Inflammation and Nitro-Oxidative Stress in Current Suicidal Attempts and Current Suicidal Ideation: a Systematic Review and Meta-Analysis.

Running title: immune activation in current suicidal behaviors

Asara Vasupanrajit, M.Sc.[a]; Ketsupar Jirakran, M.Sc.[a,b]; Chavit Tunvirachaisakul, M.D., Ph.D.[a, c]; Marco Solmi, M.D., Ph.D.[f,g,h], Michael Maes, M.D., Ph.D.[a, c, d, e]

[a] Department of Psychiatry, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

[b] Maximizing Thai Children's Developmental Potential Research Unit, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

[c] Cognitive Impairment and Dementia Research Unit, Department of Psychiatry, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

[d] IMPACT Strategies Research Center, Deakin University, Geelong, Australia.

[e] Department of Psychiatry, Medical University of Plovdiv, Plovdiv, Bulgaria.

[f] University of Ottawa, Psychiatry Department, Ottawa, Ontario, Canada

[g] The Ottawa Hospital, University of Ottawa, Ottawa, Ontario, Canada

[h] Ottawa Hospital Research Institute (OHRI), Clinical Epidemiology Program, University of Ottawa, Ottawa, Ontario, Canada

Corresponding author:

Prof. Dr. Michael Maes, M.D., Ph.D.

Department of Psychiatry, Faculty of Medicine, Chulalongkorn University,

Bangkok, 10330

Thailand

Email: Dr.michaelmaes@hotmail.com; asara.vasu@gmail.com

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Abstract

A meta-analysis showed a significant association between activated immune-inflammatory and nitro-oxidative (IO&NS) pathways and suicide attempts (SA). There are no data whether suicidal ideation (SI) is accompanied by activated IO&NS pathways and whether there are differences between SA and SI. The current study searched PubMed, Google Scholar, and Web of Science, for articles published from inception until May 10, 2021, and systematically reviewed and meta-analyzed the association between recent SA/SI (< 3 months) and IO&NS biomarkers. We included studies which compared psychiatric patients with and without SA and SI and controls (either healthy controls or patients without SA or SI) and used meta-analysis (random-effect model with restricted maximum-likelihood) to delineate effect sizes with 95% confidence intervals (CI). Our search included 59 studies comprising 4.034 SA/SI cases and 12.377 controls. Patients with SA/SI showed activated IO&NS pathways (SMD: 0.299; CI: 0.200; 0.397) when compared to controls. The immune profiles were more strongly associated with SA than with SI, particularly when compared to healthy controls, as evidenced by activated IO&NS pathways (SMD: 0.796; CI: 0.503; 1.089), an immune-inflammatory response (SMD: 1.409; CI: 0.637; 1.462), inflammation (SMD: 1.200; CI: 0.584; 1.816), and neurotoxicity (SMD: 0.904; CI: 0.431; 1.378). The effects sizes of the IO&NS, immune-inflammatory response and inflammatory profile were significantly greater in SA than in SI. In conclusion: increased neurotoxicity due to inflammation and nitro-oxidative stress and lowered neuroprotection may explain at least in part why psychiatric patients show increased SA and SI. The IO&NS pathways are more pronounced in recent SA than in SI.

Keywords: suicide, neuro-immune, inflammation, oxidative and nitrosative stress, depression, mood disorders, schizophrenia, psychiatry

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Introduction

Non-fatal suicide behaviors (SB) are self-injurious behaviors, which may be classified according to their severity into suicidal ideation (SI) and suicide attempts (SA)[1]. A study across 17 countries shows that SI has a greater lifetime prevalence than SA, namely 9.2% and 2.7%, respectively[2], indicating that not all individuals with SI will attempt suicide. Many different risk factors may lead to SB[3, 4] but psychiatric disorders are the major risk factors[5, 6]. Individuals with major depressive disorder (MDD) show an almost eight-fold increased risk of suicide, whilst bipolar disorder (BD) and schizophrenia (SCZ) show a six-fold increased risk as compared with individuals without these psychiatric disorders[6].

There is now evidence that activation of immune-inflammatory and nitro-oxidative (IO&NS) pathways is involved in the pathophysiology of major psychiatric disorders, including MDD, BD, and SCZ[7-10]. These disorders are characterized by a simultaneous activation of the immune-inflammatory response system (IRS) and the compensatory immune-regulatory system (CIRS), which may down-regulate the IRS. **Electronic Supplementary File (ESF) 1 Table 1** shows the IRS-CIRS pathways, and their features involved in those major psychiatric disoders.[11-13]. IRS activation is accompanied by the induction of nitro-oxidative (O&NS) pathways with increased production of reactive oxygen (ROS) and nitrogen species (RNS) especially when the antioxidant defenses are reduced[7]. The consequent redox disbalance may cause increased damage to lipids, proteins, DNA, and mitochondria[7]. Moreover, many IO&NS markers have neurotoxic effects, including interleukin (IL-)2, IL-6, tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), some chemokines (i.e., CCL-2, CCL-5), C-reactive protein (CRP), quinolinic acid (QA), picolinic acid (PA), malondialdehyde (MDA), and nitric oxide metabolites (NOx)[13, 14]. Increased neurotoxicity may cause dysfunctions in gray and white matter plasticity, which in turn are

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associated with affective disorders and SCZ[13-15]. In contrast, antioxidants, including albumin, vitamin-D, and high-density lipoprotein (HDL), and neurotrophic substances, including brain-derived neurotrophic factor (BDNF)[16], may have neuroprotective effects thereby protecting the central nervous system (CNS) against the neurotoxic effects of the IRS[7].

Since the 1990ties, there were also studies implicating IO&NS pathways in the pathophysiology of SB[17, 18]. Since then, a rising number of studies have examined the relationship between SB (either SA or SI) and IO&NS biomarkers, including IL-1β, IL-6, TNF-α, IFN-γ, chemokines such as IL-8, and the neutrophil-to-lymphocyte ratio; CIRS markers including IL-4, IL-10, and soluble IL-2 receptor (sIL-2R); acute phase response (APR) productions such as CRP and albumin; O&NS markers (i.e., MDA, NOx); and antioxidants or neurotrophic factors including albumin, BDNF, omega-3 polyunsaturated fatty acids (PUFAs), HDL-cholesterol, total antioxidant capacity (TAC), and vitamin D3[19,23,24]. One of the most consistently reported abnormalities in SB is the increase in IL-6 in cerebrospinal fluid (CSF), blood, and postmortem brain, whilst more controversial findings were observed for other pro-inflammatory cytokines[20, 21]. It is noteworthy that the cytokine imbalance in SB may present with activation of the tryptophan catabolite (TRYCAT) pathway leading to lowered levels of tryptophan (TRP) and increased levels of TRYCATs including QA, PA, and kynurenine (KYN)[4, 22, 23].

Meta-analyses, which examined associations with cytokines other than IL-6, frequently reported controversial findings. For example, Black and Miller[24] found significantly increased blood levels of IL-1β, whereas Ducasse et al.[25] reported a medium effect size with lower IL-2 and IL-4 but higher TGF-β plasma levels. CRP (positively)[26, 27] and BDNF (negatively)[28] were significantly associated with SB, while SB was associated with BDNF in plasma[28] but not in serum[28, 29].

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Importantly, most previous meta-analyses on IO&NS blood biomarkers and suicide examined SA and SI patients lumped together in one SB group without considering possible differences between these groups[24-26]. Hence, the current study aimed to systematically review and meta-analyze the association between IO&NS blood biomarkers and recent SB and to delineate differences among SA and SI. The examination of solitary IO&NS biomarkers is less relevant because these compounds take part in highly connected networks and subnetworks. In this regard, Maes et al.[9, 15] showed that the combination of several IO&NS biomarkers into weighted composite scores may improve our understanding of the pathways involved in affective disorders, schizophrenia and SB. Therefore, we here examine whether SA and/or SI are associated with composite scores reflecting IO&NS (the primary analyses) and its subdomains namely IRS, inflammation, neurotoxicity, and neuroprotection (the secondary analyses) as described in ESF1 Table 1 . In addition, we also examine solitary biomarkers such as CRP (part of the inflammation profile) and BDNF (part of neuroprotection profile). Based on previous knowledge, we hypothesized that a) in patients with SA and SI, IO&NS, and IRS, inflammation, neurotoxicity, and CRP are increased, whereas neuroprotection and BDNF are reduced when compared with controls; and b) that aberrations in these functional profiles are more pronounced in SA than in SI.

Materials and methods

Our methodological approach was based on the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020[30], the Cochrane Handbook for Systematic Reviews and Interventions[31], and the Meta-Analyses of Observational Studies in Epidemiology (MOOSE)[32]. We followed an a priori protocol which is available upon request from

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the last author. The draft or process of this study did not directly or indirectly involve public or patient representatives.

Scope of systematic review

This study classified SB into 2 groups, namely SA and SI[1]. We combined different biomarkers into composites according to their well-established functions (ESF 1 Table 1). This study first selected manuscripts, which were published in peer-reviewed journals, and then searched additional records in the reference lists of the studies and grey literature. We included English case-control studies or cohort studies when these included a control group and compared SB (SA+ or SI+ within 3 months before the study) with controls, including non-SB patients (SA- or SI-) and/or healthy controls (HC), alone and together. As such, we also examined differences in effect sizes between SA+ *versus* SA- and SI+ *versus* SI- within patients with psychiatric disorders. Moreover, we also examined possible differences in effect sizes between SA and SI. We reviewed papers, which included patients and controls of both sexes, all ages and ethnicities, and examined IO&NS biomarkers in blood, serum, and plasma but not CSF, urine, platelets or stimulated whole blood.

We contacted the authors of eligible studies, which did not report mean and standard deviation (SD) or standard error (SE) values and requested to provide means, SD, and number of cases and controls. When the authors did not respond to our request, we computed mean and SD values using formulas published by Wan et al.[33] for studies presenting median with either interquartile range (IQR) or minimum/maximum values. We excluded studies reporting animal models, translational and genetic research, or studies without controls. Any reasons why studies were excluded were recorded.

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Literature search and data extraction

A systematic review of studies was conducted using the electronic databases including PUBMED/MEDLINE, Google Scholar, and Web of Science from inception to 10th May 2021. The search used the major terms of IO&NS biomarkers and suicide **(ESF 1 Table 2)**, include "inflamm*" OR immun*", "cytokine", "chemokine", "IL-6", "IL-1", "interleukin", "C-Reactive Protein", "CRP", "tumor necrosis factor", "TNF", "interferon", "IFN", "Transforming growth factor", "TGF", "Tryptophan", "Oxidative stress", "Antioxidants", "Zinc", "Vitamin", "Albumin", "Nitric oxide", "Lipid hydroperoxides", "Omega 3", "Coenzyme Q10", "DHA", "suicid*". We conducted a manual search on the reference list of the studies included and previous meta-analysis studies.

The first author (AV) screened the eligibility manuscripts by considering the titles and abstracts and collected the full text of the potentially eligible papers and extracted the key data into a predefined Excel spread sheet. The second author (KJ) independently checked the extracted data once the first author (AV) completed all information. In case of disagreement, the last author (MM) was consulted. We used a methodological quality and red-point score checklist, namely the immune cofounder's scale (ICS), adapted from Andrés-Rodríguez et al.[34] and Vasupanrajit et al.[19], which was slightly modified by the last author **(ESF 1 Table 3).**

Statistical Analysis

This study performed statistical analysis using the Comprehensive meta-analysis (CMA) V3 software. The precise methods were described previously.[18] The primary outcome was the pooled standardized mean difference (SMD) of the IO&NS profiles. The secondary outcomes were

pooled SMD of the IO&NS subdomains, namely IRS, inflammation, CRP, neurotoxicity, antioxidant/neuroprotective (ANTIOXPRO), and BDNF, which were examined to explore which components of the IO&NS are more relevant to recent SA and SI. Hence, in the present MA, we employed synthetic scores which reflect outcome profiles and compared these scores between SA and SI and controls. For studies reporting more than one IO&NS biomarker, a synthetic score was computed using the mean of the outcomes, while assuming dependence. We used a random effect model with restricted maximum-likelihood because there are differences in study design, measuring time, and participants' characteristics across studies. The random-effects subgroup meta-analysis were performed, comparing patient subgroups (either SA+ or SI+) *versus* controls. This study computed the SMD values with 95% confidence intervals (CI) and used an alpha level of 0.05 indicating statistically significant results (two sided tests). The Cochrane Q test and the I^2 metric were computed, but Tau (τ) and τ^2 was used to evaluate heterogeneity[35, 36]. If τ^2 was imprecise, we investigated potential sources of heterogeneity across studies when at least 10 studies provided data of the same profile, using either subgroup meta-analysis (with minimum of three studies per sub-group) or random-effects meta-regression analyses (with minimum of ten studies).

