

Cumulative meta-analysis of interleukins 6 and 1 β , tumour necrosis factor α and C-reactive protein in patients with major depressive disorder

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Supplementary Material

Tables:

Quality assessment of included studies	2
Summary statistics for included studies	4
Inclusion and exclusion criteria in the studies and covariates included in the meta-analysis	7
Comorbid psychiatric conditions, substance use, severity of depression and medications	13

Figures:

Flow diagram on literature search strategy	16
Cumulative meta-analysis on A) IL-6, B) CRP, C) TNF- α and D) IL1 β including only studies with high quality (score ≥ 6) and subjects not using antidepressants	17
References	19

Supplementary Table 1. Quality assessment of studies included in the meta-analysis using Newcastle-Ottawa scale for case-control studies.

<i>Study</i>	<i>Selection</i>	<i>Comparability</i>	<i>Exposure</i>	<i>Total</i>
Basterzi AD et al., 2005	**	*	**	5
Carvalho LA et al., 2013	***	**	**	7
Cizza G et al., 2009	***	**	**	7
Dahl J et al., 2014	***	**	***	8
Dhabhar FS et al., 2009	****	**	**	8
Diniz BS et al., 2010a	**	*	*	4
Diniz BS et al., 2010b	**	*	*	4
Dome P et al., 2009	**	**	*	5
Dunjic-Kostic B et al., 2013	**	**	**	6
Eller T 2008	**	*	***	6
Eller T 2009	**	**	**	6
Euteneuer F et al., 2011	**	**	**	6
Fitzgerald P et al., 2006	**	*	**	5
Fornaro M et al., 2011	*	*	**	4
Fornaro M et al., 2013	*	*	***	5
Frodl T et al., 2013	**	*	**	5
Grassi-Oliveira, R et al., 2009	**	**	**	6
Hennings A et al., 2013	****	**	**	8
Hernandez ME et al., 2008	***	**	***	8
Hernandez ME et al., 2013	**	**	**	6
Hornig M et al., 1998	**		*	3
Huang T-L & Lee C-T 2007	*	**	***	6
Hughes MM et al., 2012	***	**	***	8
Häfner S et al., 2008	**		*	3
Joyce PR et al., 1992	*	**	**	5
Kagaya A 2001	**	*	**	5
Karlović D et al., 2012	**	*	***	6
Kéri S et al., 2014	***	*	**	6
Kling MA et al., 2006	***	**	**	7
Lanquillon S et al., 2000	**	**	***	7
Leo R et al., 2006	**	**	***	7
Li Z et al., 2013	**	**	**	6
Maes M et al., 1995a	**	*	***	6
Maes M et al., 1995b	***	*	***	7
Maes M et al., 1997	**	*	***	6
Maes M, Mihaylova I et al., 2012	**	*	**	5
Maes M, Ringel K et al., 2012	**	*	*	4

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<i>Study</i>	<i>Selection</i>	<i>Comparability</i>	<i>Exposure</i>	<i>Total</i>
Mikova O et al., 2001	*	*	***	5
Motivala SJ et al., 2005	***	**	**	7
Narita K et al., 2006	**	**	**	6
O'Brien S et al., 2007	**		***	5
O'Donovan A et al., 2013	**	*	***	6
Pavon L et al., 2006	***	**	***	8
Pike JL and Irwin MR 2006	***	**	**	7
Piletz JE et al., 2009	***	*	**	6
Rothermundt M et al., 2001	*	*	***	5
Rudolf S et al., 2014	**	*	**	5
Schmidt FM 2014	**	*	**	5
Simon NM et al., 2008	**	*	**	5
Sluzewska A et al., 1996	**	*	***	6
Sutcgil L et al., 2007	**	*	***	6
Thomas AJ et al., 2005	**	*	*	4
Tuglu C et al., 2003	**	*	**	5
Voderholzer U et al., 2012	**	**	**	6
Weinstein, AA et al., 2010	***	**	**	7
Yang K et al., 2007	**	**	***	7
Yoshimura R et al., 2010	*	*	**	4
Zahn D et al., 2012	*	*	**	4

Quality points for *exposure* assessment were:

- ascertainment of method (blood drawn as fasting state and use of validated assays for sample analysis) = *
- same procedures used for cases and controls (sample processing and assay performance) = *
- the representativeness of sample material (three or more immune markers analysed in the study) = *

Supplementary Table 2. Summary statistics for included studies.

<i>Study</i>	<i>Patient type</i>	<i>Immune measures</i>	<i>N (cases/contr.)</i>	<i>Gender (female/male)</i>	<i>Age (cases/controls)</i>	<i>Depression diagnosis and severity scale</i>	<i>Country</i>	<i>Quality score</i>
Basterzi AD et al., 2005 ¹	Outpatients	IL-6	46 (23/23)	40/6	33.8 ± 12.8 / 33.6 ± 12.5	DSM-IV, HAM-D	Turkey	5
Carvalho LA et al., 2013 ²	Inpatients	IL-6, IL-10, IL-4, MCP-1	40 (19/21)	28/12	49.05 ± 3.3 / 45.9 ± 2.4	DSM-IV, ICD-10, HAM-D	UK	7
Cizza G et al., 2009 ³	Outpatients	CRP	133 (89/44)	women only	35.5 ± 7 / 35.2 ± 7	DSM-IV, HAM-D	USA	7
Dahl J et al., 2014 ⁴	Outpatients	IL-1β, IL-1Ra, IL-5, IL-6, IL-7, IL-8, IL-10, G-CSF, IFN-γ, MIP-1α, TNF-α, IL-2, IL-15	84 (50/34)	57/27	40 ± 12 / 38.3 ± 13.9	MINI, MADRS, IDS	Norway	8
Dhabhar FS et al., 2009 ⁵	Outpatients	IL-6, IL-10	23 (12/11)	13/10	38.42 ± 11.03 / 38.00 ± 13.27	DSM-IV, HAM-D, IDS	USA	8
Diniz BS et al., 2010a ⁶	Outpatients	IL-1β	67 (23/44)	57/10	70.2 ± 4.9 / 69.5 ± 7.1	DSM-IV, HAM-D	Brazil	4
Diniz BS et al., 2010b ⁷	Outpatients	TNF-α, sTNFR1, sTNFR2	67 (28/39)	55/11	70.4 ± 4.38 / 70.2 ± 5.3	DSM-IV, HAM-D	Brazil	4
Dome P et al., 2009 ⁸	In- and outpatients	CRP, TNF-α	49 (33/16)	43/6	40.6 ± 10.6 / 40.3 ± 9.5	DSM-IV, BDI	Hungary	5
Dunjic-Kostic B et al., 2013 ⁹	Inpatients	IL-6, TNF-α, sIL-2R	86 (47/39)	38/48	51.27 ± 7.35 / 49.90 ± 4.99	DSM-IV, HAM-D	Serbia	6
Eller T 2008 ¹⁰	Outpatients	IL-8, TNF-α, sIL-2R	145 (100/45)	99/48	32.1 ± 11.9 / 32.9 ± 14.1	MINI, MADRS	Estonia	6
Eller T 2009 ¹¹	Outpatients	TNF-α, sIL-2R	130 (75/55)	89/41	35.2 ± 13.7 / 32.75 ± 14.10	MINI, HAM-D, BDI	Estonia	6
Euteneuer F et al., 2011 ¹²	Outpatients	IL-6, TNF-α	85 (37/48)	51/34	33.46 ± 12.77 / 35.79 ± 13.25	DSM-IV, BDI-II, SCL-90-R	Germany	6
Fitzgerald P et al., 2006 ¹³	Inpatients	IL-6, TNF-α	38 (19/19)	26/12	46.4 ± 2.92 / 40.1 ± 2.44	DSM-IV, HAM-D	Ireland	5
Fornaro M et al., 2011 ¹⁴	Outpatients	IL-6	32 (16/16)	21/11	51.1 ± 11 / 44 ± 11.6	DSM-IV, HAM-D	Italy	4
Fornaro M et al., 2013 ¹⁵	Outpatients	IL-1β, TNF-α, IFN-γ, IL-2, IL-4, IL-10, IL-12	62 (30/32)	48/14	48.27 ± 9.67 / 45.23 ± 11.62	DSM-IV, HAM-D	Italy	5
Frodl T et al., 2012 ¹⁶	Outpatients	IL-6, CRP	83 (40/43)	49/34	41.4 ± 10.9 / 37.0 ± 13.7	DSM-IV, HAM-D, BDI	Ireland	5
Grassi-Oliveira, R et al., 2009 ¹⁷	Outpatients	TNF-α, sTNFR1, sTNFR2	49 (30/19)	women only	39.21 ± 8.56 / 37.36 ± 5.48	DSM-IV, BDI	Brazil	6
Hennings A et al., 2013 ¹⁸	Outpatients	IL-6	86 (38/48)	24/62	32.08 ± 12.25 / 36.44 ± 13.28	DSM-IV, SOMS7, BDI	Germany	8
Hernandez ME et al., 2008 ¹⁹	Outpatients	IL-10, IL-4, IL-13, IL-2, IL-1β, IFN-γ	53 (31/22)	37/16	32.0 ± 9.40 / 30.75 ± 6.25	MINI, HAM-D, BDI	Mexico	8
Hernandez ME et al., 2013 ²⁰	Outpatients	IL-10, IL-4, IL-13, IL-2, IL-1β, IFN-γ	95 (65/30)	69/26	34 ± 9 / 32 ± 6	MINI, HAM-D, BDI	Mexico	6

