UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM PSIQUIATRIA E CIÊNCIAS DO COMPORTAMENTO

TESE DE DOUTORADO

MARCADORES DE INFLAMAÇÃO E ESTRESSE OXIDATIVO NO TRANSTORNO DE ESTRESSE PÓS-TRAUMÁTICO

Tatiana Lauxen Peruzzolo

Orientador: Prof. Dr. Ives Cavalcante Passos

Junho de 2022

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM PSIQUIATRIA E CIÊNCIAS DO COMPORTAMENTO

TESE DE DOUTORADO

MARCADORES DE INFLAMAÇÃO E ESTRESSE OXIDATIVO NO TRANSTORNO DE ESTRESSE PÓS-TRAUMÁTICO

Tese apresentada como requisito parcial para a obtenção do Título de Doutor em Psiquiatria à Universidade Federal do Rio Grande do Sul, Programa de Pós-Graduação em Ciências Médicas: Psiquiatria

Autora: Tatiana Lauxen Peruzzolo

Orientador: Prof. Dr. Ives Cavalcante Passos

Porto Alegre, 2022.

Catalogação Bibliográfica

CIP - Catalogação na Publicação

Peruzzolo, Tatiana Lauxen
MARCADORES DE INFLAMAÇÃO E ESTRESSE OXIDATIVO NO TRANSTORNO DE ESTRESSE PÓS-TRAUMÁTICO / Tatiana Lauxen Peruzzolo. -- 2022.
158 f.
Orientador: Ives Cavalcante Passos.

Tese (Doutorado) -- Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento, Porto Alegre, BR-RS, 2022.

1. Transtorno de Estresse Pós-traumático. 2. Marcadores Inflamatórios. 3. Estresse oxidativo. 4. Tratamento. I. Passos, Ives Cavalcante, orient. II. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os dados fornecidos pelo(a) autor(a).

FOLHA DE APROVAÇÃO

A meu esposo, Renato Salim, e a minha filha, Clara Peruzzolo Salim. Aos meus pais, Adair Caetano Peruzzolo e Eloí Terezinha Lauxen Peruzzolo.

AGRADECIMENTOS

Agradeço ao meu orientador, o Prof. Dr. Ives Cavalcante Passos, por todos os ensinamentos e, principalmente, pela paciência e compreensão. Agradeço a todo o grupo de pesquisa Alliance, fonte de novas ideias e conhecimentos. Agradeço também aos colaboradores dos dois artigos, Jairo V. Pinto, Thiago H. Roza, Ana Paula Anzolin, Vanessa Gnielka, Amanda Salvador Marin, Vitória Ruschel Lorenzon, Nicolle Mastella, Luis Francisco Ramos Lima e João Damasceno, sem os quais estes trabalhos não seriam possíveis. Incluo aqui um especial agradecimento a dois colegas: Augusto O. Shintani, colaborador nos dois artigos e um exemplo de organização e dedicação; André M. Kohmann, meu colega desde a residência de Psiquiatria da Infância e Adolescência e meu amigo.

Agradeço aos meus pais, por todo seu apoio, amor e exemplos de uma vida. Aos meus irmãos, que sempre me incentivaram e me encorajaram nessa jornada. À minha sogra, Úrsula E. Vidal de Souza, que é minha segunda mãe.

À minha filha, Clara, meu grande presente de Deus, que compreendeu e tolerou todas as vezes que a mamãe abriu mão de brincar com ela para estudar.

E, por último, mas certamente não menos importante, ao meu esposo, Renato, meu porto seguro e meu companheiro nos bons e maus momentos há 17 anos. Obrigada por estar ao meu lado e por ser fonte de força e tolerância frente aos desafios da vida.

"*Quem crê ter todas as respostas, certamente não fez todas as perguntas*."

Confúcio

SUMÁRIO

APRESENTAÇÃO

Este trabalho consiste na tese de doutorado intitulada "**Inflammatory and oxidative stress markers in post-traumatic stress disorder**", apresentada ao Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento, da Universidade Federal do Rio Grande do Sul, em junho de 2022.

O material é dividido em seis partes, na ordem que se segue: (1) Introdução, (2) Justificativa, (3) Objetivos, (4) Aspectos Éticos, (5) Artigos e (6) Considerações finais. Na seção "Artigos", estão apresentadas as seguintes publicações:

- Artigo 1. "**Inflammatory and oxidative stress markers in post-traumatic stress disorder: a systematic review and meta-analysis**."
- Artigo 2. "**Changes in Inflammatory and oxidative stress markers after treatment in posttraumatic stress disorder: a systematic review**"

LISTA DE ABREVIATURAS E SIGLAS

BHE – Barreira Hematoencefálica

CRH – Hormônio Liberador de Corticotropina

DNA – Ácido Desoxirribonucleico

DSM-DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS

GM-CSF – Fator Estimulante de Colônia de Granulócitos - Macrófagos

GR – Receptor de Glicocorticoide

GSH - Glutationa

HPA – Eixo Hipotálamo – Hipófise - Adrenal

IL - Interleucina

INF - Interferon

M-CSF - Fator Estimulante de Colônia de Macrófagos

NF- κB – Fator Nuclear Kappa B

OXS - Oxidative Stress

PCR – Proteína C Reativa

SNC – Sistema Nervoso Central

SNS – Sistema Nervosos Simpático

SOD – Superóxido Dismutase

TDM – Transtorno Depressivo Maior

TEPT - Transtorno de Estresse Pós-Traumático

TNF – Fator de Necrose Tumoral

RESUMO

O transtorno de estresse pós-traumático (TEPT) é uma condição que afeta aproximadamente 3,9% da população mundial. O TEPT está relacionado a níveis elevados de incapacidades sociais, profissionais e físicas, bem como a altos níveis de utilização de serviços médicos. Estimativas sugerem que até um terço daqueles que desenvolvem TEPT passam a experimentar uma forma crônica do transtorno que, em muitos casos, dura anos. Entre esses pacientes, comorbidades psiquiátricas e médicas são comuns, com muitos apresentando início precoce de condições relacionadas à idade, como doença cardiometabólica, transtornos neurocognitivos e demência. Novas evidências sugerem que essas consequências biológicas são devidas a elevados níveis sistêmicos de estresse oxidativo e inflamação. Assim, nosso objetivo foi realizar uma revisão sistemática atualizada e metanálise de biomarcadores inflamatórios em pacientes com TEPT, em comparação com controles saudáveis, incluindo também a avaliação de marcadores de estresse oxidativo. Após concluída esta primeira revisão, uma segunda pesquisa avaliando tratamentos para o TEPT que visassem a redução dos biomarcadores inflamatórios foi conduzida.

A metanálise incluiu 54 estudos. Os resultados confirmaram os achados do estudo anterior em relação ao aumento das concentrações de IL-6 e TNF-α no TEPT. Esses achados permaneceram significativos mesmo após a exclusão de estudos que avaliaram pacientes em uso de medicamentos psicotrópicos. Adicionalmente, constatou-se que a concentração da PCR é significativamente maior em pacientes com TEPT em comparação com controles.

Na segunda revisão, foram detectados 7 estudos que investigaram alterações nos marcadores de estresse inflamatório e oxidativo após tratamento em pacientes com TEPT. Apenas 2 estudos utilizaram medicamentos alternativos como opção de tratamento. Os demais estudos avaliaram a resposta clínica e imunológica a psicofármacos, mais especificamente aos Inibidores Seletivos de Recaptação da Serotonina (ISRS) e à vilazodona. Os resultados encontrados são promissores. Estudos com amostras maiores e com maior duração devem ser realizados para confirmar os achados.

Palavras-chave: Transtorno de estresse pós-traumático; inflamação; estresse oxidativo.

ABSTRACT

Post-traumatic stress disorder (PTSD) is a condition that affects approximately 3.9% of the world's population. PTSD is related to high levels of social, occupational, and physical disabilities, as well as high levels of use of medical services. Estimates suggest that up to a third of those who develop PTSD go on to experience a chronic form of the disorder that, in many cases, lasts for years. Among these patients, psychiatric and medical comorbidities are common, with many experiencing early-onset age-related conditions such as cardiometabolic disease, neurocognitive disorders, and dementia. New evidence suggests that these biological consequences are due to elevated systemic levels of oxidative stress (OXS) and inflammation (INF). Thus, our aim was to perform an updated systematic review and meta-analysis of inflammatory biomarkers in PTSD patients compared to healthy controls, also including the assessment of oxidative stress markers. After completing this first review, a second research evaluating treatments for PTSD aimed at reducing inflammatory biomarkers was conducted.

The meta-analysis included 54 studies. The results confirmed the findings of the previous study regarding increased concentrations of IL-6 and TNF-α in PTSD. These findings remained significant even after excluding studies that evaluated patients using psychotropic medications. Additionally, CRP concentration was found to be significantly higher in PTSD patients compared to controls.

In the second review, 7 studies were detected that investigated changes in markers of inflammatory and oxidative stress after treatment in patients with PTSD. Only two studies used alternative drugs as a treatment option. The other studies evaluated the clinical and immunological response to psychotropic drugs, more specifically to SSRIs and vilazodone. The results found are promising. Studies with larger samples and longer duration should be performed to confirm the findings.

1. INTRODUÇÃO

O transtorno de estresse pós-traumático (TEPT) é uma condição que pode se desenvolver após a exposição a eventos extremamente perturbadores, como violência interpessoal, combate, acidentes com risco de vida ou desastres naturais. É uma situação que reconhece a tragédia e o sofrimento humano, sejam eles produtos da natureza, da crueldade humana ou uma combinação deles (YEHUDA, Rachel *et al.*, 2015). Afeta aproximadamente 3,9% (0,3 a 8,8%) da população mundial (KOENEN *et al.*, 2017). História familiar de transtornos psiquiátricos, condições médicas crônicas, intensidade do evento traumático, ser mulher e experiências traumáticas cumulativas são fatores de risco associados ao seu desenvolvimento (TORTELLA-FELIU *et al.*, 2019). Os sintomas de TEPT incluem memórias angustiantes e intrusivas, pesadelos sobre o trauma, irritabilidade, hipervigilância (estado aumentado de sensibilidade à ameaça ou preocupação com o potencial de perigo), insônia, falta de concentração e retração emocional (YEHUDA, Rachel *et al.*, 2015).

O TEPT foi introduzido pela primeira vez no DSM-III em 1980, em parte devido às preocupações crescentes com as alterações emocionais em veteranos da Guerra do Vietnã (PICHOT, 1986). A psiquiatria já havia reconhecido que neuroses traumáticas de longa data podem ocorrer após a exposição ao combate, mas estava se tornando aparente que sintomas semelhantes estavam presentes em pessoas que sofreram violência interpessoal, como estupro ou agressão, sobreviveram a limpeza étnica ou genocídio, ou sofreram acidentes graves ou desastres naturais (YEHUDA, R.; MCFARLANE, 1995). O diagnóstico de TEPT foi revolucionário ao afirmar os efeitos transformativos e de longo prazo do trauma, visto que a teoria da época era de que os efeitos do estresse iriam desaparecer com a remoção do estressor. Posteriormente, estudos documentaram que, embora a exposição ao trauma fosse comum, o TEPT ocorria em apenas uma minoria dos sobreviventes. A definição do DSM-III incluiu 12 sintomas e destacou a importância dos sintomas de revivência do trauma. O afeto entorpecido e contraído era um segundo agrupamento de sintomas. Uma variedade de sintomas - como hiperexcitação, distúrbios do sono, culpa, comprometimento da memória e evitação de gatilhos traumáticos - foram descritos em um terceiro grupo inespecífico. Nos DSM-III revisado (DSM-III R (1988)) e DSM-IV (1994), ambas as definições incluíram 17 sintomas e foram baseadas em observações de que a evitação,

o entorpecimento e o estranhamento interpessoal representavam uma adaptação dinâmica com propósito de diminuir o sofrimento das memórias traumáticas. Outros sintomas foram pensados para representar expressões fisiológicas de excitação ou hipervigilância (AMERICAN PSYCHIATRIC ASSOCIATION., 1987; DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS, 4TH ED, 1994).

A primeira grande revisão da definição desde 1988 ocorreu em 2013 no DSM-5 (DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS: DSM-5, 2013). Entre as mudanças nos critérios diagnósticos para o TEPT no DSM-5, que agora inclui 20 sintomas, está a divisão dos sintomas em quatro grupos. A dimensão entorpecimento/evitação foi dividida em dois grupos distintos: evitação e alterações negativas persistentes nas cognições e no humor (YEHUDA, Rachel *et al.*, 2015).

O TEPT está relacionado a níveis elevados de incapacidades sociais, profissionais e físicas, bem como a altos níveis de utilização de serviços médicos. Em amostras da comunidade e de veteranos de guerra, o TEPT está associado a relações sociais e familiares empobrecidas, ausências ao trabalho, renda mais baixa e menor sucesso acadêmico e profissional (DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS: DSM-5, 2013). Além disso, estimativas sugerem que até um terço daqueles que desenvolvem TEPT passam a experimentar uma forma crônica do transtorno que, em muitos casos, dura anos (KESSLER, 2000; MICHOPOULOS et al., 2017). Entre esses pacientes, comorbidades psiquiátricas e médicas são comuns, com muitos apresentando início precoce de condições relacionadas à idade, como doença cardiometabólica (LOHR et al., 2015), transtornos neurocognitivos (ROSENBAUM et al., 2015) e demência (KESSLER, 2000) (PRASAD, 2015). Portanto, a carga total de doenças (deficiência mais mortalidade prematura) atribuível ao TEPT é extremamente alta (YEHUDA, Rachel *et al.*, 2015).

Novas evidências sugerem que essas consequências biológicas são devidas a elevados níveis sistêmicos de estresse oxidativo (OXS) e inflamação (INF), além do envelhecimento celular acelerado e neuroprogressão - a remodelação patológica dos circuitos neurais que ocorre durante o curso de uma doença mental crônica (MILLER, Mark W. *et al.*, 2018).

1.1.INFLAMAÇÃO E TEPT

A inflamação é uma resposta biológica complexa iniciada pelo sistema imunológico. Ela remove agentes infecciosos, como bactérias e vírus, e ajuda a reparar danos aos tecidos. No sangue periférico, são as células imunológicas, como neutrófilos, monócitos, linfócitos e macrófagos, que participam de reações inflamatórias. Já no cérebro, as micróglias são consideradas células inflamatórias. As células imunológicas são recrutadas para o local da infecção, liberando espécies reativas de oxigênio (ROS), citocinas pró-inflamatórias, prostaglandinas, moléculas de adesão e proteínas do complemento para eliminar a invasão de organismos prejudiciais ou para promover a cicatrização de tecidos lesados (MARTIN; LEIBOVICH, 2005).

Na inflamação aguda, quando o agente patogênico é removido, o processo inflamatório cessa. No entanto, em processos inflamatórios crônicos, mais tipicamente associados à maioria das doenças e condições neurodegenerativas humanas, as células imunes podem liberar quantidades excessivas de mediadores inflamatórios, podendo danificar o tecido normal, causando falência de órgãos e, eventualmente, até a morte.

Das substâncias liberadas na cadeia da reação inflamatória, as citocinas são as mais estudadas em saúde mental. As citocinas são proteínas produzidas principalmente por linfócitos e macrófagos ativados, mas também por endotélio, epitélio e células do tecido conjuntivo. No cérebro, eles são produzidos principalmente por células da microglia e alguns por neurônios. Citocinas pró-inflamatórias incluem interleucina-6 (IL-6), IL-17, IL-18, IL-23 e fator de necrose tumoral alfa (TNF-alfa), que são tóxicos para as células. As citocinas anti-inflamatórias incluem IL-1, IL-4, IL-10, IL-11 e IL-13, que auxiliam no reparo no local da lesão. Algumas citocinas pró-inflamatórias, como a IL-6, também podem atuar como fator neurotrófico. Neste caso, ela funciona como uma citocina pró-inflamatória durante a fase aguda da lesão e como um fator neurotrófico entre a fase subaguda e a fase crônica da lesão.

As citocinas desempenham um papel importante na modulação da função de muitos outros tipos de células: (1) as citocinas que regulam a ativação, o crescimento e a diferenciação dos linfócitos incluem interleucina-2 (IL-2) e IL-4 (favorece o crescimento), bem como a IL -10 que é regulador negativo das respostas imunes; (2) citocinas envolvidas com imunidade natural, como fator de necrose tumoral-alfa (TNF-alfa), IL-1Beta, interferon tipo I (IFN-alfa e IFN-beta) e IL-6; (3) citocinas que ativam células inflamatórias, como macrófagos (IFN-gama, TNF-alfa, TNF-beta, IL-5, IL-10 e IL-12); (4) citocinas que estimulam a hematopoiese (IL-3, IL-7, ligante c-kit, fator

estimulador de colônia de granulócitos-macrófagos (GM-CSF) e fator estimulador de colônias de macrófagos (M-CSF) (PRASAD, 2015).

Outro marcador de inflamação amplamente validado é a proteína C reativa (PCR), uma proteína que pode ser medida no plasma ou soro que responde a estímulos inflamatórios desencadeando respostas celulares que levam à sua eliminação. A PCR é o mais sensível dos reagentes inflamatórios do corpo, sendo capaz de proliferar até 1000 vezes em resposta a estímulos desencadeantes. Como a PCR é produzida principalmente no fígado, há muito se supôs que ela se expressasse apenas na periferia. No entanto, estudos recentes documentaram a presença de PCR em tecido cortical e subcortical de pacientes com várias doenças neurodegenerativas (STRANG *et al.*, 2012; YASOJIMA *et al.*, 2000).

Evidências emergentes também sugerem que a PCR é produzida em células endoteliais dos microvasos que formam a barreira hematoencefálica e que a PCR periférica pode afetar o sistema nervoso central por meio do rompimento da barreira hematoencefálica (MILLER, Mark W. *et al.*, 2018).

A noção de que a inflamação está envolvida na doença mental remonta pelo menos à observação de taxas aumentadas de depressão entre pacientes com hepatite C crônica tratados com interferon-α (RENAULT *et al.*, 1987). Esta ligação original entre inflamação e depressão foi apoiada por evidências subsequentes de que pacientes com transtorno depressivo maior (TDM) mostram níveis elevados de marcadores inflamatórios, incluindo citocinas pró-inflamatórias, como IL - 1β, IL - 6, e TNF - α, bem como proteínas de fase aguda, como PCR, no sangue e no líquido cefalorraquidiano (DOWLATI *et al.*, 2010; HOWREN; LAMKIN; SULS, 2009; SASAYAMA *et al.*, 2013). Além disso, estudos demonstraram que a desregulação imunológica e a inflamação estão associadas a uma série de distúrbios psiquiátricos além do TDM, incluindo esquizofrenia (MILLER, B. J. *et al.*, 2011), transtorno bipolar (MODABBERNIA *et al.*, 2013), transtorno do espectro autista (ROSSIGNOL; FRYE, 2012) e TEPT (PASSOS *et al.*, 2015).

Um número crescente de estudos mostrou que indivíduos com TEPT exibem níveis sanguíneos significativamente elevados de marcadores inflamatórios, como IL-1β, IL-6, TNF-α e PCR, em relação a controles saudáveis. Embora algumas evidências sugiram que a própria exposição ao trauma, independentemente da presença / ausência de diagnóstico de TEPT, possa levar a níveis aumentados de marcadores pró-inflamatórios, uma série de estudos comparando marcadores inflamatórios entre

pacientes com TEPT e controles não-TEPT expostos a trauma mostraram que o TEPT está associado a níveis elevados desses marcadores além do possível efeito da exposição ao trauma (TURSICH *et al.*, 2014).

Entre eles, a IL-6 é o marcador pró-inflamatório mais bem estudado, para o qual um aumento significativo em pacientes com TEPT é consistentemente mostrado em uma metanálise e na maioria dos estudos subsequentes (PASSOS *et al.*, 2015) (HORI; KIM, 2019). Além disso, os resultados de uma metanálise anterior do nosso grupo de pesquisa apontam para um uso potencial da IL-1β como biomarcador de duração da doença e IL-6 como biomarcador de gravidade (PASSOS *et al.*, 2015).

Em relação aos estudos que avaliaram os níveis de PCR no sangue em pacientes de TEPT, os resultados são mistos. Passos et al. (2015) em uma metanálise incluindo o resultado de cinco estudos avaliando PCR em pacientes com TEPT (131 casos; 136 controles no total), não encontraram diferenças significativas entre casos e controles (PASSOS *et al.*, 2015). No entanto, alguns estudos mais recentes relataram associações positivas entre a gravidade dos sintomas de TEPT e os níveis de PCR no plasma, ainda que nem todos os achados adicionais sejam uniformes (BAUMERT *et al.*, 2013; DENNIS *et al.*, 2016; MILLER, M. W. *et al.*, 2018).

Embora em menor número, há estudos que examinaram citocinas anti-inflamatórias, como IL - 4 e IL - 10, no sangue de indivíduos com TEPT em comparação aos controles. No entanto, seus resultados foram bastante controversos (HORI; KIM, 2019).

1.2. ESTRESSE OXIDATIVO E TEPT

O estresse oxidativo (Oxidative Stress - OXS) é um processo que ocorre quando os radicais livres dominam os sistemas antioxidantes protetores do corpo (por exemplo, glutationa [GSH], superóxido dismutase [SOD] e enzimas relacionadas). Existem vários tipos diferentes de radicais livres derivados de oxigênio e nitrogênio que são gerados no corpo. Normalmente, os radicais livres são gerados no corpo durante o uso de oxigênio no metabolismo de certos compostos (PRASAD, 2015). Sob estresse oxidativo agudo,

como infecção bacteriana ou viral, os antioxidantes aumentam em resposta à presença de moléculas pró-oxidantes. Quando o OXS é prolongado, ocorre a produção excessiva de radicais livres, causando danos ao DNA (ácido desoxirribonucleico), RNA (ácido ribonucleico), proteínas, carboidratos e membranas (PATEL; WINDER, 2010). Os antioxidantes se esgotam, levando à degeneração celular e apoptose, aumentando assim o risco de doença aguda e / ou crônica.

O cérebro é particularmente vulnerável a seus efeitos deletérios devido à alta demanda metabólica e à densa composição de células lipídicas suscetíveis à oxidação. Estudos ligaram o OXS a rupturas da barreira hematoencefálica, padrões alterados de crescimento neural e mudanças na morfologia cerebral (PATEL; WINDER, 2010).

O estresse oxidativo acompanha os transtornos mentais e tem chamado a atenção nos últimos anos. Vários estudos sugeriram uma associação entre o estresse oxidativo e transtornos psiquiátricos, incluindo o transtorno de ansiedade generalizada, o transtorno do pânico, transtorno obsessivo-compulsivo, fobia social e TEPT (ATLI *et al.*, 2016).

Evidências clínicas preliminares sobre o envolvimento do estresse oxidativo na fisiopatologia do TEPT vêm de estudos transversais que encontraram diferenças significativas nas concentrações de enzimas antioxidantes no sangue e na expressão gênica relacionada ao OXS entre pacientes com TEPT e controles. Por exemplo, Atli et al. relataram níveis elevados de peroxidação lipídica sérica (refletindo a quebra e oxidação de ácidos graxos poli-insaturados) e enzimas antioxidantes depletadas em sobreviventes de terremoto com TEPT em comparação com controles expostos ao terremoto (ATLI *et al.*, 2016). Da mesma forma, Stefanovic et al. mediram os níveis sanguíneos de SOD e glutationa transferase em veteranos de guerra croatas e encontraram níveis reduzidos de ambos os antioxidantes em veteranos com TEPT em comparação com os controles (BOROVAC ŠTEFANOVIĆ *et al.*, 2016).

1.3. Possíveis Mecanismos de Associação entre TEPT, Inflamação e Estresse Oxidativo Elevado

Um possível mecanismo para as associações entre TEPT, OXS e INF é a ativação crônica e repetida do eixo hipotálamo-hipófise-adrenal (HHA) que ocorre devido ao estresse excessivo associado a esse transtorno. O eixo HHA é um sistema

neuroendócrino que desempenha um papel fundamental na resposta ao estresse e na manutenção da homeostase corporal (MILLER, Mark W. *et al.*, 2018). É ativado em resposta a vários estressores, resultando em um aumento da secreção de glicocorticoide do córtex adrenal. O glicocorticoide, por sua vez, regula sua própria produção por meio de feedback negativo, ligando-se aos receptores de glicocorticoide (GRs) no hipotálamo e na hipófise. O glicocorticoide também exerce feedback negativo via GRs e receptores mineralocorticoides no hipocampo.

O estresse aumenta a síntese e a liberação do hormônio liberador de corticotropina (CRH) e arginina vasopressina no núcleo paraventricular do hipotálamo. O CRH estimula o sistema nervoso simpático (SNS) a produzir catecolaminas, incluindo norepinefrina (que leva a vários sintomas de TEPT, como hiperexcitação). Esta liberação aumentada de norepinefrina pode induzir a produção de citocinas pró-inflamatórias, como IL-1 e IL-6. Essas citocinas, por sua vez, estimulam a secreção de CRH do núcleo paraventricular hipotalâmico. Quanto à (re) ativação do eixo HHA, o aumento do CRH tipicamente estimula a secreção de adrenocorticotropina e, consequentemente, causa elevação do cortisol.

No entanto, no TEPT, evidências robustas mostram redução do cortisol em face do CRH aumentado. Como o cortisol pode diminuir a síntese e liberação de citocinas pró-inflamatórias, suprimindo a sinalização do fator nuclear - κB (NF - κB) e mediando a regulação específica da apoptose celular, a capacidade reduzida do cortisol para inibir as respostas inflamatórias no TEPT pode exacerbar o estado pró-inflamatório. Além disso, dado que o cortisol mostrou inibir a atividade do SNS, exceto quando sua elevação ocorre em sincronia com a liberação de noradrenalina, os níveis baixos de cortisol persistentes no TEPT podem contribuir para a hiperatividade do SNS, acelerando ainda mais a inflamação. Deve-se observar que o hipocortisolismo, juntamente com uma maior sensibilidade dos receptores de glicocorticoide (GR), é uma característica distintiva do TEPT (HORI; KIM, 2019).

Além disso, as citocinas liberadas da microglia inibem a neurogênese e promovem a apoptose neuronal, e esses processos têm sido implicados na neuroprogressão associada ao TEPT e distúrbios relacionados (MILLER, Mark W. *et al.*, 2018).

1.4. Atividade Inflamatória Aumentada e Neuroprogressão no TEPT

Dada a definição atualmente predominante de TEPT como um distúrbio cerebral, o conceito-chave aqui seria "neuroinflamação" ou inflamação do tecido nervoso. O cérebro já foi considerado um órgão com privilégios imunológicos, o que significaria que as células do sistema imunológico não entrariam no cérebro, exceto em certos casos de doenças e lesões. Entretanto, evidências nos últimos anos têm indicado que o cérebro e o sistema imunológico se comunicam rotineiramente, tanto na doença quanto na saúde. Na verdade, agora é bem conhecido que as citocinas pró-inflamatórias periféricas podem afetar o cérebro por meio de vários mecanismos, incluindo através do transporte ativo através da barreira hematoencefálica (BHE), através de regiões com vazamento na BHE, ou através da ativação de vias neurais, como o nervo vago (DANTZER *et al.*, 2008).

A microglia, as células imunes inatas primárias no SNC, são mediadores importantes dos processos neuroinflamatórios. Eles existem em repouso (quiescente) ou em estados ativados, dependendo do meio inflamatório (BUTOVSKY; WEINER, 2018). A microglia tem várias funções fisiológicas normais, incluindo sinaptogênese, suporte trófico, quimiotaxia e neurogênese.

No entanto, a microglia pode perder essas funções homeostáticas durante o curso de muitas doenças (BUTOVSKY; WEINER, 2018). Em cérebros doentes e estressados, a microglia pode persistir em um estado ativado, superproduzindo citocinas pró-inflamatórias e glutamato (RÉUS *et al.*, 2015; TAKAKI *et al.*, 2012). Esses mediadores pró-inflamatórios ativam astrócitos que também liberam citocinas e, posteriormente, induzem a ativação da microglia. Dessa maneira, a comunicação entre a microglia e os astrócitos pode amplificar a sinalização pró-inflamatória iniciada pela microglia, levando a alterações funcionais / estruturais do cérebro e a mudanças comportamentais associadas ao TEPT. Entre estas alterações encontram-se a ativação intensificada da amígdala em resposta a estímulos ameaçadores (INAGAKI *et al.*, 2012), e o prejuízo em uma variedade de funções cognitivas, incluindo memória / aprendizagem verbal, memória de trabalho, atenção e funções executivas, com prejuízo particularmente acentuado na memória / aprendizagem verbal.

