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THIAGO HOLANDA FREITAS

CITOCINAS E QUIMIOCINAS COMO BIOMARCADORES TERAPÊUTICOS NA DEPRESSÃO: REVISÃO SISTEMÁTICA E META-ANÁLISE

FORTALEZA

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Tese de doutorado apresentada à Universidade Federal do Ceará, como parte das exigências do Programa de Pós-Graduação em Ciências Médicas para a obtenção do título de Doutor.

Orientador: Prof. Dr. André Férrer Carvalho.

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FORTALEZA-CE
2017

“Há verdadeiramente duas coisas diferentes: saber e crer que se sabe. A ciência consiste em saber; em crer que se sabe reside a ignorância."

Hipócrates

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RESUMO

Thiago Holanda Freitas. Citocinas e quimiocinas como biomarcadores terapêuticos na depressão: Revisão Sistemática e Metanálise

Um considerável corpo de evidência sugere que alterações em vias imuno-inflamatórias contribuem para a fisiopatologia do Transtorno Depressivo Maior (TDM), e indivíduos com TDM podem ter níveis elevados predominantemente de citocinas pró-inflamatórias. Metanálises prévias sugerem que o tratamento com fármacos antidepressivos pode diminuir o nível periférico de interleucina-1 beta (IL-1β) e IL-6. Recentemente foram publicados muitos novos estudos examinando o efeito dos antidepressivos nestas citocinas e portanto foi realizada uma Metanálise de estudos que avaliaram os níveis periféricos de citocinas e quimiocinas durante tratamento antidepressivo em pacientes com TDM. As bases de dados PubMed/MEDLINE, EMBASE e PsychInfo foram utilizadas, buscando referencias do seu início até 09 de março de 2017. Quarenta e cinco estudos preencheram critérios de inclusão (N=1517). Os níveis periféricos de IL-6, Fator de necrose tumoral alfa (TNF-α), IL-1β, IL-10, IL-2, IL-4, interferon-γ, IL-8, ligante C-C de quimiocinas (CCL-2), CCL-3, antagonista do receptor de IL-1, IL-13, IL-17, IL-5, IL-7 e o receptor solúvel de IL-2 foram medidos em pelo menos três bancos de dados e então foram metanalisados. O tratamento antidepressivo reduziu significativamente os níveis de IL-6 (g de Hedge= -0,454, P< 0,001), TNF-α (g= -0,202), IL-10 (g=-0,566), e CCL-2 (g= -1,502). Estes achados indicam que o tratamento antidepressivo diminui vários marcadores periféricos de inflamação. Entretanto esta metanálise não forneceu evidências de que a redução nos níveis inflamatórios está associada com resposta terapêutica, embora uma pequena parcela de estudos separem respondedores de não-respondedores.

Palavras-Chave: depressão; Metanálise; antidepressivo; citocinas; quimiocinas.

ABSTRACT

Thiago Holanda Freitas. Inflammatory Cytokines and chemokines as response biomarkers in major depression.

Mounting evidence suggests that aberrations in immune-inflammatory pathways contribute to the pathophysiology of major depressive disorder (MDD), and individuals with MDD may have elevated levels of predominantly pro-inflammatory cytokines and C-reactive protein. In addition, previous meta-analyses suggest that antidepressant drug treatment may decrease peripheral levels of interleukin-1 beta (IL-1β) and IL-6. Recently, several new studies examining the effect of antidepressants on these cytokines have been published, and so we performed an up-dated meta-analysis of studies that measured peripheral levels of cytokines and chemokines during antidepressant treatment in patients with MDD. The PubMed/MEDLINE, EMBASE, and PsycInfo databases were searched from inception through March 9th, 2017. Forty-five studies met inclusion criteria (N=1517). Peripheral levels of IL-6, tumor necrosis factor alpha (TNF-α), IL-1β, IL-10, IL-2, IL-4, interferon-γ, IL-8, the C-C motif ligand 2 chemokine (CCL-2), CCL-3, IL-1 receptor antagonist, IL-13, IL-17, IL-5, IL-7, and the soluble IL-2 receptor were measured in at least three datasets and thus were meta-analyzed. Antidepressant treatment significantly decreased peripheral levels of IL-6 (Hedges g = -0.454, P < 0.001), TNF-α (g = -0.202), IL-10 (g = -0.566), and CCL-2 (g = -1.502). These findings indicate that antidepressants decrease several markers of peripheral inflammation. However, this meta-analysis did not provide evidence that reductions in peripheral inflammation are associated with antidepressant treatment response although few studies provided separate data for treatment responders and non-responders.

Keywords: depression; meta-analysis; antidepressant; cytokines; chemokines; inflammatio

LISTA DE SÍMBOLOS E ABREVIATURAS

APA	*American Psychiatric Association*
CID-10	Classificação Internacional de Doenças – 10ª. edição
CCL	*Chemokine ligand*
DSM	Manual Estatístico e Diagnóstico dos Transtornos Mentais
HPA	Eixo hipotálamo-hipófise-adrenal
IDO	2,3-indoleamina desoxigenasse
IFN-gama	Interferon Gama
IL	Interleucina
IL-1Ra	Antagonista do receptor de interleucina 1
sIL-2R	Receptor solúvel de interleucina 2
SNC	Sistema Nervoso Central
TDM	Transtorno Depressivo Maior
TE	Tamanho de efeito
Th	Linfócito T helper
TNF-alfa	Fator de Necrose Tumoral Alfa

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INTRODUÇÃO

A depressão é um transtorno afetivo que pode causar impacto significativo no funcionamento social, ocupacional e em outras áreas da vida do indivíduo (GOODWIN & JAMISON, 2010). A prevalência em 12 meses da Depressão Maior é de 5,5% em países desenvolvidos e de 5,9% em países em desenvolvimento. No Brasil, a taxa maior é na população mais jovens (10,9%) (KESSLER *et al.*, 2010). Segundo a Organização Mundial de Saúde (OMS), a depressão é a quarta principal causa de incapacidade no mundo, e em 2020 estima-se que seja a segunda principal causa (KESSLER & BROMET, 2013).

Seus sintomas incluem perda do prazer ou do interesse, humor deprimido, choro fácil, alterações no sono, peso e apetite, além de dificuldade de concentração, baixa auto estima e idéias de morte ou até tentativas de suicídio. A mortalidade é alta, podendo chegar a 15% dos casos (DUMAN, 1998).

A etiologia da depressão está associada a fatores de vida estressantes, personalidade, gênero, adoecimento, história familiar, aspectos sociais e uso de substâncias psicoativas (ABELAIRA *et al.*, 2014). Embora sua fisiopatologia não esteja completamente conhecida, o transtorno pode estar associado a alterações na expressão de neurotransmissores, no eixo hipotálamo-hipófise-adrenal, em genes e em estruturas cerebrais.

A ativação de resposta inflamatória no sistema nervoso central (SNC) tem sido vista também como desempenhando um papel central na patogênese da depressão, devido a achados de níveis elevados de citocinas proinflamatórias em pacientes com sintomas depressivos tais como anedonia, humor deprimido e letargia (MILLER YOUNG, 2009).

As primeiras evidências de alteração na resposta imunoiflamatóra na depressão datam do início da década de 1980, quando foram documentadas alterações na imunidade celular em pacientes deprimidos hospitalizados. Os achados incluíam resposta linfocitária reduzida, hipercortisolismo, alteração na população de linfócitos B e T e elevação nos níveis de Prostaglandina E_2 (CALABRESE *et al.*, 1986).

Evidências mostram que a depressão resulta em uma desordem inflamatória, acompanhada por ativação mediada por anticorpos e a consequente liberação de citocinas inflamatórias (POSTAL & APPENZELLER, 2014). A maioria dos estudos atuais dão suporte à hipótese de um desbalanço na resposta linfocitária Th1/Th2 na depressão – com predominância da resposta Th1, com subsequente alteração da modulação celular no cérebro durante episódios depressivos ou estresse psicológico (MYINT *et al.*, 2005). Os antidepressivos parecem atenuar a resposta inflamatória e a hipercortisolemia por reduzir a

liberação de citocinas proinflamatórias pela micróglia ativada e por sensibilizar os receptores de glicocorticoides no eixo hipotálamo-hipófise-adrenal (LEONARD, 2014).

Com a descoberta de vários auto anticorpos em pacientes deprimidos, o estudo da autoimunidade na depressão se tornou cada vez mais importante. A evidência mais convincente do papel dos auto anticorpos na depressão observa-se no estudo de Katzav e colaboradores. A injeção intraventricular cerebral de anticorpos anti-P ribossomal levou a comportamento depressivo em roedores, e os anticorpos depositavam-se tipicamente no hipocampo, córtex cingulado e córtex olfatório piriforme primário (KATZAV *et al.*, 2007; CHEN *et al.*, 2011).

As citocinas compreendem um grupo heterogêneo de mensageiros moleculares que são produzidos por células imunocompetentes como linfócitos e macrófagos e que são secretadas pelos astrócitos e pela micróglia durante o desenvolvimento fetal, o que sugere um papel destes mediadores no neurodesenvolvimento (KRONFOL & D.G., 2000). Elas podem ser divididas em dois grupos: as citocinas proinflamatórias e as anti inflamatórias. O primeiro grupo inclui aquelas diretamente envolvidas na resposta inflamatória, tais como: interleucina (IL) – 1β, IL-6, interferon (IFN)- γ e o fator de necrose tumoral (TNF)- α. O segundo grupo inclui IL-4, IL-10 e IL-13, conhecidas por diminuir a resposta inflamatória através da produção de mediadores (RAISON, CAPURON & MILLER, 2006; ABELAIRA *et al.*, 2014; ROSENBLAT *et al.*, 2014).

As citocinas proinflamatórias – tais como IL-1, IL-6 e TNF-α, influenciam o SNC por diversas vias. Uma delas é o efeito no eixo hipotalálamo-hipófise-adrenal, promovendo febre, diminuição da ingesta alimentar, isolamento social – síndrome também conhecida como "*sickness behavior*" – além de e liberação excessiva de Hormônio Liberador de Corticotrofinas (CRH), levando a um feedback negativo sobre o hipotálamo e a consequente resistência a glicocorticoides. Este processo possivelmente é responsável pelo desenvolvimento de um estado inflamatório crônico na depressão (MAES, Michael *et al.*, 2012; YOUNG, BRUNO & POMARA, 2014).

Uma série de estudos tem observado aumento de citocinas proinflamatórias no líquido cefalorraquidiano (LCR) de pacientes deprimidos, alguns inclusive em comparação com indivíduos saudáveis (FELGER & LOTRICH, 2013). Entretanto tais achados não são replicados em outros estudos (LEVINE – FELGER 2009). Tais inconsistências incluem ausência de diferença na comparação com indivíduos sem depressão, níveis menores de algumas citocinas, como IL-6 ou TNF-α inalterado.

Recentemente a compreensão da resposta inflamatória foi modificada pela descoberta das células Th17. Elas são um subtipo de célula T CD4+ e parecem contribuir para a patogênese da depressão. As células Th17 são claramente danosas ao SNC (BEUREL, HARRINGTON & JOPE, 2013). Elas produzem citocinas proinflamatórias, incluindo interleucina -17 (IL-17 A e F), IL-21 e Il-22. Assim como os outros subtipos de células T, as células Th17 tem um fator de transcrição linhagem-específico, conhecido como receptor órfão γt ácido retinóico-relacionado (ROR γt) (CHEN *et al.*, 2011). As células T helper produtoras de IL-17 desempenham um papel importante na indução de doenças autoimunes do sistema nervoso: incluindo esclerose múltipla e o seu modelo animal, chamado de encefalomielite autoimune experimental (EAE). A perda de ROR γt em ratos os faz resistentes ao desenvolvimento de EAE (IVANOV *et al.*, 2006). Foi demonstrado que as células Th17 se acumulam no cérebro de ratos, gerando comportamento depressivo em diversos modelos. Além disso, uma redução na expressão Th17 está relacionada a maior resistência ao desamparo aprendido em animais (BEUREL, HARRINGTON & JOPE, 2013).

Outro aspecto de interesse no papel da inflamação no transtorno depressivo maior é o impacto do tratamento antidepressivo nos níveis de citocinas. Em estudos longitudinais que avaliaram estes parâmetros, resultados heterogêneos são encontrados. Martinez e colaboradores não identificaram redução nos níveis de IL-1, IL-6 e TNF-α após tratamento com venlafaxina, por exemplo (MARTINEZ *et al.*, 2012).

Dowlati e colaboradores publicaram em 2010 uma importante meta-análise que avaliou a diferença na concentração de citocinas em pacientes deprimidos e controles (DOWLATI *et al.*, 2010). Nesse estudo, foram incluídos 24 artigos que avaliavam a depressão pelos critérios do DSM. As citocinas avaliadas foram TNF-α, IL-1β, IL-6, IL-4, IL-2, IL-8, IL-10 e IFN-γ. Em indivíduos deprimidos, quando comparados aos controles, as concentrações de Il-6 e TNF-α foram significativamente mais altas. O estudo não avaliou resposta terapêutica e incluiu estudos publicados até agosto de 2009. O Quadro 1 mostra os estudos de revisão que avaliaram a alteração de citocinas inflamatórias na depressão.

Tendo em vista o grande volume de publicações nos últimos anos que avaliam o papel destas citocinas na etiopatogenia da depressão (LEONARD, B & MAES, M, 2012; FELGER & LOTRICH, 2013; VALKANOVA, EBMEIER & ALLAN, 2013; POSTAL & APPENZELLER, 2014; YOUNG, BRUNO & POMARA, 2014) e considerando a inconsistência nos dados sobre o impacto do tratamento antidepressivo na atividade inflamatória, torna-se necessária uma nova metanálise (incluindo esses achados) que possa

determinar se as concentrações de determinadas citocinas são úteis como marcadores de resposta terapêutica na depressão.

Não é incomum em meta-análises que a incorporação de novos achados alterem os tamanhos de efeito e mesmo a direção dos achados. Pelo menos dois fenômenos são bem descritos, a saber: o "fenômeno de Proteus" através do qual o primeiro (ou os primeiros) estudos são enviesados em direção a um tamanho de efeito discrepante e o fenômeno da "maldição dos vencedores" em que o cientista que primeiro faz uma descoberta encontra uma tamanho de efeito inflado (usualmente associado a baixo poder estatístico), e os estudos subsequentes ocasionam uma aproximação ao tamanho de efeito "real" (BUTTON *et al.*, 2013). Ademais, a inclusão de mais estudos em uma meta-análise usualmente permite um estudo dos fatores relacionados à heterogeneidade entre os estudos (através de análise de subgrupos e meta-regressões) com maior pode estatístico e menor risco para erro do tipo I.

Quadro 01. Meta-análises que avaliam alterações de citocinas na depressão.

AUTOR	ANO	TÍTULO	PERIÓDICO	ACHADOS
Valkanova V, et al	2013	CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies.	Journal of Affect Disorders	Elevação significativa da PCR em pessoas com sintomas depressivos. Menor elevação e tamanho de efeito na associação de IL-6 e depressão.
Hiles SA, et al	2012	A meta-analysis of differences in IL-6 and IL-10 between people with and without depression: exploring the causes of heterogeneity.	*Brain, Behavior,* and *Immunity*	Elevação de IL-6 na depressão e nas pessoas sem comorbidade cardíaca em comparação com os com comorbidade cardiovascular. A diferença entre o níveis de IL-10 não foi significante.
Hiles SA, et al	2012	Interleukin-6, C-reactive protein and interleukin-10 after antidepressant treatment in people with depression: a meta-analysis.	*Psychological Medicine*	Redução significante de IL-6 (n=14, d=-0.42, p=0.02), pequena redução da PCR (n=8, d=-0.57, p=0.05) e redução não significativa de IL-10 (n=3, d=-0.45, p=0.14).
Liu Y, et al	20112	Interleukin (IL)-6, tumour necrosis factor alpha (TNF-α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression.	Journal of Affect Disorders	Níveis significativamente maiores de sIL-2R, TNF-α e IL-6 em pacientes com depressão em comparação aos controles. (SMD=0.555, p<0.001, SMD=0.567, p=0.010; SMD=0.680, p<0.001)..
Hannestad J, et al	2011	The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis.	Neuropsychopharmacology	Não houve redução dos níveis de TNFα, IL-6 e IL-1β após o tratamento.

Dowlati Y, et al	2010	A meta-analysis of cytokines in major depression.	*Biological Psychiatry*	Níveis significantemente maiores de TNF- alfa e IL-6 em pacientes com depressão em comparação aos controles. Sem diferenças significativas entre as outras citocinas.
Howren MB, et al	2009	Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis.	*Psychosomatic Medicine*	Associação positiva entre depressão e os níveis de PCR, IL-1 e IL-6. Depressão foi relacionada a PCR e IL-6 em pacientes com doença cardíaca ou cancer. Não houve associação consistente com idade, medicação e sexo.
(GOLDSMITH, RAPAPORT & MILLER)	2016	A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression.	*Molecular Psychiatry*	Os níveis de IL-6 foram significativamente maior em indivíduos com TDM quando comparados aos dos controles, e diminuíram significativamente após tratamento da fase aguda.

2. REFERENCIAL TEÓRICO

2.1. Transtorno Depressivo Maior – definição, apresentações clínicas e diagnóstico.

A Depressão maior ou Transtorno Depressivo Maior (TDM) é uma condição psiquiátrica caracterizada pela presença de períodos distintos de humor anormalmente triste ou desinteresse ou diminuição da capacidade hedônica, segundo critérios diagnósticos da 5ª. edição do Manual Diagnóstico e Estatístico dos Transtornos Mentais da *American Psychiatric Association* - APA (DSM-5) (ASSOCIATION, 2013). Outros sintomas são: choro fácil, alterações do sono, perda ou ganho de peso, alterações no apetite, dificuldade de concentração, baixa autoestima, idéias de morte e até suicídio. Os sintomas devem estar presentes na maior parte dos dias (com exceção de mudança de peso e ideação suicida), por um período de pelos menos 2 semanas.

A Organização Mundial de Saúde (OMS), na Classificação Internacional de Doenças (CID-10) (ORGANIZATION, 1993) enumera critérios para “Episódio Depressivo", que incluem: retardo psicomotor, perda do interesse em atividades usuais para o paciente, hiporreatividade emocional, alterações no ciclo circadiano, apetite, libido e diminuição da energia, por um período igual ou superior a 2 semanas.

Apesar de haver alta concordância entre estes dois sistemas de classificação (CID-10 e DSM-5) (RICHARDS, 2011), existe uma variedade de apresentações clínicas da depressão. Ainda que seja considerada uma entidade única, subtipos diferentes de síndromes são descritos, apresentando uma combinação diversa dos sintomas elencados nos critérios diagnósticos: (i) Depressão Atípica – especificada no DSM, mais frequentemente apresenta-se com reatividade do humor, ganho de peso, paralisia de chumbo, hipersonia; (ii) Depressão Melancólica – anedonia, humor anormal, piora matinal, despertar precoce, lentificação psicomotora, perda de peso e apetite. Além destas, são também descritas a depressão mista, transtorno depressivo menor e transtorno depressivo recorrente breve (BENAZZI, 2006).

2.2. Epidemiologia e impacto socioeconômico.

Segundo a APA, a prevalência em 12 meses do TDM nos Estados Unidos é de 7% (ASSOCIATION, 2013). Já Kessler & Bromet, numa revisão de dados epidemiológicos sobre depressão, apontam que a prevalência do transtorno varia de 1,5 a 19% em diferentes grupos

étnico-culturais (KESSLER & BROMET, 2013). Segundo a OMS (World Mental Health Survey), a prevalência ao longo da vida é de quatro a 10% e de 3 a 6% em 12 meses (KESSLER *et al.*, 2009), chegando a afetar mais de 120 milhões de pessoas em todo o mundo (BREDT *et al.*, 2015). Dados mais recentes sugerem que é uma das principais causas de incapacidade, chegando a 23% da população se considerada depressão comórbida em doenças clínicas (GURURAJAN *et al.*, 2016). Já a OMS ranqueou a depressão como a quarta principal causa de incapacidade no mundo, e estima-se que até 2020 seja a segunda maior causa.

Um grande número de estudos epidemiológicos demonstrou o impacto da depressão em diferentes áreas do funcionamento do indivíduo: interrupção da escolarização, impacto na estabilidade marital, associação com desemprego, prejuízo na performance parental, maior absenteísmo profissional, queda na renda individual, piora do prognóstico de doenças clínicas preexistentes (KESSLER & BROMET, 2013).

Quanto aos impactos econômicos, foi estimado nos EUA um custo anual de 83,1 bilhões de dólares, dos quais 31% relacionados a medicamentos, 7% a mortalidade e 62% a prejuízos trabalhistas (RICHARDS, 2011).

Os objetivos do tratamento da depressão são o restabelecimento funcional, remissão da crise, prevenção de novos episódios depressivos, promover um restabelecimento das emoções, alívio sintomático e devolver o indivíduo ao seu estado pré-mórbido (LAM *et al.*, 2016).

Por remissão entende-se uma melhora significativa dos sintomas e da funcionalidade por um período de tempo normalmente inferior a 8 semanas (RICHARDS, 2011). Após este período, inicia-se a recuperação. Se houver um reaparecimento dos sintomas durante o período de remissão, diz que há uma recaída (do mesmo episódio); se ocorrer depois de 8 semanas, há então uma recorrência – um novo episódio depressivo.

Devido a grande heterogeneidade de apresentação clínica, variação em fatores de risco e resposta terapêutica (ARNOW *et al.*, 2015), muitos estudos tem tentado demonstrar que fatores biológicos estão associados a melhores taxas de remissão com o tratamento.

2.3. Etiopatogenia

Embora o diagnóstico se baseie somente no exame clínico, a depressão se correlaciona com um grande número de fenômenos biológicos, resultando em uma fisiopatologia complexa e ainda não totalmente compreendida (BENTLEY, PAGALILAUAN & SIMPSON, 2014).

A hipótese mais conhecida para explicar o aparecimento de sintomas depressivos é a chamada "Hipótese Monoaminérgica", segundo a qual haveria uma deficiência na atividade de neurotransmissores, particularmente a serotonina, na fenda sináptica.

A depressão apresenta ainda associação com hipersensibilização de receptores alfa-adrenérgicos – o que resulta em diminuição na função serotoninérgica – e com *downregulation* de receptores β-adrenérgicos. Estas alterações se correlacionam com uma das funções terapêuticas dos antidepressivos, que acabam por restabelecer essa neurotransmissão com seu uso continuado.

Além das monoaminas, outro neurotransmissor que tem sido implicado na gênese da depressão é o glutamato. Um grande número de estudos demonstra disfunção do sistema glutamatérgico, alterações em seu *clearance* e metabolismo em áreas cerebrais relacionadas a comportamentos cognitivo-emocionais (SANACORA, TRECCANI & POPOLI, 2012). Na mesma direção, estudos com animais mostram que diferentes tipos de estressores aumentam a liberação e transmissão glutamatérgica em áreas límbicas e corticais, induzindo remodelação dendrítica, redução das sinapses e possivelmente reduções volumétricas que lembram aquelas de indivíduos deprimidos. A ativação glutamatérgica sofre influência também da via da quinurenina, ativada por mediadores inflamatórios (FELGER & LOTRICH, 2013).

O papel do eixo hipotálamo-hipófise-adrenal (HHA) na depressão também tem sido largamente estudado (BREDT *et al.*, 2015). Em condições estressoras, o primeiro passo da resposta imune envolve a ativação do eixo HHA pela amígdala. O hipotálamo libera então o hormônio liberador de corticotropina (CRH), que estimula a hipófise a sintetizar e secretar o hormônio adrenocorticotrópico (ACTH), que, por sua vez, estimula a glândula adrenal a sintetizar o cortisol. Em condições normais, este aumento de cortisol levaria a um feedback negativo sobre o hipotálamo, atenuando a cadeia descrita (KIM *et al.*, 2016). Em indivíduos com depressão, entretanto, este feedback está prejudicado, possivelmente por alteração nos receptores de glicocorticóide do hipotálamo em decorrência de mediadores inflamatórios (detalhado a seguir).

Desde o início da década de 90, muito interesse se voltou para a pesquisa de atividade inflamatória na depressão, desde que Smith (SMITH, 1991) publicou a "Teoria Macrofágica da Depressão", segundo a qual citocinas pró-inflamatórias produzidas por macrófagos ativados contribuem para o aparecimento de sintomas depressivos. Desde então, vários outros autores descrevem alterações imunológicas envolvidas com neste processo (MAES, STEVENS*, et al.*, 1993; DANTZER & KELLEY, 2007).

A idéia de que as citocinas inflamatórias desempenham um papel importante na patogênese da depressão se baseia em quatro grupos de achados (JEON & KIM, 2016):

I. A inoculação de citocinas em animais ou em humanos sob terapia imunológica provoca sintomas depressivos. Boa parte dos pacientes em tratamento com interferon para hepatite C preenchem critérios para TDM. Além disso, a indução da expressão de citocinas através da injeção de lipopolissacarídeos em cobaias leva a comportamento depressivo verificado no modelo do nado forçado, por exemplo.
II. Em pacientes com depressão tem sido observados níveis maiores de citocinas pró-inflamatórias quando comparados aos controles saudáveis (ABELAIRA *et al.*, 2014).
III. Citocinas desencadeiam maior atividade do eixo HPA e da produção de catecolaminas pelo sistema nervoso simpático. As citocinas estimulam a liberação de CRH, ACTH, além de ativar a enzima IDO, levando à degradação do triptofano, prejudicando a síntese cerebral de 5-HT. Juntas, as citocinas inflamatórias, NA e DA promovem liberação de CRF, desencadeando reações imunes que geram "sickness behavior" (DANTZER *et al.*, 2008): desesperança, isolamento, hipobulia, redução no apetite, concentração.
IV. Antidepressivos podem ter uma ação através da inibição na produção de citocinas anti-inflamatórias, como demonstram alguns estudos longitudinais com pacientes deprimidos antes e depois do tratamento (TUGLU, C. *et al.*, 2003; BASTERZI *et al.*, 2005; SUTCIGIL *et al.*, 2007; HIMMERICH, MILENOVIC*, et al.*, 2010).

2.4. Biomarcadores na depressão

Devido à crescente prevalência e ao impacto causado pela depressão, tem sido bastante pesquisados biomarcadores que possam auxiliar na identificação do risco, do diagnóstico ou na escolha terapêutica (UDDIN, 2014).

Biomarcador é uma característica que pode ser objetivamente mensurada e avaliada como indicador de uma resposta biológica normal, de um processo patológico ou de uma resposta a uma intervenção terapêutica (GROUP, 2001). Eles podem ter várias funções na detecção e monitorização do estado de saúde: ferramenta diagnóstica para identificação de pacientes com doença ou condição anormal (ex.: glicemia no *diabetes mellitus*), ferramenta para avaliar o estágio de uma doença (ex.: antígeno associado ao câncer CA-125), uso como indicador de prognóstico (ex.: procalcitonina na sepse) e na monitorização de resposta terapêutica (ex.: contagem de leucócitos em estados infecciosos).

Desta forma, os biomarcadores podem ser divididos em: (i) biomarcadores de risco, (ii) diagnósticos ou de traço (iii) de fase (iv) biomarcadores de estágio (v) biomarcadores de resposta terapêutica (vi) biomarcadores prognósticos (DAVIS *et al.*, 2015).

Atualmente, a avaliação de resposta terapêutica na depressão se dá através de exame

psíquico, entrevista clínica não estruturada ou com uso de escalas padronizadas (BENTLEY, PAGALILAUAN & SIMPSON, 2014). Um biomarcador de resposta estimaria a probabilidade de haver resposta ou remissão em a dado tratamento. Isso permitiria aos clínicos estratificar pacientes e escolher uma estratégia terapêutica personalizada e mais efetiva (DAVIS *et al.*, 2015).

Vários são os alvos biológicos de tais investigações: neurotrofinas, melatonina, cortisol, teste de supressão da dexametasona, folato, vitamina D, (UDDIN, 2014). Entre estes, um grupo promissor de possíveis biomarcadores tem sido amplamente estudado: as citocinas.

2.5. Resposta inflamatória na depressão.

Citocinas são proteínas secretadas pelas células do sistema de imunidade inata e adquirida. Elas efetuam mecanismos de resposta do hospedeiro a um patógeno ou lesão tecidual. Como são produzidas por monócitos, eram comumente denominadas "monocinas". São produzidas também por neurônios, células endoteliais, astrócitos e micróglia. Devido ao fato de mediarem ações de um linfócito a outro, são também chamadas interleucinas (IL), nomenclatura utilizada até hoje para muitas delas (ABBAS, LITCHMAN & PILLAI, 2008).

De forma simplificada, as citocinas são divididas em pró-inflamatórias e antiinflamatórias. Aquelas incluem IL-1, IL-2, IL-6, IFN- γ e TNF-alfa. As antiinflamatórias compreendem, entre outras, IL-4, IL-10, IL-11, IL-13 e TGF-β. As pró-inflamatórias ativam cicloxigenase-2 (COX-2), aumentam os níveis de prostaglandina E2 (PGE2), ativando células inflamatórias. Elas interagem entre si, balanceando suas ações. Por exemplo, IL-10 reduz a produção de TNF-α, ao passo que o antagonista do receptor de IL-1a bloqueia o receptor de IL-1 (JEON & KIM, 2016).

Um desbalanço destas respostas acontece em estados patológicos. Nestas situações, há também aumento na permeabilidade da barreira hematoencefálica, o que permite a passagem das citocinas periféricas para o sistema nervosa central. Além disto, as citocinas também podem afetar o SNC através de seus mediadores, como o óxido nítrico ou as prostaglandinas (DANTZER *et al.*, 2008). No cérebro, elas podem ser sintetizadas no hipotálamo, hipocampo, cerebelo, região periventricular, prosencéfalo, entre outras (MAIER & WATKINS, 1998).

Simth postulou que a administração de "monocinas" a indivíduos saudáveis era capaz de provocar sintomas depressivos e que uma desregulação na resposta inflamatória poderia explicar a elevada comorbidade de depressão com doença coronariana ou artrite reumatoide, por exemplo (SMITH, 1991).

Acredita-se que o sistema de imunidade inata tenha um papel importante na depressão e determina o tipo de resposta imune adaptativa Th1 ou Th2. Na resposta Th1, os macrófagos liberam citocinas pró-inflamatórias, tais como interferon gama (INF-γ), TNF- α, interleucina 1 e 2 (PATEL, 2013).

Como descrito anteriormente, as monoaminas desempenham um papel importante na regulação do humor. Mas de que forma a expressão de citocinas inflamatórias interfere na função destes neurotransmissores?

O triptofano é um aminoácido essencial que participa na síntese de serotonina. A biodisponibilidade do precursor de serotonina é uma medida da taxa de síntese deste neurotransmissor no SNC. A queda nos níveis de triptofano (que está relacionada ao aparecimento de sintomas depressivos) em pacientes que fazem imunoterapia pode ser decorrente da ativação enzimática da triptofano 2,3 desoxigenase (TDO) e da indoleamina 2,3 desoxigenase (IDO) (Figura 1). A IDO pode ser ativada diretamente por um número de citocinas, incluindo IFN-gama e TNF- α, está presente nos macrófagos e células dendríticas e pode ser expressa no cérebro. A ativação da IDO leva a produção de componentes que tem ação em receptores glutamatérgicos, podendo ser um *trigger* para o aparecimento de sintomas depressivos (DANTZER *et al.*, 2008).

O TNF-α altera a função do transportador de serotonina, contribuindo para aumento de sua captação e menor disponibilidade desta na fenda sináptica (POSTAL & APPENZELLER, 2014). Além disso ele contribui para a estimulação da IDO levando a produção de agonistas glutamatérgicos e depleção dos níveis de triptofano (Figura 1) (MAES *et al.*, 2011).

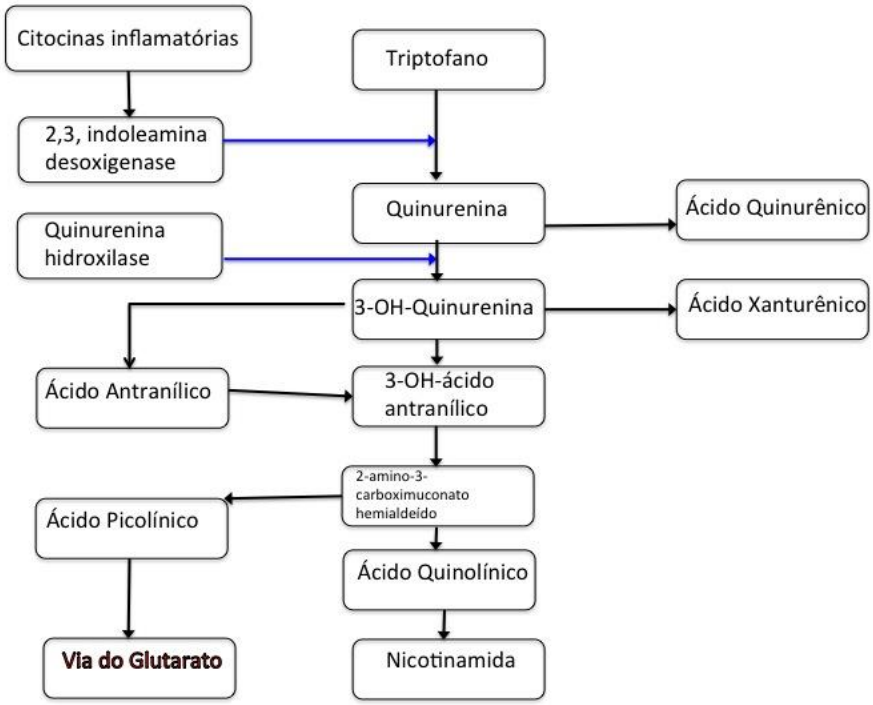


Figura 1. Via catabólica do triptofano. Citocinas proinflamatórias induzem o metabolismo do triptofano em quinurenina pela 2,3 indoleamina desoxigenase. Adaptado de Maes *et al.*, 2001. Progress in Neuro-Psychopharmacology & Biological Psychiatry.

Dantzer postula ainda que o cérebro monitora a resposta imune inata basicamente de 4 formas: (1) nervos aferentes são ativados por citocinas produzidas na periferia, (2) receptores Toll-like de células cirumventriculares e do plexo coroide respondem a padrões de molécula associadas a patógenos produzindo citocinas pro-inflamatórias, (3) transporte através da barreira hematoencefálica por meio da saturação do sistema de transporte e (4) receptores de IL-1 localizadas em macrófagos perivasculares das vênulas cerebrais.

Desta forma pode haver produção de citocinas por células da micróglia. Este processo requer ativação da via rápida neuronal aferente e uma lentificação da propagação de citocinas pelo cérebro.

Com relação a interferência dos mediadores inflamatórios no eixo HHA, já sabidamente disfuncional em indivíduos deprimidos, sabe-se que as citocinas interferem na função dos receptores de glicocorticóides, mantendo o estado de hipercortisolismo e dificultando o feedback no hipotálamo (PACE & MILLER, 2009).

Já a neurogênese está também prejudicada durante o processo patológico depressivo, e está intimamente ligada à neuroinflamação: receptores de citocinas pró-inflamatórias estão largamente presentes em regiões envolvidas com função cognitiva, tais como o hipocampo, que sofre efeito lesivo de IL-6, TNF-α e IL-1β (KIM *et al.*, 2016).

Os fármacos antidepressivos, por sua vez, parecem atuar na depressão não apenas por sua função em nível sináptico. Estes teriam efeito de atenuar a resposta inflamatória e a hipercortisolemia por redução da liberação de citocinas pró-inflamatórias na micróglia ativada e por re-sensibilizar os receptores de glicocorticóides no eixo HPA. Estas duas ações resultam em melhoria da função neurotransmissora (LEONARD, 2014). Esta ação já foi demonstrada em estudos experimentais (TYNAN, WEIDENHOFER, *et al.*, 2012), em que níveis de TNF-α induzidos por LPS foram significativamente reduzidos pela ação de inibidores de receptação de serotonina. Em estudos clínicos, foi demonstrado por exemplo que uma redução dos níveis periféricos de IL-6 estaria associada a resposta terapêutica (CATTANEO *et al.*, 2013) e que uma remissão clínica estaria acompanhada de normalização destes biomarcadores inflamatórios (HANNESTAD, DELLAGIOIA & BLOCH, 2011).

Entretanto há uma grande heterogeneidade nestes estudos (padrão de coleta de marcadores, tipo de antidepressivo usado, tempo de follow up, perfil de participantes) e desde que estas metanálises foram publicadas, novos estudos surgiram avaliando o papel dos níveis de citocinas como marcadores de resposta na depressão.

3. OBJETIVOS

3.1. Objetivo Principal

- Reavaliar as evidências existentes do efeito dos antidepressivos nos níveis periféricos de citocinas e quimiocinas em indivíduos com depressão maior.

3.2. Objetivos Secundários

- Explorar as fontes potenciais de heterogeneidade entre os estudos
- Investigar se a mudança nos níveis de citocinas e quimiocinas relacionadas aos antidepressivos difere entre indivíduos respondedores e não-respondedores.

4. MATERIAIS E MÉTODOS

O presente estudo compreendeu uma metanálise de estudos que compararam os níveis periféricos de citocinas e quimiocinas em pacientes com depressão maior antes e após tratamento com antidepressivo. Para tanto, foi seguido o protocolo PRISMA - *Preferred Reported Items for Systematic Reviews and Mata-analysis (LIBERATI et al., 2009)* (Figura 5). A busca na literatura, o *screening* por título e resumo, a decisão final após revisão de texto completo foram feitos por dois investigadores independentemente (THF e NQA). As discordâncias foram resolvidas por consenso e, quando não havia decisão consensual, um terceiro investigador independente a tomava (CAK).

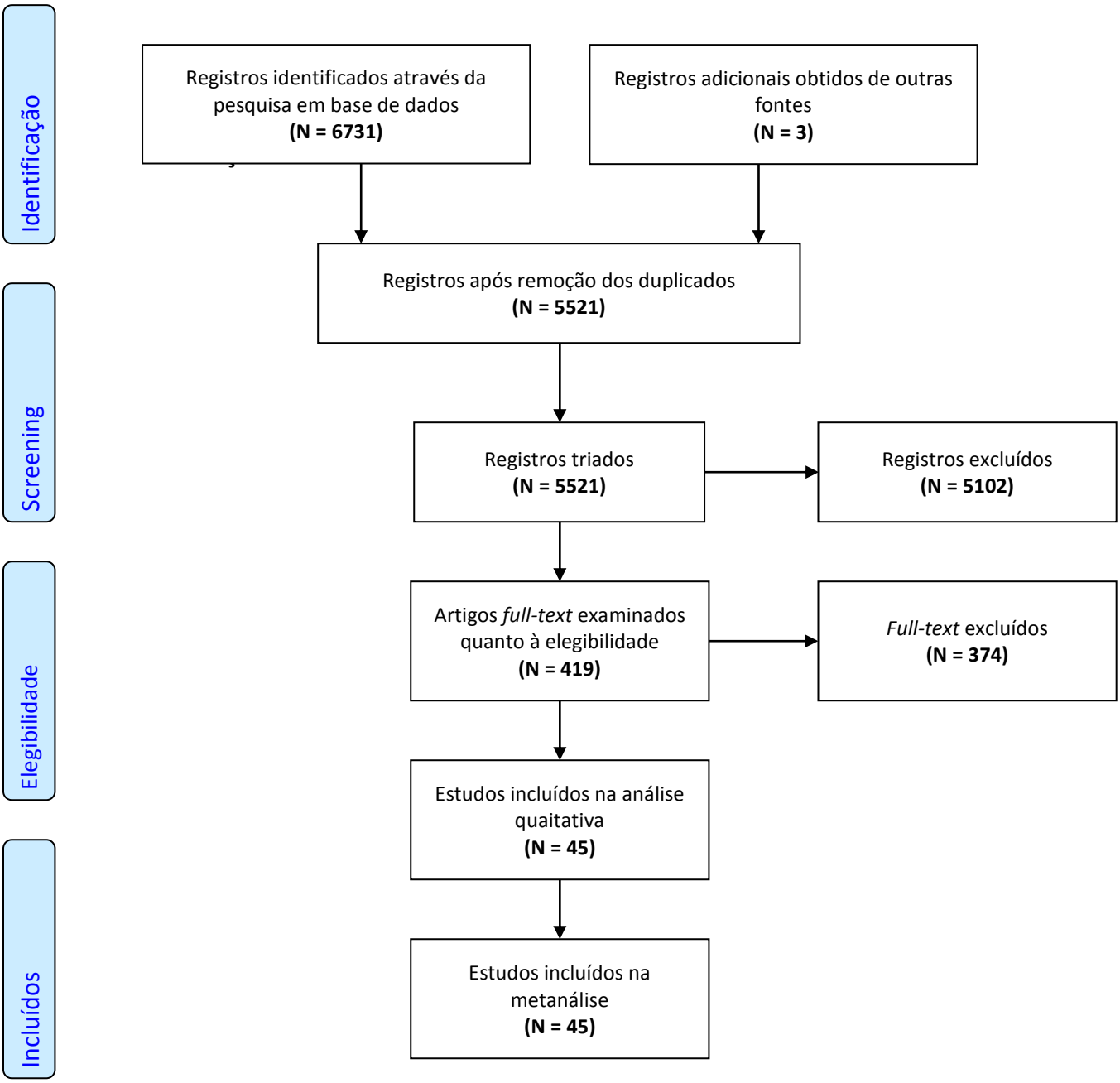
4.1.Estratégia de Busca

Uma busca sistemática foi realizada nas bases de dados PubMed/MEDLINE, EMBASE e PsychInfo desde o início até 09 de março de 2017. O protocolo de busca detalhado está no ANEXO 1. A busca foi ampliada com listas de citação de artigos incluídos no Google Scholar (BAKKALBASI *et al.*, 2006).

4.2.Seleção dos estudos

Foram incluídos artigos originais, publicados em qualquer idioma. Os estudos elegíveis teriam que mensurar níveis periféricos de citocinas ou quimiocinas em indivíduos com idade igual ou superior a 18 anos, que preenchessem critérios do DSM (ASSOCIATION, 2013), ou da CID (ORGANIZATION, 1993). Foram adotados os seguintes critérios de exclusão: (1) estudos em que os participantes tinham comorbidades clínicas ou psiquiátricas; (2) estudos que incluíam mulheres grávidas ou no período puerperal; (3) relatos ou séries de caso ($N < 10$); (4) estudos que examinavam as citocinas ou quimiocinas em outra espécime que não o sangue periférico (ex.: LCR); (5) estudos em animais ou que avaliaram a produção *in* vitro das citocinas/quimiocinas e (6) estudos que incluíram outras intervenções (ex.: exercício físico) a menos que os dados de pacientes tratados com antidepressivos fossem fornecidos à parte. Os autores de abstracts que preenchessem critérios de inclusão foram contatados por e-mail a fim de fornecerem dados para análise (não foram fornecidos dados adicionais).

Figura 2. Fluxograma de seleção, inclusão e exclusão dos estudos conforme o protocolo PRISMA



Para cada mediador imune, foram extraídos a média, estimativas de variância [desvio padrão (DP), erro padrão da média (SEM) ou intervalo de confiança de 95% (IC)] e os tamanhos da amostra. Em estudos que forneciam a mediana ± intervalo interquartil (IQR) ou média ± variância, foi estimado o valor da média ± DP seguindo-se um protocolo padrão (HOZO, DJULBEGOVIC & HOZO, 2005).

Para fins de extração, foram considerados os níveis de quimiocinas e citocinas no início (baseline) e no momento de maior duração do tratamento com maior número de participantes (tempo de *follow-up* ≥ 4 semanas). Sempre que possível, também foram extraídos os seguintes dados: (1) primeiro autor; (2) ano de publicação; (3) distribuição por sexo (% de mulheres) ; (4) idade (média e DP) ; (5) índice de massa corpórea (média e DP); (6) média de duração da doença (anos); (7) porcentagem de pacientes livre de medicamento ou virgens de terapia farmacológica antes do ensaio (*drug-free e treatment-naïve*); (8) medida de sintomas depressivos no início e no final (*endpoint*); (9) taxas de resposta (definida como o percentual de participantes que atingiram uma redução igual ou superior a 50% nos escores de depressão); (10) tempo de *follow-up (semanas);* (11) estudos em que um só antidepressivo foi usado *versus* aqueles em que havia mais de um agente antidepressivo; e (12) tabagismo atual (%). Para estudos que incluíram controles saudáveis, foram extraídos ainda os seguintes dados destes participantes: (1) tamanho da amostra e (2) níveis de citocinas/quimiocinas.

4.3.Qualidade metodológica dos estudos

Foi aplicada uma pontuação para estratificar os estudos quanto à sua qualidade, baseando-se na Escala de Newcastle-Ottawa para avaliação de estudos não randomizados em metanálises (STANG, 2010). Sete parâmetros foram usados para estimar a qualidade metodológica dos estudos incluídos: (1) amostra inicial com pelo menos 40 participantes (1=SIM; 0=NÃO); (2) *attrition rate* ≤ 20% (1=SIM; 0=NÃO); (3) forneceu as taxas de resposta terapêutica (1=SIM; 0=NÃO); (4) comparou os níveis de citocinas e quimiocinas de respondedores e não respondedores (1=SIM; 0=NÃO); (5) um período de *washout* foi conduzido antes do início do ensaio ou os pacientes eram virgens de tratamento (1=SIM; 0=NÃO); (6) o horário da coleta da amostra foi relatado (ex.: manhã ou tarde) (1=SIM; 0=NÃO); e (7) o fabricante do teste laboratorial foi informado (e os parâmetros puderam ser verificados no respectivo *site*) ou os parâmetros do teste eram fornecidos (ou seja: limite de detecção e coeficiente de variação foi informado).

4.4.Análise estatística

Como os estudos usaram diferentes métodos de medida, foi estimada uma diferença padrão e um intervalo de confiança (IC) de 95% (g de Hedge) para cada mediador imune, o que fornece um tamanho de efeito (TE) sem viés ajustado para amostras pequenas (LAU, IOANNIDIS & SCHMIDT, 1997). A heterogeneidade dos estudos foi avaliada usando-se o teste Q de Cochran, uma média ponderada dos quadrados dos desvios dos TE estimado dos estudos individuais a partir da estimativa total. Além disso, heterogeneidade entre os estudos foi quantificada pelo I2, que de maneira simplificada indica o percentual da variação total dos diversos estudos devido a heterogeneidade, e é considerado alto quando é maior ou igual a 50% (PATSOPOULOS, EVANGELOU & IOANNIDIS, 2009). Um alto grau de heterogeneidade foi estimado. Portanto o TE foi agrupado usando um modelo *random-effect* de acordo com DerSimonian e Laird, usando o método da variância inversa para estimar a heterogeneidade (DERSIMONIAN & LAIRD, 1986). Metanálises foram realizadas somente para os mediadores com pelo menos três *datasets* individuais. O modelo *random-effects* assume uma diversidade nos diversos estudos e incorpora no cálculo uma variância entre estudos (LAU, IOANNIDIS & SCHMIDT, 1997). Um TE de 0,2 foi considerado baixo, de 0,5, moderado e 0,8, alto (COHEN, 1992).

Foram computadas medidas para fornecer uma indicação do perfil de ativação imune periférica envolvida no TDM (Thelper 1 (Th1), Th2, células T reguladoras (TReg) e resposta fenotípica de macrófagos polarizados M1). Então foram calculadas as médias de TE a partir de cada estudo que contribuiu com um mediador incluído na bioassinatura previamente definida. A Tabela 1 descreve os mediadores e número de estudos que contribuíram para cada estimativa de TE.

Tabela 1. Agrupamento de citocinas consideradas em cada perfil inflamatório.

Mediador	TH_1 (k = 28)	TH_2 (k = 12)	T_{Reg} (k = 13)	M1 (k = 42)
CCL-2				X
IL-2	X			
IL-4		X		
IL-5		X		
IL-6				X
IL-8				X
IL-10			X	
IL-12				X
IL-13		X		
IL-23				X
IFN-γ	X			
TGF-β			X	
TNF-α	X			X

Abreviações**:** **CCL-2** = ligante C-C de quimiocinas 2; **IFN-γ** = interferon gama; **IL** = interleucina; **TGF-β** = Fator de crescimento transformador beta; **TNF-α** = fator de necrose tumoral alfa. O número de datasets individuais usados no cálculo de cada índice está em parênteses (k).

Estudos com resultados não significativos (negativos) tem menor probabilidade de serem publicados do que aqueles com resultados positivos (CARVALHO *et al.*, 2016). Para avaliar viés de publicação, foi inspecionada eventual assimetria no gráfico de funil (EGGER *et al.*, 1997). Evidência de efeito de pequenos estudos (indicativo de viés de publicação) foi considerado quando o valor de P do teste de Egger foi menor que 0,1 e o TE o estudo maior foi mais conservador ou mudou a direção quando comparado à estimativa geral do TE (gráficos de funil do TE estimando viés de publicação estão demonstrados nas figuras 3, 4 e 5). Utilizou-se a técnica do *trim-and-fill* procedure para estimar o TE ajustado para viés de publicação (DUVAL & TWEEDIE, 2000), ao passo que a estatística do *fail-safe N* foi utilizada para determinar quantos estudos adicionais seriam necessários para tornar não significante um TE significante (ROSENTHAL, 1979).

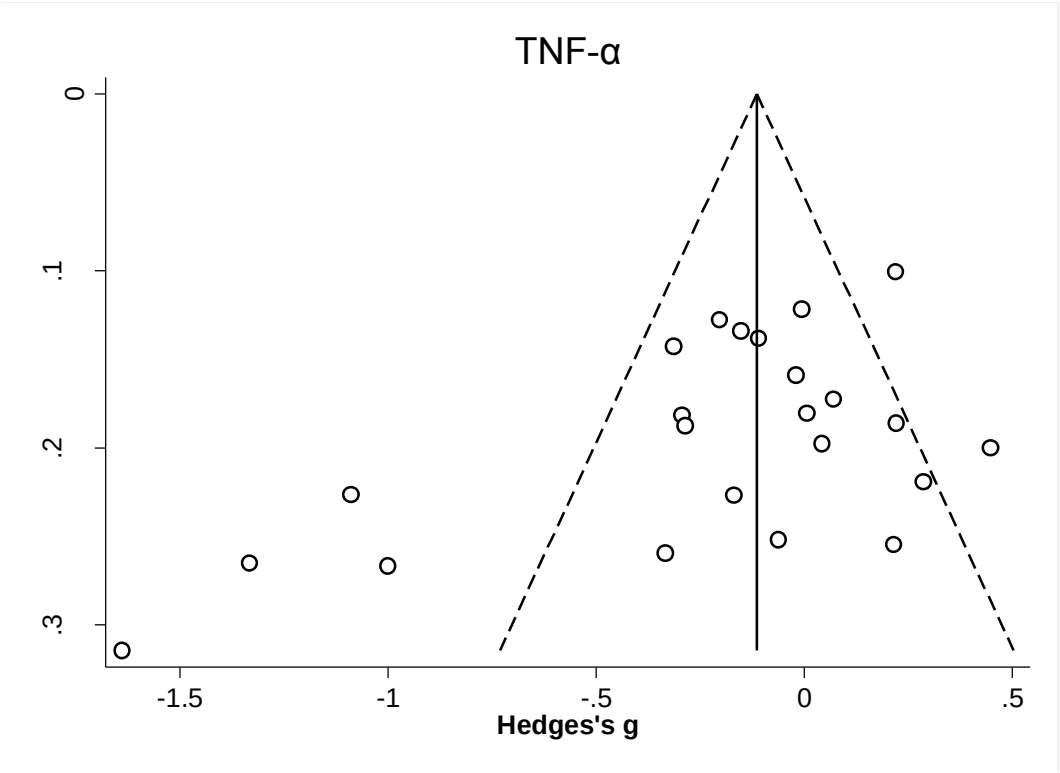


Figura 3. Gráfico de funil de estudos que investigaram TNF-α

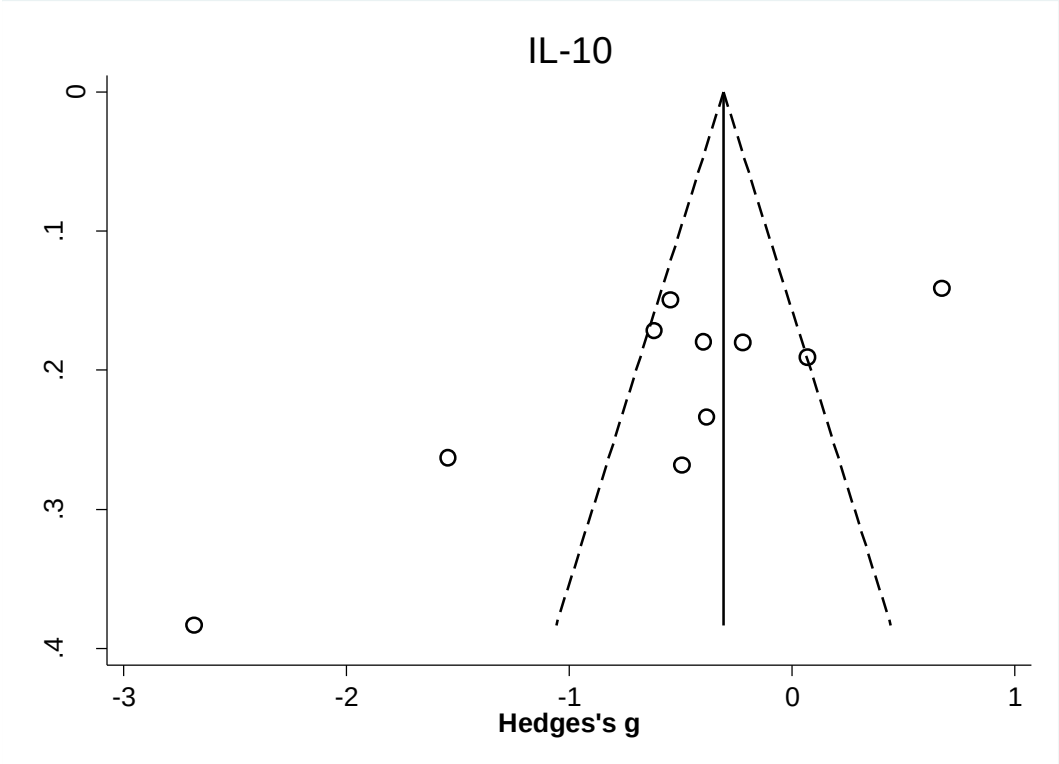


Figura 4. Gráfico de funil de estudos que investigaram IL-10

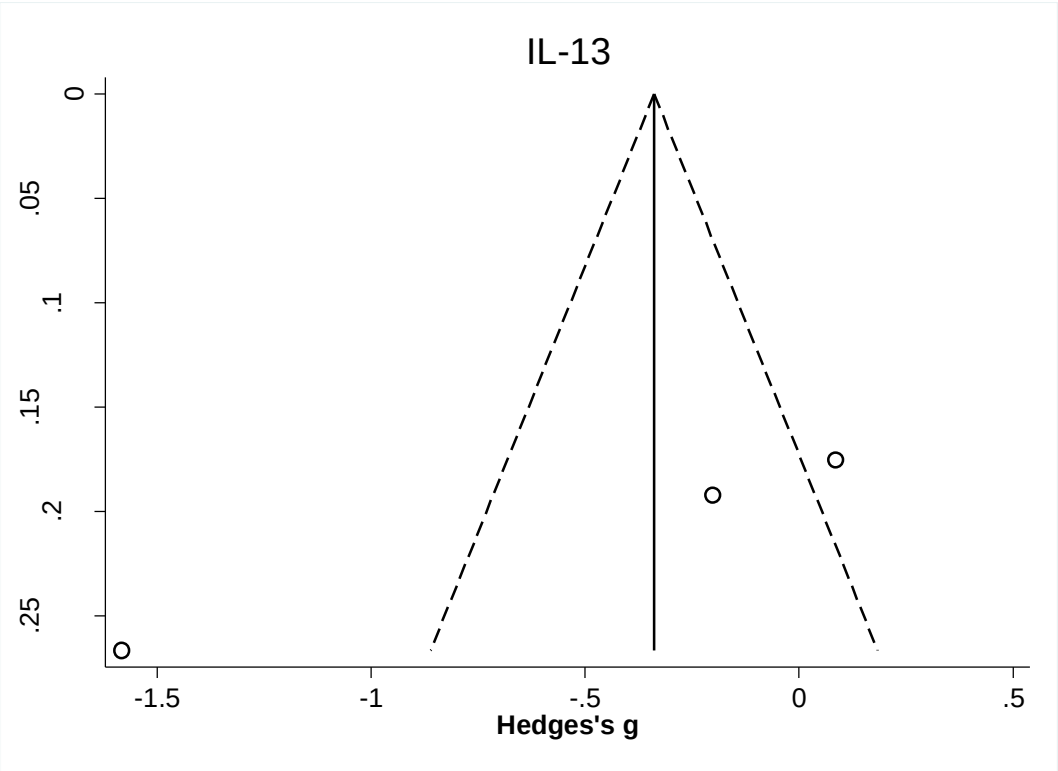


Figura 5. Gráfico de funil de estudos que investigaram IL-13

Foram exploradas as potenciais fontes de heterogeneidade dos estudos em cada mediador, usando um subgrupo (se houvesse pelo menos 3 estudos em cada subgrupo) ou uma análise de meta-regressão *random-effects (*se houvesse pelo menos 10 estudos com dados de moderador disponíveis). Os estudos em que as taxas de resposta estavam acima da mediana para um mediador imune específico foram agrupados e comparados com estudos em que as taxas de resposta estiveram abaixo da mediana. Menos *datasets* frequentemente fornecem estimativas de menor força e confiabilidade (THOMPSON & HIGGINS, 2002). As seguintes variáveis foram consideradas na análise de meta-regressão: tamanho da amostra, média de idade, média do IMC, distribuição de gênero (% mulheres), percentual de fumantes atuais, taxas de resposta (%), mudanças em sintomas depressivos (normalizadas para cada escala), média de duração da doença em anos. Os estudos foram ponderados de modo que as investigações com parâmetros mais precisos (indicados pelo tamanho da amostra e IC 95%) tivessem maior influência na análise de meta-regressão (THOMPSON & HIGGINS, 2002). Para as estimativas de TE estatisticamente significantes, foi realizada uma análise de sensibilidade em que excluíam-se os estudos das análises para verificar se um estudo único tornavam os resultados não significantes ou modificavam a direção do TE. Além disso, uma metanálise cumulativa foi foi realizada para mediadores imunológicos com TE significante e pelo menos 10 *datasets*. Essas análises avaliam a influência de novos estudos em resultados

agrupados anteriores. Para tanto, dados individuais foram colocados em ordem cronológica, com o estudo mais recente sendo colocado na análise primeiro. A cada passo seguinte, um novo estudo foi incluído na análise, e assim recalculados o TE e o IC 95%. O fenômeno de Proteus se refere à situação em que os estudos publicados primeiro são aqueles mais frequentemente enviesados, com TE superestimados (maldição dos vencedores). Estudos subsequentes tendem a ter menos viés, normalmente encontrando menores TE ou até contradizendo os achados daqueles inicialmente publicados. Uma metanálise cumulativa pode, portanto, avaliar tal fenômeno.