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<i>Study</i>	<i>Patient type</i>	<i>Immune measures</i>	<i>N (cases/contr.)</i>	<i>Gender (female/male)</i>	<i>Age (cases/controls)</i>	<i>Depression diagnosis and severity scale</i>	<i>Country</i>	<i>Quality score</i>
Hornig M et al., 1998 ²¹	Outpatients	CRP, TNF- α	68 (22/46)	33/35	44.5 $\pm$ 11.6 / 41.1 $\pm$ 11.5	DSM-III-R	USA	3
Huang T-L & Lee C-T 2007 ²²	Inpatients	IL-1 β , TNF- α , IL-10	82 (42/40)	55/27	38.0 $\pm$ 8.2 / 31.4 $\pm$ 3.9	DSM-IV, HAM-D	Taiwan	6
Hughes MM et al., 2012 ²³	Inpatients	IL-6, IL-1 β , TNF- α , IFN- γ , CRP	78 (39/39)	45/33	41.9 $\pm$ 1.8 / 37.1 $\pm$ 2.1	DSM-IV, HAM-D	Ireland	8
Häfner S et al., 2008 ²⁴	In- and outpatients	CRP	138 (70/68)	79/59	49.3 $\pm$ 13.3 / 41.3 $\pm$ 14.1	DSM-IV, HAM-D	Germany	3
Joyce PR et al., 1992 ²⁵	Outpatients	CRP, AAC, AAT, HAPT, CPM, IgG, IgA, IgM	33 (21/12)	men only	34.2 $\pm$ 10.1 / 31.5 $\pm$ 4.1	DSM-III-R, HAM-D	New Zealand	5
Kagaya A 2001 ²⁶	Outpatients	IL-6, IL-1 β , TNF- α , sIL-2R	23 (6/18)	6/18	31.1 $\pm$ 8.2 / 30.9 $\pm$ 7.0	DSM-III-R, HAM-D	Japan	5
Karlović D et al., 2012 ²⁷	In- and outpatients	CRP, IL-6, TNF- α	73 (55/18)	30/43	49.75 $\pm$ 12.2 / 45.0 $\pm$ 9.5	DSM-IV, MINI, HAM-D	Croatia	6
Kéri S et al., 2014 ²⁸	Outpatients	IL-6, CRP	80 (50/30)	52/28	22.6 $\pm$ 6.0 / 24.3 $\pm$ 8.3	DSM-IV, HAM-D	Hungary	6
Kling MA et al., 2007 ²⁹	Outpatients	CRP, SAA	36 (18/18)	women only	41 $\pm$ 12 / 36 $\pm$ 10	DSM-IV, HAM-D	USA	7
Lanquillon S et al., 2000 ³⁰	Inpatients	CRP	39 (24/15)	22/13	53.5 $\pm$ 15.2 / 48.7 $\pm$ 14.1	DSM-IV, HAM-D, MADRS	Germany	7
Leo R et al., 2006 ³¹	In- and outpatients	IL-6, IL-1 β , TNF- α , CD40L, sP-selectin	92 (46/46)	53/39	34.85 $\pm$ 5.88 / 34.11 $\pm$ 5.22	DSM-IV, HAM-D	Italy	7
Li Z et al., 2013 ³²	In- and Outpatients	TNF- α	128 (64/64)	103/25	32.1 $\pm$ 6.8 / 31.6 $\pm$ 5.9	DSM-IV, HAM-D	China	6
Maes M et al., 1995a ³³	In- and outpatients	IL-6, sIL-6R, sIL-2R, Tfr	99 (61/38)	42/57	36.6 $\pm$ 1.3 / 33.8 $\pm$ 1.5	DSM-III-R, HAM-D	Belgium	6
Maes M et al., 1995b ³⁴	Inpatients	IL-6, IL-1 β , sIL-2R, Tfr	41 (28/13)	16/25	35.2 $\pm$ 12.2 / 34.4 $\pm$ 15.1	DSM-III-R	USA	7
Maes M et al., 1997 ³⁵	Outpatients	IL-6, IL-6R, IL-1R, CC16, sCD8	50 (35/15)	21/19	50.3 $\pm$ 13.9 / 47.5 $\pm$ 15.0	DSM-III-R, HAM-D	Belgium	6
Maes M, Mihaylova I et al., 2012 ³⁶	Outpatients	IL-1 β , IL-1 α , TNF- α	111 (85/26)	64/47	42.0 $\pm$ 11.0 / 42.1 $\pm$ 12.8	DSM-IV, MINI, HAM-D	Belgium	5
Maes M, Ringel K et al., 2012 ³⁷	Outpatients	IL-1, TNF- α	144 (109/35)	82/62	43.0 $\pm$ 11.0 / 42.5 $\pm$ 12.4	DSM-IV, HAM-D	Belgium	4
Mikova O et al., 2001 ³⁸	Inpatients	IL-6, IL-8, IL-2R, TNF- α , CC16	43 (28/15)	31/12	47.3 $\pm$ 11.3 / 42.0 $\pm$ 10.9	DSM-IV, HAM-D	Bulgaria	5
Motivala SJ et al., 2005 ³⁹	Outpatients	IL-6, IL-6sR, MCP-1, sICAM	40 (22/18)	men only	44.4 $\pm$ 7.5 / 40.3 $\pm$ 9.2	DSM-IV, HAM-D	USA	7
Narita K et al., 2006 ⁴⁰	Outpatients	TNF- α	41 (21/20)	21/20	60.9 $\pm$ 7.1 / 59.4 $\pm$ 4.6	DSM-IV, HAM-D	Japan	6
O'Brien S et al., 2007 ⁴¹	Outpatients	IL-6, sIL-6R, TNF- α , IL-8, IL-10	52 (28/24)	33/19	44.15 / 35.58	DSM-IV, HAM-D	Ireland	5
O'Donovan A et al., 2013 ⁴²	Inpatients	IL-6, TNF- α , IL-10, TGF- β , CRP	124 (76/48)	86/36	50.54 $\pm$ 2.31 / 45.85 $\pm$ 2.23	MINI, HAM-D	Ireland	6