Assim, tanto a inflamação na periferia, como no SNC podem contribuir para a neuroinflamação por meio da ativação da microglia e dos astrócitos. Em particular, IL - 6, TNF - α e IL - 1β são mostrados para influenciar o cérebro nos níveis morfológico, funcional e cognitivo, afetando, por exemplo, neurogênese, plasticidade sináptica e memória / aprendizagem (LEVIN; GODUKHIN, 2017).

Consistente com essas disfunções cognitivas, estudos de neuroimagem demonstraram que indivíduos com TEPT apresentam anormalidades estruturais e funcionais nas regiões do cérebro que controlam a função cognitiva, incluindo o hipocampo e o córtex pré-frontal (AUPPERLE *et al.*, 2012; BREMNER *et al.*, 2008; LI *et al.*, 2014).

Além disso, foi demonstrado que a inflamação crônica acelera o encurtamento dos telômeros, levando ao envelhecimento celular e à senescência prematura, que tem sido implicada na perda de controle do sistema imunológico (MARSLAND *et al.*, 2017). As células senescentes são diferenciadas terminalmente e não são mais totalmente funcionais. Embora não sofram morte celular, eles causam danos ao expelir citocinas no meio celular. Uma revisão da literatura de 32 estudos entre 2001 e 2014 encontrou um encurtamento dos telômeros leucocitários, além de um aumento nos marcadores pró-inflamatórios em pacientes com TEPT, sugerindo imunosenescência precoce (KIM; LEE; YOON, 2020; PASSOS *et al.*, 2015; STEIN *et al.*, 2019).

2. JUSTIFICATIVA

Existem alguns pontos que justificam uma nova revisão e metanálise a respeito desse assunto. Uma metanálise anterior e meta-regressão mostrou níveis aumentados de IL-6, IL-1β, TNF-α e interferon-γ em pacientes com TEPT. Algumas limitações, no entanto, impediram conclusões mais robustas. Especificamente, poucos estudos foram incluídos nas metanálise e o estudo não incluiu marcadores de estresse oxidativo. Além disso, o tipo de trauma e a fração sanguínea avaliada (soro versus plasma) não foram explorados como moderadores potenciais dos tamanhos de efeito. Vale ressaltar também que diversos estudos foram publicados desde 2015, quando foi feita essa metanálise, com novos achados sobre biomarcadores periféricos no TEPT.

Embora os sintomas psicocomportamentais sejam os principais fatores considerados ao investigar o estado patológico e a gravidade de um TEPT, compreender as alterações imunológicas que ocorrem em conjunto com esses sintomas pode ser informativo. Respostas inflamatórias e de estresse oxidativo detalhadas no TEPT podem ajudar a identificar as vias potencialmente distintas ou divergentes para o desenvolvimento da patologia e revelar ainda mais a fisiopatologia do transtorno (SONG *et al.*, 2018). Por exemplo, os níveis plasmáticos de IL-1β e IL-6 mostraram se correlacionar positivamente com a duração e gravidade dos sintomas de TEPT, respectivamente, e podem, portanto, ser usados para monitorar a resposta ao tratamento (PASSOS *et al.*, 2015).

Outro ponto é que as estratégias atuais de tratamento farmacológico têm como foco o alívio dos sintomas. Alguns exemplos disso são o uso de inibidores seletivos da recaptação da serotonina para tratar ansiedade e sintomas depressivos, agonistas alfa-2 adrenérgicos e estabilizadores de humor para direcionar a hiperexcitação e antagonistas alfa-1 adrenérgicos para direcionar os distúrbios do sono (NORRHOLM; JOVANOVIC, 2010). No entanto, esses tratamentos atuais para o TEPT têm mostrado eficácia limitada, o que tem estimulado o surgimento de pesquisas sobre novas abordagens psicofarmacológicas, baseadas nos mecanismos biológicos subjacentes ao TEPT (PATEL; WINDER, 2010). Drogas destinadas a diminuir as concentrações de citocinas pró-inflamatórias ou reduzir o estresse oxidativo na circulação podem ter benefícios duplos e ajudar a aliviar a carga da doença em pacientes de TEPT.

3. **OBJETIVOS:**

3.1.Objetivos Gerais:

Nosso objetivo é realizar uma revisão sistemática atualizada e metanálise de biomarcadores inflamatórios em pacientes com TEPT, em comparação com controles saudáveis, incluindo também a avaliação de marcadores de estresse oxidativo. Após

concluída esta primeira revisão, uma segunda pesquisa avaliando tratamentos para o TEPT que visem a redução dos biomarcadores inflamatórios será conduzida.

3.2.Objetivos Específicos:

- Realizar uma revisão sistemática atualizada e metanálise de biomarcadores inflamatórios em pacientes com TEPT.
- Incluir a avaliação de marcadores de estresse oxidativo.
- Comparar os níveis de biomarcadores de estresse oxidativo e inflamatório encontrados em pacientes de TEPT com aqueles encontrados em controles saudáveis.
- Explorar a influência do transtorno depressivo maior comórbido (TDM) e o uso atual de medicamentos psicotrópicos em análises de subgrupos.
- Investigar a influência do tipo de trauma, gravidade e duração dos sintomas de TEPT, a hora do dia o sangue foi coletado, o imunoensaio usado e a fração do sangue avaliada, como fontes potenciais de heterogeneidade em análises de meta-regressão univariada.
- Em um segundo artigo, realizar uma revisão sistemática sobre os tratamentos existentes para o TEPT que busquem atuar não somente na melhora da sintomatologia clínica, como também nos mecanismos fisiopatológicos do transtorno, sejam eles a inflamação e/ou o estresse oxidativo.

4. ASPECTOS ÉTICOS:

Por se tratar de suas revisões sistemáticas com metanálise, o presente trabalho não necessitou ser submetido a aprovação do Comitê de Ética.

5. **ARTIGOS:**

5.1. Artigo 1 – "*Inflammatory and oxidative stress markers in post-traumatic stress disorder: a systematic review and meta-analysis.*"

Carta de Aceite

Data: 4 de abril de 2022

Subject: Accepted manuscript 2021MP000679RRR

Manuscript Number: 2021MP000679RRR
Title: Inflammatory and oxidative stress markers in post-traumatic stress disorder: a systematic review and meta-analysis
Author: Professor Passos

Dear Professor Passos,

I am very pleased to inform you that your above-mentioned manuscript has now been officially accepted for publication in the *Molecular Psychiatry*. The files will be forwarded to our production team within the next few hours. For further queries, please contact the *Molecular Psychiatry*'s production editor at a.yoshida@nature.com

You can now use a single sign-on for all your accounts, view the status of all your manuscript submissions and reviews, access usage statistics for your published articles and download a record of your refereeing activity for the Nature journals.

Content Sharing
To assist our authors in disseminating their research swiftly and legally to the broader community, our Sharedit initiative provides you with the ability to generate a unique shareable link that will allow anyone to read the published article. If you plan to select an Open Access option for your paper, or where an individual can view content via a personal or institutional subscription, recipients of the link will also be able to download and print the PDF.

As soon as your article is published, you can generate your shareable link by entering the DOI of your article here.

In addition, Springer Nature encourages all authors and reviewers to associate an Open Researcher and Contributor Identifier (ORCID) to their account. ORCID is a community-based initiative that provides an open, non-proprietary and transparent registry of unique identifiers to help disambiguate research contributions.

In order to extend the reach and impact of your published paper, we strongly encourage you to highlight your paper on social media and research-sharing networks. Please do Tweet about your paper and view our simple http://www.nature.com/content/authortips/index.html?WT.mc_id=WEB_AUTHORTIPS_1507_AJAUTHORPAGES">tips on how to highlight your paper.

We might distribute a press release, which may contain details of your work, to news organizations and to science journals worldwide before your paper is published. Your own institution or funding agency is free to prepare your own press release, but it must mention the embargo date to *Molecular Psychiatry*.

Please note that *Molecular Psychiatry* is a Transformative Journal (TJ). Authors may publish their research with us through the traditional subscription access route or make their paper immediately open access through payment of an article-processing charge (APC). Authors will not be required to make a final decision about access to their article until it has been accepted. Find out more about Transformative Journals

Authors may need to take specific actions to achieve compliance with funder and institutional open access mandates. If your research is supported by a funder that requires immediate open access (e.g. according to Plan S principles) then you should select the gold OA route, and we will direct you to the compliant route where possible. For authors selecting the subscription publication route, the journal's standard licensing terms will need to be accepted, including self-archiving policies. Those licensing terms will supersede any other terms that the author or any third party may assert apply to any version of the manuscript.

Thank you for submitting your work to the *Molecular Psychiatry*.

Yours sincerely,

Julio Licinio
Editor
Molecular Psychiatry

Versão do Manuscrito Aceita

Title: Inflammatory and oxidative stress markers in post-traumatic stress disorder: a systematic review and meta-analysis

Authors: Tatiana Lauxen Peruzzolo, MD[1,2,*]; Jairo Vinícius Pinto, MD[1,3*]; Thiago Henrique Roza, MD[1,2*]; Augusto Ossamu Shintani[1,2]; Ana Paula Anzolin[1,2]; Vanessa Gnielka, MD[1,2]; André Moura Kohmann, MD[1,2]; Amanda Salvador Marin[1,2]; Vitória Ruschel Lorenzon[1,2]; André Russowsky Brunoni, PhD[4,5,6]; Flávio Kapczinski, PhD[1,2,7]; Ives Cavalcante Passos, PhD[1,2,8]

1- Laboratory of Molecular Psychiatry, Centro de Pesquisa Experimental (CPE) and Centro de Pesquisa Clínica (CPC), Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, RS, Brazil.

2- Universidade Federal do Rio Grande do Sul, School of Medicine, Graduate Program in Psychiatry and Behavioral Sciences, Department of Psychiatry, Porto Alegre, RS, Brazil.

3- University Hospital, Universidade Federal de Santa Catarina, Florianópolis, SC, Brazil.

4- Centro de Pesquisas Clínicas e Epidemiológicas, Hospital Universitário, Universidade de São Paulo, São Paulo, Brasil.

5- Departamentos de Clínica Médica e Psiquiatria, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brasil.

6- Instituto Nacional de Biomarcadores em Psiquiatria (IMBION), Laboratory of Neurosciences (LIM-27), Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brasil.

7-Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada.

8-Instituto Nacional de Ciência e Tecnologia Translacional em Medicina (INCT-TM), Porto Alegre, RS, Brazil.

* Dr Tatiana Lauxen Peruzzolo, Dr Jairo Vinícius Pinto, and Dr Thiago Henrique Roza are joint first authors who contributed equally to this work. Dr Jairo Vinícius Pinto was responsible for the statistical analysis. Dr Tatiana Lauxen Peruzzolo and Dr Thiago Henrique Roza were responsible for writing the article, supervised by Dr Ives Cavalcante Passos and Dr André Russowsky Brunoni.

Corresponding author

Ives Cavalcante Passos, MD, PhD

Professor of Psychiatry, Department of Psychiatry

Federal University of Rio Grande do Sul, Hospital de Clínicas de Porto Alegre

Full address: Rua Ramiro Barcelos, 2350, Av. Protásio Alves, 211 - Santa Cecilia, Porto Alegre - RS, 90035-903. Laboratório de Psiquiatria Molecular - 1º andar CPE.

Phone number: +5551997752017

E-mail: ivescp1@gmail.com

https://orcid.org/0000-0001-6407-8219

E-mail of all authors

Tatiana Lauxen Peruzzolo: tatiperuzzolo@gmail.com

Jairo Vinícius Pinto: jairovinicius@msn.com

Thiago Henrique Roza: roza.h.thiago@gmail.com

Augusto Ossamu Shintani: ashintani@gmail.com

André Kohmann: andrekohmann@yahoo.com.br

Vanessa Gnielka: vgnielka@hcpa.edu.br

Amanda Salvador Marin: amanda.marin10@gmail.com

Vitória Ruschel Lorenzon: vitoriaruschel@gmail.com

Ana Paula Anzolin: anapaulasordianzolin@gmail.com

André Russowsky Brunoni: brunoni@usp.br

Flávio Kapczinski: flavio.kapczinski@gmail.com

Ives Cavalcante Passos: ivescp1@gmail.com

Abstract

Post-traumatic stress disorder (PTSD) has been associated with persistent, low-degree inflammation, which could explain the increased prevalence of autoimmune conditions and accelerated aging among patients. The aim of the present study is to assess which inflammatory and oxidative stress markers are associated with PTSD**.** We carried out a meta-analytic and meta-regression analysis based on a systematic review of studies comparing inflammatory and oxidative stress markers between patients with PTSD and controls. We undertook meta-analyses whenever values of inflammatory and oxidative stress markers were available in two or more studies. Overall, 28 008 abstracts were identified, and 54 studies were included, with a total of 8 394 participants. The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to evaluate the quality of the studies. Concentrations of C-reactive protein (SMD = 0.64; 95% CI: 0.21 to 1.06; p = 0.0031; k = 12), interleukin 6 (SMD = 0.94; 95% CI: 0.36 to 1.52; p=0.0014; k = 32), and tumor necrosis factor-α (SMD = 0.89; 95% CI: 0.23 to 1.55; p=0.0080; k = 24) were significantly increased in patients with PTSD in comparison with healthy controls. Interleukin 1β levels almost reached the threshold for significance (SMD = 1.20; 95% CI: -0.04 to 2.44; p = 0.0569; k = 15). No oxidative stress marker was associated with PTSD. These findings may explain why PTSD is associated with accelerated aging and illnesses in which immune activation has a key role, such as cardiovascular diseases and diabetes. Additionally, they pointed to the potential role of inflammatory markers as therapeutic targets.

Keywords: post-traumatic stress disorder; PTSD; meta-analysis; inflammation; oxidative stress; biomarkers; C-reactive protein; interleukin 6; Interleukin 1β.

1. Introduction

Post-traumatic stress disorder (PTSD) is a chronic and severe psychiatric condition, which may develop in approximately one-third of individuals who were exposed to or experienced a significant traumatic event [1, 2]. PTSD presents a lifetime prevalence of about 3.9% (0.3 to 8.8%) [3]. Family history of psychiatric disorders, chronic medical conditions, the intensity of the traumatic event, being a woman, and cumulative traumatic experiences are risk factors associated with its development [2]. In addition, PTSD has been associated with increased suicide risk [4], premature death [5], coronary heart disease, and elevated economic burden [6]. PTSD presents a complex pathophysiology, and immune activation has been associated with the disorder [1, 7]. Most of the evidence comes from empirical data on blood biomarkers, which have described increased levels of specific proinflammatory cytokines and acute-phase proteins in patients with PTSD compared with healthy controls [7, 8]. PTSD has also been associated with an increased risk of developing autoimmune conditions in longitudinal studies [9, 10]. In addition, PTSD has been linked to accelerated aging, reduced cortical thickness, and neurodegeneration [11–13].

A previous meta-analysis and meta-regression published in 2015 showed increased levels of interleukin 6 (IL-6), interleukin 1β (IL-1β), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ) in patients with PTSD.[8] Additionally, its findings suggested the use of IL-1β as biomarker of illness duration, and IL-6 as a biomarker of PTSD severity. Some limitations, however, prevent more robust conclusions. Specifically, few studies were included in the meta-analyses and meta-regression analysis of some inflammatory markers, and the study did not include oxidative stress markers. Additionally, type of trauma and the blood fraction assessed (serum *vs* plasma) were not explored as potential moderators of the effect sizes. Another systematic review and meta-

analysis was published in 2020, with the aim of providing an updated account of the presence of immune biomarkers in PTSD patients [14]. In their analysis, patients with PTSD presented significantly higher levels of C-reactive protein (CRP), TNF-α, IL-6, IL-1β, interleukin 2 (IL-2), white blood cells, and IFN-γ in comparison with healthy controls. However, this study presents important limitations, including a significantly less comprehensive search, based on references written only in English and indexed in three electronic databases. For instance, even though the authors of this 2020 paper aimed to update the prior work [8], their work was based on the screening of 2,606 references [14], whereas the study published in 2015 was based on the screening of 8,057 references [8]. Furthermore, the 2020 study also did not investigate the levels of oxidative stress markers in PTSD patients; also presenting limitations concerning methodology and data analysis that were described in the discussion of the present manuscript [14].

Therefore, aiming to address the above-described gaps, we decided to perform an updated and comprehensive systematic review and meta-analysis of inflammatory biomarkers in patients with PTSD, in comparison with healthy controls; also including the assessment of oxidative stress markers. Additionally, we explored the influence of comorbid major depressive disorder (MDD) and current use of psychotropic medication in subgroup meta-analyses. Comorbid MDD and current psychotropic use were investigated, along with type of trauma, severity, and length of PTSD symptoms, the time-of-day blood was collected, the assay used, and blood fraction assessed, as potential sources of heterogeneity in univariate meta-regression analyses.

2. Methods and Materials

2.1. Search strategy and selection criteria

The study protocol was registered at PROSPERO (CRD42020153592; August 2020). We utilized the guidelines described by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15]. The PRISMA checklist used can be found in Supplementary table 1. Furthermore, we structured our selection criteria and statistical analysis in concordance with the MOOSE guidelines for meta-analyses and systematic reviews of observational studies [16]. The methodological quality of included studies was determined using the Newcastle-Ottawa Scale (NOS) (see Supplementary table 2) [17].

A literature search was conducted in the following databases: PubMed, Embase, Scopus, Web of Science, and PsycInfo for articles published in any language between January 1, 1960, and October 6, 2021. Search terms are described in the supplementary material (see Supplementary table 3). Medical Subject Heading (MeSH) terms were used in PubMed and Emtree terms were used in Embase. We also searched the reference lists of included studies and contacted experts in the field of PTSD for unpublished data. Two pairs of investigators (TLP plus AMK, and AOS plus APSA) independently screened records identified through database searching, supervised by VG, who decided in cases of disagreement. The same pairs of investigators then assessed for eligibility the full text of all titles and abstracts included in the screening phase, supervised by ICP, and FK, who decided in cases of disagreement. Data from all eligible articles were then extracted by seven investigators (TLP, AMK, AOS, APSA, VG, ASM, VRL). Articles in languages other than English were translated. The following eligibility criteria were used: (a) observational studies that assessed peripheral blood inflammatory or oxidative stress markers in patients with PTSD (if the study had a prospective design, we included only baseline assessments) compared with controls; (b) studies that used well-validated diagnostic criteria for PTSD (Diagnostic and Statistical Manual of Mental Disorders, 4th edition - DSM-IV, DSM-5, International Classification of Diseases, 10th edition - ICD-10, or the Clinician-Administered PTSD Scale (CAPS)); (c) studies that included adult patients (aged ≥18 years); (d) studies that showed the mean and standard deviation (SD) of peripheral blood cytokines (authors were contacted if the information was missing – when there was no response from the authors, a calculation of the estimated mean and SD was made [Supplementary table 4]). Exclusion criteria were: (a) studies that assessed patients with bipolar disorder and psychotic disorders, severe medical illness, or autoimmune or inflammatory disease; (b) studies with participants who were using anti-inflammatory or immunomodulatory drugs; (c) studies with inflammatory marker concentrations measured in cerebrospinal fluid or brain tissue; (d) studies that assessed peripheral inflammatory or oxidative stress markers measured after stimulation; (e) review articles. However, we included studies that evaluated patients with PTSD and MDD. Likewise, studies that evaluated patients with anxiety disorder, alcohol dependence and substance abuse were also included, as these are comorbidities often associated with PTSD. A subgroup analysis differentiated the effect size of findings according to the presence of MDD. Subgroup analyses were not performed in relation to other comorbid disorders, as there were insufficient data in the included studies.

2.2. Data extraction

Duplicated references were removed. We used standardised spreadsheets to extract data from articles, including name of the first author; publication year; number, sex, and age of the participants; type of diagnostic instrument

used; mean and SD of peripheral blood cytokines and oxidative stress markers; type of trauma (war *vs* other than war trauma); time of day blood was collected (fasting *vs* postprandial); type of blood fraction assessed (serum *vs* plasma); type of assay undertaken (enzyme-linked immunosorbent assay - ELISA, or other than ELISA); whether the study allowed patients with comorbid MDD in the PTSD group; whether patients were medication-free; illness duration; and severity of PTSD symptoms assessed by CAPS. When an analysis was reported in more than one article, data were extracted from the most recent report.

2.3. Data analysis

Meta-analyses were performed whenever information about inflammatory or oxidative stress markers was available in two or more studies [18]. To incorporate both within-study and between-study variabilities, random-effects models with restricted maximum-likelihood estimators were used to synthesize the effect sizes [18]. The bias-corrected standardized mean difference (SMD) was used to assess the effect size, and the level of significance for the models was 0.05 [18]. For the SMD, an effect size of 0.2 was considered a small effect, 0.5 a moderate effect, and 0.8 or more as a large effect size [19]. The Q statistic was used to investigate the existence of heterogeneity, the t^2 to assess the amount of heterogeneity, and the I^2 to evaluate the proportion of variability due to heterogeneity [20]. We considered a p-value < 0.1 for the Q statistic or $I^2 > 25\%$ as thresholds for heterogeneity [21]. Egger's linear regression test was used to investigate potential small study effects in the included studies, but funnel plot inspection was used only in those meta-analyses that included 10 or more studies [22]. When a potential small study effect was identified by Egger's test ($p < 0.1$) in meta-analyses with significant effect sizes, Duval and Tweedie's trim-and-fill method was used to test the data [22][23]. The leave-one-out procedure, which consists of performing a new meta-analysis on each subset of the dataset obtained by leaving out one study at a time, was used as a sensitivity analysis to investigate the effect of each study on the main analyses [18]. This analysis tests if the effect size of the meta-analysis is driven by one study. The method should not be regarded as a way of yielding a more valid estimate of the overall effect or outcome but as a way of examining the sensitivity of the results to one particular selection mechanism. Given that meta-analyses may be susceptible to the quality of the included studies, we performed a sensitivity analysis evaluating only the high-quality studies according to the NOS.

Subgroup meta-analyses were performed to investigate the effect of comorbid MDD and current use of psychotropic medication whenever information about inflammatory or oxidative stress markers was available in two or more studies in each subgroup. Comorbid MDD and psychotropic medication use were selected as predictors since previous evidence has shown their effect on cytokines and other biomarkers [8]. Finally, univariate meta-regression analyses were used to investigate the sources of heterogeneity in meta-analyses that included at least ten studies. We analyzed methodological variables, such as type of assay undertaken (ELISA *vs* other than ELISA), blood fraction assessed (serum *vs* plasma), time of day blood was collected (fasting *vs* postprandial), and variables with clinical implications, such as presence of comorbid MDD (PTSD with comorbid MDD *vs* PTSD without MDD), current use of psychotropic medication (medication-free *vs* on psychotropic medication), illness duration (in months), PTSD symptoms assessed by CAPS, and type of trauma (war trauma vs other than war trauma), as predictors in univariate analysis. Severity of depressive symptoms, when the study included this data, was also analyzed as a variable with clinical implications. Given the great heterogeneity between the scales used to assess depressive symptoms, an effect size calculation (SMD, Hedges' g) of the difference in scale scores between patients and controls was performed. The effect size was used as a predictor of the biomarkers in question. The meta-analyses were performed using the *metafor* and the *meta* packages in R environment [24].

2.4. Role of funding source

Brazilian National Council for Scientific and Technological Development (CNPq) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES). The corresponding author had full access to all the data used in the study and had final responsibility for the decision to submit for publication. This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001.

3. Results

3.1. Systematic review – results

Figure 1 shows the full study selection process according to PRISMA. The initial literature search identified 28 008 abstracts from databases. From those, after primary and secondary screening, 54 studies (51 studies after

eligibility phase and three studies through reference review) were included, with a total of 8 394 participants (2 506 subjects with PTSD and 5 888 controls) [25-78]. Peripheral blood levels of 20 inflammatory or oxidative stress markers were assessed in two studies or more. **Table 1** presents the characteristics of included studies while Supplementary table 2 presents the quality of these studies as assessed by the NOS. The NOS evaluates three quality parameters (selection, comparability, and outcome) divided across eight specific items. Each item on the scale is scored from one point, except for comparability. The maximum score for each study is 9, with studies having less than 5 points being identified as representing a high risk of bias[79]. From the 54 studies, 37 have a NOS score greater than or equal to six, a score that signals a high quality of the study.

3.2. Meta-analysis – inflammatory markers

Meta-analyses showed that concentrations of CRP, IL-6, and TNF-α were elevated in patients with PTSD compared with controls, ranging from moderate effect size for CRP (SMD = 0.64; 95% CI: 0.21 to 1.06; p = 0.0031; k = 12) to large effect sizes for IL-6 (SMD = 0.94; 95% CI: 0.36 to 1.52; p=0.0014; k = 32) and TNF-α (SMD = 0.89; 95% CI: 0.23 to 1.55; p = 0.0080; k = 24) (**Table 2**). These comparisons presented high heterogeneity ($I^2 > 75\%$). The significance of the effect size remained robust after using the leave-one-out procedure as sensitivity analysis for IL-6, CRP, and TNF-α (Supplementary tables 5, 6, and 7). Egger's linear regression test suggested small study effects for two of the inflammatory markers with significant findings: IL-6 and TNF-α (**Table 2**). However, it was not necessary to input any studies according to the nonparametric data augmentation technique implemented in the metafor package. There were no other significant differences between groups for any of the other inflammatory or oxidative stress markers (**Table 2**); nevertheless, IL-1β almost reached the threshold for statistical significance (SMD = 1.20; 95% CI: -0.04 to 2.44; p=0.0569; k = 15). Furthermore, the levels of IL-1β became significantly higher in the PTSD group when one of the studies (Dalgard et al., 2017) was left out of the analysis (Supplementary table 8). Funnel plots of IL-6, CRP, TNF-α, and IL-1β are depicted in Supplementary figures 1–4.

Subgroup meta-analyses revealed that levels of IL-6 and TNF-α were significantly higher in patients with PTSD without comorbid MDD compared with controls (**Figure 2 and Figure 3**). On the other hand, levels of IL-6 and TNF-α were not higher in the subgroup with major depressive disorder when compared with controls (**Figures 2 and 3**). Regarding the use of medication, IL-6 was significantly higher in patients with PTSD when compared with controls, regardless of the presence of medication use (**Figure 4**). Conversely, levels of TNF-α were significantly higher than healthy controls only in those patients with PTSD who were medication-free

(**Figure 5**). Subgroup analysis showed only a marginally significant difference of IL-1β in PTSD without comorbid MDD when compared with controls (p = 0.0490) (Supplementary table 9). It was not possible to perform a subgroup meta-analysis for CRP because only one study included patients without MDD; only one study included participants who were medication-free as well. IL-1β and CRP forest plots are represented in Supplementary figures 5 and 16. Forest plots of all other cytokines are depicted in the supplemental material.

In the meta-regression analyses, the univariate models found that methodological variables explained between-study heterogeneity for IL-1β, IL-6, and TNF-α. The use of ELISA as the assay method was significantly and positively associated with IL-1β, IL-6, and TNF-α levels. On the other hand, the blood fraction investigated (serum vs plasma) was significantly associated only with IL-1β.

Among the variables with clinical implication, length of illness significantly explained heterogeneity for IL-6, IL-10, CRP, and TNF-α. While the duration of illness was negatively associated with the IL-6 levels, it was positively associated with IL-10, CRP and TNF-α levels. The severity of depressive symptoms significantly explained the heterogeneity for IL-1β and TNF-α.

Finally, the war trauma was negatively associated with TNF-α levels. The complete description of the results of the meta-regression analyses are presented in supplementary tables 10 and 11.

An assessment of the statistical power in the meta-analysis of the investigated inflammatory markers was performed (supplementary table 12). Of the 20 meta-analytic models, 17 had statistical power lower than 0.8, indicating that most analyses are underpowered. The biomarkers with statistical power above 0.8 were IL-6, CRP and TNF-α, with values of 0.99, 0.99 and 0.82, respectively.