Todas as análises foram conduzidas usando o Stata MP versão 14.0 (Stata-Corp, College Station, TX, EUA). Significância estatística foi considerada a um nível de 0,05.

5. RESULTADOS

5.1. Seleção dos estudos

Após exclusão das duplicações, foram triados título/*abstracts* de 5521 estudos originais. Um total de 5102 referências foram excluídas, ao passo que 419 textos completos foram novamente avaliados quanto à sua elegibilidade. Destes, 374 foram excluídos (ver Tabela 1 as razões de exclusão). Finalmente, quarenta e cinco estudos originais preencheram critérios de inclusão. A figura 2 mostra o fluxograma PRISMA para a seleção dos estudos.

5.2. Características e qualidade dos estudos incluídos

Um total de 45 estudos foram incluídos (N=1517). A média de tempo de seguimento (follow up em tratamento antidepressivo) foi de 7,6 semanas (DP=3,3; variando de 4 a 20). Vinte e um estudos (46,7%) incluíram somente ISRS, ao passo que cinco (11,1%) incluíram IRSN e dezenove (42,2%), diversos antidepressivos ("miscelânea"). Treze (28,9%) compararam os níveis de citocinas/quimiocinas entre pacientes respondedores e não respondedores ao tratamento. As características dos estudos incluídos estão na tabela 02.

O escore de qualidade dos estudos variou de 2 a 7 (mediana = 4). Os escores de cada estudo estão demonstrados na tabela 2.

5.3. Interleucina-6

Interleucina-6 (IL-6) foi medida em 24 estudos (N=722). O tratamento antidepressivo reduziu significativamente os níveis de Il-6, com um tamanho de efeito moderado (Hedge g = 0,454) (Tabela 3; Figura 6A). Foi grande a heterogeneidade (I^2=84,7%). Não houve evidência de viés de publicação. Na análise de meta-regressão, a diferença média de escores de sintomas depressivos foi um moderador significativo (Tabela 4). A heterogeneidade foi maior em estudos de ISRS do que naqueles de miscelânea de antidepressivos (Tabela 5). Além disso, os níveis de IL-6 diminuíram em estudos com taxas de resposta acima da mediana, ao passo que não houve diferença significativa em estudos com taxas de resposta abaixo da mediana (Tabela 5). Por fim, os níveis de IL-6 diminuíram nos estudos que a coletaram do plasma, mas não naqueles que o fizeram do soro (Tabela 5). Na análise de sensibilidade, a exclusão de um estudo de cada vez não alterou a direção ou significância estatística do tamanho de efeito

(Figura 7). Na metanálise cumulativa, o TE tem sido consistente desde 2005 (Figura 8).

5.4. Fator de necrose tumoral alfa (TNF-α)

Os níveis de TNF- α estiveram significativamente mais baixos após terapia antidepressiva (23 estudos; N=797). O TE estimado foi pequeno (Hedge g = -0,202; P=0,015) (Tabela 3; Figura 6B). houve evidência de viés de publicação, mas o TE permaneceu pequeno e significante após ajuste com o procedimento *trim-and-fill*. Houve grande heterogeneidade (I^2=80,0%). Severidade nos escores basais de sintomas depressivos foi um preditor significante das diferenças nos níveis de TNF- α entre o desfecho e o basal na análise de meta-regressão (Tabela 4). Análise de subgrupos demonstrou que a heterogeneidade foi menor nos estudos que avaliaram ISRSN ou miscelânea de antidepressivos, quando comparados àqueles que avaliaram ISRS (Tabela 5). Além disso, a heterogeneidade foi menor em estudos com taxas de resposta menores que a mediana, mas não naqueles com taxas de resposta maiores (Tabela 5). Os níveis de TNF- α diminuíram significativamente em estudos cujos ensaios foram feitos com ELISA, mas não naqueles que utilizaram outras técnicas (Tabela 5). A análise de sensibilidade revelou que a exclusão sucessiva individual de dois estudos tornou o TE não significante (Figura 9). Por fim, a metanálise cumulativa indicou que o TE não tem sido consistente ao longo do tempo (Figura 10).

5.5. Interleucina-1 Beta (IL-1β)

Os níveis de Il-1β não foram significativamente reduzidos após tratamento farmacológico antidepressivo (Hedge g = -0,255; P= 0,176; 15 estudos; N=331; Figura 6C). Não houve evidência de viés de publicação. A heterogeneidade foi grande (I^2=92%) (Tabela 3). Na análise de meta-regressão, quanto maior o tempo de seguimento (*follow*-up), maior a diferença entre os níveis de IL-1β do desfecho e basal (Tabela 4). A análise de subgrupos demonstrou que a heterogeneidade foi significativamente menor em estudos que utilizaram miscelânea de antidepressivos ou IRSN quando comparada a dos estudos usando ISRS (Tabela 5). Além disso, a heterogeneidade foi menor em estudos em que a amostra de Il-1β foi extraída do plasma, comparada àqueles em que tal citocina foi medida no soro (Tabela 5).

5.6. Interleucina-10 (IL-10)

Os níveis de Il-10 foram medidos em 10 estudos (N=331) e foram significativamente reduzidos após tratamento antidepressivo (Hedge g = -0,566) (Figura 6D). entretanto houve evidência de efeito de estudos pequenos, mas após ajuste para viés de publicação, não houve mudança no TE (Tabela 3). Na análise de meta-regressão, a média do tempo de *follow-up* foi um moderador significante (Tabela 4). Na análise de subgrupos, os níveis de IL-10 diminuíram significativamente com baixa heterogeneidade em estudos usando miscelânea de antidepressivos, mas não naqueles que avaliaram ISRS, que tiveram alta heterogeneidade. Além disso, os níveis de Il-10 diminuíram com baixa heterogeneidade em estudos que mediram a citocina no plasma, mas não naqueles que o fizeram no soro, que apresentaram alta heterogeneidade. Os níveis de IL-10 estiveram reduzidos em estudos que usaram outros tipos de ensaio, mas não naqueles que o fizeram com ELISA (Tabela 5). Análise de sensibilidade revelou um *outlier* (HERNANDEZ *et al.*, 2008a) (Figura 11), enquanto que o TE mostra-se estável desde 2009 (Figura 12).

5.7. Ligante 2 de quimiocina C-C (CCL-2)

Os níveis da quimiocina CCL-2 foram examinados em cinco estudos (N=163). O tratamento farmacológico antidepressivo significativamente reduziu os níveis de CCL-2 com uma grande estimativa de TE (Hedge g = -1,502) (Figura 6E). não houve evidência de efeitos de pequenos estudos (Tabela 3), e a heterogeneidade foi grande (i2=96,0%) mas não pode ser explorada devido a limitada quantidade de dados. Análise de sensibilidade revelou que a exclusão sucessiva de dois estudos tornou o TE não significante (Figura 13).

5.8. Outras variáveis imunológicas

Onze variáveis imunológicas adicionais (Interferon gama-IFN-γ, IL-4, IL-2, IL-8, CCL-3, antagonista do receptor de IL-1, IL-13, IL-17, IL-5, IL-7, e o receptor solúvel de IL-2) foram estudadas em pelo menos três estudos, tendo sido aqui metanalisadas.

De forma geral, os níveis destas citocinas/quimiocinas não foram significativamente alterados após farmacoterapia (Tabela 3). Os gráficos de *forest plot* estão disponíveis no material suplementar (Figuras 14 a 24). A heterogeneidade destas estimativas foi grande (I^2 entre 64,2 e 95,5%), com exceção daquela do receptor solúvel de IL-2.

5.9. Escores compilados

Medidas combinadas de perfis de citocinas/quimiocinas sugestivos da ativação de diferentes células imunes foram calculadas. Encontramos evidência de que o tratamento antidepressivo levou a redução significante em citocinas e quimiocinas predominantemente secretadas por macrófagos M1 (g de Hedge = -0,35; P<0,001), enquanto que citocinas e quimiocinas predominantemente secretadas por TH1, TH2 e TReg não foram alteradas significativamente (Figura 25).

5.10. Resposta terapêutica

Baseado em dados de estudos individuais, pode-se contrastar o TE de mudanças nos níveis de TNF- α e IL-6 entre respondedores e não-respondedores ao tratamento farmacológico. Esta estimativa de TE não foi significante (TNF-α dos respondedores: *g*=-0.346, k=8, *P*=0.115; TNF-α dos não-respondedores: *g*=-0.049, k=7, *P*=0.509; IL-6 dos respondedores: g=-0,222, k=4, P=0,480; IL-6 de não respondedores: g=-0,010, k=4, P=0,0964). Os níveis de IL-1β não foram alterados em respondedores (g=0,617, k=3, P=0,407), enquanto que os níveis periféricos desta citocina para não respondedores não estava disponível em pelo menos 3 *datasets*. Além disso, pode-se comparar os níveis basais de TNF-α e IL-8 entre respondedores e não-respondedores. Não houve diferença neste parâmetro para ambas as citocinas (TNF-α: g=0,248, k=7, P=0,353; IL-8: g=-0,082, k=3, P=0,595).

Tabela 2. Características dos estudos incluídos.

Referência	País (Idioma)	N	Idade	IMC	% fem/ % fumante	Critério diagnóstico (Entrevista estruturada)	Escala de depressão	Sintomas TDM após intervenção	Amostra (tipo de ensaio)	Tipo de intervenção	Tempo de *follow-up* (sem)	Escore de qualidade
ABBASI *et al.*, 2012	Iran (inglês)	18	34,2 ± 6,9	NA	30,0/NA	DSM-IV-TR (N/A)	HAM-D 17	11,4 ± 0,5	Soro (ELISA)	Sertralina	6	5
BASTERZI *et al.*, 2005	Turquia (inglês)	23	33,8 ± 12,8	NA	87,0/NA	DSM-IV (N/A)	HAM-D 17	10,7 ± 3,9	Soro (ELISA)	ISRS	6	5
BRUNONI *et al.*, 2014	Brasil (inglês)	18	41,0 ± 1,0	25,0 + 3,0	61,1/NA	DSM-IV (MINI)	HAM-D 17	14,0 ± 8,0	Plasma (Outro)	Sertralina	6	5
CRNKOVIC *et al.*, 2012	Croácia (inglês)	38	NA	NA	57,9/NA	DSM-IV-TR (MINI)	HAM-D	14,3 ± 2,6	Soro (Outro)	Antidepressivos	4	4
DAHL *et al.*, 2014	Noruega (inglês)	43	40,0 ± 12,0	25,8 + 5,5	76,0/NA	DSM-IV (MINI)	MADRS	13,0 ± 0,0	Plasma (Outro)	Antidepressivos	12	6
DAHL *et al.*, 2016	Noruega (inglês)	14	44,0 ± 10,0	23,8 + 4,8	78,6/NA	DSM-IV (MINI)	MADRS	12,0 ± 4,0	Plasma (Outro)	Antidepressivos	12	4
DOME *et al.*, 2012	Hungria (inglês)	24	42,7 ± 12,1	24,7 + 5,5	0,0/NA	DSM-IV (N/A)	MADRS	16,5 ± 11,1	Plasma (ELISA)	Antidepressivos	7	3
ELLER *et al.*, 2008	Estônia (inglês)	100	32,1 ± 11,9	NA	65,0/NA	DSM-IV (MINI)	MADRS	9,3 ± 9,7	Soro (Outro)	Escitalopram	12	7
ELLER *et al.*, 2009a	Estônia (inglês)	28	31,2 ± 9,5	24,3 + 3,5	60,7/NA	DSM-IV (MINI)	MADRS	13,5 ± 9,7	Soro (Outro)	Escitalopram e bupropiona	6	5
FAZZINO *et al.*, 2009	Venezuela (inglês)	20	NA	NA	0,0/NA	DSM-IV (N/A)	HAM-D	NA	Plasma (ELISA)	Venlafaxina	6	3
FORNARO *et al.*, 2011	Itália (inglês)	16	51,1 ± 11,0	NA	75,0/NA	DSM-IV (SCID)	HAM-D 17	9,1 ± 5,8	Soro (ELISA)	Duloxetina	6	6
FORNARO *et al.*, 2013	Itália (inglês)	30	48,3 ± 9,7	NA	80,0/NA	DSM-IV (SCID)	HAM-D 17	7,0 ± 3,8	Soro (ELISA)	Duloxetina	6	6
FROMMBERGER *et al.*, 1997	Alemanha (inglês)	10	46,0 ± 16,0	NA	83,3/NA	DSM-III-R (SCID)	MADRS	12,0 ± 9,0	Plasma (Outro)	Antidepressivos	7	3
(GUPTA *et al.*, 2016)	Índia (Inglês)	30	29,6 ± 9,4	NA	50,0/NA	DSM-IV (N/A)	HAM-D 21	19,5 ± 2,1	Soro (ELISA)	Mirtazapina	12	5
HERNANDEZ *et al.*,	México	24	32,0 ±	24,2 + 1,0	71,0/NA	DSM-IV	HAM-D 21	10,1 ± 1,1	Soro	ISRS	20	5

2008b	(inglês)		9,4			(MINI)			(ELISA)			
HERNANDEZ *et al.*, 2013	México (inglês)	31	35,0 ± 9,0	24,6 + 0,7	67,7/NA	DSM-IV-TR (MINI)	HAM-D	10,0 ± 2,0	Soro (ELISA)	ISRS	5	3
HIMMERICH, MILENOVIC*, et al.*, 2010	Alemanha (inglês)	16	42,0 ± 8,2	NA	68,8/NA	ICD-10 (N/A)	HAM-D 21	7,7 ± 6,0	Plasma (ELISA)	Antidepressivos	6	2
HO *et al.*, 2015	Taiwan (inglês)	26	23,2 ± 3,2	NA	0,0/NA	DSM-IV (N/A)	HAM-D 17	6,2 ± 4,6	Soro (ELISA)	Escitalopram	4	4
JAZAYERI *et al.*, 2010	Iran (inglês)	14	37,0 ± 8,5	29,6 + 6,2	71,4/NA	DSM-IV (N/A)	HAM-D 24	NA	Soro (ELISA)	Fluoxetina	8	4
KIM *et al.*, 2013	Coréia (inglês)	26	36,7 ± 9,4	24,3 + 10,2	80,8/NA	DSM-IV (N/A)	HAM-D	9,8 ± 8,3	Plasma (ELISA)	Antidepressivos	6	3
KRAUS *et al.*, 2002	Alemanha (inglês)	20	47,1 ± 16,6	23,3 + 2,5	50,0/35,0	DSM-IV (N/A)	NA	NA	Plasma (ELISA)	Mirtazapina ou Venlafaxina	4	4
LEO *et al.*, 2006	Itália (inglês)	20	34,9 ± 5,9	27,7 + 2,0	56,5/NA	DSM-IV-TR (SCID)	HAM-D 21	14,4 ± 2,1	Plasma (ELISA)	Sertralina ou citalopram	6	4
LI *et al.*, 2013	China (inglês)	61	32,1 ± 6,8	21,3 + 2,2	78,1/0,0	DSM-IV-TR (SCID)	HAM-D 17	NA	Plasma (ELISA)	Venlafaxina	8	7
(LINDQVIST *et al.*, 2017)	EUA (Inglês)	22	39,0 ± 13,4	28,2 ± 4,7	68,2/31,8	DSM-IV-TR (SCID)	HAM-D	NA	Plasma (ELISA)	ISRS	6	6
MACKAY *et al.*, 2009	Reino Unido (inglês)	28	39,0 ± 2,4	NA	82,1/NA	DSM-IV (N/A)	HAM-D 21	5,3 ± 1,4	Soro (ELISA)	Fluoxetina	18	2
MAES, MELTZER*, et al.*, 1995	USA (inglês)	17	36,6 ± 1,3	NA	41,0/NA	DSM-III-R (N/A)	HAM-D 24	14,6 ± 3,5	Plasma (ELISA)	Antidepressivos	12	4
MAES *et al.*, 1997	Bélgica (inglês)	25	50,3 ± 13,9	NA	45,7/NA	DSM-III-R (N/A)	HAM-D 17	13,3 ± 8,4	Soro (ELISA)	Antidepressivos	5	4
MIKOVA *et al.*, 2001	Bulgária (inglês)	14	47,3 ± 11,3	NA	100,0/NA	DSM-IV (N/A)	HAM-D	NA	Soro (ELISA)	Antidepressivos	6	5
(MUTHURAMALINGAM *et al.*, 2016)	Índia (Inglês)	29	NA	NA	63,8/NA	DSM-IV (MINI)	HAM-D	NA	Soro (ELISA)	Fluoxetina	6	3
MYINT *et al.*, 2005	Coréia (inglês)	22	40,7 ± 15,5	21,4 + 2,5	67,5/NA	DSM-IV (N/A)	HAM-D	5,6 ± 4,2	Plasma (ELISA)	Antidepressivos	8	3
(MYUNG *et al.*, 2016)	Coréia do Sul (Inglês)	66	68,0	NA	75,8/NA	DSM-IV-TR (N/A)	HAM-D 17	9,0	Soro (Outro)	ISRS ou mirtazapina	6	4
PILETZ *et al.*, 2009	USA	14	39,4 ±	28,1 + 1,4	86,4/18,2	DSM-IV	HAM-D 21	6,4 ± 1,1	Plasma	Venlafaxina	8	3

	(inglês)		1,9			(SCID)			(ELISA)			
ROTHERMUNDT, AROLT, PETERS*, et al.*, 2001	Alemanha (inglês)	43	44,5 ± 10,0	NA	65,1/37,2	DSM-IV (CIDI)	HAM-D 21	17,0 ± 9,0	Sangue (ELISA)	Antidepressivos	4	4
SEIDEL *et al.*, 1995	Alemanha (inglês)	39	39,9 ± 9,4	NA	69,2/NA	DSM-III-R (N/A)	HAM-D	14,9 ± 7,8	Sangue (ELISA)	Antidepressivos	6	3
SHEN *et al.*, 2010	China (inglês)	34	42,5 ± 12,1	NA	47,1/NA	DSM-IV (N/A)	HAM-D	10,1 ± 3,0	Soro (ELISA)	Fluoxetina	8	5
SLUZEWSKA, RYBAKOWSKI, LACIAK*, et al.*, 1995	Polônia (inglês)	22	42,0 ± 5,6	NA	90,9/NA	DSM-III-R (N/A)	HAM-D 17	17,0 ± 9,0	Soro (ELISA)	Fluoxetina	8	2
SONG *et al.*, 2009	China (inglês)	32	34,0 ± 13,0	NA	56,3/NA	DSM-IV (SCID)	HAM-D 21	11,3 ± 6,6	Soro (ELISA)	Fluoxetina	6	4
SUN *et al.*, 2010	China (chinês)	28	39,1 ± 13,2	NA	83,3/NA	DSM-IV (N/A)	HAM-D 24	11,8 ± 4,5	Soro (ELISA)	Fluoxetina	6	3
SUTCIGIL *et al.*, 2007	Turquia (inglês)	23	34,8 ± 7,4	NA	47,8/NA	DSM-IV (N/A)	HAM-D	13,6 ± 2,2	Soro (ELISA)	Sertralina	8	4
TUGLU, Cengiz *et al.*, 2003	Turquia (inglês)	26	39,4 ± 14,6	NA	42,3/69,2	DSM-IV (SCID)	HAM-D 17	9,0 ± 3,9	Soro (ELISA)	ISRS	6	5
USHIROYAMA *et al.*, 2004	Japão (inglês)	55	51,9 ± 5,7	23,6 + 1,1	100,0/14,5	DSM-IV (N/A)	HAM-D	9,5 ± 5,2	Plasma (ELISA)	Antidepressivos	12	4
YI *et al.*, 2015	China (inglês)	60	37,0 ± 10,0	NA	50,0/NA	ICD-10 (N/A)	MADRS	15,0 ± 5,0	Soro (ELISA)	ISRS	6	5
YOSHIMURA *et al.*, 2009	Japão (inglês)	51	39,8 ± 11,8	NA	58,8/NA	DSM-IV (MINI)	HAM-D	NA	Plasma (ELISA)	IRSN + ISRS	8	7
YOSHIMURA *et al.*, 2013	Japão (inglês)	118	44,3 ± 12,5	NA	38,0/NA	DSM-IV (N/A)	NA	NA	Plasma (ELISA)	Paroxetina ou sertralina	8	6
(YOSHIMURA *et al.*, 2017)	Japão (inglês)	30	45,0 ± 14,2	NA	56,7/NA	DSM-IV (N/A)	HAM-D 17	12,2 ± 2,8	Plasma (ELISA)	Fluvoxamina	8	4

Variáveis contínuas estão representadas como média ± DP.

Tabela 3. Metanálise primária de citocinas e quimiocinas em indivíduos com TDM tratados com antidepressivos.

Mediador	N Estudos	N Sujeitos	TE (IC 95%)	*P* (total)[a]	I^2	*P* (Egger)[b]	Efeitos de estudos pequenos[c]	Fail-safe N	TE ajustado (IC 95%)[d]
IL-6	24	722	-0,454 (-0,656 – -0,251)	**< 0,001**	84,7	0,118	N	622	NA
TNF-α	23	797	-0,202 (-0,365 – -0,039)	**0,015**	80,0	**0,018**	Y	100	-0,317 (-0,496 – -0,138)
IL-1β	15	448	-0,255 (-0,624 – 0,115)	0,176	92,0	0,780	N	90	NA
IL-10	10	331	-0,566 (-1,010 – -0,122)	**0,012**	92,5	**0,017**	Y	115	-0,566 (-1,010 – -0,122)
IL-4	10	281	0,510 (-0,176 – 1,197)	0,145	95,5	0,260	N	32	NA
IFN-γ	9	242	0,134 (-0,430 – 0,697)	0,642	93,2	0,732	N	0	NA
IL-2	8	207	-0,094 (-0,827 – 0,638)	0,800	94,8	0,358	N	0	NA
IL-8	7	298	-0,056 (-0,311 – 0,199)	0,668	76,9	0,346	N	0	NA
CCL-2	5	163	-1,502 (-2,581 – -0,422)	**0,006**	96,0	**0,019**	N	44	NA
CCL-3	4	124	-0,553 (-1,381 – 0,276)	0,191	93,6	0,409	N	12	NA
IL-1Ra	4	115	-0,166 (-0,483 – 0,151)	0,305	64,2	0,767	N	0	NA
sIL-2 receptor	4	159	-0,054 (-0,207 – 0,099)	0,490	0,0	0,177	N	0	NA
IL-13	3	88	-0,545 (-1,426 – 0,336)	0,225	92,9	**0,010**	Y	8	-0,545 (-1,426 – 0,336)
IL-17	3	70	-1,244 (-2,674 – 0,187)	0,088	94,6	0,116	N	1	NA
IL-5	3	90	-0,124 (-0,547 – 0,300)	0,567	73,3	0,597	N	0	NA
IL-7	3	90	-0,187 (-0,730 – 0,355)	0,498	83,0	0,807	N	0	NA

Abreviaturas: IC = intervalo de confiança; **TE** = tamanho do efeito; **S** = Sim; **N** = Não; **NA** = Não se aplica; Resultados estatisticamente significantes estão em negrito.

[a] Efeito global no teste Z

[b] No teste de Egger de viés de publicação

[c] $P < 0.1$ no teste de Egger de viés de publicação e tamanho de efeito do maior estudo mais conservador do que o tamanho de efeito global na direção oposta

[d] Ajustado usando o procedimento *trim-and-fill* de Duval & Tweedie

Tabela 4. Meta-regressão de citocinas e quimiocinas periféricas que modificaram após tratamento antidepressivo em indivíduos com TDM.

Variável	N		Meta-regressão				Meta-regressão		
	Estudos	Sujeitos	Slope	95% CI		*P*	Intercepto	z	*P*
IL-6									
Ano de publicação	24	722	-0,006	-0,039	0,027	0,728	11,341	0,334	0,738
Tamanho da amostra	24	722	-0,004	-0,015	0,007	0,445	-0,335	-1,602	0,109
Percentual de mulheres	24	722	-0,005	-0,016	0,006	0,380	-0,145	-0,380	0,704
Média do tempo de seguimento (semanas)	24	722	-0,011	-0,125	0,103	0,848	-0,384	-0,904	0,366
Média de idade (anos)	22	655	0,013	-0,031	0,057	0,564	-1,027	-1,127	0,260
Severidade de base da depressão [a]	21	561	0,011	-0,007	0,029	0,244	-1,564	-1,702	0,089
Diferença média de severidade da depressão [a]	17	444	-0,039	-0,069	-0,009	**0,010**	-2,334	-3,282	**0,001**
Taxa de resposta	12	414	-0,006	-0,034	0,022	0,667	-0,034	-0,041	0,968
Média de IMC	6	138	0,109	-0,107	0,324	0,322	-3,470	-1,178	0,239
TNF-α									
Ano de publicação	23	797	0,013	-0,031	0,057	0,560	-26,597	-0,588	0,556
Tamanho da amostra	23	797	0,005	-0,004	0,014	0,297	-0,392	-1,967	**0,049**
Média do tempo de seguimento (semanas)	23	797	-0,040	-0,113	0,033	0,285	0,086	0,291	0,771
Percentual de mulheres	22	773	0,002	-0,008	0,012	0,739	-0,338	-0,960	0,337
Média de idade (anos)	21	730	0,005	-0,018	0,028	0,671	-0,440	-0,893	0,372
Severidade de base da depressão [a]	20	734	-0,017	-0,027	-0,007	**0,001**	1,395	2,712	**0,007**
Diferença média de severidade da depressão [a]	16	526	0,008	-0,008	0,024	0,316	0,184	0,414	0,679
Taxa de resposta	15	568	-0,005	-0,022	0,011	0,549	0,036	0,063	0,950
Média de IMC	10	304	-0,031	-0,133	0,072	0,560	0,622	0,479	0,632
Percentual de pacientes virgens de tratamento	6	249	-0,005	-0,016	0,006	0,362	0,314	0,719	0,472
Percentual de fumantes	5	176	-0,015	-0,036	0,006	0,168	0,194	0,492	0,622
IL-1β									
Ano de publicação	15	448	-0,024	-0,109	0,062	0,586	47,357	0,542	0,588
Tamanho da amostra	15	448	-0,018	-0,053	0,018	0,336	0,264	0,453	0,651
Média de idade (anos)	15	448	-0,017	-0,098	0,065	0,688	0,388	0,242	0,809

Percentual de mulheres	15	448	-0,001	-0,025	0,023	0,936	-0,185	-0,225	0,822
Severidade de base da depressão [a]	15	448	0,011	-0,021	0,043	0,502	-1,286	-0,824	0,410
Diferença média de severidade da depressão [a]	14	434	-0,015	-0,050	0,019	0,388	-1,014	-1,139	0,255
Média do tempo de seguimento (semanas)	15	448	0,140	0,043	0,237	**0,005**	-1,314	-3,120	**0,002**
Média de IMC	7	174	-0,105	-0,511	0,301	0,613	2,718	0,496	0,620
Taxa de resposta	5	153	0,022	-0,032	0,075	0,422	-1,451	-0,681	0,496
IL-10									
Ano de publicação	10	331	0,038	-0,054	0,130	0,415	-77,364	-0,821	0,411
Tamanho da amostra	10	331	0,027	-0,013	0,068	0,190	-1,448	-2,026	**0,043**
Média de idade (anos)	10	331	0,016	-0,069	0,102	0,708	-1,199	-0,719	0,472
Percentual de mulheres	10	331	-0,014	-0,038	0,009	0,233	0,284	0,369	0,712
Severidade de base da depressão [a]	10	331	-0,002	-0,046	0,042	0,940	-0,428	-0,206	0,837
Diferença média de severidade da depressão [a]	10	331	-0,004	-0,054	0,046	0,867	-0,784	-0,636	0,525
Média do tempo de seguimento (semanas)	10	331	-0,124	-0,220	-0,029	**0,011**	0,443	0,987	0,324
Média de IMC	5	144	0,446	-0,861	1,753	0,504	-12,118	-0,735	0,462
IL-4									
Ano de publicação	10	281	0,028	-0,332	0,388	0,879	-55,697	-0,151	0,880
Tamanho da amostra	10	281	0,119	0,046	0,192	**0,001**	-2,862	-2,511	**0,012**
Média do tempo de seguimento (semanas)	10	281	0,000	-0,284	0,284	0,999	0,549	0,437	0,662
Média de idade (anos)	9	261	-0,038	-0,248	0,173	0,725	1,946	0,492	0,622
Percentual de mulheres	9	261	-0,020	-0,082	0,041	0,522	1,696	0,902	0,367
Severidade de base da depressão [a]	9	261	-0,038	-0,135	0,060	0,446	4,289	0,871	0,384
Diferença média de severidade da depressão [a]	9	261	0,025	-0,065	0,115	0,583	1,931	0,753	0,451
IFN-γ									
Ano de publicação	9	272	-0,036	-0,329	0,257	0,810	72,493	0,241	0,809
Tamanho da amostra	9	272	0,066	-0,050	0,183	0,265	-1,638	-0,985	0,324
Média de idade (anos)	9	272	-0,061	-0,199	0,077	0,387	2,423	0,900	0,368
Percentual de mulheres	9	272	-0,004	-0,048	0,040	0,848	0,400	0,270	0,787
Severidade de base da depressão [a]	9	272	-0,035	-0,121	0,051	0,421	3,414	0,831	0,406

Diferença média de severidade da depressão [a]	9	272	-0,006	-0,079	0,067	0,877	-0,167	-0,083	0,934
Média do tempo de seguimento (semanas)	9	272	-0,065	-0,271	0,141	0,537	0,708	0,668	0,504
Média de IMC	6	154	-0,060	-1,261	1,141	0,922	1,385	0,094	0,925
IL-2									
Ano de publicação	8	207	0,027	-0,368	0,422	0,894	-54,186	-0,134	0,894
Tamanho da amostra	8	207	0,179	-0,042	0,400	0,113	-4,604	-1,604	0,109
Média do tempo de seguimento (semanas)	8	207	0,073	-0,112	0,258	0,439	-0,792	-0,773	0,439
Média de idade (anos)	7	187	-0,066	-0,240	0,107	0,453	2,231	0,684	0,494
Percentual de mulheres	7	187	0,005	-0,045	0,055	0,845	-0,463	-0,281	0,779
Severidade de base da depressão [a]	7	187	-0,106	-0,151	-0,061	**< 0,001**	10,427	4,527	**< 0,001**
Diferença média de severidade da depressão [a]	7	187	0,021	-0,085	0,126	0,702	0,996	0,320	0,749
IL-8									
Ano de publicação	7	298	-0,013	-0,070	0,044	0,662	25,450	0,436	0,663
Tamanho da amostra	7	298	0,004	-0,004	0,013	0,316	-0,264	-1,073	0,283
Média de idade (anos)	7	298	-0,010	-0,029	0,008	0,277	0,367	0,890	0,374
Percentual de mulheres	7	298	-0,008	-0,016	0,000	0,058	0,451	1,580	0,114
Média do tempo de seguimento (semanas)	7	298	-0,049	-0,129	0,031	0,232	0,352	0,956	0,339
Severidade de base da depressão [a]	6	284	0,007	-0,024	0,037	0,659	-0,604	-0,472	0,637
Diferença média de severidade da depressão [a]	5	218	-0,011	-0,042	0,020	0,482	-0,541	-0,735	0,463
Taxa de resposta	5	258	0,010	-0,049	0,070	0,728	-0,752	-0,372	0,710
CCL-2									
Ano de publicação	5	163	0,340	-0,387	1,066	0,360	-684,728	-0,918	0,358
Tamanho da amostra	5	163	0,014	-0,147	0,174	0,866	-2,253	-0,737	0,461
Média de idade (anos)	5	163	0,014	-0,181	0,210	0,885	-2,402	-0,546	0,585
Percentual de mulheres	5	163	0,008	-0,088	0,105	0,868	-2,222	-0,759	0,448
Severidade de base da depressão [a]	5	163	-0,058	-0,298	0,183	0,638	4,313	0,330	0,741
Média do tempo de seguimento (semanas)	5	163	-0,851	-2,375	0,673	0,274	3,985	0,736	0,462

Abreviações: IC = intervalo de confiança; **IL** = interleucina; **TNF-α** = fator de necrose tumoral alfa; Resultados estatisticamente significantes estão em negrito. [a] O valor médio na escala de sintomas depressivos em cada estudo foi normalizada como uma percentagem do ponto de corte que define depressão severa em cada escala

Tabela 5. Análise de subgrupo de citocinas e quimiocinas em indivíduos com TDM após tratamento antidepressivo.

Variável		Metanálise				Heterogeneidade		
	gl	TE	IC 95%	P^a	I^2	Q	P^b
IL-6								
Antidepressivo								
Miscelânea	9	-0,321	-0,499	-0,143	**< 0,001**	51,2	18,46	**0,030**
ISRS	12	-0,629	-0,970	-0,288	**< 0,001**	90,1	121,18	**< 0,001**
Taxa de resposta > mediana[c]								
Sim	3	-0,442	-0,942	0,058	0,083	86,0	21,41	**< 0,001**
Não	2	-0,573	-1,379	0,233	0,164	88,7	17,63	**< 0,001**
Fonte da amostra								
Plasma	10	-0,507	-0,701	-0,313	**< 0,001**	65,2	28,71	**0,001**
Soro	11	-0,397	-0,799	0,004	0,052	90,7	118,62	**< 0,001**
Tipo de ensaio								
ELISA	18	-0,414	-0,649	-0,179	**0,001**	86,2	130,33	**< 0,001**
Outro	4	-0,613	-1,041	-0,186	**0,005**	78,6	18,68	**0,001**
Duração do tratamento > mediana[d]								
Não	13	-0,486	-0,856	-0,116	**0,010**	90,6	138,36	**< 0,001**
Sim	9	-0,418	-0,537	-0,300	**< 0,001**	14,2	10,49	0,312
TNF-α								
Antidepressivo								
Miscelânea	10	-0,128	-0,305	0,050	0,159	66,3	29,64	**0,001**
IRSN	2	-0,154	-0,391	0,084	0,204	28,9	2,81	0,245
ISRS	8	-0,367	-0,757	0,023	0,065	89,6	76,92	**< 0,002**
Taxa de resposta > mediana[c]								
SIm	3	-0,611	-1,542	0,320	0,199	94,7	57,10	**< 0,001**
Não	3	-0,186	-0,374	0,002	0,053	0,0	1,77	0,622
Fonte da amostra								
Plasma	9	-0,163	-0,329	0,002	0,053	53,0	19,14	**0,024**
Soro	12	-0,246	-0,511	0,018	0,068	86,6	89,23	**< 0,001**
Tipo de ensaio								
ELISA	15	-0,286	-0,515	-0,057	**0,015**	83,0	88,15	**< 0,001**
Outro	6	-0,027	-0,200	0,147	0,764	54,7	13,25	**0,039**
Duração do tratamento > mediana[d]								
Não	12	-0,137	-0,352	0,079	0,214	76,4	50,81	**< 0,001**
Sim	9	-0,289	-0,551	-0,027	**0,031**	84,5	58,19	**< 0,001**
IL-1β								
Antidepressivo								
Miscelânea	4	-0,148	-0,326	0,031	0,105	23,9	5,25	0,262
IRSN	1	0,060	-0,458	0,577	0,821	65,2	2,87	0,090
ISRS	7	-0,364	-1,091	0,363	0,326	95,1	143,30	**< 0,001**
Taxa de resposta > mediana[c]								
Sim	1	1,090	-1,532	3,712	0,415	97,3	37,31	**< 0,001**
Não	2	-0,386	-1,101	0,329	0,290	91,5	23,45	**< 0,001**
Fonte da amostra								
Plasma	4	-0,393	-0,603	-0,182	**< 0,001**	16,7	4,80	0,308
Soro	7	-0,213	-0,943	0,517	0,567	95,6	158,98	**< 0,001**
Sangue todo	1	0,024	-0,188	0,237	0,823	0,0	0,16	0,691

Estimulada								
SIm	2	-0,019	-0,213	0,174	0,844	0,0	1,12	0,570
Não	11	-0,300	-0,775	0,174	0,215	93,3	163,35	**< 0,001**
Duração do tratamento > mediana[d]								
Não	8	-0,568	-1,048	-0,089	**0,020**	92,3	103,55	**< 0,001**
Sim	5	0,225	-0,352	0,803	0,445	91,0	55,60	**< 0,001**
IL-10								
Antidepressivo								
Miscelânea	2	-0,563	-0,767	-0,360	**< 0,001**	0,0	0,18	0,915
ISRS	5	-0,667	-1,453	0,119	0,096	95,4	109,87	**< 0,001**
Fonte da amostra								
Plasma	2	-0,497	-0,721	-0,274	**< 0,001**	0,0	0,34	0,842
Serum	5	-0,634	-1,382	0,114	0,096	95,4	109,06	**< 0,001**
Tipo de ensaio								
ELISA	6	-0,624	-1,256	0,008	0,053	94,8	115,13	**< 0,001**
Outro	2	-0,497	-0,721	-0,274	**< 0,001**	0,0	0,34	0,842
Duração do tratamento > mediana[d]								
Não	5	-0,280	-0,831	0,271	0,319	92,3	65,34	**< 0,001**
Sim	3	-1,003	-1,666	-0,341	**0,003**	89,6	28,72	**< 0,001**
IL-4								
Fonte da amostra								
Plasma	2	-0,574	-1,747	0,599	0,337	91,9	24,77	**< 0,001**
Soro	6	0,982	0,118	1,846	**0,026**	96,4	165,53	**< 0,001**
Duração do tratamento > mediana[d]								
Não	6	0,389	-0,494	1,271	0,388	96,3	163,22	**< 0,001**
Sim	2	0,823	-0,502	2,148	0,223	93,9	32,58	**< 0,001**
IFN-γ								
Antidepressivo								
Miscelânea	2	-0,387	-0,616	-0,158	**0,001**	0,0	0,49	0,782
ISRS	4	0,415	-0,643	1,473	0,442	95,6	91,62	< **0,001**
Fonte da amostra								
Plasma	3	-0,780	-1,453	-0,107	**0,023**	84,8	19,77	**< 0,001**
Soro	4	0,855	0,159	1,550	**0,016**	92,7	54,48	**< 0,001**
Tipo de ensaio								
ELISA	5	0,679	0,062	1,297	**0,031**	91,5	59,03	**< 0,001**
Outro	2	-1,021	-1,950	-0,091	**0,031**	89,2	18,46	**< 0,001**
Duração do tratamento > mediana[d]								
Não	4	0,474	-0,555	1,503	0,366	95,3	85,18	**< 0,001**
Sim	3	-0,282	-0,476	-0,087	**0,004**	2,8	3,09	0,379

Abreviações: IC = intervalo de confiança; **TE** = tamanho do efeito; Resultados estatisticamente significantes estão em negrito

[a] Efeito global no teste Z

[b] No teste Q de heterogeneidade

[c] Valores da mediana da taxa de resposta para cada citocina foram usados para definir um ponto de corte

Figura 6. ***Forest plots*** **de estudos que medem a mudança nos níveis periféricos de (A) IL-6, (B) TNF-α, (C) IL-1β, (D) IL-10 e (E) CCl-2 em indivíduos com TDM após tratamento antidepressivo. O TE está representado como g de Hedge com IC de 95%.**

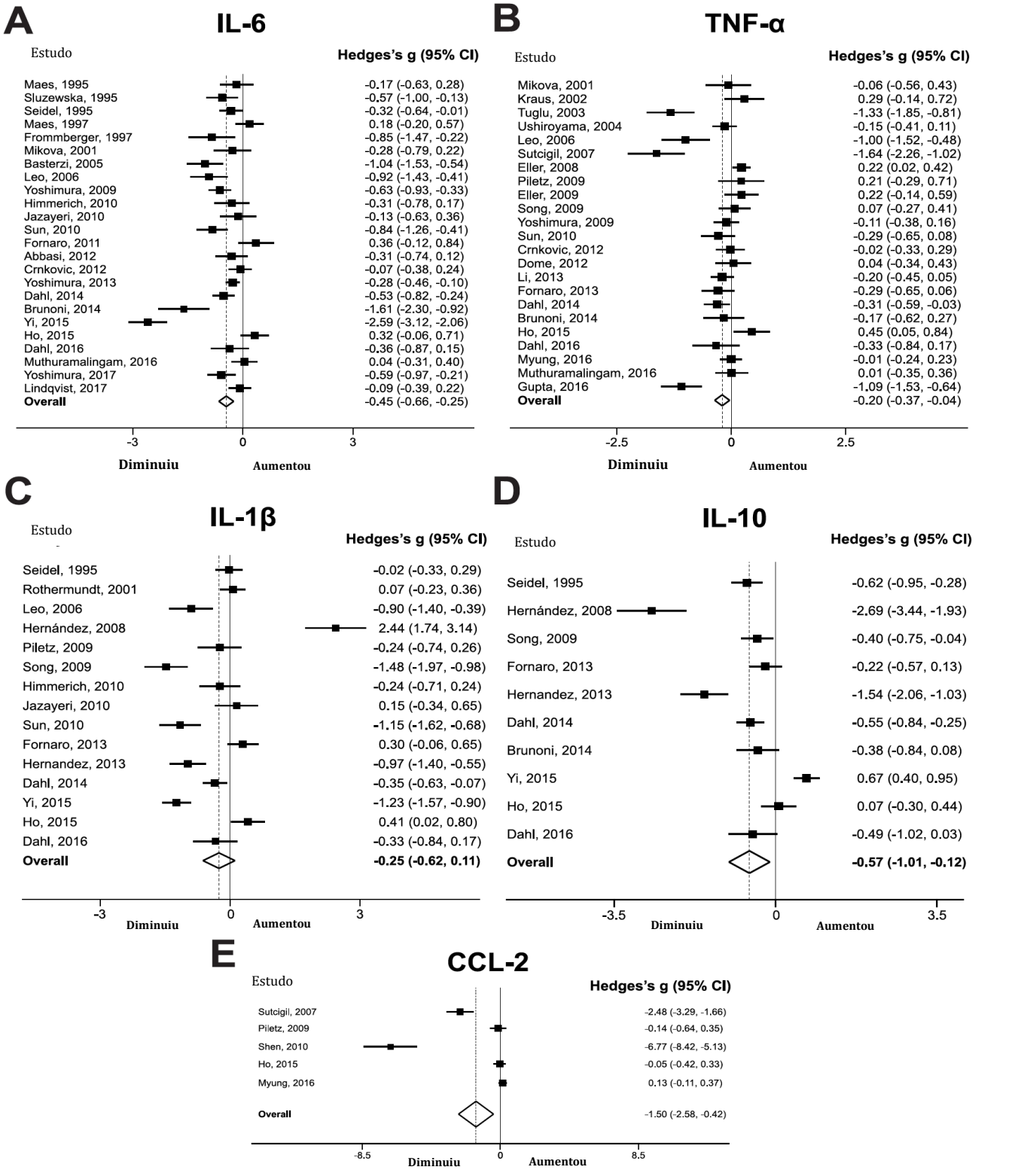


Figura 7. Análise de sensibilidade da metanálise de estudos que investigaram IL-6.

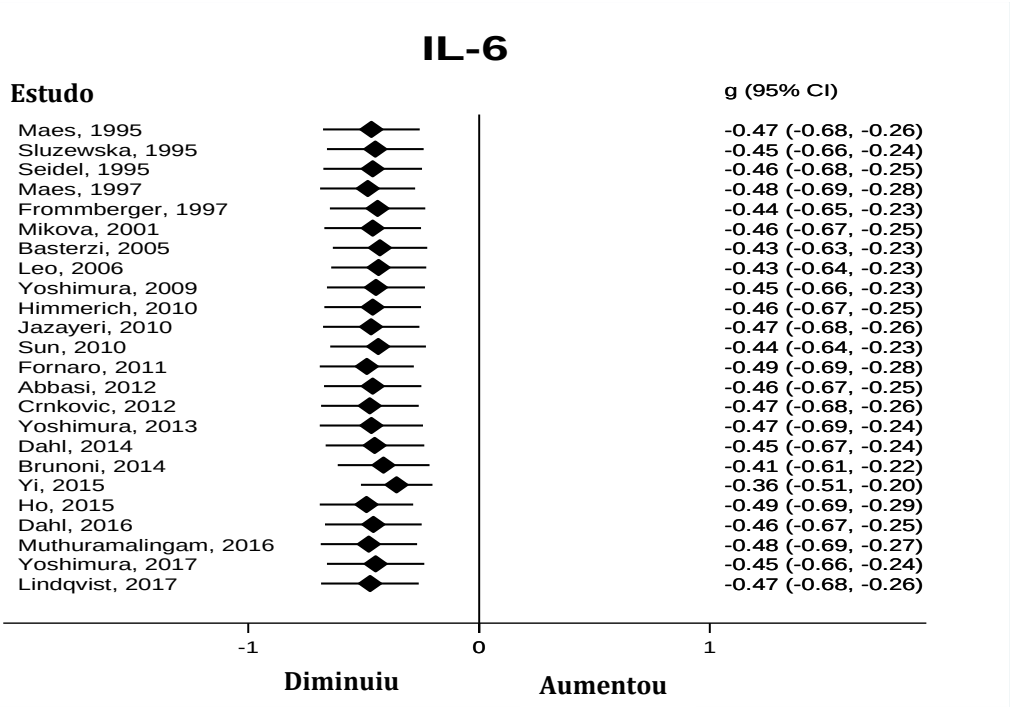


Figura 8. Metanálise cumulativa de estudos que investigaram IL-6.

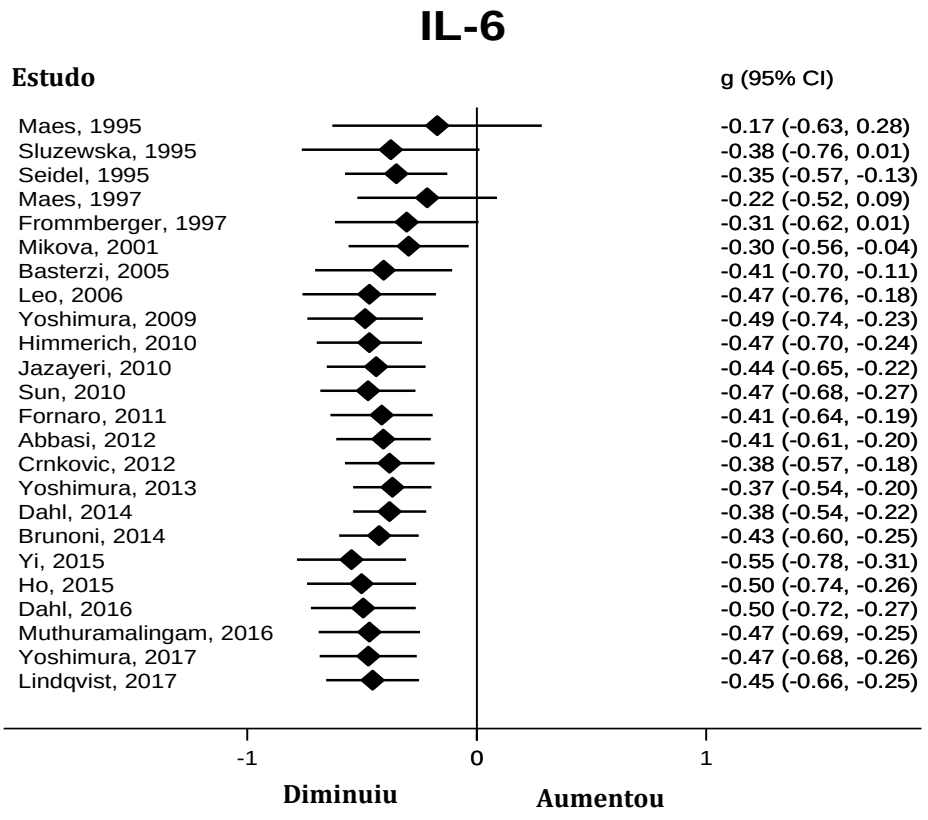


Figura 9. Análise de sensibilidade da metanálise de estudos que investigaram TNF-α.

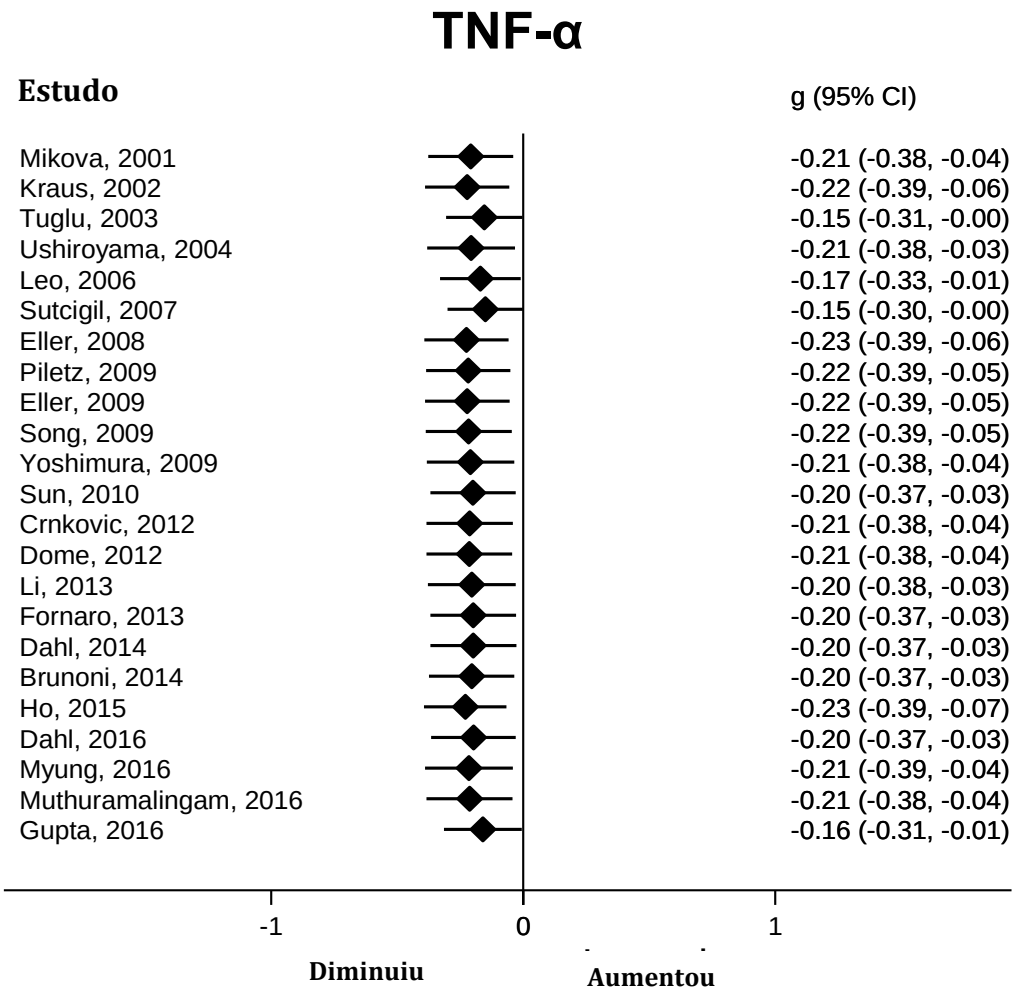


Figura 10. Metanálise cumulativa de estudos que investigaram TNF-α.

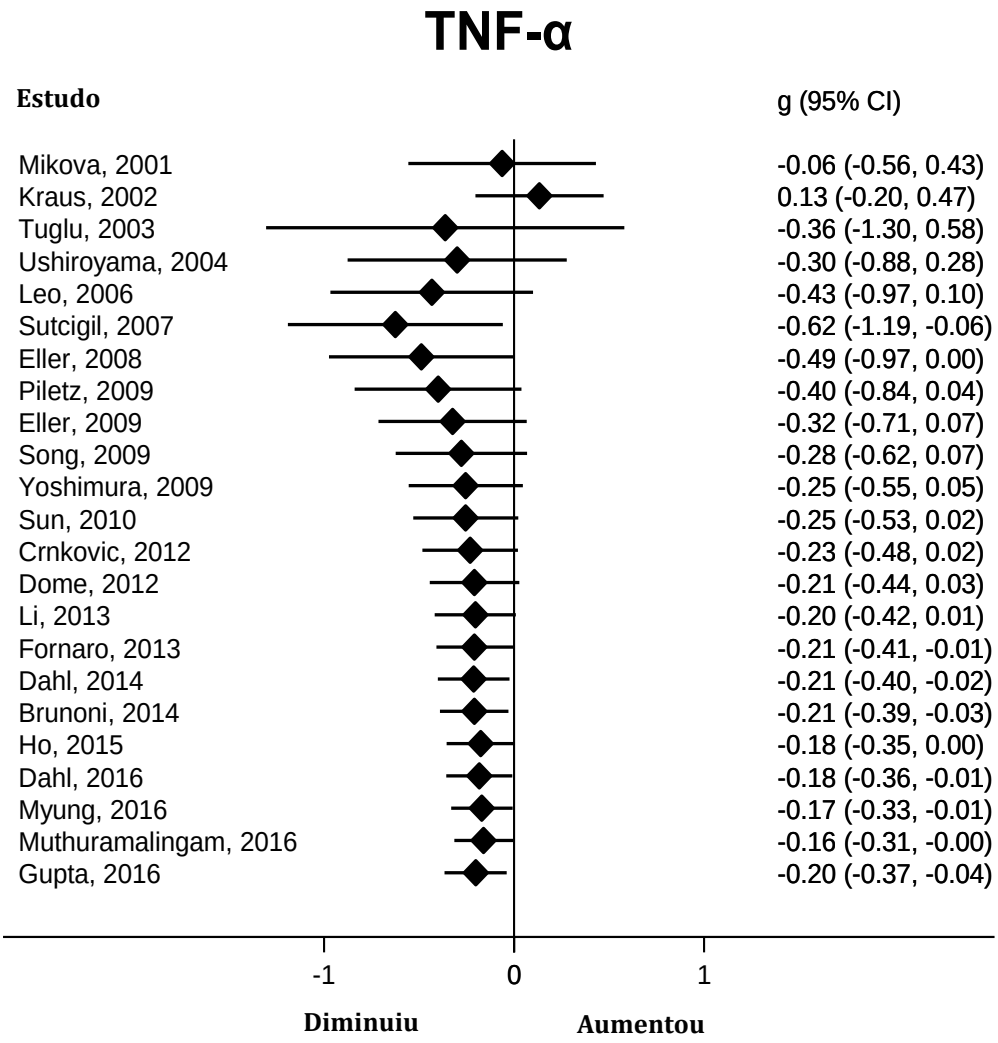


Figura 11. Análise de sensibilidade da metanálise de estudos que investigaram IL-10.