Sensitivity analyses were performed to investigate the robustness of the pooled combined meta-analysis effects and between-study heterogeneity using the leave-one-out method. We used the classical fail-safe N method, Kendall tau with continuity correction (using one-tailed p-values) and Egger's regression intercept (using one tailed p-values) to evaluate small study effects including publication bias. We also used funnel plots, which display study precision on the y-axis and the SDM on the x-axis, to detect small study effects or systemic heterogeneity by simultaneously displaying the observed studies and the imputed missing values.

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Results

Search results

Our search strategy identified 2451 reports. Of those, 64 articles[17, 18, 20, 37-97] were assessed in our systematic review after removing duplicated citations and using the selection criteria. We removed 5 articles[50, 63, 71, 75, 88] from the meta-analysis for reasons shown in the ESF 1 Table 5. Consequently, 59 articles[17, 18, 20, 37-49, 51-62, 64-70, 72-74, 76-87, 89-97] were considered in the meta-analysis (**Figure 1**).

ESF 1 Table 4 shows the characteristics of the included studies. Fifty-two articles were case control studies, and four articles were cohort studies, two were retrospective, and one was a longitudinal study. Thirty-three studies assayed the biomarkers in serum, 18 in plasma, 4 in blood, and 4 reported mixed mediums. Of these, only 35 studies samples reported the specific time for blood sampling. The age range of all participants samples was 12-89 years old. We included participants from all continents except Australasia, namely 1 study from Belgium, Croatia, Egypt, Iran, Ireland, Japan, Netherland, and Tunisia; 2 studies from Canada, France, India, Italy, Mexico, Poland, and Taiwan; 3 studies from Brazil and Iraq; 4 studies from Sweden; 6 studies from China and Turkey; 7 studies from USA; and 8 studies from South Korea. The median quality scores were 5.7 (min = 1.6, max = 9.7), whereas the median red point score was 17.5 (min = 9.0, max = 25.0).

The meta-analysis included 16.411 participants samples, namely 4.034 cases (either SA+ or SI+) and 12.377 controls. We used subgroups within the study as unit of analysis to compare 2.511 SA+ cases *versus* 7.784 SA- and heathy controls combined, and 1.523 SI+ *versus* 4.593 SI- and healthy controls combined (**Table 1**).

We found that 42.05% of the SA patients in the 59 studies belonged to a mixed group of psychiatric disorders (MIX), whereas 34.41% suffered from MDD, 19.59% of affective disorders, and 1% showed other psychiatric disorders including schizophrenia and adjustment disorders (OTHER). We found that 23.7% of the SI+ cases suffered from MDD and 23.57% from affective disorders, whilst 23.05% and 9.26% of the cases were allocated to the MIX or OTHER class. Most SA+ cases were included based on the attempted suicidal act (67.98%) and the others were included based on a semi-structure interview (32.02%), whereas most of SI+ cases were assessed by a self-report questionnaire (63.23%) and the remaining using a semi-structured interview (36.76%).

Qualitative synthesis

Table 1 shows the distribution of the SMD and confidence intervals of the outcome profiles. Inspecting the confidence intervals showed that most included studies favored SB and that only 1 or 2 studies reporting on IO&NS, IRS, inflammation, neurotoxicity, and ANTIOXPRO showed confidence intervals which were entirely located on the negative side of zero. All studies on CRP and BDNF favored SB and no studies showed a CI, which was entirely on the negative side of zero. Furthermore, there were two studies, not included in the CMA (ESF 1 Table 5), which reported no significant findings on plasma cytokines[63], chemokines[63], and TRP[88], whereas the other three studies revealed inconsistent results on plasma CRP[50, 63, 75]. Regarding the SB subtypes SA and SI, we found that most studies favor SA and that no CI was entirely located on the negative side of zero (except the ANTIOXPRO profile), whereas in the SI studies 1 or 2 confidence intervals were entirely located on the negative side of zero. In addition, there were no significant findings

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on the plasma TRP/amino acid ratio[71] in studies which were not included in the CMA (ESF 1 Table 5) and which compared SA+ cases with SA- controls.

Meta-analysis of the primary outcome: IO&NS profile

Table 2 and **Figure 2** show that there is a significant difference in the overall pooled effect size of 0.299 when comparing IO&NS in SB with controls. Since there is some heterogeneity, we used subgroup analysis within study as the unit of analysis and found that the comparison of SA+ *versus* controls yielded a SMD of 0.387, and SI+ *versus* controls a SMD of 0.167. When using the subgroups as the unit of analysis, we found that the comparison of SA+ *versus* SA- yielded a SMD of 0.255, whereas SA+ *versus* HC yielded a large, pooled effect size of 0.796. The comparison of SI+ *versus* SI- yielded a significantly but small effect size (n=21; SMD: 0.156; 95%CI: 0.016; 0.296), whereas the SMD was not significantly different when comparing SI+ with HC. **ESF 2 Figure 1** showed the differences in the effect sizes of the comparisons of SA+ vs controls (SMD=0.387) and SI+ *versus* controls (0.167) which was significant (χ^2=5.14, df=1, p=0.023), indicating that SA+ is more strongly associated with IO&NS than SI+. Sensitivity analysis using the leave-one-out method did not alter the results of these meta-analysis (and any of the meta-analyses described below). Consequently, we performed a sensitivity analysis on the high-quality studies (quality score≥7.0; redpoint score ≤18.0) and compared those with a low quality (quality score≤4.0; redpoint score>18.0). **ESF 2 Figure 2** shows the meta-analysis performed on the 13 high-quality studies[44, 46, 52, 53, 55, 64, 66, 69, 70, 72, 84, 91, 93] (SMD: 0.407; 95%CI: 0.203; 0.611; τ^2=0.092) and 5 low-quality studies[39, 73, 79, 89, 92] (SMD: 0.129; 95%CI: 0.014; 0.0.243; τ^2=0.005) when comparing SB to controls. This difference between high- and low-quality studies was significant (χ^2=5.444, df=1, p=0.020).

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Meta-analyses of the secondary outcomes

IRS profile

Table 2 reports a moderate, pooled effect size of 0.460 in overall SB cases. Subgroup analysis showed that the comparison of SA+ *versus* controls yielded a significantly effect size of 0.590, whereas SI+ *versus* controls yielded a lower effect size of 0.231. When using subgroups as the unit of analysis, we found that the comparison of SA+ *versus* SA- yielded a SMD of 0.384, whereas SA+ *versus* HC yielded a large, pooled effect size of 1.049. There was no significant difference between SI+ and SI- or HC groups. The difference in the effect sizes of the comparisons of SA+ vs controls (SMD=0.590) and SI+ *versus* controls (0.231) was significant (χ^2=6.54, df=1, p=0.011).

Inflammatory profile

We found that the inflammation score is higher in SB cases than in controls with a moderate effect size of 0.459. Subgroup analysis showed that the comparison of SA+ *versus* controls yielded a SMD of 0.623, whereas the comparison of SI+ *versus* controls yielded a SMD of 0.239 (**Figure 3**). When using the subgroups as the unit of analysis, we found that the comparison of SA+ *versus* SA- yielded a SMD of 0.414, whereas SA+ *versus* HC yielded a large, pooled effect size of 1.200. There was no significant difference between SI+ and SI- or HC groups. The difference in the effect sizes of the comparisons of SA+ vs controls (SMD=0.623) and SI+ *versus* controls (SMD=0.239) was significant (χ^2=5.048, df=1, p=0.025).

CRP

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When comparing CRP in SB with controls, we found a pooled effect size of 0.573 (table 2). Subgroup analysis showed that the comparison of SA+ *versus* controls yielded a significant pooled effect size of 0.689, whereas SI+ *versus* controls yielded a significant effect size of 0.429. When using subgroups as the unit of analysis, we found that the comparison of SA+ *versus* SA- yielded a SMD of 0.499, whereas SA+ *versus* HC yielded a large, pooled effect size of 1.311. The comparison of SI+ *versus* SI- yielded a significantly moderate effect size (n=4; SMD: 0.460; 95%CI: 0.098; 0.822). The comparison of SI+ *versus* HC showed only two studies and therefore we did not perform CMA. The difference in the effect sizes of the comparisons of SA+ vs controls and SI+ *versus* controls was not significant (χ^2=1.58, df=1, p=0.208).

Neurotoxicity profiles

Table 2 also shows that the neurotoxicity levels are significantly increased in SB as compared with controls with an overall pooled effect size of 0.403. Subgroup analysis (with the subgroup as the unit of analysis) showed that the comparison of SA+ *versus* controls yielded a significant pooled effect size of 0.524, whereas SI+ *versus* controls yielded a lower effect size of 0.243. We found that the comparison of SA+ *versus* SA- yielded a SMD of 0.403, whereas SA+ *versus* HC yielded a large, pooled effect size of 0.904. There was no significant difference between SI+ and SI- or HC groups. The difference in the effect sizes of the comparisons of SA+ vs controls and SI+ *versus* controls was not significant (χ^2=3.61, df=1, p=0.057).

ANTIOXPRO profiles

We found significant associations between ANTIOXPRO scores in SB cases with a small, pooled effect size of 0.179. The comparison of SA+ *versus* controls yielded a low but significant

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effect size of 0.199, whereas there were no significant differences when comparing SI+ and controls. When using the subgroups as the unit of analysis, we found that the comparison of SA+ *versus* SA- yielded a SMD of 0.137, whereas SA+ *versus* HC yielded a SMD of 0.476. The difference in the effect sizes of the comparisons of SA+ vs controls and SI+ *versus* controls was not significant (χ^2=0.22, df=1, p=0.636).

BDNF

Table 2 shows that SB is accompanied by the lowered BDNF levels with a SMD of 0.479. The comparison of SA+ *versus* controls yielded a SMD of 0.417, and SI+ *versus* controls yielded a SMD of 0.665. When using the subgroups as the unit of analysis, we found that the comparison of SA+ *versus* SA- yielded a SMD of 0.256, whereas SA+ *versus* HC yielded a large, pooled effect size of 0.962. The comparison of SI+ *versus* SI- yielded a significantly moderate effect size (n=3; SMD: 0.587; 95%CI: 0.324; 0.851). We are unable to perform the analyses of SI+ *versus* HC due to the small number of studies (n=2). The difference in the effect sizes of the comparisons of SA+ vs controls and SI+ *versus* controls was not significant (χ^2=1.44, df=1, p=0.230).

Other subgroup analyses and meta-regression analyses

ESF 2 Table 1 shows the association among IO&NS profiles and SB remained significant in patients with MDD and MIX, whereas in patients belonging to the affective and OTHER groups was not significant, and these differences were significant (χ^2=8.563; df=3; p=0.036). The IO&NS markers showed a significant association with SB in inpatients but not in outpatients. The comparisons of in- and outpatients in SB *versus* controls (χ^2 = 8.147; df=1; p=0.004) and SA *versus* controls (χ^2 = 5.770; df=1; p=0.016) were significantly different. There were no significant

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differences in effect sizes obtained in studies using serum, plasma, and blood (χ^2 =4.677; df=2; p=0.096). There are significant associations between IO&NS markers and SB in patients who are diagnosed based on the suicidal act or an interview, but not when the SB was assessed through self-report, and this difference was significant (χ2 = 8.479; df=2; p=0.014). In SA, the IO&NS effect size was significantly larger in studies which diagnosed SB by registering the act as compared with studies which used an interview (χ^2 =7.102; df=1; p=0.008). In SI, there was no significant difference between interview and self-report (χ^2 = 0.015; df=1; p=0.902). Meta-regression revealed no effects of latitude, quality scores, and redpoint scores.