3. Discussion

The present meta-analysis and meta-regression included 54 studies, corresponding to 34 additional studies in comparison with the prior systematic review [8], also investigating oxidative stress markers in the analysis. On the one hand, with the inclusion of more studies, we found that the concentration of CRP (k = 5 in the prior meta-analysis, while k = 12 in the present study) is significantly higher in patients with PTSD compared with controls,

with this finding not being significant in the previous study [8]. On the other hand, IFN-γ (k = 6 in the present study and k = 2 in the prior meta-analysis) and IL-1β (k = 15 in the present study and k = 7 in the prior meta-analysis) were no longer significant. IL-1β became marginally significant when assessing the difference of IL-1β in PTSD without comorbid MDD in comparison with controls. Additionally, the present study confirmed the findings of the prior study[8] with regard to the increased concentrations of IL-6 and TNF-α in PTSD. These findings remained significant even after excluding studies that assessed patients on psychotropic medications. However, we had an unexpected finding, given that levels of interleukin 6 and TNF-alpha were not higher in the subgroup with major depressive disorder when compared with controls. For most inflammatory markers, study heterogeneity was high. No oxidative stress marker was significantly associated with PTSD. Additionally, our initial purpose was to assess variables such as tobacco use or exercise as moderators in meta-regression models. However, these analyses were not performed because these variables were rarely reported. We discuss below the new findings compared with the prior meta-analysis [8].

This systematic review and meta-analysis add to the evidence of inflammation as a key factor in the pathophysiology of PTSD. The mechanism behind this association is complex, and is yet to be elucidated [80]. Nevertheless, one potential explanation would be related to an altered function in the hypothalamic-pituitary-adrenal (HPA) axis, leading to increased levels of catecholamines and decreased basal levels of cortisol, which is a highly replicated finding in patients with PTSD [1, 80, 81]. This finding has been suggested as biological vulnerability associated with increased risk of developing PTSD following the experience of a traumatic event [82]. Concerning the inflammatory markers, increased levels of norepinephrine promote the production of proinflammatory cytokines; whereas, in homeostatic states, cortisol is known to decrease the levels of proinflammatory cytokines after the initial stages of the stress response.[80, 82] These pathophysiological changes combined may be associated with the increased levels of proinflammatory markers described in this meta-analysis.

Furthermore, PTSD has been extensively associated with cardiovascular disease, being regarded as an independent risk factor for acute events, including stroke and acute coronary syndrome [83]. For instance, a meta-analysis assessed the association between incident coronary disease and PTSD in longitudinal studies, describing that the risk of coronary disease or cardiac-specific mortality was increased by 27%, after the adjustment of the estimate for specific covariates, including depression [84]. One of the potential explanatory physiological mechanisms for this association is the link between PTSD and the above-mentioned proinflammatory state [83]. Likewise, atherosclerosis, which is intimately connected with coronary syndrome and other cardiac-related

outcomes, is linked with a chronic inflammatory state by strong empirical and clinical evidence.[85] Therefore, the results of the present meta-analysis contributes to the evidence on the connection between PTSD and cardiovascular disease.

In terms of treatment, patients with PTSD have few pharmacological options to rely on, with trauma-focused psychological treatments receiving the highest recommendations in treatment guidelines, and selective serotonin reuptake inhibitors (SSRIs) usually being regarded as the most effective pharmacological options available [86]. Nevertheless, up to 70% of patients with PTSD are considered to present some level of treatment-resistance, failing to respond to these treatment options [87]. These trends highlight the need for novel strategies of treatment, including new targets of pharmacotherapy, such as the inflammatory markers described in this systematic review [88]. To date, only animal models of PTSD have explored inflammation as a treatment target, describing promising results [89, 90].

One of the main findings of this study is the significantly higher concentration of CRP in the serum of patients with PTSD compared with healthy controls. In our previous meta-analysis, this finding was not statistically significant [8]. Such a difference may be attributed to a larger number of studies included in the analysis, which had larger samples. On the one hand, CRP is the most sensitive indicator of inflammation in the organism, being widely used as a marker of infection, inflammatory reactions, chronic disease progression, and treatment response [88, 91]. On the other hand, it is a nonspecific biomarker, which has been shown to be significantly increased in patients with depressive disorders, anxiety disorders, suicidality, substance misuse, and cardiovascular disease [55, 92–96]. Furthermore, it is not known whether elevated CRP is a marker of PTSD and its underlying physiopathology or a marker of increased risk for developing PTSD [97]. For instance, a large longitudinal all-male study described that increased baseline plasma CRP levels significantly predicted post-deployment PTSD symptoms [98]. Nevertheless, this trend was not observed in another longitudinal study, in which CRP was not a significant predictor of PTSD development in an all-female sample of nurses [99]. These findings may be partially explained by differences in gender, age, or even sample size. Moreover, the value of CRP as a prognostic marker in patients with PTSD is yet to unfold. However, as suggested in a prospective cohort study of Veterans, increased baseline CRP serum levels significantly predicted a worse course of PTSD in the follow-up [36]. Another cross-sectional study, with an all-female small sample size, described that women who recovered from PTSD present similar concentrations of CRP to healthy controls, and both groups presented CRP levels significantly lower than women with current PTSD [39]. Nevertheless, further evidence from longitudinal

studies is needed to elucidate the direction of the relationship between CRP and PTSD, and the potential role of CRP in the clinical care of patients with PTSD.

Similarly to what was reported by Passos et al in 2015 [8], the present updated meta-analysis found that IL-6 and TNF-α levels were significantly higher in PTSD patients in comparison with controls. On the one hand, IL-6 is one of the most studied inflammatory markers in PTSD, with most studies consistently pointing to increased levels of this cytokine relative to controls [80]. On the other hand, the evidence on TNF-α levels is more conflicting; for instance, the 2015 meta-analysis described that the levels of this inflammatory marker was increased only in those who were medication free and in the subgroup meta-analysis in which authors excluded patients with comorbid major depression [8]. Both inflammatory markers present a variety of functions in the human homeostasis, playing important roles in immune activation, hematopoiesis and inflammation; also presenting implications in the pathophysiology of several chronic conditions [100–102]. Furthermore, there is evidence that IL-6 and TNF-α may influence neural plasticity, processes of learning and memory, as well as neurogenesis, which may be associated with the activation of microglia and astrocytes in the brain, potentially leading to neurodegeneration and decreased gray-matter volume [80, 103, 104].

Oxidative stress may also be increased in patients with PTSD [27, 88, 105]. Oxidative stress is a fundamental biological process, also induced by inflammation, that produces cellular damage due to an imbalance between levels of antioxidants and free radicals [88, 105]. It is intimately connected with neurodegeneration, aging, and implicated in the pathogenesis of several chronic conditions [88]. Most studies investigating oxidative stress in patients with PTSD described reduced levels and activity of antioxidant enzymes, differences in expression of oxidative stress-related genes, as well as higher levels of other specific biomarkers of oxidative stress in these patients [27, 106–108]. Possibly, the traumatic experience itself responds by increasing oxidative stress. Nevertheless, a cross-sectional study described significantly decreased paraoxonase-1 activity and elevated malondialdehyde concentration in earthquake-exposed individuals with PTSD in comparison with healthy controls; in the same study, such differences were not significant between healthy controls and earthquake survivors who did not develop PTSD [27]. Considering this context, our study might have been underpowered for detecting increased oxidative stress markers in patients with PTSD. Therefore, future studies with larger samples are needed to investigate the levels of these markers and the role of this biological process in PTSD, including the investigation of potential new treatment strategies to reduce the impact of such changes [105].

As mentioned in the introduction, a similar systematic review and meta-analysis was published in 2020, also investigating immune biomarkers in patients with PTSD [14]. The authors searched only for English-language papers, retrieving 2606 references from three databases, and including 40 studies in their research [14]. In their analysis, patients with PTSD presented significantly higher levels of CRP, TNF-α, IL-6, IL-1β, IL-2, white blood cells, and IFN-γ in comparison with healthy controls. Conversely, our investigation found only concentrations of CRP, IL-6, and TNF-α to be significantly increased in patients with PTSD; in addition to IL-1β levels almost reaching the threshold for significance. Such differences may be explained by the strengths that our investigation presents in comparison with their systematic review [14]. We performed a more comprehensive search, retrieving 28,008 abstracts from five different databases, including references published in any language, which yielded a total of 54 studies for the meta-analysis, corresponding to 8,394 participants. In addition, our search is more up-to-date since it covered the period up to October 6, 2021, whereas their study covered up to January 31, 2019. Our group also made an exhaustive effort to acquire data by contacting the authors. There is no information concerning registration of their systematic review's protocol on PROSPERO or a similar platform, nor did they describe any type of quality assessment procedure applied to the included studies [14]. The data analysis procedure applied in our study is also more robust, with the use of the leave-one-out procedure and the Duval and Tweedie's trim-and-fill method when applicable. Their study did not investigate oxidative stress markers' presence in PTSD; also not investigating the effect of type of trauma, illness duration and severity, as well as blood fraction assessed as sources of heterogeneity in meta-analyses [14]. Nevertheless, white blood cells were not explored in our study.

Our study presents some limitations. High levels of between-study heterogeneity were recorded for most cytokine variables measured in our analysis. According to the results of univariate meta-regression analyses, methodological variables, such as type of essay and blood fraction investigated, explained between-study heterogeneity for IL-1β, IL-6, and TNF-α. Length of illness significantly explained heterogeneity for IL-6, IL-10, CRP, and TNF-α. Duration of illness was negatively associated with the IL-6 levels, and positively associated with IL-10, CRP and TNF-α levels. Lastly, war trauma was negatively associated with TNF-α levels. Unexplained heterogeneity could be related to other factors such as body mass index, smoking status, physical activity, blood pressure, alcohol consumption, genetics, or any combination of these variables.[80] All these variables are related to inflammatory changes, but most included studies did not report them. Additionally, it is important to highlight that meta-analyses of observational studies usually describe high between-study heterogeneity, mainly in terms of methodology, population, and settings, which differ substantially across included studies.[109] This aspect may compromise the interpretation of synthesized estimates. Another limitation of our study was the small number of

studies in the meta-regression and subgroup analyses for some cytokines. In addition, as mentioned earlier, in the evaluation of statistical power in meta-analysis of the investigated inflammatory markers, 17 out of 20 meta-analytic models presented statistical power lower than 0.8, indicating that most analyses of this study are underpowered. Notably, 20 studies included in our meta-analysis allowed controls possibly exposed to trauma but without PTSD in the healthy control group. Although those controls did not have any psychiatric or physical illness, we do not know to what extent exposure to trauma can trigger long-term changes in inflammatory markers in healthy individuals, even if they have not developed PTSD.

In summary, the contribution of our study was to clarify results reported previously, showing that PTSD is associated with a pattern of immune activation characterized by increased levels of CRP, IL-6, and TNF-α. The importance of this research lies in identifying peripheral biomarkers associated with PTSD, potentially establishing early diagnoses, monitoring treatment results, and providing new targets for therapeutic interventions.

4. Acknowledgments

TLP has received a scholarship from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). JVP has received a scholarship from CNPq (Brazilian National Council for Scientific and Technological Development), Brazil. AOS has received a scholarship from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). ASM has received a scholarship from Institutional Scientific Initiation Scholarship Program (PIBIC) with support from CNPq and Universidade Federal do Rio Grande do Sul, Brazil. VRL has received a scholarship from Federal University of Rio Grande do Sul Scientific Initiation Program (BIC-UFRGS). APA has received a scholarship from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). ARB receives scholarships and support from FAPESP, the Brazilian National Council of Scientific Development (CNPq-1B), University of São Paulo Medical School (FMUSP), the UK Academy of Medical Sciences (Newton Advanced Fellowship), and the International Health Cohort Consortium (IHCC). FK has received grants from Instituto Nacional de Ciência e Tecnologia – Conselho Nacional de Desenvolvimento Científico e Tecnológico, and the Canada Foundation for Innovation (CFI). ICP is CNPq research fellow and supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Brazil and by FIPE (Fundo de Incentivo à Pesquisa e Eventos) from Hospital de Clínicas de Porto Alegre, Brazil. This work was supported by a São Paulo Research State Foundation (FAPESP) grant (20/05441-9).

5. Conflict of interests

ICP has received research support from or served as consultant, adviser or speaker for Lundbeck, EMS, Libbs, and receives authorship royalties from Springer Nature and ArtMed.

Supplementary information is available at MP's website.

6. References

1. Yehuda R, Hoge CW, McFarlane AC, Vermetten E, Lanius RA, Nievergelt CM, et al. Post-traumatic stress disorder. Nat Rev Dis Primers. 2015; 1:15057.

2. Tortella-Feliu M, Fullana MA, Pérez-Vigil A, Torres X, Chamorro J, Littarelli SA, et al. Risk factors for posttraumatic stress disorder: An umbrella review of systematic reviews and meta-analyses. Neurosci Biobehav Rev. 2019; 107:154–165.

3. Koenen KC, Ratanatharathorn A, Ng L, McLaughlin KA, Bromet EJ, Stein DJ, et al. Posttraumatic stress disorder in the World Mental Health Surveys. Psychol Med. 2017; 47:2260–2274.

4. Gradus JL. Posttraumatic Stress Disorder and Death from Suicide. Curr Psychiatry Rep. 2018; 20:98.

5. Lohr JB, Palmer BW, Eidt CA, Aailaboyina S, Mausbach BT, Wolkowitz OM, et al. Is Post-Traumatic Stress Disorder Associated with Premature Senescence? A Review of the Literature. Am J Geriatr Psychiatry. 2015; 23:709–725.

6. Dams J, Rimane E, Steil R, Renneberg B, Rosner R, König H-H. Health-Related Quality of Life and Costs of Posttraumatic Stress Disorder in Adolescents and Young Adults in Germany. Front Psychiatry. 2020; 11:697.

7. Michopoulos V, Powers A, Gillespie CF, Ressler KJ, Jovanovic T. Inflammation in Fear- and Anxiety-Based Disorders: PTSD, GAD, and Beyond. Neuropsychopharmacology. 2017; 42:254–270.

8. Passos IC, Vasconcelos-Moreno MP, Costa LG, Kunz M, Brietzke E, Quevedo J, et al. Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. The Lancet Psychiatry. 2015; 2:1002–1012.

9. Roberts AL, Malspeis S, Kubzansky LD, Feldman CH, Chang S-C, Koenen KC, et al. Association of Trauma and Posttraumatic Stress Disorder With Incident Systemic Lupus Erythematosus in a Longitudinal Cohort of Women. Arthritis Rheumatol. 2017; 69:2162–2169.

10. Song H, Fang F, Tomasson G, Arnberg FK, Mataix-Cols D, Fernández de la Cruz L, et al. Association of Stress-Related Disorders with Subsequent Autoimmune Disease. JAMA. 2018; 319:2388–2400.

11. Miller MW, Sadeh N. Traumatic stress, oxidative stress and post-traumatic stress disorder: neurodegeneration and the accelerated-aging hypothesis. Mol Psychiatry. 2014; 19:1156–1162.

12. Yang R, Wu GWY, Verhoeven JE, Gautam A, Reus VI, Kang JI, et al. A DNA methylation clock associated with age-related illnesses and mortality is accelerated in men with combat PTSD. Mol Psychiatry. 2020. 7 May 2020. https://doi.org/10.1038/s41380-020-0755-z.

13. Miller MW, Wolf EJ, Sadeh N, Logue M, Spielberg JM, Hayes JP, et al. A novel locus in the oxidative stress-related gene ALOX12 moderates the association between PTSD and thickness of the prefrontal cortex. Psychoneuroendocrinology. 2015; 62:359–365.

14. Yang J-J, Jiang W. Immune biomarkers alterations in post-traumatic stress disorder: A systematic review and meta-analysis. J Affect Disord. 2020; 268:39–46.

15. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6: e1000097.

16. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000; 283:2008–2012.

17. Ottawa Hospital Research Institute. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 13 January 2021.

18. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. J Stat Softw. 2010; 36:1–48.

19. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane Handbook for Systematic Reviews of Interventions. John Wiley & Sons; 2019.

20. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002. 2002.

21. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003; 327:557–560.

22. Higgins JPT, Green S. Recommendations on testing for funnel plot asymmetry. Cochrane Handbook for Systematic Reviews of Interventions Version. 2011;5.

23. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315:629–634.

24. Team RC. R: A Language and Environment for Statistical Computing. 887 R Foundation for Statistical Computing, Vienna, Austria. URL Https://www. 2017. 2017.

25. Spivak B, Shohat B, Mester R, Avraham S, Gil-Ad I, Bleich A, et al. Elevated levels of serum interleukin-1 beta in combat-related posttraumatic stress disorder. Biol Psychiatry. 1997; 42:345–348.

26. Muhtz C, Godemann K, von Alm C, Wittekind C, Goemann C, Wiedemann K, et al. Effects of chronic posttraumatic stress disorder on metabolic risk, quality of life, and stress hormones in aging former refugee children. J Nerv Ment Dis. 2011; 199:646–652.

27. Atli A, Bulut M, Bez Y, Kaplan İ, Özdemir PG, Uysal C, et al. Altered lipid peroxidation markers are related to post-traumatic stress disorder (PTSD) and not trauma itself in earthquake survivors. Eur Arch Psychiatry Clin Neurosci. 2016; 266:329–336.

28. Küffer A, Straus LD, Prather AA, Inslicht SS, Richards A, Shigenaga JK, et al. Altered overnight levels of pro-inflammatory cytokines in men and women with posttraumatic stress disorder. Psychoneuroendocrinology. 2019; 102:114–120.

29. Vidović A, Gotovac K, Vilibić M, Sabioncello A, Jovanović T, Rabatić S, et al. Repeated assessments of endocrine- and immune-related changes in posttraumatic stress disorder. Neuroimmunomodulation. 2011; 18:199–211.

30. Smith AK, Conneely KN, Kilaru V, Mercer KB, Weiss TE, Bradley B, et al. Differential immune system DNA methylation and cytokine regulation in post-traumatic stress disorder. Am J Med Genet B Neuropsychiatr Genet. 2011;156B:700–708.

31. Baker DG, Ekhator NN, Kasckow JW, Hill KK, Zoumakis E, Dashevsky BA, et al. Plasma and cerebrospinal fluid interleukin-6 concentrations in posttraumatic stress disorder. Neuroimmunomodulation. 2001; 9:209–217.

32. Ogłodek EA, Just MJ. The association between inflammatory markers (iNOS, HO-1, IL-33, MIP-1β) and depression with and without posttraumatic stress disorder. Pharmacol Rep. 2018; 70:1065–1072.

33. Ogłodek EA. Evaluation of ADMA, carbonyl groups, CAT and NKA in depressed patients with and without posttraumatic stress disorder. Pharmacol Rep. 2017; 69:730–737.

34. Ogłodek EA. The role of PON-1, GR, IL-18, and OxLDL in depression with and without posttraumatic stress disorder. Pharmacol Rep. 2017; 69:837–845.

35. Ogłodek EA. Changes in the concentrations of inflammatory and oxidative status biomediators (MIP-1 α, PMN elastase, MDA, and IL-12) in depressed patients with and without posttraumatic stress disorder. Pharmacol Rep. 2018; 70:110–118.

36. Eswarappa M, Neylan TC, Whooley MA, Metzler TJ, Cohen BE. Inflammation as a predictor of disease course in posttraumatic stress disorder and depression: A prospective analysis from the Mind Your Heart Study. Brain Behav Immun. 2019; 75:220–227.

37. Gill J, Vythilingam M, Page GG. Low cortisol, high DHEA, and high levels of stimulated TNF-alpha, and IL-6 in women with PTSD. J Trauma Stress. 2008; 21:530–539.

38. Gill J, Luckenbaugh D, Charney D, Vythilingam M. Sustained elevation of serum interleukin-6 and relative insensitivity to hydrocortisone differentiates posttraumatic stress disorder with and without depression. Biol Psychiatry. 2010; 68:999–1006.

39. Gill JM, Saligan L, Lee H, Rotolo S, Szanton S. Women in recovery from PTSD have similar inflammation and quality of life as non-traumatized controls. J Psychosom Res. 2013; 74:301–306.

40. Gola H, Engler H, Sommershof A, Adenauer H, Kolassa S, Schedlowski M, et al. Posttraumatic stress disorder is associated with an enhanced spontaneous production of pro-inflammatory cytokines by peripheral blood mononuclear cells. BMC Psychiatry. 2013; 13:40.

41. Guo M, Liu T, Guo J-C, Jiang X-L, Chen F, Gao Y-S. Study on serum cytokine levels in posttraumatic stress disorder patients. Asian Pac J Trop Med. 2012; 5:323–325.

42. Toft H, Bramness JG, Lien L, Abebe DS, Wampold BE, Tilden T, et al. PTSD patients show increasing cytokine levels during treatment despite reduced psychological distress. Neuropsychiatr Dis Treat. 2018; 14:2367–2378.

43. Söndergaard HP, Hansson L-O, Theorell T. The inflammatory markers C-reactive protein and serum amyloid A in refugees with and without posttraumatic stress disorder. Clin Chim Acta. 2004; 342:93–98.

44. Park J, Marvar PJ, Liao P, Kankam ML, Norrholm SD, Downey RM, et al. Baroreflex dysfunction and augmented sympathetic nerve responses during mental stress in veterans with post-traumatic stress disorder. J Physiol. 2017; 595:4893–4908.

45. Sumner JA, Chen Q, Roberts AL, Winning A, Rimm EB, Gilsanz P, et al. Cross-Sectional and Longitudinal Associations of Chronic Posttraumatic Stress Disorder With Inflammatory and Endothelial Function Markers in Women. Biol Psychiatry. 2017; 82:875–884.

46. Miller K, Driscoll D, Smith LM, Ramaswamy S. The Role of Inflammation in Late-Life Post-Traumatic Stress Disorder. Mil Med. 2017;182: e1815–e1818.

47. Oganesyan LP, Mkrtchyan GM, Sukiasyan SH, Boyajyan AS. Classic and alternative complement cascades in post-traumatic stress disorder. Bull Exp Biol Med. 2009; 148:859–861.

48. Jergović M, Tomičević M, Vidović A, Bendelja K, Savić A, Vojvoda V, et al. Telomere shortening and immune activity in war veterans with posttraumatic stress disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2014; 54:275–283.

49. Jergović M, Bendelja K, Savić Mlakar A, Vojvoda V, Aberle N, Jovanovic T, et al. Circulating levels of hormones, lipids, and immune mediators in post-traumatic stress disorder - a 3-month follow-up study. Front Psychiatry. 2015; 6:49.

50. Maes M, Lin AH, Delmeire L, Van Gastel A, Kenis G, De Jongh R, et al. Elevated serum interleukin-6 (IL-6) and IL-6 receptor concentrations in posttraumatic stress disorder following accidental man-made traumatic events. Biol Psychiatry. 1999; 45:833–839.

51. Miller MW, Maniates H, Wolf EJ, Logue MW, Schichman SA, Stone A, et al. CRP polymorphisms and DNA methylation of the AIM2 gene influence associations between trauma exposure, PTSD, and C-reactive protein. Brain Behav Immun. 2018; 67:194–202.

52. Neupane SP, Bramness JG, Lien L. Comorbid post-traumatic stress disorder in alcohol use disorder: relationships to demography, drinking and neuroimmune profile. BMC Psychiatry. 2017; 17:312.

53. Jiang D, Jiang S, Gong F, Yuan F, Zhao P, He X, et al. Correlation between Depression, Posttraumatic Stress Disorder, and Inflammatory Factors in Patients with Severe Burn Injury. Am Surg. 2018; 84:1350–1354.

54. Spitzer C, Barnow S, Völzke H, Wallaschofski H, John U, Freyberger HJ, et al. Association of posttraumatic stress disorder with low-grade elevation of C-reactive protein: evidence from the general population. J Psychiatr Res. 2010; 44:15–21.

55. Lindqvist D, Wolkowitz OM, Mellon S, Yehuda R, Flory JD, Henn-Haase C, et al. Proinflammatory milieu in combat-related PTSD is independent of depression and early life stress. Brain Behav Immun. 2014; 42:81–88.

56. Lindqvist D, Dhabhar FS, Mellon SH, Yehuda R, Grenon SM, Flory JD, et al. Increased pro-inflammatory milieu in combat related PTSD - A new cohort replication study. Brain Behav Immun. 2017; 59:260–264.

57. Hoge EA, Brandstetter K, Moshier S, Pollack MH, Wong KK, Simon NM. Broad spectrum of cytokine abnormalities in panic disorder and posttraumatic stress disorder. Depress Anxiety. 2009; 26:447–455.

58. Vidović A, Vilibić M, Sabioncello A, Gotovac K, Rabatić S, Folnegović-Šmalc V, et al. Changes in immune and endocrine systems in posttraumatic stress disorder - prospective study. Acta Neuropsychiatr. 2009;21 Suppl 2:46–50.

59. de Oliveira JF, Wiener CD, Jansen K, Portela LV, Lara DR, Souza LD de M, et al. Serum levels of interleukins IL-6 and IL-10 in individuals with posttraumatic stress disorder in a population-based sample. Psychiatry Res. 2018; 260:111–115.

60. Dalgard C, Eidelman O, Jozwik C, Olsen CH, Srivastava M, Biswas R, et al. The MCP-4/MCP-1 ratio in plasma is a candidate circadian biomarker for chronic post-traumatic stress disorder. Transl Psychiatry. 2017;7: e1025.

61. Newton TL, Fernandez-Botran R, Miller JJ, Burns VE. Interleukin-6 and soluble interleukin-6 receptor levels in posttraumatic stress disorder: associations with lifetime diagnostic status and psychological context. Biol Psychol. 2014; 99:150–159.

62. O'Donovan A, Ahmadian AJ, Neylan TC, Pacult MA, Edmondson D, Cohen BE. Current posttraumatic stress disorder and exaggerated threat sensitivity associated with elevated inflammation in the Mind Your Heart Study. Brain Behav Immun. 2017; 60:198–205.

63. Olam N, Yasar AB. The relation of trauma type on the levels of plasma C-reactive protein in patients with post-traumatic stress disorder/Travma sonrasi stres bozuklugu hastalarinda travma tipinin plazma C-reaktif protein duzeyi ile iliskisi. Anadolu Psikiyatri Dergisi. 2019; 20:573–581.

64. Tucker P, Ruwe WD, Masters B, Parker DE, Hossain A, Trautman RP, et al. Neuroimmune and cortisol changes in selective serotonin reuptake inhibitor and placebo treatment of chronic posttraumatic stress disorder. Biol Psychiatry. 2004; 56:121–128.

65. Powers A, Dixon HD, Conneely K, Gluck R, Munoz A, Rochat C, et al. The differential effects of PTSD, MDD, and dissociation on CRP in trauma-exposed women. Compr Psychiatry. 2019; 93:33–40.

66. Imai R, Hori H, Itoh M, Lin M, Niwa M, Ino K, et al. Inflammatory markers and their possible effects on cognitive function in women with posttraumatic stress disorder. J Psychiatr Res. 2018; 102:192–200.

67. Imai R, Hori H, Itoh M, Lin M, Niwa M, Ino K, et al. Relationships of blood proinflammatory markers with psychological resilience and quality of life in civilian women with posttraumatic stress disorder. Sci Rep. 2019; 9:17905.

68. von Känel R, Hepp U, Kraemer B, Traber R, Keel M, Mica L, et al. Evidence for low-grade systemic proinflammatory activity in patients with posttraumatic stress disorder. J Psychiatr Res. 2007; 41:744–752.

69. von Känel R, Begré S, Abbas CC, Saner H, Gander M-L, Schmid J-P. Inflammatory biomarkers in patients with posttraumatic stress disorder caused by myocardial infarction and the role of depressive symptoms. Neuroimmunomodulation. 2010; 17:39–46.

70. Song Y, Zhou D, Guan Z, Wang X. Disturbance of serum interleukin-2 and interleukin-8 levels in posttraumatic and non-posttraumatic stress disorder earthquake survivors in northern China. Neuroimmunomodulation. 2007; 14:248–254.

71. Wang Z, Mandel H, Levingston CA, Young MRI. An exploratory approach demonstrating immune skewing and a loss of coordination among cytokines in plasma and saliva of Veterans with combat-related PTSD. Hum Immunol. 2016; 77:652–657.

72. Wang W, Wang L, Xu H, Cao C, Liu P, Luo S, et al. Characteristics of pro- and anti-inflammatory cytokines alteration in PTSD patients exposed to a deadly earthquake. J Affect Disord. 2019; 248:52–58.

73. Teche SP, Rovaris DL, Aguiar BW, Hauck S, Vitola ES, Bau CHD, et al. Resilience to traumatic events related to urban violence and increased IL10 serum levels. Psychiatry Res. 2017; 250:136–140.

74. Chen T, Guo M, Gao Y, Chen F, Guo J, Liu T, et al. A comparative study on the levels of serum cytokines and cortisol among post-traumatic stress disorder patients of Li and Han ethnicities in Hainan. Chin Med J. 2014; 127:2771–2774.

75. Tezcan E, Atmaca M, Kuloglu M, Ustundag B. Free radicals in patients with post-traumatic stress disorder. Eur Arch Psychiatry Clin Neurosci. 2003; 253:89–91.