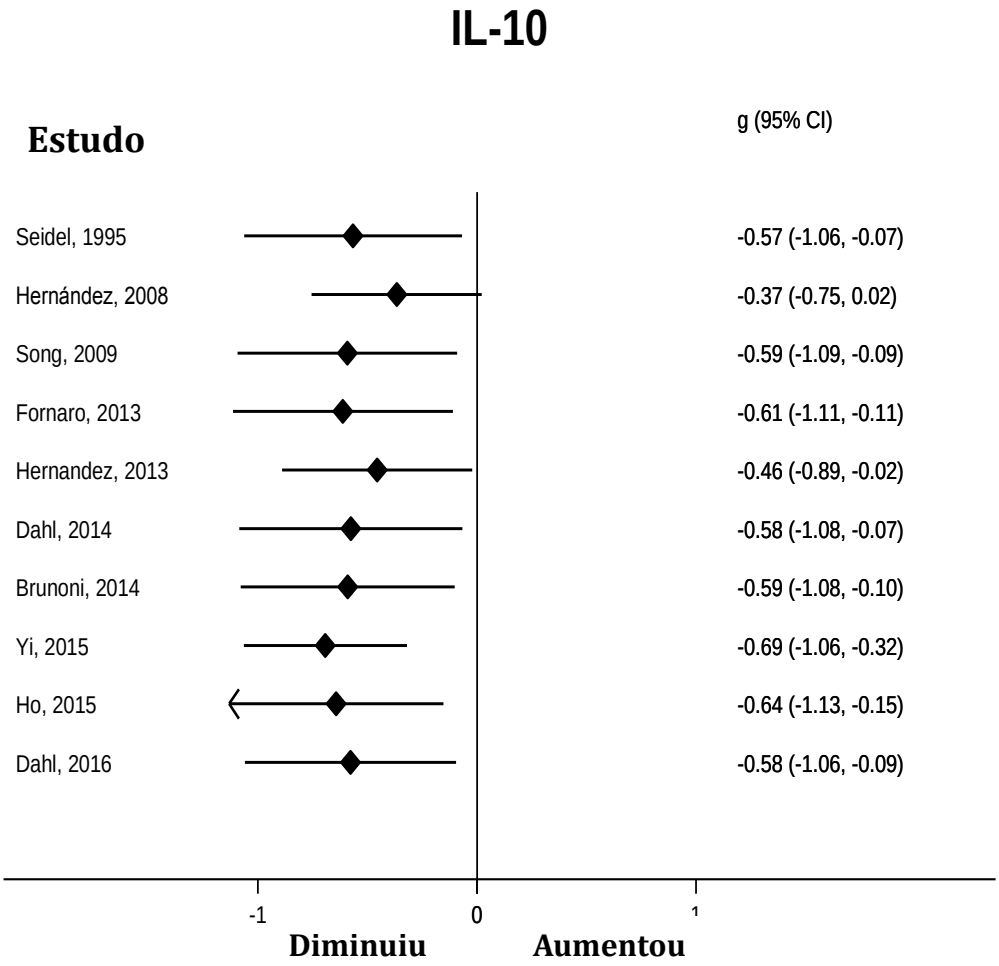


Figura 12. Metanálise cumulativa de estudos que investigaram IL-10.

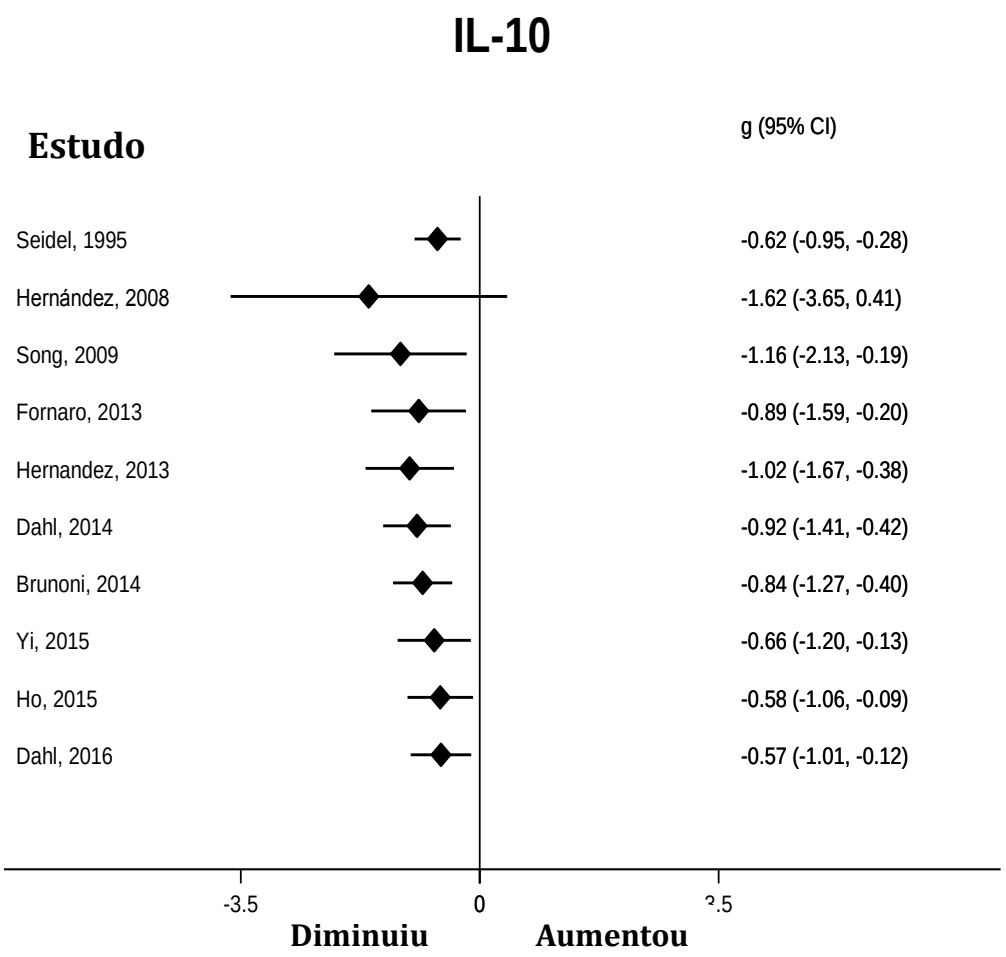


Figura 13. Análise de sensibilidade da metanálise de estudos que investigaram CCL-2.

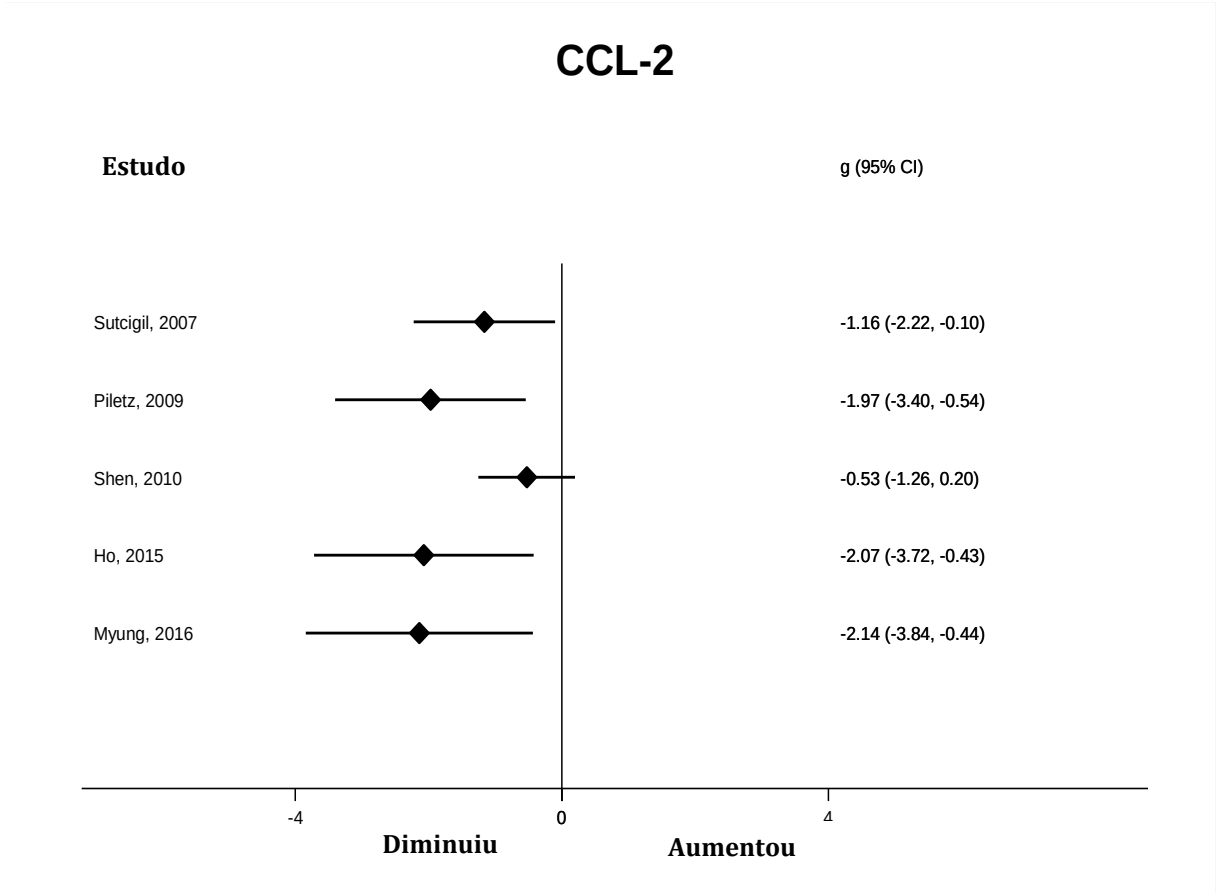


Figura 14. *Forest plot* de estudos que investigaram IL-4

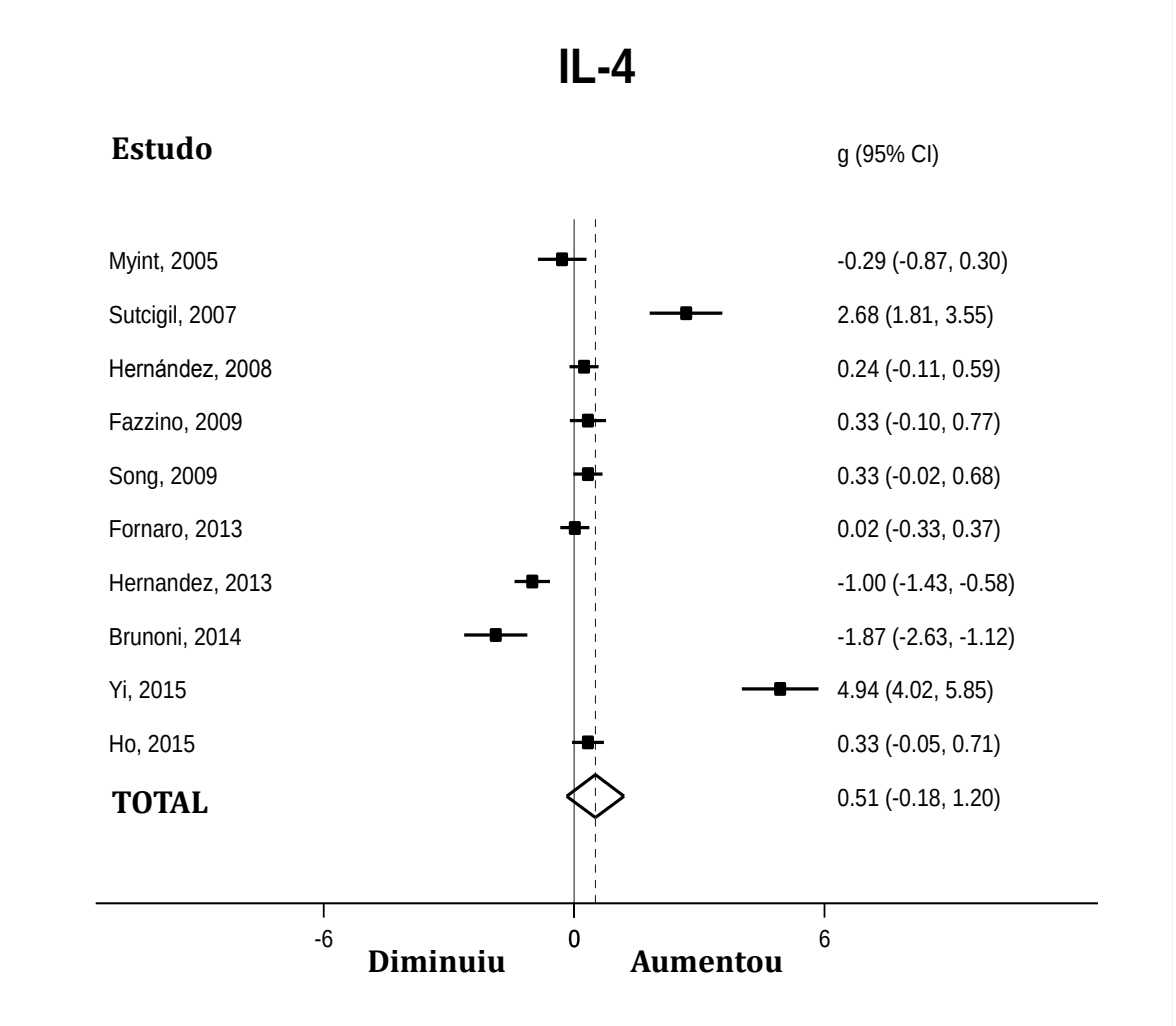


Figura 15. ***Forest plot*** **de estudos que investigaram IFN-γ.**

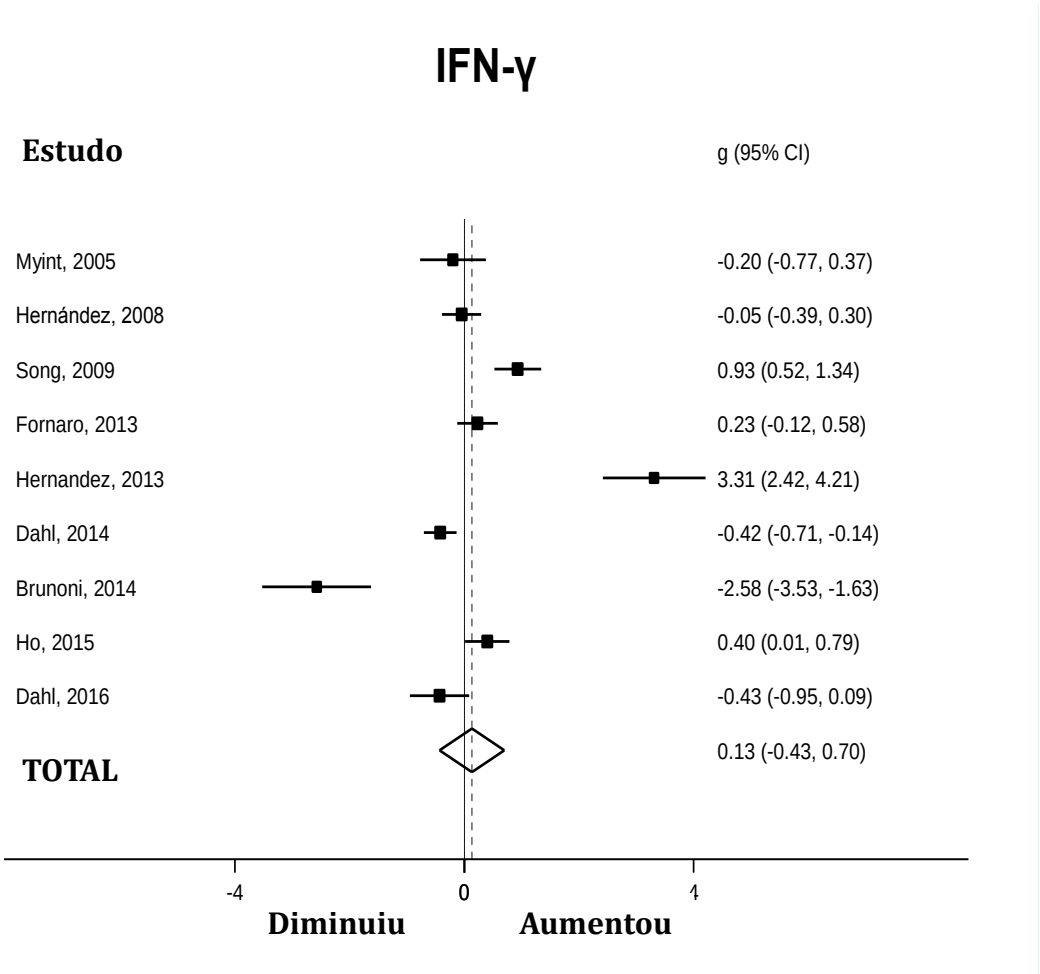


Figura 16. *Forest plot* de estudos que investigaram IL-2.

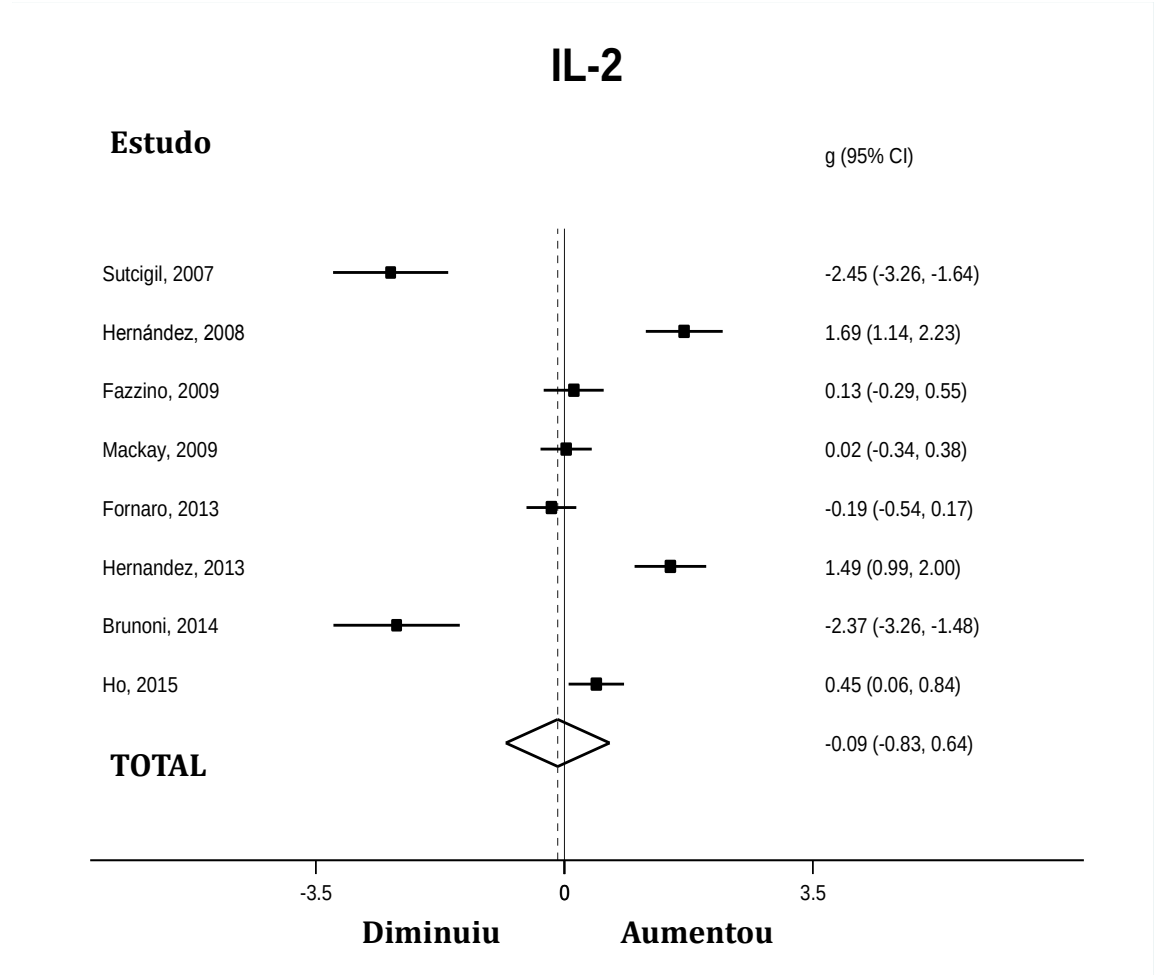


Figura 17. *Forest plot* de estudos que investigaram IL-8.

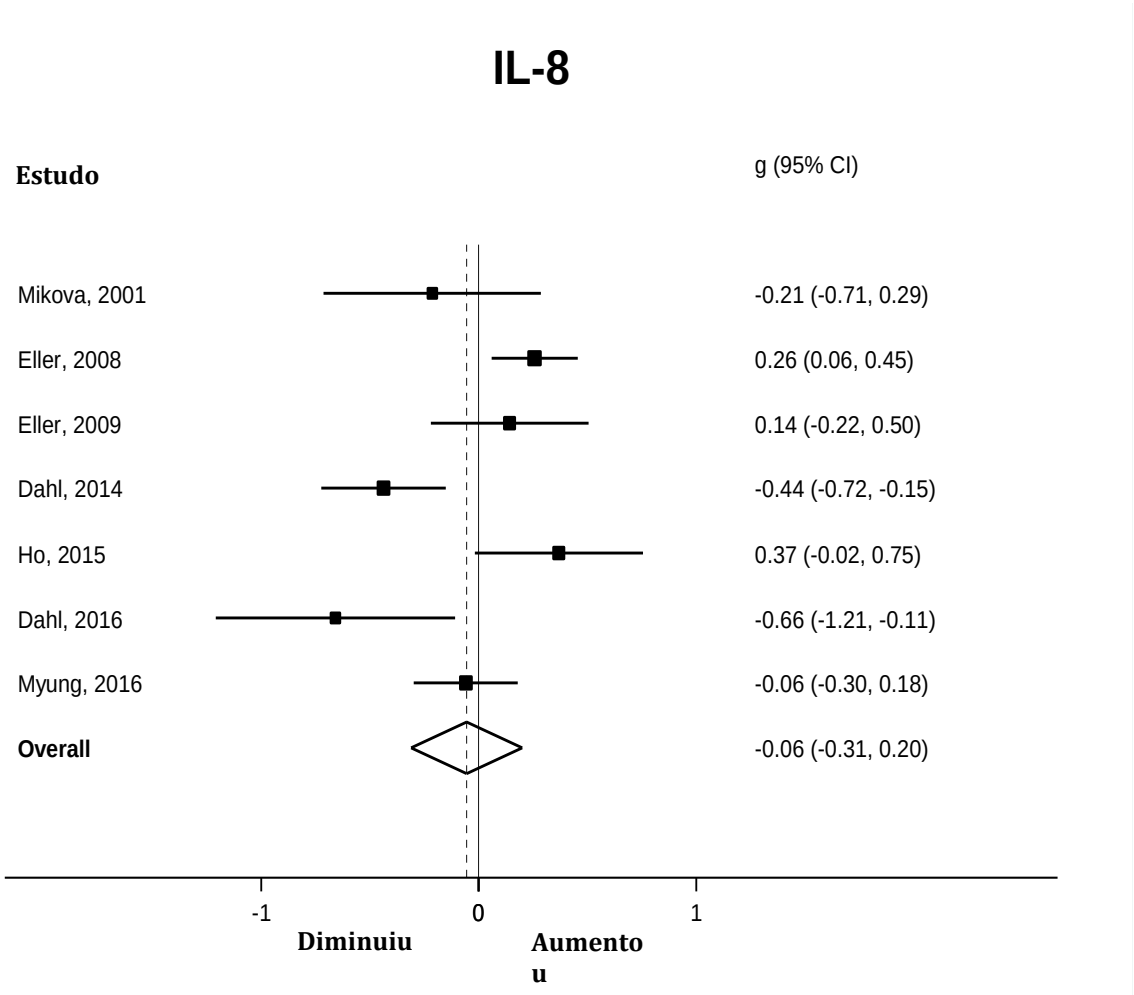


Figura 18. *Forest plot* de estudos que investigaram CCL-3.

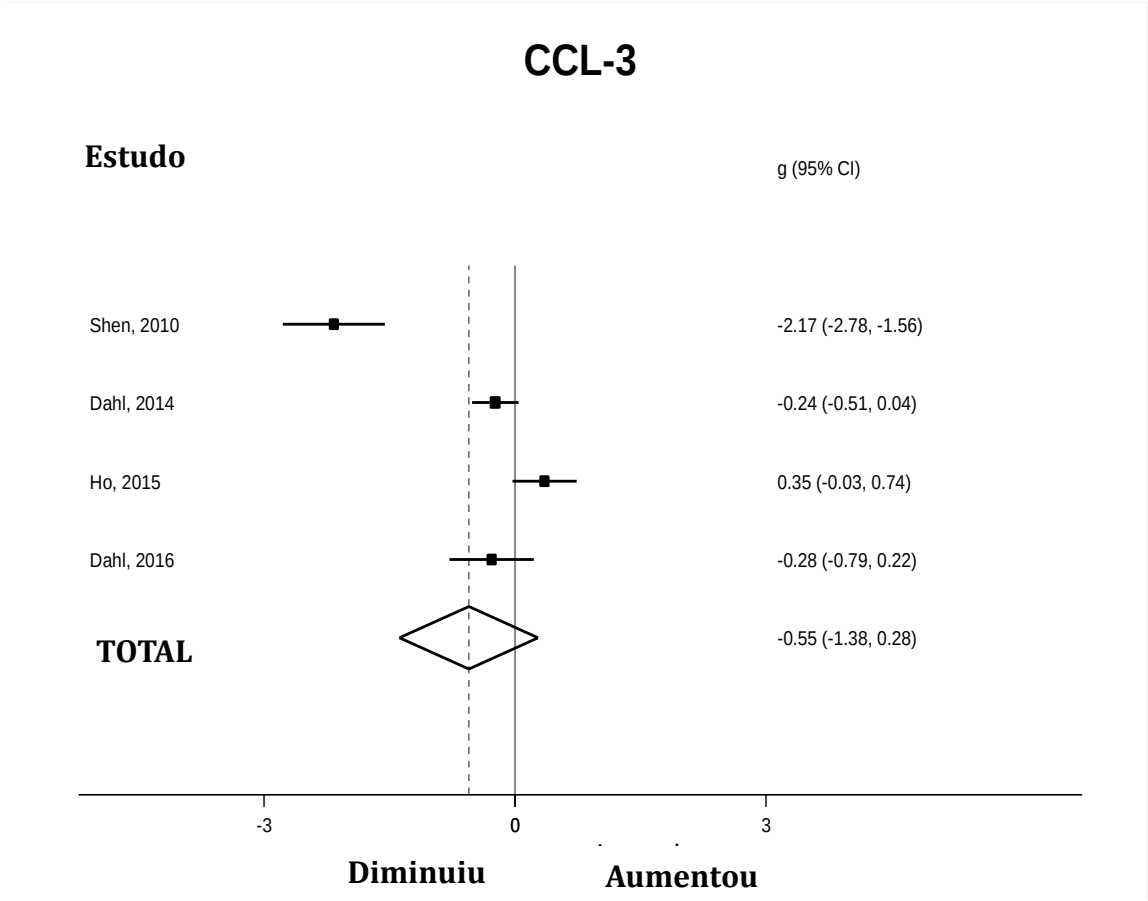


Figura 19. *Forest plot* de estudos que investigaram IL-1Ra.

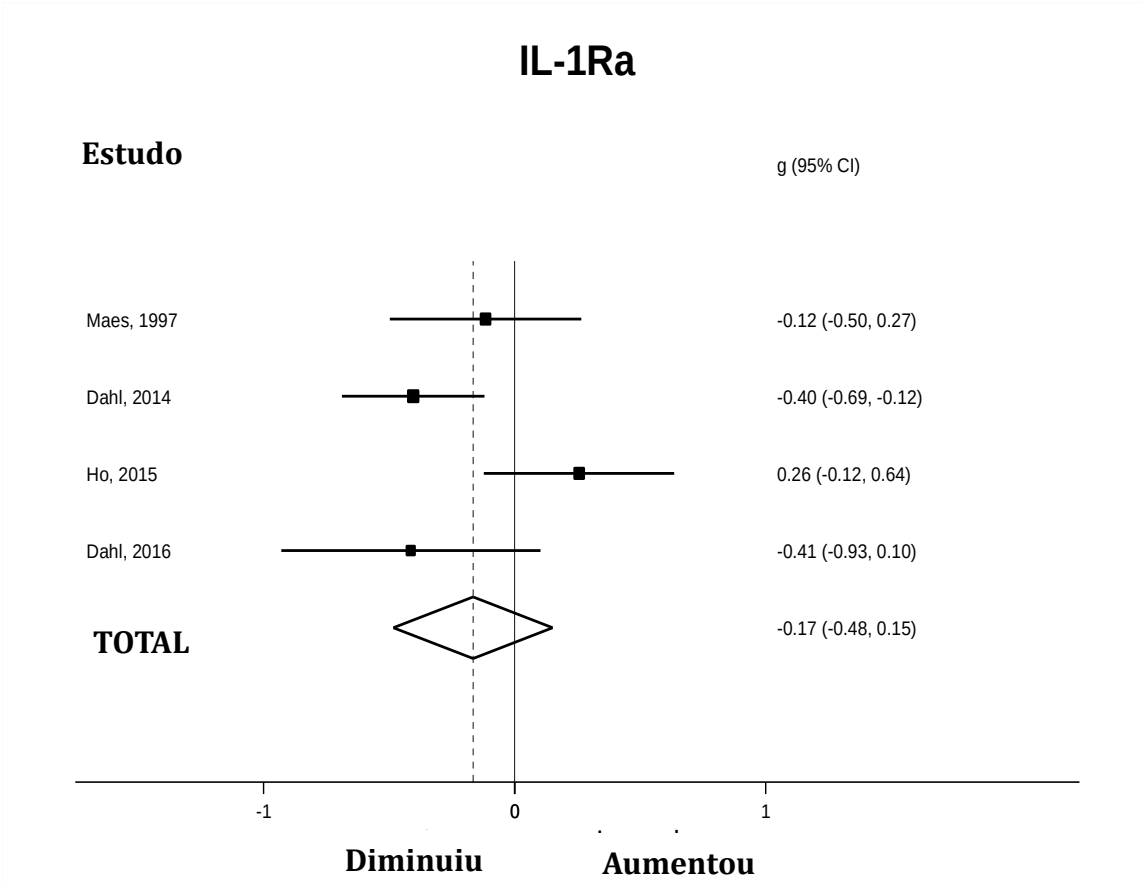


Figura 20. ***Forest plot*** **de estudos que investigaram receptor solúvel de IL-2 (sIL-2 receptor).**

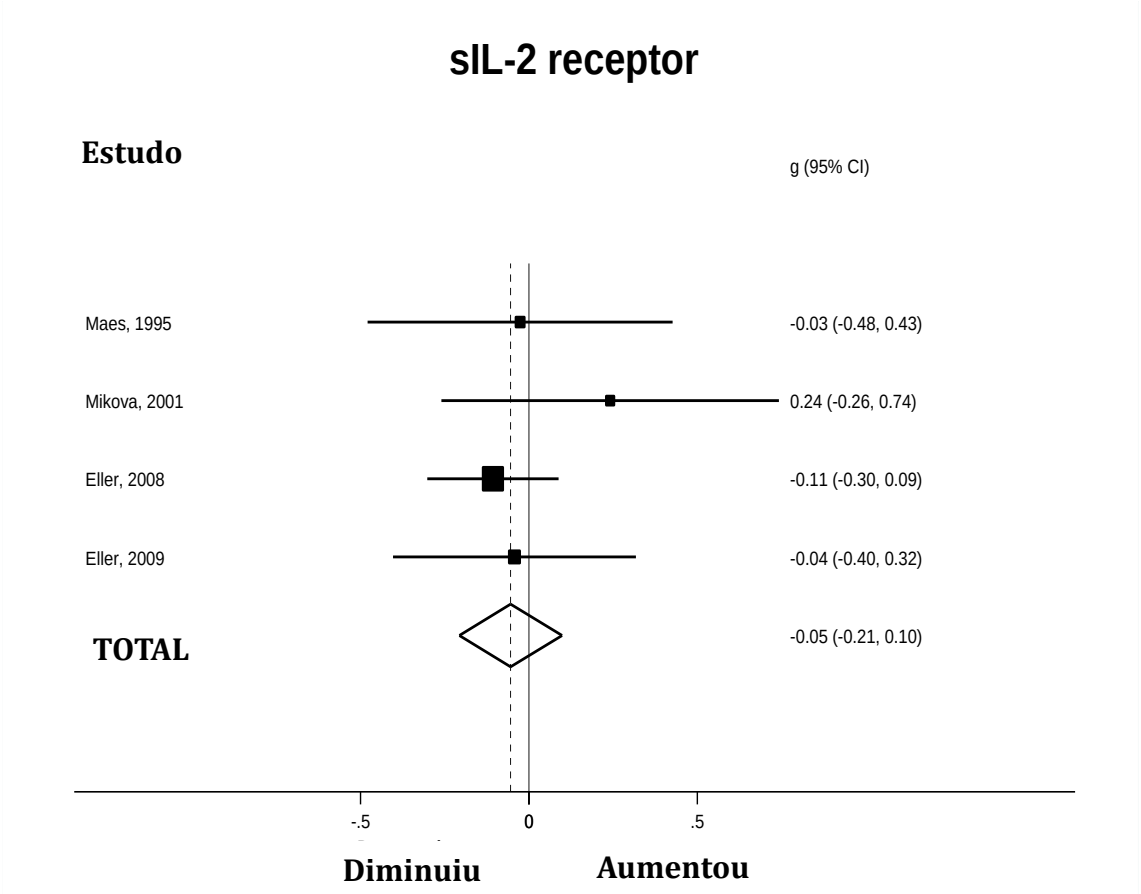


Figura 21. *Forest plot* de estudos que investigaram IL-13.

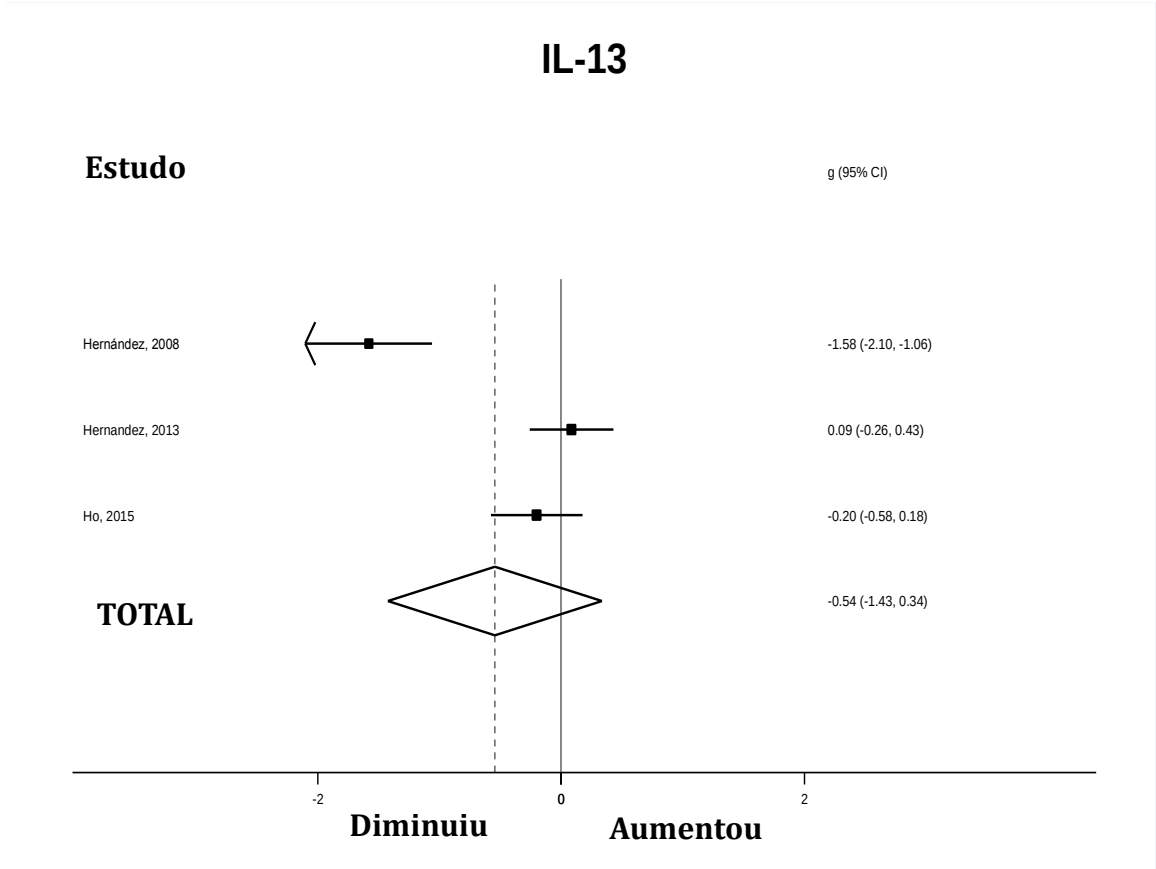


Figura 22. *Forest plot* de estudos que investigaram IL-17.

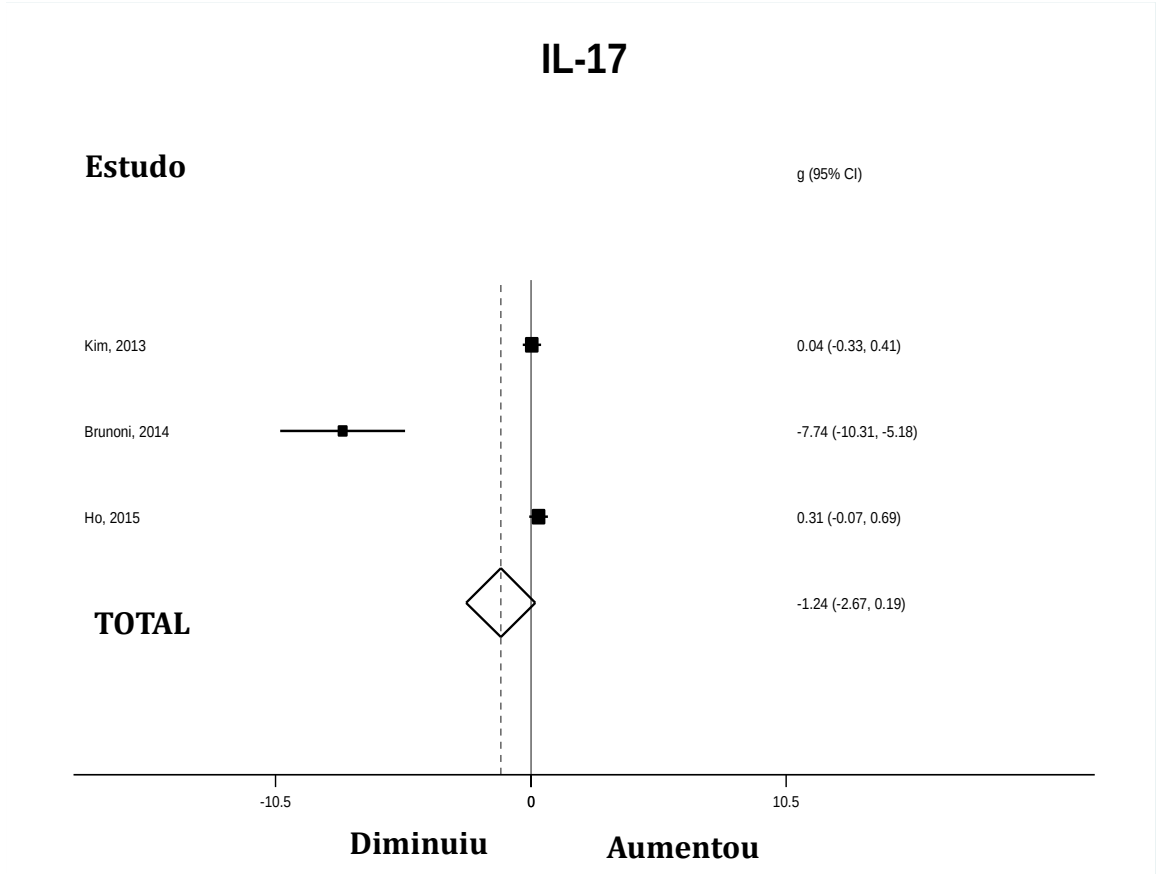


Figura 23. *Forest plot* de estudos que investigaram IL-5.

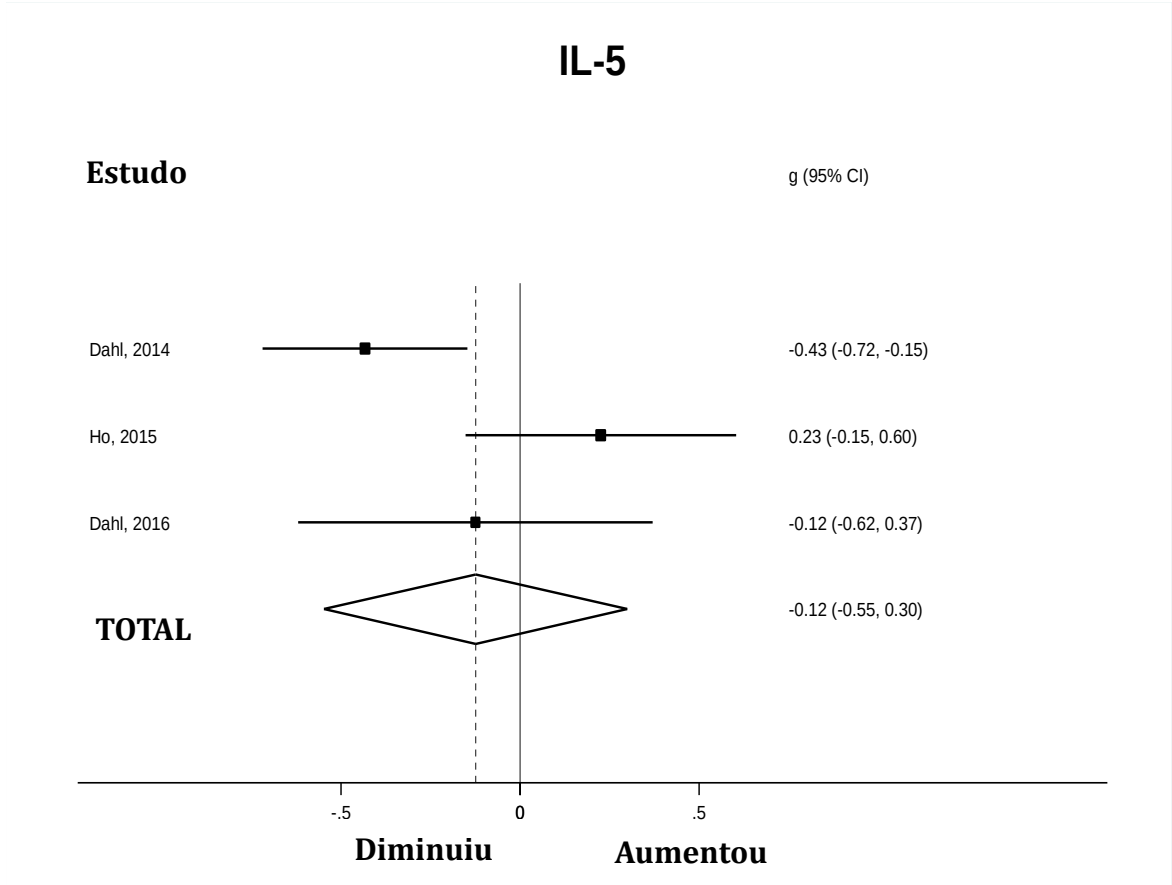


Figura 24. *Forest plot* de estudos que investigaram IL-7.

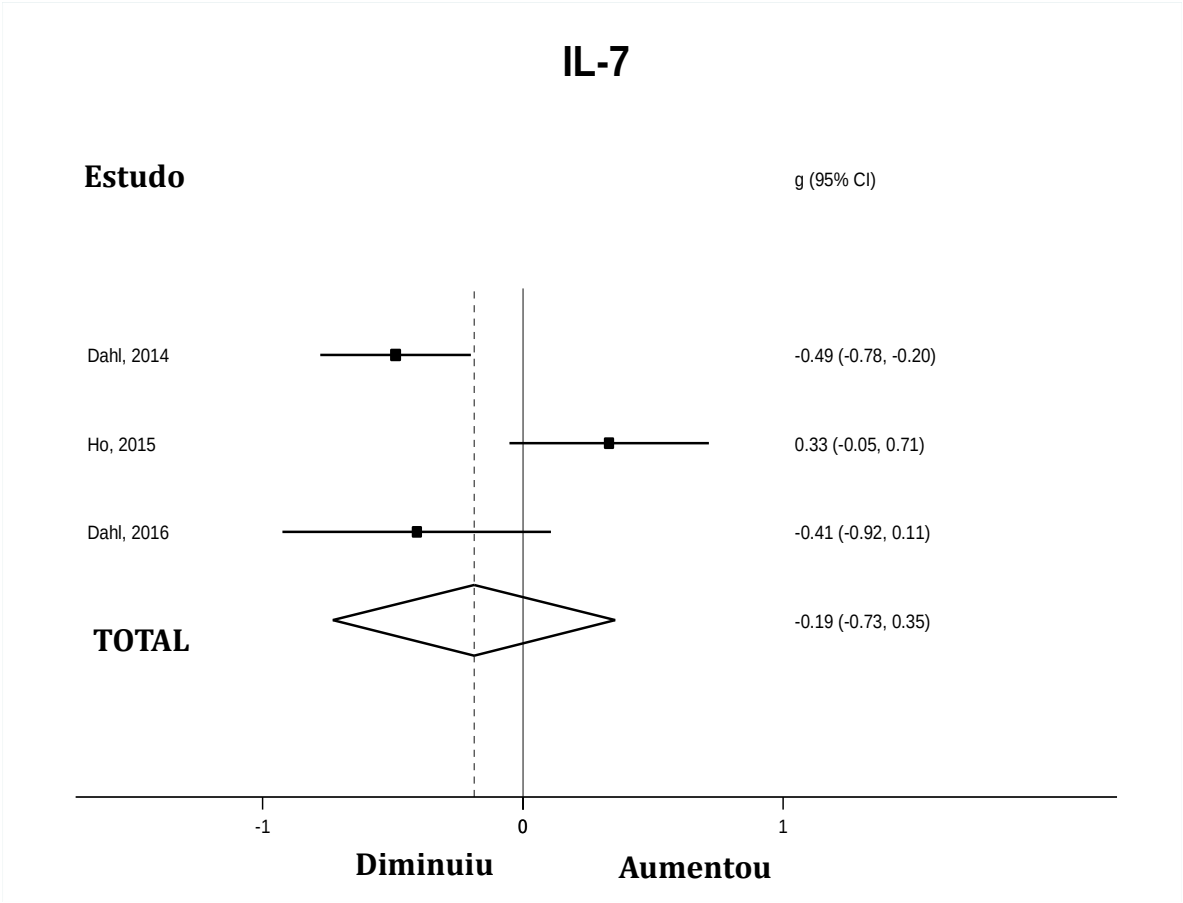
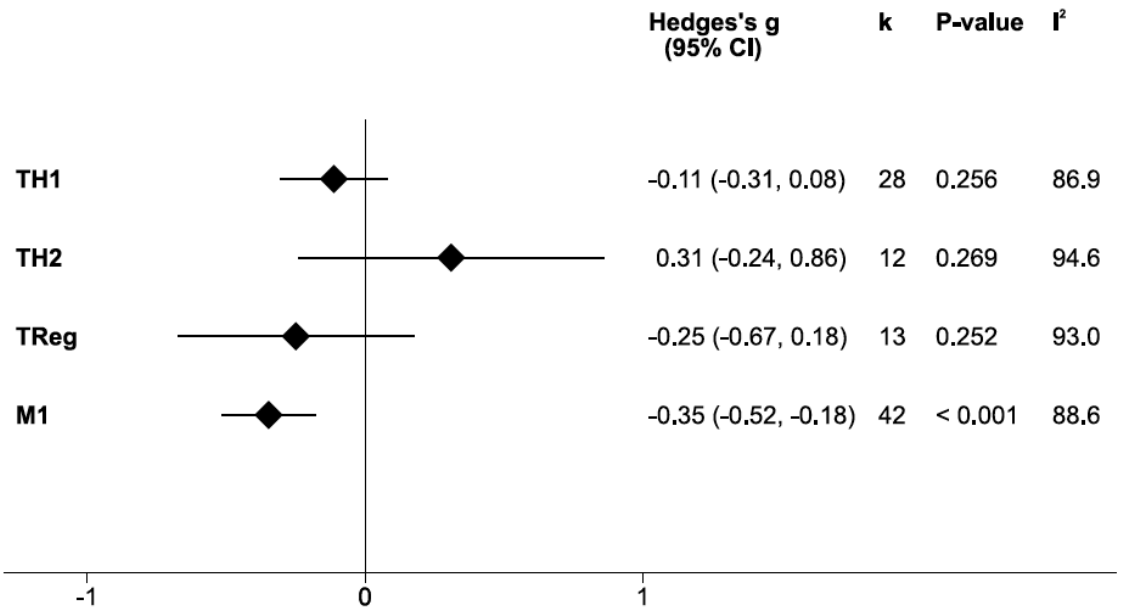


Figura 25. *Forest plot* de medidas combinadas da redução de citocinas de cada perfil celular.



6. DISCUSSÃO

Esta metanálise sugere que o tratamento farmacológico para o Transtorno Depressivo Maior é acompanhado de diminuição significante nos níveis de IL-6, TNF- α, IL-10 e CCL-2. Metanálises anteriores encontraram que o tratamento farmacológico pode reduzir TNF-α e IL-6 em indivíduos com TDM (HANNESTAD, DELLAGIOIA & BLOCH, 2011; HILES *et al.*, 2012). Tais estudos demonstraram estimativas de TE para TNF- α, IL-1β, IL-6 e IL-10. Além disso, de forma semelhante a esta metanálise, um alto grau de heterogeneidade foi observado (HANNESTAD, DELLAGIOIA & BLOCH, 2011; HILES *et al.*, 2012).

Duas metanálises recentes encontraram resultados diversos quanto à redução dos níveis de mediadores imunes após tratamento antidepressivo (STRAWBRIDGE *et al.*, 2015; GOLDSMITH, RAPAPORT & MILLER, 2016). A metanálise de Goldsmith e colaboradores verificou que o tratamento diminuiu os níveis de IL-6, IL-10 e IL-12 e aumentou os níveis de Il-1β e IL-4. Entretanto o referido estudo incluiu uma quantidade relativamente pequena de estudos e forneceu TE através de modelos de efeito fixo, que podem gerar resultados pouco confiáveis quando a heterogeneidade entre os estudos é alta. A maior metanálise até então publicada, havia incluído 35 estudos originais (STRAWBRIDGE *et al.*, 2015). Entretanto este número incluiu participantes com depressão bipolar e também outras intervenções terapêuticas. Devido à grande quantidade de dados avaliados, nós pudemos estimar o TE de dezesseis mediadores imunes. Além disso, foi possível explorar maiores fontes potenciais de heterogeneidade do que em qualquer estudo anterior.

Dados metanalíticos sugerem que níveis de IL-6, TNF- α, IL-10, sIL-2R, CCL-2, IL-12, IL-13, IL-18 e IL-1Ra e proteína C-reativa estão elevados em indivíduos com TDM quando comparados a controles saudáveis (DOWLATI *et al.*, 2010; HAAPAKOSKI *et al.*, 2015; EYRE *et al.*, 2016). Além disso, uma metanálise recente sugere que os níveis de CCL-2 podem estar significativamente elevados em indivíduos deprimidos quando comparados a controles (EYRE *et al.*, 2016). Na presente metanálise, foi demonstrado que os antidepressivos reduzem significativamente os níveis de IL-6, IL-10, TNF-α e CCL-2.

Apesar de os antidepressivos em uso atuarem principalmente via mecanismos monoaminérgicos, um corpo significativo de evidências sugerem que uma ativação de mecanismos neurotróficos cerebrais pode estar associada a seus efeitos terapêuticos (KRISHNAN & NESTLER, 2010). Evidências de estudos pré-clínicos indicam que inflamação periférica pode influenciar na plasticidade hipocampal via ativação microglial (RIAZI *et al.*,

2015). Além disso, a atividade de IL-6 e TNF-α podem reduzir a plasticidade sináptica no hipocampo (EYRE & BAUNE, 2012). Portanto nossos achados são consistentes com a teoria de que os antidepressivos podem diminuir a inflamação periférica e seu impacto no cérebro (LEONARD, 2014), embora nossa análise indique que este efeito pode não ser consistentemente associado a resposta terapêutica.

Evidências anteriores sugerem que inflamação periférica pode ser observada em uma parcela mas não em todos os indivíduos com TDM (MILLER & RAISON, 2016). Além disso, um estudo prévio sugere que indivíduos com TDM e considerável inflamação periférica podem responder ao antagonista de TNF- α infliximabe, ao passo que em pacientes com TDM e baixo grau de inflamação periférica, esta resposta é menor que a do placebo (RAISON, Charles L. *et al.*, 2013).

Portanto é possível que os efeitos terapêuticos observados no uso dos antidepressivos (isto é: um decréscimo geral de citocinas e quimiocinas inflamatórias) possa não ser o principal mecanismo que contribui para os benefícios destas drogas(MILLER & RAISON, 2016). Entretanto nenhum estudo incluso nesta metanálise estratificou os pacientes quanto ao nível de inflamação basal.

Uma metanálise prévia encontrou que níveis de TNF-α diminuíram no tratamento de respondedores, mas não naqueles refratários (STRAWBRIDGE *et al.*, 2015). Além disso, foi sugerido que o nível basal de inflamação poderia predizer a resposta ao tratamento antidepressivo. Entretanto tal metanálise incluiu vários tratamentos além de farmacológicos, bem como pacientes com depressão bipolar, além de estudos em cujas amostras havia pacientes com comorbidades significativas (STRAWBRIDGE *et al.*, 2015). A presente metanálise evitou estes potenciais confundidores e incluiu um número bem maior de estudos e participantes. Encontrou-se que embora os antidepressivos possam diminuir os níveis de TNF-α, estes resultados devem ser interpretados com cautela devido à grande heterogeneidade e ao fato de a análise de sensibilidade ter indicado que alguns estudos podem ter enviesado a estimativa de TE total.

Tem sido postulado que a migração e a redistribuição de monócitos pró-inflamatórios para o cérebro pode ativar as células microgliais de modo a contribuir para a fisiopatologia do TDM (WOHLEB & DELPECH, 2016). Os macrófagos desempenham funções de certo modo antagônicas: inibem a proliferação de patógenos, mas também promovem proliferação celular (no processo cicatricial). Eles iniciam e direcionam basicamente todos as funções imunológicas, inclusive imunidade adaptativa de células B e T. Por causa de sua atividade inibidora e reparadora, os macrófagos foram nomeados, respectivamente, M1 e M2. A resposta M1

direciona células T a produzirem IFN-γ, ao passo que a resposta M2, IL-4 e TGF-β. Achados curiosos demonstram que TNF-α, IL-6 e CCL-2 podem ser secretados predominantemente por macrófagos M1 polarizados embora não seletivamente (MILLS, 2015). Além disso, uma quantidade considerável de evidências pré-clínicas sugerem que os ISRS podem diminuir a secreção de mediadores inflamatórios pelas células microgliais estimuladas por lipopolissacarídeos (TYNAN, WEIDENHOFER, *et al.*, 2012; DURAIRAJ, STEURY & PARAMESWARAN, 2015). Desta forma, nosso resultados estão em conformidade com estes dados experimentais, embora não tenhamos encontrado evidência conclusiva para demonstrar diferença neste efeito de uma classe de entidepressivo para outra.

Nós encontramos evidências de que os antidepressivos podem diminuir os níveis periféricos da quimiocina CCL-2. Esta quimiocina é predominantemente pró-inflamatória e está envolvida na quimiotaxia de monócitos periféricos para o cérebro (GE *et al.*, 2008). A inibição do transporte de monócitos periféricos para o cérebro pode tornar-se um mecanismo de ação promissor para novas modalidades terapêuticas no TDM (WOHLEB *et al.*, 2016). De qualquer modo, tais achados devem ser interpretados cuidadosamente devido ao número limitado de estudos e pelo fato de que o TE não se manteve após análise de sensibilidade.

A interleucina-10 é predominantemente secretada pelas células T reguladores (TRegs) e exerce predominantemente funções antiinflamatórias (SAKAGUCHI *et al.*, 2010). No TDM, tem-se postulado que ocorre um efeito conhecido como sistema compensador anti inflamatório reflexo (compensatory antiinflamatory reflex system – CIRS) (MAES, M. *et al.*, 2012). Segundo esta hipótese, este sistema tem um papel homeostático contrarregulador em indivíduos com TDM. Nosso estudo encontrou que os antidepressivos podem reduzir os níveis de IL-10 em pacientes deprimidos, o que corrobora a tese de que o efeito de tais fármacos se deva à redução nos níveis de inflamação periféricos por eles promovida.

Pontos fortes e limitações do estudo

O principal ponto forte desta metanálise foi a inclusão da maior quantidade de dados atualmente disponível, além da adequada exploração das fontes potenciais de heterogeneidade. Entretanto algumas potenciais fontes de heterogeneidade podem não ter sido exploradas devido a insuficiência de dados em alguns estudos. Por exemplo: o índice de massa corporal parece influenciar tanto a resposta ao tratamento antidepressivo (UHER *et al.*, 2009) como a inflamação periférica (ORENES-PINERO *et al.*, 2015). Além disso, a qualidade metodológica dos estudos

incluídos variou significativamente. Na análise de metarregressão, a média de IMC não moderou significativamente as mudanças nos níveis periféricos de IL-6, TNF-α, IFN-γ e IL-10. Ela não demonstrou também se as diferenças observadas nos níveis de TNF-α são moderadas pelo percentual de fumantes. Outra limitação foi devido a diferenças na padronização dos ensaios por diferentes laboratórios bem como dificuldades técnicas em alguns mediadores (p.ex.: IL-2 e IFN-γ), o que pode ter contribuído para heterogeneidade nos achados (ELLER *et al.*, 2009b). Por fim, não foi possível comparar as diferenças nos níveis dos mediadores imunes em pacientes com depressão melancólica com estes níveis em paciente com depressão atípica (devido à insuficiência de dados).