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Study	Patient type	Immune measures	N (cases/contr.)	Gender (female/male)	Age (cases/controls)	Depression diagnosis and severity scale	Country	Quality score
Pavon L et al., 2006 ⁴³	Outpatients	IL-6, TNF- α , IL-1 β , IL-2, IFN- γ , IL-4, IL-13	66 (33/33)	56/5	33.6 $\pm$ 10.2 / 24.2 $\pm$ 1.98	DSM-IV, HAM-D	Mexico	8
Pike JL and Irwin MR 2006 ⁴⁴	Outpatients	IL-6, IL-2r, haptoglobin, AAT, AAG	50 (25/25)	men only	42.5 $\pm$ 9.2 / 42.7 $\pm$ 12.0	DSM-IV, HAM-D	USA	7
Piletz JE et al., 2009 ⁴⁵	Outpatients	CRP, TNF- α , IL-1 β , MCP-1, CD40L	39 (22/17)	33/6	39.4 $\pm$ 1.9 / 39.7 $\pm$ 2.1	DSM-IV, HAM-D	USA	6
Rothermundt M et al., 2001 ⁴⁶	Inpatients	CRP, A2M, HB	86 (43/43)	56/30	44.45 $\pm$ 9.95 / 44.45 $\pm$ 9.95	DSM-IV, ICD-10	Germany	5
Rudolf S et al., 2014 ⁴⁷	Inpatients	CRP, IL-6	56 (32/24)	28/28	34.6 $\pm$ 11.7 / 30.8 $\pm$ 9.5	DSM-IV	Germany	5
Schmidt FM 2014 ⁴⁸	In- and outpatients	IL-2, IL-4, IL-5, IL-10, IL-12, IL-13, GM-CSF, IFN- γ , TNF- α	270 (64/206)	163/107	39.09 $\pm$ 12.86 / 37.73 $\pm$ 12.97	DSM-IV, HAM-D, BDI-II	Germany	5
Simon NM et al., 2008 ⁴⁹	Outpatients	MCP-1 α , MIP-1 α , IL-1 α , IL-1 β , IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p70, IL-13, IL-15, Eotaxin, GM-CSF, IFN- γ , IP-10, TNF- α	98 (49/49)	41/57	41.65 $\pm$ 11.07 / 41.69 $\pm$ 11.28	DSM-IV	USA	5
Sluzewska A et al., 1996 ⁵⁰	Inpatients	IL-6, sIL-6, sIL-2R, Tfr, CRP, AGP	64 (49/15)	49/15	42.3 $\pm$ 6.5 / n/a	DSM-III-R, HAM-D	Poland	6
Sutcgil L et al., 2007 ⁵¹	Outpatients	IL-2, IL-4, IL-12, TNF- α , TGF- β , MCP-1	48 (23/25)	23/25	34.78 $\pm$ 7.42 / 34.32 $\pm$ 7.80	DSM-IV, HAM-D	Turkey	6
Thomas AJ et al., 2005 ⁵²	Outpatients	IL-1 β , CRP	40 (21/19)	25/15	76.4 $\pm$ 7.3 / 74.9 $\pm$ 7.0	DSM-IV, MADRS	UK	4
Tuglu C et al., 2003 ⁵³	Inpatients	CRP, TNF- α	43 (26/17)	17/26	39.38 $\pm$ 14.56 / 37.11 $\pm$ 11.08	DSM-IV, HAM-D, BDI	Turkey	5
Voderholzer U et al., 2012 ⁵⁴	Outpatients	IL-6, IL-1RA, IL-2R	33 (16/17)	21/11	34 $\pm$ 13 / 27 $\pm$ 8	DSM-IV, HAM-D	Germany	6
Weinstein, AA et al., 2010 ⁵⁵	Outpatients	IL-6, TNF- α , CRP	28 (14/14)	14/14	41.7 $\pm$ 9.6 / 39.3 $\pm$ 5.6	DSM-IV, HAM-D, BDI-II	USA	7
Yang K et al., 2007 ⁵⁶	Inpatients	IL-6, TNF- α , IL-1 β	46 (23/23)	30/16	42.12 $\pm$ 2.27 / 38.39 $\pm$ 1.76	DSM-IV, HAM-D	China	7
Yoshimura R et al., 2010 ⁵⁷	Outpatients	IL-6	40 (20/20)	14/26	39.2 $\pm$ 10.6 / 36.7 $\pm$ 10.1	DSM-IV, HAM-D	Japan	4
Zahn D et al., 2013 ⁵⁸	Outpatients	CRP	46 (21/25)	25/21	49.5 $\pm$ 8.0 / 54.0 $\pm$ 8.4	DSM-IV, QIDS	Germany	4

Diagnostic criteria for depression: DSM: the Diagnostic and Statistical Manual of Mental Disorders; MINI: The Mini International Neuropsychiatric Interview

Depression severity assessment: HAMD: the Hamilton Rating Scale for Depression; MADRS: Montgomery–Åsberg Depression Rating Scale; BDI: the Beck Depression Inventory; ICD: the International Classification of Diseases; IDS: Inventory of Depressive Symptomatology; QIDS: Quick Inventory of Depressive Symptomatology; SCL-90-R: Symptom Checklist-90-Revised

Supplementary Table 3. Inclusion and exclusion criteria in the studies and covariates included in the meta-analysis.