76. McD Young R, Lawford B, Mellor R, Morris CP, Voisey J, PTSD Initiative. Investigation of C-reactive protein and AIM2 methylation as a marker for PTSD in Australian Vietnam veterans. Gene. 2021; 803:145898.

77. Mehta ND, Stevens JS, Li Z, Gillespie CF, Fani N, Michopoulos V, et al. Inflammation, reward circuitry and symptoms of anhedonia and PTSD in trauma-exposed women. Soc Cogn Affect Neurosci. 2020; 15:1046–1055.

78. Yang, L., Wu, X., Wang, X., Hu, S., Liu, G., Ma, W., and Zhang, Y. Controlled study on serum cytokine levels in stress-related disorders. Chinese Mental Health Journal. 2001; 15:295–296.

79. Luchini C, Stubbs B, Solmi M, Veronese N. Assessing the quality of studies in meta-analyses: Advantages and limitations of the Newcastle Ottawa Scale. World J Metaanal. 2017; 5:80.

80. Hori H, Kim Y. Inflammation and post-traumatic stress disorder. Psychiatry Clin Neurosci. 2019; 73:143–153.

81. Daskalakis NP, Cohen H, Nievergelt CM, Baker DG, Buxbaum JD, Russo SJ, et al. New translational perspectives for blood-based biomarkers of PTSD: From glucocorticoid to immune mediators of stress susceptibility. Exp Neurol. 2016; 284:133–140.

82. Daskalakis NP, Lehrner A, Yehuda R. Endocrine aspects of post-traumatic stress disorder and implications for diagnosis and treatment. Endocrinol Metab Clin North Am. 2013; 42:503–513.

83. Edmondson D, von Känel R. Post-traumatic stress disorder and cardiovascular disease. Lancet Psychiatry. 2017; 4:320–329.

84. Edmondson D, Kronish IM, Shaffer JA, Falzon L, Burg MM. Posttraumatic stress disorder and risk for coronary heart disease: a meta-analytic review. Am Heart J. 2013; 166:806–814.

85. Wolf D, Ley K. Immunity and Inflammation in Atherosclerosis. Circ Res. 2019; 124:315–327.

86. Hamblen JL, Norman SB, Sonis JH, Phelps AJ, Bisson JI, Nunes VD, et al. A guide to guidelines for the treatment of posttraumatic stress disorder in adults: An update. Psychotherapy. 2019; 56:359–373.

87. Starke JA, Stein DJ. Management of Treatment-Resistant Posttraumatic Stress Disorder. Current Treatment Options in Psychiatry. 2017; 4:387–403.

88. Miller MW, Lin AP, Wolf EJ, Miller DR. Oxidative Stress, Inflammation, and Neuroprogression in Chronic PTSD. Harv Rev Psychiatry. 2018; 26:57–69.

89. Ebenezer PJ, Wilson CB, Wilson LD, Nair AR, J F. The Anti-Inflammatory Effects of Blueberries in an Animal Model of Post-Traumatic Stress Disorder (PTSD). PLoS One. 2016;11: e0160923.

90. Monsey MS, Gerhard DM, Boyle LM, Briones MA, Seligsohn M 'ayan, Schafe GE. A diet enriched with curcumin impairs newly acquired and reactivated fear memories. Neuropsychopharmacology. 2015; 40:1278–1288.

91. Wu Y, Potempa LA, El Kebir D, Filep JG. C-reactive protein and inflammation: conformational changes affect function. Biol Chem. 2015; 396:1181–1197.

92. Chen X, Pu J, Liu Y, Tian L, Chen Y, Gui S, et al. Increased C-reactive protein concentrations were associated with suicidal behavior in patients with depressive disorders: a meta-analysis. Psychiatry Res. 2020; 292:113320.

93. Costello H, Gould RL, Abrol E, Howard R. Systematic review and meta-analysis of the association between peripheral inflammatory cytokines and generalised anxiety disorder. BMJ Open. 2019;9: e027925.

94. Osimo EF, Baxter LJ, Lewis G, Jones PB, Khandaker GM. Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. Psychol Med. 2019; 49:1958–1970.

95. Zhou J, Lu Y, Wang S, Chen K. Association between serum amyloid A levels and coronary heart disease: a systematic review and meta-analysis of 26 studies. Inflamm Res. 2020; 69:331–345.

96. Costello EJ, Copeland WE, Shanahan L, Worthman CM, Angold A. C-reactive protein and substance use disorders in adolescence and early adulthood: a prospective analysis. Drug Alcohol Depend. 2013; 133:712–717.

97. Friend SF, Nachnani R, Powell SB, Risbrough VB. C-Reactive Protein: Marker of risk for post-traumatic stress disorder and its potential for a mechanistic role in trauma response and recovery. Eur J Neurosci. 2020. 1 November 2020. https://doi.org/10.1111/ejn.15031.

98. Eraly SA, Nievergelt CM, Maihofer AX, Barkauskas DA Biswas N, Agorastos A, et al. Assessment of plasma C-reactive protein as a biomarker of posttraumatic stress disorder risk. JAMA Psychiatry. 2014; 71:423–431.

99. Sumner JA, Chen Q, Roberts AL, Winning A, Rimm EB, Gilsanz P, et al. Posttraumatic stress disorder onset and inflammatory and endothelial function biomarkers in women. Brain Behav Immun. 2018; 69:203–209.

100. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol. 2014;6: a016295.

101. Hunter CA, Jones SA. IL-6 as a keystone cytokine in health and disease. Nat Immunol. 2015; 16:448–457.

102. Winsauer C, Kruglov AA, Chashchina AA, Drutskaya MS, Nedospasov SA. Cellular sources of pathogenic and protective TNF and experimental strategies based on utilization of TNF humanized mice. Cytokine Growth Factor Rev. 2014; 25:115–123.

103. Marsland AL, Gianaros PJ, Abramowitch SM, Manuck SB, Hariri AR. Interleukin-6 covaries inversely with hippocampal grey matter volume in middle-aged adults. Biol Psychiatry. 2008; 64:484–490.

104. Baune BT, Konrad C, Grotegerd D, Suslow T, Ohrmann P, Bauer J, et al. Tumor necrosis factor gene variation predicts hippocampus volume in healthy individuals. Biol Psychiatry. 2012; 72:655–662.

105. Maier A, Dharan A, Oliver G, Berk M, Redston S, Back SE, et al. A multi-centre, double-blind, 12-week, randomized, placebo-controlled trial to assess the efficacy of adjunctive N-Acetylcysteine for treatment-resistant PTSD: a study protocol. BMC Psychiatry. 2020; 20:397.

106. Borovac Štefanović L, Kalinić D, Mimica N, Beer Ljubić B, Aladrović J, Mandelsamen Perica M, et al. Oxidative status and the severity of clinical symptoms in patients with post-traumatic stress disorder. Ann Clin Biochem. 2015; 52:95–104.

107. Zieker J, Zieker D, Jatzko A, Dietzsch J, Nieselt K, Schmitt A, et al. Differential gene expression in peripheral blood of patients suffering from post-traumatic stress disorder. Mol Psychiatry. 2007; 12:116–118.

108. Tylee DS, Chandler SD, Nievergelt CM, Liu X, Pazol J, Woelk CH, et al. Blood-based gene-expression biomarkers of post-traumatic stress disorder among deployed marines: A pilot study. Psychoneuroendocrinology. 2015; 51:472–494.

109. Metelli S, Chaimani A. Challenges in meta-analyses with observational studies. Evid Based Ment Health. 2020; 23:83–87.

7. Figures

Figure 1. Study selection flowchart.

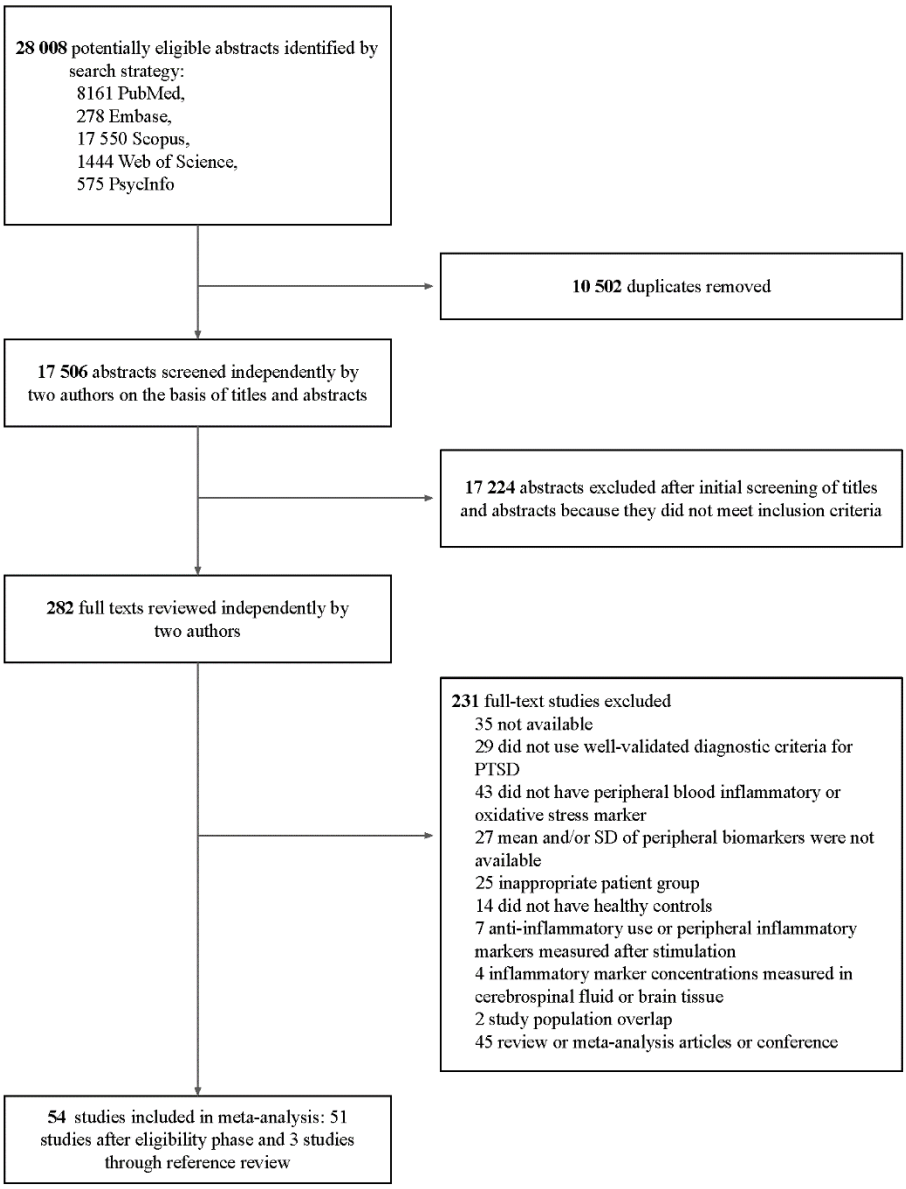


Figure 1. Study selection

Figure 2. Subgroup meta-analysis of interleukin 6 with comorbid MDD as a predictor. SMD: standardized mean difference; PTSD: post-traumatic stress disorder; MDD: major depressive disorder; RE: random effects; SMD: Standardized Mean Difference.

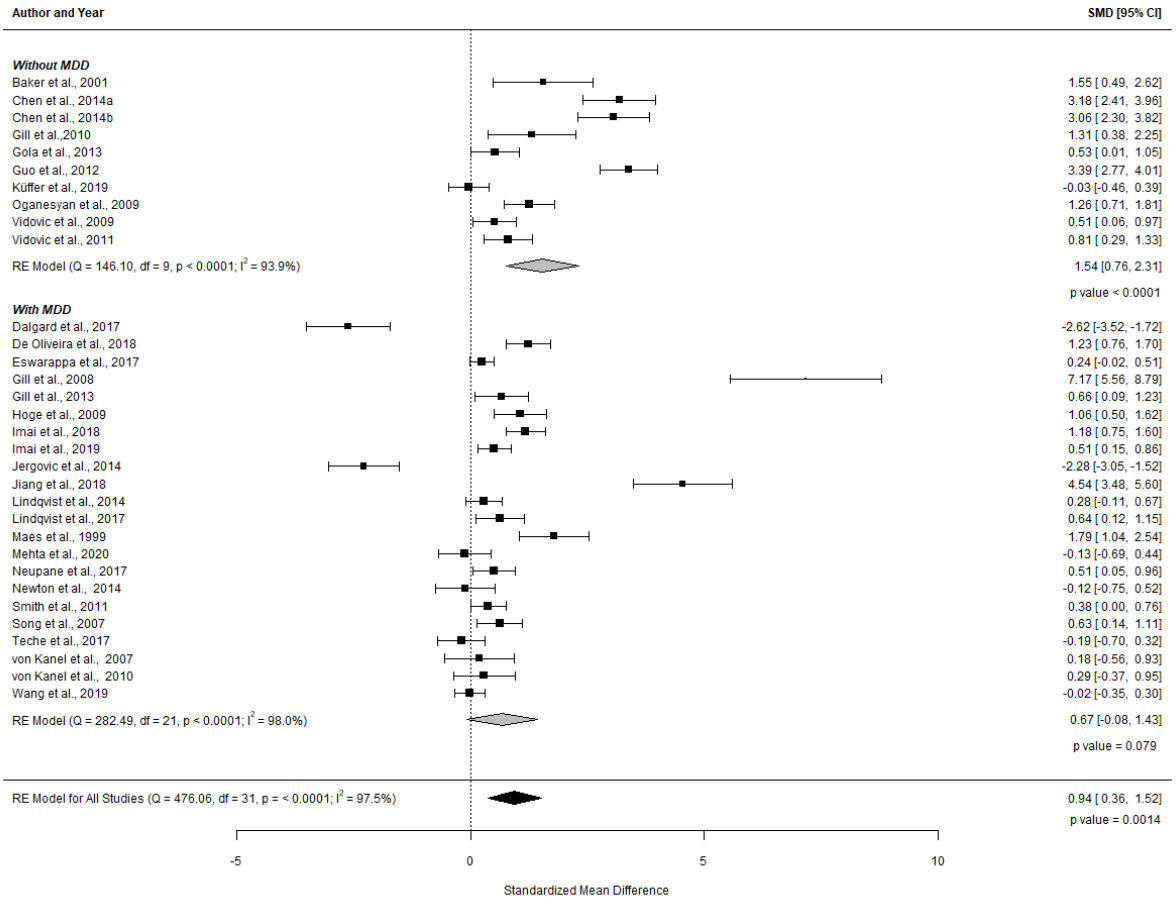


Figure 3. Subgroup meta-analysis of Tumor Necrosis Factor-α with comorbid MDD as a predictor. MDD: major depressive disorder; RE: random effects. SMD: Standardized Mean Difference.

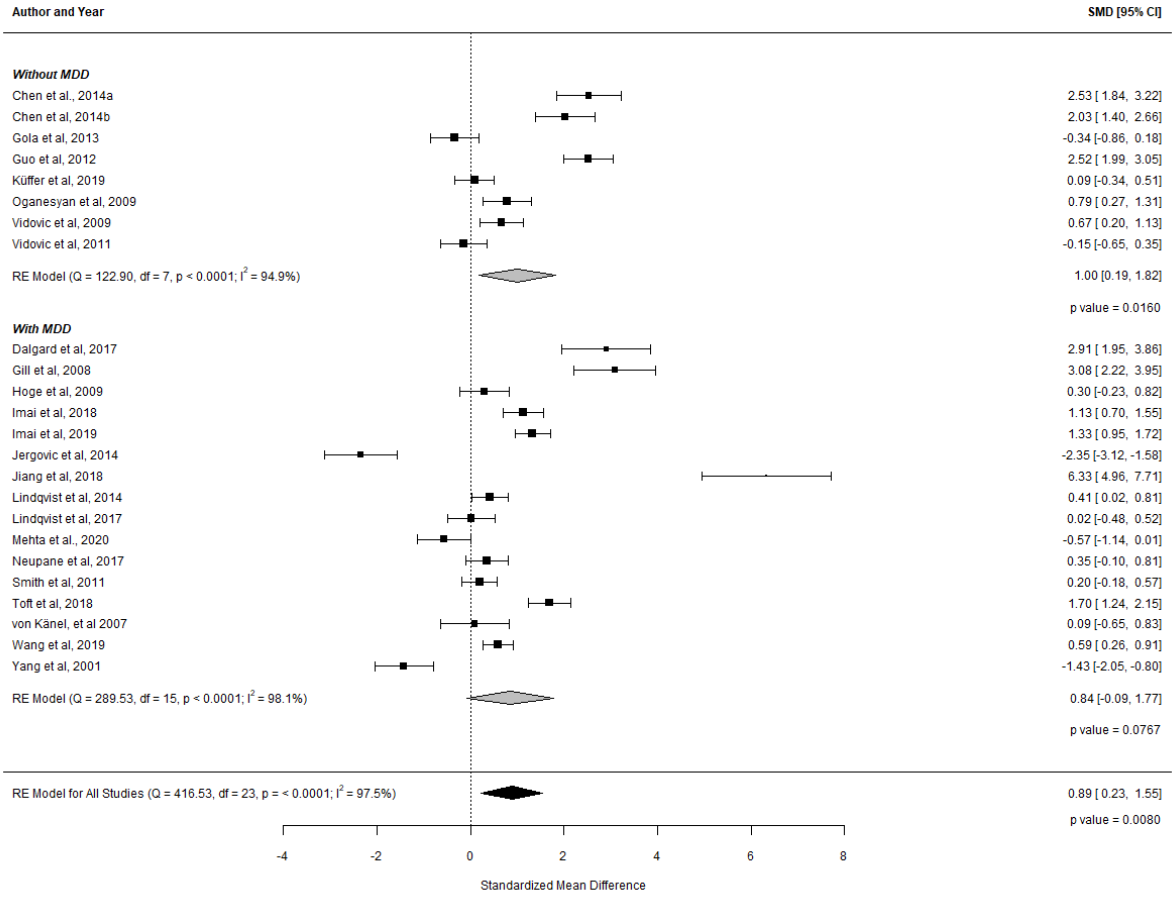

Author and Year
SMD [95% CI]
Without MDD
Chen et al., 2014a
2.53 [1.84, 3.22]
Chen et al, 2014b
2.03 [1.40, 2.66]
Gola et al, 2013
-0.34 [-0.86, 0.18]
Guo et al, 2012
2.52 [1.99, 3.05]
Küffer et al, 2019
0.09 [-0.34, 0.51]
Oganesyan et al, 2009
0.79 [0.27, 1.31]
Vidovic et al, 2009
0.67 [0.20, 1.13]
Vidovic et al, 2011
-0.15 [-0.65, 0.35]
RE Model (Q = 122.90, df = 7, p < 0.0001; I² = 94.9%)
1.00 [0.19, 1.82]
p value = 0.0160
With MDD
Dalgard et al, 2017
2.91 [1.95, 3.86]
Gill et al, 2008
3.08 [2.22, 3.95]
Hoge et al, 2009
0.30 [-0.23, 0.82]
Imai et al, 2018
1.13 [0.70, 1.55]
Imai et al, 2019
1.33 [0.95, 1.72]
Jergovic et al, 2014
-2.35 [-3.12, -1.58]
Jiang et al, 2018
6.33 [4.96, 7.71]
Lindqvist et al, 2014
0.41 [0.02, 0.81]
Lindqvist et al, 2017
0.02 [-0.48, 0.52]
Mehta et al., 2020
-0.57 [-1.14, 0.01]
Neupane et al, 2017
0.35 [-0.10, 0.81]
Smith et al, 2011
0.20 [-0.18, 0.57]
Toft et al, 2018
1.70 [1.24, 2.15]
von Känel, et al 2007
0.09 [-0.65, 0.83]
Wang et al, 2019
0.59 [0.26, 0.91]
Yang et al, 2001
-1.43 [-2.05, -0.80]
RE Model (Q = 289.53, df = 15, p < 0.0001; I² = 98.1%)
0.84 [-0.09, 1.77]
p value = 0.0767
RE Model for All Studies (Q = 416.53, df = 23, p = < 0.0001; I² = 97.5%)
0.89 [0.23, 1.55]
p value = 0.0080
-4
-2
0
2
4
6
8
Standardized Mean Difference

Figure 4: Subgroup meta-analysis of interleukin 6 with use of psychotropic medications as a predictor. PTSD: post-traumatic stress disorder; MDD: major depressive disorder; RE: random effects. SMD: Standardized Mean Difference.

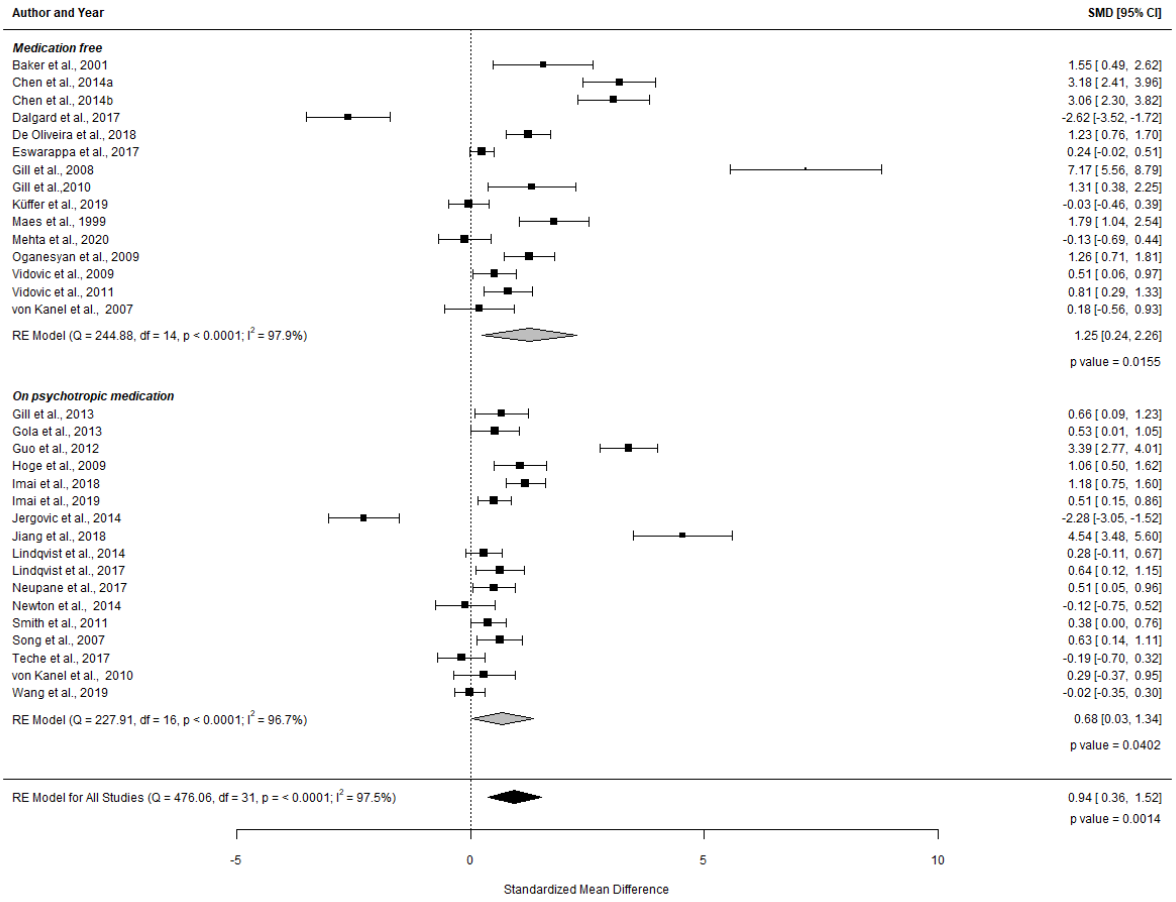
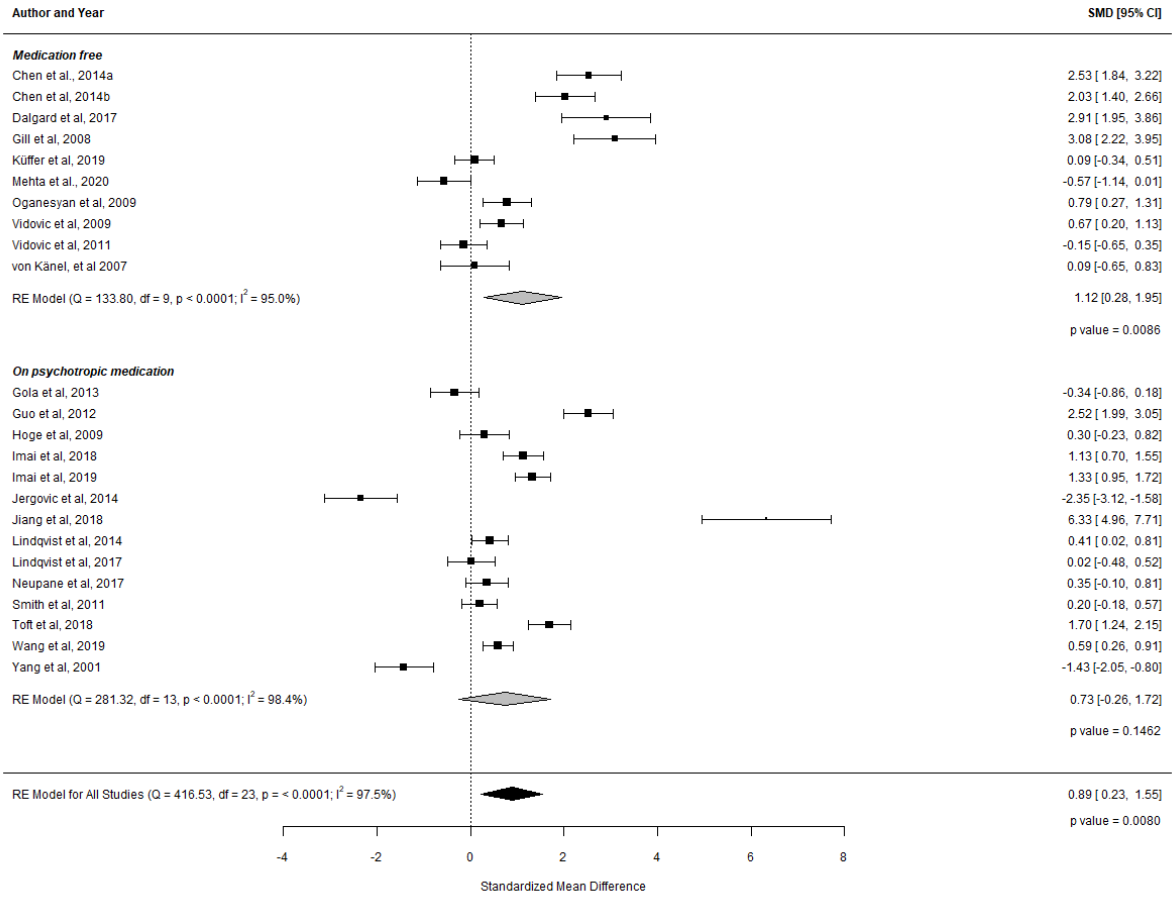


Figure 5: Subgroup meta-analysis of Tumor Necrosis Factor-α with use of psychotropic medications as a predictor. RE: random effects. SMD: Standardized Mean Difference.