7. CONCLUSÃO

Em resumo, esta meta-análise mostrou que, globalmente, os antidepressivos diminuíram os níveis periféricos de IL-6, TNF-α, IL-10 e CCL-2. Esta meta-análise sugere que os antidepressivos podem diminuir a inflamação periférica. No entanto, este efeito não parece ser consistentemente diferente entre respondedores e não respondedores. Além disso, os níveis basais de TNF-α não prediziam a resposta ao tratamento antidepressivo. Estudos futuros devem contrastar os níveis periféricos de citocinas / quimiocinas entre respondedores e não respondedores.

Além disso, uma meta-análise de pacientes individuais em que os participantes são estratificados de acordo com o grau de inflamação basal poderia representar um próximo passo para investigar a hipótese de que os antidepressivos podem ser mais eficazes para pacientes com menor inflamação periférica, enquanto os antiinflamatórios podem ser promissores para aqueles pacientes com maior ativação imune (MILLER & RAISON, 2016).

Por fim, outras modalidades comprovadamente eficazes, como a eletroconvulsoterapia (ECT) podem também impactar a ativação imune periférica, embora as evidências sejam limitadas (JÄRVENTAUSTA *et al.*, 2017).

REFERÊNCIAS BIBLIOGRÁFICAS

ABBAS, A. K.; LITCHMAN, A. H.; PILLAI, S. **Imunologia Celular e Molecular**. 6a. edição. Rio de Janeiro: Elsevier, 2008. ISBN 978-85-352-2244-9.

ABBASI, S. H. et al. Effect of celecoxib add-on treatment on symptoms and serum IL-6 concentrations in patients with major depressive disorder: randomized double-blind placebo-controlled study. **J Affect Disord,** v. 141, n. 2-3, p. 308-14, Dec 10 2012. ISSN 0165-0327.

ABELAIRA, H. M. et al. Neuroimmunomodulation in depression: a review of inflammatory cytokines involved in this process. **Neurochem Res,** v. 39, n. 9, p. 1634-9, Sep 2014. ISSN 0364-3190.

ADLER, U. C.; MARQUES, A. H.; CALIL, H. M. Inflammatory aspects of depression. Netherlands, p. 19-23, 2008. ISSN 1871-5281. Disponível em: < http://www.ingentaconnect.com/content/ben/iadt/2008/00000007/00000001/art00003 http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS=N&AN=2008239927 >. Acesso em: (Adler, Calil) Department of Psychobiology, UNIFESP/EPM, R. Napoleao de Barros 925, Sao Paulo, SP 04024-002, Brazil.

AGUILAR-ZAVALA, H. et al. Stress, inflammatory markers and factors associated in patients with type 2 diabetes mellitus. **Stress and Health: Journal of the International Society for the Investigation of Stress,** v. 24, n. 1, p. 49-54, Feb 2008. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc6&AN=2008-03190-006 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc6&rft.genre=article&rft_id=info:doi/10.1002%2Fsmi.1162&rft_id=info:pmid/&rft.issn=1532-3005&rft.volume=24&rft.issue=1&rft.spage=49&rft.pages=49-54&rft.date=2008&rft.jtitle=Stress+and+Health%3A+Journal+of+the+International+Society+for+the+Investigation+of+Stress&rft.atitle=Stress%2C+inflammatory+markers+and+factors+associated+in+patients+with+type+2 >.

AJILORE, O. The neural correlates of altered immune function in major depression: The impact of age and medical co-morbidities. p. 240S, 2014. ISSN 0006-3223. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=71434561 >. Acesso em: (Ajilore) University of Illinois at Chicago, Chicago, IL, United States.

AJILORE, O. et al. Neuroanatomical correlates of altered immune function in late-life depression. p. S262, 2012. ISSN 0893-133X. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=70948336 >. Acesso em: (Ajilore, Pandey, Charlton, Korthauer, Lamar, Yang, Ren, Kumar) University of Illinois at Chicago, Chicago, IL, United States.

ALESCI, S. et al. Major depression is associated with significant diurnal elevations in plasma interleukin-6 levels, a shift of its circadian rhythm, and loss of physiological complexity in its secretion: clinical implications. **J Clin Endocrinol Metab,** v. 90, n. 5, p. 2522-30, May 2005. ISSN 0021-972X (Print) 0021-972x.

ANDERSON, G. et al. Increased IL-6 trans-signaling in depression: focus on the tryptophan catabolite pathway, melatonin and neuroprogression. **Pharmacol Rep,** v. 65, n. 6, p. 1647-54, 2013. ISSN 1734-1140 (Print) 1734-1140.

ANDRADE, C. Tumor necrosis factor-alpha, depression, and ECT: toward a better understanding of the relationships. **J ect,** v. 20, n. 3, p. 197-8, Sep 2004. ISSN 1095-0680 (Print) 1095-0680.

ANDROSOVA, L. V. et al. Interleukin level in endogenous depression. Russian Federation, p. 45-48, 2001. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed5&NEWS=N&AN=11586704 >.

ANISMAN, H. Cascading effects of stressors and inflammatory immune system activation: Implications for major depressive disorder. Canada, p. 4-20, 2009. ISSN 1180-4882. Disponível em: < http://www.cma.ca/multimedia/staticContent/HTML/N0/l2/jpn/vol-34/issue-1/pdf/pg4.pdf http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=2009227899 >. Acesso em: (Anisman) Institute of Neuroscience, Carleton University, Life Science Research Centre, Ottawa, ON K1S 5B6, Canada.

ANISMAN, H.; HAYLEY, S. Inflammatory factors contribute to depression and its comorbid conditions. **Sci Signal,** v. 5, n. 244, p. pe45, Oct 2 2012. Disponível em: < http://stke.sciencemag.org/content/sigtrans/5/244/pe45.full.pdf >.

ANISMAN, H. et al. Cytokines as a stressor: implications for depressive illness. **Int J Neuropsychopharmacol,** v. 5, n. 4, p. 357-73, Dec 2002. ISSN 1461-1457 (Print)
1461-1457. Disponível em: < http://ijnp.oxfordjournals.org/content/ijnp/5/4/357.full.pdf >.

ANISMAN, H.; KOKKINIDIS, L.; MERALI, Z. Further evidence for the depressive effects of cytokines: anhedonia and neurochemical changes. **Brain Behav Immun,** v. 16, n. 5, p. 544-56, Oct 2002. ISSN 0889-1591 (Print)
0889-1591.

ANISMAN, H.; MERALI, Z. Cytokines, stress, and depressive illness. United States, p. 513-524, 2002. ISSN 0889-1591. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed5&NEWS=N&AN=2002414779 >. Acesso em: (Anisman) Institute of Neuroscience, Carleton University, Ottawa, Ont. K1S 5B6, Canada.

ANISMAN, H. et al. Endocrine and cytokine correlates of major depression and dysthymia with typical or atypical features. **Mol Psychiatry,** v. 4, n. 2, p. 182-8, Mar 1999. ISSN 1359-4184 (Print)
1359-4184.

ARNOW, B. A. et al. Depression Subtypes in Predicting Antidepressant Response: A Report From the iSPOT-D Trial. **Am J Psychiatry,** v. 172, n. 8, p. 743-50, Aug 1 2015. ISSN 0002-953x.

ARTS, M. H. et al. Relationship Between Physical Frailty and Low-Grade Inflammation in Late-Life Depression. **J Am Geriatr Soc,** v. 63, n. 8, p. 1652-7, Aug 2015. ISSN 0002-8614. Disponível em: < http://onlinelibrary.wiley.com/store/10.1111/jgs.13528/asset/jgs13528.pdf?v=1&t=ilu4d1ww&s=0b0ef3efae597374151545cdd161d2000e8a561d >.

ARTS, M. H. L. et al. Inflammaging: Associated with physical frailty in late-life depression. p. S133-S134, 2014. ISSN 1064-7481. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=71442059 >. Acesso em: (Arts) Mental Health Center Friesland, Department of Old Age Psychiatry, Leeuwarden, Netherlands.

ASCHBACHER, K. et al. Interleukin-1 beta responses to acute stress are associated with increases in depressive symptoms one year later. p. 97S, 2011. ISSN 0006-3223. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70402323 >. Acesso em: (Aschbacher, Epel, Wolkowitz) Psychiatry, University of California San Francisco, San Francisco, CA, United States.

ASSOCIATION, A. P. **DSM V American Psychiatric Association**. 2013.

AUDET, M. C. et al. Cytokine variations and mood disorders: Influence of social stressors and social support. Switzerland, 2014. ISSN 1662-4548. Disponível em: < http://journal.frontiersin.org/Journal/10.3389/fnins.2014.00416/full http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=2015658488 >. Acesso em: (Audet, Merali) Institute of Mental Health Research, Ottawa, ON, Canada.

AZAR, R.; NOLAN, R. P.; STEWART, D. E. Listening to the heart-brain talk: persistent depressive symptoms are associated with hsCRP in apparently healthy individuals at high risk for coronary artery disease. **Eur J Prev Cardiol,** v. 19, n. 4, p. 857-63, Aug 2012. ISSN 2047-4873. Disponível em: < http://cpr.sagepub.com/content/19/4/857.full.pdf >.

BAGHAI, T. C. et al. Major depression, cardiovascular risk factors and the omega-3 index. 2011. ISSN 0924-9338. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70416785 >. Acesso em: (Baghai, Born, Haefner, Schule, Eser, Rupprecht, Bondy) Psychiatry and Psychotherapy, LMU-Munich, Munich, Germany.

BAHRINI, L. et al. The relationship between smoking and inflammation in depression. p. 1570, 2015. ISSN 0924-9338. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=71930842 >. Acesso em: (Bahrini, Ouanes, Robbana, Trabelsi, Ghachem) Psychiatry, Razi Hospital, Tunis, Tunisia.

BAKKALBASI, N. et al. Three options for citation tracking: Google Scholar, Scopus and Web of Science. **Biomedical Digital Libraries,** v. 3, n. 1, p. 7, 2006. ISSN 1742-5581. Disponível em: < http://dx.doi.org/10.1186/1742-5581-3-7 >.

BARON, D. A.; HARDIE, T.; BARON, S. H. Possible association of interleukin-2 treatment with depression and suicide. United States, p. 799-800, 1993. ISSN 0098-6151. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed3&NEWS=N&AN=1993213608 >. Acesso em: (Baron, Hardie, Baron) Horsham Clinic, 722 East Butler Pike, Ambler, PA 19002, United States.

BASTERZI, A. D. et al. IL-6 levels decrease with SSRI treatment in patients with major depression. **Hum Psychopharmacol,** v. 20, n. 7, p. 473-6, Oct 2005. ISSN 0885-6222 (Print)
0885-6222.

BAUER, J. et al. Induction of cytokine synthesis and fever suppresses REM sleep and improves mood in patients with major depression. **Biol Psychiatry,** v. 38, n. 9, p. 611-21, Nov 1 1995. ISSN 0006-3223 (Print)
0006-3223. Disponível em: < http://www.biologicalpsychiatryjournal.com/article/0006-3223(95)00374-X/abstract >.

BAUNE, B.; AIR, T.; JAWAHAR, C. Inflammation impacts on social cognition in major depressive disorder. **Biological Psychiatry,** v. 1), p. 8S-9S, May 2016. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed14&AN=72256158 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:emed14&rft.genre=article&rft_id=info:doi/10.1016%2Fj.biopsych.2016.03.1748&rft_id=info:pmid/&rft.issn=0006-3223&rft.volume=79&rft.issue=9+SUPPL.+1&rft.spage=8S&rft.pages=8S-9S&rft.date=2016&rft.jtitle=Biological+Psychiatry&rft.atitle=Inflammation+impacts+on+social+cognition+in+major+depressive+disorder&rft.aulast=Baune%3C1070. > >.

BAUNE, B. et al. Inflammatory biomarkers predict depressive, but not anxiety symptoms during aging: The prospective Sydney Memory and Aging Study. **Psychoneuroendocrinology,** v. 37, n. 9, p. 1521-1530, Sep 2012. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc9&AN=2012-06668-001 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc9&rft.genre=article&rft_id=info:doi/10.1016%2Fj.psyneuen.2012.02.006&rft_id=info:pmid/&rft.issn=0306-4530&rft.volume=37&rft.issue=9&rft.spage=1521&rft.pages=1521-1530&rft.date=2012&rft.jtitle=Psychoneuroendocrinology&rft.atitle=Inflammatory+biomarkers+predict+depressive%2C+but+not+anxiety+symptoms+during+aging%3A+The+prospective+Sydney+Memory+and+A http://www.psyneuen-journal.com/article/S0306-4530(12)00060-1/abstract >.

BAUNE, B. T. et al. The interleukin 1 beta (IL1B) gene is associated with failure to achieve remission and impaired emotion processing in major depression. **Biol Psychiatry,** v. 67, n. 6, p. 543-9, Mar 15 2010. ISSN 0006-3223.

BAY-RICHTER, C. et al. Peripheral inflammation induces depressive-like behaviour and alters peripheral and central cytokine expression - Implications for the cytokine theory of depression. p. S27, 2010. ISSN 0889-1591. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=70268248 >. Acesso em: (Bay-Richter, Janelidze, Hallberg, Traskman Bendz, Brundin) Psychoimmunology Unit, Department of Psychiatry, Lund University, Solvesgatan 17, Lund 211 84, Sweden.

BAY-RICHTER, C. et al. Garden rehabilitation stabilises INF-gamma and IL-2 levels but does not relieve depressive-symptoms. p. 37, 2012. ISSN 0941-9500. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70703429 >. Acesso em: (Bay-Richter, Traskman-Bendz, Grahn, Brundin) Lund University, Sweden.

BEASLEY, C.; MA, C.; SHAO, L. Cytokine expression in cingulate cortex in major depressive disorder with and without psychosis. p. 114, 2014. ISSN 1461-1457. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=71910087 >. Acesso em: (Beasley, Ma, Shao) UBC, Vancouver, Canada.

BECKING, K. et al. Disturbances in hypothalamic-pituitary-adrenal axis and immunological activity differentiating between unipolar and bipolar depressive episodes. **PLoS ONE,** v. 10 (7) (no pagination), n. 0133898, 21 Jul 2015. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed13&AN=2015370100 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:emed13&rft.genre=article&rft_id=info:doi/10.1371%2Fjournal.pone.0133898&rft_id=info:pmid/&rft.issn=1932-6203&rft.volume=10&rft.issue=7&rft.spage=no+pagination&rft.pages=no+pagination&rft.date=2015&rft.jtitle=PLoS+ONE&rft.atitle=Disturbances+in+hypothalamic-pituitary-adrenal+axis+and+immunological+activity+differentiating+between+unipolar+and+bipolar+de. > >.

BEHR, G. A. et al. Peripheral biomarkers in new onset of major depressive disorder in midlife women: The harvard study of moods and cycles. p. 278S, 2012. ISSN 0006-3223. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70718825 >. Acesso em: (Behr, Frey, Soares) Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada.

BELZEAUX, R. et al. Responder and nonresponder patients exhibit different peripheral transcriptional signatures during major depressive episode. **Transl Psychiatry,** v. 2, p. e185, 2012. ISSN 2158-3188. Disponível em: < http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3565773/pdf/tp2012112a.pdf >.

BENAZZI, F. Various forms of depression. **Dialogues Clin Neurosci,** v. 8, n. 2, p. 151-61, 2006. ISSN 1294-8322 (Print)
1294-8322.

BENEDETTI, F. et al. Interleukine-6 serum levels correlate with response to antidepressant sleep deprivation and sleep phase advance. **Prog Neuropsychopharmacol Biol Psychiatry,** v. 26, n. 6, p. 1167-70, Oct 2002. ISSN 0278-5846 (Print)
0278-5846.

BENTLEY, S. M.; PAGALILAUAN, G. L.; SIMPSON, S. A. Major depression. **Med Clin North Am,** v. 98, n. 5, p. 981-1005, Sep 2014. ISSN 0025-7125.

BERK, M. et al. Acute phase proteins in major depression. **Journal of Psychosomatic Research,** v. 43, n. 5, p. 529-534, Nov 1997. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc3&AN=1997-43433-010 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc3&rft.genre=article&rft_id=info:doi/10.1016%2FS0022-3999%2897%2900139-6&rft_id=info:pmid/&rft.issn=0022-3999&rft.volume=43&rft.issue=5&rft.spage=529&rft.pages=529-534&rft.date=1997&rft.jtitle=Journal+of+Psychosomatic+Research&rft.atitle=Acute+phase+proteins+in+major+depression.&rft.aulast=Berk >.

BERMUDEZ, C. M. Clinical applications of peripheral markers of response in antidepressant treatment: Neurotrophins and cytokines. **Revista Colombiana de Psiquiatria,** v. 41, n. 1, p. 165-184, Jan-Apr 2012. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc9&AN=2013-20649-010 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc9&rft.genre=article&rft_id=info:doi/&rft_id=info:pmid/&rft.issn=0034-7450&rft.volume=41&rft.issue=1&rft.spage=165&rft.pages=165-

184&rft.date=2012&rft.jtitle=Revista+Colombiana+de+Psiquiatria&rft.atitle=Clinical+applications+of+peripheral+markers+of+response+in+antidepressant+treatment%3A+Neurotrophins+and+cytokines.&rft.aulast=Bermudez >.

BERTHOLD-LOSLEBEN, M.; HIMMERICH, H. The TNF-alpha system: Functional aspects in depression, narcolepsy and psychopharmacology. Netherlands, p. 193-202, 2008. ISSN 1570-159X. Disponível em: < http://www.ingentaconnect.com/content/ben/cn/2008/00000006/00000003/art00002 http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS=N&AN=2008467155 >. Acesso em: (Berthold-Losleben, Himmerich) Department of Psychiatry and Psychotherapy, RWTH Aachen University, Pauwelsstrase 30, 52074 Aachen, Germany.

BEUREL, E.; HARRINGTON, L. E.; JOPE, R. S. Inflammatory T Helper 17 Cells Promote Depression-like Behavior in Mice. **Biological Psychiatry,** v. 73, n. 7, p. 622-630, 4/1/ 2013. ISSN 0006-3223. Disponível em: < http://www.sciencedirect.com/science/article/pii/S0006322312008475 >.

BIZIK, G. et al. Dissociative symptoms reflect levels of tumor necrosis factor alpha in patients with unipolar depression. New Zealand, p. 675-679, 2014. ISSN 1176-6328. Disponível em: < http://www.dovepress.com/getfile.php?fileID=19775 http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=2014299799 >. Acesso em: (Bizik, Bob, Raboch, Pavlat) Center for Neuropsychiatric research of Traumatic Stress, Department of psychiatry and UHSL, Czech Republic.

BLOM, E. H. et al. Pro-inflammatory cytokines are elevated in adolescent females with emotional disorders not treated with SSRIs. **Journal of Affective Disorders,** v. 136, n. 3, p. 716-723, Feb 2012. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc9&AN=2011-25983-001 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc9&rft.genre=article&rft_id=info:doi/10.1016%2Fj.jad.2011.10.002&rft_id=info:pmid/&rft.issn=0165-0327&rft.volume=136&rft.issue=3&rft.spage=716&rft.pages=716-723&rft.date=2012&rft.jtitle=Journal+of+Affective+Disorders&rft.atitle=Pro-inflammatory+cytokines+are+elevated+in+adolescent+females+with+emotional+disorders+not+treated+with+SSRIs.&rft.aulast=B >.

BLUME, J.; DOUGLAS, S. D.; EVANS, D. L. Immune suppression and immune activation in depression. United States, p. 221-229, 2011. ISSN 0889-1591. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=2011036021 >. Acesso em: (Blume) Department of Psychiatry, University of Pennsylvania School of Medicine, 423 Guardian Drive, 305 Blockley Hall, Philadelphia, PA 19104, United States.

BLUME, J. et al. Interaction effects between sex and depression on chemokine and cytokine production. p. 286S, 2011. ISSN 0006-3223. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70402913 >. Acesso em: (Blume, Lynch, Gettes, Dube, Benton, Flanagan, Brown, Metzger) Department of Psychiatry, University of Pennsylvania, School of Medicine, Philadelphia, PA, United States.

BOB, P. et al. Depression, traumatic stress and interleukin-6. **J Affect Disord,** v. 120, n. 1-3, p. 231-4, Jan 2010. ISSN 0165-0327.

BOT, M. et al. Serum proteomic profiling of major depressive disorder. p. 332S, 2015. ISSN 0006-3223. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=71846995 >. Acesso em: (Bot, Jansen, Lamers, Vogelzangs, Penninx) Department of Psychiatry, VU University Medical Center and GGZ inGeest, Amsterdam, Netherlands.

BOUFIDOU, F. et al. Immune changes related to tryptophan metabolism after electroconvulsive therapy (ECT) in major depressive disorder (MDD) patients. p. 7-8, 2014. ISSN 0941-9500. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=71369897 >. Acesso em: (Oulis, Papadimitriou) 1st Department of Psychiatry, Athens University Medical School, Eginition Hospital, Vas. Sophias 74, Athens 11528, Greece.

BOUHUYS, A. L. et al. Potential psychosocial mechanisms linking depression to immune function in elderly

subjects. **Psychiatry Res,** v. 127, n. 3, p. 237-45, Jul 15 2004. ISSN 0165-1781 (Print)
0165-1781.

BRAMBILLA, F.; MAGGIONI, M. Blood levels of cytokines in elderly patients with major depressive disorder. **Acta Psychiatr Scand,** v. 97, n. 4, p. 309-13, Apr 1998. ISSN 0001-690X (Print)
0001-690x. Disponível em: < http://onlinelibrary.wiley.com/store/10.1111/j.1600-0447.1998.tb10005.x/asset/j.1600-0447.1998.tb10005.x.pdf?v=1&t=iebjfy12&s=c36e0bd34716fafd0cdea1cee5f987c1c391c1c5 >.

BRAMBILLA, F. et al. Immune aspects in elderly depression: peripheral blood mononuclear cell responses to mitogen stimulation and cytokine plasma concentrations. **Aging (Milano),** v. 9, n. 4 Suppl, p. 34-5, 1997. ISSN 0394-9532 (Print)
0394-9532.

BRAMBILLA, F.; MONTELEONE, P.; MAJ, M. Interleukin-1beta and tumor necrosis factor-alpha in children with major depressive disorder or dysthymia. **J Affect Disord,** v. 78, n. 3, p. 273-7, Mar 2004. ISSN 0165-0327 (Print)
0165-0327.

BREDT, D. S. et al. Translating depression biomarkers for improved targeted therapies. **Neurosci Biobehav Rev,** v. 59, p. 1-15, Dec 2015. ISSN 0149-7634.

BREMMER, M. et al. Inflammatory markers in late-life depression: Results from a population-based study. **Journal of Affective Disorders,** v. 106, n. 3, p. 249-255, Mar 2008. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc6&AN=2008-01271-005 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc6&rft.genre=article&rft_id=info:doi/10.1016%2Fj.jad.2007.07.002&rft_id=info:pmid/&rft.issn=0165-0327&rft.volume=106&rft.issue=3&rft.spage=249&rft.pages=249-255&rft.date=2008&rft.jtitle=Journal+of+Affective+Disorders&rft.atitle=Inflammatory+markers+in+late-life+depression%3A+Results+from+a+population-based+study.&rft.aulast=Bremmer >.

BRIETZKE, E. et al. Interleukin-6 and verbal memory in recurrent major depressive disorder. p. 47S-48S, 2011. ISSN 0006-3223. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70402167 >. Acesso em: (Brietzke, Lafer) Psychiatry, University of Sao Paulo, Sao Paulo, Brazil.

BROWN, P. J. et al. Inflammation, Depression, and Slow Gait: A High Mortality Phenotype in Later Life. **J Gerontol A Biol Sci Med Sci,** v. 71, n. 2, p. 221-7, Feb 2016. ISSN 1079-5006. Disponível em: < http://biomedgerontology.oxfordjournals.org/content/71/2/221.full.pdf >.

BRUNONI, A. R. et al. Cytokines plasma levels during antidepressant treatment with sertraline and transcranial direct current stimulation (tDCS): Results from a factorial, randomized, controlled trial. Germany, p. 1315-1323, 2014. ISSN 0033-3158. Disponível em: < link.springer.de/link/service/journals/00213/index.htm http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=2014201024 >. Acesso em: (Brunoni, Valiengo, Bensenor, Lotufo) Center for Clinical and Epidemiological Research and Interdisciplinary, Center for Applied Neuromodulation (CINA), University Hospital, University of Sao Paulo, Av. Prof Lineu Prestes 2565, 3o andar, CEP 05508-000 Sao Paulo Sao Paulo, Brazil.

BUTTON, K. S. et al. Power failure: why small sample size undermines the reliability of neuroscience. **Nat Rev Neurosci,** v. 14, n. 5, p. 365-76, May 2013. ISSN 1471-003x.

BYRNE, M. L. et al. Acute phase protein and cytokine levels in serum and saliva: A comparison of detectable levels and correlations in a depressed and healthy adolescent sample. United States, p. 164-175, 2013. ISSN 0889-1591. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=2013629791 >. Acesso em: (Byrne, Waloszek, Woods, Trinder, Allen) Melbourne School of Psychological Sciences, University of Melbourne, Victoria 3010, Australia.

CALABRESE, J. R. et al. Depression, immunocompetence, and prostaglandins of the E series. **Psychiatry Res,** v. 17, n. 1, p. 41-7, Jan 1986. ISSN 0165-1781 (Print)

0165-1781.

CAMACHO, A. et al. Association of subsyndromal and depressive symptoms with inflammatory markers among different ethnic groups: the multi-ethnic study of atherosclerosis (MESA). **J Affect Disord,** v. 164, p. 165-70, Aug 2014. ISSN 0165-0327. Disponível em: < http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4079665/pdf/nihms593273.pdf >.

CAMPOS, A. C. et al. Further evidence for the role of interferon-gamma on anxiety- and depressive-like behaviors: involvement of hippocampal neurogenesis and NGF production. **Neurosci Lett,** v. 578, p. 100-5, Aug 22 2014. ISSN 0304-3940.

CAPURON, L. et al. Does cytokine-induced depression differ from idiopathic major depression in medically healthy individuals? **J Affect Disord,** v. 119, n. 1-3, p. 181-5, Dec 2009. ISSN 0165-0327. Disponível em: < http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2763953/pdf/nihms99484.pdf >.

CAPURON, L. et al. Depressive symptoms and metabolic syndrome: Is inflammation the underlying link? **Biological Psychiatry,** v. 64, n. 10, p. 896-900, Nov 2008. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc6&AN=2008-15613-020 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc6&rft.genre=article&rft_id=info:doi/10.1016%2Fj.biopsych.2008.05.019&rft_id=info:pmid/&rft.issn=0006-3223&rft.volume=64&rft.issue=10&rft.spage=896&rft.pages=896-900&rft.date=2008&rft.jtitle=Biological+Psychiatry&rft.atitle=Depressive+symptoms+and+metabolic+syndrome%3A+Is+inflammation+the+underlying+link%3F&rft.aulast=Capuron http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2621309/pdf/nihms78136.pdf >.

CARUNCHO, H. J.; RIVERA-BALTANAS, T. Biomarkers of depression. Spain, p. 470-476, 2010. ISSN 0210-0010. Disponível em: < http://www.neurologia.com/pdf/Web/5008/bd080470.pdf http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=2010267851 >. Acesso em: (Caruncho, Rivera-Baltanas) Departamento de Biologia Celular, Grupo de Investigacion, Universidad de Santiago de Compostela, E-15782 Santiago de Compostela (A Coruna), Spain.

CARVALHO, A. F. et al. Bias in Peripheral Depression Biomarkers. **Psychother Psychosom,** v. 85, n. 2, p. 81-90, 2016. ISSN 0033-3190.

CARVALHO, L. et al. Antidepressants, but not antipsychotics, modulate GR function in human whole blood: An insight into molecular mechanisms. **European Neuropsychopharmacology,** v. 20, n. 6, p. 379-387, Jun 2010. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc7&AN=2010-08994-007 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc7&rft.genre=article&rft_id=info:doi/10.1016%2Fj.euroneuro.2010.02.006&rft_id=info:pmid/&rft.issn=0924-977X&rft.volume=20&rft.issue=6&rft.spage=379&rft.pages=379-387&rft.date=2010&rft.jtitle=European+Neuropsychopharmacology&rft.atitle=Antidepressants%2C+but+not+antipsychotics%2C+modulate+GR+function+in+human+whole+blood%3A+An+insight+into+molecular+ http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2982744/pdf/ukmss-32289.pdf >.

CARVALHO, L. A. et al. Cytokine profile in treatment-resistant depression. p. S342-S343, 2010. ISSN 0924-977X. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=70311472 >. Acesso em: (Carvalho, Torre, Pariante) Institute of Psychiatry Kings College London, Department of Psychological Medicine (CCBB), James Black Centre Institute of Psychiatry, London, United Kingdom.

CASALE, C. et al. Depression in morbid obesity is associated a with worsening metabolic profile, not ameliorated by treatment with selective serotonin reuptake inhibitors. p. 1015-1016, 2011. ISSN 0960-8923. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70529942 >. Acesso em: (Casale, Malik, Lei, Mohamed-Ali) University College London, Medicine, London, United Kingdom.

CASERTA, M. T. et al. Associations among depression, perceived self-efficacy, and immune function and health in preadolescent children. **Dev Psychopathol,** v. 23, n. 4, p. 1139-47, Nov 2011. ISSN 0954-5794. Disponível em: <

http://journals.cambridge.org/download.php?file=%2FDPP%2FDPP23_04%2FS0954579411000526a.pdf&code=824a5c24c34127248eb4aa14d4bda045 >.

CASTILLA-CORTAZAR, I.; CASTILLA, A.; GURPEGUI, M. Opioid peptides and immunodysfunction in patients with major depression and anxiety disorders. **J Physiol Biochem,** v. 54, n. 4, p. 203-15, Dec 1998. ISSN 1138-7548 (Print)
1138-7548.

CATENA-DELL'OSSO, M. et al. Inflammatory and neurodegenerative pathways in depression: A new avenue for antidepressant development? , Netherlands, p. 245-255, 2011. ISSN 0929-8673. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=2011041166 >. Acesso em: (Catena-Dell'Osso, Consoli, Baroni, Marazziti) Dipartimento di Psichiatria, Neurobiologia, Farmacologia e Biotecnologie, Universita di Pisa, via Roma, 67, I-56100 Pisa, Italy.

CATENA-DELL'OSSO, M. et al. Inflammation, Serotonin and Major Depression. Netherlands, p. 571-577, 2013. ISSN 1389-4501. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=2013266534 >. Acesso em: (Catena-Dell'Osso, Marazziti) Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy.

CATTANEO, A. et al. Candidate genes expression profile associated with antidepressants response in the GENDEP study: differentiating between baseline 'predictors' and longitudinal 'targets'. **Neuropsychopharmacology,** v. 38, n. 3, p. 377-85, Feb 2013. ISSN 0893-133x.

CATTANEO, A. et al. Gene expression profile associated with major depression and with antidepressant response. p. S95-S96, 2012. ISSN 0924-977X. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70701863 >. Acesso em: (Cattaneo) University of Brescia, Genetic and Biological Section, Brescia, Italy.

CATTANEO, E. et al. Polymorphisms of the MCP-1 and IL-10 genes and mood disorders: An association study. Italy, p. 149-151, 2008. ISSN 0393-0645. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS=N&AN=2009030756 >. Acesso em: (Cattaneo, Pozzoli, Mundo, Altamura) Dipartimento di Psichiatria, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Universita degli Studi di Milano, via Francesco Sforza 35, 20122 Milano, Italy.

CHANG, H. H. et al. Raised C-reactive protein levels associated higher HbAc1 after antidepressant treatment in major depressive patients. p. 72, 2010. ISSN 1461-1457. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=70220424 >. Acesso em: (Chang) Institute of Biopharmaceutical, Tainan, Taiwan (Republic of China).

CHANG, M. Y.; TSENG, C. H.; CHIOU, Y. L. The Plasma Concentration of Copper and Prevalence of Depression Were Positively Correlated in Shift Nurses. p. 175-181, 2014. ISSN 1099-8004. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=23460604 >. Acesso em: (Chang, Tseng) Department of Nursing, Taichung Veterans General Hospital, Taichung, Taiwan (Republic of China).

CHEN, Y. et al. Emerging tendency towards autoimmune process in major depressive patients: a novel insight from Th17 cells. **Psychiatry Res,** v. 188, n. 2, p. 224-30, Jul 30 2011. ISSN 0165-1781 (Print)
0165-1781.

CHEN, Y. C. et al. Antidepressant effects on insulin sensitivity and proinflammatory cytokines in the depressed males. **Mediators Inflamm,** v. 2010, p. 573594, 2010. ISSN 0962-9351. Disponível em: < http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2872762/pdf/MI2010-573594.pdf >.

CHO, E. Y. N. et al. Interleukin-6 is lowered in individuals with depressive personality disorder from a population-based sample. p. A-112, 2014. ISSN 0033-3174. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=71438143 >. Acesso em: (Cho, Von Kanel) Department of General Internal Medicine, Division of Psychosomatic Medicine, Bern University Hospital, Inselspital, Bern, Switzerland.

CHOCANO-BEDOYA, P. O. et al. C-reactive protein, interleukin-6, soluble tumor necrosis factor alpha receptor 2 and incident clinical depression. **J Affect Disord,** v. 163, p. 25-32, Jul 2014. ISSN 0165-0327. Disponível em: < http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4029945/pdf/nihms-581472.pdf >.

CHRISTOPOULOS, P. et al. Immune system dysregulation and major depressive disorder: IL-1 as a potential target of antidepressant agents. p. 72-73, 2010. ISSN 1461-1457. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=70220426 >. Acesso em: (Christopoulos, Panagoutsos, Papadopoulos) Psychiatry hospital of Tripoli, Tripolis, Greece.

CHUNG, Y. et al. Simultaneous measurement of 23 plasma cytokines in late-life depression patients. p. S366, 2009. ISSN 0924-977X. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=70044582 >. Acesso em: (Chung, Lim, Hong) Ajou University School of Medicine, Psychiatry, Suwon, South Korea.

CLARK, M. C. et al. Psychosocial and biological indicators of depression in the caregiving population. **Biol Res Nurs,** v. 15, n. 1, p. 112-21, Jan 2013. ISSN 1099-8004. Disponível em: < http://brn.sagepub.com/content/15/1/112.full.pdf >.

CLERICI, M. et al. Cytokine polymorphisms in the pathophysiology of mood disorders. **CNS Spectrums,** v. 14, n. 8, p. 419-425, Aug 2009. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc6&AN=2009-17937-006 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc6&rft.genre=article&rft_id=info:doi/&rft_id=info:pmid/&rft.issn=1092-8529&rft.volume=14&rft.issue=8&rft.spage=419&rft.pages=419-425&rft.date=2009&rft.jtitle=CNS+Spectrums&rft.atitle=Cytokine+polymorphisms+in+the+pathophysiology+of+mood+disorders.&rft.aulast=Clerici >.

COHEN, J. A power primer. **Psychol Bull,** v. 112, n. 1, p. 155-9, Jul 1992. ISSN 0033-2909 (Print) 0033-2909.

CONNOR, T. J.; LEONARD, B. E. Depression, stress and immunological activation: The role of cytokines in depressive disorders. United States, p. 583-606, 1998. ISSN 0024-3205. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed4&NEWS=N&AN=1998031251 >. Acesso em: (Connor, Leonard) Department of Pharmacology, National University of Ireland, Galway, Ireland.

COSTI, S. et al. Association between peripheral interleukin 6 and brain response to positive stimuli in a depressive spectrum. **European Neuropsychopharmacology,** v. 25, p. S235-S236, September 2015. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed13&AN=72129348 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:emed13&rft.genre=article&rft_id=info:doi/&rft_id=info:pmid/&rft.issn=0924-977X&rft.volume=25&rft.issue=&rft.spage=S235&rft.pages=S235-S236&rft.date=2015&rft.jtitle=European+Neuropsychopharmacology&rft.atitle=Association+between+peripheral+interleukin+6+and+brain+response+to+positive+stimuli+in+a+depressive+spectrum&rft.aulast=Costi%3C1065. > >.

CRADDOCK, D.; THOMAS, A. Cytokines and late-life depression. United States, p. 42-52, 2006. ISSN 1087-495X. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed7&NEWS=N&AN=16989292 >. Acesso em: (Craddock, Thomas) Bensham Hospital, Gateshead, United Kingdom.

CRNKOVIC, D. et al. Connection between inflammatory markers, antidepressants and depression. **Acta Clin Croat,** v. 51, n. 1, p. 25-33, Mar 2012. ISSN 0353-9466 (Print) 0353-9466.

DAHL, J. et al. Recovery from major depressive disorder episode after non-pharmacological treatment is associated with normalized cytokine levels. **Acta Psychiatrica Scandinavica Mar**, n. Pagination, p. No Pagination Specified, Mar 2016. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc12&AN=2016-16296-001 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-

2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc12&rft.genre=article&rft_id=info:doi/10.1111%2Facps.12576&rft_id=info:pmid/&rft.issn=0001-690X&rft.volume=&rft.issue=&rft.spage=No&rft.pages=No+Pagination+Specified&rft.date=2016&rft.jtitle=Acta+Psychiatrica+Scandinavica&rft.atitle=Recovery+from+major+depressive+disorder+episode+after+non-pharmacological+treatment+is+associated+with+normalized+cyto >.

DAHL, J. et al. The plasma levels of various cytokines are increased during ongoing depression and are reduced to normal levels after recovery. United Kingdom, p. 77-86, 2014. ISSN 0306-4530. Disponível em: < http://www.elsevier.com/locate/psyneuen http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=2014350812 >. Acesso em: (Dahl) Ringerike Psychiatric Center, Vestre Viken Hospital Trust, Norway.

DANTZER, R. Cytokine, Sickness Behavior, and Depression. United States, p. 247-264, 2009. ISSN 0889-8561. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=2009185155 >. Acesso em: (Dantzer) Integrative Immunology and Behavior Program, University of Illinois at Urbana-Champaign, 212 ERML, 1201 W Gregory Drive, Urbana, IL 61801, United States.

_____. Inflammation-induced depression: Evidence and mechanisms. p. 28, 2012. ISSN 1461-1457. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=71592022 >. Acesso em: (Dantzer) MD Anderson Cancer Center, Department of Symptom Research, Houston, TX, United States.

DANTZER, R.; KELLEY, K. W. Twenty years of research on cytokine-induced sickness behavior. **Brain Behav Immun,** v. 21, n. 2, p. 153-60, Feb 2007. ISSN 0889-1591 (Print) 0889-1591.

DANTZER, R. et al. From inflammation to sickness and depression: when the immune system subjugates the brain. **Nat Rev Neurosci,** v. 9, n. 1, p. 46-56, Jan 2008. ISSN 1471-003x.

DARKO, D. F. et al. Mitogen-stimulated lymphocyte proliferation and pituitary hormones in major depression. United States, p. 145-155, 1989. ISSN 0006-3223. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed2&NEWS=N&AN=1989151160 >. Acesso em: (Darko, Gillin, Risch, Bulloch, Golshan, Tasevska, Hamburger) San Diego Veterans Administration Medical Center, UCSD School of Medicine, San Diego, CA United States.

DARKO, D. F. et al. Cellular immunity and the hypothalamic-pituitary axis in major affective disorder: A preliminary study. **Psychiatry Research,** v. 25, n. 1, p. 1-9, Jul 1988. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc3&AN=1989-15657-001 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc3&rft.genre=article&rft_id=info:doi/10.1016%2F0165-1781%2888%2990152-7&rft_id=info:pmid/&rft.issn=0165-1781&rft.volume=25&rft.issue=1&rft.spage=1&rft.pages=1-9&rft.date=1988&rft.jtitle=Psychiatry+Research&rft.atitle=Cellular+immunity+and+the+hypothalamic-pituitary+axis+in+major+affective+disorder%3A+A+preliminary+study.&rft.aulast=Darko >.

DAVIS, J. et al. Towards a classification of biomarkers of neuropsychiatric disease: from encompass to compass. **Mol Psychiatry,** v. 20, n. 2, p. 152-3, Feb 2015. ISSN 1359-4184.

DE MELLO, A. S. et al. A nested population-based case-control study on inflammation markers in early-stage mood disorders. p. e35, 2012. ISSN 0268-1315. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=70966808 >. Acesso em: (De Mello, Ghislani, Oses, Kaster, Jansen, Wiener, Kapczinski, Magalhaes, Branco, Pinheiro, Da Silva Rua) Brazil.

DEL GRANDE DA SILVA, G. et al. Pro-inflammatory cytokines and psychotherapy in depression: Results from a randomized clinical trial. **Journal of Psychiatric Research,** v. 75, p. 57-64, Apr 2016. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc12&AN=2016-11334-012 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-

2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc12&rft.genre=article&rft_id=info:doi/10.1016%2Fj.jpsychires.2016.01.008&rft_id=info:pmid/&rft.issn=0022-3956&rft.volume=75&rft.issue=1&rft.spage=57&rft.pages=57-64&rft.date=2016&rft.jtitle=Journal+of+Psychiatric+Research&rft.atitle=Pro-inflammatory+cytokines+and+psychotherapy+in+depression%3A+Results+from+a+randomized+clinical+trial.&rft.aulast=Del
http://ac.els-cdn.com/S0022395616300073/1-s2.0-S0022395616300073-main.pdf?_tid=c26e8f44-27f5-11e6-a243-00000aacb35d&acdnat=1464784896_57c9afe1943897067379649a38e13e0f >.

DELLAGIOIA, N.; HANNESTAD, J. Citalopram pre-treatment does not reduce endotoxin-induced depressive symptoms. p. 242S, 2010. ISSN 0006-3223. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=70130242 >. Acesso em: (DellaGioia, Hannestad) Psychiatry, Yale University, New Haven, CT, United States.

DEMIR, S. et al. Neutrophil-lymphocyte ratio in patients with major depressive disorder undergoing no pharmacological therapy. **Neuropsychiatric Disease and Treatment,** v. 11, p. 2253-2258, Aug 2015. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc11&AN=2015-40105-001
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc11&rft.genre=article&rft_id=info:doi/&rft_id=info:pmid/&rft.issn=1176-6328&rft.volume=11&rft.issue=&rft.spage=2253&rft.pages=&rft.date=2015&rft.jtitle=Neuropsychiatric+Disease+and+Treatment&rft.atitle=Neutrophil-lymphocyte+ratio+in+patients+with+major+depressive+disorder+undergoing+no+pharmacological+therapy.&rft.aulast=Demir
https://www.dovepress.com/getfile.php?fileID=26772 >.

DENTINO, A. N. et al. Association of interleukin-6 and other biologic variables with depression in older people living in the community. **Journal of the American Geriatrics Society,** v. 47, n. 1, p. 6-11, Jan 1999. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc3&AN=1999-00224-002
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc3&rft.genre=article&rft_id=info:doi/&rft_id=info:pmid/&rft.issn=0002-8614&rft.volume=47&rft.issue=1&rft.spage=6&rft.pages=6-11&rft.date=1999&rft.jtitle=Journal+of+the+American+Geriatrics+Society&rft.atitle=Association+of+interleukin-6+and+other+biologic+variables+with+depression+in+older+people+living+in+the+community.&rft.aulast=Dentino >.

DERSIMONIAN, R.; LAIRD, N. Meta-analysis in clinical trials. **Control Clin Trials,** v. 7, n. 3, p. 177-88, Sep 1986. ISSN 0197-2456 (Print)
0197-2456.

DIMOPOULOS, N. et al. Increased plasma levels of 8-iso-PGF2alpha and IL-6 in an elderly population with depression. **Psychiatry Res,** v. 161, n. 1, p. 59-66, Oct 30 2008. ISSN 0165-1781 (Print)
0165-1781.

DINAN, T. G. Inflammatory markers in depression. **Current Opinion in Psychiatry,** v. 22, n. 1, p. 32-36, Jan 2009. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc6&AN=2008-17624-006
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc6&rft.genre=article&rft_id=info:doi/10.1097%2FYCO.0b013e328315a561&rft_id=info:pmid/&rft.issn=0951-7367&rft.volume=22&rft.issue=1&rft.spage=32&rft.pages=32-36&rft.date=2009&rft.jtitle=Current+Opinion+in+Psychiatry&rft.atitle=Inflammatory+markers+in+depression.&rft.aulast=Dinan
http://graphics.tx.ovid.com/ovftpdfs/FPDDNCLBEFGADB00/fs046/ovft/live/gv023/00001504/00001504-200901000-00007.pdf >.

DOME, P. et al. Investigation of circulating endothelial progenitor cells and angiogenic and inflammatory cytokines during recovery from an episode of major depression. **J Affect Disord,** v. 136, n. 3, p. 1159-63, Feb 2012. ISSN

0165-0327.

DOWLATI, Y. et al. A meta-analysis of cytokines in major depression. **Biol Psychiatry,** v. 67, n. 5, p. 446-57, Mar 1 2010. ISSN 0006-3223.

DOYLE, T. A. et al. Diabetes, depressive symptoms, and inflammation in older adults: results from the Health, Aging, and Body Composition Study. **J Psychosom Res,** v. 75, n. 5, p. 419-24, Nov 2013. ISSN 0022-3999. Disponível em: < http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3817497/pdf/nihms516755.pdf >.

DUIVIS, H. E. et al. Differential association of somatic and cognitive symptoms of depression and anxiety with inflammation: findings from the Netherlands Study of Depression and Anxiety (NESDA). **Psychoneuroendocrinology,** v. 38, n. 9, p. 1573-85, Sep 2013. ISSN 0306-4530.

DUMAN, R. S. Novel therapeutic aproaches beyond the serotonin receptor. **Biol Pshychiatry,** v. 44, p. 324-335, 1998.

DUNJIC-KOSTIC, B. et al. Is tumor necrosis factor-alpha a sensitive marker of acute exacerbation of severe mental illnesses? **European Neuropsychopharmacology,** v. 25, p. S230-S231, September 2015. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed13&AN=72129340 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:emed13&rft.genre=article&rft_id=info:doi/&rft_id=info:pmid/&rft.issn=0924-977X&rft.volume=25&rft.issue=&rft.spage=S230&rft.pages=S230-S231&rft.date=2015&rft.jtitle=European+Neuropsychopharmacology&rft.atitle=Is+tumor+necrosis+factor-alpha+a+sensitive+marker+of+acute+exacerbation+of+severe+mental+illnesses%3F&rft.aulast=Dunjic-Kostic%3C1066. > >.

DURAIRAJ, H.; STEURY, M. D.; PARAMESWARAN, N. Paroxetine differentially modulates LPS-induced TNFalpha and IL-6 production in mouse macrophages. **Int Immunopharmacol,** v. 25, n. 2, p. 485-92, Apr 2015. ISSN 1567-5769.

DUSEJA, R. et al. Astrocytic TNFalpha regulates the behavioral response to antidepressants. United States, p. 187-194, 2015. ISSN 0889-1591. Disponível em: < http://www.elsevier.com/inca/publications/store/6/2/2/8/0/0/index.htt http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=2014980241 >. Acesso em: (Duseja, Heir, Lewitus, Altimimi, Stellwagen) Centre for Research in Neuroscience, Dept of Neurology and Neurosurgery, McGill University Health Centre, Montreal, QC H3G 1A4, Canada.

DUVAL, S.; TWEEDIE, R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. **Biometrics,** v. 56, n. 2, p. 455-63, Jun 2000. ISSN 0006-341X (Print)
0006-341x.

EGGER, M. et al. Bias in meta-analysis detected by a simple, graphical test. **Bmj,** v. 315, n. 7109, p. 629-34, Sep 13 1997. ISSN 0959-8138 (Print)
0959-535x.

EINVIK, G. et al. Circulating cytokine concentrations are not associated with major depressive disorder in a community-based cohort. United States, p. 262-267, 2012. ISSN 0163-8343. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=2012247124 >. Acesso em: (Einvik, Randby, Namtvedt, Omland) Division of Medicine, Akershus University Hospital, Lorenskog, Norway.

EISENBERGER, N. I. et al. Inflammation and social experience: an inflammatory challenge induces feelings of social disconnection in addition to depressed mood. **Brain Behav Immun,** v. 24, n. 4, p. 558-63, May 2010. ISSN 0889-1591. Disponível em: < http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2856755/pdf/nihms171761.pdf >.

ELLER, T. et al. Pro-inflammatory cytokines and treatment response to escitalopram in major depressive disorder. **Prog Neuropsychopharmacol Biol Psychiatry,** v. 32, n. 2, p. 445-50, Feb 15 2008. ISSN 0278-5846 (Print)
0278-5846.

_____. Effects of bupropion augmentation on pro-inflammatory cytokines in escitalopram-resistant patients with

major depressive disorder. United Kingdom, p. 854-858, 2009a. ISSN 0269-8811. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=2009445582 >. Acesso em: (Eller, Vasar, Maron) Department of Psychiatry, University of Tartu, Tartu, Estonia.

_____. The role of IL-2 and soluble IL-2R in depression and antidepressant response. **Curr Opin Investig Drugs,** v. 10, n. 7, p. 638-43, Jul 2009b. ISSN 1472-4472.

ELOMAA, A. P. et al. Elevated levels of serum IL-5 are associated with an increased likelihood of major depressive disorder. **BMC Psychiatry,** v. 12, p. 2, 2012. ISSN 1471-244x. Disponível em: < http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3266629/pdf/1471-244X-12-2.pdf >.

ERHARDT, S. et al. Inflammatory mechanism in depression. p. 13, 2012. ISSN 0924-2708. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70760121 >. Acesso em: (Erhardt, Brundin, Landen, Guillemin, Engberg) Lund University, Dept of Physiology and Pharmacology, Karolinska Institutet, Stockholm SE 17177, Sweden.

EUTENEUER, F. et al. Effects of cognitive-behavioral therapy with physical activity promotion on immunological markers in major depression: A randomized controlled trial. **Psychosomatic Medicine,** v. 78 (3), p. A79, April 2016. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed14&AN=72259997 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:emed14&rft.genre=article&rft_id=info:doi/10.1097%2FPSY.0000000000000343&rft_id=info:pmid/&rft.issn=0033-3174&rft.volume=78&rft.issue=3&rft.spage=A79&rft.pages=A79&rft.date=2016&rft.jtitle=Psychosomatic+Medicine&rft.atitle=Effects+of+cognitive-behavioral+therapy+with+physical+activity+promotion+on+immunological+markers+in+major+depression%3A+A+randomize. > >.

EUTENEUER, F. et al. Psychobiological aspects of somatization syndromes: Contributions of inflammatory cytokines and neopterin. Ireland, p. 60-65, 2012. ISSN 0165-1781. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=2012069791 >. Acesso em: (Euteneuer, Hennings, Riemer, Rief) Division of Clinical Psychology and Psychotherapy, Philipps University of Marburg, Germany.

EYRE, H.; BAUNE, B. T. Neuroplastic changes in depression: a role for the immune system. **Psychoneuroendocrinology,** v. 37, n. 9, p. 1397-416, Sep 2012. ISSN 0306-4530.

EYRE, H. A. et al. A meta-analysis of chemokines in major depression. **Prog Neuropsychopharmacol Biol Psychiatry,** v. 68, p. 1-8, Jul 04 2016. ISSN 0278-5846.

FAGUNDES, C. P. et al. Depressive symptoms enhance stress-induced inflammatory responses. p. S35, 2012. ISSN 0889-1591. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70937033 >. Acesso em: (Fagundes, Glaser, Hwang, Malarkey, Kiecolt-Glaser) Ohio State University, School of Medicine, 460 Medical Center Drive, Room 144B, Columbus, OH 43210, United States.

FANG, C. K. et al. Mirtazapine inhibits tumor growth via immune response and serotonergic system. United States, 2012. Disponível em: < http://www.plosone.org/article/fetchObjectAttachment.action?uri=info%3Adoi%2F10.1371%2Fjournal.pone.0038886&representation=PDF http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=2012406859 >. Acesso em: (Fang, Chiang, Tung, Hwang) Department of Biomedical Imaging and Radiological Sciences, National Yang-Ming University, Taipei, Taiwan (Republic of China).

FAREED, J. et al. C-reactive protein: A marker of inflammation in depression. p. S392, 2010. ISSN 0893-133X. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70807907 >. Acesso em: (Fareed, Halaris, Piletz, Meresh, Hoppensteadt, Al-Duwaisan, Sinacore) Loyola University Chicago, Maywood, IL, United States.

FASICK, V. et al. The hippocampus and TNF: Common links between chronic pain and depression. United Kingdom, p. 139-159, 2015. ISSN 0149-7634. Disponível em: < http://www.elsevier.com/locate/neubiorev http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=2015959646 >. Acesso em: (Fasick, Samankan, Nader, Ignatowski) Department of Pathology and Anatomical Sciences, School of Medicine and Biomedical Sciences, University at Buffalo, The State University of New York, Buffalo, NY 14214, United States.

FAZZINO, F. et al. Taurine transporter in lymphocytes of patients with major depression treated with venlafaxine plus psychotherapy. **Adv Exp Med Biol,** v. 643, p. 217-24, 2009. ISSN 0065-2598 (Print) 0065-2598. Disponível em: < http://link.springer.com/chapter/10.1007%2F978-0-387-75681-3_22 >.

FELGER, J. C.; LOTRICH, F. E. Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. **Neuroscience,** v. 246, p. 199-229, Aug 29 2013. ISSN 0306-4522.

FIGNOLE LOFTON, M. Inflammation, altruism, religiousness, and the beck depression Inventory-II in urban African Americans. **Dissertation Abstracts International: Section B: The Sciences and Engineering,** v. 73, n. 6-B, p. 3998, 2012. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc9&AN=2012-99240-521 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc9&rft.genre=article&rft_id=info:doi/&rft_id=info:pmid/&rft.issn=0419-4217&rft.volume=73&rft.issue=6-B&rft.spage=3998&rft.pages=3998&rft.date=2012&rft.jtitle=Dissertation+Abstracts+International%3A+Section+B%3A+The+Sciences+and+Engineering&rft.atitle=Inflammation%2C+altruism%2C+religiousness%2C+and+the+beck+depression+Inventory-II+in+urban+African+A >.

FIGUEROA, N.; MORENO, C.; MALACARA, J. M. Association of inflammatory markers with symptoms and hormones at postmenopause. 2013. ISSN 0163-769X. Disponível em: < http://press.endocrine.org/doi/abs/10.1210/endo-meetings.2013.RE.3.SAT-508 http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=71785645 >. Acesso em: (Figueroa, Moreno, Malacara) University of Guanajuato, Campus Len, Len, Mexico.

FISCHER, C. W. et al. Investigating depression-like and metabolic parameters in a chronic low-grade inflammation model. p. 28, 2012. ISSN 0924-2708. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70760150 >. Acesso em: (Fischer, Elfving, Lund, Wegener) Centre for Psychiatric Research, Aarhus University Hospital, Skovagervej 2, Risskov 8240, Denmark.

FITZGERALD, P. et al. Cutaneous glucocorticoid receptor sensitivity and pro-inflammatory cytokine levels in antidepressant-resistant depression. **Psychol Med,** v. 36, n. 1, p. 37-43, Jan 2006. ISSN 0033-2917 (Print) 0033-2917. Disponível em: < http://journals.cambridge.org/download.php?file=%2FPSM%2FPSM36_01%2FS003329170500632Xa.pdf&code=4506b3de7407057de6bbfbf916a408e1 >.

FLUITMAN, S. B. et al. Electroconvulsive therapy has acute immunological and neuroendocrine effects in patients with major depressive disorder. **J Affect Disord,** v. 131, n. 1-3, p. 388-92, Jun 2011. ISSN 0165-0327.

FONSEKA, T. M. et al. Novel investigational drugs targeting IL-6 signaling for the treatment of depression. United Kingdom, p. 459-475, 2014. ISSN 1354-3784. Disponível em: < http://informahealthcare.com/loi/eid http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=2015830639 >. Acesso em: (Fonseka, Kennedy) University of Toronto, University Health Network, Department of Psychiatry, 200 Elizabeth Street, 8-EN-238, Toronto, ON M5G 2C4, Canada.

_____. Evidence to support peripheral and central IL-6 signaling targets to treat depression. United Kingdom, p. 991-992, 2015. ISSN 1354-3784. Disponível em: < http://informahealthcare.com/loi/eid http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=2015147348 >. Acesso em: (Fonseka, Kennedy) University Health Network, University of Toronto, Department of Psychiatry, 200 Elizabeth Street, 8-EN-238, Toronto, ON M5G 2C4, Canada.

FORNARO, M. et al. Increase in IL-6 levels among major depressive disorder patients after a 6-week treatment with duloxetine 60 mg/day: A preliminary observation. New Zealand, p. 51-56, 2011. ISSN 1176-6328. Disponível

em: < http://www.dovepress.com/getfile.php?fileID=8416
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=2011097427 >. Acesso em: (Fornaro, Martino) Department of Neuroscience, Section of Psychiatry, University of Genova, Genoa, Italy.

FORNARO, M. et al. Might different cytokine trends in depressed patients receiving duloxetine indicate differential biological backgrounds. **J Affect Disord,** v. 145, n. 3, p. 300-7, Mar 5 2013. ISSN 0165-0327.