Study	Inclusion criteria	Exclusion criteria	Covariates identified and/or controlled in the study	Covariates included in the meta-analysis
Basterzi AD et al., 2005 ¹	MDD outpatients	Any other axis I/II DSM-IV diagnosis; current pregnancy; acute or chronic infections; autoimmune, allergic, neoplastic or endocrine diseases; acute physical disorders; surgery; infarction within 3 months	Age; sex; HAMD score	Age; sex; patient type; medications; HAMD score
Carvalho LA et al., 2013 ²	Treatment resistant MDD inpatients; receipt of intensive inpatient treatment; diagnosis of primary affective disorder; failure to respond to at least one medication trial; HAMD score ≥ 16	Significant physical illnesses; history of hypersensitivity to corticosteroids or steroid use; heavy smoker; use of drugs with known immune/endocrine function: e.g. oral contraceptives; pregnant/lactating women; alcohol dependence	Age; sex; BMI; BDI score; HAMD score; BHS; BAI; RLCQ; BSI; duration of episode; number of previous hospital admissions; ECT in the past; medications	Age; sex; BMI; patient type; BDI score; medications; HAMD score
Cizza G et al., 2009 ³	Female MDD outpatients who had experienced depressive episode in the past three years	Coronary artery disease	Age; BMI; race; smoking; drinking; education; cooper test score; medications; HAMD/HAMA score; age of onset; no of episodes; duration of depression; antidepressant use	Age; BMI, HAMD score; patient type; medications
Dahl J et al., 2014 ⁴	MDD outpatients with age 18-60 years, score ≥ 22 on the IDS scale; minimum of 3 weeks washout period	Present or previous hypomania or mania; psychotic symptoms; autoimmune disorder; chronic inflammation; severe metabolic syndrome; BMI $> 34 \text{ kg/m}^2$; psychotic disorder; alcohol/drug dependence; receiving anti-inflammatory, antiviral, antibiotic or immune modulating drugs; inability to provide informed consent	Age; sex; BMI; MADRS score; IDS score	Age; sex; BMI; patient type; medications; MADRS score; IDS score
Dhabhar FS et al., 2009 ⁵	MDD outpatients; HAMD score ≥ 17 ; medically healthy; no clinically significant abnormalities; negative urine toxicology; age 19-69 years; English speaking; ability to provide informed consent	Pregnancy; medical illnesses (e.g. autoimmune disease, diabetes, HIV, endocrine disorders, hepatitis, cancer, chronic infections); use of steroids, psychotropic meds, antioxidants, corticosteroids, contraceptives, immunotherapy or antibiotics; febrile illness or elevated WBC counts; immunizations within 4 weeks; DSM-IV criteria for psychotic, bipolar or PTSD; drug/alcohol abuse	Age; sex; BMI; IDS score; HAMD score; marital status; ethnicity; education	Age; sex; BMI; patient type; IDS score; HAMD score; medications
Diniz BS et al., 2010a ⁶	Elderly MDD outpatients (first or recurrent episode)	History of disorders of chronic inflammatory disorders or uncontrolled clinical diseases; antidepressant or anti-inflammatory medication	Age; sex; education; depression episode duration; MMSE; CAMCOG; CDT; VF; HAMD score	Age; sex; patient type; HAMD score; medications
Diniz BS et al., 2010b ⁷	Elderly MDD outpatients (first or recurrent episode)	History of disorders of chronic inflammatory disorders or uncontrolled clinical diseases; antidepressant or anti-inflammatory medication	Age; sex; education; depression episode duration; MMSE; CAMCOG; CDT; VF; HAMD score	Age; sex; patient type; HAMD score; medications
Dome P et al., 2009 ⁸	MDD in- and outpatients	Elevated levels of fasting blood glucose, creatinine or urea nitrogen or liver functions; hypertension; psychiatric diagnoses; BMI $> 30 \text{ kg/m}^2$, high cholesterol or triglyceride levels; hypertriglyceridemia; signs of infection; $> 20 \text{ mm h}$ erythrocyte sedimentation rate; cardiovascular risk factors or CVD; medications with known effects on EPC numbers	Age; sex; BMI; smoking; BUN; WBC count; total cholesterol; triglycerides; BDI score; medications	Age; sex; BMI; BDI score; medications

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Study	Inclusion criteria	Exclusion criteria	Covariates identified and/or controlled in the study	Covariates included in the meta-analysis
Dunjic-Kostic B et al., 2013 ⁹	MDD inpatients; HAMD score ≥ 17 ; examination and diagnosis for the same type of depression; refractory patients	History of any other psychiatric disorder e.g. schizophrenia, other psychosis or substance/alcohol abuse, OCD or organic mental disorder; acute or chronic physical disease; pregnancy or breast feeding; history of systemic, endocrine or immune disorder; cancer; infections; allergies; obesity; under-nutrition; heavy smoker; anti-inflammatory or immunosuppressive therapy	Age; sex; BMI; smoking; marital state; education; employment; age of onset; duration of depression; subtype of depression; HAMD score; duration and class of antidepressant treatment; heredity; suicidal risk	Age; sex; BMI; patient type; HAMD score; medications
Eller T 2008 ¹⁰	MDD Outpatients; score ≥ 23 in MADRS	Acute infections; neurological or immunological disorders; substance abuse; bipolar depression; panic disorder	Age; sex; number of episodes; age of onset; duration of episode; subtype of depression; drug naïve vs. previously treated; MADRS score	Age; sex; patient type; MADRS score; medications
Eller T 2009 ¹¹	MDD outpatients; HAMD score < 20 ; physically healthy patients not receiving physical therapy	Substance abuse; acute infections; neurological or immunological disorders; bipolar disorder; panic disorder; antidepressant or anti-inflammatory medication	Age; sex; BMI; smoking; subtype of depression; HAMD score; BDI score	Age; sex; BMI; patient type; HAMD score; BDI score; medications
Euteneuer F et al., 2011 ¹²	MDD outpatients	Organic illnesses involving CNS or affecting immune status; psychotic symptoms; somatization or pain disorder; alcohol/drug abuse; analgesics; antipsychotics; stimulants; anxiolytics; current psychotherapy; pregnancy and lactation	Age; sex; BMI; physical activity; years of education; contraceptives; anxiety disorders comorbidity; antidepressants; BDI score; SCL-90-R GSI; pressure pain threshold	Age; sex; BMI; BDI score; patient type; medications
Fitzgerald P et al., 2006 ¹³	Physically healthy subjects with MDD and without psychotic features; age 25-65 years	Other psychiatric disorders ; inflammatory or allergic conditions; recent or current use of corticosteroids; concurrent physical illness	Age; sex; class and dose of antidepressant medications; HAMD score; severity of depression; SIV score	Age; sex; patient type; HAMD score; medications
Fornaro M et al., 2011 ¹⁴	Outpatients diagnosed with single or recurrent, drug naïve MDD episode; age 18-65 years; able to give informed consent; HAMD score ≥ 18	Pregnancy; breast feeding; bipolar disorder; any anxiety or schizoaffective disorder; schizophrenia; dementia; current suicidal and/or psychotic ideation; other non-psychotropic medications; history of medical comorbidities	Age; sex; HAMD score; YMRS	Age; sex; patient type; HAMD score; medications
Fornaro M et al., 2013 ¹⁵	MDD outpatients diagnosed with single or recurrent, drug naïve MDD episode; age 18-65 years; able to give informed consent; HAMD score ≥ 18	Pregnancy; breast feeding; bipolar disorder; any anxiety or schizoaffective disorder; schizophrenia; dementia; current suicidal and/or psychotic ideation; substance use disorder; other non-psychotropic medications; history of medical comorbidities	Age; sex; HAMD score; YMRS	Age; sex; patient type; HAMD score; medications
Frodl T et al., 2012 ¹⁶	MDD outpatients	Antipsychotics or mood stabilizers; age < 18 or > 65 ; history of neurological or comorbid psychiatric Axis I/II disorders; severe medical illness; head injury; substance abuse	Age; sex; height; weight; drinking; HAMD score; BDI score; CTQ; childhood maltreatment; age of onset; duration of depression; medications, GILZ; SGK-1; GR	Age; sex; patient type; BDI score; HAMD score; medications
Grassi-Oliveira, R et al., 2009 ¹⁷	Female MDD outpatients; 20-55 years of age	Axis I comorbidities; severe or unstable clinical illness; illness associated with abnormal immunological parameters; neurological disorder; psychotic symptoms; any psychoactive substance use in the last 30 days	Age; BMI; education; social status; PCL-C scores; BDI score; PTSD; PCL-C; CTQ; antidepressants	Age; BMI; BDI score; patient type; medications
Hennings A et al., 2013 ¹⁸	MDD outpatients with a maximum of three persistent medically unexplained bodily symptoms	Current delusional disorders; alcohol/substance abuse or dependence; persistent medical illnesses that could affect immune status; ongoing psychotherapy; medical illnesses or injuries in the last two week; medication with opiates	Age; sex; BMI; BDI score; fitness status; chronic stress; antidepressants; comorbid Axis I disorder	Age; sex; BMI; patient type; BDI score; medications