8. Tables

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

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

Study, Year	Inflammatory markers /Oxidative stress markers assessed	N		Age (total sample mean/SD)	CAPS score (Mean/ SD)	Blood fraction	Medication-free	Excluded MDD
		PTSD	Controls					
Spivak, 1997[25]	IL-1β, sIL-2R	19	19	28.5/NA	NA/NA	Serum	Yes	Yes
Muhtz, 2011 [26]	hsCRP	25	25	71/NA	NA/NA	Serum	No	No
Atli, 2016[27]	MDA, PON-1	32	38	33/NA	NA/NA	Serum	NA	NA
Küffer, 2019[28]	IL-6, TNF-α	42	43	30.55/NA	54/14.91	Serum	Yes	Yes
Vidovic,	IL-6, TNF-	39	25	41.91/N	58.7/7.	Serum	Yes	Yes

2011[29]	α			A	5			
Smith, 2011[30]	IL-6, IFNa, IL-1β, IL-2, TNF-α, IL-4 e IL-10	50	60	41.32/NA	93.24/NA	Plasma	NA	No
Baker, 2001[31]	IL-6	11	8	41.82/NA	82.1/6.7	Plasma	Yes	Yes
Oglodek, 2018[a][32]	MIP-1β	60	40	45.2/4.5	NA/NA	Plasma	Yes	No
Oglodek, 2017[a][33]	CAT	60	40	45.2/4.5	NA/NA	Plasma	Yes	No
Oglodek, 2017[b][34]	PON-1, IL-18	60	40	45.2/4.5	NA/NA	Plasma	Yes	No
Oglodek, 2018[b][35]	MIP-1α, MDA, IL-12	60	40	45.2/4.5	NA/NA	Plasma	Yes	No
Eswarappa, 2019[36]	CRP, IL-6	64	396	56.6/10.9	NA/NA	Serum	Yes	No
Gill,	TNF-α, IL-	26	21	44.	NA/NA	NA	Yes	No

2008[37]	1β, IL-6			.3/NA				
Gill, 2010[38]	IL-6	9	14	34.39/NA	69/10	Plasma	Yes	No
Gill, 2013[39]	IL-6, CRP	26	24	34.81/NA	NA/NA	Plasma	No	Yes
Gola, 2013[40]	IL-6, IL-8, IL-10, TNF-α, MCP-1	35	25	31.14/NA	80/17.5	Plasma	No	Yes
Guo, 2012[41]	IL-2, IL-4, IL-6, IL-8, IL-10, TNF-α	50	50	41.5/13.04	NA/NA	Serum	NA	Yes
Toft, 2018[42]	IL-1β, IL-1R, MCP-1, TNF-α	39	69	41.91/10.79	NA/NA	Serum	NA	No
Söndergaard, 2004 [43]	hsCRP	25	38	NA/NA	NA/NA	Serum	NA	No
Park, 2017 [44]	hsCRP, IL-2, IL-6	14	14	33.3/1.6	81/9	NA	NA	No

Sumner, 2017 [45]	CRP, TNF-α	174	175	43.45/4.7	NA/NA	Plasma	No	No
Miller, 2017 [46]	CRP	16	16	67.4/2.28	38.6/11.3	Serum	No	No
Oganesyan, 2009 [47]	TNF-α, IL-1β, IL-6	31	31	40.5/3.92	NA/NA	Serum	NA	Yes
Jergovic, 2014 [48]	IFN-γ, IL-4, IL-2, TNF-α, IL-6	30	17	NA/NA	56.7/14.8	Serum	NA	No
Jergovic, 2015 [49]	CRP, MIP-1α, IL-8, IL-1β, IL-2, TNF-α, IFN-γ, IL-4, IL-6	69	32	NA/NA	NA/NA	Serum	No	No
Maes, 1999 [50]	IL-6, sIL-6R, sIL-1RA	13	32	NA/NA	NA/NA	Serum	Yes	No
Miller, 2018 [51]	CRP	163	123	32.08/8.358	69.06/NA	Serum	NA	NA

Neupane, 2017 [52]	CRP, IL-1RA, IL-6, IL-10, TNF-α, IFN-γ	32	47	35.5/10.1	NA/NA	Serum	No	No
Jiang, 2018 [53]	IL-1β, IL-6, IL-8, TNF-α	27	25	38.35/8.27	NA/NA	Serum	NA	No
Spitzer, 2010 [54]	CRP	55	2994	53.53/15	NA/NA	Serum	NA	No
Lindqvist, 2014 [55]	IL-6; IL-1β; TNF-α, CRP, IL-10, IFN-γ	51	51	33.9/8.85	67.8/16.9	Serum	No	No
Lindqvist, 2017 [56]	IL-6, TNF-α, IFN-γ, hsCRP	31	30	31.00/5.5	92.7/17.1	Serum	No	No
Hoge, 2009 [57]	IL-6, TNF-α, IL-10, hsCRP, IL-1β; IFN-γ, MCP-1, MIP-1 α, GM-CSF	28	28	31/11.15	NA/NA	Serum	No	No

Vidovic, 2009 [58]	IL-6, TNF-α	39	37	39.28/9.95	68.02/NA	Serum	Yes	Yes
De Oliveira, 2018 [59]	IL-6, IL-10.	41	41	27.26/5.09	NA/NA	Serum	Yes	NA
Dalgard, 2017 [60]	IL-2, IL-8, IL-1β, IFN-γ, IL-6, IL-10, TNF-α, MIP-1β, TARC, IL-8, MCP-1	20	17	30.35/11.54	70/NA	Plasma	Yes	No
Newton, 2014 [61]	IL-6	15	26	NA/NA	32/13	Plasma	NA	No
O'Donovan, 2017 [62]	hsCRP	257	363	59/11	NA/NA	NA	NA	No
Olam, 2019 [63]	CRP	73	69	31.94/8.78	97.69/12.89	Serum	NA	No
Tucker, 2004[64]	IL-1B, sIL-2R	58	21	NA/NA	88.74/14.2	Serum	NA	No

Powers, 2019 [65]	hsCRP	18	16	50.89/8.86	16.32/NA	Serum	NA	No
Imai, 2018 [66]	IL-1B, IL-6, TNF-α, hsCRP, sIL-6R	40	65	NA/NA	NA/NA	Serum	No	No
Imai, 2019 [67]	IL-6, TNF-α, hsCRP	56	73	37.16/NA	NA/NA	Serum	No	No
Von Kanel, 2007 [68]	CRP, IL-1β, IL-6, TNF-α, IL-4, IL-10	14	14	NA/NA	NA/NA	Plasma	NA	No
Von Kanel, 2010 [69]	IL-6, CRP	15	29	NA/NA	43/NA	Plasma	NA	No
Song, 2007 [70]	IL-2, IL-6, IL-8	34	34	39/NA	NA/NA	Serum	NA	No
Wang, 2016 [71]	IL-2, IFN-γ, IL-6, IL-7, TNF-alpha, IL-4, IL-10	7	6	41.7/NA	75.9/13.3	Plasma	Yes	No

Wang, 2019 [72]	TNF-α, IL-1β, IL-2, IL-6, IL-8, IFN-γ, IL-4, IL-10	51	136	48.8/7.6	NA/NA	Serum	NA	No
Teche, 2017 [73]	IL-6, IL-10, cortisol	30	30	42.65/NA	NA/NA	Serum	No	No
Chen, 2014 [74]	IL-2, IL-6, IL-8, TNF-α	60	60	37.82/NA	NA/NA	Serum	Yes	Yes
Tezcan,2003 [75]	CAT, MDA	14	14	31.18/NA	NA/NA	Plasma	Yes	NA
McD Young, 2021 [76]	CRP	159	140	68.82/4.2	15.59/0.8	Plasma	No	No
Mehta, 2020 [77]	hs-CRP, IL-6, TNF-α, IL-1β	18	36	39.6/11.8	NA/NA	Serum	Yes	No
Yang, 2001 [78]	TNF-α, IL-2, GM-CSF	21	31	NA/NA	NA/NA	Serum	NA	NA

Oglodek 2017[a]: Evaluation of ADMA, carbonyl groups, CAT, and NKA in depressed patients with and without post-traumatic stress disorder. **Oglodek 2017[b]**: The role of PON-1, GR, IL-18, and OxLDL in depression with and without post-traumatic stress disorder; **Oglodek 2018[a]**: The association between inflammatory markers (iNOS, HO-1, IL-33, MIP-1beta) and depression with and without post-traumatic stress disorder. **Oglodek 2018[b]**: Changes in the concentrations of inflammatory and oxidative status biomediators (MIP-1 alpha, PMN elastase, MDA, and IL-12) in depressed patients with and without post-traumatic stress disorder. MDA: Malondialdehyde; CAT: Catalase; PON-1: paraoxonase-1.

Table 2. Meta-analysis of inflammatory and oxidative stress markers in PTSD

Table 2. Meta-analysis of inflammatory and oxidative stress markers in PTSD

	Studies	Sample size		Effect size			Heterogeneity			Egger's test
	k	PTSD	Controls	SMD	95% CI	*p*-value	Q statistic (*df*; *p* value)	t^2	I^2	*z* statistic (*p*-value)
Interleukin 1β	15	541	625	1.20	[-0.04 to 2.44]	0.0569	359.10 (14, $p < 0.0001$)	5.87	98.80%	2.8681 ($p = 0.0041$)
Interleukin 1RA	2	45	79	0.11	[-0.45 to 0.67]	0.7040	2.04 (1, $p = 0.1531$)	0.08	51.01%	*NA*

Interleukin 2	8	284	373	-0.46	[-1.61 to 0.70]	0.4383	164.55 (7, $p < 0.0001$)	2.67	97.66%	-2.5295 ($p = 0.0114$)
Interleukin 4	6	223	305	-0.40	[-1.99 to 1.19]	0.6211	143.72 (5, $p < 0.0001$)	3.85	98.38%	-1.9427 ($p = 0.0520$)
Interleukin 6	32	1028	1518	0.94	[0.36 to 1.52]	0.0014	476.06 (31, $p < 0.0001$)	2.66	97.47%	3.6277 ($p = 0.0003$)
Interleukin 8	7	287	322	-0.29	[-1.45 to 0.87]	0.6252	199.50 (6, $p < 0.0001$)	2.37	97.54%	-0.6195 ($p = 0.5356$)
Interleukin 10	11	401	482	0.36	[-0.27 to 0.99]	0.2682	144.51 (10, $p < 0.0001$)	1.07	94.73%	0.5741 ($p = 0.5659$)
Soluble IL-2 receptor	2	71	53	-2.14	[-7.68 to 3.40]	0.4484	93.11 (1, $p < 0.0001$)	15.81	98.93%	*NA*
Soluble IL-6 receptor	2	53	97	0.31	[-0.27 to 0.89]	0.2968	2.38 (1, $p = 0.1225$)	0.11	58.08%	*NA*
Interferon-γ	6	223	309	-0.19	[-1.66 o 1.28]	0.7983	80.31 (5, $p < 0.0001$)	3.28	98.26%	-4.2688 ($p < 0.0001$)
C-reactive protein	12	737	3935	0.64	[0.21 to 1.06]	0.0031	179.09 (11, $p < 0.0001$)	0.50	93.26%	-0.7926 ($p = 0.4280$)

hs-C-reactive protein	8	459	643	0.26	[-0.51 to 1.02]	0.5131	59.64 (6, $p < 0.0001$)	1.13	96.31%	2.2854 ($p = 0.0223$)
Tumor necrosis factor-α	24	830	991	0.89	[0.23 to 1.55]	0.0080	416.53 (23, $p < 0.0001$)	2.60	97.49%	3.2535 ($p = 0.0011$)
MCP-1	4	122	139	-0.66	[-1.53 to 0.22]	0.1430	20.61 (3, $p < 0.0001$)	0.71	90.65%	-1.8715 ($p = 0.0613$)
MIP-1 α (or CCL3)	3	157	100	4.37	[-4.05 to 12.79]	0.3088	188.98 (2, $p < 0.0001$)	55.02	99.80%	13.7462 ($p < 0.0001$)
MIP-1 β (or CCL4)	2	80	57	7.01	[-3.61 to 17.63]	0.1959	117.87 (1, $p < 0.0001$)	58.25	99.15%	*NA*
Malondialdehyde	3	104	92	-0.15	[-1.33 to 1.02]	0.8005	35.88 (2, $p < 0.0001$)	1.00	92.95%	0.4429 ($p = 0.6579$)
GM-CSF	2	49	59	-0.27	[-1.23 to 0.68]	0.5720	5.98 (1, $p = 0.0143$)	0.39	83.28%	*NA*
Catalase	2	74	54	2.64	[-2.87 to 8.14]	0.3474	92.94 (2, $p < 0.0001$)	15.61	98.92%	*NA*
Paraoxonase-1	2	90	78	-5.35	[-14.78 to 4.08]	0.2661	144.00 (1, $p < 0.0001$)	45.98	99.31%	*NA*

CCL3: chemokine C-C motif ligand 3; CCL4: chemokine CC motif ligand 4; CI: confidence interval; df:

degrees of freedom; GM-CSF: granulocyte-macrophage colony-stimulating factor; hs: high sensitivity; IL: interleukin; MCP-1: monocyte chemoattractant protein-1; MIP-1 α: macrophage inflammatory protein 1 alpha; MIP-1 β: macrophage inflammatory protein 1 beta; NA: not applicable; PTSD: post-traumatic stress disorder; SMD: standardised mean difference.

5.5.1. Material Suplementar ao Artigo 1

Inflammatory and oxidative stress markers in post-traumatic stress disorder: a systematic review and meta-analysis (Supplementary Material)

Authors: Tatiana Lauxen Peruzzolo, MD*; Jairo Vinícius Pinto, MD*; Thiago Henrique Roza, MD*; Augusto Ossamu Shintani; Ana Paula Anzolin; Vanessa Gnielka, MD; André Moura Kohmann, MD; Amanda Salvador Marin; Vitória Ruschel Lorenzon; André Russowsky Brunoni, PhD; Flávio Kapczinski, PhD; Ives Cavalcante Passos, PhD

*Dr Tatiana Lauxen Peruzzolo, Dr Jairo Vinícius Pinto, and Dr Thiago Henrique Roza are joint first authors who contributed equally to this work.

Table of Contents

1.Supplementary table 1. PRISMA checklist

Section/Topic	#	Checklist Item	*Reported on Page #
Title			
Title	01	Identify the report as a systematic review, meta-analysis, or both.	01
Abstract			
Structured summary	02	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	03
Introduction			
Rationale	03	Describe the rationale for the review in the context of what is already known.	04
Objectives	04	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design.	05

Methods			
Protocol and registration	05	Indicate if a review protocol exists, if and where it can be and, if available, provide registration information including registration number.	06
Eligibility criteria	06	Specify study characteristics and report characteristics used as criteria for eligibility, giving rationale.	06
Information sources	07	Describe all information sources in the search and date last searched.	06
Search	08	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	06 Supplemental information table 3
Study selection	09	State the process for selecting studies.	06
Data collection process	10	Describe method of data extraction from reports and any processes for obtaining and confirming data from investigators.	07
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	07
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies, and how this information is to be used in any data synthesis.	07-08

Summary measures	13	State the principle summary measures.	07-08
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency for each meta-analysis.	07-08
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence.	---
Additional analyses	16	Describe methods of additional analyses, if done, indicating which were pre-specified.	08
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10 Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment.	---
Results of individual studies	20	For all outcomes considered, present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2

Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies.	10-11
Additional analysis	23	Give results of additional analyses, if done.	10-11
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups.	12-16
Limitations	25	Discuss limitations at study and outcome level, and at review level.	15-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-16
Funding			
Funding	27	Describe sources of funding for the systematic review and other support; role of funders for the systematic review.	08-09, 17

*Page numbers reported on this checklist refer to the manuscript in its submitted version and may not reflect the page numbers on the published version of the manuscript.

2.Supplementary table 2. The Newcastle-Ottawa Scale (NOS) for assessing the quality of included studies.

Overall, the quality of the studies included in this meta-analysis is high. The vast majority of articles in the meta-analysis, 37 out of 54, have a NOS score greater than or equal to six, a score that signals a high quality of the study. Articles with scores lower than five may eventually contribute to a bias in the meta-analysis, however only 6 of the 54 articles in the meta-analysis present this risk.

	Selection	Comparability	Outcome	Total Score
Atli, 2016	****	**	***	9
Baker, 2001	***	**	***	8
Chen, 2014	****	*	**	7
Dalgard, 2017	**	*	**	5
De Oliveira, 2018	***	*	***	7
Eswarappa, 2017	**	*	***	6
Gill, 2008	****	*	***	8
Gill, 2010	***	---	*	4
Gill, 2013	****	*	***	8
Gola, 2013	****	*	***	8

Guo, 2012	**	*	*	4
Hoge, 2009	**	*	**	5
Imai, 2018	**	**	*	5
Imai, 2019	***	*	*	5
Jergovic, 2014	****	*	**	7
Jergovic, 2015	****	*	**	7
Jiang, 2018	***	*	**	6
Küffer, 2019	****	*	***	8
Lindqvist, 2014	**	*	***	6
Lindqvist, 2017	**	*	***	6
Maes, 1999	***	*	***	7
McD Young, 2019	**	*	**	5
Mehta, 2020	**	*	***	6
Miller, 2017	**	*	*	4
Miller, 2018	****	---	**	6

Muhtz, 2011	***	**	**	7
Neupane, 2017	***	---	**	5
Newton, 2014	****	*	**	7
O'Donovan, 2017	****	*	***	8
Oganesyan, 2009	**	*	---	3
Oglodek, 2017[a]	****	*	***	8
Oglodek, 2017[b]	****	*	***	8
Oglodek, 2018[a]	****	*	***	8
Oglodek, 2018[b]	****	*	***	8
Olam, 2019	****	---	*	5
Park, 2017	***	*	*	5
Powers, 2019	**	*	*	4
Smith, 2011	***	---	*	4
Söndergaard, 2004	***	*	**	6
Song, 2007	***	**	**	7

Spitzer, 2010	***	*	***	7
Spivak, 1997	****	**	**	8
Sumner, 2017	****	**	**	8
Teche, 2017	***	*	**	6
Tezcan,2003	***	---	**	5
Toft, 2018	***	*	***	7
Tucker, 2004	****	---	*	5
Vidovic, 2009	***	*	***	7
Vidovic, 2011	****	*	***	8
Von Kanel, 2007	***	*	**	6
Von Kanel, 2010	****	*	**	7
Wang, 2016	***	*	**	6
Wang, 2019	****	**	**	8
Yang, 2001*	NA	NA	NA	NA

Yang 2001*: It was not possible to assess the quality of the paper, as we were unable to obtain the full article. Data for analysis were obtained from the database of the previous study conducted by our group.[8]

1. Supplementary table 3. Search terms.

("Inflammation" OR "Immune Activation" OR "Interleukin" OR "Cytokine" OR "Interferon" OR "Tumor Necrosis Factor-alpha" OR "C-Reactive Protein" OR "Oxidative Stress" OR "Reactive Oxygen Species" OR "antioxidant" OR "Superoxide Dismutase" OR "Glutathione Peroxidase" OR "Selenoglutathione Peroxidase" OR "Glutathione Lipoperoxidase" OR "Catalase" OR "Free Radicals" OR "Nitric Oxide" OR "Mononitrogen Monoxide" OR "Nitrogen Monoxide" OR "Endothelium-Derived Nitric Oxide" OR "Lipid Peroxidation" OR "Lipid Peroxidations" OR "malonyldialdehyde" OR "Malonaldehyde" OR "Malonylaldehyde" OR "Sodium Malondialdehyde" OR "Thiobarbituric Acid Reactive Substances" OR "TBARs" OR "nitrotyrosine" OR "3-nitrotyrosine" OR "3-mononitrotyrosine" OR "3-nitro-L-tyrosine" OR "glutathione" OR "protein carbonyl" OR "DNA oxidation" OR "DNA damage" OR "DNA fragmentation") AND ("Posttraumatic Stress Disorder" OR "PTSD").

2. Supplementary table 4. Studies in which the mean and the standard deviation of the inflammatory markers or oxidative stress markers were estimated from the median, range, and the size of the respective sample.

Study, Year	Inflammatory Markers / Oxidative Stress Markers Assessed in the study
Vidovic, 2011	IL-6, TNF-α
Hoge, 2009	IL-6, TNF-α, IL-10, hsCRP, IL-1β; IFN-γ, MCP-1, MIP-1 α, GM-CSF
Neupane, 2017	CRP, IL-1RA, IL-6, IL-10, TNF-α, IFN-γ
Imai, 2018	IL-1B, IL-6, TNF-α, hsCRP, sIL-6R
Von Kanel, 2007	CRP, IL-1β, IL-6, TNF-α, IL-4, IL-10
Jergovic, 2015	CRP, MIP-1α, IL-8, IL-1β, IL-2, TNF-α, IFN-γ, IL-4, IL-6
De Oliveira, 2018	IL-6, IL-10

Imai, 2019	IL-6, TNF-α, hsCRP

The methodology used to estimate the mean and standard deviation are described in the article of Hozo et al. 2005.

3. Supplementary table 5. Sensitivity analysis – leave one out procedure for interleukin 6.

	Effect size			Heterogeneity		
	SMD	95% CI	*p* value	Q statistic (*df*; *p* value)	t^2	I^2
Baker et al; 2001	0.92	[0.33 to 1.52]	0.0023	472.89 (30, $p < 0.0001$)	2.74	97.61%
Chen et al; 2014a	0.87	[0.29 to 1.44]	0.0031	432.58 (30, $p < 0.0001$)	2.56	97.42%
Chen et al; 2014b	0.87	[0.29 to 1.45]	0.0031	434.79 (30, $p < 0.0001$)	2.58	97.44%
Dalgard et al; 2017	1.05	[0.50 to 1.59]	0.0002	426.96 (30, $p < 0.0001$)	2.30	97.15%
De Oliveira et al; 2018	0.93	[0.34 to 1.53]	0.0022	468.81 (30, $p < 0.0001$)	2.76	97.55%
Eswarappa et al; 2017	0.97	[0.37 to 1.56]	0.0015	468.44 (30, $p < 0.0001$)	2.75	97.34%
Gill et al; 2008	0.77	[0.3 to 1.25]	0.0017	412.22 (30, $p < 0.0001$)	2.77	96.36%
Gill et al; 2010	0.93	[0.29 to 1.53]	0.0022	473.75 (30, $p < 0.0001$)	2.75	97.61%
Gill et al; 2013	0.95	[0.35 to 1.55]	0.0018	476.00 (30, $p < 0.0001$)	2.76	97.58%
Gola et al; 2013	0.96	[0.36 to 1.55]	0.0017	476.00 (30, $p < 0.0001$)	2.76	97.57%

Guo et al; 2012	0.86	[0.29 to 1.43]	0.0032	395.80 (30, $p < 0.0001$)	2.51	97.36%
Hoge et al; 2009	0.94	[0.34 to 1.54]	0.0021	473.28 (30, $p < 0.0001$)	2.77	97.58%
Imai et al; 2018	0.93	[0.34 to 1.53]	0.0022	468.42 (30, $p < 0.0001$)	2.76	97.53%
Imai et al; 2019	0.96	[0.36 to 1.55]	0.0017	475.83 (30, $p < 0.0001$)	2.76	97.48%
Jergovic et al; 2015	1.04	[0.48 to 1.59]	0.0002	421.08 (30, $p < 0.0001$)	2.37	97.22%
Jiang et al; 2018	0.83	[0.28 to 1.37]	0.0030	422.00 (30, $p < 0.0001$)	2.29	97.15%
Küffer et al; 2019	0.97	[0.38 to 1.57]	0.0013	467.38 (30, $p < 0.0001$)	2.73	97.50%
Lindqvist et al; 2014	0.96	[0.37 to 1.56]	0.0015	473.47 (30, $p < 0.0001$)	2.75	97.50%
Lindqvist et al; 2017	0.95	[0.35 to 1.55]	0.0018	476.02 (30, $p < 0.0001$)	2.76	97.57%
Maes et al; 1999	0.91	[0.32 to 1.51]	0.0025	466.17 (30, $p < 0.0001$)	2.73	97.58%
Mehta et al., 2020	0.98	[0.38 to 1.57]	0.0013	469.70 (30, $p < 0.0001$)	2.72	97.54%
Neupane et al; 2017	0.96	[0.36 to 1.55]	0.0170	475.91 (30, $p < 0.0001$)	2.76	97.54%
Newton et al; 2014	0.98	[0.38 to 1.57]	0.0013	471.21 (30, $p < 0.0001$)	2.72	97.56%
Oganesyan et al; 2009	0.93	[0.33 to 1.53]	0.0022	470.20 (30, $p < 0.0001$)	2.76	97.57%
Smith et al; 2011	0.96	[0.36 to 1.56]	0.0016	474.82 (30, $p < 0.0001$)	2.76	97.49%

Song et al; 2007	0.95	[0.36 to 1.55]	0.0018	476.04 (30, $p < 0.0001$)	2.76	97.56%
Teche et al; 2017	0.98	[0.39 to 1.57]	0.0012	466.65 (30, $p < 0.0001$)	2.72	97.52%
Vidovic et al; 2009	0.96	[0.36 to 1.55]	0.0017	475.94 (30, $p < 0.0001$)	2.76	97.54%
Vidovic et al; 2011	0.95	[0.35 to 1.54]	0.0019	475.37 (30, $p < 0.0001$)	2.77	97.57%
von Kanel et al; 2007	0.97	[0.37 to 1.56]	0.0015	474.89 (30, $p < 0.0001$)	2.74	97.59%
von Kanel et al; 2010	0.96	[0.37 to 1.56]	0.0015	475.23 (30, $p < 0.0001$)	2.75	97.58%
Wang et al; 2019	0.97	[0.38 to 1.57]	0.0013	460.84 (30, $p < 0.0001$)	2.73	97.42%

CI: confidence interval; df: degrees of freedom; SMD: standardised mean difference.

4. Supplementary table 6. Sensitivity analysis – leave one out procedure for C-reactive protein.

	Effect size			Heterogeneity		
	SMD	95% CI	*p* value	Q statistic (*df*; *p* value)	t^2	I^2
Eswarappa et al; 2017	0.69	[0.24to 1.14]	0.0028	157.35 (10, $p < 0.0001$)	0.52	92.92%
Gill et al; 2013	0.63	[0.17 to 1.09]	0.0073	179.09 (10, $p < 0.0001$)	0.55	94.15%
Jergovic et al; 2015	0.62	[0.16 to 1.08]	0.0085	178.78 (10, $p < 0.0001$)	0.55	93.98%
Lindqvist et al; 2014	0.67	[0.21 to 1.12]	0.0042	174.95 (10, $p < 0.0001$)	0.54	93.75%
McD Young et al.,	0.49	[0.15 to 0.83]	0.0044	64.48 (10, $p < 0.0001$)	0.27	87.46%
Miller et al; 2017	0.60	[0.15 to 1.06]	0.0087	178.29 (10, $p < 0.0001$)	0.53	94.09%
Miller et al; 2018	0.66	[0.20 to 1.12]	0.0052	171.99 (10, $p < 0.0001$)	0.55	93.02%
Neupane et al; 2017	0.63	[0.17 to 1.09]	0.0075	179.09 (10, $p < 0.0001$)	0.55	94.05%
Olam et al; 2019	0.54	[0.12 to 0.96]	0.0110	153.56 (10, $p < 0.0001$)	0.44	92.50%
Spitzer et al; 2010	0.67	[0.21 to 1.12]	0.0044	170.18 (10, $p < 0.0001$)	0.54	93.21%
von Kanel et al; 2007	0.68	[0.23 to 1.12]	0.0029	176.50 (10, $p < 0.0001$)	0.52	93.93%

von Kanel et al; 2010	0.75	[0.35 to 1.14]	0.0002	161.26 (10, $p < 0.0001$)	0.40	93.14%

CI: confidence interval; df: degrees of freedom; SMD: standardised mean difference.