Publication bias

ESF 2 Table 2 shows the impact of publication bias on the studies under the random-effect model. There is some degree of publication bias for IO&NS, IRS, inflammation, CRP, neurotoxicity, and ANTIOXPRO studies with 6, 5, 3, 2, 4, and 4 missing studies samples on the right side of the funnel plot, respectively, and correction yielded an increase in the overall adjusted point estimate. There was no impact of publication bias on the BDNF studies.

Discussion

The first major finding of this systematic review and meta-analysis is that SB (namely SA and SI) is accompanied by significantly increased levels of the primary outcome variable, the IO&NS profile, albeit with a small effect size. In addition, also the IRS, inflammation (including CRP), neurotoxicity, ANTIOXPRO (including BDNF) profiles were significantly associated with SB, with small to moderate effect sizes. Our meta-analysis thus confirms that the pathophysiology of SB is related to activated IO&NS pathways [4, 22, 98] with elevated CRP[26] and reduced BDNF

levels.[28] Most importantly, our results show that suicidal behaviors are associated with an inflammatory response which is mainly driven by M1 macrophage-derived cytokines[11, 99] including IL-1β, IL-6, and TNF-α, which induce the production of acute phase proteins such as CRP and downregulate albumin, and by Th-1 cells with increased production of IFN-γ[11]. These products of activated macrophages and T cells exert neurotoxic effects thereby affecting white and gray matter plasticity[11]. Moreover, both M1 and Th-1 cytokines may stimulate indoleamine 2,3-dioxygenase (IDO), thereby lowering plasma TRP and inhibiting 5-HT synthesis, and increasing the production of neurotoxic TRYCATs including KYN, and QA, which may result in N-Methyl-D-Aspartic acid (NMDA)-induced neurotoxicity[8, 99]. Furthermore, increased indicants of nitro-oxidative stress with increased lipid peroxidation and lowered antioxidant levels, further contribute to increased neurotoxicity and reduced neuroprotection.[7] Chronically elevated IO&NS pathways cause breakdown of the blood brain barrier (BBB), which allows neurotoxic molecules to enter the brain thereby contributing to the neurotoxic effects. Previously, it was shown that activated IO&NS pathways are associated with major depressive and bipolar disorder, staging of affective disorders, neurodegenerative processes, and schizophrenia.[11, 99, 100]

We should stress that the present meta-analysis study used composite scores reflecting IO&NS profiles.[11, 12, 101] Previously, we have discussed the many advantages of using composite scores instead of solitary markers in case-control studies [11, 12, 101] and in meta-analysis as well.[18] For example, if a study would report on 2 inflammatory markers (e.g. CRP and albumin) with one being significantly associated with SA and the other not, it would mean that selecting only one biomarker in a meta-analysis may yield erroneous conclusions with regard to “inflammation”[19]. Therefore, performing meta-analyses on one biomarker only may not allow to generalize the findings because the results may by quite different after including all biomarkers of the same

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profile. Moreover, the selection of only one biomarker per study may induce more biological between-study variance because different confounding variables may differently affect the biomarkers of the same profile.[19] For example, selecting CRP as an index of inflammation is prone to bias because CRP is affected by many confounding variables including early lifetime trauma, sex, age and especially body mass index[19, 102, 103]. In our study, the different biomarker scores were not only averaged in one and the same study but also averaged over all studies. As such, our meta-analyses used more robust synthetic indices of IO&NS and its subdomains based on all available data and, therefore, these data allow to generalize the findings to the functional profiles specified in our study.

The second major finding of this study is that the effects sizes of the IO&NS, IRS, inflammation, CRP, and neurotoxicity scores were higher in SA than in SI, and that the effect sizes of IO&NS, IRS and inflammation were significantly greater in SA than in SI. These findings may indicate that IRS and inflammatory processes are more tightly associated with SA than with SI. This may point towards differences in the severity with SA being more severe than SI[1]. On the other hand, the effects sizes of the comparisons between SA and SI were not significant when considering CRP, neurotoxicity, ANTIOXPRO and BDNF. Therefore, the results of the current meta-analysis do not confirm the results of Gibbs et al.[57] who reported significant differences in serum hs-CRP levels between SA and SI. All in all, these results show that the higher IO&NS and IRS profiles in SA *versus* SI should be attributed to smaller but cumulative effects of inflammation, neurotoxicity, and lowered neuroprotection in SA.

The study showed some statistical heterogeneity as assessed using the tau (τ) statistic, which represents a precise measurement of heterogeneity and which is insensitive to the number of patients or studies in the meta-analysis.[35, 36] On the other hand, Q-values and the I^2 metric do

not reflect the degree of heterogeneity, although frequently employed as such.[18] Nevertheless, the current meta-analysis was able to detect five possible sources of statistical heterogeneity. Firstly, differences in outpatient *versus* inpatient status with higher effect sizes in the latter. This may be explained by effects of severity of illness which is higher in inpatients than outpatients[104], and the higher frequency of SA in inpatients[104]. The second source of heterogeneity concerns the assessment of SB with a greater effect size when the diagnosis of SA was based on the suicidal act rather than on an interview. These results show that the assessment of SB based on interview and self-report may largely underestimate the actual effect sizes and, therefore, are inaccurate assessment methods. Future research on SB should recruit patients with SA based on the registered suicidal act.

Thirdly, the quality of the included papers contributed to heterogeneity as evidenced by higher pooled effect sizes of IO&NS in high-quality studies than low-quality studies. The fourth source of statistical heterogeneity is due to the choice of controls, namely patients without SB *versus* heathy controls. As such we found that that the pooled effect sizes of the IO&NS, IRS, inflammation (including), CRP, and neurotoxicity profiles were larger when comparing SB with healthy controls as reference group (between 0.796 and 1.311), whereas lower effect sizes were obtained when comparing patients with and without SB (between 0.3 to 0.5). The comparisons with normal controls show that activated IO&NS pathways are strongly associated with SA in patients with psychiatric disorders, and the comparisons obtained with patients without SB show that SB is accompanied by aberrations in IO&NS pathways above and beyond the increased levels in psychiatric patients. Therefore, it is safe to conclude that activated IO&NS, IRS, inflammatory and neurotoxic pathways and lowered neuroprotection are strongly associated not only with the major psychiatric disorders [11, 101] but also with the SB which are associated with those disorders.

Fifthly, inspection of the forest plots shows that the heterogeneity is increased by a number of heterogeneity-influencing studies which favor SA. Previously, we performed sensitivity analyses on the included studies after deselecting a few heterogeneity-influencing studies and found that the prediction intervals no longer overlapped with the zero SMD but fell completely on the right site of zero. Indeed, a few small n studies that favor SA and show a very large effect size may bias SMD whereby the heterogeneity may increase in a random effect model and the latter may be more biased that when using a fixed effect model[19]. It should be added that there is probably nothing wrong with these heterogeneity-influencing studies, they only show a large SMD.

Several limitations should be considered when discussing our findings. Firstly, there are very few studies which assayed IL-4[56, 72] and TGF-β1[78] and therefore these important Th-2 and T regulatory (Treg) cytokines could not be included in the CMA. Secondly, key biomarkers of other profiles were also missing. For example, haptoglobin, transferrin, and zinc were missing as inflammatory biomarkers (and its parent profiles). Vitamin E, coenzyme Q10, glutathione, catalase, MPO and xanthine oxidase were missing as O&NS biomarkers. In fact, we were even unable to compute a CIRS profile, although most important to evaluate the homeostatic processes in the immune system.[11] Therefore, future research should focus on the missing biomarkers, i.e., Treg cytokines such as IL-10 and TGF-β1, Th-2 cytokines including IL-4, IL-5 and IL-13 (see also ESF Table 1; column “what is missing in SB research”). Thirdly, this study did not include other potential variables regarding severity of SB, including lifetime SB[19], staging of the major psychiatric disorders[13], and stressful live events, including early lifetime trauma[4]. Further studies should also include those covariates.

In conclusion, this is the first meta-analysis to explore IO&NS pathways in SA *versus* SI. Recent SB (within 3 months) is accompanied by aberrations in IO&NS profiles, which are more

strongly associated with SA than SI. Increased neurotoxicity due to inflammation and nitro-oxidative stress may explain why psychiatric patients are at higher risk of SA and SI than healthy controls. As such, we have delineated new drug targets to treat SB, namely the IO&NS subdomains.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. MS received honoraria and has been a consultant for Angelini, Lundbeck.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The dataset (CMA file) generated during and/or analyzed during the current study will be available from MM upon reasonable request and once the dataset has been fully exploited by the authors.

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Author's contributions

All authors contributed to the writing up of the paper. The work was designed by MM and AV. Data were collected by AV and KJ. Statistical analyses were performed by MM and AV. All authors revised and approved the final draft.

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Compliance with Ethical Standards/Disclosure of potential conflicts of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Research involving Human Participants and/or Animals

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Figure 1. PRISMA 2020 diagram

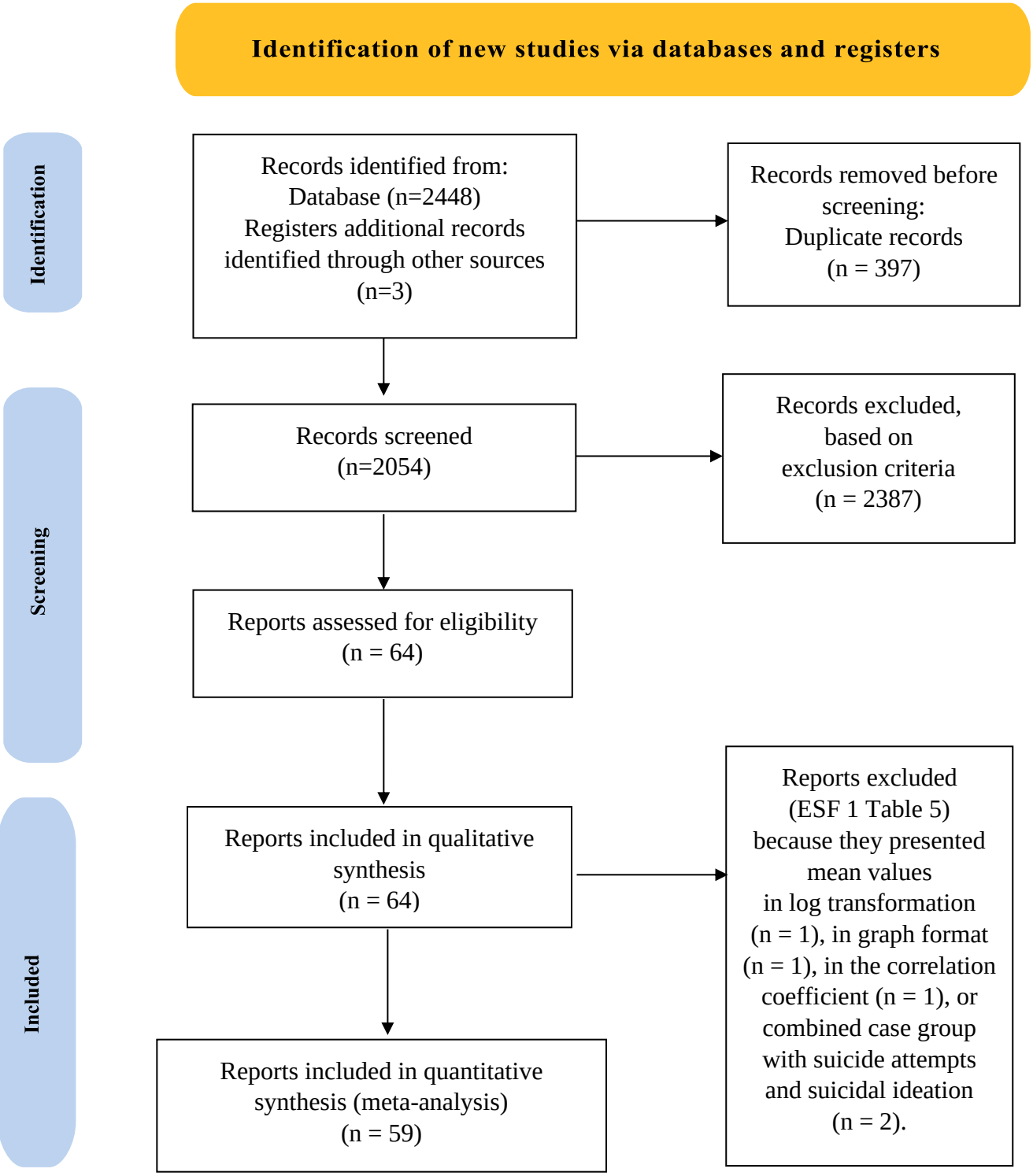

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Table 1. Number of cases with suicidal attempts (SA+), suicidal ideation (SI+) and controls in the different meta-analyses and side of standardized mean difference (SMD) and the 95% confidence intervals with respect to zero SMD.