FORTI, P. et al. Blood inflammatory proteins and risk of incident depression in the elderly. Switzerland, p. 11-20, 2010. ISSN 1420-8008. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=2010151916 >. Acesso em: (Forti, Rietti, Pisacane, Olivelli, Ravaglia) Department of Internal Medicine, Ageing and Nephrology, University Hospital St. Orsola-Malpighi, Via Massarenti, 9, IT-40138 Bologna, Italy.

FROMMBERGER, U. H. et al. Interleukin-6-(IL-6) plasma levels in depression and schizophrenia: comparison between the acute state and after remission. **Eur Arch Psychiatry Clin Neurosci,** v. 247, n. 4, p. 228-33, 1997. ISSN 0940-1334 (Print)
0940-1334. Disponível em: < http://download.springer.com/static/pdf/35/art%3A10.1007%2FBF02900219.pdf?originUrl=http%3A%2F%2Flink.springer.com%2Farticle%2F10.1007%2FBF02900219&token2=exp=1441740475~acl=%2Fstatic%2Fpdf%2F35%2Fart%3A10.1007%2FBF02900219.pdf%3ForiginUrl%3Dhttp%3A%2F%2Flink.springer.com%2Farticle%2F10.1007%2FBF02900219*~hmac=a1508353010291758e459a86ee5e53529cff782b1811af818f2d73c33d5e5540 >.

GABBAY, V. et al. Immune system dysregulation in adolescent major depressive disorder. **Journal of Affective Disorders,** v. 115, n. 1-2, p. 177-182, May 2009. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc6&AN=2009-04616-021
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc6&rft.genre=article&rft_id=info:doi/10.1016%2Fj.jad.2008.07.022&rft_id=info:pmid/&rft.issn=0165-0327&rft.volume=115&rft.issue=1-2&rft.spage=177&rft.pages=177-182&rft.date=2009&rft.jtitle=Journal+of+Affective+Disorders&rft.atitle=Immune+system+dysregulation+in+adolescent+major+depressive+disorder.&rft.aulast=Gabbay
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2770721/pdf/nihms146404.pdf >.

GABBAY, V. et al. A preliminary study of cytokines in suicidal and nonsuicidal adolescents with major depression. **J Child Adolesc Psychopharmacol,** v. 19, n. 4, p. 423-30, Aug 2009. ISSN 1044-5463. Disponível em: < http://online.liebertpub.com/doi/pdfplus/10.1089/cap.2008.0140 >.

GAZAL, M. et al. Association of interleukin-10 levels with age of onset and duration of illness in patients with major depressive disorder. **Revista Brasileira de Psiquiatria,** v. 37, n. 4, p. 296-302, October 2015. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed13&AN=20151050747
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:emed13&rft.genre=article&rft_id=info:doi/10.1590%2F1516-4446-2014-1452&rft_id=info:pmid/&rft.issn=1516-4446&rft.volume=37&rft.issue=4&rft.spage=296&rft.pages=296-302&rft.date=2015&rft.jtitle=Revista+Brasileira+de+Psiquiatria&rft.atitle=Association+of+interleukin-10+levels+with+age+of+onset+and+duration+of+illness+in+patients+with+major+depressive+disor. >
http://www.scielo.br/pdf/rbp/v37n4/1516-4446-rbp-1516444620141452.pdf >.

GAZAL, M. et al. The impact of cognitive behavioral therapy on IL-6 levels in unmedicated women experiencing the first episode of depression: a pilot study. **Psychiatry Res,** v. 209, n. 3, p. 742-5, Oct 30 2013. ISSN 0165-1781.

GE, S. et al. Transcellular transport of CCL2 across brain microvascular endothelial cells. **J Neurochem,** v. 104, n. 5, p. 1219-32, Mar 2008. ISSN 0022-3042.

GIBNEY, S. et al. Poly I: C-induced activation of the innate immune response is accompanied by symptoms of depression and anxiety. p. S222, 2011. ISSN 0889-1591. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70531584 >. Acesso em: (Gibney, McGuinness, Prendergast, Harkin, Connor) Trinity College Institute for Neuroscience, Trinity College, Dublin 2, Ireland.

GILBEY, M. P. et al. Prevalence and treatment of depression are differentially associated with insulin resistance and obesity. p. 255-256, 2011. ISSN 0959-9851. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70529587 >. Acesso em: (Gilbey, Marina, Cotena) University College London, Neuroscience, Physiology and Pharmacology, United Kingdom.

GIMENO, D. et al. Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. **Psychological Medicine,** v. 39, n. 3, p. 413-423, Mar 2009. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc6&AN=2009-03827-008
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc6&rft.genre=article&rft_id=info:doi/10.1017%2FS0033291708003723&rft_id=info:pmid/&rft.issn=0033-2917&rft.volume=39&rft.issue=3&rft.spage=413&rft.pages=413-423&rft.date=2009&rft.jtitle=Psychological+Medicine&rft.atitle=Associations+of+C-reactive+protein+and+interleukin-6+with+cognitive+symptoms+of+depression%3A+12-year+follow-up+of+the+Whitehall+II+
http://journals.cambridge.org/download.php?file=%2FPSM%2FPSM39_03%2FS0033291708003723a.pdf&code=ad6c35b36278c6b9bcc11dafcdd37ae9 >.

GLAUS, J. et al. Associations between mood, anxiety or substance use disorders and inflammatory markers after adjustment for multiple covariates in a population-based study. United Kingdom, p. 36-45, 2014. ISSN 0022-3956. Disponível em: < http://www.elsevier.com/locate/jpsychires
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=2014709036 >. Acesso em: (Glaus, Vandeleur, Lasserre, Strippoli, Gholam-Rezaee, Castelao, Preisig) Department of Psychiatry, Lausanne University Hospital, Switzerland.

GLAUS, J. et al. Prospective associations between inflammatory markers, cardiovascular risk factors and common mental disorders in the lausanne cohort study (COLAUS). **Biological Psychiatry,** v. 1), p. 176S, May 2016. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed14&AN=72256581
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:emed14&rft.genre=article&rft_id=info:doi/10.1016%2Fj.biopsych.2016.03.1054&rft_id=info:pmid/&rft.issn=0006-3223&rft.volume=79&rft.issue=9+SUPPL.+1&rft.spage=176S&rft.pages=176S&rft.date=2016&rft.jtitle=Biological+Psychiatry&rft.atitle=Prospective+associations+between+inflammatory+markers%2C+cardiovascular+risk+factors+and+common+mental+disorders+in+the. > >.

GOLDSCHMIED, J. R. et al. A preliminary study exploring the relationships among markers of cardiovascular dysfunction, sleep-disordered breathing, and depression. p. A169, 2013. ISSN 0161-8105. Disponível em: < http://www.journalsleep.org/Resources/Documents/2013AbstractSupplement.pdf
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=71513303 >. Acesso em: (Goldschmied, Arnedt, Ehrmann, Pitt, D'Alecy, Sen, Dalack, Deldin) University of Michigan, Ann Arbor, MI, United States.

GOLDSMITH, D. et al. Inflammatory cytokines are associated with decreased psychomotor speed in female, but not male, patients with major depression. **Neuropsychopharmacology,** v. 40, p. S339-S340, December 2015. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed13&AN=72133044
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:emed13&rft.genre=article&rft_id=info:doi/10.1038%2Fnpp.2015.326&rft_id=info:pmid/&rft.issn=0893-133X&rft.volume=40&rft.issue=&rft.spage=S339&rft.pages=S339-S340&rft.date=2015&rft.jtitle=Neuropsychopharmacology&rft.atitle=Inflammatory+cytokines+are+associated+with+decreased+psychomotor+speed+in+female%2C+but+not+male%2C+patients+with+major+depression&rf. > >.

GOLDSMITH, D. R. et al. Inflammatory markers are associated with decreased psychomotor speed in patients with major depressive disorder. **Biological Psychiatry,** v. 1), p. 53S, May 2016. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed14&AN=72256269

http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:emed14&rft.genre=article&rft_id=info:doi/10.1016%2Fj.biopsych.2016.03.1748&rft_id=info:pmid/&rft.issn=0006-3223&rft.volume=79&rft.issue=9+SUPPL.+1&rft.spage=53S&rft.pages=53S&rft.date=2016&rft.jtitle=Biological+Psychiatry&rft.atitle=Inflammatory+markers+are+associated+with+decreased+psychomotor+speed+in+patients+with+major+depressive+disorder&rft.aulas. > >.

GOLDSMITH, D. R.; RAPAPORT, M. H.; MILLER, B. J. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. **Mol Psychiatry**, Feb 23 2016. ISSN 1359-4184.

GOODWIN, F. K.; JAMISON, K. R. **Doença maníaco-depressiva: transtorno bipolar e depressão recorrente**. 2. ed. Porto Algre: Artmed, 2010. 1359 ISBN 978-85-363-2202-5.

GRASSI-OLIVEIRA, R. et al. Interleukin-6 and verbal memory in recurrent major depressive disorder. **Neuro Endocrinol Lett,** v. 32, n. 4, p. 540-4, 2011. ISSN 0172-780X (Print)
0172-780x.

GRASSI-OLIVEIRA, R. et al. Differences in chemokine levels in individuals with recurrent major depression disorder with and without suicide ideation. p. 178S, 2011. ISSN 0006-3223. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70402578 >. Acesso em: (Grassi-Oliveira, Vieira) Developmental Cognitive Neuroscience, Postgraduate Program in Psychology - Human Cognition, Pontifical Catholic University of Rio Grande do Sul, Porto Alegre, Brazil.

GROER, M. et al. High C-reactive protein levels in active duty soldiers are associated with depression, PTSD and combat exposure. p. S22, 2012. ISSN 0889-1591. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70936983 >. Acesso em: (Groer, Radford) University of South Florida, College of Nursing, 12910 Bruce B Downs Blvd, Tampa, FL 33612, United States.

GROUP, B. D. W. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. **Clin Pharmacol Ther,** v. 69, n. 3, p. 89-95, Mar 2001. ISSN 0009-9236 (Print)
0009-9236.

GRUDET, C. et al. Suicidal patients are deficient in vitamin D, associated with a pro-inflammatory status in the blood. United Kingdom, p. 210-219, 2014. ISSN 0306-4530. Disponível em: < http://www.elsevier.com/locate/psyneuen
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=2014871044 >. Acesso em: (Grudet, Westrin) Department of Clinical Sciences, Lund, Psychiatry, Lund University, Lund 221 85, Sweden.

GUIDI, L. et al. Impairment of lymphocyte activities in depressed aged subjects. Ireland, p. 13-24, 1991. ISSN 0047-6374. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed2&NEWS=N&AN=1991303268 >. Acesso em: (Guidi, Baroloni, Frasca, Antico, Pili, Cursi, Tempesta, Rumi, Menini, Carbonin, Doria, Gambassi) Istituto di Clinica Medica, Universita Cattolica, del Sacro Cuore, Largo A. Gemelli 8, I-00168 Roma, Italy.

GUPTA, R. et al. Effect of Mirtazapine Treatment on Serum Levels of Brain-Derived Neurotrophic Factor and Tumor Necrosis Factor-alpha in Patients of Major Depressive Disorder with Severe Depression. **Pharmacology,** v. 97, n. 3-4, p. 184-8, 2016. ISSN 0031-7012.

GURURAJAN, A. et al. Molecular biomarkers of depression. **Neurosci Biobehav Rev,** v. 64, p. 101-33, May 2016. ISSN 0149-7634.

HAACK, M. et al. Plasma levels of cytokines and soluble cytokine receptors in psychiatric patients upon hospital admission: Effects of confounding factors and diagnosis. United Kingdom, p. 407-418, 1999. ISSN 0022-3956. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed4&NEWS=N&AN=1999291715 >. Acesso em: (Haack, Hinze-Selch, Fenzel, Kraus, Kuhn, Schuld, Pollmacher) Max Planck Institute of Psychiatry, Kraepelinstrasse 10, 80804, Munich, Germany.

HAAPAKOSKI, R. et al. Cumulative meta-analysis of interleukins 6 and 1beta, tumour necrosis factor alpha and C-reactive protein in patients with major depressive disorder. **Brain Behav Immun,** v. 49, p. 206-15, Oct 2015. ISSN 0889-1591.

HAASTRUP, E. et al. Promoter variants in IL18 are associated with onset of depression in patients previously exposed to stressful-life events. **J Affect Disord,** v. 136, n. 1-2, p. 134-8, Jan 2012. ISSN 0165-0327.

HAFNER, S. et al. Association between social isolation and inflammatory markers in depressed and non-depressed individuals: Results from the MONICA/KORA study. **Brain, Behavior, and Immunity,** v. 25, n. 8, p. 1701-1707, Nov 2011. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc8&AN=2011-23405-022 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc8&rft.genre=article&rft_id=info:doi/10.1016%2Fj.bbi.2011.06.017&rft_id=info:pmid/&rft.issn=0889-1591&rft.volume=25&rft.issue=8&rft.spage=1701&rft.pages=1701-1707&rft.date=2011&rft.jtitle=Brain%2C+Behavior%2C+and+Immunity&rft.atitle=Association+between+social+isolation+and+inflammatory+markers+in+depressed+and+non-depressed+individuals%3A+Results+fr http://ac.els-cdn.com/S088915911100239X/1-s2.0-S088915911100239X-main.pdf?_tid=b78c76b0-5684-11e5-a8ac-00000aacb35e&acdnat=1441756552_c247c04e07194e06717fedd529222f66 >.

HALARIS, A. et al. Relationship of vascular endothelial growth factor and inflammation in depression. p. 221S, 2014. ISSN 0006-3223. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=71434502 >. Acesso em: (Halaris, Clark-Raymond, Meresh, Sharma, Hage, Morrissey, Hoppensteadt, Fareed, Sinacore) Psychiatry and Behavioral Neuroscience, Loyola University, Stritch School of Medicine, Maywood, IL, United States.

HALARIS, A. et al. Inflammation and endothelial dysfunction in depression: Factors contributing to cardiovascular disease co-morbidity. p. 614, 2009. ISSN 1538-7933. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=70051320 >. Acesso em: (Halaris, Piletz, Tobin) Psychiatry, Loyola University Medical Center, Maywood, United States.

HALARIS, A. et al. Interleukin-6 as a biomarker in major depressive disorder. p. S1, 2012. ISSN 0889-1591. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70936907 >. Acesso em: (Halaris, Meresh, Fareed, Hoppenstead, Kimmons, Sinacore) Loyala University Stritch School of Medicine, Psychiatry, 2160 South First Avenue, Maywood, IL 60153, United States.

HALARIS, A. et al. Inflammation and endothelial dysfunction in depression and anxiety disorders. p. S237, 2011. ISSN 0889-1591. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70531636 >. Acesso em: (Halaris, Meresh, Fareed, Hoppenstead, Kimmons, Sinacore, Ruys) Loyola University, Stritch School of Medicine, Psychiatry, 2160 South First Avenue, Maywood, IL 60153, United States.

HALARIS, A. et al. Tumor necrosis factor alpha as a biomarker in major depressive disorder. p. S1, 2012. ISSN 0889-1591. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70936908 >. Acesso em: (Halaris, Meresh, Fareed, Hoppensteadt, Kimmons, Sinacore) Loyola University Stritch School of Medicine, Psychiatry, 2160 South First Avenue, Maywood, IL 60153, United States.

HALARIS, A. et al. Plasma interleukin-6 as a biomarker in the treatment of major depressive disorder. p. 179, 2012. ISSN 1461-1457. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=71592577 >. Acesso em: (Halaris) Loyola University Medical Center, Maywood, United States.

HALLBERG, L. et al. Exercise-induced release of cytokines in patients with major depressive disorder. **J Affect Disord,** v. 126, n. 1-2, p. 262-7, Oct 2010. ISSN 0165-0327.

HANNESTAD, J.; DELLAGIOIA, N.; BLOCH, M. The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis. **Neuropsychopharmacology,** v. 36, n. 12, p. 2452-9, Nov 2011. ISSN 0893-133x.

HAROON, E. et al. Conceptual convergence: Increased inflammation is associated with increased basal ganglia glutamate in patients with major depression. **Neuropsychopharmacology,** v. 40, p. S335-S336, December 2015. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed13&AN=72133039 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:emed13&rft.genre=article&rft_id=info:doi/10.1038%2Fnpp.2015.326&rft_id=info:pmid/&rft.issn=0893-133X&rft.volume=40&rft.issue=&rft.spage=S335&rft.pages=S335-S336&rft.date=2015&rft.jtitle=Neuropsychopharmacology&rft.atitle=Conceptual+convergence%3A+Increased+inflammation+is+associated+with+increased+basal+ganglia+glutamate+in+patients+with+major+depressi. > >.

HASHIMOTO, T. et al. Milnacipran treatment and potential biomarkers in depressed patients following an initial SSRI treatment failure: A prospective, open-label, 24-week study. **Neuropsychiatric Disease and Treatment,** v. 11, p. 3031-3040, Dec 2015. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc11&AN=2015-56854-001 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc11&rft.genre=article&rft_id=info:doi/&rft_id=info:pmid/&rft.issn=1176-6328&rft.volume=11&rft.issue=&rft.spage=3031&rft.pages=&rft.date=2015&rft.jtitle=Neuropsychiatric+Disease+and+Treatment&rft.atitle=Milnacipran+treatment+and+potential+biomarkers+in+depressed+patients+following+an+initial+SSRI+treatment+failure%3A+A+prospective%2C+open-label%2C+24 https://www.dovepress.com/getfile.php?fileID=28314 >.

HASHIOKA, S. et al. Antidepressants inhibit interferon-gamma-induced microglial production of IL-6 and nitric oxide. **Exp Neurol,** v. 206, n. 1, p. 33-42, Jul 2007. ISSN 0014-4886 (Print) 0014-4886.

HAYLEY, S. Toward an anti-inflammatory strategy for depression. Switzerland, 2011. ISSN 1662-5153. Disponível em: < http://www.frontiersin.org/behavioral_neuroscience/10.3389/fnbeh.2011.00019/abstract http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=2011673935 >. Acesso em: (Hayley) Department of Neuroscience, Carleton University, Ottawa, ON, Canada.

HAYLEY, S.; MERALI, Z.; ANISMAN, H. Stress and cytokine-elicited neuroendocrine and neurotransmitter sensitization: Implications for depressive illness. United Kingdom, p. 19-32, 2003. ISSN 1025-3890. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed6&NEWS=N&AN=2003148393 >. Acesso em: (Hayley, Anisman) Institute of Neuroscience, Carleton University, Ottawa, Ont., Canada.

HEISER, P. et al. Differential modulation of cytokine production in major depressive disorder by cortisol and dexamethasone. **European Neuropsychopharmacology,** v. 18, n. 12, p. 860-870, Dec 2008. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc6&AN=2008-15162-006 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc6&rft.genre=article&rft_id=info:doi/10.1016%2Fj.euroneuro.2008.07.003&rft_id=info:pmid/&rft.issn=0924-977X&rft.volume=18&rft.issue=12&rft.spage=860&rft.pages=860-870&rft.date=2008&rft.jtitle=European+Neuropsychopharmacology&rft.atitle=Differential+modulation+of+cytokine+production+in+major+depressive+disorder+by+cortisol+and+dexamethasone.&rft.aula http://www.europeanneuropsychopharmacology.com/article/S0924-977X(08)00174-0/abstract >.

HENJE BLOM, E. et al. Elevated levels of IL-6 is related to clinical depression and anxiety in adolescent girls. p. S212-S213, 2011. ISSN 0889-1591. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70531552 >. Acesso em: (Henje Blom, Serlachius, Lekander, Mobarrez, Ingvar) Karolinska Institutet, Department of Clinical Neuroscience, Retzius v 8, A2:3, Stockholm, Sweden.

HENNESSY, M. B. et al. Proinflammatory activity and the sensitization of depressive-like behavior during maternal separation. **Behav Neurosci,** v. 125, n. 3, p. 426-33, Jun 2011. ISSN 0735-7044. Disponível em: < http://psycnet.apa.org/journals/bne/125/3/426.pdf >.

HENNINGS, A. et al. Exercise affects symptom severity but not biological measures in depression and somatization - Results on IL-6, neopterin, tryptophan, kynurenine and 5-HIAA. Ireland, p. 925-933, 2013. ISSN 0165-1781. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=2013746703 >. Acesso em: (Hennings, Riemer, Rief) Division of Clinical Psychology and Psychotherapy, Philipps University of Marburg, Gutenbergstrasse 18, 35032 Marburg, Germany.

HERNANDEZ, M. E. et al. Variations in circulating cytokine levels during 52 week course of treatment with SSRI for major depressive disorder. **Eur Neuropsychopharmacol,** v. 18, n. 12, p. 917-24, Dec 2008a. ISSN 0924-977X (Print)
0924-977x.

_____. Variations in circulating cytokine levels during 52 week course of treatment with SSRI for major depressive disorder. Netherlands, p. 917-924, 2008b. ISSN 0924-977X. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS=N&AN=2008478653 >. Acesso em: (Hernandez, Loria, Pavon) Department of Psychoimmunology, National Institute of Psychiatry Ramon de la Fuente, Mexico.

HERNANDEZ, M. E. et al. Effect of selective serotonin reuptake inhibitors and immunomodulator on cytokines levels: an alternative therapy for patients with major depressive disorder. p. 267871, 2013. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=24348675 >. Acesso em: (Hernandez) Department of Psychoimmunology, National Institute of Psychiatry "Ramon de la Fuente", Calzada Mexico-Xochimilco 101, Col. San Lorenzo Huipulco, Tlalpan, 14370 Mexico City, DF, Mexico ; Universidad Autonoma Metropolitana. Avenida San Rafael Atlixco No. 186, Col. Vicentina, Iztapalapa, 09340 Mexico City, DF, Mexico.

HERRAN, A. et al. Increased bone remodeling in first-episode major depressive disorder. United States, p. 779-782, 2000. ISSN 0033-3174. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed5&NEWS=N&AN=2001006232 >. Acesso em: (Herran, Vazquez-Barquero) Department of Psychiatry, University Hospital Marques de Valdecilla, Santander, Spain.

HESTAD, K. A. et al. Raised plasma levels of tumor necrosis factor alpha in patients with depression: normalization during electroconvulsive therapy. **J ect,** v. 19, n. 4, p. 183-8, Dec 2003. ISSN 1095-0680 (Print)
1095-0680.

_____. Inflammation and depression: further studies are needed. **J ect,** v. 21, n. 1, p. 52, Mar 2005. ISSN 1095-0680 (Print)
1095-0680.

HILES, S. A. et al. A meta-analysis of differences in IL-6 and IL-10 between people with and without depression: exploring the causes of heterogeneity. **Brain Behav Immun,** v. 26, n. 7, p. 1180-8, Oct 2012. ISSN 0889-1591.

HILES, S. A. et al. Unhealthy lifestyle may increase later depression via inflammation in older women but not men. United Kingdom, p. 65-74, 2015. ISSN 0022-3956. Disponível em: < http://www.elsevier.com/locate/jpsychires http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=2015833109 >. Acesso em: (Hiles, Baker) Priority Research Centre for Translational Neuroscience and Mental Health, Faculty of Health, University of Newcastle, New South Wales, Australia.

HIMMERICH, H.; BERTHOLD-LOSLEBEN, M.; POLLMACHER, T. The relevance of the TNF-alpha system in psychiatric disorders. Germany, p. 334-345, 2009. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=19415585 >. Acesso em: (Himmerich, Berthold-Losleben, Pollmacher) Klinik fur Psychiatrie und Psychotherapie, Universitatsklinikum der RWTH Aachen.

HIMMERICH, H. et al. Depression, comorbidities and the TNF-alpha system. **Eur Psychiatry,** v. 23, n. 6, p. 421-9, Sep 2008. ISSN 0924-9338 (Print)
0924-9338.

HIMMERICH, H. et al. Antidepressant activity of venlafaxine is independent of IFN-gamma reduction. p. S63,

2010a. ISSN 0165-0327. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=70140875 >. Acesso em: (Himmerich, Sheldrick, Plumakers, Rink) RWTH Aachen University, Germany.

_____. IFN-gamma reduction by tricyclic antidepressants. **Int J Psychiatry Med,** v. 40, n. 4, p. 413-24, 2010b. ISSN 0091-2174 (Print)
0091-2174.

HIMMERICH, H. et al. Regulatory T cells increased while IL-1beta decreased during antidepressant therapy. **J Psychiatr Res,** v. 44, n. 15, p. 1052-7, Nov 2010. ISSN 0022-3956.

HIMMERICH, H. et al. Early prediction of changes in weight during six weeks of treatment with antidepressants. **J Psychiatr Res,** v. 38, n. 5, p. 485-9, Sep-Oct 2004. ISSN 0022-3956 (Print)
0022-3956.

HO, P. S. et al. A shift toward T helper 2 responses and an increase in modulators of innate immunity in depressed patients treated with escitalopram. United Kingdom, p. 246-255, 2015. ISSN 0306-4530. Disponível em: < http://www.elsevier.com/locate/psyneuen
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=2015750223 >. Acesso em: (Ho, Liang) Department of Psychiatry, Beitou Branch, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan (Republic of China).

HO, R. Cytokines in depressive disorder. p. S8, 2014. ISSN 0304-4602. Disponível em: < http://www.annals.edu.sg/pdf/43VolNo10Oct2014/NUHS2014.pdf
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=71798657 >.

HODES, G. E. et al. A functional role for interleukin 6 in susceptibility to depression. p. S202, 2011. ISSN 0893-133X. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70607455 >. Acesso em: (Hodes, Steizhammer, Golden, Christoffel, Magida, Kluge, Tamminga, Ghose, Wong, Lee, Bahn, Russo) Mt. Sinai School Medicine, New York, United States.

HOZO, S. P.; DJULBEGOVIC, B.; HOZO, I. Estimating the mean and variance from the median, range, and the size of a sample. **BMC Medical Research Methodology,** v. 5, n. 1, p. 13, 2005. ISSN 1471-2288. Disponível em: < http://dx.doi.org/10.1186/1471-2288-5-13 >.

HUFNER, K. et al. Bioprofiling of platelets in medicated patients with depression. **Journal of Affective Disorders,** v. 172, p. 81-88, Feb 2015. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc11&AN=2014-54092-013
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc11&rft.genre=article&rft_id=info:doi/10.1016%2Fj.jad.2014.09.029&rft_id=info:pmid/&rft.issn=0165-0327&rft.volume=172&rft.issue=&rft.spage=81&rft.pages=81-88&rft.date=2015&rft.jtitle=Journal+of+Affective+Disorders&rft.atitle=Bioprofiling+of+platelets+in+medicated+patients+with+depression.&rft.aulast=Hufner >.

HUGHES, M. et al. Depressed patients with a mild inflammatory phenotype display robust tryptophan depletion in the absence of kynurenine pathway activation. p. 186, 2012. ISSN 1461-1457. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=71592602 >. Acesso em: (Hughes) Institute of Neuroscience, Dublin, Ireland.

HUGHES, M. M. et al. Childhood trauma and depression are associated with a dysregulated inflammatory profile. p. e32, 2013. ISSN 0889-1591. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=71206289 >. Acesso em: (Hughes, Carballedo, McLoughlin, Frodl, Connor) Trinity College Institute of Neuroscience, Trinity College, Dublin 2, Ireland.

HUMPHREYS, D. et al. Interleukin-6 production and deregulation of the hypothalamic-pituitary-adrenal axis in patients with major depressive disorders. **Endocrine,** v. 30, n. 3, p. 371-6, Dec 2006. ISSN 1355-008X (Print)

1355-008x.

HWANG, J. P. et al. Interleukin-1 beta -511C/T genetic polymorphism is associated with age of onset of geriatric depression. **Neuromolecular Med,** v. 11, n. 4, p. 322-7, 2009. ISSN 1535-1084. Disponível em: < http://download.springer.com/static/pdf/384/art%3A10.1007%2Fs12017-009-8078-x.pdf?originUrl=http%3A%2F%2Flink.springer.com%2Farticle%2F10.1007%2Fs12017-009-8078-x&token2=exp=1441668321~acl=%2Fstatic%2Fpdf%2F384%2Fart%3A10.1007%2Fs12017-009-8078-x.pdf%3ForiginUrl%3Dhttp%3A%2F%2Flink.springer.com%2Farticle%2F10.1007%2Fs12017-009-8078-x*~hmac=91d78057082d80475236c13e6072adb75ddb1c558f8212fd2221420daa810670 >.

IACOB, E. Gene expression dysregulation in medication refractory depression. **Dissertation Abstracts International: Section B: The Sciences and Engineering,** v. 74, n. 9-B(E), p. No Pagination Specified, 2014. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc11&AN=2014-99060-235
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc11&rft.genre=article&rft_id=info:doi/&rft_id=info:pmid/&rft.issn=0419-4217&rft.volume=74&rft.issue=9-B%28E%29&rft.spage=No&rft.pages=No+Pagination+Specified&rft.date=2014&rft.jtitle=Dissertation+Abstracts+International%3A+Section+B%3A+The+Sciences+and+Engineering&rft.atitle=Gene+expression+dysregulation+in+medication+refractory+depression.&rft.aula >.

ISUNG, J. et al. Low vascular endothelial growth factor and interleukin-8 in cerebrospinal fluid of suicide attempters. **Transl Psychiatry,** v. 2, p. e196, 2012. ISSN 2158-3188. Disponível em: < http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3565771/pdf/tp2012123a.pdf >.

IVANOV, II et al. The orphan nuclear receptor RORgammat directs the differentiation program of proinflammatory IL-17+ T helper cells. **Cell,** v. 126, n. 6, p. 1121-33, Sep 22 2006. ISSN 0092-8674 (Print)
0092-8674.

IWATA, M.; OTA, K. T.; DUMAN, R. S. The inflammasome: Pathways linking psychological stress, depression, and systemic illnesses. United States, p. 105-114, 2013. ISSN 0889-1591. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=2013331079 >. Acesso em: (Iwata, Ota, Duman) Dept Psychiatry, Yale University School of Medicine, New Haven, CT, United States.

JANELIDZE, S. et al. Cytokine levels in the blood may distinguish suicide attempters from depressed patients. **Brain Behav Immun,** v. 25, n. 2, p. 335-9, Feb 2011. ISSN 0889-1591.

JANGPANGI, D. et al. To measure changes in inflammatory markers in patients of depression. p. 79-80, 2012. ISSN 0019-5499. Disponível em: < http://www.ijpp.com/IJPP archives/2012_56_4_Oct - Dec/APPICON 2012_proceedings.pdf
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=71829393 >. Acesso em: (Jangpangi, Mondal, Bandhu, Kataria, Bhattacharjee) Department of Physiology, Lady Hardinge Medical College, New Delhi, India.

JÄRVENTAUSTA, K. et al. Changes in interleukin-6 levels during electroconvulsive therapy may reflect the therapeutic response in major depression. **Acta Psychiatrica Scandinavica,** v. 135, n. 1, p. 87-92, 2017. ISSN 1600-0447. Disponível em: < http://dx.doi.org/10.1111/acps.12665 >.

JAZAYERI, S. et al. Effects of eicosapentaenoic acid and fluoxetine on plasma cortisol, serum interleukin-1beta and interleukin-6 concentrations in patients with major depressive disorder. **Psychiatry Res,** v. 178, n. 1, p. 112-5, Jun 30 2010. ISSN 0165-1781 (Print)
0165-1781.

JEON, S. W.; KIM, Y. K. Neuroinflammation and cytokine abnormality in major depression: Cause or consequence in that illness? **World J Psychiatry,** v. 6, n. 3, p. 283-93, Sep 22 2016. ISSN 2220-3206.

JOHNSON, S. M. Proinflammatory cytokines, glucocorticoids and depression. **Dissertation Abstracts International: Section B: The Sciences and Engineering,** v. 69, n. 12-B, p. 7840, 2009. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc6&AN=2009-99120-048

http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc6&rft.genre=article&rft_id=info:doi/&rft_id=info:pmid/&rft.issn=0419-4217&rft.volume=69&rft.issue=12-B&rft.spage=7840&rft.pages=7840&rft.date=2009&rft.jtitle=Dissertation+Abstracts+International%3A+Section+B%3A+The+Sciences+and+Engineering&rft.atitle=Proinflammatory+cytokines%2C+glucocorticoids+and+depression.&rft.aulast=Johnson >.

JOZUKA, H. et al. Psychoneuroimmunoendocrinological study of major depression. **Seishin Igaku (Clinical Psychiatry),** v. 42, n. 6, p. 599-604, Jun 2000. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc3&AN=2000-08992-003 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc3&rft.genre=article&rft_id=info:doi/&rft_id=info:pmid/&rft.issn=0488-1281&rft.volume=42&rft.issue=6&rft.spage=599&rft.pages=599-604&rft.date=2000&rft.jtitle=Seishin+Igaku+%28Clinical+Psychiatry%29&rft.atitle=Psychoneuroimmunoendocrinological+study+of+major+depression.&rft.aulast=Jozuka >.

JOZUKA, H. et al. Comparison of immunological and endocrinological markers associated with major depression. United Kingdom, p. 36-41, 2003. ISSN 0300-0605. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed6&NEWS=N&AN=2003120234 >. Acesso em: (Jozuka, Jozuka) Dept. Psychiat./Psychosomatic Med., Jozuka Mental Clinic, JMC Stress Medical Institute, 1-18 Hananokicho, Nishio, Aichi, Japan.

KABANCHIK, A. et al. [Importance of interleukin 2 soluble receptors determination in patients over 60 years with untreated depression]. **Vertex,** v. 15 Suppl 1, p. 41-4, 2004. ISSN 0327-6139 (Print) 0327-6139.

KAGAYA, A. et al. Plasma concentrations of interleukin-1beta, interleukin-6, soluble interleukin-2 receptor and tumor necrosis factor alpha of depressed patients in Japan. **Neuropsychobiology,** v. 43, n. 2, p. 59-62, 2001. ISSN 0302-282X (Print) 0302-282x. Disponível em: < http://www.karger.com/Article/Pdf/54867 >.

KAMINSKA, T. et al. Cytokine production in major depression. The role of proinflammatory cytokines and Th1/Th2 dysfunction. Poland, p. 84-89, 2002. ISSN 1426-3912. Disponível em: < http://www.termedia.pl/Journal/-10 http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed5&NEWS=N&AN=2003195334 >. Acesso em: (Kaminska, Kandefer-Szerszen) Department of Virology, Maria Curie-Sklodowska University, Akademicka 19, 20-033 Lublin, Poland.

KANG, A. et al. Peripheral anti-inflammatory effects explain the ginsenosides paradox between poor brain distribution and anti-depression efficacy. United Kingdom, 2011. Disponível em: < http://www.jneuroinflammation.com/content/8/1/100 http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=2011508812 >. Acesso em: (Kang, Hao, Zheng, Liang, Xie, Xie, Dai, Zhao, Wu, Xie, Wang) Key Laboratory of Drug Metabolism and Pharmacokinetics, State Key Laboratory of Natural Medicines, China Pharmaceutical University, Nanjing 210009, Jiangsu, China.

KARAOULANIS, S. E. et al. The role of cytokines and hot flashes in perimenopausal depression. United Kingdom, 2012. Disponível em: < http://www.annals-general-psychiatry.com/content/11/1/9 http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=2012262175 >. Acesso em: (Karaoulanis, Angelopoulos) Department of Psychiatry, University Hospital of Larissa, University of Thessaly, Larissa, Greece.

KARRENBAUER, D. et al. Interleukin-2 reduces extracellular cortical serotonin: Impact on depressive-related and anxiety-like behaviour. p. S16, 2010. ISSN 0889-1591. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=70268210 >. Acesso em: (Karrenbauer, Schwarting) Physiological Psychology, Philipps University, Marburg, Germany.

KAST, R. E. Anti- and pro-inflammatory considerations in antidepressant use during medical illness: bupropion lowers and mirtazapine increases circulating tumor necrosis factor-alpha levels. **Gen Hosp Psychiatry,** v. 25, n. 6, p. 495-6, Nov-Dec 2003. ISSN 0163-8343 (Print)

0163-8343.

KATZAV, A. et al. Induction of autoimmune depression in mice by anti-ribosomal P antibodies via the limbic system. **Arthritis Rheum,** v. 56, n. 3, p. 938-48, Mar 2007. ISSN 0004-3591 (Print)
0004-3591.

KEMP, D. E. et al. Baseline interleukin-6, cortisol, and insulin in major depressive disorder and response to pioglitazone: Preliminary support for insulin sensitizers as modulators of mood. p. S353-S354, 2011. ISSN 0893-133X. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70607731 >. Acesso em: (Kemp, Ganocy, Gao, Ismail-Beigi, Conroy, Obral, Calabrese) Case Western Reserve University, Cleveland, United States.

KENIS, G.; MAES, M. Effects of antidepressants on the production of cytokines. United Kingdom, p. 401-412, 2002. ISSN 1461-1457. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed5&NEWS=N&AN=2002458596 >. Acesso em: (Kenis, Maes) Department of Psychiatry, University of Maastricht, 6200 MD Maastricht, Netherlands.

KESSLER, R. C. et al. The WHO World Mental Health (WMH) Surveys. **Psychiatrie (Stuttg),** v. 6, n. 1, p. 5-9, Jan 1 2009. ISSN 1614-4864 (Print)
1614-4864.

KESSLER, R. C. et al. Age differences in the prevalence and co-morbidity of DSM-IV major depressive episodes: results from the WHO World Mental Health Survey Initiative. **Depress Anxiety,** v. 27, n. 4, p. 351-64, Apr 2010. ISSN 1091-4269.

KESSLER, R. C.; BROMET, E. J. The epidemiology of depression across cultures. **Annu Rev Public Health,** v. 34, p. 119-38, 2013. ISSN 0163-7525.

KHAIROVA, R. A. et al. A potential role for pro-inflammatory cytokines in regulating synaptic plasticity in major depressive disorder. United Kingdom, p. 561-578, 2009. ISSN 1461-1457. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=2009468243 >. Acesso em: (Khairova, MacHado-Vieira, Du, Manji) Mood and Anxiety Disorders Program, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, United States.

KHAN, M. H. et al. Inflammation as common denominator of ED and MDD. 2013. ISSN 0924-9338. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=71172087 >. Acesso em: (Khan) Psychiatry, Sexual Health Institute of Pakistan, Lahore, Pakistan.

KIM, J. W. et al. Plasma levels of IL-23 and IL-17 before and after antidepressant treatment in patients with major depressive disorder. South Korea, p. 294-299, 2013. ISSN 1738-3684. Disponível em: < http://www.psychiatryinvestigation.org/html/pdfdown.asp?pn=0502013045
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=2013656655 >. Acesso em: (Kim, Kim, Hwang, Yoon, Ko, Han) Department of Psychiatry, Korea University, College of Medicine, Ansan Hospital, Ansan, South Korea.

KIM, Y. K. et al. The role of pro-inflammatory cytokines in neuroinflammation, neurogenesis and the neuroendocrine system in major depression. **Prog Neuropsychopharmacol Biol Psychiatry,** v. 64, p. 277-84, Jan 4 2016. ISSN 0278-5846.

KIM, Y. K. et al. Cytokine imbalance in the pathophysiology of major depressive disorder. United States, p. 1044-1053, 2007. ISSN 0278-5846. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS=N&AN=2007257764 >. Acesso em: (Kim, Na) Department of Psychiatry, Korea University Ansan Hospital, College of Medicine, South Korea.

KIM, Y. K. et al. Exploration of biological markers of suicidal behavior in major depressive disorder. South Korea, p. 13-21, 2007. ISSN 1738-3684. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS=N&AN=2007190583 >. Acesso em: (Kim, Won, Hur, Lee, Lee) Department of Psychiatry, Korea University, Ansan Hospital, Ansan, South Korea.

KIRALY, D. D. et al. Changes in inflammatory biomarkers in patients with treatment-resistant depression before and after therapeutic ketamine infusion. **Biological Psychiatry,** v. 1), p. 132S, May 2016. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed14&AN=72256475 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:emed14&rft.genre=article&rft_id=info:doi/10.1016%2Fj.biopsych.2016.03.1748&rft_id=info:pmid/&rft.issn=0006-3223&rft.volume=79&rft.issue=9+SUPPL.+1&rft.spage=132S&rft.pages=132S&rft.date=2016&rft.jtitle=Biological+Psychiatry&rft.atitle=Changes+in+inflammatory+biomarkers+in+patients+with+treatment-resistant+depression+before+and+after+therapeutic+ketamin. > >.

KLOIBER, S. et al. Hormones, cytokines, and adipokines in the course of depression-potential biomarkers for treatment response? , p. 187, 2012. ISSN 1461-1457. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=71592606 >. Acesso em: (Kloiber, Hennings, Uhr, Lucae) Max-Planck-Institute, Munich, Germany.

KOO, J. W.; DUMAN, R. S. Evidence for IL-1 receptor blockade as a therapeutic strategy for the treatment of depression. **Curr Opin Investig Drugs,** v. 10, n. 7, p. 664-71, Jul 2009. ISSN 1472-4472. Disponível em: < http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3673287/pdf/nihms-479149.pdf >.

KOO, J. W. et al. Nuclear factor-kappaB is a critical mediator of stress-impaired neurogenesis and depressive behavior. **Proc Natl Acad Sci U S A,** v. 107, n. 6, p. 2669-74, Feb 9 2010. ISSN 0027-8424. Disponível em: < http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2823860/pdf/pnas.200910658.pdf >.

KRAUS, T. et al. Body weight, the tumor necrosis factor system, and leptin production during treatment with mirtazapine or venlafaxine. **Pharmacopsychiatry,** v. 35, n. 6, p. 220-5, Nov 2002. ISSN 0176-3679 (Print) 0176-3679. Disponível em: < https://www.thieme-connect.com/DOI/DOI?10.1055/s-2002-36390 >.

KRISHNAN, V.; NESTLER, E. J. Linking Molecules to Mood: New Insight Into the Biology of Depression. **The American journal of psychiatry,** v. 167, n. 11, p. 1305-1320, 09/15 2010. ISSN 0002-953X 1535-7228. Disponível em: < http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3031089/ >.

KROGH, J.; NORDENTOFT, M. Interleukin 6, crp, and tnf-in patients with depression and the effect of a randomized exercise intervention. p. 386-387, 2011. ISSN 1021-7401. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70554237 >. Acesso em: (Krogh, Nordentoft) Psychiatric Center Copenhagen, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark.

KRONFOL, Z.; D.G., R. Cytokines and the brain: implications for clinical psychiatry. **Am J Psychiatr,** v. 157, p. 683-694, 2000.

KUBERA, M. et al. Stimulatory effect of antidepressants on the production of IL-6. **Int Immunopharmacol,** v. 4, n. 2, p. 185-92, Feb 2004. ISSN 1567-5769 (Print) 1567-5769.

KUBERA, M. et al. Effects of serotonin and serotonergic agonists and antagonists on the production of interferon-gamma and interleukin-10. United States, p. 89-98, 2000. ISSN 0893-133X. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed5&NEWS=N&AN=2000219413 >. Acesso em: (Kubera) Clin. Res. Center for Mental Health, Anwerp, Belgium.

KUBERA, M. et al. Plasma levels of interleukin-6, interleukin-10, and interleukin-1 receptor antagonist in depression: comparison between the acute state and after remission. **Pol J Pharmacol,** v. 52, n. 3, p. 237-41, May-Jun 2000. ISSN 1230-6002 (Print) 1230-6002.

KUBERA, M. et al. Anti-Inflammatory effects of antidepressants through suppression of the interferon-gamma/interleukin-10 production ratio. **J Clin Psychopharmacol,** v. 21, n. 2, p. 199-206, Apr 2001. ISSN 0271-0749 (Print) 0271-0749. Disponível em: < http://graphics.tx.ovid.com/ovftpdfs/FPDDNCMCBGOCAA00/fs036/ovft/live/gv019/00004714/00004714-200104000-00012.pdf >.

KUBERA, M. et al. Effects of serotonin and serotonergic agonists and antagonists on the production of tumor necrosis factor alpha and interleukin-6. **Psychiatry Res,** v. 134, n. 3, p. 251-8, Apr 30 2005. ISSN 0165-1781 (Print) 0165-1781.

KUSUNOKI, K. et al. Serum levels of dihydroneopterin and soluble cytokine receptors in major depression. Germany, p. 24-26, 1999. ISSN 0933-4807. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed4&NEWS=N&AN=1999206483 >. Acesso em: (Kusunoki, Ozaki, Sato, Hirano, Narita) Department of Psychiatry, Fujita Health University, School of Medicine, Toyoake, Aichi 470-1192, Japan.

LAI, J. S. et al. Inflammation mediates the association between fatty acid intake and depression in older men and women. **Nutrition Research,** v. 36, n. 3, p. 234-245, March 01 2016. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed13&AN=20160170190 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:emed13&rft.genre=article&rft_id=info:doi/10.1016%2Fj.nutres.2015.11.017&rft_id=info:pmid/&rft.issn=0271-5317&rft.volume=36&rft.issue=3&rft.spage=234&rft.pages=234-245&rft.date=2016&rft.jtitle=Nutrition+Research&rft.atitle=Inflammation+mediates+the+association+between+fatty+acid+intake+and+depression+in+older+men+and+women&rft.aulast=Lai%3C1198. > http://ac.els-cdn.com/S0271531715002973/1-s2.0-S0271531715002973-main.pdf?_tid=2fdf250c-27f6-11e6-aa61-00000aab0f02&acdnat=1464785080_7dfd11dbb66bca3655d25c4700e454af >.

LAM, R. W. et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 1. Disease Burden and Principles of Care. **Can J Psychiatry,** v. 61, n. 9, p. 510-23, Sep 2016. ISSN 0706-7437.

LAMERS, F. et al. Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. **Molecular Psychiatry,** v. 18, n. 6, p. 692-699, Jun 2013. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc10&AN=2013-20409-012 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc10&rft.genre=article&rft_id=info:doi/&rft_id=info:pmid/&rft.issn=1359-4184&rft.volume=18&rft.issue=6&rft.spage=692&rft.pages=692-699&rft.date=2013&rft.jtitle=Molecular+Psychiatry&rft.atitle=Evidence+for+a+differential+role+of+HPA-axis+function%2C+inflammation+and+metabolic+syndrome+in+melancholic+versus+atypical+depression.&rft.aulast=Lamers >.

LANDMANN, R. et al. Unaltered monocyte function in patients with major depression before and after three months of antidepressive therapy. **Biol Psychiatry,** v. 41, n. 6, p. 675-81, Mar 15 1997. ISSN 0006-3223 (Print) 0006-3223.

LANQUILLON, S. et al. Cytokine production and treatment response in major depressive disorder. **Neuropsychopharmacology,** v. 22, n. 4, p. 370-379, Apr 2000. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc3&AN=2000-08048-004 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc3&rft.genre=article&rft_id=info:doi/10.1016%2FS0893-133X%2899%2900134-7&rft_id=info:pmid/&rft.issn=0893-133X&rft.volume=22&rft.issue=4&rft.spage=370&rft.pages=370-379&rft.date=2000&rft.jtitle=Neuropsychopharmacology&rft.atitle=Cytokine+production+and+treatment+response+in+major+depressive+disorder.&rft.aulast=Lanquillon http://www.nature.com/npp/journal/v22/n4/pdf/1395458a.pdf >.

LAU, J.; IOANNIDIS, J. P.; SCHMIDT, C. H. Quantitative synthesis in systematic reviews. **Annals of Internal Medicine,** v. 127, n. 9, p. 820-826, 1997.

LAZARY, J. et al. Major depressive disorder is influenced by a genetic interaction of VEGF and TNF alpha. 2012. ISSN 0924-9338. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70794141 >. Acesso em: (Lazary, Dome, Gonda, Sarosi, Faludi) Department of Theoretical and Mental Health, Budapest, Hungary.

LEE, H. et al. Physical health and incident late-life depression: Modification by cytokine genes. p. S85, 2013. ISSN 1041-6102. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=71303484 >. Acesso em: (Lee) Gwangju Samsung Hospital, South Korea.

LEHTIMAKI, K. et al. Increase in plasma proinflammatory cytokines after electroconvulsive therapy in patients with depressive disorder. **J ect,** v. 24, n. 1, p. 88-91, Mar 2008. ISSN 1095-0680 (Print)
1095-0680.

LEHTO, S. M. et al. Serum chemokine levels in major depressive disorder. **Psychoneuroendocrinology,** v. 35, n. 2, p. 226-32, Feb 2010. ISSN 0306-4530.

LEHTO, S. M. et al. Serum anti-inflammatory markers in general population subjects with elevated depressive symptoms. **Neurosci Lett,** v. 484, n. 3, p. 201-5, Nov 5 2010. ISSN 0304-3940.

LEO, R. et al. Association between enhanced soluble CD40 ligand and proinflammatory and prothrombotic states in major depressive disorder: Pilot observations on the effects of selective serotonin reuptake inhibitor therapy. **Journal of Clinical Psychiatry,** v. 67, n. 11, p. 1760-1766, Nov 2006. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc5&AN=2007-07420-014 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc5&rft.genre=article&rft_id=info:doi/10.4088%2FJCP.v67n1114&rft_id=info:pmid/&rft.issn=0160-6689&rft.volume=67&rft.issue=11&rft.spage=1760&rft.pages=1760-1766&rft.date=2006&rft.jtitle=Journal+of+Clinical+Psychiatry&rft.atitle=Association+between+enhanced+soluble+CD40+ligand+and+proinflammatory+and+prothrombotic+states+in+major+depressive+disorder%3A >.

LEONARD, B. Antinflammatory mechanisms of antidepressants. p. 13, 2012. ISSN 0924-2708. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70760122 >. Acesso em: (Leonard) Pharmacology Department, National University of Ireland, Galway, Ireland.

LEONARD, B.; MAES, M. Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concomitants play a role in the pathophysiology of unipolar depression. United Kingdom, p. 764-785, 2012. ISSN 0149-7634. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=2012049709 >. Acesso em: (Leonard) Pharmacology Department, National University of Ireland, Galway, Ireland.

LEONARD, B.; MAES, M. Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concomitants play a role in the pathophysiology of unipolar depression. **Neurosci Biobehav Rev,** v. 36, p. 764 - 785, 2012.

LEONARD, B. E. Are antidepressants anti-inflammatory drugs? A critical look at the evidence. p. 69, 2012. ISSN 0941-9500. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70703453 >. Acesso em: (Leonard) Pharmacology Department, National University of Ireland, Galway, Ireland.

_____. Impact of inflammation on neurotransmitter changes in major depression: an insight into the action of antidepressants. **Prog Neuropsychopharmacol Biol Psychiatry,** v. 48, p. 261-7, Jan 3 2014. ISSN 0278-5846.

LEVANDOVSKI, R. et al. The effect of sunlight exposure on interleukin-6 levels in depressive and non-depressive subjects. **BMC Psychiatry,** v. 13, p. 75, 2013. ISSN 1471-244x. Disponível em: < http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3599872/pdf/1471-244X-13-75.pdf >.

LI, Z. et al. Venlafaxine inhibits the upregulation of plasma tumor necrosis factor-alpha (TNF-alpha) in the Chinese patients with major depressive disorder: a prospective longitudinal study. **Psychoneuroendocrinology,** v. 38, n. 1, p. 107-14, Jan 2013. ISSN 0306-4530.

LIATIS, A. I. Norepinephrine regulation of inflammatory responses during monocyte activation and differentiation and during acute stress in patients with major depression. **Dissertation Abstracts International: Section B: The Sciences and Engineering,** v. 73, n. 7-B(E), p. No Pagination Specified, 2013. Disponível em: <

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc10&AN=2013-99020-150
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc10&rft.genre=article&rft_id=info:doi/&rft_id=info:pmid/&rft.issn=0419-4217&rft.volume=73&rft.issue=7-B%28E%29&rft.spage=No&rft.pages=No+Pagination+Specified&rft.date=2013&rft.jtitle=Dissertation+Abstracts+International%3A+Section+B%3A+The+Sciences+and+Engineering&rft.atitle=Norepinephrine+regulation+of+inflammatory+responses+during+monocyte+activat >.

LIBERATI, A. et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. **Bmj,** v. 339, p. b2700, Jul 21 2009. ISSN 0959-535x.

LICHTBLAU, N. et al. Cytokines as biomarkers in depressive disorder: Current standing and prospects. United Kingdom, p. 592-603, 2013. ISSN 0954-0261. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=2013685315 >. Acesso em: (Lichtblau, Schmidt, Schumann, Himmerich) Department of Psychiatry and Psychotherapy, University Hospital Leipzig, Semmelweisstra s e 10, 04103 Leipzig, Germany.

LICINIO, J.; WONG, M. L. The role of inflammatory mediators in the biology of major depression: Central nervous system cytokines modulate the biological substrate of depressive symptoms, regulate stress-responsive systems, and contribute to neurotoxicity and neuroprotection. United Kingdom, p. 317-327, 1999. ISSN 1359-4184. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed4&NEWS=N&AN=1999326985 >. Acesso em: (Licinio, Wong) Clinical Neuroendocrinology Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892, United States.

LINDQVIST, D. et al. Oxidative stress, inflammation and treatment response in major depression. **Psychoneuroendocrinology,** v. 76, p. 197-205, Feb 2017. ISSN 0306-4530.

LIU, Y. et al. [Impact on serum 5-HT and TH1/TH2 in patients of depressive disorder at acute stage treated with acupuncture and western medication]. **Zhongguo Zhen Jiu,** v. 35, n. 6, p. 539-43, Jun 2015. ISSN 0255-2930 (Print)
0255-2930.

LIU, Y. et al. [Effect of acupuncture on early onset of SSRIs treating depressive disorder and related indicators of neuroimmunology]. **Zhongguo Zhong Xi Yi Jie He Za Zhi,** v. 35, n. 3, p. 299-303, Mar 2015. ISSN 1003-5370 (Print)
1003-5370.

LOTRICH, F. Depression symptoms, low-grade inflammatory activity, and new targets for clinical intervention. **Biological Psychiatry,** v. 70, n. 2, p. 111-112, Jul 2011. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc8&AN=2011-13389-009
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc8&rft.genre=article&rft_id=info:doi/10.1016%2Fj.biopsych.2011.05.022&rft_id=info:pmid/&rft.issn=0006-3223&rft.volume=70&rft.issue=2&rft.spage=111&rft.pages=111-112&rft.date=2011&rft.jtitle=Biological+Psychiatry&rft.atitle=Depression+symptoms%2C+low-grade+inflammatory+activity%2C+and+new+targets+for+clinical+intervention.&rft.aulast=Lotrich
http://www.biologicalpsychiatryjournal.com/article/S0006-3223(11)00551-8/abstract >.

LUCAS, M. et al. Inflammatory dietary pattern and risk of depression among women. **Brain Behav Immun,** v. 36, p. 46-53, Feb 2014. ISSN 0889-1591. Disponível em: < http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3947176/pdf/nihms530243.pdf >.

LUTGENDORF, S. K. et al. Life stress, mood disturbance, and elevated interleukin-6 in healthy older women. United States, p. M434-M439, 1999. ISSN 1079-5006. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed4&NEWS=N&AN=1999364571 >. Acesso em: (Lutgendorf) Department of Psychology, University of Iowa, E11 Seashore Hall, Iowa City, IA 52242, United States.

MACIUKIEWICZ, M. et al. Genetic variation in IL-1beta, IL-2, IL-6, TSPO and BDNF and response to duloxetine or placebo treatment in major depressive disorder. **Pharmacogenomics,** v. 16, n. 17, p. 1919-1929, November 2015. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed13&AN=2015540422 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:emed13&rft.genre=article&rft_id=info:doi/10.2217%2Fpgs.15.136&rft_id=info:pmid/&rft.issn=1462-2416&rft.volume=16&rft.issue=17&rft.spage=1919&rft.pages=1919-1929&rft.date=2015&rft.jtitle=Pharmacogenomics&rft.atitle=Genetic+variation+in+IL-1beta%2C+IL-2%2C+IL-6%2C+TSPO+and+BDNF+and+response+to+duloxetine+or+placebo+treatment+in+major+depressive+disorder&.> >.

MACKAY, G. M. et al. Kynurenine metabolites and inflammation markers in depressed patients treated with fluoxetine or counselling. Australia, p. 425-435, 2009. ISSN 0305-1870. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=2009432622 >. Acesso em: (MacKay, Forrest, Stone) Institute of Biomedical and Life Sciences, University of Glasgow, Glasgow, United Kingdom.

MAES, M. Increased serum interleukin-1-receptor-antagonist concentrations in major depression. Netherlands, p. 29-36, 1995. ISSN 0165-0327. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed3&NEWS=N&AN=1996014911 >. Acesso em: (Maes) Laboratory of Biological Psychiatry, CWRU, Cleveland, OH, United States.

_____. Interleukin-1beta and the etiology of depression. **Acta Psychiatr Scand,** v. 103, n. 3, p. 161-2, Mar 2001. ISSN 0001-690X (Print)
0001-690x. Disponível em: < http://onlinelibrary.wiley.com/store/10.1034/j.1600-0447.2001.00005.x/asset/j.1600-0447.2001.00005.x.pdf?v=1&t=ieak96d2&s=ed2feea3c22671edcd6050b7c00019cc78461e71 >.

MAES, M. et al. Targeting classical IL-6 signalling or IL-6 trans-signalling in depression? **Expert Opin Ther Targets,** v. 18, n. 5, p. 495-512, May 2014. ISSN 1472-8222.

MAES, M. et al. Depression and sickness behavior are Janus-faced responses to shared inflammatory pathways. **BMC Medicine,** v. 10, n. 1, p. 66, 2012. ISSN 1741-7015. Disponível em: < http://www.biomedcentral.com/1741-7015/10/66 >.