5. Supplementary table 7. Sensitivity analysis – leave one out procedure for tumour necrosis factor-α.

	Effect size			Heterogeneity		
	SMD	95% CI	*p* value	Q statistic (*df*; *p* value)	t^2	I^2
Chen et al; 2014a	0.82	[0.15 to 1.49]	0.0167	387.31 (22, $p < 0.0001$)	2.59	97.53%
Chen et al; 2014b	0.84	[0.16 to 1.52]	0.0153	397.69 (22, $p < 0.0001$)	2.67	97.58%
Dalgard et al; 2017	0.81	[0.14 to 1.47]	0.0171	394.73 (22, $p < 0.0001$)	2.53	97.50%
Gill et al; 2008	0.80	[0.14 to 145]	0.0175	385.93 (22, $p < 0.0001$)	2.49	97.45%
Gola et al; 2013	0.94	[0.27 to 1.62]	0.0064	401.85 (22, $p < 0.0001$)	2.66	97.55%
Guo et al; 2012	0.82	[0.15 to 1.49]	0.0168	366.73 (22, $p < 0.0001$)	2.59	97.49%
Hoge et al; 2009	0.92	[0.23 to 1.60]	0.0089	414.70 (22, $p < 0.0001$)	2.73	97.60%
Imai et al; 2018	0.88	[0.19 to 1.57]	0.0122	411.39 (22, $p < 0.0001$)	2.74	97.56%
Imai et al; 2019	0.87	[0.18 to 1. 56]	0.0130	403.63 (22, $p < 0.0001$)	2.73	97.53%
Jergovic et al; 2014	1.02	[0.40 to 1.64]	0.0013	357.72 (22, $p < 0.0001$)	2.21	97.13%
Jiang et al; 2018	0.68	[0.15 to 1.21]	0.0121	350.65 (22, $p < 0.0001$)	1.61	96.15%

Küffer et al; 2019	0.93	[0.24 to 1.61]	0.0080	409.34 (22, $p < 0.0001$)	2.71	97.54%
Lindqvist et al; 2014	0.91	[0.22 to 1.60]	0.0093	415.02 (22, $p < 0.0001$)	2.73	97.53%
Lindqvist et al; 2017	0.93	[0.24 to 1.61]	0.0078	410.18 (22, $p < 0.0001$)	2.70	97.58%
Mehta et al., 2020	0.95	[0.28 to 1.63]	0.0056	398.79 (22, $p < 0.0001$)	2.63	97.54%
Neupane et al; 2017	0.92	[0.23 to 1.60]	0.0091	414.77 (22, $p < 0.0001$)	2.73	97.57%
Oganesyan et al; 2009	0.90	[0.21 to 1.59]	0.0108	416.25 (22, $p < 0.0001$)	2.74	97.62%
Smith et al; 2011	0.92	[0.24 to 1. 61]	0.0085	410.44 (22, $p < 0.0001$)	2.72	97.51%
Toft et al; 2018	0.86	[0.17 to 1.54]	0.0143	395.22 (22, $p < 0.0001$)	2.71	97.55%
Vidovic et al; 2009	0.90	[0.21 to 1.59]	0.0103	416.52 (22, $p < 0.0001$)	2.74	97.59%
Vidovic et al; 2011	0.94	[0.25 to 1.62]	0.0071	406.34 (22, $p < 0.0001$)	2.69	97.56%
von Kanel et al; 2007	0.93	[0.24 to 1.61]	0.0081	414.30 (22, $p < 0.0001$)	2.71	97.64%
Wang et al; 2019	0.91	[0.22 to 1.59]	0.0100	416.36 (22, $p < 0.0001$)	2.74	97.47%
Yang et al; 2001	0.99	[0.33 to 1.64]	0.0031	372.56 (22, $p < 0.0001$)	2.46	97.39%

CI: confidence interval; df: degrees of freedom; SMD: standardised mean difference.

6. Supplementary table 8. Sensitivity analysis – leave one out procedure for interleukin 1β.

	Effect size			Heterogeneity		
	SMD	95% CI	*p* value	Q statistic (*df*; *p* value)	t^2	I^2
Dalgard et al; 2017	1.50	[0.35 to 2.65]	0.0109	303.92 (13, $p < 0.0001$)	4.73	98.58%
Gill et al; 2008	1.26	[-0.07 to 2.59]	0.0643	359.03 (13, $p < 0.0001$)	6.34	98.89%
Hoge et al; 2009	1.27	[-0.06 to 2.60]	0.0603	357.73 (13, $p < 0.0001$)	6.30	98.87%
Imai et al; 2018	1.30	[-0.02 to 2.62]	0.0539	346.71 (13, $p < 0.0001$)	6.23	98.79%
Jergovic et al; 2015	1.28	[-0.04 to 2.61]	0.0580	354.54 (13, $p < 0.0001$)	6.28	98.82%
Jiang et al; 2018	0.77	[-0.18 to 1.72]	0.1115	284.69 (13, $p < 0.0001$)	3.19	97.93%
Lindqvist et al; 2014	1.28	[-0.05 to 2.61]	0.0592	355.22 (13, $p < 0.0001$)	6.29	98.80%
Mehta et al., 2020	1.32	[-0.00 to 2.63]	0.0504	349.49 (13, $p < 0.0001$)	6.18	98.86%
Oganesyan et al; 2009	1.04	[-0.24 to 2.32]	0.1126	306.70 (13, $p < 0.0001$)	5.86	98.84%
Smith et al; 2011	1.31	[-0.01 to 2.63]	0.0524	341.44 (13, $p < 0.0001$)	6.21	98.77%

Spivak et al; 1997	1.21	[-0.13 to 2.55]	0.0758	356.28 (13, $p < 0.0001$)	6.37	98.92%
Toft et al; 2018	1.11	[-0.21 to 2.44]	0.0983	303.12 (13, $p < 0.0001$)	6.22	98.85%
Tucker et al; 2004	0.96	[-0.26 to 2.18]	0.1237	277.85 (13, $p < 0.0001$)	5.28	98.72%
Von Kanel et al; 2007	1.23	[-0.10 to 2.57]	0.0704	358.59 (13, $p < 0.0001$)	6.36	98.92%
Wang et al; 2019	1.24	[-0.09 to 2.58]	0.0683	358.25 (13, $p < 0.0001$)	6.36	98.76%

CI: confidence interval; df: degrees of freedom; SMD: standardised mean difference.

7. Supplementary table 9. Subgroup meta-analysis of inflammatory markers in PTSD.

	Studies	Sample size		Effect size			Heterogeneity			Egger's Test
	K	PTSD	Controls	SMD	95% CI	*p* value	Q statistic (*df*; *p* value)	t^2	I^2	*z* statistic (*p* value)
Interleukin 1β	----	----	----	----	----	----	----	----	----	----
Complete (full sample)	15	541	625	1.20	[-0.04 to 2.44]	0.0569	359.10 (14, $p < 0.0001$)	5.87	98.80%	2.8681 ($p = 0.0041$)
With MDD	13	491	575	1.03	[-0.36 to 2.42]	0.1458	303.03 (12, $p < 0.0001$)	6.42	98.97%	----
Without MDD	2	50	50	2.35	[0.01 to 4.68]	0.0490	19.08 (01, $p < 0.0001$)	2.69	94.76%	----
Medication Free	7	186	159	1.04	[-0.84 to 2.91]	0.2780	191.11 (06, $p < 0.0001$)	6.26	97.83%	----
On psychotropic medication	8	355	466	1.36	[-0.42 to 3.13]	0.1345	160.26 (07, $p < 0.0001$)	6.45	99.22%	----

Interleukin 6	----	----	----	----	----	----	----	----	----	----
Complete (full sample)	32	1028	1518	0.94	[0.36 to 1.52]	0.0014	476.06 (31, $p < 0.0001$)	2.66	97.47%	3.6277 ($p = 0.0003$)
With MDD*	22	712	1225	0.67	[-0.08 to 1.43]	0.0790	282.49 (31, $p < 0.0001$)	3.14	98.04%	----
With MDD**	22	705	1225	1.80	[-0.06 to 1.47]	0.0723	284.16 (21, $p < 0.0001$)	3.24	98.08%	----
Without MDD*	10	316	293	1.54	[0.76 to 2.31]	<0.0001	146.10 (09, $p < 0.0001$)	1.44	93.50%	----
Without MDD**	11	323	325	1.59	[0.88 to 2.30]	<0.0001	150.29 (10, $p < 0.0001$)	1.33	93.12%	----
Medication Free	15	427	775	1.25	[0.24 to 2.26]	0.0155	244.88 (14, $p < 0.0001$)	3.85	97.86%	----
On psychotropic medication	17	601	743	0.68	[0.03 to 1.34]	0.0402	227.91 (16, $p < 0.0001$)	1.81	96.72%	----
Tumor necrosis factor-α	----	----	----	----	----	----	----	----	----	----
Complete (full	24	830	991	0.89	[0.23 to	0.0080	416.53 (23, p	2.60	97.49%	3.2535 (p

sample)					1.55]		< 0.0001)			= 0.0011)
With MDD	16	534	720	0.84	[-0.09 to 1.77]	0.0767	289.83 (15, *p* < 0.0001)	3.50	98.14%	----
Without MDD	8	296	271	1.00	[0.19 to 1.82]	0.0160	122.90 (7, *p* < 0.0001)	1.31	94.89%	----
Medication Free	10	289	284	1.12	[0.28 to 1.95]	0.0086	133.80 (9, *p* < 0.0001)	1.69	94.97%	----
On psychotropic medication	14	541	707	0.73	[-0.26 to 1.72]	0.1462	281.32 (13, *p* < 0.0001)	3.47	98.37%	----

CI: confidence interval; df: degrees of freedom; MDD: major depressive disorder; PTSD: post-traumatic stress disorder; SMD: standardised mean difference.

*The complete sample of Maes et al., 1999 was used. **The separated samples of patients with and without comorbid MDD from study Maes et al., 1999 were used.

8. Supplementary table 10. Univariate meta-regression analysis with methodological variables.

					Studies	
Interleukin 1β	Estimate	SE	95% CI	p-value	Total	Included
Assay used (ELISA *vs* other)	2.44	1.13	[0.22 to 4.66]	0.0313	15	15
Blood collection (fasting *vs* postprandial)	0.03	2.04	[-3.98 to 4.03]	0.9901	15	11
Blood fraction (serum *vs* plasma)	2.70	1.25	[0.25 to 5.15]	0.0308	15	14
Interleukin 6	----	----	----	----	----	----
Assay used (ELISA *vs* other)	1.43	0.54	[0.38 to 2.49]	0.0077	32	32
Blood collection (fasting *vs* postprandial)	1.05	0.98	[-0.87 to 2.97]	0.2825	32	23
Blood fraction (serum *vs* plasma)	0.95	0.51	[-0.04 to 1.95]	0.0606	32	30
Interleukin 10	----	----	----	----	----	----
Assay used (ELISA *vs* other)	1.05	0.61	[-0.16 to 2.25]	0.0886	11	11
Blood collection (fasting *vs* postprandial) *	----	----	----	----	----	----
Blood fraction (serum *vs* plasma)	0.93	0.61	[-0.26 to 2.13]	0.1247	11	11

C-reactive protein	----	----	----	----	----	----
Assay used (ELISA *vs* other)	0.70	0.59	[-0.46 to 1.86]	0.2358	12	11
Blood collection (fasting *vs* postprandial) *	----	----	----	----	---	----
Blood fraction (serum *vs* plasma)	0.77	0.49	[-0.18 to 1.72]	0.1122	12	12
Tumor necrosis factor-α	----	----	----	----	----	----
Assay used (ELISA *vs* other)	1.43	0.62	[0.21 to 2.64]	0.0210	24	24
Blood collection (fasting *vs* postprandial)	0.27	1.40	[-2.48 to 3.03]	0.8450	24	17
Blood fraction (serum *vs* plasma)	0.51	0.80	[-1.06 to 2.09]	0.5221	24	22
CI: confidence interval; ELISA: enzyme-linked immunosorbent assay; PTSD: post-traumatic stress disorder; SE: standard error; SMD: standardised mean difference. *Blood collection (fasting *vs* postprandial) was not tested since all studies included presented fasting as the method of blood collection.						

9. Supplementary table 11. Univariate meta-regression analysis – variables with clinical implications.

		Studies

Interleukin 1β	Estimate	SE	95% CI	p-value	Total	Included
Presence of comorbid MDD (yes *vs* no)	-1.32	1.90	[-5.04 to 2.40]	0.4870	15	15
Medication-free (yes *vs* no)	0.90	1.27	[-1.60 to 3.40]	0.7069	15	11
Type of trauma (war *vs* other)	-0.74	1.97	[-4.60 to 3.12]	0.7082	15	11
Length of illness (measured in months)	-0.04	0.02	[-0.09 to 0.01]	0.0858	15	04
CAPS score	0.13	0.15	[-0.16 to 0.42]	0.3680	15	04
Depression severity	1.58	0.52	[0.55 to 2.61]	0.0026	15	09
Interleukin 6	----	----	----	----	----	----
Presence of comorbid MDD (yes *vs* no)	-0.91	0.64	[-2.16 to 0.34]	0.1552	32	31
Medication free (yes *vs* no)	0.67	0.61	[-0.52 to 1.86]	0.2694	32	25
Type of trauma (war *vs* other)	-0.88	0.67	[-2.20 to 0.44]	0.1903	32	32
Length of illness (measured in months)	-0.02	0.01	[-0.04 to -0.01]	0.0369	32	09
CAPS score	0.02	0.02	[-0.02 to 0.05]	0.3100	32	14
Depression severity	0.32	0.26	[-0.19 to 0.84]	0.2179	32	11

Interleukin 10	----	----	----	----	----	----
Presence of comorbid MDD (yes *vs* no)	-0.35	0.58	[-1.47 to 0.78]	0.5491	11	10
Medication-free (yes *vs* no)	1.69	0.85	[0.02 to 3.36]	0.0470	11	07
Type of trauma (war *vs* other)	-0.39	0.48	[-1.34 to 0.56]	0.4266	11	09
Length of illness (measured in months)	0.01	0.01	[0.01 to 0.03]	0.0256	11	05
CAPS score	-0.01	0.02	[-0.05 to 0.02]	0.4656	11	05
Depression severity	-0.15	0.22	[-0.58 to 0.27]	0.4775	11	06
C-reactive protein	----	----	----	----	----	----
Presence of comorbid MDD (yes *vs* no)	-0.04	0.87	[-1.75 to 1.67]	0.9618	12	11
Medication-free (yes *vs* no)	-0.62	0.88	[-2.34 to 1.11]	0.4819	12	08
Type of trauma (war *vs* other)	-0.10	0.44	[-0.97 to 0.77]	0.8271	12	11
Length of illness (measured in months)	0.03	0.01	[0.02 to 0.04]	<0.0001	12	04
CAPS score	-0.01	0.02	[-0.03 to 0.03]	0.9904	12	06
Depression severity	0.09	0.09	[-0.08 to 0.26]	0.2957	12	07
Tumor necrosis factor-α	----	----	----	----	----	----

Presence of comorbid MDD (yes *vs* no)	-0.03	0.72	[-1.44 to 1.38]	0.9670	24	23
Medication free (yes *vs* no)	0.75	0.55	[-0.32 to 1.82]	0.1714	24	16
Type of trauma (war *vs* other)	-1.55	0.72	[-2.95 to -0.15]	0.0302	24	24
Length of illness (measured in months)	0.03	0.01	[0.01 to 0.06]	0.0317	23	06
CAPS score	0.02	0.03	[-0.05 to 0.08]	0.6381	23	09
Depression severity	1.14	0.47	[0.23 to 2.05]	0.0144	23	10

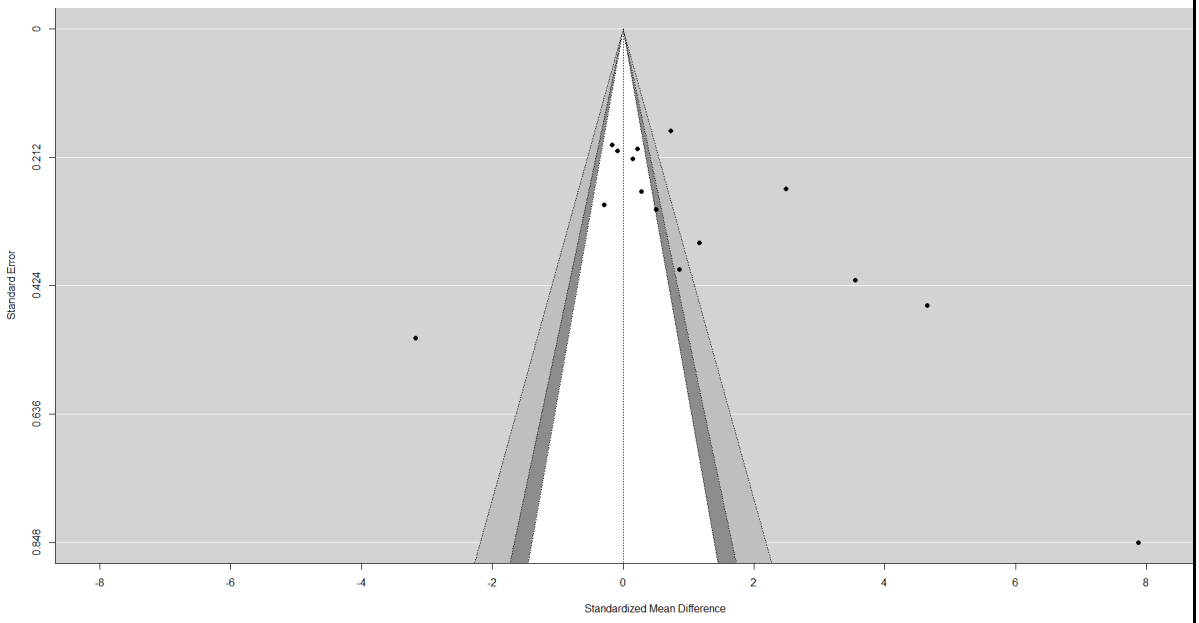
CAPS: Clinician-Administered PTSD Scale; CI: confidence interval; MDD: major depressive disorder; PTSD: post-traumatic stress disorder; SE: standard error; SMD: standardised mean difference.

10. Supplementary table 12. Statistical power in meta-analysis.

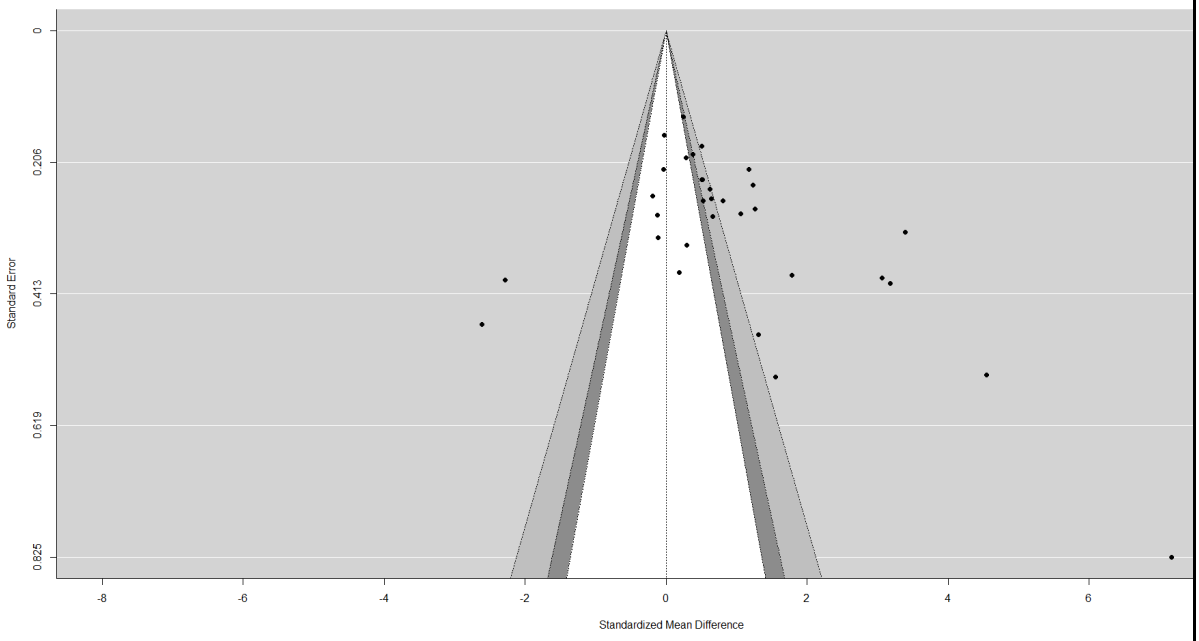
	Studies included	Average sample size	Effect size	I^2	Statistical power
Interleukin 1β	15	77.7	1.20	0.988	0.56
Interleukin 1RA	2	62.0	0.11	0.510	0.14
Interleukin 2	8	82.1	-0.46	0.977	0.20
Interleukin 4	6	88.0	-0.40	0.984	0.15
Interleukin 6	32	79.6	0.94	0.935	0.99
Interleukin 8	7	87.0	-0.29	0.974	0.14
Interleukin 10	11	80.3	0.36	0.947	0.27
Soluble IL-2 receptor	2	62.0	-2.14	0.989	0.41
Soluble IL-6 receptor	2	75.0	0.31	0.581	0.34
Interferon-γ	6	88.7	-0.19	0.983	0.12
C-reactive protein	12	381.0	0.64	0.933	0.99
hs-C-reactive protein	8	137.8	0.26	0.963	0.19

Tumor necrosis factor-α	24	75.9	0.89	0.975	0.82
MCP-1	4	65.3	-0.66	0.907	0.45
MIP-1 α (or CCL3)	3	85.7	4.37	0.998	0.28
MIP-1 β (or CCL4)	2	68.5	7.01	0.992	0.50
Malondialdehyde	3	65.3	-0.15	0.930	0.19
GM-CSF	2	54.0	-0.27	0.823	0.27
Catalase	2	64.0	2.64	0.989	0.44
Paraoxonase-1	2	84.0	-5.35	0.993	0.49

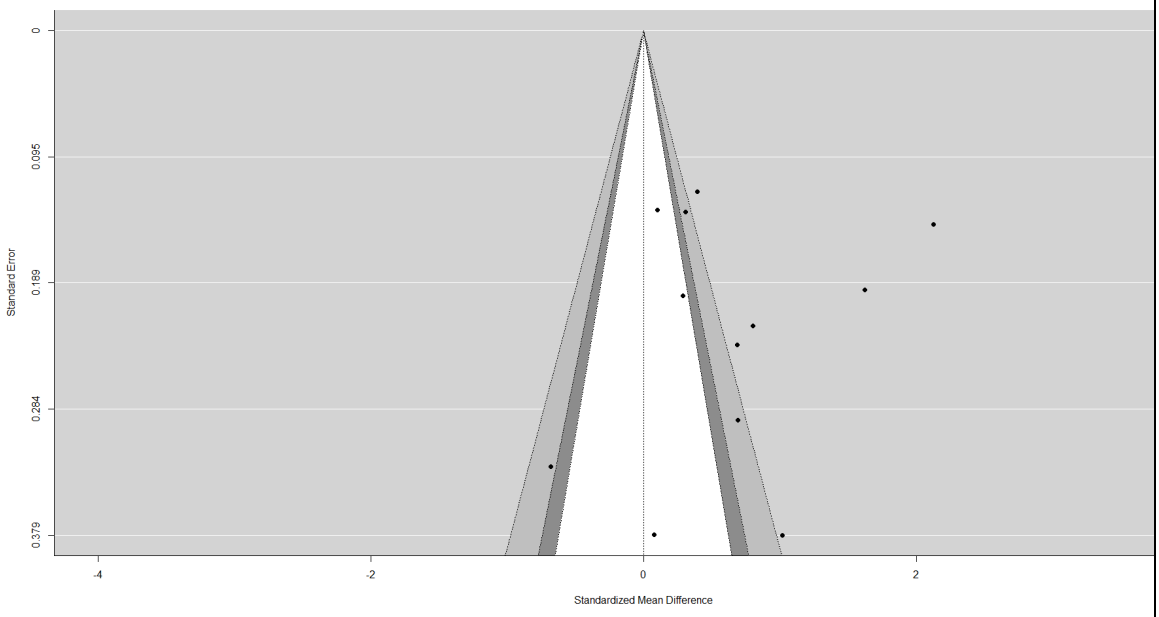
CCL3: chemokine C-C motif ligand 3; CCL4: chemokine CC motif ligand 4; GM-CSF: granulocyte-macrophage colony-stimulating factor; hs: high sensitivity; IL: interleukin; MCP-1: monocyte chemoattractant protein-1; MIP-1 α: macrophage inflammatory protein 1 alpha; MIP-1 β: macrophage inflammatory protein 1 beta.



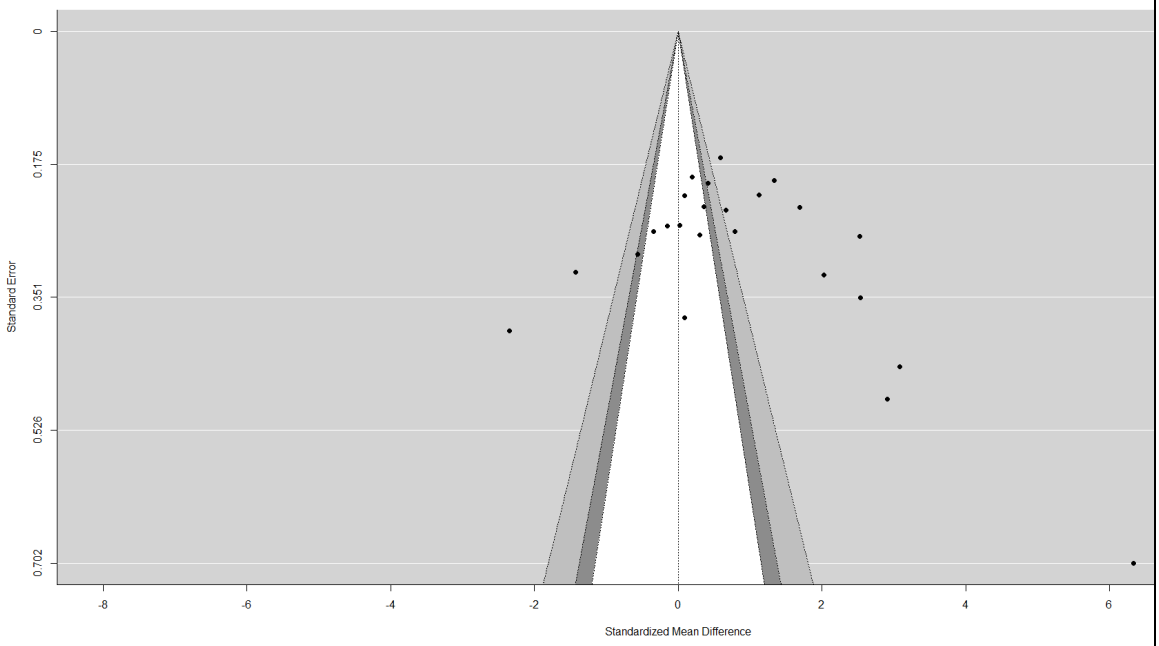
13. Supplementary figure 1 – Funnel Plot – Interleukin 1β



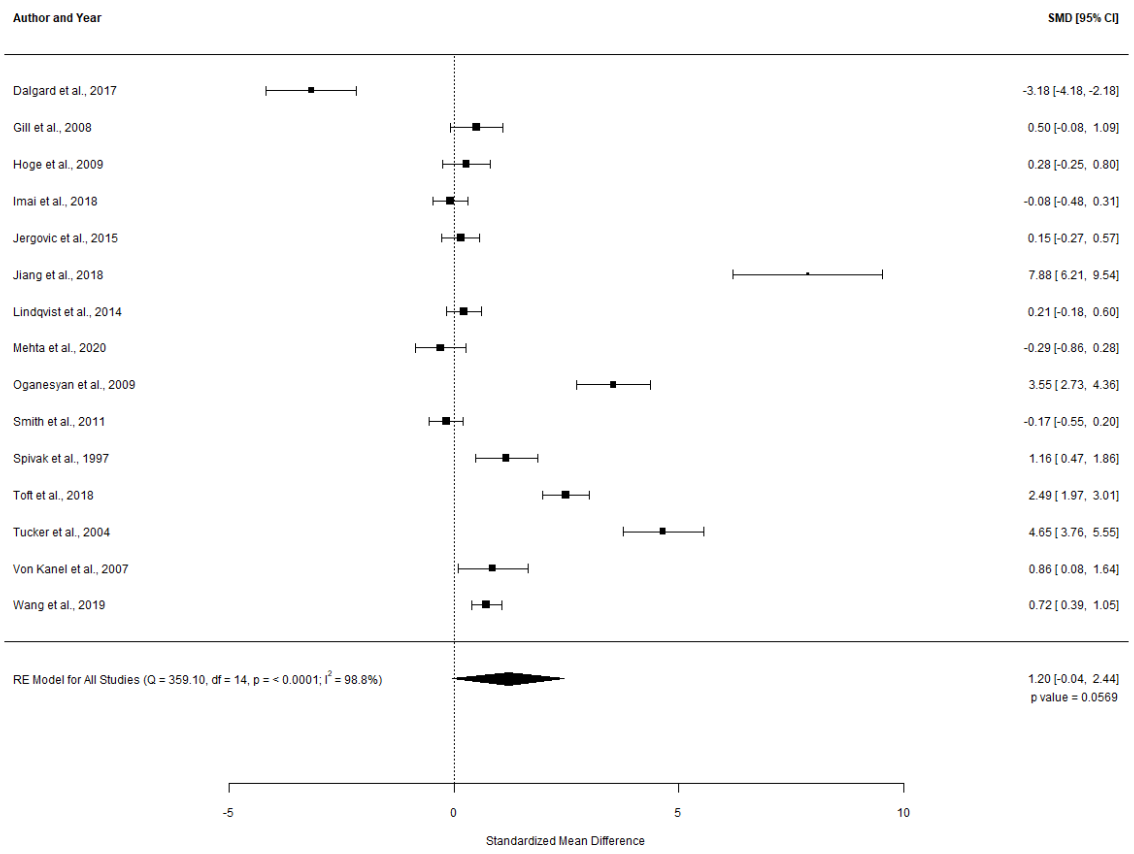
14. Supplementary figure 2 – Funnel Plot – Interleukin 6



15. Supplementary figure 3 – Funnel Plot – C-reactive protein

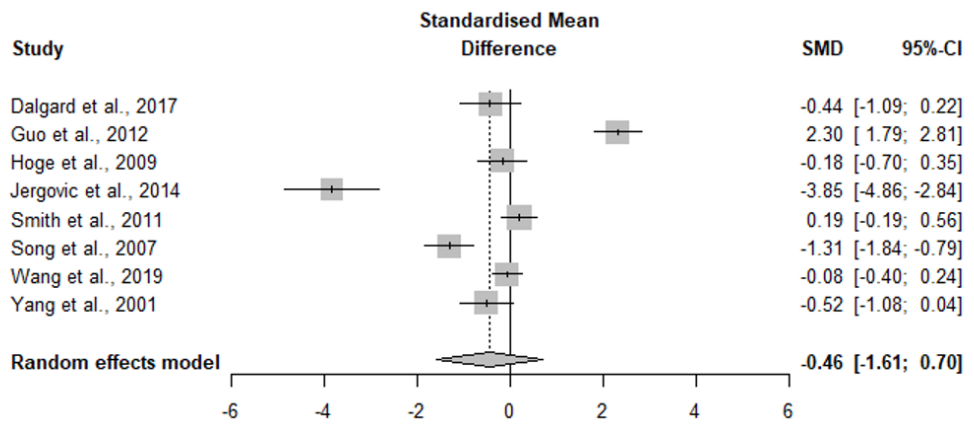


16. Supplementary figure 4 – Funnel Plot – Tumour necrosis factor-α



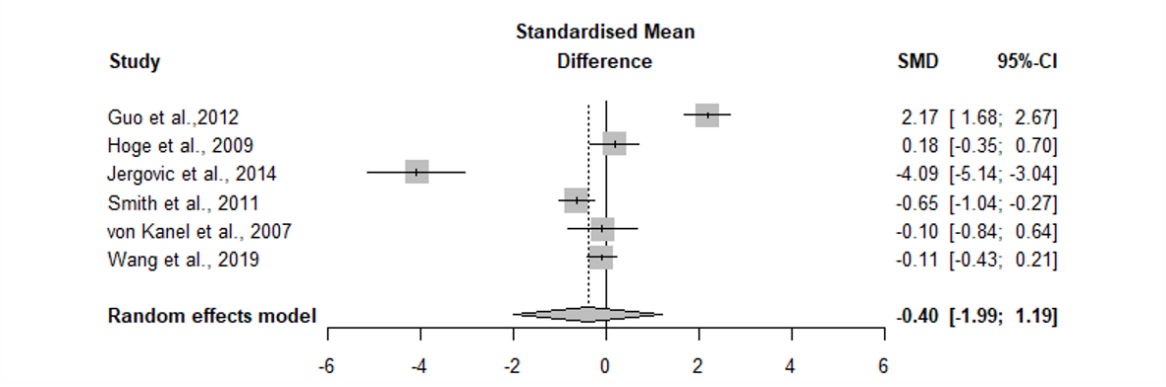
17. Supplementary figure 5 – Forest Plot – Meta-analysis of interleukin 1β

Meta-analysis comparing patients and controls. PTSD: post-traumatic stress disorder; SD: standard deviation; SMD: standardised mean difference.