Outcome profiles	n studies	Side of 95% confidence intervals				Case numbers	Control numbers	Total number of participants
		SMD < 0	Overlap 0 and SMD < 0	Overlap 0 and SMD > 0	SMD > 0			
Overall								
IO&NS	59	2	11	25	21	4034	12377	16411
IRS	33	1	2	14	16	2394	7739	10133
Inflammation	25	1	1	11	12	1762	4803	6564
CRP	15	0	1	4	10	1399	3955	5354
Neurotoxicity	29	1	3	11	13	1870	4620	6489
ANTIOXPRO	40	2	12	16	10	2985	9401	12386
BDNF	10	0	1	4	5	489	780	1269
SA+								
IO&NS	37	0	7	14	16	2511	7784	10295
IRS	23	0	1	9	13	1732	5483	7215
Inflammation	16	0	1	6	9	1117	2576	3693
CRP	10	0	1	2	7	914	1925	2839
Neurotoxicity	19	0	2	7	10	1209	2361	3570
ANTIOXPRO	26	1	8	10	7	1976	6953	8929
BDNF	7	0	1	3	3	363	481	844
SI+								
IO&NS	24	2	5	12	5	1523	4593	6116
IRS	11	1	1	6	3	662	2256	2918
Inflammation	9	1	0	6	3	645	2227	2872
CRP	6	0	0	3	3	485	2030	2515
Neurotoxicity	11	1	1	6	3	661	2259	2919
ANTIOXPRO	16	1	6	6	3	1010	2448	3458
BDNF	3	0	0	1	2	126	300	426

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IO&NS: immune-inflammatory and oxidative and nitrosative stress

IRS: immune-inflammatory response system

ANTIOXPRO: protection via antioxidants and neurotrophic products.

CRP: C-reactive protein

BDNF: Brain-derived neurotrophic factor

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Table 2. Results of meta-analysis performed on different outcome variables (immune and oxidative and nitrosative stress profiles, IO&NS, and subdomains)

Outcome feature sets	n studies	Groups, subgroups	SMD	95% CI	z	p	Q	df	p	I^2 (%)	τ^2	T
IO&NS	59	Overall	0.299	0.200; 0.397	5.933	<0.001	276.474	58	<0.001	79.022	0.100	0.316
	37	SA+ *vs.* Controls	0.387	0.256; 0.519	5.771	<0.001	176.200	36	<0.001	79.569	0.114	0.337
	21	SA+ *vs.* HC	0.796	0.503; 1.089	5.322	<0.001	152. 636	20	<0.001	86.897	0.393	0.627
	29	SA+ *vs.* SA-	0.255	0.140; 0.370	4.344	<0.001	90.748	28	<0.001	69.145	0.056	0.238
	24	SI+ *vs.* Controls	0.167	0.030; 0.304	2.396	0.017	83.446	23	<0.001	72.437	0.071	0.267
IRS	33	Overall	0.460	0.314; 0.605	6.186	<0.001	174.008	32	<0.001	81.610	0.128	0.358
	23	SA+ *vs.* Controls	0.590	0.400; 0.779	6.101	<0.001	133.065	22	<0.001	83.467	0.158	0.398
	14	SA+ *vs.* HC	1.049	0.637; 1.462	4.983	<0.001	118.960	13	<0.001	89.072	0.534	0.731
	17	SA+ *vs.* SA-	0.384	0.229; 0.538	4.855	<0.001	56.249	16	<0.001	71.555	0.064	0.254
	11	SI+ *vs.* Controls	0.231	0.033; 0.430	2.281	0.023	28.265	10	0.002	64.621	0.063	0.251
Inflammation	25	Overall	0.459	0.284; 0.633	5.142	<0.001	147.659	24	<0.001	83.746	0.146	0.382
	16	SA+ *vs.* Controls	0.623	0.388; 0.858	5.199	<0.001	95.325	15	<0.001	84.264	0.173	0.415
	9	SA+ *vs.* HC	1.200	0.584; 1.816	3.820	<0.001	90.393	8	<0.001	91.150	0.791	0.889
	13	SA+ *vs.* SA-	0.414	0.223; 0.605	4.250	<0.001	47.029	12	<0.001	74.484	0.080	0.282
	10	SI+ *vs.* Controls	0.239	0.000; 0.478	1.962	0.050	36.317	9	<0.001	75.218	0.099	0.315
CRP	15	Overall	0.573	0.366; 0.780	5.433	<0.001	99.036	14	<0.001	85.864	0.128	0.358
	10	SA+ *vs.* Controls	0.689	0.386; 0.991	4.463	<0.001	78.523	9	<0.001	88.538	0.194	0.440
	4	SA+ *vs.* HC	1.311	0.446; 2.177	2.969	0.003	32.712	3	<0.001	90.829	0.704	0.839
	8	SA+ *vs.* SA-	0.499	0.234; 0.764	3.696	<0.001	43.082	7	<0.001	83.752	0.110	0.331
	6	SI+ *vs.* Controls	0.429	0.161; 0.697	3.138	0.002	18.524	5	0.002	73.009	0.075	0.274
Neurotoxicity	29	Overall	0.403	0.253; 0.553	5.262	<0.001	133.901	28	<0.001	79.089	0.116	0.340
	19	SA+ *vs.* Controls	0.524	0.320; 0.727	5.048	<0.001	94.676	18	<0.001	80.988	0.147	0.383
	12	SA+ *vs.* HC	0.904	0.431; 1.378	3.745	<0.001	106.480	11	<0.001	89.669	0.607	0.779

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	14	SA+ *vs.* SA-	0.403	0.218; 0.588	4.278	<0.001	49.022	13	<0.001	73.481	0.079	0.282
	11	SI+ *vs.* Controls	0.243	0.036; 0.449	2.299	0.021	30.692	10	0.001	67.418	0.072	0.268
ANTIOXPRO	40	Overall	0.179	0.063; 0.294	3.031	0.002	196.268	39	<0.001	80.129	0.095	0.308
	26	SA+ *vs.* Controls	0.199	0.058; 0.341	2.761	0.006	119.840	25	<0.001	79.139	0.091	0.302
	13	SA+ *vs.* HC	0.476	0.083; 0.869	2.372	0.018	118.374	12	<0.001	89.863	0.461	0.679
	22	SA+ *vs.* SA-	0.137	0.021; 0.253	2.322	0.020	58.340	21	<0.001	64.004	0.039	1.197
	16	SI+ *vs.* Controls	0.141	-0.056; 0.338	1.401	0.161	73.159	15	<0.001	79.497	0.113	0.336
BDNF	10	Overall	0.479	0.224; 0.735	3.681	<0.001	34.811	9	<0.001	74.146	0.118	0.344
	7	SA+ *vs.* Controls	0.417	0.102; 0.733	2.590	0.010	25.883	6	<0.001	76.819	0.131	0.362
	4	SA+ *vs.* HC	0.962	0.708; 1.217	7.416	<0.001	2.628	3	0.453	0.000	0.000	0.000
	6	SA+ *vs.* SA-	0.256	-0.026; 0.538	1.779	0.075	14.800	5	0.011	66.217	0.076	0.275
	3	SI+ *vs.* Controls	0.665	0.413; 0.917	5.169	<0.001	2.039	2	0.361	1.934	0.001	0.032

SMD: standardized mean difference, 95% CI: 95% confidence intervals

IO&NS: immune-inflammatory and oxidative and nitrosative stress

IRS: immune-inflammatory response system

ANTIOXPRO: protection via antioxidants and neurotrophic products.

CRP: C-reactive protein

BDNF: Brain-derived neurotrophic factor

We used the study as well as the prespecified subgroups as the units of analysis. Thus, patients with suicide behaviors (SB) were first (overall) compared with controls. Second, we performed subgroup analyses comparing the pooled effect size of IO&NS, IRS, inflammation, CRP, neurotoxicity, ANTIOXPRO and BDNF profiles in a) SA+ *versus* SA- patients or healthy controls); and b) SI+ *versus* SI- patients or healthy controls.

IO&NS profile in suicide behaviors

Study name	Year	Subgroup within study	Outcome	Statistics for each study	
				Std diff in means	p-Value
Maes	1989	SI	Combined	-0,266	0,440
Nassberger	1993	SA	sIL-2R	1,632	0,000
Verma	1999	SA	HDL	0,073	0,743
Almeida-Montes	2000	SA	HDL	-0,121	0,729
Ozer	2004	SI	Combined	-0,422	0,299
Kim (a)	2006	SA	Combined	0,600	0,005
Lee (a)	2006	SA	Combined	0,635	0,001
Roy	2006	SI	HDL	-0,027	0,842
Devici	2007	SA	Combined	0,516	0,179
Kim (b)	2007	SA	Combined	0,856	0,001
Lee (b)	2007	SA	Combined	1,006	0,000
Gabbay	2009	SA	Combined	0,024	0,951
Grassi-Oliveira	2012	SI	Combined	-0,813	0,036
Pinheiro	2012	SI	BDNF	0,637	0,023
O'Donovan	2013	SI	Combined	0,471	0,048
Ruljancic	2013	SA	Combined	1,142	0,000
Ainiyet	2014	Combined	Combined	0,142	0,383
Baek	2014	SA	Combined	-0,330	0,132
De Berardis	2014	SI	HDL	0,214	0,271
Grudet	2014	SA	Combined	0,770	0,009
Kim (c)	2014	SI	HDL	0,096	0,386
Park	2014	SI	Combined	-0,026	0,925
Bradley	2015	SI	Combined	0,481	0,135
Graça Cantarelli	2015	SA	Combined	0,058	0,792
Janelidze	2015	SA	CXCL8	0,101	0,747
Brundin	2016	SA	Combined	-0,145	0,638
Eisen	2016	SA	Combined	0,016	0,917
Gibbs	2016	Combined	Combined	0,300	0,032
Loas	2016	SA	hs-CRP	0,513	0,008
Mensi	2016	SA	HDL	-0,021	0,940
Priya	2016	SA	Combined	0,897	0,000
Chang	2017	SI	Combined	0,539	0,004
Ekinci	2017	SA	Combined	0,286	0,165
Gundogdu Meydaneri	2018	SA	Combined	0,208	0,452
Kurosawa	2018	SA	Combined	0,148	0,443
Peng	2018	SA	Combined	0,060	0,665
Segoviano-Mendoza	2018	SA	Combined	-0,071	0,632
Sowa-Kucma	2018	SI	Combined	0,205	0,196
Aguglia	2019	SA	Combined	0,148	0,084
Ai	2019	SI	Combined	0,827	0,000
Al-Amarei	2019	SA	Combined	2,195	0,000
Eidan	2019	SA	Combined	1,732	0,000
Fang	2019	SI	HDL	0,097	0,649
Khan	2019	SI	Combined	0,404	0,089
Rasheed	2019	SA	Combined	0,240	0,395
Su	2019	SI	HDL	-0,458	0,000
Atik	2020	SA	VitD	0,779	0,000
Dolsen	2020	SI	Combined	0,030	0,661
Liu	2020	SI	Combined	0,151	0,567
Ma	2020	SA	HDL	0,357	0,000
Mohamed	2020	SI	hs-CRP	0,983	0,000
Oh	2020	SA	Combined	0,147	0,021
Oshnokhah	2020	SA	Combined	-0,190	0,382
Pasyk	2020	SA	BDNF	0,109	0,363
Si	2020	SI	HDL	0,073	0,362
Velasco	2020	SA	Combined	0,068	0,585
Choi	2021	SI	Combined	0,176	0,485
Gananca	2021	SI	Combined	-0,162	0,569
Yagci	2021	SA	Combined	0,799	0,001
				0,299	0,000