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Study	Inclusion criteria	Exclusion criteria	Covariates identified and/or controlled in the study	Covariates included in the meta-analysis
Hernandez ME et al., 2008 ¹⁹	MDD outpatients with BMI≤25; low coffee, alcohol and tobacco intake; free of antidepressants for at least 3 weeks	Pregnancy; medical illnesses; pharmacological treatments; history of allergies or allergic reactions; mental disorders including symptoms of dysthymia or chronic depression	Age; sex; BMI; HAMD score; BDI score; education; family history of depression; first or recurrent depression episode	Age; sex; BMI; patient type; HAMD score; BDI score; medications
Hernandez ME et al., 2013 ²⁰	MDD outpatients who were free of antidepressants for at least 3 weeks	Medical illnesses	Age; sex; BMI; HAMD score; BDI score; education; family history of depression; first or recurrent depression episode	Age; sex; BMI; patient type; HAMD score; medications
Hornig M et al., 1998 ²¹	MDD outpatients	Inflammatory, infectious or allergic diseases in the past two weeks; free of drugs known to affect immune function for four weeks; chronic medical illnesses known to affect immune system	Age; sex; affective subtypes; medications	Age; sex; ; patient type; medications
Huang T-L & Lee C-T 2007 ²²	MDD inpatients without any medication two weeks before the study	Chronic medical illnesses including heart, lung, liver, kidney and metabolic diseases; free of acute infections or allergic reactions	Age; sex; BMI; duration of illness; HAMD score	Age; sex; BMI; patient type; HAMD score; medications
Hughes MM et al., 2012 ²³	MDD inpatients	Age <18 or >65; history of neurological or comorbid psychiatric disorders (Axis I or Axis II); other severe medical illness; head injury; substance abuse; antipsychotics or mood stabilizers	Age; sex; BMI; smoking; drinking; age of onset; depression duration; HAMD score; antidepressants	Age; sex; BMI; patient type; HAMD score; medications
Häfner S et al., 2008 ²⁴	In- and outpatients with acute MDD	Severe medical disorders and infections; antihypertensive medication such as ACE inhibitors or angiotensin receptor blockers; hormone replacement therapy	Age; sex; BMI; smoking; HAMD score; ACE; hyperlipidemia	Age; sex; BMI; HAMD score; medications
Joyce PR et al., 1992 ²⁵	Male MDD outpatients free of medication for a minimum of two weeks	Physical illnesses	Age; BMI; mean cortisol; delta TSH; HAMD score	Age; BMI; patient type; HAMD score; medications
Kagaya A 2001 ²⁶	MDD outpatients free of antidepressants for more than 1 week at the beginning of the study	Other psychiatric disorders; endocrine and other medical disturbances; bipolar disorders; manic episodes; history of treatment with electroconvulsive therapy or lithium carbonate	Age; sex; HAMD score	Age; sex; patient type; HAMD score; medications
Karlović D et al., 2012 ²⁷	MDD in- and outpatients without psychotropic medication for at least 30 days prior the study	Other psychiatric disorders; alcohol or substance abuse; past and chronic illnesses or any other medical problems	Age; sex; smoking; education; marital status; working status; place of living; severity and subtypes of depression; number of depression episodes; duration of the disorder; psychiatric familiarity; age of onset; HAMD score	Age; sex; HAMD score; medications
Kéri S et al., 2014 ²⁸	First-episode MDD outpatients without a history of previous treatment and not receiving any pharmacological treatment or psychotherapy	Presence and history of psychotic or manic symptoms; severe suicidality requiring emergency treatment; substance misuse in the past 6 months; general health problems requiring medications; inability to participate in the psychotherapeutic process	Age; sex; education; socioeconomic status; smoking; drinking; BMI; waist-to-hip ratio; oral contraceptives; HAMD score	Age; sex; BMI; patient type; HAMD score; medications
Kling MA et al., 2007 ²⁹	Female MDD outpatients with at least 2 previous episodes and off psychotropic medication for ≥3 months	Potentially confounding illnesses; pregnancy; lactating women; smokers; medication for treatment or for prevention of medical condition	Age; BMI; ethnicity; HAMD score	Age; BMI; patient type; HAMD score; medications
Lanquillon S et al., 2000 ³⁰	MDD inpatients free of antidepressant medication for at least 6 weeks before hospital admission	Negative serum and urine screens for antidepressants and substances typical of drug abuse; other Axis I or Axis II diagnosis; pregnancy; acute or chronic infectious, autoimmune, allergic, neoplastic or endocrine diseases; other acute physical diseases	Age; sex; number of depression episodes; duration of current episode; weight loss; HAMD score, MADRS score	Age; sex; patient type; HAMD score; medications

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Study	Inclusion criteria	Exclusion criteria	Covariates identified and/or controlled in the study	Covariates included in the meta-analysis
Leo R et al., 2006 ³¹	First-episode MDD in- and outpatients not using psychotropic medication	Medical or neurological diseases; other psychiatric disorders; conventional risk factors for CAD incl. hypertension, hyperlipidemia, obesity, diabetes, family history and smoking; use of steroids, NSAIDs or antibiotics during the 2 preceding weeks; contraceptive hormonal therapy	Age; sex; BMI; total cholesterol; LDL cholesterol; triglycerides; HAMD score	Age; sex; BMI; HAMD score; medications
Li Z et al., 2013 ³²	First-episode and drug naive MDD in- and outpatients; age 18-60	HAMD score <17; smoking, drinking or substance dependence; severe medical illness such as cancer, diabetes; brain disease; pregnancy; infectious, auto-immunological, endocrinological, pulmonary, cardiac or haematological disease	Age; sex; BMI; duration of depression; HAMD score	Age; sex; BMI; HAMD score; medications
Maes M et al., 1995a ³³	MDD in- and outpatients	Other Axis I diagnosis; e.g. substance use disorder; organic mental disorder, schizophrenia; abnormal SGPT, SGOT, GGT, hematologic measures and renal function test; drugs known to interfere with immune or endocrine function; chronic illnesses known to affect immune status; acute infectious or allergic reactions for at least 2 weeks before the study	Age; sex; length of wash-out period	Age; sex; medications
Maes M et al., 1995b ³⁴	MDD inpatients in acute phase of illness and free from antidepressants for at least 1 week before the study	Medical illnesses	Age; sex; smoking;	Age; sex; patient type; medications
Maes M et al., 1997 ³⁵	MDD inpatients	Medical illnesses; infections; inflammatory or allergic reactions for at least 2 weeks before blood sampling; drugs known to affect immune or endocrine function; glucocorticoids; anticonceptive drugs; other Axis I diagnoses (organic mental disorders; schizophrenia; primary anxiety disorders) ; psychoactive substance use disorders within past 6 months; eating disorders	Age; sex; number of depressive episodes; duration of depression; HAMD score	Age; sex; patient type; HAMD score; medications
Maes M, Mihaylova I et al., 2012 ³⁶	MDD outpatients	Medical illnesses; mood stabilizers or immunomodulatory drugs; alcohol abuse and smoking; inflammatory or allergic reactions two months prior study; BMI>30; current and lifetime diagnosis of other Axis I disorders (psychotic, and lifetime diagnoses of anxiety disorders)	Age; sex; depression subtype; number of depressive episodes; duration of depression; HAMD score; use of antidepressants; treatment resistance; CF	Age; sex; HAMD score; patient type; medications
Maes M, Ringel K et al., 2012 ³⁷	MDD outpatients	Medical illnesses; mood stabilizers or immunomodulatory drugs; alcohol abuse and smoking; inflammatory or allergic reactions two months prior study; BMI>30; current and lifetime diagnosis of other Axis I disorders e.g. psychotic, substance use disorders, organic and substance use disorders	Age; sex; depression duration and subtype; number of depressive episodes; HAMD score; use of antidepressants; lysozyme; CF; 5-HT autoimmunity	Age; sex; HAMD score; patient type; medications
Mikova O et al., 2001 ³⁸	MDD inpatients; HAMD score ≥18	Physical illness; MAO inhibitors, antipsychotics, lithium, anticonvulsants during the last 6 months; antidepressants; treated for MS with glucocorticoids during the month before the study; infection; allergic responses for 2 weeks prior study	Age; sex; HAMD score	Age; sex; patient type; HAMD score; medications
Motivala SJ et al., 2005 ³⁹	Male MDD outpatients	Current or history of alcohol dependence; recent viral infections; chronic medical conditions such as diabetes, cancer or COPD; hypertension; antihypertensive medication; antidepressants; aspirin use for 7 days before immune assessment; HIV negativity	Age; weight; ethnicity; education; smoking; drinking; HAMD score; EEG sleep variables	Age; BMI; patient type; HAMD score; medications
Narita K et al., 2006 ⁴⁰	MDD outpatients with complete remission and receiving antidepressant treatment over 6 months	History of chronic inflammatory disease; collagen disease; cardiac disease; atherosclerotic risk factors; diabetes; chronic alcoholism; smoking; BMI >26; use of antipsychotics, statins or antihypertensive drugs	Age; sex; BMI; fasting glucose; HbA1c; number and duration of depression; duration of pharmacotherapy; adiponectin; SSRI/SNRI; HAMD score	Age; sex; BMI; HAMD score; patient type; medications