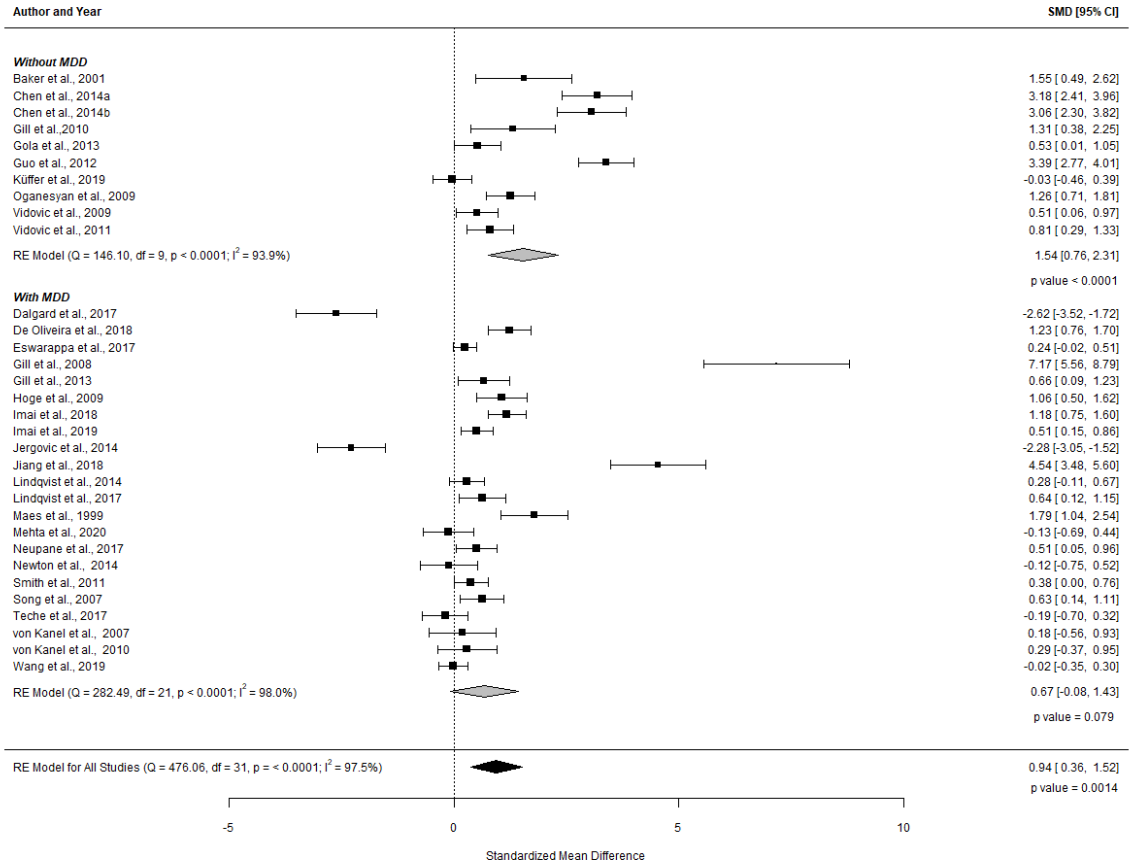
18. Supplementary figure 6 – Forest Plot – Meta-analysis of interleukin 2

Meta-analysis comparing patients and controls. PTSD: post-traumatic stress disorder; SD: standard deviation; SMD: standardised mean difference.



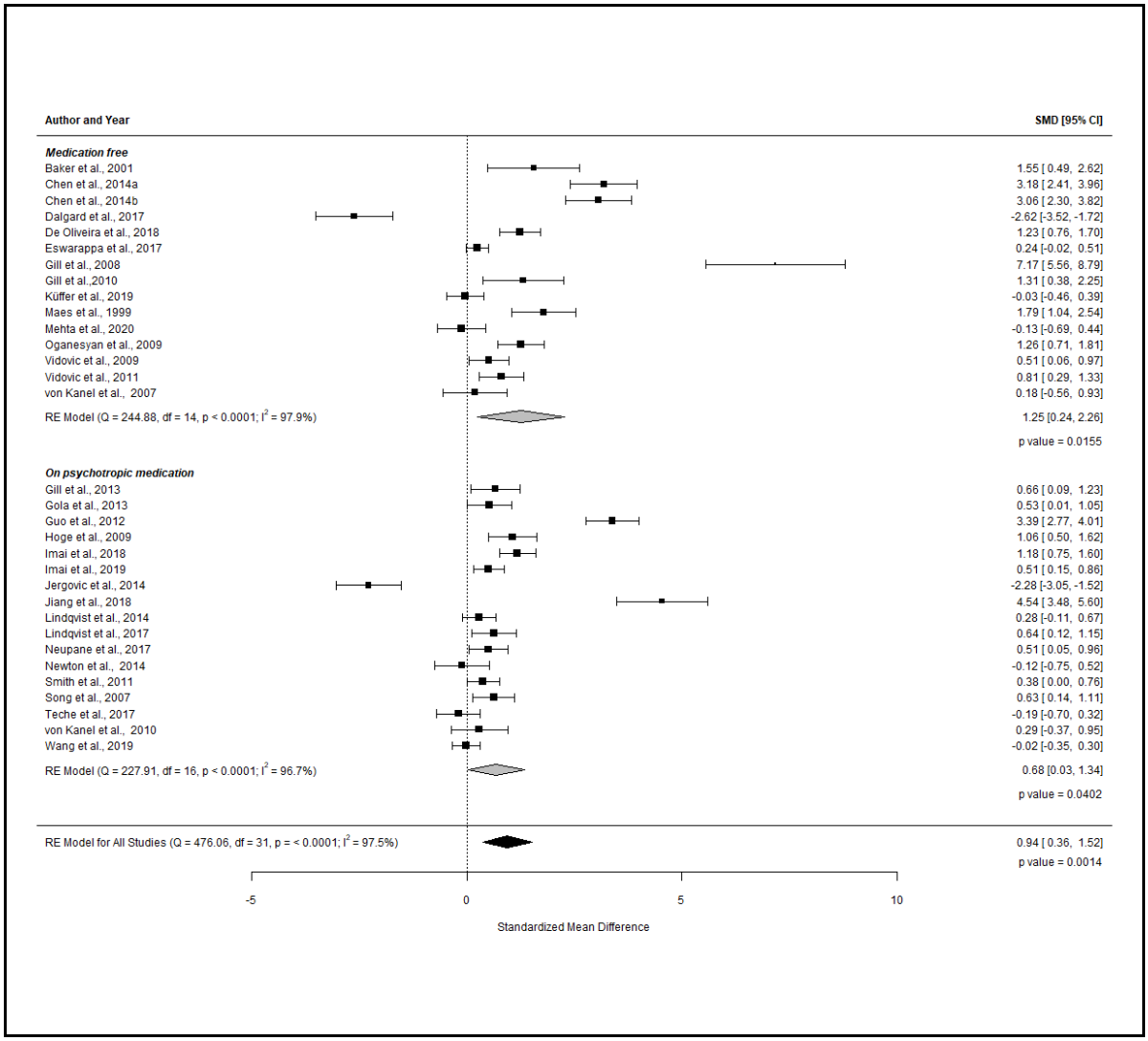
19. Supplementary figure 7 – Forest Plot – Meta-analysis of interleukin 4

Meta-analysis comparing patients and controls. PTSD: post-traumatic stress disorder; SD: standard deviation; SMD: standardised mean difference.



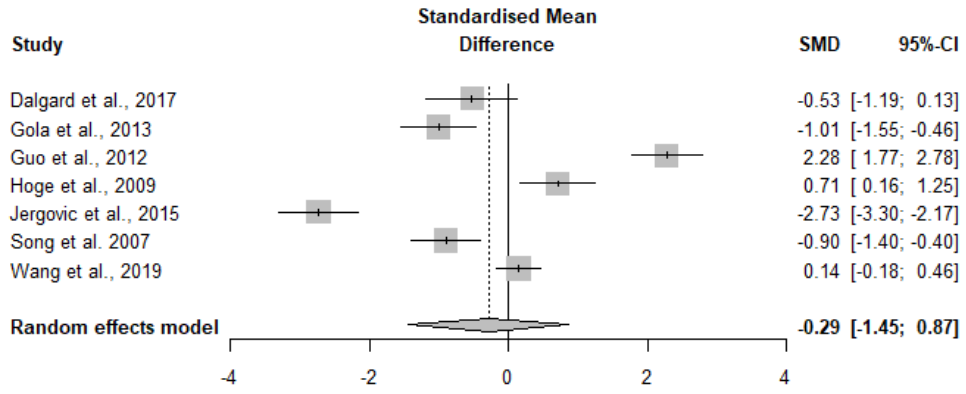
20. Supplementary figure 8 – Forest Plot – Subgroup meta-analysis of interleukin 6 with and without MDD.

MDD: major depressive disorder; SD: standard deviation; SMD: standardised mean difference.



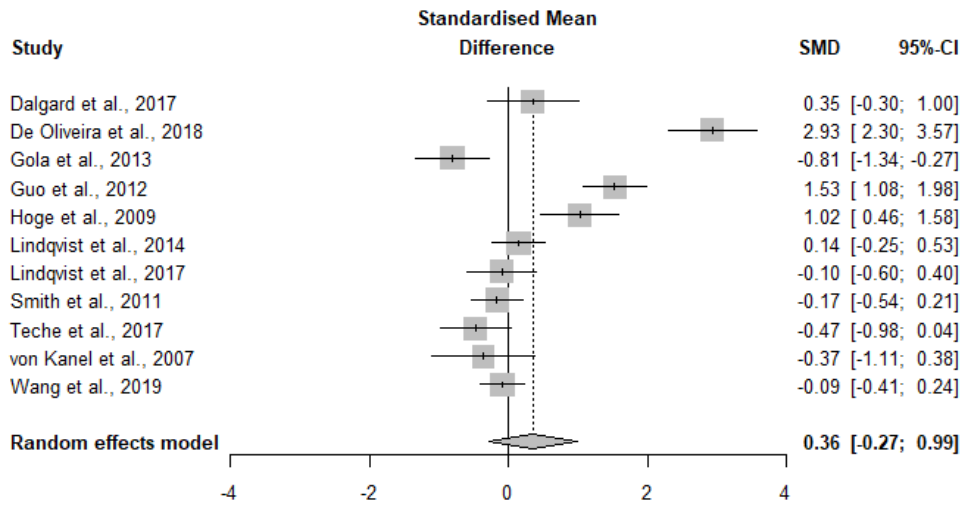
21. Supplementary figure 9 – Forest Plot – Subgroup meta-analysis of interleukin 6 with and without medication.

SD: standard deviation; SMD: standardised mean difference.



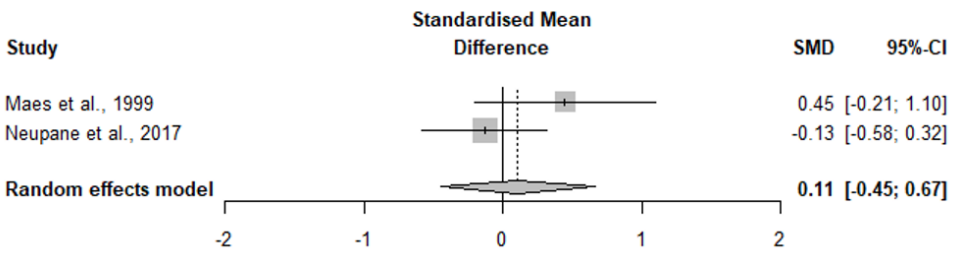
22. Supplementary figure 10 – Forest Plot – Meta-analysis of interleukin 8.

Meta-analysis comparing patients and controls. PTSD: post-traumatic stress disorder; SD: standard deviation; SMD: standardised mean difference.



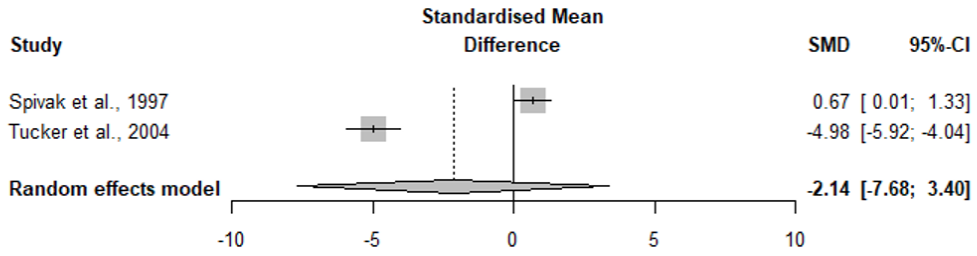
23. Supplementary figure 11 – Forest Plot – Meta-analysis of interleukin 10

Meta-analysis comparing patients and controls. PTSD: post-traumatic stress disorder; SD: standard deviation; SMD: standardised mean difference.



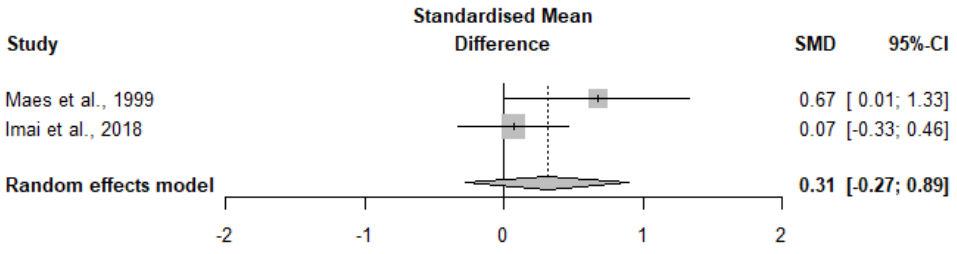
24. Supplementary figure 12 – Forest Plot – Meta-analysis of interleukin 1RA

Meta-analysis comparing patients and controls. PTSD: post-traumatic stress disorder; SD: standard deviation; SMD: standardised mean difference.



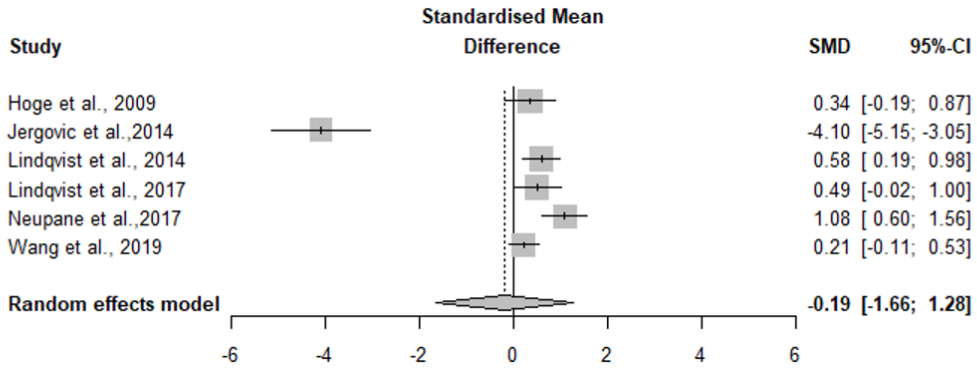
25. Supplementary figure 13 – Forest Plot – Meta-analysis of soluble IL-2 receptor

Meta-analysis comparing patients and controls. IL: interleukin; PTSD: post-traumatic stress disorder; SD: standard deviation; SMD: standardised mean difference.



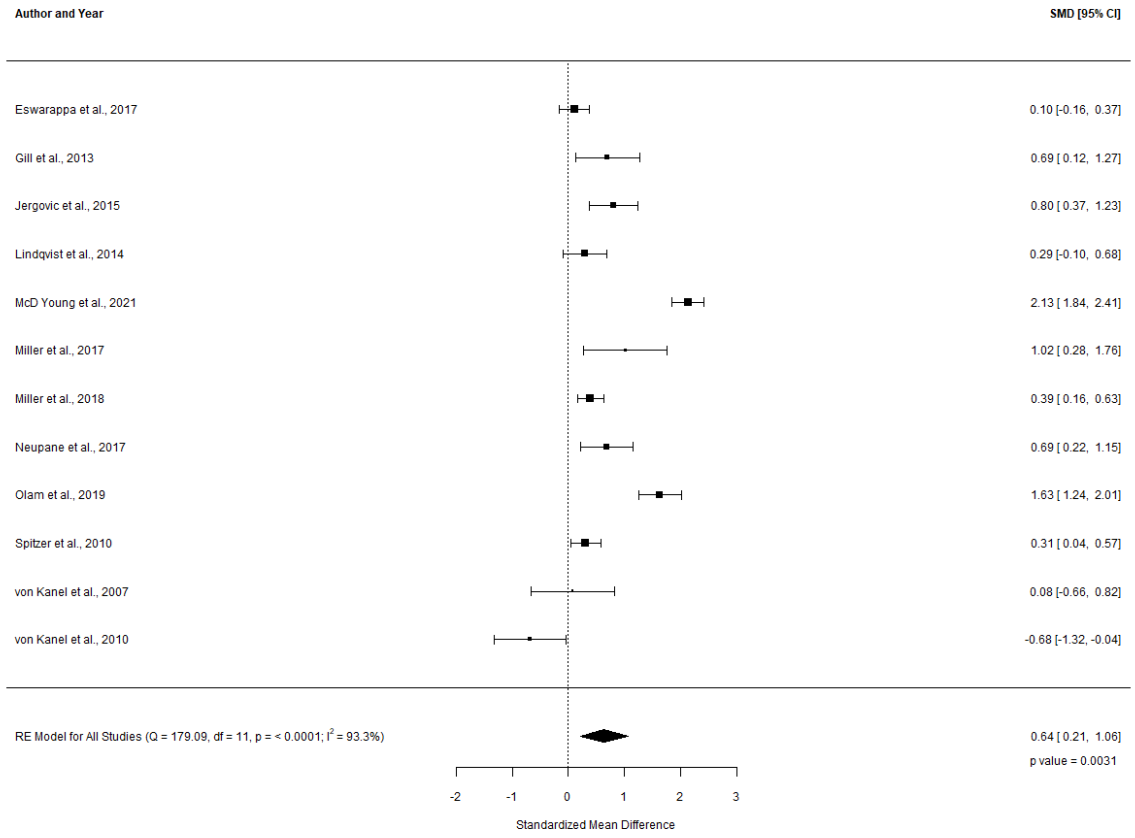
26. Supplementary figure 14 – Forest Plot – Meta-analysis of soluble IL-6 receptor

Meta-analysis comparing patients and controls. IL: interleukin; PTSD: post-traumatic stress disorder; SD: standard deviation; SMD: standardised mean difference.



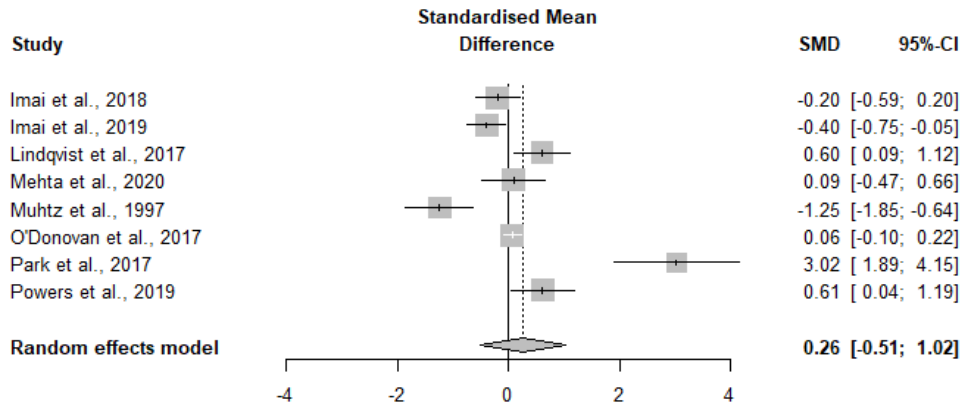
27. Supplementary figure 15 – Forest Plot – Meta-analysis of interferon-γ

Meta-analysis comparing patients and controls. PTSD: post-traumatic stress disorder; SD: standard deviation; SMD: standardised mean difference.



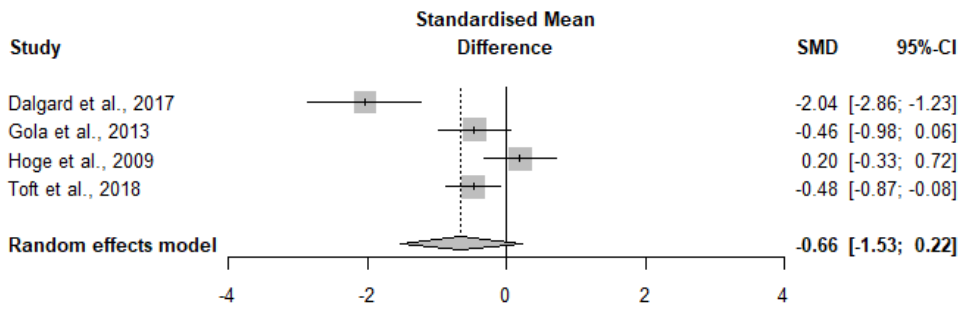
28. Supplementary figure 16 – Forest Plot – Meta-analysis of C-reactive protein.

Meta-analysis comparing patients and controls. PTSD: post-traumatic stress disorder; SD: standard deviation; SMD: standardised mean difference.



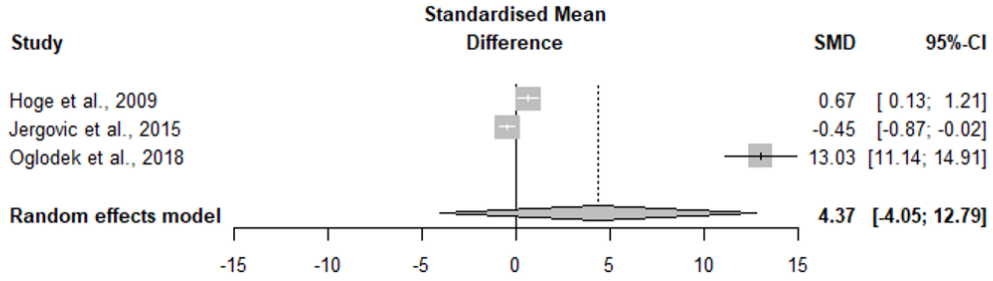
29. Supplementary figure 17 – Forest Plot – Meta-analysis of hs-C-reactive protein

Meta-analysis comparing patients and controls. hs: high sensitivity; PTSD: post-traumatic stress disorder; SD: standard deviation; SMD: standardised mean difference.



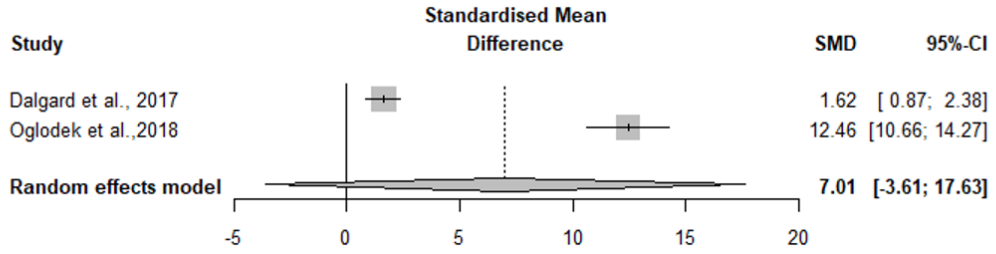
30. Supplementary figure 18 – Forest Plot – Meta-analysis of MCP-1

Meta-analysis comparing patients and controls. MCP-1: monocyte chemoattractant protein-1; PTSD: post-traumatic stress disorder; SD: standard deviation; SMD: standardised mean difference.



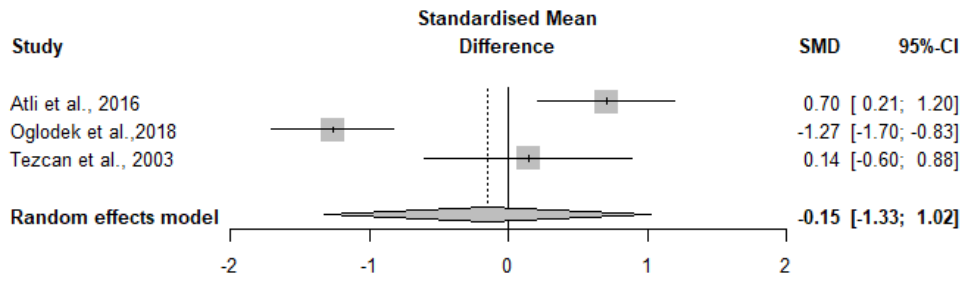
31. Supplementary figure 19 – Forest Plot – Meta-analysis of MIP-1 α (or CCL3)

Meta-analysis comparing patients and controls. MIP-1 α: macrophage inflammatory protein 1 alpha; PTSD: post-traumatic stress disorder; SD: standard deviation; SMD: standardised mean difference.