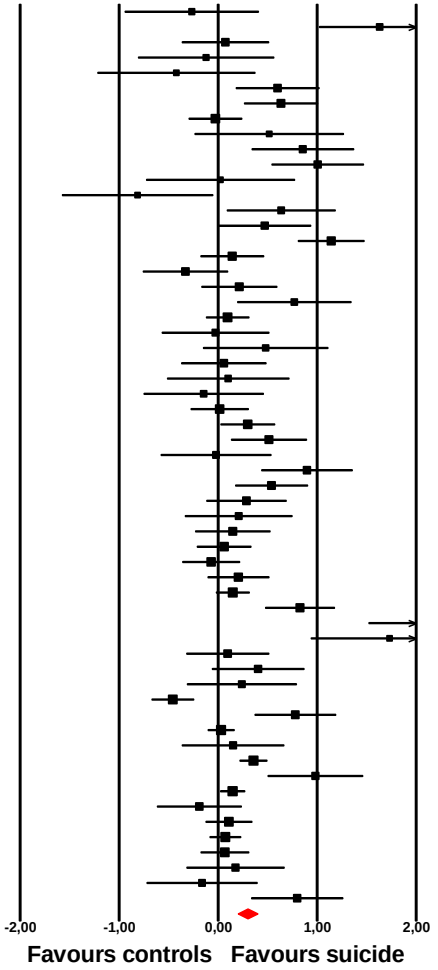

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Figure 2. Forest plot with results of meta-analysis performed on 59 studies reporting immune-inflammatory and oxidative & nitrosative stress (IO&NS) biomarkers.

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Inflammation in SA/SI

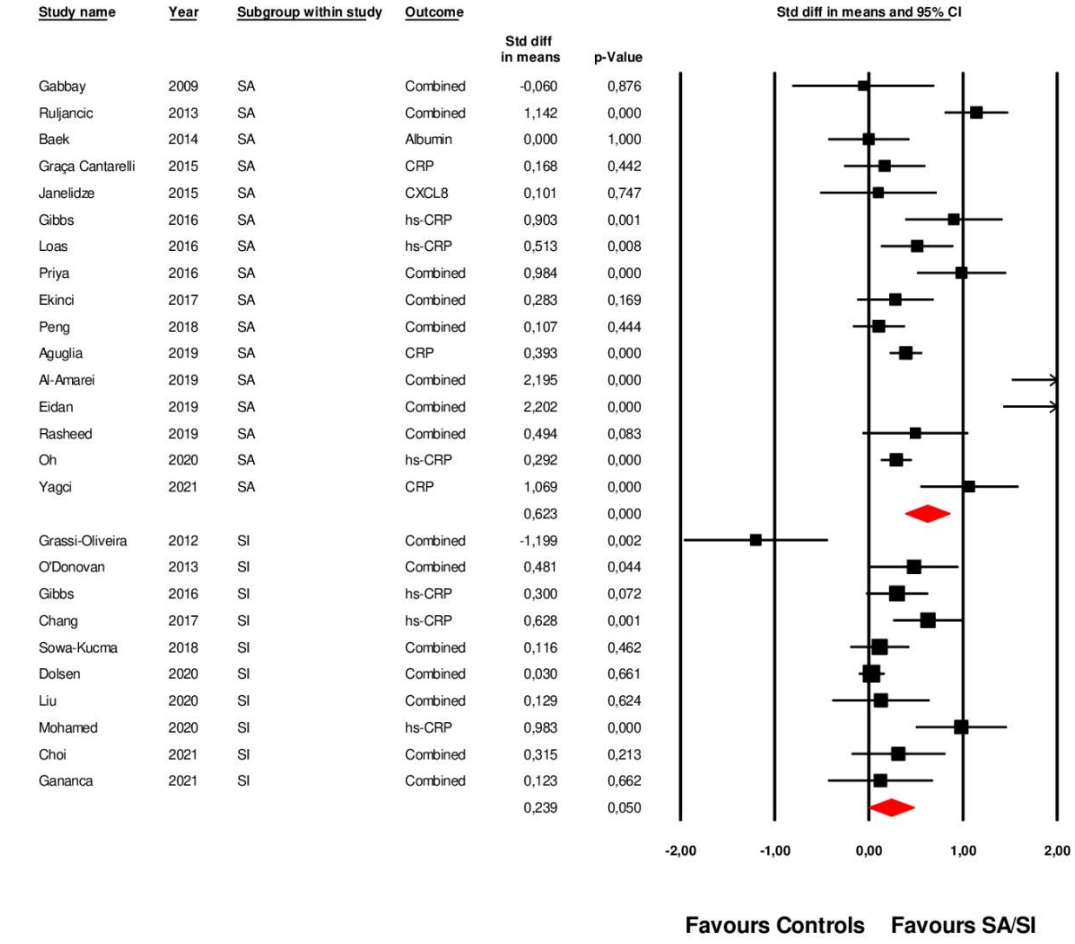

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Figure 3. Forest plot with results of meta-analysis (subgroup analysis) performed on 26 studies reporting inflammation profile.

Electronic Supplementary Information File (ESF) 1

Activated immune, oxidative and nitrosative stress pathways are strongly associated with suicidal attempts and less with suicidal ideation: a meta-analysis and meta-regression.

Running title: immune activation in suicidal behaviors

Asara Vasupanrajit, M.Sc.[a]; Ketsupar Jirakran, M.Sc.[a,b]; Chavit Tunvirachaisakul, M.D., Ph.D.[a, c]; Michael Maes, M.D., Ph.D.[a, c, d, e]

[a] Department of Psychiatry, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

[b] Maximizing Thai Children's Developmental Potential Research Unit, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

[c] Cognitive Impairment and Dementia Research Unit, Department of Psychiatry, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

[d] IMPACT Strategies Research Center, Deakin University, Geelong, Australia.

[e] Department of Psychiatry, Medical University of Plovdiv, Plovdiv, Bulgaria.

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ESF 1 Table 1. Explanation of peripheral immune and O&NS phenotypes.

Immune and O&NS phenotype		What is	What examined	What is missing in SA research
IRS[1, 2]	Inflammation (M1)	M1 cytokines, Acute Phase Proteins (APR), Complement	Interleukin (IL)-6, Tumor necrosis factor (TNF)-α, IL-1β, C-reactive protein (CRP), Albumin, CCL2, CXCL8	Fibrinogen sIL-6R, soluble gp130, sTNF-αR1, sIL-1RA, complement factors
	T helper (Th)-1	IL-2, Interferon (IFN)-γ, IL-12	IL-2, IFN-γ, IL2/IL4, IFN-γ/IL4	IL-12
	Cell-mediated immunity (CMI)	Interaction M1 and Th1	IL-6, TNF-α, IL-1, IL-2, IFN-γ, sIL-2R, TRYCATS (i.e., PA, QA, KYN), Tryptophan	Neopterin
	Th-17	IL-6, IL-17	IL-6	IL-17
	Chemokines	CXCL-8, eotaxin	CXCL-8, CCL2, CCL11, RANTES	eotaxin, etc
	APR proteins	Plasminogen Activator Inhibitor-1 (PAI-1), Haptoglobin (Hp), serum amyloid A and P, alpha-1 acid, complement system (such as C3 and C4), CRP, Fb, Albumin	CRP, Albumin	Fibrinogen, Hp, PAI-1, retinol binding protein (RBP)
CIRS[1, 2]	Regulatory T cells (T-reg)	IL-10, Transforming growth factor (TGF)-β	TGF-β	T-reg cells CD4, CD25, Forkhead box P3 (FOXP3), TGF-β
	Th-2	IL-4, IL-5, IL-9, IL-10, IL-13 and IL-25	IL-4	IL-13, IL-5, IL-9
O&NS[1, 2]	Nitro-oxidative stress	Advanced oxidation protein products (AOPP), Homocysteine, Lipid Hydroperoxide (LOOH), 3,4-Methylenedioxyamphetamine (MDA), Nitric oxide metabolites (NOx)	MDA, NOx, TBARS	DNA oxidation damage to mitochondria, AOPP, Homocysteine, LOOH
	Antioxidant	Albumin, BDNF, HDL-c, total reactive antioxidant potential (TRAP), Vitamin D	Albumin, BDNF, DHA, EPA, HDL-c, TAC, Tryptophan, Vitamin D	Catalase, Vitamin A, Vitamin C, Vitamin E, Coenzyme Q10, Zinc, Glutathione
NT	Neurotoxicity[3]	IRS, CIRS, Nitro-oxidative stress	AA, CCL1, CCL2, CCL3, RANTES, CCL11, CCL17, CCL22, CCL23, CCL24, CCL27, CX3CL1, CXCL2, CXCL5, CXCL8, CXCL10, CXCL12,	LPS bacteria, indicants BBB, AOPP, Homocysteine, LOOH,

			CXCL16, CRP, IFN-γ, IL-1β, IL-2, IL-6, TNF-α, TRYCATS (i.e., PA, QA, KYN), MDA, NOx, TBARS, TNFR60, TNFR80	
NP	Neuroprotection[3]	Antioxidant	Albumin, BDNF, DHA, EPA, HDL-c, TAC, Trytophan, Vitamin D	Vitamin E, Coenzyme Q10, Zinc, Glutathione

Note: Further explanation of the function of the peripheral immune and O&NS phenotypes can be found in Maes and Carvalho, 2018[1]; Roomruangwong et al., 2020[2] and Maes et al., 2021[3]

1. Maes M, Carvalho AF. The Compensatory Immune-Regulatory Reflex System (CIRS) in Depression and Bipolar Disorder. Mol Neurobiol 2018; 55(12): 8885-8903.
2. Roomruangwong C, Noto C, Kanchanatawan B, Anderson G, Kubera M, Carvalho AF et al. The Role of Aberrations in the Immune-Inflammatory Response System (IRS) and the Compensatory Immune-Regulatory Reflex System (CIRS) in Different Phenotypes of Schizophrenia: the IRS-CIRS Theory of Schizophrenia. Mol Neurobiol 2020; 57(2): 778-797.
3. Maes M, Moraes JB, Bonifacio KL, Barbosa DS, Vargas HO, Michelin AP et al. Towards a new model and classification of mood disorders based on risk resilience, neuro-affective toxicity, staging, and phenome features using the nomothetic network psychiatry approach. Metabolic brain disease 2021; 36(3): 509-521.