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Study	Inclusion criteria	Exclusion criteria	Covariates identified and/or controlled in the study	Covariates included in the meta-analysis
O'Brien S et al., 2007 ⁴¹	MDD outpatients with HAMD score >20	Significant physical illness including acute or chronic infections, inflammatory or immune disorders; >10% above ideal body weight; endocrine, immune or metabolic disorder; IBD; acquired immunodeficiency syndrome; allergic, infectious or inflammatory response in last 2 weeks; other Axis I disorders; substance abuse	Age; sex; smoking; HAMD score	Age; sex; HAMD score; medications
O'Donovan A et al., 2013 ⁴²	MDD inpatients	Lack of primary diagnosis of MDD; acute physical illness; age <18 years	Age; sex; BMI; HAMD score, suicidal ideation; attempted suicide; number of depression episodes; duration of MDD; medications	Age; sex; BMI; HAMD score, patient type; medications
Pavon L et al., 2006 ⁴³	MDD outpatients free of medication for at least three weeks; HAMD score ≥22	Past and present neurological, psychiatric or substance abuse; physical illnesses; no comorbid diagnoses besides anxiety; low coffee, tobacco and alcohol consumption	Age; sex; ethnicity; socio-economic class; education	Age; sex; patient type; medications
Pike JL and Irwin MR 2006 ⁴⁴	MDD male outpatients in good health and not using antidepressants for at least 19 days prior to evaluation	Alcohol or substance abuse or dependence; psychiatric comorbidity; recent <10 days viral illness; immunosuppressive medications;	Age; weight; smoking; drinking; HAMD score; medications	Age; sex; patient type; HAMD score; medications
Piletz JE et al., 2009 ⁴⁵	MDD outpatients with wash-out period for at least 2 weeks; HAMD score ≥19	Medical illness such as CAD, diabetes, arthritis or hypertension; any diagnosis other than MDD; clinically significant abnormalities; history of seizures; pregnancy; allergy to antidepressants; abnormality on ECG; history of substance abuse/dependence; PTSD; psychosis; bleeding diathesis; history of heart or vascular disease; family history of early-onset heart or vascular disease; heavy smoking (>1 pack of cigarettes/day)	Age; sex; BMI; systolic and diastolic BP; HAMD score; medications	Age; sex; BMI; HAMD score; patient type; medications
Rothermundt M et al., 2001 ⁴⁶	MDD inpatients	Acute infectious diseases; past physical illnesses e.g. acute or chronic infections, autoimmune diseases, cancer); medications with potential immune effects	Age; sex; HAMD score; depression subtype; medications	Age; sex; HAMD score; patient type; medications
Rudolf S et al., 2014 ⁴⁷	MDD inpatients	Schizophrenia; mental retardation; alcohol or drug abuse for at least 3 months prior to the study; diabetes; inflammatory of infectious disease; CVD; pregnancy; age ≤17 years; polypharmacy	Age; sex; height; weight; BMI; sport; alcohol; pack years; waist girth; systolic/diastolic BP; cholesterol; HDL; LDL; triglycerides; HbA1c; glucose; insulin; cortisol; depression subtype; medications	Age; sex; BMI; patient type; medications
Schmidt FM 2014 ⁴⁸	MDD in- and outpatients free of psychoactive medication for at least 7 days prior the examination	Other DSM-IV Axis I disorders; use of illegal drugs: alcohol abuse within the past 6 months; history of head injury with loss of consciousness >1h; acute or chronic infection; major somatic disorders; diagnosed sleep apnea; obesity hypoventilation syndrome	Age; sex; BMI; smoking; employment; activity; age at onset; duration of depression; number of episodes; duration of current episode; sleep patterns; appetite; HAMD score; BDI score;	Age; sex; BMI; HAMD score; BDI score; patient type; medications
Simon NM et al., 2008 ⁴⁹	MDD outpatients free of antidepressants for a minimum of 1 week at entry	Pregnancy; significant medical or substance use disorder	Age; sex; ethnicity; duration of depression; HAMD score	Age; sex; HAMD score; patient type; medications
Sluzewska A et al., 1996 ⁵⁰	MDD inpatients who were drug-free for at least 10 days	Chronic or acute infection; allergic disease or other condition affecting immune system for at least 2 weeks before the study; major medical illness; oral contraceptives	Age; sex; HAMD score	Age; sex; HAMD score; patient type; medications