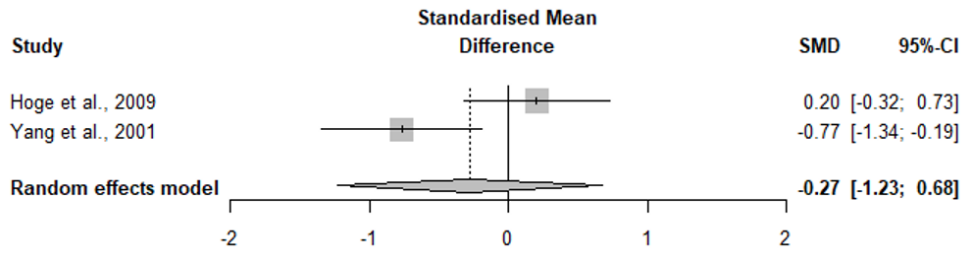
32. Supplementary figure 20 – Forest Plot – Meta-analysis of MIP-1 β (or CCL4)

Meta-analysis comparing patients and controls. MIP-1 β: macrophage inflammatory protein 1 beta; PTSD: post-traumatic stress disorder; SD: standard deviation; SMD: standardised mean difference.



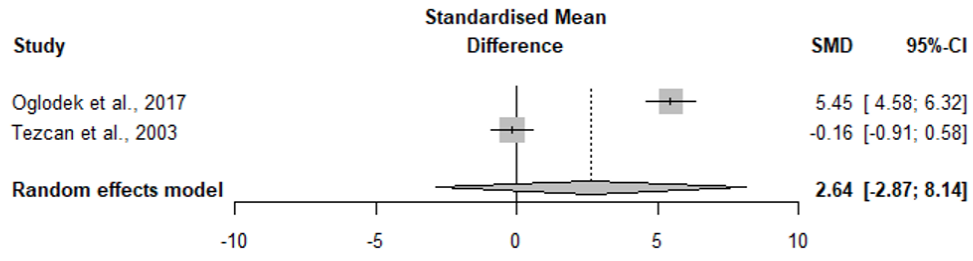
33. Supplementary figure 21 – Forest Plot – Meta-analysis of Malondialdehyde

Meta-analysis comparing patients and controls. PTSD: post-traumatic stress disorder; SD: standard deviation; SMD: standardised mean difference.



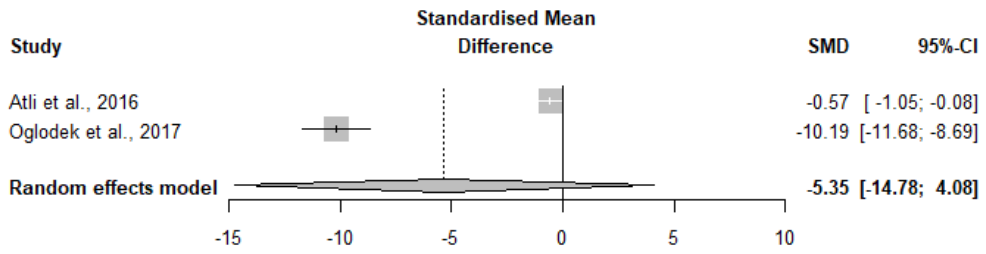
34. Supplementary figure 22 – Forest Plot – Meta-analysis of GM-CSF

Meta-analysis comparing patients and controls. GM-CSF: granulocyte-macrophage colony-stimulating factor; PTSD: post-traumatic stress disorder; SD: standard deviation; SMD: standardised mean difference.



35. Supplementary figure 23 – Forest Plot – Meta-analysis of catalase

Meta-analysis comparing patients and controls. PTSD: post-traumatic stress disorder; SD: standard deviation; SMD: standardised mean difference.



36. Supplementary figure 24 – Forest Plot – Meta-analysis of paraoxonase-1

Meta-analysis comparing patients and controls. PTSD: post-traumatic stress disorder; SD: standard deviation; SMD: standardised mean difference.

5.2.Artigo 2 – "*Changes in Inflammatory and oxidative stress markers after treatment in posttraumatic stress disorder: a systematic review*."

Carta de Submissão

Manuscript Number: PSY-D-22-00849
Changes in Inflammatory and oxidative stress markers after treatment in posttraumatic stress disorder: a systematic review.

Dear Professor Passos,

Your above-referenced submission has been assigned a manuscript number: PSY-D-22-00849.

To track the status of your manuscript, please log in as an author at https://www.editorialmanager.com/psy/, and navigate to the "Submissions Being Processed" folder.

Thank you for submitting your work to this journal.

Kind regards,
Psychiatry Research

6. CONSIDERAÇÕES FINAIS

O Transtorno de Estresse Pós-Traumático é um transtorno debilitante que se desenvolve após a exposição a eventos traumáticos, com importantes impactos sociais e econômicos, podendo esses efeitos ser duradouros. Por exemplo, estudos mostraram que sobreviventes de terremoto exibiram sintomas de ansiedade, de TEPT e redução da qualidade de vida mesmo após 23 anos após o incidente (KHACHADOURIAN et al., 2015).

O diagnóstico de TEPT é baseado na exposição a um trauma grave, juntamente com sintomas de reexperiência intrusiva, evitação e alterações negativas persistentes na cognição, humor e excitação (DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS: DSM-5, 2013). Esses critérios não levam em conta anormalidades biológicas subjacentes. Isso dificulta o tratamento farmacológico, pois não são identificados "alvos" bioquímicos claros para a farmacoterapia. Além disso, pacientes com TEPT frequentemente exibem comorbidades clínicas, tais como doença cardiovascular, síndrome metabólica, diabetes mellitus tipo II e doenças autoimunes (BERSANI et al. 2020). Todas essas patologias estão intimamente relacionadas ao estresse oxidativo e à inflamação. Pode-se, então, presumir que os mecanismos subjacentes do TEPT envolvem a desregulação do sistema imunológico (KIM et al. 2020), o que sugere que o TEPT é um distúrbio sistêmico, e não apenas cerebral (MELLON et al. 2018), podendo contribuir para o envelhecimento acelerado (LOHR et al. 2015).

Assim, embora os sintomas psicocomportamentais sejam os principais fatores considerados ao investigar o estado patológico e a gravidade do TEPT, entender as alterações imunológicas que ocorrem em conjunto com esses sintomas pode ser elucidativo (KIM et al. 2019) (QUINONES et al. 2020). As causas da inflamação no TEPT não são claras, mas podem envolver determinantes genéticos associados a uma "inflamação estéril" em resposta a padrões moleculares associados a danos, estados hipercatecolaminérgicos e hipocortisolêmicos induzidos pelo estresse crônico (MELLON et al. 2018).

Passos e colaboradores (2015) publicaram uma metanálise prévia, examinando marcadores inflamatórios no TEPT (PASSOS et al. 2015). Este estudo destacou que o peso das evidências apoia o conceito de que o TEPT é associado a níveis elevados de citocinas pró-inflamatórias, como IL-6, IL-1β, TNF-α e IFN-γ. Contudo, o estudo apresentou algumas

limitações: poucos estudos foram incluídos nas metanálises e o estudo não incluiu marcadores de estresse oxidativo. Além disso, o tipo de trauma e a fração sanguínea avaliada (soro versus plasma) não foram explorados como potenciais moderadores dos tamanhos de efeito. A presente metanálise incluiu 34 estudos adicionais em comparação com a revisão sistemática anterior, também investigando marcadores de estresse oxidativo na análise. Os resultados confirmaram os achados do estudo anterior em relação ao aumento das concentrações de IL-6 e TNF-α no TEPT. Esses achados permaneceram significativos mesmo após a exclusão de estudos que avaliaram pacientes em uso de medicamentos psicotrópicos. No entanto, tivemos um achado inesperado, uma vez que os níveis de IL-6 e TNF-α não foram maiores no subgrupo com transtorno depressivo maior quando comparados aos controles. Adicionalmente, com a inclusão de mais estudos, constatou-se que a concentração da PCR é significativamente maior em pacientes com TEPT em comparação com controles, diferentemente do encontrado no estudo anterior. Por outro lado, IFN-γ e IL-1β deixaram de ser significativos. IL-1β tornou-se marginalmente significativo ao avaliar a diferença de IL-1β em pacientes com TEPT sem TDM comórbido em comparação aos controles. Nenhum marcador de estresse oxidativo foi significativamente associado ao TEPT. Além disso, nosso objetivo inicial era avaliar variáveis como uso de tabaco ou exercícios como moderadores em modelos de meta-regressão. No entanto, essas análises não foram realizadas porque essas variáveis raramente foram relatadas.

Embora os estudos incluídos tenham avaliado marcadores sanguíneos, a ativação imune também pode ser encontrada no líquido cefalorraquidiano no TEPT (BAKER et al. 2012) Além disso, existem vários mecanismos para a comunicação do sistema imunológico periférico com o cérebro, incluindo o transporte através de regiões com vazamento da barreira hematoencefálica, como os órgãos circunventriculares, estimulação de aferentes vagais e tráfico de monócitos ativados ou outras células imunes para o cérebro (BERSANI et al. 2020). A neuroinflamação, por sua vez, pode alterar o funcionamento cerebral, como impactar a disponibilidade de serotonina, catecolamina e glutamato, aumentar o estresse oxidativo e o metabólito neurotóxico ácido quinolínico e acentuar a resposta da amígdala a situações ameaçadoras (HORI and KIM 2019).

Com base nesses achados e no fato de que os medicamentos convencionalmente indicados para o TEPT têm mostrado eficácia limitada, um segundo estudo foi desenvolvido, com objetivo de avaliar estudos que pesquisassem opções de tratamento farmacológico para o TEPT com ação nos marcadores inflamatórios e de estresse oxidativo. Nesta segunda revisão, foram detectados 7 estudos que investigaram alterações nos marcadores de estresse inflamatório e oxidativo após tratamento em pacientes com TEPT. A maioria deles procurou avaliar

alterações no cortisol. Quatro estudos incluíram alterações nos níveis de citocinas em sua análise e 3 estudos analisaram a PCR. Nenhum dos estudos avaliou o efeito do tratamento medicamentoso no estresse oxidativo. Cerca de 85% dos estudos utilizaram o DSM-IV como critério diagnóstico. Os estudos foram homogêneos em termos de instrumentos utilizados para avaliar a gravidade dos sintomas de TEPT e a resposta clínica ao tratamento. Apenas 2 estudos utilizaram medicamentos alternativos como opção de tratamento. Em ambos os casos, foram utilizados probióticos. Embora os resultados desses 2 estudos tenham sido discrepantes, algumas diferenças entre os dois ensaios podem ser responsáveis pelas respostas distintas encontradas, como os critérios de seleção da amostra e a gravidade dos sintomas de TEPT. Os demais estudos avaliaram a resposta clínica e imunológica a psicofármacos, mais especificamente aos ISRS e à vilazodona. Em todos esses artigos, houve melhora nos sintomas do TEPT. No entanto, os marcadores inflamatórios observados foram significativamente alterados em apenas duas análises: o estudo de Vermetten et al., que avaliou o uso de paroxetina em pacientes por 12 meses, e o estudo de Tucker et al., que avaliou a uso dos ISRS sertralina e citalopram. Assim, embora nesses estudos os ISRS tenham provado sua eficácia clínica, seu potencial como agente anti-inflamatório e as possíveis explicações para isso permanecem sendo objeto de pesquisa. Possíveis explicações para a redução da neuroinflamação são a redução das citocinas circulantes no sangue e tecido cerebral, assim como através da regulação de vias inflamatórias complexas. Além disso, uma questão chave a ser avaliada em estudos futuros é se os resultados positivos encontrados com o tratamento com ISRSs é uma consequência da modulação imunológica e se os mecanismos imunológicos são responsáveis quando o tratamento com ISRS é ineficaz (WANG and YOUNG 2016).

Não foram encontrados ensaios clínicos randomizados (ECR) investigando agentes anti-inflamatórios, como anti-inflamatórios não esteroides, inibidores da ciclooxigenase-2 e outros medicamentos que já demonstraram ter associação a efeitos antidepressivos em indivíduos deprimidos cujos marcadores inflamatórios prévios ao tratamento encontravam-se elevados (KOHLER et al. 2016). A hidrocortisona tem sido estudada no TEPT como agente potencializador em tratamentos psicoterapêuticos ou como agente de prevenção ao TEPT em indivíduos submetidos a situações traumáticas com alguma evidência de eficácia. Porém em nenhum deles os marcadores inflamatórios foram avaliados antes e depois do tratamento (YEHUDA et al. 2015; SURÍS et al. 2010; KOTHGASSNER et al. 2021). Devido à relativa segurança de vários anti-inflamatórios, acreditamos que ensaios com anti-inflamatórios devem ser futuramente conduzidos em pacientes com TEPT. Um cuidado deve ser tomado, selecionando-se pacientes com hiperativação imunológica basal, visto que estudos no TDM

utilizando o infliximabe, um bloqueador de TNF-α, melhorou significativamente os sintomas depressivos apenas no subgrupo de pacientes com marcadores inflamatórios elevados previamente ao tratamento (RAISON et al. 2013).

Em resumo, há fortes evidências que demonstram que tanto a exposição a traumas, quanto o desenvolvimento de TEPT estão associados a fatores imunológicos pró-inflamatórios, com consequências sistêmicas importantes para os pacientes (WANG and YOUNG 2016). Estudos futuros irão precisar buscar entender quais sintomas específicos são provocados por citocinas e quais circuitos no cérebro são afetados pela passagem de citocinas através da barreira hematoencefálica (NEYLAN and O'DONOVAN 2019). Sabemos que um dos desafios significativos para estudar a associação imune com TEPT é a variabilidade no tipo e gravidade da exposição ao trauma que levou ao TEPT. Resultados mais conclusivos podem ser obtidos com uma população de indivíduos rigidamente controlada e relativamente homogênea, com alguns tendo TEPT e outros não (WANG and YOUNG 2016). Além disso, os níveis de resposta abaixo do esperado nos tratamentos atualmente disponíveis para TEPT exige a exploração de tratamentos alternativos. Assim, fatores imunológicos devem ser direcionados em novas terapêuticas para evitar o acúmulo de comorbidades e declínio cognitivo decorrente da neuroprogressão em pacientes que permanecem cronicamente sintomáticos.

7. REFERÊNCIAS

AMERICAN PSYCHIATRIC ASSOCIATION. (org.). **Diagnostic and Statistical Manual of Mental Disorders (3rd ed. revised). DSM-III-R**. [*S. l.: s. n.*], 1987.

ATLI, Abdullah *et al.* Altered lipid peroxidation markers are related to post-traumatic stress disorder (PTSD) and not trauma itself in earthquake survivors. **European archives of psychiatry and clinical neuroscience**, [*s. l.*], v. 266, n. 4, p. 329–336, 2016. Disponível em: https://doi.org/10.1007/s00406-015-0638-5

AUPPERLE, Robin L. *et al.* Dorsolateral prefrontal cortex activation during emotional anticipation and neuropsychological performance in posttraumatic stress disorder. **Archives of general psychiatry**, [*s. l.*], v. 69, n. 4, p. 360–371, 2012. Disponível em: https://doi.org/10.1001/archgenpsychiatry.2011.1539

BAUMERT, Jens *et al.* No evidence for an association of posttraumatic stress disorder with circulating levels of CRP and IL-18 in a population-based study. **Cytokine**, [*s. l.*], v. 63, n. 2, p. 201–208, 2013. Disponível em: https://doi.org/10.1016/j.cyto.2013.04.033

BOROVAC ŠTEFANOVIĆ, Leda *et al.* Cytokines and metabolic syndrome in Croatian war veterans with post-traumatic stress disorder (PTSD). **Abstracts HDBMB**, [*s. l.*], p. 75, 2016. Disponível em: https://www.bib.irb.hr/821169?rad=821169. Acesso em: 12 abr. 2021.

BREMNER, J. Douglas *et al.* Structural and functional plasticity of the human brain in posttraumatic stress disorder. **Progress in brain research**, [*s. l.*], v. 167, p. 171–186, 2008. Disponível em: https://doi.org/10.1016/S0079-6123(07)67012-5

BUTOVSKY, Oleg; WEINER, Howard L. Microglial signatures and their role in health and disease. **Nature reviews. Neuroscience**, [*s. l.*], v. 19, n. 10, p. 622–635, 2018. Disponível em: https://doi.org/10.1038/s41583-018-0057-5

DANTZER, Robert *et al.* From inflammation to sickness and depression: when the immune

system subjugates the brain. **Nature reviews. Neuroscience**, [*s. l.*], v. 9, n. 1, p. 46–56, 2008. Disponível em: https://doi.org/10.1038/nrn2297

DENNIS, Paul A. *et al.* An investigation of vago-regulatory and health-behavior accounts for increased inflammation in posttraumatic stress disorder. **Journal of psychosomatic research**, [*s. l.*], v. 83, p. 33–39, 2016. Disponível em: https://doi.org/10.1016/j.jpsychores.2016.02.008

DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS, 4TH ED. **https://psycnet.apa.org › record › 1...https://psycnet.apa.org › record › 1...**, Arlington, VA, US, v. 4, p. 886, 1994. Disponível em: https://psycnet.apa.org/fulltext/1994-97698-000.pdf

DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS: DSM-5. [*S. l.*]: Amer Psychiatric Pub Incorporated, 2013. Disponível em: https://doi.org/10.1176/appi.books.9780890425596

DOWLATI, Yekta *et al.* A meta-analysis of cytokines in major depression. **Biological psychiatry**, [*s. l.*], v. 67, n. 5, p. 446–457, 2010. Disponível em: https://doi.org/10.1016/j.biopsych.2009.09.033

EGGER, M. *et al.* Bias in meta-analysis detected by a simple, graphical test. **BMJ** , [*s. l.*], v. 315, n. 7109, p. 629–634, 1997. Disponível em: https://doi.org/10.1136/bmj.315.7109.629

HIGGINS, J. P. T.; GREEN, S. Recommendations on testing for funnel plot asymmetry. **Cochrane Handbook for Systematic Reviews of Interventions Version**, [*s. l.*], v. 5, n. 0, 2011.

HIGGINS, J. P. T.; THOMPSON, S. G. Quantifying heterogeneity in a meta-analysis. **Statistics in medicine**, [*s. l.*], 2002. Disponível em: https://onlinelibrary.wiley.com/doi/abs/10.1002/sim.1186?casa_token=zIEJCR6wg8gAAAAA:sScSNrdy7PwC8qFJ0uP7DyHMFLsSYZBuZYsB_J-nYULRcKhvHKdKD53Y5J7c5-aWXMvJ54_Pmz4LDA

HIGGINS, Julian P. T. *et al.* **Cochrane Handbook for Systematic Reviews of Interventions**. [*S. l.*]: John Wiley & Sons, 2019. *E-book*.

HIGGINS, Julian P. T. *et al.* Measuring inconsistency in meta-analyses. **BMJ** , [*s. l.*], v. 327, n. 7414, p. 557–560, 2003. Disponível em: https://doi.org/10.1136/bmj.327.7414.557

HORI, H.; KIM, Y. Inflammation and post-traumatic stress disorder. **Psychiatry and clinical neurosciences**, [*s. l.*], 2019. Disponível em: https://onlinelibrary.wiley.com/doi/abs/10.1111/pcn.12820

HOWREN, M. Bryant; LAMKIN, Donald M.; SULS, Jerry. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. **Psychosomatic medicine**, [*s. l.*], v. 71, n. 2, p. 171–186, 2009. Disponível em: https://journals.lww.com/psychosomaticmedicine/Fulltext/2009/02000/Associations_of_Depression_With_C_Reactive.6.aspx?casa_token=agG0wQr3tXUAAAAA:3pOeo1LWHHJgfg5qIx7_KI469JD5EesjFspTZM5K8GBgFHuYKUGzVYZcf-bqbBfYXxHZYoo0EqEpWBIepSIlwwoJHFHRHg

INAGAKI, Tristen K. *et al.* Inflammation selectively enhances amygdala activity to socially threatening images. **NeuroImage**, [*s. l.*], v. 59, n. 4, p. 3222–3226, 2012. Disponível em: https://doi.org/10.1016/j.neuroimage.2011.10.090

KIM, Tammy D.; LEE, Suji; YOON, Sujung. Inflammation in Post-Traumatic Stress Disorder (PTSD): A Review of Potential Correlates of PTSD with a Neurological Perspective. **Antioxidants (Basel, Switzerland)**, [*s. l.*], v. 9, n. 2, 2020. Disponível em: https://doi.org/10.3390/antiox9020107

KOENEN, K. C. *et al.* Posttraumatic stress disorder in the World Mental Health Surveys. **Psychological medicine**, [*s. l.*], v. 47, n. 13, p. 2260–2274, 2017. Disponível em: https://doi.org/10.1017/S0033291717000708

LEVIN, S. G.; GODUKHIN, O. V. Modulating Effect of Cytokines on Mechanisms of Synaptic Plasticity in the Brain. **Biochemistry. Biokhimiia**, [*s. l.*], v. 82, n. 3, p. 264–274, 2017. Disponível em: https://doi.org/10.1134/S000629791703004X

LI, Lei *et al.* Grey matter reduction associated with posttraumatic stress disorder and traumatic stress. **Neuroscience and biobehavioral reviews**, [*s. l.*], v. 43, p. 163–172, 2014. Disponível em: https://doi.org/10.1016/j.neubiorev.2014.04.003

MARSLAND, Anna L. *et al.* **The effects of acute psychological stress on circulating and stimulated inflammatory markers: A systematic review and meta-analysis**. [*S. l.: s. n.*], 2017. Disponível em: https://doi.org/10.1016/j.bbi.2017.01.011

MARTIN, Paul; LEIBOVICH, S. Joseph. Inflammatory cells during wound repair: the good, the bad and the ugly. **Trends in cell biology**, [*s. l.*], v. 15, n. 11, p. 599–607, 2005. Disponível em: https://doi.org/10.1016/j.tcb.2005.09.002

MILLER, Brian J. *et al.* **Meta-Analysis of Cytokine Alterations in Schizophrenia: Clinical Status and Antipsychotic Effects**. [*S. l.: s. n.*], 2011. Disponível em: https://doi.org/10.1016/j.biopsych.2011.04.013

MILLER, Mark W. *et al.* Oxidative Stress, Inflammation, and Neuroprogression in Chronic PTSD. **Harvard review of psychiatry**, [*s. l.*], v. 26, n. 2, p. 57–69, 2018. Disponível em: https://doi.org/10.1097/HRP.0000000000000167

MILLER, M. W. *et al.* CRP polymorphisms and DNA methylation of the AIM2 gene influence associations between trauma exposure, PTSD, and C-reactive protein. **Brain, behavior, and immunity**, [*s. l.*], v. 67, p. 194–202, 2018. Disponível em: https://doi.org/10.1016/j.bbi.2017.08.022

MODABBERNIA, Amirhossein *et al.* Cytokine alterations in bipolar disorder: a meta-analysis of 30 studies. **Biological psychiatry**, [*s. l.*], v. 74, n. 1, p. 15–25, 2013. Disponível em: https://doi.org/10.1016/j.biopsych.2013.01.007

MOHER, David *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. **PLoS medicine**, [*s. l.*], v. 6, n. 7, p. e1000097, 2009. Disponível em: https://doi.org/10.1371/journal.pmed.1000097

NORRHOLM, Seth D.; JOVANOVIC, Tanja. Tailoring therapeutic strategies for treating posttraumatic stress disorder symptom clusters. **Neuropsychiatric disease and treatment**, [*s. l.*], v. 6, p. 517–532, 2010. Disponível em: https://doi.org/10.2147/NDT.S10951

PASSOS, Ives Cavalcante *et al.* Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. **The lancet. Psychiatry**, [*s. l.*], v. 2, n. 11, p. 1002–1012, 2015. Disponível em: https://doi.org/10.1016/S2215-0366(15)00309-0

PATEL, Sachin; WINDER, Danny G. **An odyssey of fear: Homer stresses new mechanisms**. **Biological psychiatry**, 2010. Disponível em: https://doi.org/10.1016/j.biopsych.2010.10.005

PICHOT, P. [DSM-III: the 3d edition of the Diagnostic and Statistical Manual of Mental Disorders from the American Psychiatric Association]. **Revue neurologique**, [*s. l.*], v. 142, n. 5, p. 489–499, 1986. Disponível em: https://www.ncbi.nlm.nih.gov/pubmed/3787052

PRASAD, Kedar N. **Treat Concussion, TBI, and PTSD with Vitamins and Antioxidants**. [*S. l.*]: Simon and Schuster, 2015. *E-book*.

RENAULT, P. F. *et al.* Psychiatric complications of long-term interferon alfa therapy. **Archives of internal medicine**, [*s. l.*], v. 147, n. 9, p. 1577–1580, 1987. Disponível em: https://www.ncbi.nlm.nih.gov/pubmed/3307672

RÉUS, G. Z. *et al.* The role of inflammation and microglial activation in the pathophysiology

of psychiatric disorders. **Neuroscience**, [*s. l.*], v. 300, p. 141–154, 2015. Disponível em: https://doi.org/10.1016/j.neuroscience.2015.05.018

ROSSIGNOL, D. A.; FRYE, R. E. A review of research trends in physiological abnormalities in autism spectrum disorders: immune dysregulation, inflammation, oxidative stress, mitochondrial dysfunction and environmental toxicant exposures. **Molecular psychiatry**, [*s. l.*], v. 17, n. 4, p. 389–401, 2012. Disponível em: https://doi.org/10.1038/mp.2011.165

SASAYAMA, Daimei *et al.* Increased cerebrospinal fluid interleukin-6 levels in patients with schizophrenia and those with major depressive disorder. **Journal of psychiatric research**, [*s. l.*], v. 47, n. 3, p. 401–406, 2013. Disponível em: https://doi.org/10.1016/j.jpsychires.2012.12.001

SONG, Huan *et al.* Association of Stress-Related Disorders With Subsequent Autoimmune Disease. **JAMA: the journal of the American Medical Association**, [*s. l.*], v. 319, n. 23, p. 2388–2400, 2018. Disponível em: https://doi.org/10.1001/jama.2018.7028

STEIN, Dan J. *et al.* Integrating mental health with other non-communicable diseases. **BMJ** , [*s. l.*], v. 364, p. l295, 2019. Disponível em: https://doi.org/10.1136/bmj.l295

STRANG, F. *et al.* Amyloid plaques dissociate pentameric to monomeric C-reactive protein: a novel pathomechanism driving cortical inflammation in Alzheimer's disease? **Brain: a journal of neurology**, [*s. l.*], 2012. Disponível em: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1750-3639.2011.00539.x

TAKAKI, Junpei *et al.* **L-glutamate released from activated microglia downregulates astrocytic L-glutamate transporter expression in neuroinflammation: the "collusion" hypothesis for increased extracellular L-glutamate concentration in neuroinflammation**. [*S. l.: s. n.*], 2012. Disponível em: https://doi.org/10.1186/1742-2094-9-275

TEAM, R. C. R: A Language and Environment for Statistical Computing. 887 R Foundation for Statistical Computing, Vienna, Austria. **URL https://www**, [*s. l.*], 2017. Disponível em: https://scholar.google.ca/scholar?cluster=6111971073386142988&hl=en&as_sdt=0,5&sciodt=0,5

TORTELLA-FELIU, Miquel *et al.* Risk factors for posttraumatic stress disorder: An umbrella review of systematic reviews and meta-analyses. **Neuroscience and biobehavioral reviews**, [*s. l.*], v. 107, p. 154–165, 2019. Disponível em: https://doi.org/10.1016/j.neubiorev.2019.09.013

TURSICH, M. *et al.* Association of trauma exposure with proinflammatory activity: a

transdiagnostic meta-analysis. **Translational psychiatry**, [*s. l.*], v. 4, p. e413, 2014. Disponível em: https://doi.org/10.1038/tp.2014.56

VIECHTBAUER, Wolfgang. Conducting Meta-Analyses inRwith themetaforPackage. **Journal of statistical software**, [*s. l.*], v. 36, n. 3, p. 1–48, 2010. Disponível em: https://doi.org/10.18637/jss.v036.i03. Acesso em: 13 jan. 2021.

YASOJIMA, K. *et al.* Human neurons generate C-reactive protein and amyloid P: upregulation in Alzheimer's disease. **Brain research**, [*s. l.*], v. 887, n. 1, p. 80–89, 2000. Disponível em: https://doi.org/10.1016/s0006-8993(00)02970-x

YEHUDA, Rachel *et al.* Post-traumatic stress disorder. **Nature reviews. Disease primers**, [*s. l.*], v. 1, p. 15057, 2015. Disponível em: https://doi.org/10.1038/nrdp.2015.57

YEHUDA, R.; MCFARLANE, A. C. Conflict between current knowledge about posttraumatic stress disorder and its original conceptual basis. **The American journal of psychiatry**, [*s. l.*], v. 152, n. 12, p. 1705–1713, 1995. Disponível em: https://doi.org/10.1176/ajp.152.12.1705