Abbreviations:
AA: Arachidonic acid (omega-6 fatty acid)
APR: the acute phase response
BBB: Blood-Brain Barrier
BDNF: Brain-derived neurotrophic factor
CCL: The C–C motif chemokine ligand
CIRS: The compensatory immune-regulatory reflex system
CXCL: The chemokine C-X-C motif ligand
CX3CL1: The C-X3-C Motif Chemokine Ligand 1/Fractalkine
DHA: Docosahexaenoic acid (omega-3 fatty acid)
EPA: Eicosapentaenoic acid (omega-3 fatty acid)
HDL-c: High-density lipoprotein cholesterol
IRS: The immune-inflammatory response system
KYN: Kynurenine
LPS: Lipopolysaccharides
MDA: Malondialdehyde
NOx: Nitric oxide metabolites
NT: Neurotoxicity
NP: Neuroprotection
O&NS: Antioxidants and nitro-oxidative stress
PA: Picolinic acid
QA: Quinolinic acid
RANTES: Regulated on Activation, Normal T Cell Expressed and Secreted
SA: Suicide attempts
SI: Suicide ideation
sIL2R: Soluble Interleukin 2 Receptor
sIL6R: Soluble Interleukin 6 Receptor
sTNF-αR1: Soluble tumor necrosis factor alpha receptor 1
TAC: Total antioxidant capacity
TBARS: Thiobarbituric acid reactive substances
TNFR: Tumor necrosis factor receptors
TRYCATs: The tryptophan catabolites

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ESF 1 Table 2. Specific search for each database.

PubMed/Medline
((inflamm* OR immun*) AND (cytokine OR chemokine OR il-6 OR il-1 OR interleukin OR (c-reactive protein OR CRP) OR (Tumor necrosis factor OR tnf) OR (interferon OR ifn) OR (Transforming growth factor OR tgf) OR Tryptophan AND (suicid*)) **1072**
PubMed/Medline
((Oxidative stress OR Antioxidants) AND (Zinc) OR (Vitamin C) OR (Albumin) OR (Nitric oxide metabolites) OR (Lipid hydroperoxides) OR (Omega 3) OR (Coenzyme Q10) OR (DHA) AND (suicid*) **406**
Google Scholar
Suicide AND [inflamm*] OR [immun*] AND [oxidative stress biomarkers] AND antioxidants OR [cytokine] OR chemokine] OR [il-6 OR il-1 OR interleukin] OR [(c-reactive protein) OR CRP] OR [(Tumor necrosis factor) OR tnf] OR [interferon OR ifn] OR (Transforming) **617**
WEB OF SCIENCE
TOPIC: (Suicide AND Oxidative Stress) **353**

ESF 1 Table 3. Immune confounder of suicide behaviors scale (ICS); applied from Andrés-Rodríguez, et al., 2019[a] and Vasupanrajit et al., 2021[b]

Methodological quality of the study		
1	Study sample ≥ 128 participants including patients and controls (1= Yes, 0 = No)	
2	Did the study control results for potential confounders (e.g., age, BMI, gender, race)? (1= Yes, 0 = No)	
3	Were participants with suicide attempts (SA) and controls age- and-gender-matched or statistically controlled? (1= Yes, 0 = No)	
4	Was the time of sample collection specified (e.g., morning vs. evening)? (1= Yes, 0 = No)	
5	Were participants with SA free of immunomodulatory drugs including anti-cytokines, corticoids, immunoglobulins, and immunosuppressants, been through a medication washout or the intake was statistically controlled? (1= Yes, 0 = No)	
6	Were participants with suicidal behaviour free of antidepressants and mood stabilizers or statistically controlled? (1= Yes, 0 = No)	
7	Reporting of either the manufacturer of the test or its parameters (detection limit and coefficient of variation) (1= Yes, 0 = No)	
8	Reporting how data under detection limit was handled (1 = Yes, 0 = No)	
9	Reporting % of the sample under detection limit (1=Yes, 0= No)	
10	Reporting blood fraction (serum, plasma, culture supernatant or whole blood) (1= Yes, 0 = No)	
	Total quality score (10 points)	
Biomarker confounders red points *The red points should not be given if the item is statistically controlled*		
1	3 red points for comorbid illnesses such as autoimmune disorders & other immune disorders including RA, psoriasis, IBD, COPD, MS	
2	3 red points for use of recreational drugs such as methamphetamine or opioids (Not applicable if psychiatric disorders are excluded)	
3	2 red points when groups were significantly difference or there was no statistically controlled for age	
4	2 red points when groups were significantly difference or there was no statistically controlled for sex	
5	2 red points for medication use as for example immunomodulators	
6	2 red points for early traumatic life events	
7	2 red points for shift work and primary sleep disorders	

8	1.5 red points for antidepressants	
9	1 red point for more common systemic immune disorders including diabetes type 1/2, essential hypertension, metabolic syndrome	
10	1 red point for not fasting (8 hours before blood extraction)	
11	1 red point for use of omega-3 and antioxidant supplements	
12	1 red point when groups were significantly difference or there was no statistically controlled for BMI	
13	1 red point for physical activity or sedentary life	
14	1 red point for smoking	
15	1 red point for use of oral contraceptives or NSAIDs	
16	0.5 red points for ethnicity in countries such as US, Brazil (not China or Japan)	
17	0.5 red points for seasonality	
18	0.5 red points for diurnal variation (8-10 a.m. versus all other time points)	
	Total red point score (26 points)	

Note: Threshold of study samples is stablished as it is the minimum needed for statistical power. Confounders red points should be given when the item is not reported (or statistically controlled).

[a] Andrés-Rodríguez L, Borràs X, Feliu-Soler A, Pérez-Aranda A, Angarita-Osorio N, Moreno-Peral P et al. Peripheral immune aberrations in fibromyalgia: A systematic review, meta-analysis and meta-regression. Brain, Behavior, and Immunity 2020; **87**: 881-889.
[b] Vasupanrajit A, Jirakran K, Tunvirachaisakul C, Maes M. Suicide attempts are associated with activated immune-inflammatory, nitro-oxidative, and neurotoxic pathways: A systematic review and meta-analysis. Journal of Affective Disorders 2021; **295**: 80-92.

ESF 1 Table 4. Characteristics of 59 studies included in quantitative synthesis (meta-analysis).

Authors (Year)	Sub groups	N		Psychiatric disorders in cases	Suicide assessment	Exclusion of comorbid illnesses	Specific time of blood sample	Medium	IO&NS markers	Key findings	Quality score (max=10)	Redpoint score (max=26)
		Cases	Controls									
Aguglia et al. (2019)	SA	432	200	Mixed	After SA	No	Yes	Serum	- CRP - HDL	- CRP levels in SA+ were significantly higher than in SA-, whereas no significant difference in HDL.	6.9	18.5
Ai et al. (2019)	SI	84	66	MDD	Self-report	No	No	Plasma	- BDNF	- No significant difference in BDNF between SI+ and SI-.	4.7	18.0
Ainiyet & Rybakowski (2014)	SA, SI	65	159	Affective	Interview	Partly	Yes	Serum	- HDL	- No significant difference in HDL was observed.	3.8	19.5
Al-Amarei et al. (2019)	SA	22	34	MDD	After SA	Partly	Partly	Plasma	- CRP	- CRP levels in SA+ were significantly higher than in SA- or HC.	4.0	15.0
Almeida-Montes et al. (2000)	SA	18	15	MDD	After SA	Yes	Yes	Serum	- HDL	- No significant difference in HDL between SA+ and SA-.	6.3	11.5
Atik et al. (2020)	SA	59	42	Mixed	After SA	No	No	Serum	- Vitamin D	- Vitamin D levels in SA+ were significantly lower than in HC.	4.1	20.5
Baek et al. (2014)	SA	22	464	MDD	Interview	No	Yes	Serum	- Albumin - HDL	- HDL levels in SA+ were significantly higher than in SA-. - Albumin levels were not significantly different.	5.7	19.0
Bradley et al. (2015)	SI	19	26	MDD	Self-report	Partly	Yes	Plasma	- KYN - TRP - KYN/TRP	- TRP levels in SA+ were significantly lower than in SA- or HC, whereas KYN levels were not substantially different. - KYN/TRP ratio in SA+ were significantly higher than in SA- or HC.	7.2	12.0
Brundin et al. (2016)	SA	18	29	MDD, Affective	After SA	No	Yes	Plasma	- PA - QA	- PA levels in SA+ with mixed group of psychiatric disorders were significantly lower than in HC, whereas QA levels were not substantially different.	6.3	23.8
Chang et al. (2017)	SI	58	61	MDD	Interview	Partly	Yes	Blood Serum	- ESR - hs-CRP	- ESR and hs-CRP levels in SI+ were significantly higher than in SI-.	7.0	10.8
Choi et al. (2021)	SI	23	59	MDD, Other	Self-report	Partly	Yes	Serum	- hs-CRP - IFN-γ - IL-10 - IL-6 - TNF-α	- Higher TNF-α levels were a significant indicator of SI in MDD patients. - No significant findings in SI+ patients with panic disorders.	5.0	22.5
De Beradis et al. (2014)	SI	79	40	Other	Self-report	Partly	Yes	Serum	- HDL	- No significant findings in SI+ patients with OCD. However, alexithymia patients with OCD showed significant lower HDL levels than HC.	6.0	14.5
Devici et al. (2007)	SA	10	25	Other	After SA	No	Yes	Serum	- BDNF	- Lower BDNF levels were observed in SA+ and MDD patients than in HC.	5.0	22.5

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Dolsen et al. (2020)	SI	244	1733	Mixed	Self-report	No	Yes	Plasma	- hs-CRP - IL-6 - TNF-α	- Higher IL-6 levels were associated with SI+ in the past week.	6.8	21.0
Eidan et al. (2019)	SA	22	34	MDD	After SA	Partly	Yes	Plasma	- IL-6 - IFN-γ - HDL	- Higher IL-6 and IFN-γ levels were found in SA+ than in HC. - No significant difference in HDL was observed.	7.5	14.5
Eisen et al. (2016)	SA	84	99	Mixed	After SA	No	Yes	Serum	- BDNF	- No significant association between BDNF and SA.	6.6	19.0
Ekinci & Ekinci (2017)	SA	37	76	MDD	After SA	Partly	Yes	Serum Blood	- HDL - hs-CRP - NLR	- NLR and hs-CRP levels in SA+ were significantly higher than in SA- or HC after adjusting the confounding factors.	8.8	9.0
Fang et al. (2019)	SI	26	148	Other	Interview	Partly	Yes	Serum	- HDL	- No significant association between HDL and SI+ in schizophrenia patients.	9.4	9.0
Gabbay et al. (2009)	SA	12	17	MDD	After SA	Partly	Yes	Plasma	- IFN-γ - TNF-α - IL-1β - IL-6 - IFN-γ/IL-4	- After adjusting confounding variables, IFN-γ levels in SA+ were significantly higher than in HC and TNF-α levels in SA+ were significantly lower than in SA-.	4.8	17.0
Ganança et al. (2021)	SI	22	31	MDD	Interview	Partly	No	Serum Plasma	- IL-1β - IL-6 - TNF-α - AA - EPA - DHA	- Inflammatory and lipid markers revealed no significant differences in SI+ when compared with SI- or HC. - DHA% and IL-1β showed lower in patient with history of SA+ (within 5 years) when compared with SI+.	5.0	15.0
Gibbs et al. (2016)	SA, SI	129	110	Mixed	After SA, Interview	No	No	Serum	- HDL - hs-CRP	- hs-CRP levels showed significantly higher in patient with SA+ when compared with SI+. - hs-CRP levels in SA+ were significantly higher than in SA- or HC.	5.9	18.0
Graça Cantarelli et al. (2015)	SA	50	36	Affective	After SA	No	Yes	Serum	- BDNF - HDL	- No significant differences of BDNF and HDL between SA+ and SA-.	5.9	19.3
Grassi-Oliveira et al. (2012)	SI	18	14	MDD	Interview, Self-report	Yes	No	Plasma	- CCL2 - RANTES - CCL11	- Lower CCL2 and RANTES levels were detected in SI+, compared with SA- and HC.	4.8	12.0
Grudet et al. (2014)	SA	59	16	Mixed	After SA	No	Yes	Serum	- Vitamin D	- Vitamin D levels in SA+ were significantly lower than in SA- or HC.	4.1	21
Gundogdu Meydaneri et al. (2018)	SA	27	26	MDD	After SA	Partly	No	Blood	- WBC - NPs - Lymphs - Monocytes - NLR	- No significant differences of those biomarkers between groups.	4.5	17.5