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Study	Inclusion criteria	Exclusion criteria	Covariates identified and/or controlled in the study	Covariates included in the meta-analysis
Sutcgil L et al., 2007 ⁵¹	First episode MDD outpatients	Other Axis I or Axis II diagnosis; pregnancy; acute or chronic infections within the past month; autoimmune, allergic, neoplastic or endocrine diseases and other acute physical disorders within past 3 months; use of antidepressants, NSAIDs or oral contraceptives in the past 6 weeks	Sex; age; HAMD score	Sex; age; HAMD score; patient type; medications
Thomas AJ et al., 2005 ⁵²	>60 years old MDD outpatients with score ≥ 20 on the MADRS	Dementia or other neurological diseases; conditions associated with inflammation such as rheumatoid arthritis; oral steroids	Age; sex; cognitive performance; MADRS; mini-mental state examination; geriatric depression scale; the age at onset; duration of depression; medications	Age; sex; MADRS; patient type; medications
Tuglu C et al., 2003 ⁵³	MDD inpatients without antidepressive medications for the last 6 weeks	Other Axis I or Axis II DSM-IV diagnosis; pregnancy; chronic or acute disease in the last 3 months; neuroleptics (past 6 months)	Age; sex; HAMD score; BDI score; ESR; leukocytes	Age; sex; HAMD score; BDI score; patient type; medications
Voderholzer U et al., 2012 ⁵⁴	Drug-free MDD outpatients	Significant medical disorder or infectious disease; smoking; history of drug/alcohol abuse; psychotropic or anti-inflammatory drugs within 7 days; restless leg syndrome, sleep apnea	Age; sex; BMI; HAMD score; TSD	Age; sex; BMI; patient type; HAMD score; medications
Weinstein, AA et al., 2010 ⁵⁵	MDD outpatients	Age <18 or >80 years; history of CAD; antihypertensive, immunomodulatory or anti-inflammatory medications other than aspirin; current or past diagnosis or treatment of bipolar disorder or psychosis; active suicidal ideation	Age; sex; BMI; race; smoking; activity level; mental stress; HAMD score; medications	Age; sex; BMI; HAMD score; patient type; medications
Yang K et al., 2007 ⁵⁶	MDD inpatients with HAMD score ≥ 20 and free of major psychotropic drugs for at least 4 weeks (fluoxetine ≥ 5 weeks)	Significant physical or neurological illness; acute or chronic infections; inflammatory and immune disorders; aspirin and NSAIDs for at least 2 weeks; therapeutic corticosteroids for at least 6 months prior testings; schizophrenia or other psychoses; organic mental disorders; substance dependence; OCD or any other primary psychiatric disorder	Age; sex; BMI; education; menostasis; age of onset; duration of illness and current episode; number of episodes; family history; HAMD score	Age; sex; BMI; HAMD score; patient type; medications
Yoshimura R et al., 2010 ⁵⁷	MDD outpatients without any medications for at least 2 weeks before the blood samplings	Physical illnesses; alcohol/drug abuse;	Age; sex; HAMD score; duration of the illness; age of onset; plasma BDNF levels	Age; sex; BMI; HAMD score; patient type; medications
Zahn D et al., 2013 ⁵⁸	Untreated MDD outpatients	History of coronary heart, cerebrovascular or peripheral artery disease; current substance abuse; psychotic illness; suicidal tendencies; use of platelet aggregation inhibitors; anticoagulant or antidepressant medication; cognitive impairment; severe medical conditions other than hypertension and dyslipidaemia	Age; sex; BMI; education; smoking; HbA1c; HDL; LDL; triglycerides; CD40; quick inventory of depressive symptomology (QIDS); medications	Age; sex; BMI; patient type; medications

Abbreviations: ACE: angiotensin-converting enzyme; ACTH: adrenocorticotrophic hormone; BAI: Beck anxiety inventory; BDI: Beck depression inventory; BDNF: brain-derived neurotrophic factor; BHS: Beck hopelessness scale; BMI: body mass index; BP: blood pressure; BSI: Beck suicide scale; BUN: blood urea nitrogen; CAMCOG: Cambridge cognitive examination; CDT: clock drawing test; CF: chronic fatigue; COPD: chronic obstructive pulmonary disease; CTQ: childhood trauma questionnaire; CVD: cardiovascular disease; ECG: electrocardiogram; ECT: electroconvulsotherapy; EEG: electroencephalography; EPC: endothelial progenitor cells; ESR: erythrocyte sedimentation rate; GGT: The gamma-glutamyl transferase; GILZ: glucocorticoid-inducible genes Leucine Zipper; GR: glucocorticoid receptor; GSI: global severity index; HAMA: Hamilton anxiety scale; HAMD: Hamilton depression scale; HbA1c: glycosylated haemoglobin A1c; HDL: high-density lipoprotein; 5-HT: 5-hydroxytryptamine; IBD: inflammatory bowel disease; IDS: inventory of depressive symptomology; LDL: low-density lipoprotein; MADRS: Montgomery Åsberg depression scale; MAOI: monoamine oxidase inhibitor; MMSE: mini mental state examination; NSAID: non-steroidal anti-inflammatory drug; OCD: obsessive-compulsive disorder; PCL-C: PTSD checklist-civilian version; PTSD: post-traumatic stress disorder; RLCQ: recent life changes questionnaire; SCL: symptom check list; SGK-1: serum and glucocorticoid-inducible kinase-1; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase; SIV: steroid-induced vasoconstriction; TSD: total sleep deprivation; TSH: thyroid stimulating hormone; SSRI: selective serotonin reuptake inhibitor; SRNI: serotonin-norepinephrine reuptake inhibitors; VF: verbal fluency; WBC: white blood cells; YMRS: young mania rating scale.

Supplementary Table 4. Other Axis I or Axis II disorders, subtypes and the severity of depression, substance use and medications..

Study	Any other Axis I or Axis II disorder*	Depression subtype provided*	Depression severity informed[§]	Substance use~	Medications not used at the time of assessment[†]	Wash-out period time (min)	Medications used at the time of assessment[^]	Medication use (Yes/No category)
Basterzi AD et al., 2005 ¹	No	n/a	Yes (S)	n/a	1, 2, 6, 7	6wk	n/a	No
Carvalho LA et al., 2013 ²	n/a	Yes 4 (100%)	Yes (S)	No (1, 2)	7	n/a	1, 2, 3, 4, 5, 6	Yes
Cizza G et al., 2009 ³	Yes 1B (50%)	n/a	Yes (M)	Yes (1)	n/a	n/a	2, 7	Yes
Dahl J et al., 2014 ⁴	No (2, 3)	Yes 1 (76%)	Yes (M)	No (2, 3)	1, 2, 6, 8, 11	3wk	n/a	No
Dhabhar FS et al., 2009 ⁵	No (2, 3, 4)	n/a	Yes (S)	No (2, 3)	1, 2, 3, 5, 7, 8, 9	6wk	n/a	No
Diniz BS et al., 2010a ⁶	n/a	n/a	Yes (M)	n/a	1, 2, 6	n/a	n/a	No
Diniz BS et al., 2010b ⁷	n/a	n/a	Yes (S)	n/a	1, 2, 6	n/a	n/a	No
Dome P et al., 2009 ⁸	No	n/a	Yes (S)	Yes (1)	n/a	n/a	1, 2, 3, 4, 5, 6, 10	Yes
Dunjic-Kostic B et al., 2013 ⁹	No (3, 5, 7)	Yes 1 (62%) 2 (38%)	Yes (S)	Yes (1) No (2, 3)	1, 2, 3, 4, 5, 6, 9	4wk	n/a	No
Eller T 2008 ¹⁰	No (2, 6)	Yes 1 (73%)	Yes (M)	No (2, 3)	6	n/a	1, 7, 11	Yes
Eller T 2009 ¹¹	No (2, 6)	Yes 1 (85%)	Yes (S)	Yes (1) No (2, 3)	1, 2, 6, 9	2wk	7	No
Euteneuer F et al., 2011 ¹²	Yes 1A (5.3%), 6 (8.1%), 4 (10.5%), 8 (18.5%) No 3	n/a	Yes (M)	No (2, 3)	4, 5, 6, 11	n/a	1, 2	Yes
Fitzgerald P et al., 2006 ¹³	No (3)	Yes (4)	Yes (S)	n/a	9	n/a	1, 2	Yes
Fornaro M et al., 2011 ¹⁴	No (1B, 2, 5)	n/a	Yes (S)	n/a	1, 2, 6, 7	15d	4, 11 (sedative)	No
Fornaro M et al., 2013 ¹⁵	No (1B, 2, 5)	n/a	Yes (S)	No (2, 3)	1, 2, 6, 7	15d	4, 11 (sedative)	No
Frodl T et al., 2013 ¹⁶	No	n/a	Yes (S)	No (2, 3)	3, 5	n/a	1, 2	Yes
Grassi-Oliveira, R et al., 2009 ¹⁷	No (3) Yes (4)	n/a	Yes (M)	Yes (1)	5	n/a	1, 2	Yes
Hennings A et al., 2013 ¹⁸	Yes (57.9%) No (3)	n/a	Yes (M)	No (2, 3)	11 (opiates)	n/a	1, 2	Yes
Hernandez ME et al., 2008 ¹⁹	No	n/a	Yes (S)	Yes (1) No (2)	1, 2, 5	3wk	n/a	No
Hernandez ME et al., 2013 ²⁰	n/a	n/a	Yes (S)	n/a	1, 2	3wk	n/a	No
Hornig M et al., 1998 ²¹	No (2)	n/a	n/a	n/a	n/a	n/a	1, 2, 4, 5	Yes

