, because the results also do not show elevated IL-6 in PD nonattempters compared with healthy volunteers, one cannot conclude that the effect is due to PD. A more nuanced understanding of cytokine changes in PD may be necessary. A recent meta-analysis found higher serum and CSF IL-6 levels (but not plasma) in SB compared to control subjects (González-Castro et al., 2021). In our meta-analysis study, the blood samples included serum (19 studies) or plasma (17 studies) assuming no differences between the levels of IL-6 in serum and plasma. Confidence in these findings of a relationship of higher levels to SB and not to the associated psychiatric disorder is increased because positive studies included patients with suicidal ideation and suicide attempt and different psychiatric diagnoses in addition to MDD, meaning that MDD alone did not account for the findings. If the psychiatric diagnoses vary, and the common factor is SB, that increases the possibility that SB is the reason for higher levels of IL-6.

There is a question of whether the SB-related inflammation/immune abnormality is in brain or peripheral blood. Perhaps the brain is involved because higher IL-6, a pro-

inflammatory cytokine has been found in association with SB in blood, CSF and postmortem brain (Ganança et al., 2016). Our review did not identify a sufficient number of studies comparing brain levels of cytokines or immune markers to determine if there is neuroinflammation associated with suicidal behavior and how the brain findings compare with peripheral immune parameters. A recent genetic study suggests that upregulation of IL-6 signaling may be causally related to suicidality (Kappelmann et al., 2021). It has also been observed that higher IL-6 level correlates positively with impulsive suicidal attempters, and higher levels of IL-6 and IL-10 levels are associated with higher suicidal ideation (O'Donovan et al., 2013). Importantly, higher IL-6 levels could potentially mediate the elevated CRP observed in association with SB independently of psychiatric disorder including MDD.

Neither TNF-α nor IL-1β was associated specifically with SB. IL-1β is an acute phase pro-inflammatory cytokine; therefore, it would be expected to be higher in MDD and/or SB. Animal models of depression find higher IL-1β levels, as well as efficacy of IL-1 pathway inhibitors for inflammation-induced depression (Mazarati et al., 2010). An earlier meta-analysis reported higher IL-1β in MDD, but no differences between MDD with and without suicidal behavior (Ellul et al., 2016). Since IL-1β is a far less stable molecule than CRP and IL-6, these findings based on circulatory levels of IL-1β are less reliable.

One of the strengths of the present meta-analysis study is that we focus on SB. SB is more closely related to suicide attempts or death than ideation. Many previous studies and subsequent meta-analyses (Black and Miller, 2015; Chen et al., 2020; Vasupanrajit et al., 2022) employed broader definitions like "suicidality" or combined patients with suicidal ideation and behavior, representing a more heterogeneous group. To focus on SB, we included fewer studies and that limited the statistical power of comparisons. We did include comparison groups to separate the SB effect from the psychiatric disorder effect. Although this meta-analysis included all immune biomarkers and various tissues and biological samples, only a few markers were analyzed in more than three studies, which limited our study to fewer biomarkers, but to those with sufficient data.

Other limitations should be noted. Most of the studies employed a cross-sectional design, making it impossible to observe how these biomarkers behave over time and how sensitive they are to changes in the clinical status of the patients. We did report the new finding that CRP elevation was associated only with recent SB and therefore may be a state-dependent marker with potential for predicting acute or imminent risk of SB. Second, most studies had a low number of participants. Third, biomarkers, like CRP, are subject to potential confounders such as age, obesity, physical activity, diet, and child abuse, and most studies do not adjust for these potential confounders. Fourth, psychotropic medications affect the inflammatory status, and most studies did not report how many patients were medicated and with what medication. Finally, we lacked the data to control for severity of psychiatric illness or comorbidities associated with MDD.

In conclusion, CRP is easy to assay and showed the most robust SB-specific effects. It is a general marker of acute phase response. Large effect sizes were found for IL-6, and this cytokine has a pleiotropic function with pro- and anti-inflammatory effects (Kim and Maes, 2003). Future studies should examine longitudinal associations between SB and biomarker levels because little is known of the state-trait relationships of these markers to suicide risk or their capacity to predict future suicidal behavior. From a pathogenesis perspective, it is not known if the emotional stress of psychiatric illness and suicidal ideation drive the inflammatory response via a sterile stress response, or whether inflammation causes illness and suicidal ideation and behavior. Furthermore, relationships of peripheral inflammation with brain inflammatory markers need to be determined because not all immune biomarkers in the periphery will be reflective of immune-inflammatory response in the brain. Finally, future studies need to determine if brain inflammation or peripheral inflammation is a driver of suicidal behavior.

Contributors

All authors jointly conceived and designed the study. All authors gathered data, analysed and interpreted or wrote manuscript. Analyses were performed by SPN, FMD and HH. Initial drafts were prepared by SPN and FMD. All authors were involved in revising the draft critically for important intellectual content and approved the final version to be submitted for publication. All authors agreed to be accountable for all aspects of the work.

Conflict of interest

Dr. Mann receives royalties from the Research Foundation for Mental Hygiene for commercial use of the Columbia-Suicide Severity Rating Scale. The remaining authors have nothing to disclose.

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Author contributions were funded through affiliated academic or health care institutions that had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2023.05.009.

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