Janelidze et al. (2015)	SA	46	13	Mixed	After SA	No	Yes	Plasma	- IL-8	- No significant differences of IL-8 between SA+ and HC.	6.3	17.3
Khan et al. (2019)	SI	28	58	MDD	Interview	Yes	Yes	Serum	- BDNF	- BDNF levels in SI+ were significantly lower than in SI-.	9.4	9.0
Kim et al (2006) [a]	SA	39	57	MDD	After SA	Partly	Yes	Plasma	- NOx	- NOx levels in SA+ were significantly higher than in SA- or HC.	8.4	16.0
Kim et al. (2007) [b]	SA	32	31	MDD	After SA	Partly	No	Plasma	- BDNF	- BDNF levels in SA+ were significantly lower than in SA- or HC.	4.7	17.5
Kim et al. (2014) [c]	SI	93	639	Not Applicable	Interview	No	Yes	Serum	- HDL	- No significant differences of HDL between groups.	5.3	21.5
Kurosawa et al. (2018)	SA	33	146	Mixed	After SA	No	No	Plasma	- AA - EPA - DHA	- EPA levels were negatively associated with SA+, whilst DHA levels were positively associated.	4.4	19.5
Lee at al. (2006) [a]	SA	53	67	Mixed	After SA	Partly	Yes	Plasma	- NOx	- NOx levels in SA+ were significantly higher than in SA- or HC.	8.1	15.5
Lee et al. (2007) [b]	SA	28	72	MDD	After SA	Partly	Yes	Plasma	- BDNF	- BDNF levels in SA+ were significantly lower than in SA-.	9.7	10.5
Liu et al. (2020)	SI	24	61	MDD	Self-report	Yes	No	Serum	- IL-1β - IL-6 - IFN-γ - TNF-α - Chemokines (i.e., CCL8, IL-8, etc.)	- CCL8 levels in SI+ were significantly higher than in SI- or HC. - No further significant finding was observed between SI+ and SI- or HC.	7.0	9.8
Loas et al. (2016)	SA	41	81	Mixed	After SA	No	Yes	Serum	- hs-CRP	- hs-CRP levels in SA+ were significantly higher than in SA-.	3.0	19.0
Ma et al. (2020)	SA	235	1372	MDD	Interview	Partly	Yes	Plasma	- HDL	- HDL levels in SA+ were significantly lower than in SA-.	5.9	17.5
Maes et al. (1989)	SI	17	17	MDD	Interview	Partly	Yes	Blood	- TRP - TRP/CAA	- No significant differences between SI+ and SI- in TRP or TRP/CAA.	4.7	13.5
Mensi et al. (2016)	SA	15	71	Other	After SA	Partly	Yes	Serum	- HDL	- HDL had no significant association with SA in schizophrenia patients.	4.1	22.5
Mohamed et al. (2020)	SI	24	74	MDD	Self-report	Partly	No	Serum	- hs-CRP	- hs-CRP levels in SI+ were significantly higher than in SI-.	4.1	18.5
Nässberger & Träskman-Bendz(1993)	SA	30	25	Mixed	After SA	Partly	No	Plasma	- sIL-2R	- sIL-2R levels in SA+ were significantly higher than in HC.	4.5	21.5
O'Donovan et al. (2013)	SI	29	48	MDD	Interview	Partly	Yes	Plasma	- hs-CRP - IL-6 - IL-10 - TNF-α	- IL-6 and hs-CRP levels in SI+ were significantly higher than in HC.	6.0	21.0
Oh et al. (2020)	SA	405	3584	Affective	Interview	No	No	Blood	- hs-CRP - ESR - WBC - Vitamin D	- hs-CRP and ESR levels in SA+ were significantly higher than in SA-.	1.6	25
Oshnokhah et al. (2020)	SA	50	40	Excluded psychiatric disorders group	After SA	Yes	Yes	Serum	- MDA - NOx - TAC	- MDA and TAC levels were substantially lower in SA+ than in HC, whereas NOx levels were significantly higher.	6.9	14.0
Özer et al. (2004)	SI	10	17	Other	Interview	Partly	Yes	Serum	- HDL	- No significant association between HDL and SI+ in panic patients.	5.9	14.0
Park et al. (2014)	SI	18	56	MDD	Interview, Self-report	No	Yes	Serum	- HDL	- No significant differences of HDL between groups.	5.0	18.5

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Pasyk et al. (2020)	SA	117	176	Mixed	After SA	No	Yes	Serum	- BDNF	- BDNF levels were shown to be significantly associated with self-reported impulsivity scores, but not with SA.	6.6	19.0
Peng et al. (2018)	SA	69	202	MDD	After SA	Partly	Yes	Serum	- hs-CRP - HDL - Albumin	- No significant differences among those biomarkers between SA+ and SA-.	8.8	14.0
Pinheiro et al. (2012)	SI	14	176	Affective	Interview	No	Yes	Serum	- BDNF	- BDNF levels were significant lower in SI+ than in SI-.	7.2	21.5
Priya et al. (2016)	SA	42	42	Not Applicable	After SA	No	No	Serum	- BDNF - hs-CRP - IL-6	- BDNF levels were substantially lower in SA+ than in HC, whereas hs-CRP and IL-6 levels were significantly higher. - After adjusting for confounder factors, linear regression indicated hs-CRP as a predictor of suicide risk.	5.6	18.0
Rasheed et al. (2019)	SA	22	34	MDD	After SA	Partly	Yes	Plasma	- HDL - IL-1β - TNF-α	- TNF- levels were significantly higher in SA+ than in SA- or HC, while there were no significant differences in IL-6 or HDL levels between the groups.	6.0	12.0
Roy & Roy (2006)	SI	61	397	Affective	Self-report	No	No	Serum	- HDL	- No significant association between HDL and SI+ in depressive patients with Type I Diabetes.	2.8	24.5
Ruljancic et al. (2013)	SA	79	89	MDD	After SA	No	No	Serum	- Albumin	- Albumin levels were significantly lower in SA+ than in SA- or HC.	5.3	18.4
Segoviano-Mendoza et al. (2018)	SA	59	204	MDD	After SA	Partly	Yes	Serum	- HDL	- No significant differences of HDL between groups.	7.5	16.5
Si et al. (2020)	SI	241	441	Not Applicable	Self-report	No	Yes	Serum	- HDL	- No significant differences of HDL between SI+ and SI-. - Females with SI had higher HDL concentrations than males with SI, but females and males without SI revealed no significant differences.	4.0	20.5
Sowa-Kucma et al. (2018)	SI	93	95	Affective	Interview	Partly	Yes	Serum	- zCMI+TBARS - sIL-1RA - sIL-2R - sIL-6R - IL-1α - TBARS - sTNFR60 - sTNFR80	- Increased TBARS was associated with SI. - In SI, there were no significant differences in other biomarkers across groups.	9.3	9.0
Su et al. (2019)	SI	143	219	Affective	Self-report	No	No	Serum	- HDL	- HDL levels were significant higher in SI+ than in SI-.	5.3	20.5
Velasco et al. (2020)	SA	126	136	MDD	Interview	Yes	Yes	Blood	- Leukocytes - Lymphs - Monocytes - NPs - NLR - MLR	- Lymphs and NLR were significant differences between SA+ and SA-, whilst there were no significant differences in other biomarkers across groups.	5.5	16.0
Verma et al. (1999)	SA	40	40	Mixed	After SA	No	Yes	Serum	- HDL	- HDL levels revealed no significant differences between SA+ and SA-.	5.0	12.5
Yagci & Avci (2021)	SA	40	41	Mixed	After SA	Partly	Yes	Blood	- CRP - Leukocytes - NLR	- CRP, leukocytes, and NLR concentrations were significant higher in SA+ than in HC.	3.8	12.5

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Abbreviations:
AA: Arachidonic acid (omega-6 fatty acid)
BDNF: Brain-derived neurotrophic factor
CCL: The C–C motif chemokine ligand
CRP: C-reactive protein
DHA: Docosahexaenoic acid (omega-3 fatty acid)
EPA: Eicosapentaenoic acid (omega-3 fatty acid)
HDL-c: High-density lipoprotein cholesterol
hsCRP: The high-sensitivity C-reactive protein
IL: Interleukin
IFN: Interferon
KYN: Kynurenine
Lymphs: Lymphocytes
MDA: Malondialdehyde
MLR: Monocyte to lymphocyte ratio
NLR: Neutrophil-to-lymphocyte ratio
NOx: Nitric oxide metabolites
NPs: Neutrophils
PA: Picolinic acid
QA: Quinolinic acid
RANTES: Regulated on Activation, Normal T Cell Expressed and Secreted
SA: Suicide attempts
SI: Suicide ideation
sIL2R: Soluble Interleukin 2 Receptor
sIL6R: Soluble Interleukin 6 Receptor
sTNF-αR1: Soluble tumor necrosis factor alpha receptor 1
TAC: Total antioxidant capacity
TBARS: Thiobarbituric acid reactive substances
TNF: Tumor necrosis factor
TNFR: Tumor necrosis factor receptors
TRYCATs: The tryptophan catabolites
TRP: Tryptophans

ESF 1 Table 5. Excluded studies.

Authors, year	Reason why excluded	Key findings
Dickerson et al., 2017[a]	Graph format.	There was a significantly higher level of CRP in the patients with history of suicide attempts more than 1 month (coefficient=0.87, 95% CI 0.25, 1.50, p=0.006) compared with the control group but not in the other two psychiatric groups (p > 0.05), including patients with history of suicide attempts in 1 month and without history of suicide attempts, when adjusting for age, gender, race, smoking status, and BMI
Jha et al., 2020[b]	Combined case group with suicide attempts and suicidal ideation.	After adjustment, only IL-4 revealed significantly differences between healthy control (n=39), those at risk of MDD group (n=33), and those at risk of MDD with recent suicide attempts or suicidal ideation group (n=37), whereas the other cytokines and chemokines did not. Plasma IL-4 levels of recent suicide group had lower than healthy controls and at risk of MDD group.
Lauterbach et al., 2006[c]	Correlation coefficient.	There is a modest correlation between suicidal ideation and low plasma trytophan/amino acid ratio (*r*=0.39, p=0.042).
Melhem et al., 2017[d]	Logarithmic trasformation. The authors did dot provide mean (SD) values upon request.	Patients with suicide attempts showed significantly higher CRP [95% CI (0.15, 1.84), p = 0.02] compared to patients with suicidal ideation and healthy controls.
Roggenbach et al., 2007[e]	Combined case group with suicide attempts and suicidal ideation.	There is no significant different between depression patients with suicide group and healthy control in plasma tryptophan.

a. Dickerson F, Adamos M, Katsafanas E, Khushalani S, Origoni A, Savage C et al. The association between immune markers and recent suicide attempts in patients with serious mental illness: A pilot study. Psychiatry Res 2017; **255**: 8-12.
b. Jha MK, Cai L, Minhajuddin A, Fatt CC, Furman JL, Gadad BS et al. Dysfunctional adaptive immune response in adolescents and young adults with suicide behavior. Psychoneuroendocrinology 2020; **111**: 104487.
c. Lauterbach E, Brunner J, Hawellek B, Lewitzka U, Ising M, Bondy B et al. Platelet 5-HT2A receptor binding and tryptophan availability in depression are not associated with recent history of suicide attempts but with personality traits characteristic for suicidal behavior. Journal of Affective Disorders **2006**; 91(1): 57-62.
d. Melhem NM, Munroe S, Marsland A, Gray K, Brent D, Porta G et al. Blunted HPA axis activity prior to suicide attempt and increased inflammation in attempters. Psychoneuroendocrinology 2017; **77**: 284-294.
e. Roggenbach J, Müller-Oerlinghausen B, Franke L, Uebelhack R, Blank S, Ahrens B. Peripheral serotonergic markers in acutely suicidal patients. 1. Comparison of serotonergic platelet measures between suicidal individuals, nonsuicidal patients with major depression and healthy subjects. Journal of Neural Transmission 2007; **114**(4): 479-487.