MAES, M. et al. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. **Cytokine,** v. 9, n. 11, p. 853-8, Nov 1997. ISSN 1043-4666 (Print)
1043-4666.

MAES, M. et al. Plasma soluble interleukin-2-receptor in depression: Relationships to plasma neopterin and serum IL-2 concentrations and HPA-axis activity. France, p. 397-403, 1995. ISSN 0924-9338. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed3&NEWS=N&AN=1996002503 >. Acesso em: (Maes, Bosmans, Scharpe, D'Hondt, Desnyder) University Department of Psychiatry, AZ Stuivenberg, 267 Lange Beeldekensstraat, 2060 Antwerp, Belgium.

MAES, M. et al. Immune disturbances during major depression: upregulated expression of interleukin-2 receptors. **Neuropsychobiology,** v. 24, n. 3, p. 115-20, 1990. ISSN 0302-282X (Print)
0302-282x.

MAES, M. et al. Depression-related disturbances in mitogen-induced lymphocyte responses and interleukin-1 beta and soluble interleukin-2 receptor production. **Acta Psychiatr Scand,** v. 84, n. 4, p. 379-86, Oct 1991. ISSN 0001-690X (Print)
0001-690x. Disponível em: < http://onlinelibrary.wiley.com/doi/10.1111/j.1600-0447.1991.tb03163.x/abstract?systemMessage=Wiley+Online+Library+and+related+systems+will+have+3+hours+of+downtime+on+Saturday+12th+September+2015+from+10%3A00-13%3A00+BST+%2F+05%3A00-08%3A00+EDT+%2F+17%3A00-20%3A00+SGT+for+essential+maintenance.++Apologies+for+the+inconvenience. http://onlinelibrary.wiley.com/doi/10.1111/j.1600-0447.1991.tb03163.x/abstract >.

MAES, M. et al. Alterations in plasma dipeptidyl peptidase IV enzyme activity in depression and schizophrenia:

Effects of antidepressants and antipsychotic drugs. Denmark, p. 1-8, 1996. ISSN 0001-690X. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed4&NEWS=N&AN=1996051369 >. Acesso em: (Maes, Ranjan, Meltzer) Department of Psychiatry, Case Western Reserve University, Cleveland, OH, United States.

MAES, M. et al. Lower serum zinc in major depression in relation to changes in serum acute phase proteins. **J Affect Disord,** v. 56, n. 2-3, p. 189-94, Dec 1999. ISSN 0165-0327 (Print)
0165-0327. Disponível em: < http://ac.els-cdn.com/S0165032799000117/1-s2.0-S0165032799000117-main.pdf?_tid=e2fc9ac6-563b-11e5-aa32-00000aab0f02&acdnat=1441725271_2b96873458ae529af7860ca0a4306972 >.

MAES, M. et al. The new '5-HT' hypothesis of depression: Cell-mediated immune activation induces indoleamine 2,3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression. **Progress in Neuro-Psychopharmacology and Biological Psychiatry,** v. 35, n. 3, p. 702-721, 4/29/ 2011. ISSN 0278-5846. Disponível em: < http://www.sciencedirect.com/science/article/pii/S0278584610005117 >.

MAES, M. et al. Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. **J Affect Disord,** v. 34, n. 4, p. 301-9, Aug 18 1995. ISSN 0165-0327 (Print)
0165-0327. Disponível em: < http://www.jad-journal.com/article/0165-0327(95)00028-L/abstract >.

MAES, M. et al. Activation of cell-mediated immunity in depression: association with inflammation, melancholia, clinical staging and the fatigue and somatic symptom cluster of depression. **Prog Neuropsychopharmacol Biol Psychiatry,** v. 36, n. 1, p. 169-75, Jan 10 2012. ISSN 0278-5846.

MAES, M. et al. Disturbances in acute phase plasma proteins during melancholia: Additional evidence for the presence of an inflammatory process during that illness. United Kingdom, p. 501-515, 1992. ISSN 0278-5846. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed2&NEWS=N&AN=1992182306 >. Acesso em: (Maes, Scharpe, Bosmans, Vandewoude, Suy, Uyttenbroeck, Cooreman, Vandervorst, Raus) Dept. of Biological Psychiatry, Case Western Reserve University, 2040, Abington Road, Cleveland, OH, Belgium.

MAES, M. et al. Relationships between interleukin-6 activity, acute phase proteins, and function of the hypothalamic-pituitary-adrenal axis in severe depression. **Psychiatry Res,** v. 49, n. 1, p. 11-27, Oct 1993. ISSN 0165-1781 (Print)
0165-1781. Disponível em: < http://www.psy-journal.com/article/0165-1781(93)90027-E/abstract >.

MAES, M.; SONG, C.; YIRMIYA, R. Targeting IL-1 in depression. **Expert Opin Ther Targets,** v. 16, n. 11, p. 1097-112, Nov 2012. ISSN 1472-8222.

MAES, M. et al. Significantly increased expression of T-cell activation markers (interleukin-2 and HLA-DR) in depression: further evidence for an inflammatory process during that illness. **Prog Neuropsychopharmacol Biol Psychiatry,** v. 17, n. 2, p. 241-55, Mar 1993. ISSN 0278-5846 (Print)
0278-5846.

MAES, M. et al. Increased serum interleukin-1-receptor-antagonist concentrations in major depression. **J Affect Disord,** v. 36, n. 1-2, p. 29-36, Dec 24 1995. ISSN 0165-0327 (Print)
0165-0327.

MAGALHAES, P. V. S. et al. Peripheral eotaxin-1 (CCL11) levels and mood disorder diagnosis in a population-based sample of young adults. p. 68, ISSN 1398-5647. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=71096449 >. Acesso em: (Magalhaes) National Institute for Translational Medicine, Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil.

MAIER, S. F.; WATKINS, L. R. Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. **Psychol Rev,** v. 105, n. 1, p. 83-107, Jan 1998. ISSN 0033-295X (Print)
0033-295x.

MANOHARAN, A. et al. Evaluation of interleukin-6 and serotonin as biomarkers to predict response to fluoxetine. **Human Psychopharmacology: Clinical and Experimental Mar**, n. Pagination, p. No Pagination Specified, Mar 2016. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc12&AN=2016-15455-001
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc12&rft.genre=article&rft_id=info:doi/10.1002%2Fhup.2525&rft_id=info:pmid/&rft.issn=0885-6222&rft.volume=31&rft.issue=3&rft.spage=No&rft.pages=No+Pagination+Specified&rft.date=2016&rft.jtitle=Human+Psychopharmacology%3A+Clinical+and+Experimental&rft.atitle=Evaluation+of+interleukin-6+and+serotonin+as+biomarkers+to+predict+response+to+fluoxetine.&rft >.

MARQUES-DEAK, A. et al. Cytokine profiles in women with different subtypes of major depressive disorder. **Journal of Psychiatric Research,** v. 41, n. 1-2, p. 152-159, Jan-Feb 2007. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc5&AN=2006-21757-019
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc5&rft.genre=article&rft_id=info:doi/10.1016%2Fj.jpsychires.2005.11.003&rft_id=info:pmid/&rft.issn=0022-3956&rft.volume=41&rft.issue=1-2&rft.spage=152&rft.pages=152-159&rft.date=2007&rft.jtitle=Journal+of+Psychiatric+Research&rft.atitle=Cytokine+profiles+in+women+with+different+subtypes+of+major+depressive+disorder.&rft.aulast=Marques-Deak >.

MARTINEZ, J. M. et al. Proinflammatory and "resiliency" proteins in the CSF of patients with major depression. **Depress Anxiety,** v. 29, n. 1, p. 32-8, Jan 2012. ISSN 1091-4269.

MATSUSHIMA, J. et al. Association of inflammatory biomarkers with depressive symptoms and cognitive decline in a community-dwelling healthy older sample: A 3-year follow-up study. Netherlands, p. 9-14, 2015. ISSN 0165-0327. Disponível em: < http://www.elsevier.com/locate/jad
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=2014918287 >. Acesso em: (Matsushima, Kawashima, Nabeta, Imamura, Watanabe, Mizoguchi, Monji) Department of Psychiatry, Faculty of Medicine, Saga University, 5-1-1 Nabeshima, Saga 849-8501, Japan.

MCDADE, T. W. et al. Depressive symptoms are not associated with inflammation in younger and older adults in the Philippines. United Kingdom, p. 18-23, 2013. Disponível em: < http://www.oxfordjournals.org/our_journals/emph/
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=2014515116 >. Acesso em: (McDade, Kuzawa) Department of Anthropology, Northwestern University, Evanston, IL 60208, United States.

MERENDINO, R. A. et al. Involvement of fractalkine and macrophage inflammatory protein-1 alpha in moderate-severe depression. **Mediators Inflamm,** v. 13, n. 3, p. 205-7, Jun 2004. ISSN 0962-9351 (Print)
0962-9351. Disponível em: < http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1781561/pdf/15223613.pdf >.

MESQUITA, A. R. et al. IL-10 modulates depressive-like behavior. **J Psychiatr Res,** v. 43, n. 2, p. 89-97, Dec 2008. ISSN 0022-3956 (Print)
0022-3956.

MIKOVA, O. et al. Increased serum tumor necrosis factor alpha concentrations in major depression and multiple sclerosis. **Eur Neuropsychopharmacol,** v. 11, n. 3, p. 203-8, Jun 2001. ISSN 0924-977X (Print)
0924-977x.

MILANESCHI, Y. et al. Interleukin-1 receptor antagonist and incident depressive symptoms over 6 years in older persons: the InCHIANTI study. **Biol Psychiatry,** v. 65, n. 11, p. 973-8, Jun 1 2009. ISSN 0006-3223. Disponível em: < http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2682634/pdf/nihms93738.pdf >.

MILLER, A. H.; RAISON, C. L. The role of inflammation in depression: from evolutionary imperative to modern treatment target. **Nat Rev Immunol,** v. 16, n. 1, p. 22-34, 01//print 2016. ISSN 1474-1733. Disponível em: < http://dx.doi.org/10.1038/nri.2015.5 >.

MILLER, G. E.; COHEN, S.; HERBERT, T. B. Pathways linking major depression and immunity in ambulatory

female patients. **Psychosom Med,** v. 61, n. 6, p. 850-60, Nov-Dec 1999. ISSN 0033-3174 (Print)
0033-3174. Disponível em: < http://graphics.tx.ovid.com/ovftpdfs/FPDDNCFBIACABO00/fs046/ovft/live/gv023/00006842/00006842-199911000-00021.pdf >.

MILLER, G. E.; COLE, S. W. Clustering of depression and inflammation in adolescents previously exposed to childhood adversity. **Biol Psychiatry,** v. 72, n. 1, p. 34-40, Jul 1 2012. ISSN 0006-3223. Disponível em: < http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3493164/pdf/nihms416336.pdf >.

MILLER, G. E. et al. Cynical hostility, depressive symptoms, and the expression of inflammatory risk markers for coronary heart disease. **J Behav Med,** v. 26, n. 6, p. 501-15, Dec 2003a. ISSN 0160-7715 (Print)
0160-7715.

_____. Pathways linking depression, adiposity, and inflammatory markers in healthy young adults. **Brain Behav Immun,** v. 17, n. 4, p. 276-85, Aug 2003b. ISSN 0889-1591 (Print)
0889-1591.

MILLER, G. E. et al. Clinical depression and regulation of the inflammatory response during acute stress. **Psychosom Med,** v. 67, n. 5, p. 679-87, Sep-Oct 2005. ISSN 0033-3174. Disponível em: < http://graphics.tx.ovid.com/ovftpdfs/FPDDNCMCBGOCAA00/fs047/ovft/live/gv031/00006842/00006842-200509000-00001.pdf >.

MILLER, G. E. et al. Clinical depression and inflammatory risk markers for coronary heart disease. **Am J Cardiol,** v. 90, n. 12, p. 1279-83, Dec 15 2002. ISSN 0002-9149 (Print)
0002-9149.

MILLS, C. D. Anatomy of a discovery: m1 and m2 macrophages. **Front Immunol,** v. 6, p. 212, 2015. ISSN 1664-3224.

MISCHOULON, D. Depression, inflammation, and omega-3 fatty acids. **Neuropsychopharmacology,** v. 40, p. S46, December 2015. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed13&AN=72125918 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:emed13&rft.genre=article&rft_id=info:doi/10.1038%2Fnpp.2015.324&rft_id=info:pmid/&rft.issn=0893-133X&rft.volume=40&rft.issue=&rft.spage=S46&rft.pages=S46&rft.date=2015&rft.jtitle=Neuropsychopharmacology&rft.atitle=Depression%2C+inflammation%2C+and+omega-3+fatty+acids&rft.aulast=Mischoulon%3C1076. > >.

MISHRA, K. K. et al. Serum cytokine levels in drug naive first episode depressive patients in comparison to healthy controls and changes following treatment with antidepressants. p. S3-S4, 2015. ISSN 0019-5545. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=71768858 >. Acesso em: (Mishra, Pawar, Ryalli, Alhuwalia, Rathod) Department of Psychiatry, MGIMS, Sevagram, India.

MISHRA, K. S. K.; PAWAR, A. A.; RYLI, V. S. S. R. Significance of serum cytokines estimation in depressive episode. p. S35, 2013. ISSN 0019-5545. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=70991065 >. Acesso em: (Mishra, Pawar, Ryli) Military Hospital Barrackpore, Kolkata, West Bengal, India.

MITCHELL, A. M. et al. Hopelessness the "active ingredient"? Associations of hopelessness and depressive symptoms with interleukin-6. **Int J Psychiatry Med,** v. 46, n. 1, p. 109-17, 2013. ISSN 0091-2174 (Print)
0091-2174.

MOLTENI, R. et al. Antidepressant and anti-inflammatory properties in the action of agomelatine. p. S541-S542, 2013. ISSN 0893-133X. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=71278719 >. Acesso em: (Molteni, Macchi, Rossetti, Colombo, Dell'Agli, Riva, Racagni) University of Milan, Milan, Italy.

MOMENI, M. et al. Differential pattern of cytokine production by depressed medical students; evidence for

involvement of cytokine network in pathology of depression. Germany, p. 435-440, 2014. ISSN 1433-6510. Disponível em: < http://www.clin-lab-publications.com/
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=2014201614 >. Acesso em: (Momeni, Ghorban) Department of Immunology, Medical School, AJA University of Medical Sciences, Tehran, Iran, Islamic Republic of.

MOREIRA, F. P. et al. The effect of proinflammatory cytokines in Cognitive Behavioral Therapy. **Journal of Neuroimmunology,** v. 285, p. 143-146, Aug 2015. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc11&AN=2015-33606-022
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc11&rft.genre=article&rft_id=info:doi/10.1016%2Fj.jneuroim.2015.06.004&rft_id=info:pmid/&rft.issn=0165-5728&rft.volume=285&rft.issue=&rft.spage=143&rft.pages=143-146&rft.date=2015&rft.jtitle=Journal+of+Neuroimmunology&rft.atitle=The+effect+of+proinflammatory+cytokines+in+Cognitive+Behavioral+Therapy.&rft.aulast=Moreira
http://ac.els-cdn.com/S0165572815001617/1-s2.0-S0165572815001617-main.pdf?_tid=2de0deea-eb0f-11e5-a5dc-00000aab0f26&acdnat=1458088793_3c8285b26287b48b35edc09edd4401e5 >.

MULLER, N. Immunology of major depression. Switzerland, p. 123-130, 2014. ISSN 1021-7401. Disponível em: < http://www.karger.com/journals/nim/nim_jh.htm
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=2015941640 >. Acesso em: (Muller) Department of Psychiatry and Psychotherapy, Ludwig-Maximilian University of Munich, Nussbaumstrasse 7, Munich DE-80336, Germany.

MUTHURAMALINGAM, A. et al. Effect of Fluoxetine on Inflammatory Cytokines in Drug-Naive Major Depression: A Short-Term Prospective Study from South India. **Journal of Clinical Psychopharmacology,** v. 36, n. 6, p. 726-728, 2016. ISSN 0271-0749. Disponível em: < http://journals.lww.com/psychopharmacology/Fulltext/2016/12000/Effect_of_Fluoxetine_on_Inflammatory_Cytokines_in.30.aspx >.

MYINT, A. M. et al. Th1, Th2, and Th3 cytokine alterations in major depression. **J Affect Disord,** v. 88, n. 2, p. 167-73, Oct 2005. ISSN 0165-0327 (Print)
0165-0327.

MYUNG, W. et al. Serum Cytokine Levels in Major Depressive Disorder and Its Role in Antidepressant Response. **Psychiatry Investigation,** v. 13, n. 6, p. 644-651, 11/24
10/20/received
02/02/revised
03/28/accepted 2016. ISSN 1738-3684
1976-3026. Disponível em: < http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5128353/ >.

NASSAN, M. et al. A feasibility study evaluating peripheral biomarkers in depression subtypes. **Bipolar Disorders,** v. 17, p. 102, June 2015. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed13&AN=72167659
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:emed13&rft.genre=article&rft_id=info:doi/10.1111%2Fbdi.12309&rft_id=info:pmid/&rft.issn=1398-5647&rft.volume=17&rft.issue=&rft.spage=102&rft.pages=102&rft.date=2015&rft.jtitle=Bipolar+Disorders&rft.atitle=A+feasibility+study+evaluating+peripheral+biomarkers+in+depression+subtypes&rft.aulast=Nassan%3C1014.> >.

NEBBIA, G.; PARIANTE, C. M.; KERWIN, R. W. The molecular mechanisms by which the proinflammatory cytokine, interleukin-1, influences the glucocorticoid receptor: Relevance for glucocorticoid resistance and major depression. Italy, p. 10-16, 2000. ISSN 1122-2247. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed5&NEWS=N&AN=2001164601 >. Acesso em: (Nebbia, Pariante, Kerwin) Institute of Psychiatry, King's College London, 1 Windsor Walk, London SE5 8AF, United Kingdom.

NIEDZWIECKI, M. et al. Anti-inflammatory response to antidepressant vs antipsychotic drug treatment in obese

MDD patients. p. 210S, 2013. ISSN 0006-3223. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=71149101 >. Acesso em: (Niedzwiecki, Meresh, Fareed, Halaris) Psychiatry and Behavioral Neurosciences, Loyola University, Stritch School of Medicine, Maywood, IL, United States.

NINAN, P. et al. Brain-derived neurotrophic factor, interleukin-6, and salivary cortisol levels in patients with major depressive disorder treated with desvenlafaxine vs placebo. p. S97, 2012. ISSN 0893-133X. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=70948038 >. Acesso em: (Ninan, Shelton, Bao, Guico-Pabia) University of Alabama at Birmingham, Birmingham, AL, United States.

NOTO, C. et al. Major depression: An immune-inflammatory disorder. **Muller, Norbert [Ed]**, p. 147-159, 2015. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc11&AN=2015-20994-008
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc11&rft.genre=article&rft_id=info:doi/&rft_id=info:pmid/&rft.issn=2363-9563&rft.volume=&rft.issue=&rft.spage=147&rft.pages=147-159&rft.date=2015&rft.jtitle=&rft.atitle=Major+depression%3A+An+immune-inflammatory+disorder.&rft.aulast=Noto >.

NUNES, S. et al. Immune and hormonal activity in adults suffering from depression. **Brazilian Journal of Medical and Biological Research,** v. 35, n. 5, p. 581-587, May 2002. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc4&AN=2002-01700-001
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc4&rft.genre=article&rft_id=info:doi/10.1590%2FS0100-879X2002000500011&rft_id=info:pmid/&rft.issn=0100-879X&rft.volume=35&rft.issue=5&rft.spage=581&rft.pages=581-587&rft.date=2002&rft.jtitle=Brazilian+Journal+of+Medical+and+Biological+Research&rft.atitle=Immune+and+hormonal+activity+in+adults+suffering+from+depression.&rft.aulast=Nunes
http://www.scielo.br/pdf/bjmbr/v35n5/4352.pdf >.

O'DONOVAN, A. et al. Does suicidal ideation exacerbate depression-related inflammatory activity? , p. S26, 2010. ISSN 0889-1591. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=70268243 >. Acesso em: (O'Donovan) San Francisco Veteran's Affairs Medical Center, University of California, San Francisco, San Francisco, United States.

OGLODEK, E. A. et al. Comparison of chemokines (CCL-5 and SDF-1), chemokine receptors (CCR-5 and CXCR-4) and IL-6 levels in patients with different severities of depression. **Pharmacol Rep,** v. 66, n. 5, p. 920-6, Oct 2014. ISSN 1734-1140 (Print)
1734-1140.

OLAJOSSY, M. et al. The level of kynurenic acid and selected cytokines during antidepressive treatment. Poland, p. 55-61, 2014. ISSN 1896-6764. Disponível em: < http://www.termedia.pl/Journal/46/pdf-23685-10?filename=stezeniekwasu.pdf
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=2014837286 >. Acesso em: (Olajossy, Potembska, Skoczen) II Klinika Psychiatrii i Rehabilitacji Psychiatrycznej, Uniwersytet Medyczny w Lublinie, ul. Gluska 1, Lublin 20-439, Poland.

ORENES-PINERO, E. et al. Effects of Body Mass Index on the Lipid Profile and Biomarkers of Inflammation and a Fibrinolytic and Prothrombotic State. **J Atheroscler Thromb,** v. 22, n. 6, p. 610-7, 2015. ISSN 1340-3478.

ORGANIZATION, W. H. The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research. In: (Ed.), 1993.

OSES, J. P. et al. Pro-inflammatory cytokines and psychotherapy in depression: Preliminary results from a randomized clinical trial. **Biological Psychiatry,** v. 1), p. 71S, May 2016. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed14&AN=72256318
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:emed14&rft.genre=article&rft_id=info:doi/1

0.1016%2Fj.biopsych.2016.03.1748&rft_id=info:pmid/&rft.issn=0006-3223&rft.volume=79&rft.issue=9+SUPPL.+1&rft.spage=71S&rft.pages=71S&rft.date=2016&rft.jtitle=Biological+Psychiatry&rft.atitle=Pro-inflammatory+cytokines+and+psychotherapy+in+depression%3A+Preliminary+results+from+a+randomized+clinical+trial&rft.au. > >.

OVASKAINEN, Y. et al. Depressive symptomatology is associated with decreased interleukin-1 beta and increased interleukin-1 receptor antagonist levels in males. **Psychiatry Res,** v. 167, n. 1-2, p. 73-9, May 15 2009. ISSN 0165-1781 (Print)
0165-1781.

PACE, T. et al. Psychosocial stressor-induced plasma cortisol concentrations predict stressor-induced plasma IL-6 concentrations in patients with major depression and increased early life stress. p. S69, 2010. ISSN 0889-1591. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=70268391 >. Acesso em: (Pace, Mletzko, Bonsall, Vogt, Miller, Heim) Emory University, School of Medicine, Department of Psychiatry and Behavioral Sciences, Atlanta, GA 30322, United States.

PACE, T. W.; MILLER, A. H. Cytokines and glucocorticoid receptor signaling. Relevance to major depression. **Ann N Y Acad Sci,** v. 1179, p. 86-105, Oct 2009. ISSN 0077-8923.

PACE, T. W. et al. Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. **Am J Psychiatry,** v. 163, n. 9, p. 1630-3, Sep 2006. ISSN 0002-953X (Print)
0002-953x. Disponível em: < http://graphics.tx.ovid.com/ovftpdfs/FPDDNCMCBGOCAA00/fs046/ovft/live/gv023/00000465/00000465-200609000-00026.pdf >.

PALLAVI, P. A randomized, single-blind, trial of yoga therapy as an adjunct to SSRI treatment for adolescent depression patients: Variations in serum cytokine and neurotrophin levels. p. 118S, 2014. ISSN 0006-3223. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=71434193 >. Acesso em: (Pallavi) Department of Laboratory Medicine, All India Institute of Medical Sciences, New Delhi, India.

PALLAVI, P. et al. Serum cytokines and anxiety in adolescent depression patients: Gender effect. **Psychiatry Research Jun**, n. Pagination, p. No Pagination Specified, Jun 2015. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc11&AN=2015-31055-001
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc11&rft.genre=article&rft_id=info:doi/10.1016%2Fj.psychres.2015.06.036&rft_id=info:pmid/&rft.issn=0165-1781&rft.volume=&rft.issue=&rft.spage=No&rft.pages=No+Pagination+Specified&rft.date=2015&rft.jtitle=Psychiatry+Research&rft.atitle=Serum+cytokines+and+anxiety+in+adolescent+depression+patients%3A+Gender+effect.&rft.aulast=Pallavi >.

PANDEY, G. Central and peripheral inflammation biomarkers in depression and suicide. p. 296S, 2015. ISSN 0006-3223. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=71846902 >. Acesso em: (Pandey) Psychiatry, University of Illinois Chicago, Chicago, IL, United States.

PANTOVIC, M. et al. The role of age and gender in predicting serum levels of IL-6 and TNF-alpha in patients with schizophrenia and major depression. 2013. ISSN 0924-9338. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=71173086 >. Acesso em: (Pantovic, Dunjic-Kostic, Vukovic, Damjanovic, Ivkovic) Department for Affective Disorders, Clinic of Psychiatry, Clinical Center of Serbia, Belgrade, Serbia.

PARK, M. et al. Change in cytokine levels is not associated with antidepressant response to ketamine in patients with treatment resistant depression. **Biological Psychiatry,** v. 1), p. 69S-70S, May 2016. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed14&AN=72256313
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:emed14&rft.genre=article&rft_id=info:doi/1

0.1016%2Fj.biopsych.2016.03.1748&rft_id=info:pmid/&rft.issn=0006-3223&rft.volume=79&rft.issue=9+SUPPL.+1&rft.spage=69S&rft.pages=69S-70S&rft.date=2016&rft.jtitle=Biological+Psychiatry&rft.atitle=Change+in+cytokine+levels+is+not+associated+with+antidepressant+response+to+ketamine+in+patients+with+treatment+resis. > >.

PARK, Y.; BAEK, D. Erythrocyte levels of N-3 polyunsaturated fatty acids and biomarkers of inflammation and oxidative stress in patients with and without depression. p. 1150, 2013. ISSN 0250-6807. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=71179911 >. Acesso em: (Park, Baek) Department of Food and Nutrition, Hanyang University, Seoul, South Korea.

PATAS, K. et al. Association between serum brain-derived neurotrophic factor and plasma interleukin-6 in major depressive disorder with melancholic features. **Brain Behav Immun,** v. 36, p. 71-9, Feb 2014. ISSN 0889-1591.

PATEL, A. Review: the role of inflammation in depression. **Psychiatr Danub,** v. 25 Suppl 2, p. S216-23, Sep 2013. ISSN 0353-5053 (Print)
0353-5053.

PATSOPOULOS, N. A.; EVANGELOU, E.; IOANNIDIS, J. P. Heterogeneous views on heterogeneity. **Int J Epidemiol,** v. 38, n. 6, p. 1740-2, Dec 2009. ISSN 0300-5771.

PAVON, L. et al. Chronic intake of selective serotonin reuptake inhibitors leads to variations in the expression of 5-HTT, IFN-gamma, and IL- 2 genetic message in major depression patients. p. S235, 2011. ISSN 0889-1591. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70531630 >. Acesso em: (Pavon, Hernandez, Becerril) Laboratorio de Psicoinmunologia, Instituto Nacional de Psiquiatria. Mexico, Clz. Mexico-Xochilico 101, Tlalpan, Mexico DF 14370, Mexico.

PAVON, L. et al. Effect of combined treatment of selective serotonin reuptake inhibitors plus immunomodulator on circulating cytokines levels in patients with major depressive disorder along 52 weeks of follow up (P4521). 2013. ISSN 0022-1767. Disponível em: < http://www.jimmunol.org/cgi/content/meeting_abstract/190/1_MeetingAbstracts/178.15?sid=adeed275-fcf6-479e-be38-3dadf3d3d997
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=71202411 >. Acesso em: (Pavon, Hernandez, Mendieta) Laboratorio de Psicoinmunologia, Instituto Nacional de Psiquiatria. Mexico, Mexico, Mexico.

PAVON ROMERO, L. et al. Cortisol and cytokines changes in patients with major depression during pharmacological treatment. p. 396, 2011. ISSN 1021-7401. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70554265 >. Acesso em: (Pavon Romero, Hernandez, Becerril Villanueva) Department of Psychoimmunology, National Institute of Psychiatry Ramon de la Fuente, Mexico.

PENNINX, B. W. et al. Depression, antidepressant treatment and inflammation. p. A120, 2011. ISSN 0033-3174. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70399645 >. Acesso em: (Penninx, Vogelzangs) Psychiatry, VU University Medical Center, Amsterdam NH, Netherlands.

PENNINX, B. W. et al. Inflammatory markers and depressed mood in older persons: results from the Health, Aging and Body Composition study. **Biol Psychiatry,** v. 54, n. 5, p. 566-72, Sep 1 2003. ISSN 0006-3223 (Print)
0006-3223.

PILETZ, J. E. et al. Pro-inflammatory biomakers in depression: Treatment with venlafaxine. Norway, p. 313-323, 2009. ISSN 1562-2975. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=2009603262 >. Acesso em: (Piletz, Halaris, Zhu) Department of Psychiatry, Stritch School of Medicine, Loyola University Chicago, 2160 South First Ave, Maywood, IL, United States.

PODLIPNY, J. et al. Lower serum levels of interleukin-6 in a population sample with symptoms of depression than in a population sample without symptoms of depression. **Physiol Res,** v. 59, n. 1, p. 121-6, 2010. ISSN 0862-8408 (Print)

0862-8408.

POLESHUCK, E. L. et al. Depressive symptoms, pain, chronic medical morbidity, and interleukin-6 among primary care patients. **Pain Med,** v. 14, n. 5, p. 686-91, May 2013. ISSN 1526-2375. Disponível em: < http://onlinelibrary.wiley.com/store/10.1111/pme.12089/asset/pme12089.pdf?v=1&t=ieaj1d7s&s=7c429d2cd51432 6ec45d0836230c65f9ec08182f >.

POSTAL, M.; APPENZELLER, S. The importance of cytokines and autoantibodies in depression. **Autoimmun Rev**, Sep 18 2014. ISSN 1568-9972.

_____. The importance of cytokines and autoantibodies in depression. **Autoimmun Rev,** v. 14, n. 1, p. 30-5, Jan 2015. ISSN 1568-9972.

POSTOLACHE, T. T. et al. Inflammation, mood disorders and suicide. p. 31, 2009. ISSN 0933-4807. Disponível em: < http://www.pteridines.sk/bild/2009/A/20090101_abstracts.pdf http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=70007947 >.

PRATHER, A. A.; VOGELZANGS, N.; PENNINX, B. W. Sleep duration, insomnia, and markers of systemic inflammation: Results from the Netherlands study of depression and anxiety (NESDA). **Journal of Psychiatric Research,** v. 60, p. 95-102, Jan 2015. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc11&AN=2014-43446-001 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc11&rft.genre=article&rft_id=info:doi/10.1016%2Fj.jpsychires.2014.09.018&rft_id=info:pmid/&rft.issn=0022-3956&rft.volume=60&rft.issue=1&rft.spage=95&rft.pages=95-102&rft.date=2015&rft.jtitle=Journal+of+Psychiatric+Research&rft.atitle=Sleep+duration%2C+insomnia%2C+and+markers+of+systemic+inflammation%3A+Results+from+the+Netherlands+study+of+depressio http://www.journalofpsychiatricresearch.com/article/S0022-3956(14)00285-4/abstract >.

PROSSIN, A. et al. Experimental sadness induces plasma il-18 elevation and co-varying modulation of limbic endogenous opioid function in major depression. p. S194-S195, 2012. ISSN 0893-133X. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=70948215 >. Acesso em: (Prossin, Koch, Zalcman, Campbell, Zubieta) University of Michigan Medical School, Ann Arbor, MI, United States.

PROSSIN, R. et al. Pro-inflammatory cytokines correlate with baseline and sadness induced central Mu-opioid neurotransmission in unmedicated major depression. p. S37-S38, 2010. ISSN 0889-1591. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=70268284 >. Acesso em: (Prossin, Zubieta) Comprehensive Depression Center, Department of Psychiatry, University of Michigan Medical School, 4250 Plymouth Rd, Ann Arbor, MI 48105, United States.

PUCAK, M. L.; KAPLIN, A. I. Unkind cytokines: current evidence for the potential role of cytokines in immune-mediated depression. **Int Rev Psychiatry,** v. 17, n. 6, p. 477-83, Dec 2005. ISSN 0954-0261 (Print) 0954-0261.

QI, F. S. et al. Relationship of sleep disorder with plasma interleukin-2 and soluble interleukine-2 receptor in patients with depression. China, p. 244-245, 2005. ISSN 1671-5926. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed7&NEWS=N&AN=2005266011 >. Acesso em: (Qi, Jia, Li) Department of Psychiatry, Hospital of Xinxiang Medical College, Xinxiang 453002 Henan Province, China.

QUAK, J. et al. Does tryptophan degradation along the kynurenine pathway mediate the association between pro-inflammatory immune activity and depressive symptoms? , United Kingdom, p. 202-210, 2014. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=24845191 >. Acesso em: (Quak) Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.

QUINONES, M. P. et al. Role of the immunomodulatory cytokines interferon alpha (IFNalpha)-2 and interleukin (IL)-10. In the pathogenesis of anxiety and depression symptoms in adolescents: Effect of familial risk and stress. p.

215S-216S, 2012. ISSN 0006-3223. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70718634 >. Acesso em: (Quinones, Williamson, Livi, Olvera, Walss-Bass) Psychiatry, UTHSCSA, San Antonio, TX, United States.

RAGHUVANSHI, V. S. et al. A randomized controlled study to evaluate the efficacy of celecoxib add-on in patients of depression partially responding to escitalopram. p. S243, 2013. ISSN 0253-7613. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=71395112 >. Acesso em: (Raghuvanshi, Nischal, Nischal, Pant, Agarwal, Mahadi, Singh, Raghuvanshi) King George's Medical University, Lucknow, Uttar Pradesh, India.

RAISON, C. et al. The tumor necrosis factor-alpha antagonist infliximab reduces depressive symptoms in patients with treatment resistant depression and high inflammation. p. S49, 2012. ISSN 0889-1591. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70937082 >. Acesso em: (Raison) University of Arizona, College of Medicine, Atlanta, United States.

RAISON, C. L.; CAPURON, L.; MILLER, A. H. Cytokines sing the blues: inflammation and the pathogenesis of depression. **Trends Immunol,** v. 27, n. 1, p. 24-31, Jan 2006. ISSN 1471-4906 (Print)
1471-4906.

RAISON, C. L. et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. **JAMA Psychiatry,** v. 70, n. 1, p. 31-41, Jan 2013. ISSN 2168-622x. Disponível em: < http://archpsyc.jamanetwork.com/data/Journals/PSYCH/926165/yoa120056_31_41.pdf >.

RAISON, C. L. et al. A Randomized Controlled Trial of the Tumor Necrosis Factor-alpha Antagonist Infliximab in Treatment Resistant Depression: Role of Baseline Inflammatory Biomarkers. **JAMA psychiatry,** v. 70, n. 1, p. 31-41, 2013. ISSN 2168-622X
2168-6238. Disponível em: < http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4015348/ >.

RANJBAR, E. et al. Effects of zinc supplementation on efficacy of antidepressant therapy, inflammatory cytokines, and brain-derived neurotrophic factor in patients with major depression. **Nutr Neurosci,** v. 17, n. 2, p. 65-71, Feb 2014. ISSN 1028-415x.

RAPAPORT, M. et al. Inflammation as a predictive biomarker for response to omega-3 fatty acids in major depressive disorder: A proof-of-concept study. **Molecular Psychiatry,** v. 21, n. 1, p. 71-79, Jan 2016. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc12&AN=2016-00822-008
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc12&rft.genre=article&rft_id=info:doi/10.1038%2Fmp.2015.22&rft_id=info:pmid/&rft.issn=1359-4184&rft.volume=21&rft.issue=1&rft.spage=71&rft.pages=71-79&rft.date=2016&rft.jtitle=Molecular+Psychiatry&rft.atitle=Inflammation+as+a+predictive+biomarker+for+response+to+omega-3+fatty+acids+in+major+depressive+disorder%3A+A+proof-of-concept+study.&rft.aulast
http://www.nature.com/mp/journal/v21/n1/pdf/mp201522a.pdf >.

RAPAPORT, M. H. Inflammation as a predictive biomarker for response to omega-3 fatty acids in major depressive disorder. p. 146S-147S, 2015. ISSN 0006-3223. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=71846534 >. Acesso em: (Rapaport) Department of Psychiatry and Behavioral Sciences, EmoryUniversity, Atlanta, GA, United States.

RAWDIN, B. et al. Dysregulated relationship of inflammation and oxidative stress in major depression. **Brain, Behavior, and Immunity,** v. 31, p. 143-152, Jul 2013. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc10&AN=2013-19048-017
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc10&rft.genre=article&rft_id=info:doi/10.1016%2Fj.bbi.2012.11.011&rft_id=info:pmid/&rft.issn=0889-1591&rft.volume=31&rft.issue=&rft.spage=143&rft.pages=143-152&rft.date=2013&rft.jtitle=Brain%2C+Behavior%2C+and+Immunity&rft.atitle=Dysregulated+relationship+of+inflammation+and+oxidative+stress+in+major+depression.&rft.aulast=Rawdin

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3669232/pdf/nihms430636.pdf >.

RAWDIN, B. et al. Inflammatory and oxidative stress are highly correlated in unmedicated major depression. p. S47, 2012. ISSN 0889-1591. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70937075 >. Acesso em: (Rawdin, Mellon, Epel, Rosser, Burke, Reus, Hamilton, Nelson, Wolkowitz) Department of Psychiatry, University of California,San Francisco, 401 Parnassus Avenue, Box 0984, San Francisco, CA 94143-0984, United States.

RETHORST, C. et al. Pro-inflammatory cytokines as predictors of antidepressant effects of exercise in major depressive disorder. **Molecular Psychiatry,** v. 18, n. 10, p. 1119-1124, Oct 2013. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc10&AN=2013-35997-012
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc10&rft.genre=article&rft_id=info:doi/10.1038%2Fmp.2012.125&rft_id=info:pmid/&rft.issn=1359-4184&rft.volume=18&rft.issue=10&rft.spage=1119&rft.pages=1119-1124&rft.date=2013&rft.jtitle=Molecular+Psychiatry&rft.atitle=Pro-inflammatory+cytokines+as+predictors+of+antidepressant+effects+of+exercise+in+major+depressive+disorder.&rft.aulast=Rethorst
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3511631/pdf/nihms-391603.pdf >.

RETHORST, C. D. et al. IL-1beta and BDNF are associated with improvement in hypersomnia but not insomnia following exercise in major depressive disorder. **Transl Psychiatry,** v. 5, p. e611, 2015a. ISSN 2158-3188. Disponível em: < http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4564559/pdf/tp2015104a.pdf >.

RETHORST, C. D. et al. IL-1beta and BDNF are associated with improvement in hypersomnia but not insomnia following exercise in major depressive disorder. **Translational Psychiatry,** v. 5 (no pagination), n. e611, 04 Aug 2015b. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed13&AN=2015254915
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:emed13&rft.genre=article&rft_id=info:doi/10.1038%2Ftp.2015.104&rft_id=info:pmid/&rft.issn=2158-3188&rft.volume=5&rft.issue=&rft.spage=no+pagination&rft.pages=no+pagination&rft.date=2015&rft.jtitle=Translational+Psychiatry&rft.atitle=IL-1beta+and+BDNF+are+associated+with+improvement+in+hypersomnia+but+not+insomnia+following+exercise+in+major+depressive+. > >.

RETHORST, C. D. et al. Moderating effects of moderate-intensity physical activity in the relationship between depressive symptoms and interleukin-6 in primary care patients. **Psychosom Med,** v. 73, n. 3, p. 265-9, Apr 2011. ISSN 0033-3174. Disponível em: < http://graphics.tx.ovid.com/ovftpdfs/FPDDNCMCBGOCAA00/fs047/ovft/live/gv024/00006842/00006842-201104000-00008.pdf >.

REYES-ORTIZ, C. A. Interleukin-6, depression, and hypocholesterolemia. **J Am Geriatr Soc,** v. 47, n. 9, p. 1161, Sep 1999. ISSN 0002-8614 (Print)
0002-8614. Disponível em: < http://onlinelibrary.wiley.com/store/10.1111/j.1532-5415.1999.tb05254.x/asset/j.1532-5415.1999.tb05254.x.pdf?v=1&t=iebicait&s=22a4854a07b9c81bcb8db1820bca97b3d9e699e7 >.

RIAZI, K. et al. Microglia-dependent alteration of glutamatergic synaptic transmission and plasticity in the hippocampus during peripheral inflammation. **J Neurosci,** v. 35, n. 12, p. 4942-52, Mar 25 2015. ISSN 0270-6474.

RICHARDS, D. Prevalence and clinical course of depression: a review. **Clin Psychol Rev,** v. 31, n. 7, p. 1117-25, Nov 2011. ISSN 0272-7358.

RIEF, W. et al. Immunological differences between patients with major depression and somatization syndrome. Ireland, p. 165-174, 2001. ISSN 0165-1781. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed5&NEWS=N&AN=2002051465 >. Acesso em: (Rief, Pilger, Ihle) Klinik Roseneck, Center for Behavioral Medicine, Prien Am Chiemsee, Germany.

ROSENBLAT, J. D. et al. Inflamed moods: a review of the interactions between inflammation and mood disorders. **Prog Neuropsychopharmacol Biol Psychiatry,** v. 53, p. 23-34, Aug 4 2014. ISSN 0278-5846.

ROSENTHAL, R. The file drawer problem and tolerance for null results. **Psychological bulletin,** v. 86, n. 3, p. 638, 1979. ISSN 1939-1455.

ROTHENHAUSLER, H. B.; STEPAN, A.; KAPFHAMMER, H. P. Soluble interleukin 2 receptor levels, temperament and character in formerly depressed suicide attempters compared with normal controls. **Suicide Life Threat Behav,** v. 36, n. 4, p. 455-66, Aug 2006. ISSN 0363-0234 (Print)
0363-0234.

ROTHERMUNDT, M. et al. Different immune patterns in melancholic and non-melancholic major depression. Germany, p. 90-97, 2001. ISSN 0940-1334. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed5&NEWS=N&AN=2001193015 >. Acesso em: (Rothermundt, Arolt) Department of Psychiatry, Westfaelische Wilhelms-Universitaet, Albert-Schweitzer-Str. 11, 48129 Muenster, Germany.

ROTHERMUNDT, M. et al. Inflammatory markers in major depression and melancholia. **J Affect Disord,** v. 63, n. 1-3, p. 93-102, Mar 2001. ISSN 0165-0327 (Print)
0165-0327.

ROTTER, A. et al. Changes of cytokine profiles during electroconvulsive therapy in patients with major depression. **J ect,** v. 29, n. 3, p. 162-9, Sep 2013. ISSN 1095-0680.

RULJANCIC, N. et al. Serum levels of cytokines in depressed patients with or without suicidal behavior. p. S854, 2011. ISSN 1434-6621. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=70517926 >. Acesso em: (Ruljancic, Bakliza) Psychiatric hospital Sveti Ivan, Department of Clinical Chemistry, Jankomir 11, Zagreb, Croatia.

RUSH, G. et al. Melancholia is characterised by increased IL-6 and decreased TGF-beta compared to healthy controls. p. S31-S32, 2010. ISSN 0889-1591. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=70268263 >. Acesso em: (Rush, Smith, Lucey) St Patrick's University Hospital, James's Street, Dublin 8, Ireland.

RYBKA, J. HMGB1 and IL-17 are the mediators linking redox signalling and inflammation in depression. p. S414, 2013. ISSN 0924-977X. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=71205323 >. Acesso em: (Rybka) Nicolaus Copernicus University, Collegium Medicum, Department of Biochemistry, Bydgoszcz, Poland.

RYBKA, J. et al. Redox imbalance activates high mobility group box protein 1 which modulates T cells phenotype and cytokine profile in depressed patients. the impact on glucocorticoids response. p. S78, 2012. ISSN 0891-5849. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70923865 >. Acesso em: (Rybka, Kedziora-Kornatowska, Kupczyk, Kedziora) Collegium Medicum in Bydgoszcz, Poland.

SAKAGUCHI, S. et al. FOXP3+ regulatory T cells in the human immune system. **Nat Rev Immunol,** v. 10, n. 7, p. 490-500, Jul 2010. ISSN 1474-1733.

SANACORA, G.; TRECCANI, G.; POPOLI, M. Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. **Neuropharmacology,** v. 62, n. 1, p. 63-77, Jan 2012. ISSN 0028-3908.

SAVITZ, J. et al. Putative neuroprotective and neurotoxic kynurenine pathway metabolites are associated with hippocampal and amygdalar volumes in subjects with major depressive disorder. **Neuropsychopharmacology,** v. 40, n. 2, p. 463-471, Jan 2015. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc11&AN=2014-56334-023

http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc11&rft.genre=article&rft_id=info:doi/10.1038%2Fnpp.2014.194&rft_id=info:pmid/&rft.issn=0893-133X&rft.volume=40&rft.issue=2&rft.spage=463&rft.pages=463-471&rft.date=2015&rft.jtitle=Neuropsychopharmacology&rft.atitle=Putative+neuroprotective+and+neurotoxic+kynurenine+pathway+metabolites+are+associated+with+hippocampal+and+amygdalar+volumes+in+subject http://www.nature.com/npp/journal/vaop/naam/pdf/npp2014194a.pdf >.

SCHIEPERS, O. J. G.; WICHERS, M. C.; MAES, M. Cytokines and major depression. United States, p. 201-217, 2005. ISSN 0278-5846. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed7&NEWS=N&AN=2005066824 >. Acesso em: (Schiepers, Wichers, Maes) Dept. of Psychiat. and Neuropsychol., Maastricht University, P.O. BOX 616, 6200 MD Maastricht, Netherlands.

SCHILLING PANIZZUTTI, B. et al. Evaluation of peripheral biomarkers in bipolar and unipolar depression. p. S361-S362, 2013. ISSN 0924-977X. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=71205238 >. Acesso em: (Schilling Panizzutti) Universidade Federal do Rio Grande do Sul-INCT Translational Medicine, Programa de Pos-Graduacao em Ciencias Medicas: Psiquiatria, Porto Alegre, Brazil.

SCHLATTER, J.; ORTUNO, F.; CERVERA-ENGUIX, S. Differences in interleukins' patterns between dysthymia and major depression. France, p. 317-319, 2001. ISSN 0924-9338. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed5&NEWS=N&AN=2001285592 >. Acesso em: (Schlatter, Ortuno, Cervera-Enguix) Department of Psychiatry and Medical Psychology, University Clinic, University of Navarra, 31080-Pamplona, Spain.

_____. Lymphocyte subsets and lymphokine production in patients with melancholic versus nonmelancholic depression. **Psychiatry Res,** v. 128, n. 3, p. 259-65, Oct 30 2004a. ISSN 0165-1781 (Print) 0165-1781.

_____. Monocytic parameters in patients with dysthymia versus major depression. Netherlands, p. 243-247, 2004b. ISSN 0165-0327. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed6&NEWS=N&AN=2004060318 >. Acesso em: (Schlatter, Ortuno, Cervera-Enguix) Dept. of Psychiat. and Med. Psychol., University Clinic, University of Navarra, 31080 Pamplona, Spain.

SCHLATTER, J. et al. Parameters of natural immunity as biological markers of depression. Spain, p. 158-166, 2006. ISSN 1134-5934. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed7&NEWS=N&AN=2006563919 >. Acesso em: (Schlatter, Ortuno, Pla, Cervera-Enguix) Departamento de Psiquiatria y Psicologia Medica, Clinica Universitaria, Universidad de Navarra, Pamplona, Spain.

SCHMIDT, F. M. et al. Impact of serum cytokine levels on EEG-measured arousal regulation in patients with major depressive disorder and healthy controls. **Neuropsychobiology,** v. 73, n. 1, p. 1-9, 2016. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc12&AN=2016-17421-002 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc12&rft.genre=article&rft_id=info:doi/10.1159%2F000441190&rft_id=info:pmid/&rft.issn=0302-282X&rft.volume=73&rft.issue=1&rft.spage=1&rft.pages=1-9&rft.date=2016&rft.jtitle=Neuropsychobiology&rft.atitle=Impact+of+serum+cytokine+levels+on+EEG-measured+arousal+regulation+in+patients+with+major+depressive+disorder+and+healthy+controls.&rft.aulast=Schmid >.

SCHMIDT, F. M. et al. Pro- and anti-inflammatory cytokines, but not CRP, are inversely correlated with severity and symptoms of major depression. **Psychiatry Research,** v. 239, p. 85-91, May 30 2016. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed13&AN=20160203868 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:emed13&rft.genre=article&rft_id=info:doi/10.1016%2Fj.psychres.2016.02.052&rft_id=info:pmid/&rft.issn=0165-

1781&rft.volume=239&rft.issue=&rft.spage=85&rft.pages=85-91&rft.date=2016&rft.jtitle=Psychiatry+Research&rft.atitle=Pro-+and+anti-inflammatory+cytokines%2C+but+not+CRP%2C+are+inversely+correlated+with+severity+and+symptoms+of+major+depression&rft.a. > http://ac.els-cdn.com/S0165178116303304/1-s2.0-S0165178116303304-main.pdf?_tid=1f3b9c80-27f6-11e6-a867-00000aacb360&acdnat=1464785052_926417a563b232da99326529c5aae548 >.

SCHULD, A. et al. Effects of dexamethasone on cytokine plasma levels and white blood cell counts in depressed patients. **Psychoneuroendocrinology,** v. 26, n. 1, p. 65-76, Jan 2001. ISSN 0306-4530 (Print) 0306-4530.

SCHULD, A. et al. Hypothalamo-pituitary-adrenal function in patients with depressive disorders is correlated with baseline cytokine levels, but not with cytokine responses to hydrocortisone. **J Psychiatr Res,** v. 37, n. 6, p. 463-70, Nov-Dec 2003. ISSN 0022-3956 (Print) 0022-3956.

SEIDEL, A. et al. Cytokine production and serum proteins in depression. United Kingdom, p. 534-538, 1995. ISSN 0300-9475. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed3&NEWS=N&AN=1995172682 >. Acesso em: (Seidel, Arolt, Hunstiger, Rink, Behnisch, Kirchner) Ist. Immunology/Transfusion Medicine, University Lubeck, School of Medicine, Ratzeburger Allee 160, 23538 Lubeck, Germany.

_____. Increased CD56+ natural killer cells and related cytokines in major depression. **Clin Immunol Immunopathol,** v. 78, n. 1, p. 83-5, Jan 1996. ISSN 0090-1229 (Print) 0090-1229. Disponível em: < http://ac.els-cdn.com/S0090122996900124/1-s2.0-S0090122996900124-main.pdf?_tid=192cc510-5684-11e5-b93c-00000aab0f27&acdnat=1441756286_702f289015bc12d45c75e33d525f2d39 >.

SEKIYAMA, A. et al. Loss of association between levels of interleukin (IL) -6 and IL-1b in plasma in major depressive disorder. p. 233S-234S, 2009. ISSN 0006-3223. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=70111038 >. Acesso em: (Sekiyama, Kasahara, Inoue) Department of Molecular Pathology and Biochemistry, Osaka City University, Graduate School of Medicine, Osaka, Japan.

SHARMA, A. et al. The efficacy of a comprehensive yogic intervention on major depression-a randomized pilot study with inflammatory biomarkers. **Neuropsychopharmacology,** v. 40, p. S500, December 2015. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed13&AN=72133287 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:emed13&rft.genre=article&rft_id=info:doi/10.1038%2Fnpp.2015.327&rft_id=info:pmid/&rft.issn=0893-133X&rft.volume=40&rft.issue=&rft.spage=S500&rft.pages=S500&rft.date=2015&rft.jtitle=Neuropsychopharmacology&rft.atitle=The+efficacy+of+a+comprehensive+yogic+intervention+on+major+depression-a+randomized+pilot+study+with+inflammatory+biomarkers&rft.aulast=Sh. > >.

SHEN, Y. et al. Fluoxetine treatment for major depression decreases the plasma levels of cytokines. Kenya, p. 7346-7351, 2010. ISSN 1684-5315. Disponível em: < http://www.academicjournals.org/AJB/PDF/pdf2010/25Oct/Shen et al.pdf http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=2010637534 >. Acesso em: (Shen) Department of Diagnostics, Clinical Medical School, Hangzhou Normal University, Hangzhou, Zhejiang 310036, China.

SILIC, A.; KARLOVIC, D.; SERRETTI, A. Increased inflammation and lower platelet 5-HT in depression with metabolic syndrome. **J Affect Disord,** v. 141, n. 1, p. 72-8, Dec 1 2012. ISSN 0165-0327.

SLUZEWSKA, A. et al. Interleukin-6 serum levels in depressed patients before and after treatment with fluoxetine. **Ann N Y Acad Sci,** v. 762, p. 474-6, Jul 21 1995. ISSN 0077-8923 (Print) 0077-8923. Disponível em: < http://onlinelibrary.wiley.com/doi/10.1111/j.1749-6632.1995.tb32372.x/abstract?systemMessage=Wiley+Online+Library+and+related+systems+will+have+3+hours+of+downtime+on+Saturday+12th+September+2015+from+10%3A00-13%3A00+BST+%2F+05%3A00-08%3A00+EDT+%2F+17%3A00-

20%3A00+SGT+for+essential+maintenance.++Apologies+for+the+inconvenience. >.

SLUZEWSKA, A. et al. Increased levels of alpha-1-acid glycoprotein and interleukin-6 in refractory depression. United States, p. 170-175, 1995. ISSN 1062-6417. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed3&NEWS=N&AN=1996130635 >. Acesso em: (Sluzewska, Rybakowski, Sobieska, Bosmans, Pollet, Wiktorowicz) Department of Adult Psychiatry, K. Marcinkowski University, Medical Sciences, Szpitalna Street 27/33, 60-572 Poznan, Poland.

SLUZEWSKA, A. et al. Serotonin antibodies in relation to immune activation in major depression. **Human Psychopharmacology: Clinical and Experimental,** v. 12, n. 5, p. 453-458, Sep-Oct 1997. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc3&AN=1997-43693-005 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc3&rft.genre=article&rft_id=info:doi/10.1002%2F%28SICI%291099-1077%28199709%2F10%2912%3A5%3C453%3A%3AAID-HUP888%3E3.0.CO%3B2-4&rft_id=info:pmid/&rft.issn=0885-6222&rft.volume=12&rft.issue=5&rft.spage=453&rft.pages=453-458&rft.date=1997&rft.jtitle=Human+Psychopharmacology%3A+Clinical+and+Experimental&rft.atitle=Serotonin+antibodies+in+rel >.

SMITH, R. S. The macrophage theory of depression. **Med Hypotheses,** v. 35, n. 4, p. 298-306, Aug 1991. ISSN 0306-9877 (Print)
0306-9877.

SONG, C. et al. Imbalance between pro- and anti-inflammatory cytokines, and between Th1 and Th2 cytokines in depressed patients: The effect of electroacupuncture or fluoxetine treatment. **Pharmacopsychiatry,** v. 42, n. 5, p. 182-188, Sep 2009. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc6&AN=2009-18348-003 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc6&rft.genre=article&rft_id=info:doi/10.1055%2Fs-0029-1202263&rft_id=info:pmid/&rft.issn=0176-3679&rft.volume=42&rft.issue=5&rft.spage=182&rft.pages=182-188&rft.date=2009&rft.jtitle=Pharmacopsychiatry&rft.atitle=Imbalance+between+pro-+and+anti-inflammatory+cytokines%2C+and+between+Th1+and+Th2+cytokines+in+depressed+patients%3A+The+effect+of+electroa
https://www.thieme-connect.com/DOI/DOI?10.1055/s-0029-1202263 >.

SONG, C. et al. The inflammatory response system and the availability of plasma tryptophan in patients with primary sleep disorders and major depression. Netherlands, p. 211-219, 1998. ISSN 0165-0327. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed4&NEWS=N&AN=1998160369 >. Acesso em: (Song, Lin, Bonaccorso, Maes) Clin. Res. Ctr. Mental Hlth. (CRC-M., University Department of Psychiatry, Antwerp, Belgium.

STANG, A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. **European Journal of Epidemiology,** v. 25, n. 9, p. 603-605, 2010. ISSN 1573-7284. Disponível em: < http://dx.doi.org/10.1007/s10654-010-9491-z >.

STELZHAMMER, V. et al. Electroconvulsive therapy exerts mainly acute molecular changes in serum of major depressive disorder patients. Netherlands, p. 1199-1207, 2013. ISSN 0924-977X. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=2013589193 >. Acesso em: (Stelzhammer, Guest, Schwarz, Rahmoune, Bahn) Department of Chemical Engineering and Biotechnology, University of Cambridge, Cambridge, United Kingdom.

STEPTOE, A.; KUNZ-EBRECHT, S.; OWEN, N. Lack of association between depressive symptoms and markers of immune and vascular inflammation in middle-aged men and women. **Psychological Medicine,** v. 33, n. 4, p. 667-674, May 2003. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc4&AN=2003-05628-012 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc4&rft.genre=article&rft_id=info:doi/10.1017%2FS0033291702007250&rft_id=info:pmid/&rft.issn=0033-2917&rft.volume=33&rft.issue=4&rft.spage=667&rft.pages=667-

674&rft.date=2003&rft.jtitle=Psychological+Medicine&rft.atitle=Lack+of+association+between+depressive+symptoms+and+markers+of+immune+and+vascular+inflammation+in+middle-aged+men+and+women.&rft.au >.