Electronic Supplementary Information File (ESF) 2

Activated immune, oxidative and nitrosative stress pathways are strongly associated with suicidal attempts and less with suicidal ideation: a meta-analysis and meta-regression.

Running title: immune activation in suicidal behaviors

Asara Vasupanrajit, M.Sc.[a]; Ketsupar Jirakran, M.Sc.[a,b]; Chavit Tunvirachaisakul, M.D., Ph.D.[a, c]; Michael Maes, M.D., Ph.D.[a, c, d, e]

[a] Department of Psychiatry, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

[b] Maximizing Thai Children's Developmental Potential Research Unit, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

[c] Cognitive Impairment and Dementia Research Unit, Department of Psychiatry, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

[d] IMPACT Strategies Research Center, Deakin University, Geelong, Australia.

[e] Department of Psychiatry, Medical University of Plovdiv, Plovdiv, Bulgaria.

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ESF 2 Table 1. Results of other subgroup analyses performed on IO&NS profile.

Comparison	n studies	subgroups	SMD	95% CI	z	p	Q	df	p	I^2 (%)	τ^2	T
Subgroups by psychiatric groups												
SB *versus* Controls (χ^2 =8.563; df=3; p=0.036)	29	MDD	0.370	0.195; 0.546	4.135	<0.001	141.577	28	<0.001	80.223	0.168	0.410
	15	MIX	0.372	0.201; 0.543	4.267	<0.001	57.569	14	<0.001	75.681	0.075	0.274
	9	Affective	0.049	-0.156; 0.254	0.470	0.639	30.696	8	<0.001	73.938	0.063	0.251
	6	OTHER	0.140	-0.067; 0.346	1.326	0.185	3.577	5	0.612	0.000	0.000	0.000
Subgroups by participants groups												
SB *versus* Controls (χ^2 = 8.147; df=1; p=0.004)	33	In-patient	0.442	0.264; 0.620	4.862	<0.001	203.090	32	<0.001	84.243	0.215	0.464
	18	Out-patient	0.128	0.007; 0.249	2.080	0.038	37.804	17	0.003	55.031	0.027	0.165
SA *versus* Controls (χ^2 = 5.770; df=1; p=0.016)	26	In-patient	0.505	0.312; 0.698	5.126	<0.001	137.711	25	<0.001	81.846	0.193	0.439
	5	Out-patient	0.151	-0.064; 0.366	1.375	0.169	12.688	4	0.013	68.474	0.031	0.177
Subgroups by medium												
SB *versus* Controls (χ^2 =4.677; df=2; p=0.096)	7	Blood	0.229	0.066; 0.391	2.759	0.006	10.229	6	0.115	41.341	0.018	0.132
	19	Plasma	0.509	0.275; 0.742	4.270	<0.001	123.125	18	<0.001	85.381	0.199	0.446
	39	Serum	0.232	0.117; 0.347	3.958	<0.001	147.864	38	<0.001	74.301	0.089	0.298
Subgroups by the assessment of suicide behaviors												
SB *versus* Controls (χ^2 = 8.479; df=2; p=0.014)	32	Suicidal act	0.456	0.291; 0.622	5.409	<0.001	155.948	31	<0.001	80.122	0.168	0.410
	18	Interview	0.173	0.070; 0.275	3.304	0.001	28.494	17	0.039	40.338	0.016	0.126
	11	Self-report	0.184	-0.031; 0.400	1.676	0.094	58.554	10	<0.001	82.922	0.096	0.310
SA *versus* Controls (χ^2 =7.102; df=1; p=0.008)	32	Suicidal act	0.456	0.291; 0.622	5.409	<0.001	155.948	31	<0.001	80.122	0.168	0.410
	5	Interview	0.120	-0.064; 0.304	1.277	0.201	13.129	4	0.011	69.533	0.026	0.161

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SI *versus* Controls	13	Interview	0.200	0.069; 0.331	3.003	0.003	15.362	12	0.222	21.886	0.012	0.110
(χ^2 = 0.015; df=1; p=0.902)	11	Self-report	0.184	-0.031; 0.400	1.676	0.094	58.554	10	<0.001	82.922	0.096	0.310

SMD: standardized mean difference, 95% CI: 95% confidence intervals

IO&NS: immune-inflammatory and oxidative and nitrosative stress

SB: suicide behaviors

SA: suicide attempts

SI: suicidal ideation

We used the prespecified subgroups as the units of analysis. Thus, patients with suicide behaviors were first compared with controls. Second, we compared a) SA+ *versus* controls); and b) SI+ *versus* controls.

ESF 2 Table 2. Results on publication bias.

Outcome feature sets	Fail safe n	Z Kendall's τ	p-value (1-tailed)	Egger's t test (df)	p-value (1-tailed)	Missing studies (side)	Adjusted SMD (95%CI)
IO&NS	1829	1.44	0.075	2.50 (57)	0.008	6 (R)	0.371 (0.263; 0.479)
IRS	1304	0.73	0.233	2.67 (31)	0.006	5 (R)	0.551 (0.403; 0.710)
Inflammation	828	1.06	0.145	2.07 (24)	0.025	3 (R)	0.556 (0.376; 0.737)
CRP	529	2.57	0.005	3.24 (13)	0.003	2 (R)	0.692 (0.428; 0.956)
Neurotoxicity	776	0.13	0.448	1.93 (27)	0.032	4 (R)	0.490 (0.335; 0.645)
ANTIOXPRO	319	0.72	0.235	1.03 (38)	0.154	4 (R)	0.249 (0.124; 0.374)
BDNF	110	0.89	0.186	1.99 (8)	0.041	0	-

SMD: standardized mean difference, 95% CI: 95% confidence intervals
IO&NS: immune-inflammatory and oxidative and nitrosative stress
IRS: immune-inflammatory response system
ANTIOXPRO: protection via antioxidants and neurotrophic products.
CRP: C-reactive protein
BDNF: Brain-derived neurotrophic factor

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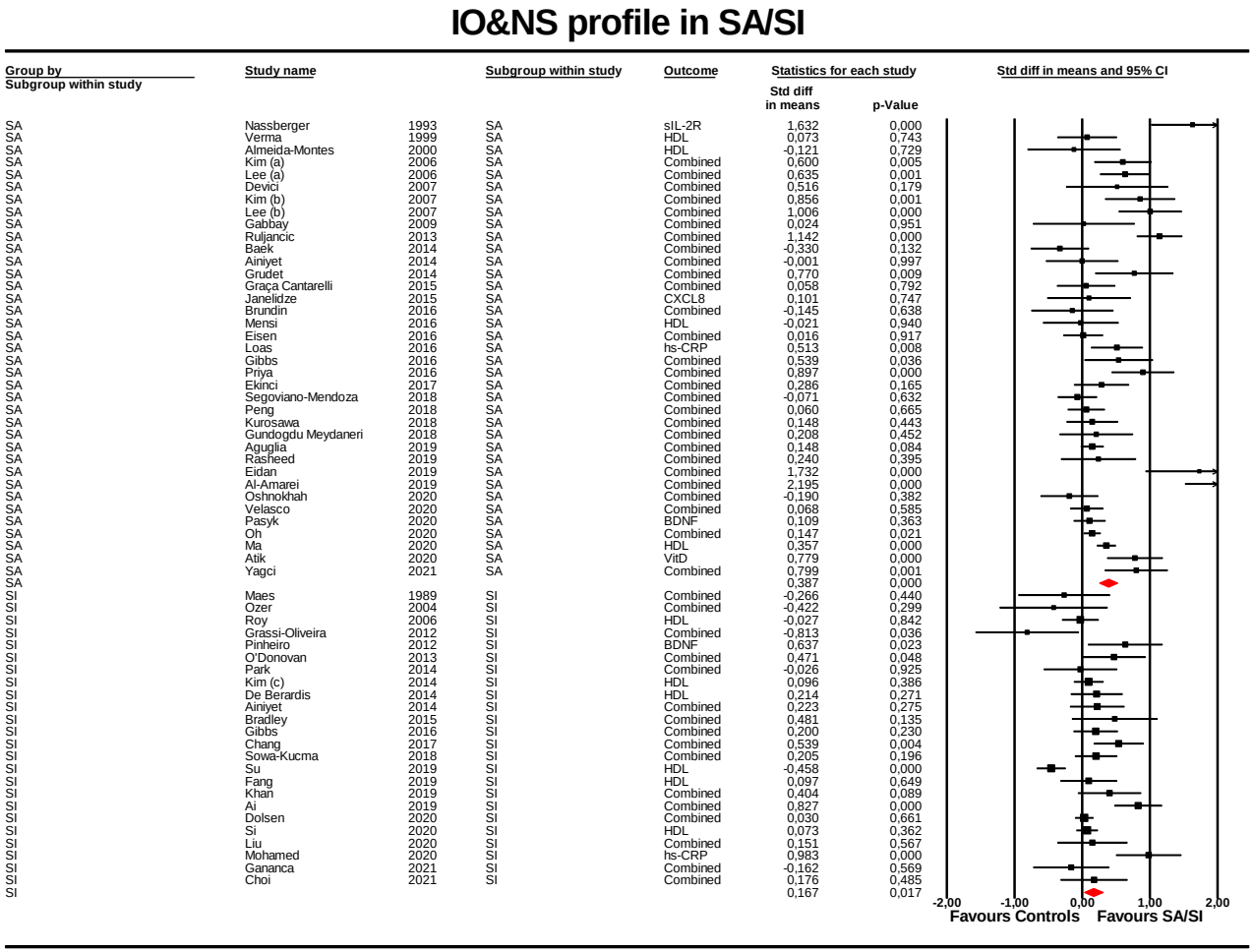

ESF 2 Figure 1. Forest plot with results of subgroup analysis performed on 61 suicide attempts (SA) or suicidal ideation (SI) studies reporting immune-inflammatory and oxidative & nitrosative stress (IO&NS) biomarkers.

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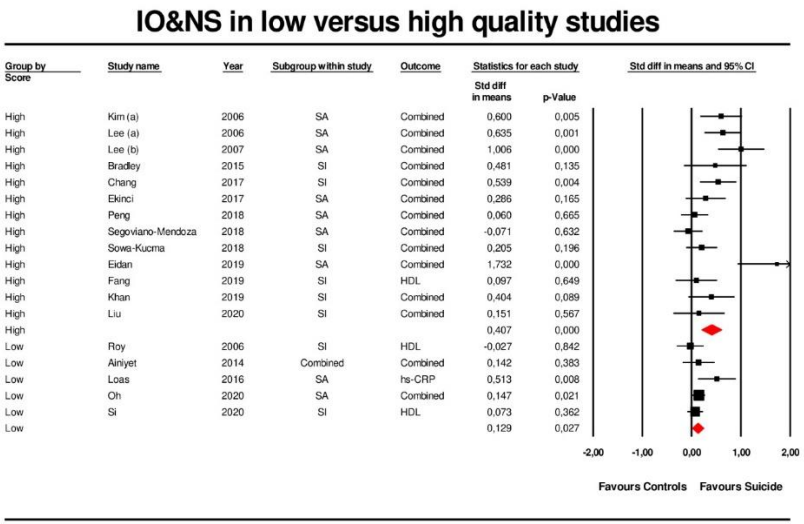

ESF 2 Figure 2. Forest plot with results of meta-analysis performed on 13 high- and 5 low-quality studies reporting immune-inflammatory and oxidative & nitrosative stress (IO&NS) biomarkers when comparing suicide behaviors to controls.