STEWART, J. C. et al. Depressive symptoms moderate the influence of hostility on serum interleukin-6 and C-reactive protein. **Psychosom Med,** v. 70, n. 2, p. 197-204, Feb 2008. ISSN 0033-3174. Disponível em: < http://graphics.tx.ovid.com/ovftpdfs/FPDDNCMCBGOCAA00/fs046/ovft/live/gv023/00006842/00006842-200802000-00010.pdf >.

STRAWBRIDGE, R. et al. Inflammation and clinical response to treatment in depression: A meta-analysis. **Eur Neuropsychopharmacol,** v. 25, n. 10, p. 1532-43, Oct 2015. ISSN 0924-977x.

SU, S. et al. Common genetic contributions to depressive symptoms and inflammatory markers in middle-aged men: The Twins Heart Study. **Psychosomatic Medicine,** v. 71, n. 2, p. 152-158, Feb-Mar 2009. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc6&AN=2009-02605-003 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc6&rft.genre=article&rft_id=info:doi/10.1097%2FPSY.0b013e31819082ef&rft_id=info:pmid/&rft.issn=0033-3174&rft.volume=71&rft.issue=2&rft.spage=152&rft.pages=152-158&rft.date=2009&rft.jtitle=Psychosomatic+Medicine&rft.atitle=Common+genetic+contributions+to+depressive+symptoms+and+inflammatory+markers+in+middle-aged+men%3A+The+Twins+Heart+Study.&rft.aul http://graphics.tx.ovid.com/ovftpdfs/FPDDNCLBEFGADB00/fs047/ovft/live/gv024/00006842/00006842-200902000-00003.pdf >.

SU, S. C. et al. Brain-derived neurotrophic factor, adiponectin, and proinflammatory markers in various subtypes of depression in young men. **Int J Psychiatry Med,** v. 42, n. 3, p. 211-26, 2011. ISSN 0091-2174 (Print) 0091-2174.

SUAREZ, E. C. Joint effect of hostility and severity of depressive symptoms on plasma interleukin-6 concentration. **Psychosom Med,** v. 65, n. 4, p. 523-7, Jul-Aug 2003. ISSN 0033-3174. Disponível em: < http://graphics.tx.ovid.com/ovftpdfs/FPDDNCGCAFBHMP00/fs046/ovft/live/gv023/00006842/00006842-200307000-00008.pdf >.

SUN, H. et al. Effect of acupuncture at Baihui (GV 20) and Zusanli (ST 36) on the level of serum inflammatory cytokines in patients with depression. China, p. 195-199, 2010. ISSN 0255-2930. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=20496732 >. Acesso em: (Sun) Department of TCM, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing 100730, China.

SUTCIGIL, L. et al. Pro- and anti-inflammatory cytokine balance in major depression: effect of sertraline therapy. **Clin Dev Immunol,** v. 2007, p. 76396, 2007. ISSN 1740-2522.

TALAIE, H. et al. Alteration of serum levels of interlukin 1 and tumor necrosis factor in depression independent of treatment or overdose of tricyclic antidepressants. Pakistan, p. 287-292, 2008. ISSN 1682-4474. Disponível em: < http://scialert.net/pdfs/jms/2008/287-292.pdf http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS=N&AN=2010016609 >. Acesso em: (Talaie, Pajoumand, Panahandeh, Abdollahi) Toxicological Research Center, Loghman-Hakim Hospital, Shaheed Beheshti University of Medical Sciences, Tehran, Iran, Islamic Republic of.

THIAGARAJAH, A. et al. Detection of GILZ, IL-6 and TNF-a in the context of depression subtypes. p. 126-127, 2014. ISSN 0004-8674. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=71565478 >. Acesso em: (Thiagarajah, Eades, Thomas, Jones, Yang, Harris, Morand, Clarke, Leech) Monash University, Melbourne, Australia.

THOMPSON, S. G.; HIGGINS, J. P. How should meta-regression analyses be undertaken and interpreted? **Stat Med,** v. 21, n. 11, p. 1559-73, Jun 15 2002. ISSN 0277-6715 (Print) 0277-6715.

TIEMEIER, H. et al. Inflammatory proteins and depression in the elderly. **Epidemiology,** v. 14, n. 1, p. 103-7, Jan 2003. ISSN 1044-3983 (Print)

1044-3983.

TOUPS, M. S. P. et al. Cytokines in the relationship between exercise treatment and anhedonia and changes in arousal in depressed subjects. p. 48S, 2014. ISSN 0006-3223. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=71433979 >. Acesso em: (Toups, Rethorst, Carmody, Trivedi) Psychiatry, UT Southwestern, Dallas, TX, United States.

TOUPS, M. S. P. et al. Inflammatory cytokines are associated with exercise augmentation treatment outcome for major depressive disorder. p. S413, 2011. ISSN 0893-133X. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70607836 >. Acesso em: (Toups, Rethorst, Greer, Huebinger, Grannemann, Kurian, Trivedi) UT Southwestern, Dallas, United States.

TRZONKOWSKI, P. et al. Immune consequences of the spontaneous pro-inflammatory status in depressed elderly patients. **Brain Behav Immun,** v. 18, n. 2, p. 135-48, Mar 2004. ISSN 0889-1591 (Print)
0889-1591.

TSAO, C. W. et al. Cytokines and serotonin transporter in patients with major depression. United States, p. 899-905, 2006. ISSN 0278-5846. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed7&NEWS=N&AN=2006254201 >. Acesso em: (Tsao) Department of Nursing, Chung Hwa College of Medical Technology, Tainan County, Taiwan (Republic of China).

TUGLU, C. et al. Increased serum tumor necrosis factor-alpha levels and treatment response in major depressive disorder. **Psychopharmacology,** v. 170, n. 4, p. 429-433, Dec 2003. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc4&AN=2003-11021-012 http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc4&rft.genre=article&rft_id=info:doi/10.1007%2Fs00213-003-1566-z&rft_id=info:pmid/&rft.issn=0033-3158&rft.volume=170&rft.issue=4&rft.spage=429&rft.pages=429-433&rft.date=2003&rft.jtitle=Psychopharmacology&rft.atitle=Increased+serum+tumor+necrosis+factor-alpha+levels+and+treatment+response+in+major+depressive+disorder.&rft.aulast=Tuglu http://download.springer.com/static/pdf/268/art%3A10.1007%2Fs00213-003-1566-z.pdf?originUrl=http%3A%2F%2Flink.springer.com%2Farticle%2F10.1007%2Fs00213-003-1566-z&token2=exp=1441743292~acl=%2Fstatic%2Fpdf%2F268%2Fart%3A10.1007%2Fs00213-003-1566-z.pdf%3ForiginUrl%3Dhttp%3A%2F%2Flink.springer.com%2Farticle%2F10.1007%2Fs00213-003-1566-z*~hmac=d7303dad49ebabe46f7544890885d61cb1a759f504687f253e0c73d0da25c898 >.

TUGLU, C. et al. Increased serum tumor necrosis factor-alpha levels and treatment response in major depressive disorder. **Psychopharmacology (Berl),** v. 170, n. 4, p. 429-33, Dec 2003. ISSN 0033-3158 (Print)
0033-3158.

TULLY, P. J. et al. The longitudinal association between inflammation and incident depressive symptoms in men: The effects of hs-CRP are independent of abdominal obesity and metabolic disturbances. United States, p. 328-335, 2015. ISSN 0031-9384. Disponível em: < http://www.elsevier.com/locate/physbeh http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=2014626044 >. Acesso em: (Tully, Martin, Wittert) Freemasons Foundation Centre for Men's Health, Discipline of Medicine, School of Medicine, The University of Adelaide, Adelaide, Australia.

TYNAN, R. J. et al. A comparative examination of the anti-inflammatory effects of SSRI and SNRI antidepressants on microglia. p. S34-S35, 2012. ISSN 0889-1591. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=70937030 >. Acesso em: (Tynan, Hinwood, Weidenhofer, Cairns, Walker) School of Biomedical Sciences and Pharmacy, Univeristy of Newcastle, Newcastle, NSW, Australia.

TYNAN, R. J. et al. A comparative examination of the anti-inflammatory effects of SSRI and SNRI antidepressants on LPS stimulated microglia. **Brain Behav Immun,** v. 26, n. 3, p. 469-79, Mar 2012. ISSN 0889-1591.

UDDIN, M. Blood-based biomarkers in depression: emerging themes in clinical research. **Mol Diagn Ther,** v. 18, n. 5, p. 469-82, Oct 2014. ISSN 1177-1062.

UHER, R. et al. Body weight as a predictor of antidepressant efficacy in the GENDEP project. **J Affect Disord,** v. 118, n. 1-3, p. 147-54, Nov 2009. ISSN 0165-0327.

USHIROYAMA, T. et al. Changes in serum tumor necrosis factor (TNF-alpha) with kami-shoyo-san administration in depressed climacteric patients. **Am J Chin Med,** v. 32, n. 4, p. 621-9, 2004. ISSN 0192-415X (Print)
0192-415x. Disponível em: < http://www.worldscientific.com/doi/pdfplus/10.1142/S0192415X04002259 >.

_____. Chai-hu-gui-zhi-gan-jiang-tang regulates plasma interleukin-6 and soluble interleukin-6 receptor concentrations and improves depressed mood in climacteric women with insomnia. **Am J Chin Med,** v. 33, n. 5, p. 703-11, 2005. ISSN 0192-415X (Print)
0192-415x. Disponível em: < http://www.worldscientific.com/doi/pdfplus/10.1142/S0192415X05003338 >.

USHIROYAMA, T.; IKEDA, A.; UEKI, M. Elevated plasma interleukin-6 (IL-6) and soluble IL-6 receptor concentrations in menopausal women with and without depression. **Int J Gynaecol Obstet,** v. 79, n. 1, p. 51-2, Oct 2002. ISSN 0020-7292 (Print)
0020-7292.

VACCARINO, V. et al. Association of major depressive disorder with serum myeloperoxidase and other markers of inflammation: a twin study. **Biol Psychiatry,** v. 64, n. 6, p. 476-83, Sep 15 2008. ISSN 0006-3223. Disponível em: < http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2597204/pdf/nihms68000.pdf >.

VALKANOVA, V.; EBMEIER, K. P.; ALLAN, C. L. CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. **J Affect Disord,** v. 150, n. 3, p. 736-44, Sep 25 2013. ISSN 0165-0327.

VARMA, G. S. Neuroinflammatory hypothesis in major depressive disorder. **Psikiyatride Guncel Yaklasimlar,** v. 6, n. 1, p. 1-9, 2014. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc11&AN=2014-29656-001
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc11&rft.genre=article&rft_id=info:doi/&rft_id=info:pmid/&rft.issn=1309-0658&rft.volume=6&rft.issue=1&rft.spage=1&rft.pages=1-9&rft.date=2014&rft.jtitle=Psikiyatride+Guncel+Yaklasimlar&rft.atitle=Neuroinflammatory+hypothesis+in+major+depressive+disorder.&rft.aulast=Varma >.

VETTA, F. et al. Tumor necrosis factor-alpha and mood disorders in the elderly. Ireland, p. 435-442, 2001. ISSN 0167-4943. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed5&NEWS=N&AN=2001278891 >. Acesso em: (Vetta, Ronzoni, Lupattelli, Novi, Fabbriconi, Ficoneri, Cicconetti, Bruno, Russo, Bollea) Via Emilio De Marchi, 81, I-00141 Roma, Italy.

VINBERG, M. et al. Does long-term treatment with recombinant human erythropoietin (EPO) impact on inflammatory markers and plasma brain derived neurotrophic factor (BDNF) levels in patients with affective disorders? **Bipolar Disorders,** v. 17, p. 104, June 2015. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed13&AN=72167664
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:emed13&rft.genre=article&rft_id=info:doi/10.1111%2Fbdi.12309&rft_id=info:pmid/&rft.issn=1398-5647&rft.volume=17&rft.issue=&rft.spage=104&rft.pages=104&rft.date=2015&rft.jtitle=Bipolar+Disorders&rft.atitle=Does+long-term+treatment+with+recombinant+human+erythropoietin+%28EPO%29+impact+on+inflammatory+markers+and+plasma+brain+derived+neurotrophic+factor+. > >.

VODERHOLZER, U. et al. Effects of sleep deprivation on nocturnal cytokine concentrations in depressed patients and healthy control subjects. United States, p. 354-366, 2012. ISSN 0895-0172. Disponível em: < http://neuro.psychiatryonline.org/data/Journals/NP/24991/354.pdf
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=2012610562 >. Acesso em: (Voderholzer, Fiebich, Dersch, Feige, Piosczyk, Kopasz, Riemann, Lieb) Dept. of Psychiatry and Psychotherapy, University Medical Center Freiburg, Freiburg, Germany.

VOGELZANGS, N. et al. Inflammatory and metabolic dysregulation and the 2-year course of depressive disorders

in antidepressant users. **Neuropsychopharmacology,** v. 39, n. 7, p. 1624-1634, Jun 2014. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc11&AN=2014-23007-008
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc11&rft.genre=article&rft_id=info:doi/10.1038%2Fnpp.2014.9&rft_id=info:pmid/&rft.issn=0893-133X&rft.volume=39&rft.issue=7&rft.spage=1624&rft.pages=1624-1634&rft.date=2014&rft.jtitle=Neuropsychopharmacology&rft.atitle=Inflammatory+and+metabolic+dysregulation+and+the+2-year+course+of+depressive+disorders+in+antidepressant+users.&rft.aulast=Vogelzangs
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4023159/pdf/npp20149a.pdf >.

VOGELZANGS, N. et al. Inflammatory and metabolic dysregulation and the 2-year course of depressive disorders in antidepressant users. United Kingdom, p. 1624-1634, 2014. ISSN 0893-133X. Disponível em: < http://www.nature.com/npp/index.html
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=2014333716 >. Acesso em: (Vogelzangs, Beekman, Van Reedt Dortland, Penninx) Department of Psychiatry, EMGO Institute for Health and Care Research, VU University Medical Center, AJ Ernststraat 1187, 1081 HL Amsterdam, Netherlands.

VOGELZANGS, N. et al. Association of depressive disorders, depression characteristics and antidepressant medication with inflammation. United Kingdom, p. e79, 2012. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=2012102962 >. Acesso em: (Vogelzangs, Beekman, Smit, Penninx) Department of Psychiatry, EMGO Institute for Health and Care Research, VU University Medical Center, AJ Ernststraat 1187, Amsterdam 1081 HL, Netherlands.

VOGELZANGS, N. et al. Associations between depressive and anxiety disorders and characteristics with inflammatory markers. p. 674, 2010. ISSN 0022-3999. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=70419933 >. Acesso em: (Vogelzangs, Beekman, Smit, Penninx) Department of Psychiatry, EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam, Netherlands.

WALKER, A. J. et al. Peripheral proinflammatory markers associated with ketamine response in a preclinical model of antidepressant-resistance. **Behavioural Brain Research,** v. 293, p. 198-202, Oct 2015. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc11&AN=2015-40654-026
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc11&rft.genre=article&rft_id=info:doi/10.1016%2Fj.bbr.2015.07.026&rft_id=info:pmid/&rft.issn=0166-4328&rft.volume=293&rft.issue=&rft.spage=198&rft.pages=198-202&rft.date=2015&rft.jtitle=Behavioural+Brain+Research&rft.atitle=Peripheral+proinflammatory+markers+associated+with+ketamine+response+in+a+preclinical+model+of+antidepressant-resistance.&rft.a
http://ac.els-cdn.com/S0166432815300978/1-s2.0-S0166432815300978-main.pdf?_tid=2ab2925e-eb0f-11e5-b759-00000aacb35e&acdnat=1458088787_8a9008d9fd9937aefdc0567ed54a43a7 >.

WANG, H. et al. Patterns of circulating cytokines in patients with chronic low back pain and depression - A prospective longitudinal study of 6 months. p. 126-127, 2009. ISSN 1530-7085. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=70207325 >. Acesso em: (Wang, Ahrens, Schiltenwolf) Orthopaedic Surgery, University of Heidelberg, Heidelberg, Germany.

WEIZMAN, R. et al. Cytokine production in major depressed patients before and after clomipramine treatment. **Biol Psychiatry,** v. 35, n. 1, p. 42-7, Jan 1 1994. ISSN 0006-3223 (Print)
0006-3223. Disponível em: < http://www.biologicalpsychiatryjournal.com/article/0006-3223(94)91166-5/abstract >.

WEST, D.; MAES, M. Major depression and activation of the inflammatory response system. Czech Republic, p. 233-243, 1999. ISSN 1212-0383. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed4&NEWS=N&AN=1999202026 >. Acesso em: (West, Maes) Clinic. Res. Ctr. for Mental Health, Antwerp University, Department of Psychiatry, 267 Lange Beeldekensstraat, 2060 Antwerp, Belgium.

WOHLEB, E. S.; DELPECH, J. C. Dynamic cross-talk between microglia and peripheral monocytes underlies stress-induced neuroinflammation and behavioral consequences. **Prog Neuropsychopharmacol Biol Psychiatry**,

May 03 2016. ISSN 0278-5846.

WOHLEB, E. S. et al. Integrating neuroimmune systems in the neurobiology of depression. **Nat Rev Neurosci,** v. 17, n. 8, p. 497-511, Aug 2016. ISSN 1471-003x.

WOJCIAK, P. et al. [Evaluation of the activity of selected elements of the immune system in depression]. **Psychiatr Pol,** v. 41, n. 5, p. 637-49, Sep-Oct 2007. ISSN 0033-2674 (Print)
0033-2674.

YANG, J. J. et al. Serum interleukin-6 is a predictive biomarker for ketamine's antidepressant effect in treatment-resistant patients with major depression. United States, p. e19-e20, 2015. ISSN 0006-3223. Disponível em: < http://www.elsevier.com/locate/biopsychiat
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=2014716248 >. Acesso em: (Yang, Wang, Shi) Department of Anesthesiology, Jinling Hospital, Nanjing University, Nanjing, China.

YANG, L. et al. Depression is associated with lower circulating endothelial progenitor cells and increased inflammatory markers. United Kingdom, p. 235-240, 2011. ISSN 0924-2708. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=2011525411 >. Acesso em: (Yang, Ruan, Ji, Li) Department of Psychology, Ningbo First Hospital, Ningbo, Zhejiang 315010, China.

YASUI, T. et al. Changes in circulating cytokine levels in midlife women with psychological symptoms with selective serotonin reuptake inhibitor and Japanese traditional medicine. Ireland, p. 146-152, 2009. ISSN 0378-5122. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=2009097659 >. Acesso em: (Yasui, Yamada, Irahara) Department of Obstetrics and Gynecology, Course of Human Development, Human Development and Health Science, 3-18-15 Kuramoto, Tokushima 770-8503, Japan.

YI, L. et al. Effect of soothing-liver and nourishing-heart acupuncture on early selective serotonin reuptake inhibitor treatment onset for depressive disorder and related indicators of neuroimmunology: a randomized controlled clinical trial. **J Tradit Chin Med,** v. 35, n. 5, p. 507-13, Oct 2015. ISSN 0255-2922 (Print)
0255-2922.

YOON, H. K. et al. Role of cytokines in atypical depression. **Nord J Psychiatry,** v. 66, n. 3, p. 183-8, Jun 2012. ISSN 0803-9488.

YOSHIMURA, R. et al. Higher plasma interleukin-6 level is associated with SSRI- or SNRI-refractory depression. p. 85, 2010. ISSN 1461-1457. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=70220472 >. Acesso em: (Yoshimura) Psychiatry, UOEH, Kitakyushu, Japan.

YOSHIMURA, R. et al. Plasma levels of interleukin-6 and selective serotonin reuptake inhibitor response in patients with major depressive disorder. **Hum Psychopharmacol,** v. 28, n. 5, p. 466-70, Sep 2013. ISSN 0885-6222. Disponível em: < http://onlinelibrary.wiley.com/store/10.1002/hup.2333/asset/hup2333.pdf?v=1&t=ieaj1xxs&s=ea3c47fc589e15512b7ab541f06c98275dd2a55a >.

YOSHIMURA, R. et al. Higher plasma interleukin-6 (IL-6) level is associated with SSRI- or SNRI-refractory depression. **Prog Neuropsychopharmacol Biol Psychiatry,** v. 33, n. 4, p. 722-6, Jun 15 2009. ISSN 0278-5846.

YOSHIMURA, R. et al. Influence of fluvoxamine on plasma interleukin-6 or clinical improvement in patients with major depressive disorder. **Neuropsychiatric Disease and Treatment,** v. 13, p. 437-441, 02/14 2017. ISSN 1176-6328
1178-2021. Disponível em: < http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5317346/ >.

YOSHIMURA, R.; NAKAMURA, J. Plasma levels of IL-6, 5-HTT gene polymorphism, and SSRIs responses in patients with major depressive disorder. p. S398, 2013. ISSN 0924-977X. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=71205297 >. Acesso em: (Yoshimura, Nakamura) University of Occupational, Dept of Psychiatry, Kitakyushu, Japan.

YOUNG, J. J.; BRUNO, D.; POMARA, N. A review of the relationship between proinflammatory cytokines and

major depressive disorder. **Journal of Affective Disorders,** v. 169, n. 0, p. 15-20, 12/1/ 2014. ISSN 0165-0327. Disponível em: < http://www.sciencedirect.com/science/article/pii/S0165032714004704 >.

YU, J.-J. et al. Chronic supplementation of curcumin enhances the efficacy of antidepressants in major depressive disorder: A randomized, double-blind, placebo-controlled pilot study. **Journal of Clinical Psychopharmacology,** v. 35, n. 4, p. 406-410, Aug 2015. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc11&AN=2015-29391-009
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc11&rft.genre=article&rft_id=info:doi/&rft_id=info:pmid/&rft.issn=0271-0749&rft.volume=35&rft.issue=4&rft.spage=406&rft.pages=406-410&rft.date=2015&rft.jtitle=Journal+of+Clinical+Psychopharmacology&rft.atitle=Chronic+supplementation+of+curcumin+enhances+the+efficacy+of+antidepressants+in+major+depressive+disorder%3A+A+randomized%2C+double-blind%2C+p
http://graphics.tx.ovid.com/ovftpdfs/FPDDNCJCAAOIKJ00/fs046/ovft/live/gv023/00004714/00004714-201508000-00009.pdf >.

ZALLI, A. et al. Low-grade inflammation predicts persistence of depressive symptoms. **Psychopharmacology Apr**, n. Pagination, p. No Pagination Specified, Apr 2015. Disponível em: < http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc11&AN=2015-17095-001
http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:psyc11&rft.genre=article&rft_id=info:doi/10.1007%2Fs00213-015-3919-9&rft_id=info:pmid/&rft.issn=0033-3158&rft.volume=&rft.issue=&rft.spage=No&rft.pages=No+Pagination+Specified&rft.date=2015&rft.jtitle=Psychopharmacology&rft.atitle=Low-grade+inflammation+predicts+persistence+of+depressive+symptoms.&rft.aulast=Zalli >.

ZEUGMANN, S. et al. Childhood maltreatment and adult proinflammatory status in patients with major depression. Croatia, p. 227-235, 2013. ISSN 0353-5053. Disponível em: < http://www.hdbp.org/psychiatria_danubina/pdf/dnb_vol25_no3/dnb_vol25_no3_227.pdf
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=2013638319 >. Acesso em: (Zeugmann, Buehrsch, Bajbouj, Heuser, Anghelescu, Quante) Department of Psychiatry and Psychotherapy, Charite, University Medicine Berlin Campus Benjamin Franklin, Berlin, Germany.

ZEUGMANN, S. et al. Inflammatory biomarkers in 70 depressed inpatients with and without the metabolic syndrome. **J Clin Psychiatry,** v. 71, n. 8, p. 1007-16, Aug 2010. ISSN 0160-6689. Disponível em: < http://www.psychiatrist.com/JCP/article/Pages/2010/v71n08/v71n0807.aspx >.

ZHANG, L. et al. Detection of proinflammatory cytokines in serum samples from patients with primary major depressive disorder. China, p. 33-36, 2015. ISSN 0254-5101. Disponível em: < http://zhwswxhmyx.periodicals.net.cn/default.html
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=2015865719 >. Acesso em: (Zhang, He, Bi, Zhang, Xu) Department of Clinical Laboratory, The Second People's Hospital of Guizhou Province, Guiyang 550004, China.

ZOGA, M. et al. Indoleamine 2,3-dioxygenase and immune changes under antidepressive treatment in major depression in females. Greece, p. 633-638, 2014. ISSN 0258-851X. Disponível em: < http://iv.iiarjournals.org/content/28/4/633.full.pdf+html
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=2014976007 >. Acesso em: (Zoga, Chatzipanagiotou, Pliatsika, Boufidou, Foteli, Nikolaou) Laboratory of Biopathology and Immunology, Athens University Medical School, Eginition Hospital, Vas. Sofias Ave. 72-74, Athens 11526, Greece.

ZUBAREVA, O. E. et al. [Interleukin-1beta and depressive states]. **Ross Fiziol Zh Im I M Sechenova,** v. 87, n. 10, p. 1450-6, Oct 2001. ISSN 0869-8139 (Print)
0869-8139.

ANEXO 1. Protocolo detalhado de busca nas bases de dados (do início até maio / 2016)

Pubmed/MEDLINE
#1: ("Tumor Necrosis Factor-alpha"[Mesh] OR "Interleukin-1"[Mesh] OR "Interleukin-4"[Mesh] OR "Interleukin-6"[Mesh] OR "Interleukin-8"[Mesh] OR "Interleukin-10"[Mesh] OR "Interferons"[Mesh] OR "Receptors, Interleukin-2"[Mesh] OR "Chemokine CCL2"[Mesh] OR "Chemokine CCL3"[Mesh] OR "Chemokine CCL11"[Mesh] OR CXCL-8[Title/Abstract] OR CXCL-10[Title/Abstract]) **Field:** Title/Abstract
#2: ("Depression"[Mesh] OR "Depressive Disorder"[Mesh] OR "Depressive Disorder, Major"[Mesh]) **Field:** Title/Abstract
#3: #1 AND #2

EMBASE Classic plus EMBASE through OVID (from 1947) and PsycInfo through OVID (from 1806)
#1: (interleukin-2 or IL-2 or interleukin-1 or IL-1 or IL-4 or Interleukin-4 or IL-6 or Interleukin-6 or IL-8 or Interleukin-8 or IL-10 or Interleukin-10 or IFN-gamma or interferon gamma or TNF-alpha or tumor necrosis factor-alpha or IL-2 receptor or CCL-2 or CCL-3 or CXCL-8 or CCL-11 or CCL-10 or chemokine).ti,ab,kw
#2: (depression or major depression or depressive disorder).ti,ab,kw
#3: #1 and #2

ANEXO 2. Estudos excluídos e suas razões de exclusão

Referência	Razão de exclusão
ADLER, MARQUES & CALIL, 2008	Não é estudo original
AGUILAR-ZAVALA *et al.*, 2008	Não avaliou TDM
AJILORE, 2014	*Abstract.* Dados indisponíveis
AJILORE *et al.*, 2012	*Abstract.* Dados indisponíveis
ALESCI *et al.*, 2005	n < 10
ANDERSON *et al.*, 2013	Não é estudo original
ANDRADE, 2004	Não é estudo original
ANDROSOVA *et al.*, 2001	Comorbidades clínicas ou psiquiátricas
ANISMAN, 2009	Não é estudo original
ANISMAN & HAYLEY, 2012	Não é estudo original
ANISMAN & MERALI, 2002	Não é estudo original
ANISMAN *et al.*, 1999	Estudo *in vitro*
ANISMAN *et al.*, 2002	Não é estudo original
ANISMAN, KOKKINIDIS & MERALI, 2002	Não é estudo original
ARTS *et al.*, 2014	*Abstract.* Dados indisponíveis
ARTS *et al.*, 2015	Não avaliou TDM
ASCHBACHER *et al.*, 2011	Não avaliou TDM
(AUDET *et al.*, 2014)	Não é estudo original
AZAR, NOLAN & STEWART, 2012	Não avaliou TDM
BAGHAI *et al.*, 2011	Comorbidades clínicas ou psiquiátricas
BAHRINI *et al.*, 2015	*Abstract.* Dados indisponíveis
BARON, HARDIE & BARON, 1993	Comorbidades clínicas ou psiquiátricas
BAUER *et al.*, 1995	n < 10
BAUNE *et al.*, 2010	Não mediu citocinas
BAUNE *et al.*, 2012	Não avaliou TDM
BAUNE, AIR & JAWAHAR, 2016	*Abstract.* Dados indisponíveis
BAY-RICHTER *et al.*, 2010	Estudo com animais
BAY-RICHTER *et al.*, 2012	Não avaliou TDM
BEASLEY, MA & SHAO, 2014	*Abstract.* Dados indisponíveis
BECKING *et al.*, 2015	Não é estudo de intervenção
BEHR *et al.*, 2012	*Abstract.* Dados indisponíveis
BELZEAUX *et al.*, 2012	Não mediu citocinas
BENEDETTI *et al.*, 2002	Não avaliou TDM
BERK *et al.*, 1997	Não avaliou TDM
BERMUDEZ, 2012	Não é estudo original
BERTHOLD-LOSLEBEN & HIMMERICH, 2008	Não é estudo original
BIZIK *et al.*, 2014	Dados insuficientes para análise
BLOM *et al.*, 2012	Comorbidades clínicas ou psiquiátricas
BLUME, DOUGLAS & EVANS, 2011	Não é estudo original
BLUME *et al.*, 2011	*Abstract.* Dados indisponíveis
BOB *et al.*, 2010	Não é estudo de intervenção
BOT *et al.*, 2015	Comorbidades clínicas ou psiquiátricas
BOUFIDOU *et al.*, 2014	*Abstract.* Dados indisponíveis
BOUHUYS *et al.*, 2004	Comorbidades clínicas ou psiquiátricas

BRAMBILLA & MAGGIONI, 1998	n < 10
BRAMBILLA *et al.*, 1997	Não avaliou TDM
BRAMBILLA, MONTELEONE & MAJ, 2004	Dados insuficientes para análise
BREMMER *et al.*, 2008	Comorbidades clínicas ou psiquiátricas
BRIETZKE *et al.*, 2011	Não avaliou TDM
BROWN *et al.*, 2016	Não avaliou TDM
BRUNONI *et al.*, 2014	Terapia antidepressiva não padrão
BYRNE *et al.*, 2013	Não avaliou TDM
CAMACHO *et al.*, 2014	Não avaliou TDM
CAMPOS *et al.*, 2014	Estudo com animais
CAPURON *et al.*, 2008	Dados insuficientes para análise
CAPURON *et al.*, 2009	Comorbidades clínicas ou psiquiátricas
CARUNCHO & RIVERA-BALTANAS, 2010	Não é estudo original
CARVALHO, L. *et al.*, 2010	Não avaliou TDM
CARVALHO, L. A. *et al.*, 2010	*Abstract.* Dados indisponíveis
CASALE *et al.*, 2011	Não mediu citocinas
CASERTA *et al.*, 2011	Não avaliou TDM
CASTILLA-CORTAZAR, CASTILLA & GURPEGUI, 1998	Estudo *in vitro*
CATENA-DELL'OSSO *et al.*, 2011	Não é estudo original
CATENA-DELL'OSSO *et al.*, 2013	Não é estudo original
CATTANEO *et al.*, 2008	Não mediu citocinas
CATTANEO *et al.*, 2012	Não mediu citocinas
CATTANEO *et al.*, 2013	Não mediu citocinas
CHANG *et al.*, 2010	*Abstract.* Dados indisponíveis
CHANG, TSENG & CHIOU, 2014	Não avaliou TDM
CHEN *et al.*, 2010	Terapia antidepressiva não padrão
CHO *et al.*, 2014	Não avaliou TDM
CHOCANO-BEDOYA *et al.*, 2014	Não avaliou TDM
CHRISTOPOULOS *et al.*, 2010	*Abstract.* Dados indisponíveis
CHUNG *et al.*, 2009	*Abstract.* Dados indisponíveis
CLARK *et al.*, 2013	Não avaliou TDM
CLERICI *et al.*, 2009	Não mediu citocinas
CONNOR & LEONARD, 1998	Não é estudo original
COSTI *et al.*, 2015	*Abstract.* Dados indisponíveis
CRADDOCK & THOMAS, 2006	Não é estudo original
DANTZER, 2009	Não é estudo original
DANTZER, 2012	Não é estudo original
DARKO *et al.*, 1988	Estudo *in vitro*
DARKO *et al.*, 1989	Não mediu citocinas
DE MELLO *et al.*, 2012	Não avaliou TDM
DEL GRANDE DA SILVA *et al.*, 2016	Terapia antidepressiva não padrão
DELLAGIOIA & HANNESTAD, 2010	Não avaliou TDM
DEMIR *et al.*, 2015	Não mediu citocinas
DENTINO *et al.*, 1999	Não avaliou TDM
DIMOPOULOS *et al.*, 2008	Comorbidades clínicas ou psiquiátricas
DINAN, 2009	Não é estudo original

DOYLE *et al.*, 2013	Não avaliou TDM
DUIVIS *et al.*, 2013	Não avaliou TDM
DUNJIC-KOSTIC *et al.*, 2015	*Abstract.* Dados indisponíveis
DUSEJA *et al.*, 2015	Estudo com animais
EINVIK *et al.*, 2012	Comorbidades clínicas ou psiquiátricas
EISENBERGER *et al.*, 2010	Não avaliou TDM
ELLER *et al.*, 2009b	Não é estudo original
ELOMAA *et al.*, 2012	Comorbidades clínicas ou psiquiátricas
ERHARDT *et al.*, 2012	Não mediu citocinas
EUTENEUER *et al.*, 2012	Comorbidades clínicas ou psiquiátricas
EUTENEUER *et al.*, 2016	Terapia antidepressiva não padrão
EYRE & BAUNE, 2012	Não é estudo original
FAGUNDES *et al.*, 2012	Não avaliou TDM
FANG *et al.*, 2012	Estudo com animais
FAREED *et al.*, 2010	*Abstract.* Dados indisponíveis
FASICK *et al.*, 2015	Não é estudo original
FIGNOLE LOFTON, 2012	Não avaliou TDM
FIGUEROA, MORENO & MALACARA, 2013	Não avaliou TDM
FISCHER *et al.*, 2012	Não avaliou TDM
FITZGERALD *et al.*, 2006	Terapia antidepressiva não padrão
FLUITMAN *et al.*, 2011	Dados insuficientes para análise
FONSEKA *et al.*, 2014	Não é estudo original
FONSEKA *et al.*, 2015	Não é estudo original
FORTI *et al.*, 2010	Comorbidades clínicas ou psiquiátricas
FROMMBERGER *et al.*, 1997	n < 10
GABBAY, Vilma *et al.*, 2009	Dados insuficientes para análise
GABBAY, V. *et al.*, 2009	Dados insuficientes para análise
GAZAL *et al.*, 2013	Terapia antidepressiva não padrão
GAZAL *et al.*, 2015	Comorbidades clínicas ou psiquiátricas
GIBNEY *et al.*, 2011	Estudo com animais
GILBEY *et al.*, 2011	Não mediu citocinas
GIMENO *et al.*, 2009	Terapia antidepressiva não padrão
GLAUS *et al.*, 2014	Comorbidades clínicas ou psiquiátricas
GLAUS *et al.*, 2016	*Abstract.* Dados indisponíveis
GOLDSCHMIED *et al.*, 2013	*Abstract.* Dados indisponíveis
GOLDSMITH *et al.*, 2015	*Abstract.* Dados indisponíveis
GOLDSMITH *et al.*, 2016	Não avaliou TDM
GRASSI-OLIVEIRA, BAUER*, et al.*, 2011	Dados insuficientes para análise
GRASSI-OLIVEIRA, BRIETZKE*, et al.*, 2011	*Abstract.* Dados indisponíveis
GROER *et al.*, 2012	Não avaliou TDM
GRUDET *et al.*, 2014	Não avaliou TDM
GUIDI *et al.*, 1991	Estudo *in vitro*
HAACK *et al.*, 1999	Comorbidades clínicas ou psiquiátricas
HAASTRUP *et al.*, 2012	Dados insuficientes para análise
HAFNER *et al.*, 2011	Não avaliou TDM
HALARIS *et al.*, 2009	Não é estudo original
HALARIS *et al.*, 2011	*Abstract.* Dados indisponíveis

HALARIS, MERESH, FAREED, HOPPENSTEAD*, et al.*, 2012	*Abstract.* Dados indisponíveis
HALARIS, MERESH, FAREED, HOPPENSTEADT, KIMMONS*, et al.*, 2012	*Abstract.* Dados indisponíveis
HALARIS, MERESH, FAREED, HOPPENSTEADT & SINACORE, 2012	*Abstract.* Dados indisponíveis
HALARIS *et al.*, 2014	Dados insuficientes para análise
HALLBERG *et al.*, 2010	Dados insuficientes para análise
HAROON *et al.*, 2015	*Abstract.* Dados indisponíveis
HASHIMOTO *et al.*, 2015	Dados insuficientes para análise
HASHIOKA *et al.*, 2007	Não avaliou TDM
HAYLEY, 2011	Não é estudo original
HAYLEY, MERALI & ANISMAN, 2003	Não é estudo original
HEISER *et al.*, 2008	Administração prévia de corticosteróide
HENJE BLOM *et al.*, 2011	Comorbidades clínicas ou psiquiátricas
HENNESSY *et al.*, 2011	Estudo com animais
HENNINGS *et al.*, 2013	Comorbidades clínicas ou psiquiátricas
HERRAN *et al.*, 2000	Dados insuficientes para análise
HESTAD *et al.*, 2003	Não avaliou TDM
HESTAD *et al.*, 2005	Não é estudo original
HILES *et al.*, 2015	Não avaliou TDM
HIMMERICH *et al.*, 2004	Não avaliou TDM
HIMMERICH *et al.*, 2008	Comorbidades clínicas ou psiquiátricas
HIMMERICH, BERTHOLD-LOSLEBEN & POLLMACHER, 2009	Não é estudo original
HIMMERICH, FULDA*, et al.*, 2010a	Dados insuficientes para análise
HIMMERICH, FULDA*, et al.*, 2010b	Não avaliou TDM
HO, 2014	Não é estudo original
HODES *et al.*, 2011	Estudo com animais
HUFNER *et al.*, 2015	Não mediu citocinas
HUGHES *et al.*, 2012	*Abstract.* Dados indisponíveis
HUGHES *et al.*, 2013	Não avaliou TDM
HUMPHREYS *et al.*, 2006	n < 10
HWANG *et al.*, 2009	Não mediu citocinas
IACOB, 2014	Não mediu citocinas
ISUNG *et al.*, 2012	Não avaliou TDM
IWATA, OTA & DUMAN, 2013	Não é estudo original
JANELIDZE *et al.*, 2011	Comorbidades clínicas ou psiquiátricas
JANGPANGI *et al.*, 2012	*Abstract.* Dados indisponíveis
JOHNSON, 2009	Não avaliou TDM
JOZUKA *et al.*, 2000	Não avaliou TDM
JOZUKA *et al.*, 2003	Dados insuficientes para análise
KABANCHIK *et al.*, 2004	Dados indisponíveis
KAGAYA *et al.*, 2001	n < 10
KAMINSKA *et al.*, 2002	Dados indisponíveis
KANG *et al.*, 2011	Estudo com animais
KARAOULANIS *et al.*, 2012	Comorbidades clínicas ou psiquiátricas
KARRENBAUER *et al.*, 2010	Estudo com animais

KAST, 2003	Não avaliou TDM
KEMP *et al.*, 2011	Terapia antidepressiva não padrão
KENIS & MAES, 2002	Não é estudo original
KHAIROVA *et al.*, 2009	Não é estudo original
KHAN *et al.*, 2013	Não é estudo original
KIM, NA*, et al.*, 2007	Amostra tratada com anticorpo monoclonal
KIM, WON*, et al.*, 2007	Não avaliou TDM
KIRALY *et al.*, 2016	*Abstract.* Dados indisponíveis
KLOIBER *et al.*, 2012	*Abstract.* Dados indisponíveis
KOO & DUMAN, 2009	Não é estudo original
KOO *et al.*, 2010	Não avaliou TDM
KROGH & NORDENTOFT, 2011	*Abstract.* Dados indisponíveis
KUBERA, KENIS, BOSMANS, SCHARPE*, et al.*, 2000	Estudo *in vitro*
KUBERA, KENIS, BOSMANS, ZIEBA*, et al.*, 2000	Dados indisponíveis
KUBERA *et al.*, 2001	n < 10
KUBERA *et al.*, 2004	Estudo *in vitro*
KUBERA *et al.*, 2005	Estudo *in vitro*
KUSUNOKI *et al.*, 1999	Dados insuficientes para análise
LAI *et al.*, 2016	Não avaliou TDM
LAMERS *et al.*, 2013	Não avaliou TDM
LANDMANN *et al.*, 1997	Estudo *in vitro*
LANQUILLON *et al.*, 2000	Estudo *in vitro*
LAZARY *et al.*, 2012	Não mediu citocinas
LEE *et al.*, 2013	Não mediu citocinas
LEHTIMAKI *et al.*, 2008	n < 10
LEHTO, NISKANEN, HERZIG*, et al.*, 2010	Não é estudo original
LEHTO, NISKANEN, MIETTOLA*, et al.*, 2010	Não avaliou TDM
LEONARD, B., 2012	Não é estudo original
LEONARD, B. E., 2012	Não é estudo original
LEONARD, B. & MAES, M., 2012	Não é estudo original
LEVANDOVSKI *et al.*, 2013	Não avaliou TDM
LIATIS, 2013	Não avaliou TDM
LICHTBLAU *et al.*, 2013	Não é estudo original
LICINIO & WONG, 1999	Não é estudo original
LIU, FENG, MAO*, et al.*, 2015	Diagnóstico de TDM com instrumentos não padrão
YI *et al.*, 2015	Terapia antidepressiva não padrão
LIU, FENG, MO*, et al.*, 2015	Diagnóstico de TDM com instrumentos não padrão
LOTRICH, 2011	Não é estudo original
LUCAS *et al.*, 2014	Não avaliou TDM
LUTGENDORF *et al.*, 1999	Não avaliou TDM
MACIUKIEWICZ *et al.*, 2015	Não mediu citocinas
MAES, 1995	Não mediu citocinas
MAES, 2001	Não é estudo original
MAES *et al.*, 1990	Administração prévia de corticosteróide
MAES *et al.*, 1991	Estudo *in vitro*
MAES *et al.*, 1992	Dados insuficientes para análise

MAES, SCHARPE*, et al.*, 1993	Estudo *in vitro*
MAES, STEVENS*, et al.*, 1993	Não mediu citocinas
MAES, BOSMANS*, et al.*, 1995	Administração prévia de corticosteróide
MAES, VANDOOLAEGHE*, et al.*, 1995	Dados insuficientes para análise
MAES *et al.*, 1996	Dados insuficientes para análise
MAES *et al.*, 1999	Não mediu citocinas
MAES, SONG & YIRMIYA, 2012	Não é estudo original
MAES *et al.*, 2014	Não é estudo original
MAGALHAES *et al.*,	*Abstract.* Dados indisponíveis
MANOHARAN *et al.*, 2016	Comorbidades clínicas ou psiquiátricas
MARQUES-DEAK *et al.*, 2007	Comorbidades clínicas ou psiquiátricas
MARTINEZ *et al.*, 2012	Mediu citocinas no líquor
MATSUSHIMA *et al.*, 2015	Não avaliou TDM
MCDADE *et al.*, 2013	Não avaliou TDM
MERENDINO *et al.*, 2004	n < 10
MESQUITA *et al.*, 2008	Estudo com animais
MILANESCHI *et al.*, 2009	Não avaliou TDM
MILLER & COLE, 2012	Terapia antidepressiva não padrão
MILLER, COHEN & HERBERT, 1999	Não mediu citocinas
MILLER *et al.*, 2002	Não avaliou TDM
MILLER *et al.*, 2003a	Não avaliou TDM
MILLER *et al.*, 2003b	Não avaliou TDM
MILLER *et al.*, 2005	Não avaliou TDM
MISCHOULON, 2015	*Abstract.* Dados indisponíveis
MISHRA, PAWAR & RYLI, 2013	*Abstract.* Dados indisponíveis
MISHRA *et al.*, 2015	*Abstract.* Dados indisponíveis
MITCHELL *et al.*, 2013	Dados insuficientes para análise
MOLTENI *et al.*, 2013	Estudo com animais
MOMENI *et al.*, 2014	Não avaliou TDM
MOREIRA *et al.*, 2015	Terapia antidepressiva não padrão
MULLER, 2014	Não é estudo original
NASSAN *et al.*, 2015	*Abstract.* Dados indisponíveis
NEBBIA, PARIANTE & KERWIN, 2000	Não é estudo original
NIEDZWIECKI *et al.*, 2013	*Abstract.* Dados indisponíveis
NINAN *et al.*, 2012	Não mediu citocinas
NOTO *et al.*, 2015	Não é estudo original
NUNES *et al.*, 2002	Dados insuficientes para análise
O'DONOVAN *et al.*, 2010	*Abstract.* Dados indisponíveis
OGLODEK *et al.*, 2014	Não é estudo de intervenção
OLAJOSSY *et al.*, 2014	Comorbidades clínicas ou psiquiátricas
OSES *et al.*, 2016	Terapia antidepressiva não padrão
OVASKAINEN *et al.*, 2009	Não avaliou TDM
PACE *et al.*, 2006	Dados insuficientes para análise
PACE *et al.*, 2010	Terapia antidepressiva não padrão
PALLAVI, 2014	*Abstract.* Dados indisponíveis
PALLAVI *et al.*, 2015	Dados insuficientes para análise
PANDEY, 2015	Não mediu citocinas

PANTOVIC *et al.*, 2013	Dados insuficientes para análise
PARK & BAEK, 2013	Não avaliou TDM
PARK *et al.*, 2016	Comorbidades clínicas ou psiquiátricas
PATAS *et al.*, 2014	Comorbidades clínicas ou psiquiátricas
PAVON *et al.*, 2011	Não mediu citocinas
PAVON *et al.*, 2013	*Abstract.* Dados indisponíveis
PAVON ROMERO *et al.*, 2011	*Abstract.* Dados indisponíveis
PENNINX *et al.*, 2003	Comorbidades clínicas ou psiquiátricas
PENNINX *et al.*, 2011	*Abstract.* Dados indisponíveis
PODLIPNY *et al.*, 2010	Não avaliou TDM
POLESHUCK *et al.*, 2013	Não avaliou TDM
POSTAL & APPENZELLER, 2015	Não é estudo original
POSTOLACHE *et al.*, 2009	Não é estudo original
PRATHER, VOGELZANGS & PENNINX, 2015	Não avaliou TDM
PROSSIN *et al.*, 2010	Terapia antidepressiva não padrão
PROSSIN *et al.*, 2012	Terapia antidepressiva não padrão
PUCAK & KAPLIN, 2005	Não é estudo original
QI *et al.*, 2005	Dados insuficientes para análise
QUAK *et al.*, 2014	Não avaliou TDM
QUINONES *et al.*, 2012	Dados insuficientes para análise
RAGHUVANSHI *et al.*, 2013	Terapia antidepressiva não padrão
RAISON *et al.*, 2012	Terapia antidepressiva não padrão
RAISON, C. L. *et al.*, 2013	Terapia antidepressiva não padrão
RANJBAR *et al.*, 2014	Dados insuficientes para análise
RAPAPORT, 2015	Terapia antidepressiva não padrão
RAPAPORT *et al.*, 2016	Terapia antidepressiva não padrão
RAWDIN *et al.*, 2012	*Abstract.* Dados indisponíveis
RAWDIN *et al.*, 2013	Comorbidades clínicas ou psiquiátricas
RETHORST *et al.*, 2011	Não avaliou TDM
RETHORST *et al.*, 2013	Terapia antidepressiva não padrão
RETHORST *et al.*, 2015a	Terapia antidepressiva não padrão
RETHORST *et al.*, 2015b	Terapia antidepressiva não padrão
REYES-ORTIZ, 1999	Não é estudo original
RIEF *et al.*, 2001	Comorbidades clínicas ou psiquiátricas
ROTHENHAUSLER, STEPAN & KAPFHAMMER, 2006	Não avaliou TDM
ROTHERMUNDT, AROLT, FENKER*, et al.*, 2001	Dados insuficientes para análise
ROTTER *et al.*, 2013	Eletroconvulsoterapia como intervenção
RULJANCIC *et al.*, 2011	*Abstract.* Dados indisponíveis
RUSH *et al.*, 2010	*Abstract.* Dados indisponíveis
RYBKA, 2013	*Abstract.* Dados indisponíveis
RYBKA *et al.*, 2012	*Abstract.* Dados indisponíveis
SAVITZ *et al.*, 2015	Não mediu citocinas
SCHIEPERS, WICHERS & MAES, 2005	Não é estudo original
SCHILLING PANIZZUTTI *et al.*, 2013	*Abstract.* Dados indisponíveis
SCHLATTER, ORTUNO & CERVERA-ENGUIX, 2001	Estudo *in vitro*
SCHLATTER, ORTUNO & CERVERA-ENGUIX,	Estudo *in vitro*

2004a	
SCHLATTER, ORTUNO & CERVERA-ENGUIX, 2004b	Estudo *in vitro*
SCHLATTER *et al.*, 2006	Estudo *in vitro*
SCHMIDT, Frank M. *et al.*, 2016	Dados insuficientes para análise
SCHMIDT, F. M. *et al.*, 2016	Comorbidades clínicas ou psiquiátricas
SCHULD *et al.*, 2001	Terapia antidepressiva não padrão
SCHULD *et al.*, 2003	Administração prévia de corticosteróide
SEIDEL *et al.*, 1996	Estudo *in vitro*
SEKIYAMA *et al.*, 2009	*Abstract.* Dados indisponíveis
SHARMA *et al.*, 2015	*Abstract.* Dados indisponíveis
SILIC, KARLOVIC & SERRETTI, 2012	Dados insuficientes para análise
SLUZEWSKA, RYBAKOWSKI, SOBIESKA*, et al.*, 1995	Comorbidades clínicas ou psiquiátricas
SLUZEWSKA *et al.*, 1997	Não avaliou TDM
SONG *et al.*, 1998	n < 10
STELZHAMMER *et al.*, 2013	n < 10
STEPTOE, KUNZ-EBRECHT & OWEN, 2003	Não avaliou TDM
STEWART *et al.*, 2008	Não avaliou TDM
SU *et al.*, 2009	Não avaliou TDM
SU *et al.*, 2011	Não avaliou TDM
SUAREZ, 2003	Não avaliou TDM
TALAIE *et al.*, 2008	Não avaliou TDM
THIAGARAJAH *et al.*, 2014	Não mediu citocinas
TIEMEIER *et al.*, 2003	Não avaliou TDM
TOUPS *et al.*, 2011	Dados insuficientes para análise
TOUPS *et al.*, 2014	Dados insuficientes para análise
TRZONKOWSKI *et al.*, 2004	Comorbidades clínicas ou psiquiátricas
TSAO *et al.*, 2006	Não mediu citocinas
TULLY *et al.*, 2015	Não avaliou TDM
TYNAN, HINWOOD*, et al.*, 2012	Não avaliou TDM
USHIROYAMA, IKEDA & UEKI, 2002	Não avaliou TDM
USHIROYAMA *et al.*, 2005	Não avaliou TDM
VACCARINO *et al.*, 2008	Comorbidades clínicas ou psiquiátricas
VARMA, 2014	Não é estudo original
VETTA *et al.*, 2001	Dados insuficientes para análise
VINBERG *et al.*, 2015	*Abstract.* Dados indisponíveis
VODERHOLZER *et al.*, 2012	Terapia antidepressiva não padrão
VOGELZANGS *et al.*, 2010	Comorbidades clínicas ou psiquiátricas
VOGELZANGS *et al.*, 2012	Não avaliou TDM
VOGELZANGS, Nicole *et al.*, 2014	Dados insuficientes para análise
VOGELZANGS, N. *et al.*, 2014	Não avaliou TDM
WALKER *et al.*, 2015	Estudo com animais
WANG *et al.*, 2009	Comorbidades clínicas ou psiquiátricas
WEIZMAN *et al.*, 1994	Estudo *in vitro*
WEST & MAES, 1999	Não é estudo original
WOJCIAK *et al.*, 2007	Comorbidades clínicas ou psiquiátricas
YANG *et al.*, 2011	Não mediu citocinas

YANG *et al.*, 2015	Não é estudo original
YASUI *et al.*, 2009	Não avaliou TDM
YOON *et al.*, 2012	Dados insuficientes para análise
YOSHIMURA & NAKAMURA, 2013	*Abstract.* Dados indisponíveis
YOSHIMURA *et al.*, 2010	*Abstract.* Dados indisponíveis
YU *et al.*, 2015	Terapia antidepressiva não padrão
ZALLI *et al.*, 2015	Não avaliou TDM
ZEUGMANN *et al.*, 2010	Dados insuficientes para análise
ZEUGMANN *et al.*, 2013	Não avaliou TDM
ZHANG *et al.*, 2015	Comorbidades clínicas ou psiquiátricas
ZOGA *et al.*, 2014	Terapia combinada ECT e antidepressivos
ZUBAREVA *et al.*, 2001	n < 10

ANEXO 3. Manuscrito publicado em *Acta Psychiatrica Scandinavica* (Metanálise que aborda o papel das citocinas e quimiocinas como biomarcadores diagnósticos no TDM).

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Meta-analysis

Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies

Köhler CA, Freitas TH, Maes M, de Andrade NQ, Liu CS, Fernandes BS, Stubbs B, Solmi M, Veronese N, Herrmann N, Raison CL, Miller BJ, Lanctôt KL, Carvalho AF. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies.

Objective: To conduct a systematic review and meta-analysis of studies that measured cytokine and chemokine levels in individuals with major depressive disorder (MDD) compared to healthy controls (HCs).
Method: The PubMed/MEDLINE, EMBASE, and PsycINFO databases were searched up until May 30, 2016. Effect sizes were estimated with random-effects models.
Result: Eighty-two studies comprising 3212 participants with MDD and 2798 HCs met inclusion criteria. Peripheral levels of interleukin-6 (IL-6), tumor necrosis factor (TNF)-alpha, IL-10, the soluble IL-2 receptor, C-C chemokine ligand 2, IL-13, IL-18, IL-12, the IL-1 receptor antagonist, and the soluble TNF receptor 2 were elevated in patients with MDD compared to HCs, whereas interferon-gamma levels were lower in MDD (Hedge's $g = -0.477$, $P = 0.043$). Levels of IL-1β, IL-2, IL-4, IL-8, the soluble IL-6 receptor (sIL-6R), IL-5, CCL-3, IL-17, and transforming growth factor-beta 1 were not significantly altered in individuals with MDD compared to HCs. Heterogeneity was large (I^2: 51.6–97.7%), and sources of heterogeneity were explored (e.g., age, smoking status, and body mass index).
Conclusion: Our results further characterize a cytokine/chemokine profile associated with MDD. Future studies are warranted to further elucidate sources of heterogeneity, as well as biosignature cytokines secreted by other immune cells.

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Key words: cytokines; chemokines; inflammation meta-analysis; depression

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Summations

- Evidence indicates that peripheral immune activation may be involved in the pathophysiology of major depressive disorder.
- Herein, we conducted an updated meta-analytic review of 82 studies that measured cytokines and/or chemokines in individuals with major depressive disorder and healthy controls.
- Levels of IL-6, TNF-α, 10, the soluble IL-2 receptor, C-C chemokine ligand 2, IL-13, IL-18, IL-12, the IL-1 receptor antagonist, and the soluble TNF receptor 2 were elevated, whereas interferon-γ levels were reduced in individuals with major depressive disorder compared to controls. These results add in the characterization of a putative cytokine/chemokine profile for major depressive disorder.

Considerations

- A large degree of heterogeneity was evident in this literature. Potential sources of heterogeneity were not consistently reported across included studies.
- Methodological quality has varied across included studies.

Introduction

In the past two decades, an increasing body of evidence indicates that aberrations in immune-inflammatory pathways and activation of cell-mediated immunity represent important pathophysiological pathways for the development of major depressive disorder (MDD) (1, 2). In addition, converging experimental and clinical research points that reciprocal neuroimmune interactions may contribute to the neurobiology of MDD (3, 4). A low-grade inflammatory response characterized by increased numbers of granulocytes and monocytes (1), as well as the elevated levels of acute phase reactants (e.g., C-reactive protein and haptoglobin) (5, 6), inflammatory cytokines (7), and possibly chemokines (8), has been demonstrated in groups of individuals with MDD compared to healthy controls (HCs). These peripheral immune abnormalities may influence brain function through several mechanisms. For example, evidence indicates that cytokines may cross the blood-brain barrier, while certain cytokines (e.g., IL-1β) may convey signals to the brain via afferent nerves like the vagus (2, 4). The pathophysiological role of proinflammatory cytokines in MDD is further supported by preclinical research indicating that proinflammatory cytokines may promote depressive-like behaviours, whereas TNF-α and IL-6 receptor knockout mice exhibit resilience to stress-induced depressive-like behaviours (9–11). In addition, a recent meta-analysis estimates that ~25% of patients with chronic hepatitis C develop depression after treatment with the proinflammatory cytokine interferon-α (IFN-α) (12). The common denominator among these findings is that peripheral immune dysregulation may represent an important pathway for inducing functional and structural brain changes that underpin the pathophysiology of MDD. Perhaps as a consequence of this, peripheral inflammatory mediators have emerged as promising candidate biomarkers for MDD (13), although evidence of bias may limit inferences derived from the literature on peripheral biomarkers for MDD (14).

A meta-analysis that included 24 studies provided evidence that peripheral levels of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) are significantly elevated in individuals with MDD compared to healthy controls (HCs) (7). However,

between-study heterogeneity for these estimates was high (7). A more recent cumulative meta-analysis confirmed that peripheral levels of IL-6 are elevated in individuals with MDD and HCs, whereas no consistent evidence of changes in TNF-α and IL-1β in patients with MDD compared to controls was found (5). This significant degree of heterogeneity could be explained by a number of factors including but not limited to the following: differences in assay methods across laboratories, medication status, and potential confounders (e.g., body mass index and smoking). Furthermore, it has been increasingly recognized that the phenotypic heterogeneity of MDD may contribute to discrepant findings. For example, melancholic depression is associated with elevated HPA axis activity (15, 16), whereas individuals with atypical depression appear to have higher levels of proinflammatory markers (16). In addition, each individual cytokine/chemokine may have different functions relevant to the pathophysiology of MDD. For example, some cytokines/chemokines are predominantly proinflammatory, whereas others are mainly anti-inflammatory, and some of these immune mediators have been increasingly implicated in neuroplasticity mechanisms (17, 18). Therefore, the characterization of peripheral levels of a wider array of cytokines and chemokines may be of particular relevance to this field.

Aims of the study

Since the publication of these previous meta-analyses (5, 7, 19, 20), additional studies have been conducted examining a wider range of immune biomarkers. Therefore, the aims of this large, collaborative meta-analysis were to investigate differences in peripheral levels of a wider range of cytokines and chemokines among individuals with major depressive disorder compared to healthy controls and to explore potential sources of heterogeneity across studies. We anticipated that the large number of new studies would allow for a more precise characterization of the role of cytokines and chemokines as peripheral biomarkers for major depressive disorder.

Methods

This study comprised a between-group meta-analysis of studies that compared cytokine or chemokine levels between adults with MDD and healthy controls. We complied with the Preferred Reported Items for Systematic Reviews and Meta-analysis (PRISMA) statement (21). The literature search, title/abstract screening, final decision on eligibility after full-text review, and data extraction were independently performed by two investigators. An *a priori* defined yet unpublished protocol was followed.

Search strategy

A systematic search was conducted in the PubMed/MEDLINE, EMBASE, and PsycINFO databases from inception up until May 30, 2016. The detailed search strings used in this review are presented in the supporting information that accompanies the online version of this article. This search strategy was augmented through tracking the citation of included articles in Google Scholar (22).

Study selection

We included original references published in any language. Eligible studies had to measure peripheral cytokine or chemokine levels in adult subjects (age ≥ 18 years old) that met either DSM (23) or ICD (24) criteria for MDD, and a comparison group of healthy controls (HCs). The following exclusion criteria were adopted: (i) studies that reported that participants had medical and/or psychiatric comorbidities were excluded (except current smoking); (ii) studies that included pregnant women or women in the postpartum period; (iii) case reports or case series ($N < 10$); (iv) studies that assayed the mediators in specimens/tissues other than blood; and (v) studies in animals. The authors of meeting abstracts that met inclusion criteria were contacted by e-mail to provide data for analysis (no additional data were provided).

Data extraction

For each cytokine/chemokine, we extracted the means, variance estimates [standard deviation (SD), standard error of the mean (SEM), or 95% confidence interval (CI)], and sample sizes for both MDD and HC groups. From studies that presented only results of the comparison of the MDD and HC groups, we extracted the appropriate measure (z-score or t-score). In studies that provided median ± IQR or median ± range, we estimated the mean ± SD following a standard method (25). We also extracted the following data whenever available: (i) first author, (ii) publication year, (iii) gender distribution of study sample (% females), (iv) mean age and BMI, (v) mean illness duration (years), (vi) treatment status (drug-free during assessment and/or treatment-naïve), (vii) percentage of the sample with atypical and/or melancholic depression, (viii) measurement of depressive symptoms, and (ix) % of current smokers.

Methodological quality of included studies

We devised a score to estimate the methodological quality of each study based on the following

parameters: (i) study sample ≥ 50 participants (1 = Yes; 0 = No); (ii) Did the study control results for potential confounders (e.g., age, BMI, gender, race)? (1 = Y; 0 = No); (iii) Were participants with MDD and HCs age- and gender-matched? (1 = Y; 0 = No); (iv) Was the time of sample collection specified? (e.g., morning vs. evening) (1 = Y; 0 = No); (v) Were participants with MDD free of antidepressant drugs during sample collection? (1 = Y; 0 = No); and (vi) Reporting of either the manufacturer of the test or its parameters (detection limit and coefficient of variation) (1 = Y; 0 = No). Thus, the score may vary from 0 to 6, with higher scores indicating better methodological quality.

Statistical analysis

Because studies used different measurement methods, we estimated a standardized mean difference and 95% CI (Hedges's *g*) for each immune mediator, which provides an unbiased effect size (ES) adjusted for small sample sizes (26). We assessed the heterogeneity across studies using the Cochran *Q* test, which provides a weighted sum of the squares of the deviations of individual study ES estimates from the overall estimate. In addition, heterogeneity across studies was quantified with the I^2 statistic, which indicates the percentage of total variation across several studies due to heterogeneity and which is considered high when ≥50% (27). We anticipated a high degree of heterogeneity. Therefore, we pooled ES using a random-effects model according to the DerSimonian and Laird method (28). Meta-analyses were conducted only for immune mediators with at least three individual datasets.

Studies with statistically non-significant (i.e., negative) results are less likely to be published than studies with significant results (14, 29). To assess publication bias, we inspected a funnel plot graph for asymmetry and calculated the Egger's regression test for funnel plot asymmetry (30). Evidence of small-study effects (indicative of publication bias) was considered when the *P*-value of the Egger's test was <0.1, and the ES of the largest study was more conservative or changed direction when compared with the overall ES estimate (funnel plots of ES estimates in which evidence of publication bias was observed are illustrated in Figs S10–S14) (14). The trim-and-fill procedure was used to estimate the ES adjusting for publication bias (31), while the fail-safe N (i.e., the file drawer statistic) was used to determine how many additional studies would be necessary to turn a significant ES non-significant (32).

We explored potential sources of heterogeneity across studies for each ES estimate, using either subgroup (if there were at least three studies in each subgroup) or random-effects meta-regression analyses. Meta-regression analyses were conducted only when at least 10 studies provided moderator; this decision was made *a priori* because with fewer datasets, this analytic tool may provide spurious results (33). The following variables were considered in meta-regression analyses: sample size, mean age of MDD group, mean age of the HC group, differences in mean age (MDD group *minus* HC group), mean body mass index (BMI) of MDD group, mean BMI of the HC group, differences in mean BMI (MDD group *minus* HC group), % of females in the MDD group, % of females in the HC group, difference in % of females (MDD group *minus* HC group), % of current smokers, latitude of the country where the study was executed, depression severity (expressed as a percentage of the cutoff for severe depression in the rating scale), methodological quality of each included study, and mean illness duration in years. Studies were weighted in such a way that investigations with more precise parameters (indicated by sample size and 95% CI) had more influence in meta-regression analyses (34). For statistically significant ES estimates, we performed sensitivity analyses in which we excluded each study from analyses to verify whether a single study turned results non-significant or otherwise changed the direction of the ES. In addition, cumulative meta-analysis was performed for significant ES with at least 10 datasets.

All analyses were conducted in Stata MP software version 14.0 (Stata Corp, College Station, TX, USA) using the metan package. Statistical significance was considered at an alpha level of 0.05.

Results

Study selection

Following removal of duplicates, the title/abstracts of 4911 unique references were screened for eligibility. A total of 4432 references were excluded, while 479 full texts were retrieved and screened for eligibility. Of those articles, 397 were excluded (see Table S1 for reasons for exclusion). Finally, 82 original studies met inclusion criteria, which provided data from 6010 participants (3212 participants with MDD and 2798 HCs). Figure 1 provides the PRISMA flowchart for study selection.

Characteristics and methodological quality of included studies

Of the 82 studies included in our meta-analysis, in 43 studies (52.4%), participants with MDD and HCs were age- and gender-matched, while 35

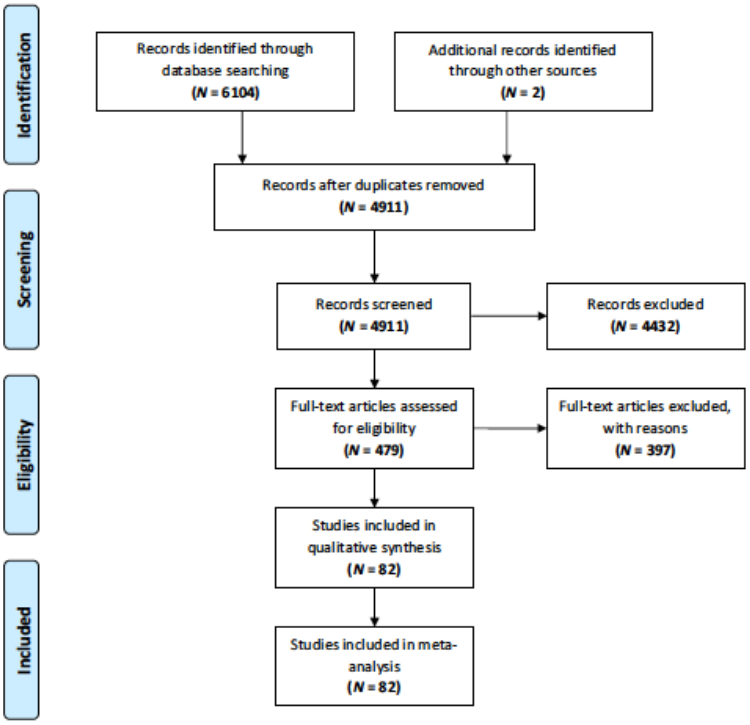

Fig. 1. PRISMA flowchart of study selection for systematic review and meta-analysis. [Colour figure can be viewed at wileyonlinelibrary.com]

studies (42.7%) adjusted results for potential confounders (e.g., age, gender distribution, depressive symptom scores, or BMI). In addition, most studies (k = 81; 98.8%) either reported the manufacturer of the assay or provided values of the coefficient of variation (CV) of the test. In addition, most studies (k = 65; 79.3%) provided data regarding medication status, whereas three (3.7%) included only treatment-naïve (i.e., never treated with antidepressants) participants with MDD. Finally, most studies did not provide information on illness duration (k = 56; 68.3%); the remaining studies included MDD participants with illness duration of 2.97 ± 6.15 (mean ± SD) years. The methodological quality scores of each study varied from 1 to 6 (median: 4) (Table S2).

Studies of IL-6

Il-6 measurements were extracted from 42 studies (1587 cases and 1183 controls). Participants with MDD had higher concentrations compared to HCs (g = 0.621; P < 0.001; Table 1 and Fig. 2a). No evidence of small-study effects (which provides an indication of publication bias) was observed. Possible sources for the large heterogeneity (I^2 = 64.9%) were explored using meta-regression and subgroup analyses (Tables S3 and S4). In meta-regression analyses, differences in gender distribution (% females) in the MDD and HC groups emerged as a significant moderator (P = 0.046). Subgroup analyses showed that heterogeneity was smaller in studies that measured IL-6 in serum and whole blood samples compared to plasma, while results suggest that the measurement of IL-6 with ELISA is associated with higher heterogeneity compared to other types of assay.

Of 42 studies that measured IL-6, 10 provided adjusted differences in peripheral levels of this cytokine to confounders (e.g., age, gender, BMI, smoking, among other variables specific to the study) (35–44). We re-calculated this ES considering those adjusted values. Then, the overall ES of IL-6 was 0.543 (95% CI = 0.435 0.651; P < 0.001). The I^2 value was 49.8% (P < 0.001). In addition, we performed a subgroup analysis considering studies which did vs. did not adjust comparisons to confounders. The overall ES for the unadjusted studies was 0.574 (95% CI = 0.437–0.711; P < 0.001; k = 32), with an I^2 of 52.3% (P < 0.001). The overall ES for the adjusted studies was 0.467 (95% CI = 0.303–0.631; P < 0.001; k = 10), with a I^2 of 38.6% (P = 0.101). Therefore, studies that adjusted to potential confounders had a lower degree of heterogeneity.

In sensitivity analysis, the exclusion of any individual study from the analysis did not alter the direction or statistical significance of the ES

Table 1. Primary meta-analyses of studies measuring peripheral cytokines and chemokines in individuals with MDD vs. healthy controls

Mediator	*N* Studies	*N* MDD	*N* Controls	ES (95% CI)	*P*-value (overall)*	I^2	*P*-value (Egger)†	Small-study effects‡	Fail-safe N	Adjusted ES (95% CI)§
IL-6	42	1587	1183	0.621 (0.486–0.755)	**<0.001**	64.9	0.950	N	2497	0.621 (0.486–0.755)
TNF-α	42	1620	1457	0.675 (0.431–0.919)	**<0.001**	90.0	**0.009**	Y	2431	0.675 (0.431–0.919)
IL-1β	22	779	727	0.032 (−0.291–0.354)	0.847	89.3	0.180	N	0	−0.152 (−0.477–0.173)
IFN-γ	17	700	770	−0.477 (−0.939 to −0.015)	**0.043**	94.0	**<0.001**	Y	95	−0.477 (−0.939 to −0.015)
IL-10	17	608	675	0.375 (0.008–0.742)	**0.045**	89.2	0.277	N	107	0.375 (0.008–0.742)
IL-2	10	357	476	−0.108 (−0.900–0.683)	0.789	95.8	0.918	N	1	−0.108 (−0.900–0.683)
IL-4	10	350	450	−0.533 (−1.073–0.007)	0.053	91.0	**0.085**	Y	41	−0.533 (−1.073–0.007)
sIL-2 receptor	10	489	391	0.735 (0.418–1.052)	**<0.001**	77.5	0.741	N	224	0.735 (0.418–1.052)
CCL-2	8	285	287	1.718 (0.641–2.794)	**0.002**	96.3	**0.044**	Y	144	1.718 (0.641–2.794)
IL-8	7	306	217	0.032 (−0.346–0.410)	0.869	76.9	0.229	N	0	0.032 (−0.346–0.410)
sIL-6 receptor	7	344	256	0.330 (−0.008–0.667)	0.055	71.3	0.115	N	12	0.330 (−0.008–0.667)
IL-13	6	243	373	1.836 (0.812–2.861)	**<0.001**	96.0	**0.009**	Y	255	1.432 (0.445–2.418)
IL-18	5	135	143	1.720 (0.379–3.062)	**0.012**	95.3	0.105	N	114	1.720 (0.379–3.062)
IL-12	4	135	301	1.229 (0.275–2.182)	**0.012**	92.9	0.609	N	71	1.229 (0.275–2.182)
IL-1Ra	4	148	110	0.449 (0.082–0.815)	**0.016**	51.6	0.986	N	9	0.449 (0.082–0.815)
IL-5	4	198	322	0.396 (−0.072–0.865)	0.097	82.1	0.105	N	18	0.396 (−0.072–0.865)
CCL-3	3	110	98	1.974 (−0.231–4.179)	0.079	97.5	0.180	N	52	1.974 (−0.231–4.179)
IL-17	3	85	106	−0.121 (−0.537–0.295)	0.569	51.6	0.212	N	0	−0.121 (−0.537–0.295)
TGF-β1	3	110	68	−1.480 (−4.756–1.797)	0.376	97.7	0.367	N	5	−1.480 (−4.756–1.797)
sTNFR2	3	94	101	1.173 (0.409–1.938)	**0.003**	83.2	0.368	N	36	1.173 (0.409–1.938)

CI, confidence interval; ES, effect size; MDD, major depressive disorder; Y, Yes; N, No; NA, Not applicable; statistically significant results are in bold.
*In *Z*-test of overall effect.
†In Egger's test of publication bias.
‡$P < 0.1$ in Egger's test of publication bias and effect size of the largest study more conservative than the overall effect size or in the opposite direction.
§Adjusted using Duval and Tweedie's trim-and-fill procedure.

estimate (Fig. S15). Cumulative meta-analysis indicated that ES estimates are consistent across studies since 1996 (Fig. S26).

Studies of TNF-α

TNF-α was investigated across 42 studies, and levels were significantly higher in the MDD group compared to HCs, while there was evidence of small-study effects ($g = 0.638$; $P < 0.001$; Table 1 and Fig. 2b); the ES was unaltered after adjustment for publication bias (Table 1). Heterogeneity was large ($I^2 = 90.0\%$). The percentage of current smokers in both the MDD and HC groups moderated the ES; in both groups, a higher prevalence of smokers was associated with a higher ES estimate (Table S3). The methodological quality of included studies also emerged as a significant moderator (Table S3). The ES estimate was smaller in studies with better methodological quality. In addition, levels of TNF-α were not significantly altered in individuals with melancholic depression compared to controls ($g = 0.141$; $k = 4$; $P = 0.418$). Sensitivity analysis indicated that the exclusion of any single study (one at a time) did not alter the direction or statistical significance of the ES estimate (Fig. S16). In the cumulative meta-analysis, this ES estimate remained consistent (moderate) after the addition of the most recent eight studies, which had similar ES estimates (Fig. S27).

Studies of IL-1β

Levels of IL-1β did not significantly differ between MDD and HC groups across 22 included studies (Hedge's $g = 0.032$, $P = 0.847$; Table 1; Fig. S1). No evidence of small-study effects was observed (Table 1). The heterogeneity was large ($I^2 = 89.3\%$). The mean BMI of participants with MDD emerged as a potential source of heterogeneity in meta-regression analysis; a larger BMI was associated with a higher ES estimate (Table S3). In addition, subgroup analyses suggest that heterogeneity is lower in studies that measured this immune mediator in whole blood (compared to studies that assayed IL-1β in serum or plasma) and in studies that used stimulated leukocytes (Table S4).

Studies of IFN-γ

Data for IFN-γ were extracted from 17 studies, and levels were reduced in subjects with MDD compared to the HCs (Table 1; Fig. 3a). There was evidence of small-study effects, but adjustment for publication bias did not change the ES

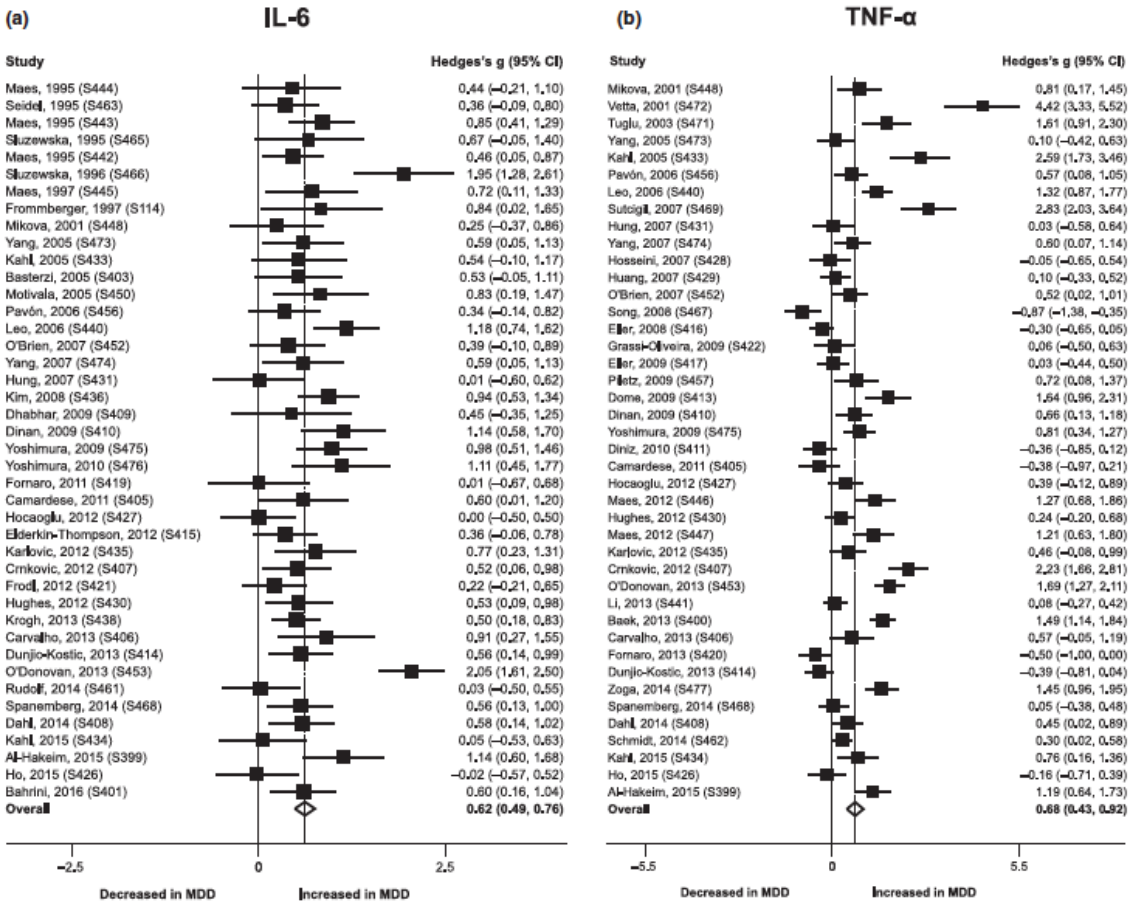

Fig. 2. Forest plots of studies which measured (a) IL-6 or (b) TNF-α or in participants with MDD compared to HCs. Effect size estimates are presented as Hedge's *g* with 95% confidence intervals (CIs). Square sizes are proportional to the ES of each study. References are presented in the supporting information.

(g = −0.452; Table 1 and Fig. 3a). Heterogeneity was large (I^2 = 94.0%). Mean BMI of the HC group, publication year, sample size, and mean age of the MDD and HC groups emerged as potential sources of heterogeneity in meta-regression analyses (Table S3). Sensitivity analysis revealed that the exclusion of 10 studies from analysis one by one rendered the ES estimate non-significant (Fig. S17). In addition, the cumulative meta-analysis indicates that the ES estimates for IFN-γ have not been consistent over time (Fig. S28).

Studies of IL-10

IL-10 levels were investigated in 17 studies, and levels were significantly higher in the MDD group compared to HCs, with a small ES (g = 0.375, P = 0.045) (Table 1 and Fig. 3b). No evidence of small-study effects was verified (Table 1). Heterogeneity was large (I^2 = 89.2%), and subgroup analyses suggest that heterogeneity is lower in studies that assayed IL-10 in plasma compared to serum. In addition, the ES was significant only in studies that followed a non-matched design (Table S4). Furthermore, IL-10 levels were not significantly altered in participants with MDD who were antidepressant-free when this cytokine was assayed, whereas these levels remained significantly elevated in participants with MDD who were using antidepressants (Table S4). Sensitivity analyses showed that the exclusion of 11 of 17 studies one at a time rendered the ES estimate non-significant (Fig. S18). In addition, the cumulative meta-analysis indicates that the ES has not been consistent over time (Fig. S29).

Studies of soluble IL-2 (sIL-2) receptor

We found evidence that sIL-2 receptor levels were significantly higher in the MDD group

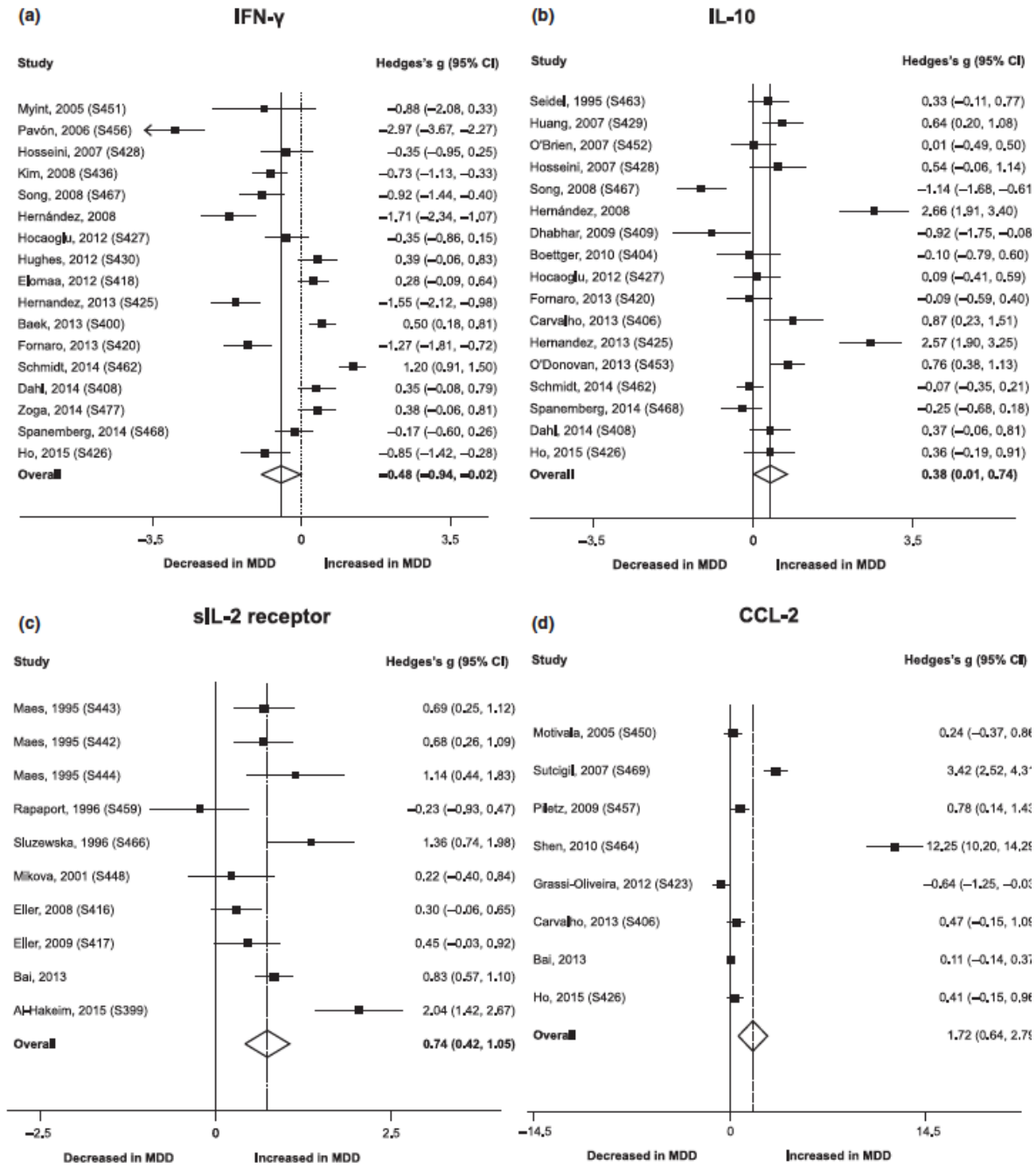

Fig. 3. Forest plots of studies which measured (a) IFN-γ or (b) IL-10 or (c) sIL-2R or (d) CCL-2 in participants with MDD com pared to HCs. Effect size estimates are presented as Hedge's *g* with 95% confidence intervals (CIs). Square sizes are proportional t the ES of each study. References are presented in the supporting information.

compared to HCs with a moderate ES estimate (Hedge's $g = 0.735$, $P < 0.001$) (Table 1; Fig. 3c). No evidence of small-study effects was observed, and between-study heterogeneity was large ($I^2 = 77.5\%$). Subgroup analyses suggested that heterogeneity was lower in studies that measured sIL2 in plasma (compared to serum as well as in studies in which MDD and HC groups were not age- and gender-matche (Table S4). In sensitivity analysis, the exclusio of included studies one at a time did not alte the direction or significant of the ES estimate

Moreover, the cumulative meta-analysis indicated that this ES estimate has been consistent over time (Fig. S30).

Studies of C-C chemokine ligand 2 (CCL-2)

Levels of CCL-2 were significantly higher in participants with MDD compared to HCs with a large ES ($g = 1.718$; $P = 0.045$) (Table 1; Fig. 3d). There was evidence of small-study effects (Table 1). However, the ES was not altered after adjustment for publication bias. Heterogeneity was large ($I^2 = 96.3\%$). The ES was not significant in studies which utilized a matched design (Table S4). In sensitivity analysis, we found that the exclusion of the study by Shen et al. (45) from the analysis turned this ES non-significant (Fig. S20).

Studies of IL-13

Levels of IL-13 were significantly higher in participants with MDD compared to HCs ($g = 1.836$; $P < 0.001$) (Table 1; Fig. 4a). The ES estimate remained large even after adjustment for publication bias ($g = 1.432$). The heterogeneity was large ($I^2 = 96.0\%$), but could not be reliably explored due to the limited number of included studies ($k = 6$).

Studies of IL-18

Levels of IL-18 were significantly higher in the MDD group compared to the HC group (Table 1; Fig. 4b). The ES estimate was high ($g = 1.720$; $P = 0.012$), although a limited number of studies were included in this meta-analysis ($k = 5$). Heterogeneity was large ($I^2 = 95.3\%$), and no evidence of small-study effects was observed (Table 1).

Studies of IL-12

Peripheral levels of IL-12 were significantly more elevated in individuals with MDD compared to HCs, with a large ES estimate ($g = 1.229$; $P = 0.012$) (Table 1; Fig. 4c). The heterogeneity was large ($I^2 = 92.9\%$), and no evidence of small-study effects was observed (Table 1). In addition, sensitivity analysis revealed that this ES could be biased by a possible outlier (46) (Fig. S22).

Studies of IL-1 receptor antagonist (IL-1Ra)

Peripheral levels of IL-1Ra were higher in the MDD group compared to HCs ($g = 0.449$; $P = 0.016$) (Table 1; Fig. 4d). Heterogeneity was large ($I^2 = 51.6\%$), while no evidence of small-study effects was observed (Table 1). However, sensitivity analyses revealed that this ES could be biased by at least three possible outliers (42, 47, 48) (Fig. S24).

Studies of soluble TNF receptor 2 (sTNFR2)

Three studies indicate that sTNFR2 levels are higher in individuals with MDD compared to HCs with a large ES ($g = 1.173$; $P = 0.003$), but high heterogeneity ($I^2 = 83.2\%$) (Table 1; Fig. 4e). No evidence of small-study effects was observed. However, sensitivity analysis shows that removal of the study by Papakostas et al. (49) turned this ES estimate non-significant (Fig. S25).

Other mediators

Levels of IL-2, IL-4, the soluble IL-6 receptor (sIL-6R), IL-8, IL-5, CCL-3, IL-17, and transforming growth factor-β (TGF-β) were measured in at least three studies and were thus meta-analyzed. Levels of these immune mediators did not significantly differ between individuals with MDD and HCs (Table 1). Forest plots for these meta-analyses are provided in the supporting information (Figs S2–S9).

Discussion

This meta-analysis provides the largest evidence synthesis conducted to date of studies that have investigated peripheral levels of cytokines and chemokine peripheral levels in individuals with MDD compared to HCs. Our results suggest that levels of IL-6, TNF-α, IL-10, the sIL-2R, CCL-2, IL-13, IL-18, IL-12, and the sTNFR2 can be significantly elevated in individuals with MDD compared to HCs, while IFN-γ levels may be slightly reduced in the MDD group compared to HCs.

The results of our meta-analysis add significant evidence to a previous meta-analysis (7), while a recent meta-analysis was limited to studies which investigated IL-1β, TNF-α, and IL-6 (5). The previous meta-analysis found elevated levels of TNF-α and IL-6 in depressive patients compared to HCs (7). A recent meta-analysis aimed to compare peripheral levels of cytokines among patients with schizophrenia, bipolar disorder, and also MDD (50). This recent meta-analysis also investigated the effects of antidepressant treatment on blood cytokine levels in patients with MDD (50). However, this meta-analysis included only 30 studies. In addition, a fixed-effects models were used to estimate ESs, which may be inaccurate when

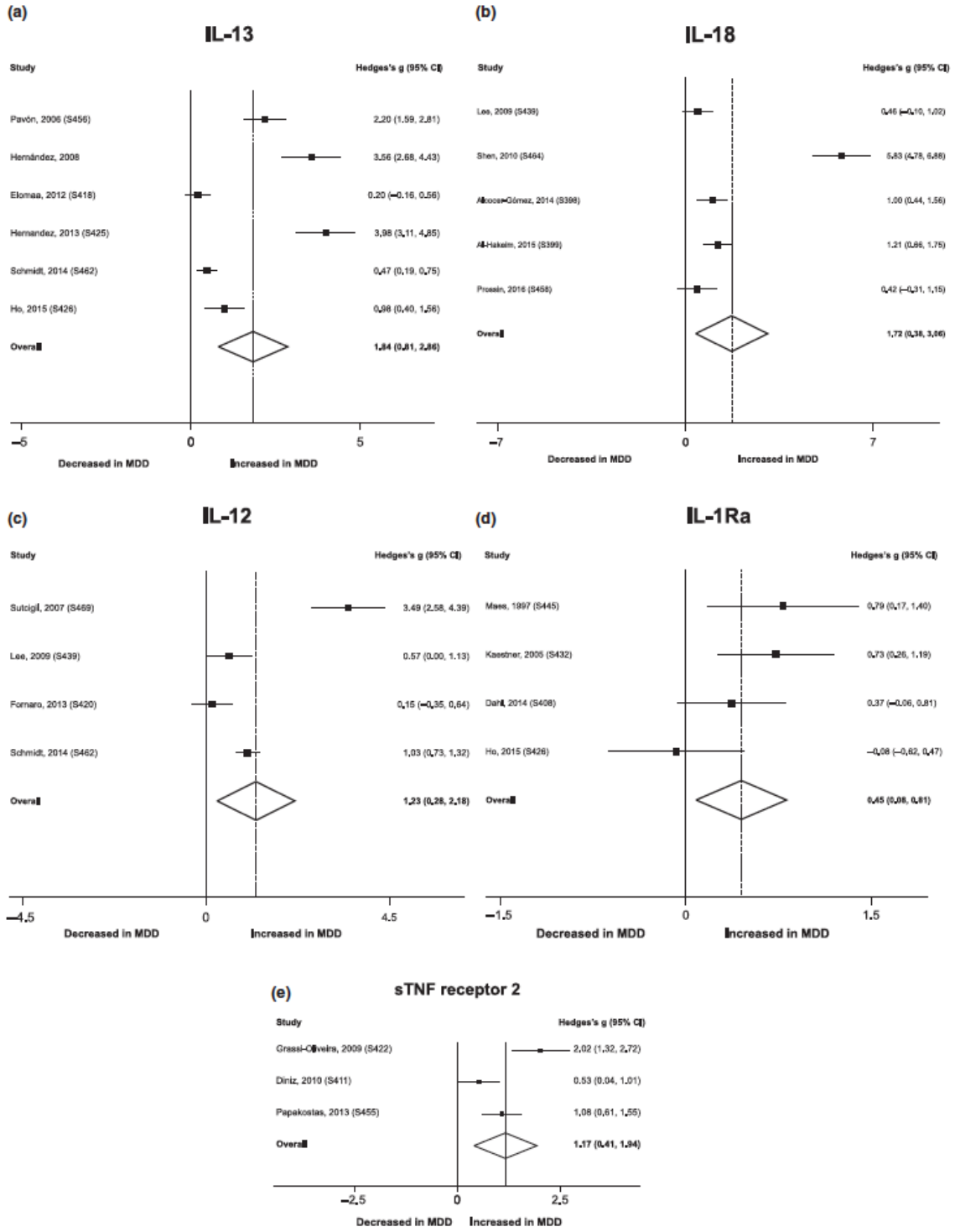

Fig. 4. Forest plots of studies which measured (a) IL-13 or (b) IL-18 or (c) IL-12 or (d) IL-1Ra or (e) sTNFR2 in participants with MDD compared to HCs. Effect size estimates are presented as Hedge's *g* with 95% confidence intervals (CIs). Square sizes are proportional to the ES of each study. References are presented in the supporting information.

heterogeneity is large (27). We confirmed that a high level of heterogeneity across studies characterizes this evolving field (5, 7). In addition, due to the larger number of included studies, we could more accurately explore potential sources of heterogeneity than has previously been possible.

A significant proportion of individuals with MDD exhibits a high prevalence of comorbid medical (e.g., metabolic) and psychiatric conditions (51, 52), which may contribute to immune activation in MDD. For example, it has been postulated that comorbid obesity may lead to a more pernicious outcome in MDD in part due to shared immune-inflammatory pathways (53, 54). Therefore, we *a priori* excluded studies in which participants with MDD had clearly identified comorbidities and examined the influence of other relevant confounders. This approach identified the fact that mean BMI values of the MDD group (IL-1β and IFN-γ), mean BMI of the HC control group (IFN-γ), and current smoking (TNF-α) significantly moderated these estimates. These findings are consistent with the hypothesis that adiposity-driven inflammation may contribute to MDD-related morbidity (55, 56). In addition, it has been postulated that smoking and an unhealthy lifestyle (e.g., poor diet) could be relevant sources of immune activation in MDD (57).

Cytokines and chemokines have been classically subdivided as anti-inflammatory and proinflammatory. However, emerging evidence indicates that this subdivision may be overly simplistic. For example, IL-6 may activate a classical pathway and a trans-signaling pathway, which may have predominantly anti- and proinflammatory activities respectively (58). We found elevated IL-6 levels in participants with MDD compared to HCs. The sIL-6R was examined in relatively few studies, and its peripheral levels were more elevated in the MDD group compared to HCs at the trend level. It is worthy to note that IL-6 was cytokine more extensively investigated in this meta-analysis, with a consistent moderate ES observed in cumulative meta-analysis. In addition, IL-6 and IL-1β may contribute to the pathophysiology of a subset of patients with MDD via excessive release of corticotrophin-releasing hormone (CRH) and by the promotion glucocorticoid receptor resistance, which may ultimately impair the negative feedback regulation of the HPA axis (59, 60).

We found evidence that IFN-γ may be reduced in participants with MDD compared to HCs. However, the ES was small and sensitivity analyses pointed to significant outliers. Furthermore, levels of IFN-γ were most often close to the limit of detection of previously available assay kits, which may lead to analytical variability. In addition, previous studies found elevated levels of IFN-γ in stimulated peripheral blood mononuclear cells (PBMCs) of individuals with MDD compared to healthy controls, which may provide a more accurate measure of this cytokine (61, 62).

Ronald Smith was the first to propose a macrophage theory for depression in the early 1990's (63). Macrophages and their counterparts in the CNS are crucial cells of the innate immune system, which can alter and adapt their phenotypes depending on their prime activity (a M1-activated phenotype has a primary role in acute defense against pathogens, whereas a M2 phenotype is primarily involved in clearing damaged tissues and repairing activities) (64). Evidence pointing to a role of M1 cells (including microglial cells and CNS macrophages) in MDD has accumulated (2, 65). A clear limitation of this meta-analysis rests on fact that the periphery may not reflect pathophysiological events in the CNS. However, preclinical studies indicate that the blockade of the trafficking of peripheral monocytes to the brain reduced proinflammatory cytokine production and decreased depressive-like behaviours in rodent stress models (66). Thus, peripheral M1 cells could be a main source of elevated cytokines in MDD (4). This meta-analysis evidenced elevated levels of CCL-2, IL-6, IL-12, TNF-α, and IL-1β, which are immune mediators secreted by M1 macrophages albeit not selectively (67).

The inflammatory response is tightly controlled at critical set points, and the maintenance of a healthy immune state is not a passive state, but may require an active expression of immunoregulatory genes (68). Regulatory T-cells (TRegs) are master immune regulators and play a significant role in immune tolerance (69). We found an elevation of IL-10 levels in individuals with MDD compared to HCs. This cytokine is predominantly secreted by TRegs (70). However, subgroup analyses found that this cytokine was not elevated in antidepressant-free participants with MDD, which may underscore an indirect effect of antidepressant drugs. In addition, TGF-β that is another biosignature cytokine of TRegs was not significantly altered in participants with MDD compared to HCs. Thus, a relative lack of counter-regulatory immune mechanisms may contribute to peripheral inflammation in MDD.

The main limitation of this meta-analysis is the high degree of heterogeneity of some estimates. Although we have identified some significant moderators, some possible sources of heterogeneity could not be investigated due to the lack of data across studies, while data on other potential

moderators (e.g., physical activity and diet quality) (57) were not provided by included studies and thus could not be controlled for. Notwithstanding, we could not investigate whether length of disease and number of affective episodes as possible moderators of ESs estimates due to the lack of data across studies, a previous meta-analysis, which used a different definition had found suggestive that some differences in peripheral levels of cytokines may occur in acute compared to chronic MDD relative to HCs (50). Furthermore, the current use of antidepressant drugs did not emerge as a significant moderator in our analyses. However, our exploratory meta-regressions could have limited power to detect this effect, and previous evidence indicates that antidepressant drugs may impact peripheral cytokine levels at follow-up (50). It has been postulated that melancholic depression is associated with an overactive HPA axis and possibly lower inflammation due to the modulatory effects of cortisol (15, 71). We found that few studies have categorized patients in melancholic vs. atypical depression, although we found that TNF-α levels did not differ when individuals with melancholic depression were compared to HCs. In addition, cytokines/chemokines appear to be involved in the pathophysiology of suicidal behaviour (72). Furthermore, technical challenges in the assessment of certain mediators (e.g., IL-2 and IFN-γ) (73) as well as differences in the standardization of assays across different laboratories could have contributed to the heterogeneity of some estimates. It is worthy to note that although a predefined protocol was followed, we did not publish or otherwise registered it in a public database. Finally, the methodological quality of included studies has varied, and in our exploratory meta-regression analyses, this factor emerged as a significant moderator of differences in TNF-α levels between participants with MDD and HCs.

In conclusion, this meta-analysis indicates that several cytokines and CCL-2 are elevated in MDD. Our results confirm that cell-mediated immune activation may be an important pathophysiological aspect of MDD. In addition, our results provide directions for further research. For example, emerging preclinical evidence and a recent theoretical framework indicate that TH17 cells could play a significant role in the biology of depression (74, 75). However, few studies have investigated peripheral levels of IL-17, IL-17F, and IL-22, which are biosignature cytokines of TH17 cells (76). Thus, the characterization of the precise peripheral immune profile associated with MDD remains a work in progress.

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Declaration of interests

In the past 3 years, CLR has served on the scientific advisory board for Usona Institute. In addition, he has served on the speaker's bureau of Merck and Sunovion and on the advisory board of Otsuka and Pamlab. All other authors report no conflict of interests.

References

1. Maes M. Evidence for an immune response in major depression: a review and hypothesis. Prog Neuropsychopharmacol Biol Psychiatry 1995;**19**:11–38.
2. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat Rev Immunol 2016;**16**:22–34.
3. Haroon E, Fleischer CC, Felger JC et al. Conceptual convergence: increased inflammation is associated with increased basal ganglia glutamate in patients with major depression. Mol Psychiatry 2016;**21**:1351–1357.
4. Wohleb ES, Franklin T, Iwata M, Duman RS. Integrating neuroimmune systems in the neurobiology of depression. Nat Rev Neurosci 2016;**17**:497–511.
5. Haapakoski R, Mathieu J, Ebmeier KP, Alenius H, Kivimaki M. Cumulative meta-analysis of interleukins 6 and 1beta, tumour necrosis factor alpha and C-reactive protein in patients with major depressive disorder. Brain Behav Immun 2015;**49**:206–215.
6. Maes M, Scharpe S, van Grootel L et al. Higher alpha 1-antitrypsin, haptoglobin, ceruloplasmin and lower retinol binding protein plasma levels during depression: further evidence for the existence of an inflammatory response during that illness. J Affect Disord 1992;**24**:183–192.
7. Dowlati Y, Herrmann N, Swardfager W et al. A meta-analysis of cytokines in major depression. Biol Psychiatry 2010;**67**:446–457.
8. Stuart MJ, Baune BT. Chemokines and chemokine receptors in mood disorders, schizophrenia, and cognitive impairment: a systematic review of biomarker studies. Neurosci Biobehav Rev 2014;**42**:93–115.
9. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 2008;**9**:46–56.
10. Simen BB, Duman CH, Simen AA, Duman RS. TNFalpha signaling in depression and anxiety: behavioral consequences of individual receptor targeting. Biol Psychiatry 2006;**59**:775–785.
11. Chourbaji S, Urani A, Inta I et al. IL-6 knockout mice exhibit resistance to stress-induced development of depression-like behaviors. Neurobiol Dis 2006;**23**:587–594.
12. Udina M, Castellvi P, Moreno-Espana J et al. Interferon-induced depression in chronic hepatitis C: a systematic review and meta-analysis. J Clin Psychiatry 2012;**73**:1128–1138.

13. Thase ME. Using biomarkers to predict treatment response in major depressive disorder: evidence from past and present studies. Dialogues Clin Neurosci 2014;**16**:539–544.
14. Carvalho AF, Kohler CA, Brunoni AR et al. Bias in peripheral depression biomarkers. Psychother Psychosom 2016;**85**:81–90.
15. Gold PW. The organization of the stress system and its dysregulation in depressive illness. Mol Psychiatry 2015;**20**:32–47.
16. Lamers F, Vogelzangs N, Merikangas KR, de Jonge P, Beekman AT, Penninx BW. Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. Mol Psychiatry 2013;**18**:692–699.
17. Stuart MJ, Singhal G, Baune BT. Systematic review of the neurobiological relevance of chemokines to psychiatric disorders. Frontiers Cellular Neurosci 2015;**9**:357.
18. Sochocka M, Diniz BS, Leszek J. Inflammatory response in the CNS: friend or foe? Mol Neurobiol 2016. doi: 10.1007/s12035-016-0297-1 [Epub ahead of print].
19. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med 2009;**71**:171–186.
20. Hiles SA, Baker AL, de Malmanche T, Attia J. A meta-analysis of differences in IL-6 and IL-10 between people with and without depression: exploring the causes of heterogeneity. Brain Behav Immun 2012;**26**:1180–1188.
21. Liberati A, Altman DG, Tetzlaff J et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;**339**:b2700.
22. Bakkalbasi N, Bauer K, Glover J, Wang L. Three options for citation tracking: Google Scholar, Scopus and Web of Science. Biomed Digit Libr 2006;**3**:7.
23. ASSOCIATION AP. DSM 5. American Psychiatric Association; 2013.
24. ORGANIZATION WH. The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research; 1993.
25. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;**5**:13.
26. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med 1997;**127**:820–826.
27. Patsopoulos NA, Evangelou E, Ioannidis JP. Heterogeneous views on heterogeneity. Int J Epidemiol 2009;**38**:1740–1742.
28. Dersimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;**7**:177–188.
29. Carvalho AF, Kohler CA, Fernandes BS et al. Bias in emerging biomarkers for bipolar disorder. Psychol Med 2016;**46**:2287–2297.
30. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;**315**:629–634.
31. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;**56**:455–463.
32. Rosenthal R. The file drawer problem and tolerance for null results. Psychol Bull 1979;**86**:638.
33. Higgins JP, Thompson SG. Controlling the risk of spurious findings from meta-regression. Stat Med 2004;**23**:1663–1682.
34. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? Stat Med 2002;**21**:1559–1573.
35. Krogh J, Benros ME, Jorgensen MB, Vesterager L, Elfving B, Nordentoft M. The association between depressive symptoms, cognitive function, and inflammation in major depression. Brain Behav Immun 2014;**35**:70–76.
36. O'Donovan A, Rush G, Hoatam G et al. Suicidal ideation is associated with elevated inflammation in patients with major depressive disorder. Depress Anxiety 2013;**30**:307–314.
37. Dunjic-Kostic B, Ivkovic M, Radonjic NV et al. Melancholic and atypical major depression–connection between cytokines, psychopathology and treatment. Prog Neuropsychopharmacol Biol Psychiatry 2013;**43**:1–6.
38. Elderkin-Thompson V, Irwin MR, Hellemann G, Kumar A. Interleukin-6 and memory functions of encoding and recall in healthy and depressed elderly adults. Am J Geriatr Psychiatry 2012;**20**:753–763.
39. Kahl KG, Bester M, Greggersen W et al. Visceral fat deposition and insulin sensitivity in depressed women with and without comorbid borderline personality disorder. Psychosom Med 2005;**67**:407–412.
40. Motivala SJ, Sarfatti A, Olmos L, Irwin MR. Inflammatory markers and sleep disturbance in major depression. Psychosom Med 2005;**67**:187–194.
41. Mikova O, Yakimova R, Bosmans E, Kenis G, Maes M. Increased serum tumor necrosis factor alpha concentrations in major depression and multiple sclerosis. Eur Neuropsychopharmacol 2001;**11**:203–208.
42. Maes M, Bosmans E, de Jongh R, Kenis G, Vandoolaeghe E, Neels H. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. Cytokine 1997;**9**:853–858.
43. Maes M, Meltzer HY, Bosmans E et al. Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. J Affect Disord 1995;**34**:301–309.
44. Leo R, di Lorenzo G, Tesauro M et al. Association between enhanced soluble CD40 ligand and proinflammatory and prothrombotic states in major depressive disorder: pilot observations on the effects of selective serotonin reuptake inhibitor therapy. J Clin Psychiatry 2006;**67**:1760–1766.
45. Shen Y, Lu P, Wei L, Hu X, Chen W. Fluoxetine treatment for major depression decreases the plasma levels of cytokines. Afr J Biotechnol 2010;**9**:7346–7351.
46. Schmidt FM, Lichtblau N, Minkwitz J et al. Cytokine levels in depressed and non-depressed subjects, and masking effects of obesity. J Psychiatr Res 2014;**55**:29–34.
47. Kaestner F, Hettich M, Peters M et al. Different activation patterns of proinflammatory cytokines in melancholic and non-melancholic major depression are associated with HPA axis activity. J Affect Disord 2005;**87**:305–311.
48. Ho PS, Yeh YW, Huang SY, Liang CS. A shift toward T helper 2 responses and an increase in modulators of innate immunity in depressed patients treated with escitalopram. Psychoneuroendocrinology 2015;**53**:246–255.
49. Papakostas GI, Shelton RC, Kinrys G et al. Assessment of a multi-assay, serum-based biological diagnostic test for major depressive disorder: a pilot and replication study. Mol Psychiatry 2013;**18**:332–339.
50. Goldsmith DR, Rapaport MH, Miller BJ. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. Mol Psychiatry 2016;**21**:1696–1709.
51. Kessler RC, Merikangas KR, Wang PS. Prevalence, comorbidity, and service utilization for mood disorders in the United States at the beginning of the twenty-first century. Ann Rev Clin Psychol 2007;**3**:137–158.

52. Vancampfort D, Correll CU, Wampers M et al. Metabolic syndrome and metabolic abnormalities in patients with major depressive disorder: a meta-analysis of prevalences and moderating variables. Psychol Med 2014;**44**: 2017–2028.
53. Du YJ, Yang CJ, Li B et al. Association of pro-inflammatory cytokines, cortisol and depression in patients with chronic obstructive pulmonary disease. Psychoneuroendocrinology 2014;**46**:141–152.
54. Mansur RB, Brietzke E, McIntyre RS. Is there a "metabolic-mood syndrome"? A review of the relationship between obesity and mood disorders. Neurosci Biobehav Rev 2015;**52**:89–104.
55. Capuron L, Lasselin J, Castanon N. Role of adiposity-driven inflammation in depressive morbidity. Neuropsychopharmacology 2017;**42**:115–128.
56. Liu CS, Carvalho AF, McIntyre RS. Towards a "metabolic" subtype of major depressive disorder: shared pathophysiological mechanisms may contribute to cognitive dysfunction. CNS Neurol Disord Drug Targets 2014;**13**:1693–1707.
57. Berk M, Williams LJ, Jacka FN et al. So depression is an inflammatory disease, but where does the inflammation come from? BMC Med 2013;**11**:200.
58. Maes M, Anderson G, Kubera M, Berk M. Targeting classical IL-6 signalling or IL-6 trans-signalling in depression? Expert Opin Ther Targets 2014;**18**:495–512.
59. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatry 2009;**65**:732–741.
60. Horowitz MA, Zunszain PA, Anacker C, Musaelyan K, Pariante CM. Glucocorticoids and inflammation: a double-headed sword in depression? How do neuroendocrine and inflammatory pathways interact during stress to contribute to the pathogenesis of depression? Mod Trends Pharmacopsychiat 2013;**28**:127–143.
61. Maes M, Scharpe S, Meltzer HY et al. Increased neopterin and interferon-gamma secretion and lower availability of L-tryptophan in major depression: further evidence for an immune response. Psychiatry Res 1994;**54**:143–160.
62. Seidel A, Arolt V, Hunstiger M, Rink L, Behnisch A, Kirchner H. Cytokine production and serum proteins in depression. Scand J Immunol 1995;**41**:534–538.
63. Smith RS. The macrophage theory of depression. Med Hypotheses 1991;**35**:298–306.
64. Kalkman HO, Feuerbach D. Antidepressant therapies inhibit inflammation and microglial M1-polarization. Pharmacol Ther 2016;**163**:82–93.
65. Yirmiya R, Rimmerman N, Reshef R. Depression as a microglial disease. Trends Neurosci 2015;**38**:637–658.
66. Wohleb ES, McKim DB, Sheridan JF, Godbout JP. Monocyte trafficking to the brain with stress and inflammation: a novel axis of immune-to-brain communication that influences mood and behavior. Frontiers Neurosci 2014;**8**:447.
67. Mills CD. Anatomy of a discovery: m1 and m2 macrophages. Front Immunol 2015;**6**:212.
68. Nathan C. Points of control in inflammation. Nature 2002;**420**:846–852.
69. Sakaguchi S, Yamaguchi T, Nomura T, Ono M. Regulatory T cells and immune tolerance. Cell 2008;**133**:775–787.
70. Sakaguchi S, Miyara M, Costantino CM, Hafler DA. FOXP3+ regulatory T cells in the human immune system. Nat Rev Immunol 2010;**10**:490–500.
71. Stetler C, Miller GE. Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. Psychosom Med 2011;**73**:114–126.
72. Black C, Miller BJ. Meta-Analysis of Cytokines and Chemokines in Suicidality: distinguishing Suicidal Versus Nonsuicidal Patients. Biol Psychiatry 2015;**78**: 28–37.
73. Eller T, Vasar V, Shlik J, Maron E. The role of IL-2 and soluble IL-2R in depression and antidepressant response. Curr Opin Investig Drugs 2009;**10**:638–643.
74. Slyepchenko A, Maes M, Kohler CA et al. T helper 17 cells may drive neuroprogression in major depressive disorder: proposal of an integrative model. Neurosci Biobehav Rev 2016;**64**:83–100.
75. Beurel E, Harrington LE, Jope RS. Inflammatory T helper 17 cells promote depression-like behavior in mice. Biol Psychiatry 2013;**73**:622–630.
76. Korn T, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 cells. Annu Rev Immunol 2009;**27**:485–517.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Forest plot of studies that investigated IL-1β.
Fig. S2. Forest plot of studies that investigated IL-2.
Fig. S3. Forest plot of studies that investigated IL-4.
Fig. S4. Forest plot of studies that investigated soluble IL-6 receptor (sIL-6 receptor).
Fig. S5. Forest plot of studies that investigated IL-8.
Fig. S6. Forest plot of studies that investigated IL-5.
Fig. S7. Forest plot of studies that investigated CCL-3.
Fig. S8. Forest plot of studies that investigated IL-17.
Fig. S9. Forest plot of studies that investigated TGF-β1.
Fig. S10. Funnel plot of studies that investigated TNF-α.
Fig. S11. Funnel plot of studies that investigated IFN-γ.
Fig. S12. Funnel plot of studies that investigated IL-4.
Fig. S13. Funnel plot of studies that investigated CCL-2.
Fig. S14. Funnel plot of studies that investigated IL-13.
Fig. S15. Sensitivity analysis for the meta-analysis of studies that investigated IL-6.
Fig. S16. Sensitivity analysis for the meta-analysis of studies that investigated TNF-α.
Fig. S17. Sensitivity analysis for the meta-analysis of studies that investigated IFN-γ.
Fig. S18. Sensitivity analysis for the meta-analysis of studies that investigated IL-10.
Fig. S19. Sensitivity analysis for the meta-analysis of studies that investigated soluble IL-2 receptor (sIL-2 receptor).
Fig. S20. Sensitivity analysis for the meta-analysis of studies that investigated CCL-2.
Fig. S21. Sensitivity analysis for the meta-analysis of studies that investigated IL-13.
Fig. S22. Sensitivity analysis for the meta-analysis of studies that investigated IL-18.
Fig. S23. Sensitivity analysis for the meta-analysis of studies that investigated IL-12.
Fig. S24. Sensitivity analysis for the meta-analysis of studies that investigated IL-1 receptor antagonist (IL-1Ra).
Fig. S25. Sensitivity analysis for the meta-analysis of studies that investigated sTNF receptor 2.
Fig. S26. Cummulative meta-analysis of studies that investigated IL-6.
Fig. S27. Cummulative meta-analysis of studies that investigated TNF-α.
Fig. S28. Cummulative meta-analysis of studies that investigated IFN-γ.
Fig. S29. Cummulative meta-analysis of studies that investigated IL-10.