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Study	Any other Axis I or Axis II disorder*	Depression subtype provided*	Depression severity informed⁶	Substance use~	Medications not used at the time of assessment⁷	Wash-out period time (min)	Medications used at the time of assessment⁸	Medication use (Yes/No category)
Huang T-L & Lee C-T 2007 ²²	n/a	Yes 1 (60%) 3 (26%)	Yes (S)	n/a	Subjects "medication free"	2wk	n/a	No
Hughes MM et al., 2012 ²³	No	n/a	Yes (S)	Yes (1) No (2)	2	n/a	1, 2	Yes/No
Häfner S et al., 2008 ²⁴	n/a	n/a	Yes (S)	n/a	10	n/a	1, 2	Yes
Joyce PR et al., 1992 ²⁵	n/a	n/a	Yes (S)	n/a	1, 11 (anticonvulsants)	2wk	n/a	No
Kagaya A 2001 ²⁶	No (2)	n/a	Yes (S)	n/a	1, 2	1wk	n/a	No
Karlović D et al., 2012 ²⁷	No	Yes 1 (58%) 2 (42%)	Yes (S)	Yes (1) No (2, 3)	1, 2, 4	30d	n/a	No
Kéri S et al., 2014 ²⁸	No (2, 3)	n/a	Yes (S)	Yes (1) No (2)	1, 2, 3	n/a	7	No
Kling MA et al., 2007 ²⁹	n/a	n/a	Yes (M)	No (1)	1, 2	3mo	n/a	No
Lanquillon S et al., 2000 ³⁰	No	n/a	Yes (S)	No (2, 3)	1, 2	6wk	n/a	No
Leo R et al., 2006 ³¹	No	n/a	Yes (S)	No (1)	1, 2, 4, 6, 7, 8	2wk	n/a	No
Li Z et al., 2013 ³²	n/a	Yes 3 (70%)	Yes (S)	No (2, 3)	1, 2	n/a	n/a	No
Maes M et al., 1995a ³³	No (5)	n/a	n/a	No (2, 3)	1, 2	1wk	n/a	No
Maes M et al., 1995b ³⁴	No (5)	n/a	n/a	Yes (1)	1, 2, 5	1wk	n/a	No
Maes M et al., 1997 ³⁵	No (1B, 5)	Yes 4 (80%)	Yes (S)	No (3)	2, 7, 9	n/a	n/a	No
Maes M, Mihaylova I et al., 2012 ³⁶	No (1B, 3)	Yes 1 (68%), 4 (68%)	Yes (S)	No (1, 2)	2, 3, 6, 9, 10	n/a	n/a	Yes/No
Maes M, Ringel K et al., 2012 ³⁷	No (3)	Yes 1 (83%), 4 (54%)	Yes (S)	No (1, 2, 3)	9, 10	n/a	1, 2	Yes
Mikova O et al., 2001 ³⁸	No	n/a	n/a	n/a	1, 2, 3, 10	n/a	n/a	No
Motivala SJ et al., 2005 ³⁹	n/a	n/a	Yes (S)	Yes (1) No (2)	1, 2, 4, 10, 11 (aspirin)	n/a	n/a	No
Narita K et al., 2006 ⁴⁰	n/a	No	Yes (M)	No (1, 2)	5, 10, 11 (statins)	n/a	1, 2, 4	Yes
O'Brien S et al., 2007 ⁴¹	No	n/a	Yes (S)	Yes (1) No (2, 3)	n/a	n/a	1, 2, 11 (lithium)	Yes
O'Donovan A et al., 2013 ⁴²	n/a	Yes 3 (38%)	Yes (S)	n/a	n/a	n/a	6, 11 (statins)	Yes
Pavon L et al., 2006 ⁴³	Yes (1B)	n/a	Yes (S)	Yes (1) No (2, 3)	Subjects "medication free"	3wk	n/a	No
Pike JL and Irwin MR 2006 ⁴⁴	No	n/a	Yes (S)	Yes (1) No (2, 3)	1, 2, 4	7d	9, 11 (diuretic, β -agonist)	No

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Study	Any other Axis I or Axis II disorder*	Depression subtype provided*	Depression severity informed^b	Substance use[~]	Medications not used at the time of assessment[†]	Wash-out period time (min)	Medications used at the time of assessment[^]	Medication use (Yes/No category)
Piletz JE et al., 2009 ⁴⁵	No (3, 4)	n/a	Yes (S)	Yes (1) No (2, 3)	1, 2 (6, 10)	2wk (3d)	n/a	No
Rothermundt M et al., 2001 ⁴⁶	No (3)	Yes 1 (51%)	Yes (S)	Yes (1)	n/a	n/a	1, 2	Yes
Rudolf S et al., 2014 ⁴⁷	No (5)	Yes 2 (25%)	n/a	Yes (1) No (2, 3)	2, 4	n/a	1	Yes
Schmidt FM 2014 ⁴⁸	No	n/a	Yes (M)	Yes (1) No (2, 3)	1, 2, 4	7d	n/a	No
Simon NM et al., 2008 ⁴⁹	Yes 1B (48%) 6 (15%) 9 (35%) 4 (18%)	n/a	Yes (S)	Yes 2, 3 (35%)	1, 2	1wk	(6, not assessed)	No
Sluzewska A et al., 1996 ⁵⁰	n/a	n/a	Yes (S)	n/a	7 (subjects "medication free")	10d	n/a	No
Sutcgil L et al., 2007 ⁵¹	No	n/a	Yes (S)	n/a	1, 2, 6, 7	6wk	n/a	No
Thomas AJ et al., 2005 ⁵²	n/a	n/a	Yes (M)	Yes (1)	11 (steroids)	n/a	1, 2, 4, 6	Yes
Tuglu C et al., 2003 ⁵³	No	n/a	Yes (S)	n/a	1, 2, 11 (neuroleptics)	6wk	n/a	No
Voderholzer U et al., 2012 ⁵⁴	n/a	n/a	Yes (M)	Yes(1) No (2, 3)	1, 2, 4, 6	7d	7	No
Weinstein, AA et al., 2010 ⁵⁵	No (2, 3)	n/a	Yes (M)	Yes (1)	6, 10	n/a	1, 2, aspirin	Yes
Yang K et al., 2007 ⁵⁶	No (3, 5, 7)	n/a	Yes (S)	No	1, 2, 4, 6, 9	2wk	4 (benzodiazepines)	No
Yoshimura R et al., 2010 ⁵⁷	n/a	n/a	Yes (M)	No (2, 3)	Subjects "medication free"	2wk	n/a	No
Zahn D et al., 2013 ⁵⁸	No (3)	n/a	Yes (M)	Yes (1) No (2, 3)	1, 2, 11 (anticoagulant)	n/a	n/a	No

* 1A: generalized anxiety disorder, 1B: "anxiety disorder" 2: bipolar disorder, 3: "psychotic disorder" or "psychoses", 4: post-traumatic stress disorder, 5: schizophrenia, 6: panic disorder, 7: obsessive-compulsive disorder, 8: phobia, 9: social anxiety

* 1 = melancholic, 2 = atypical, 3 = suicidal, 4 = treatment resistant depression

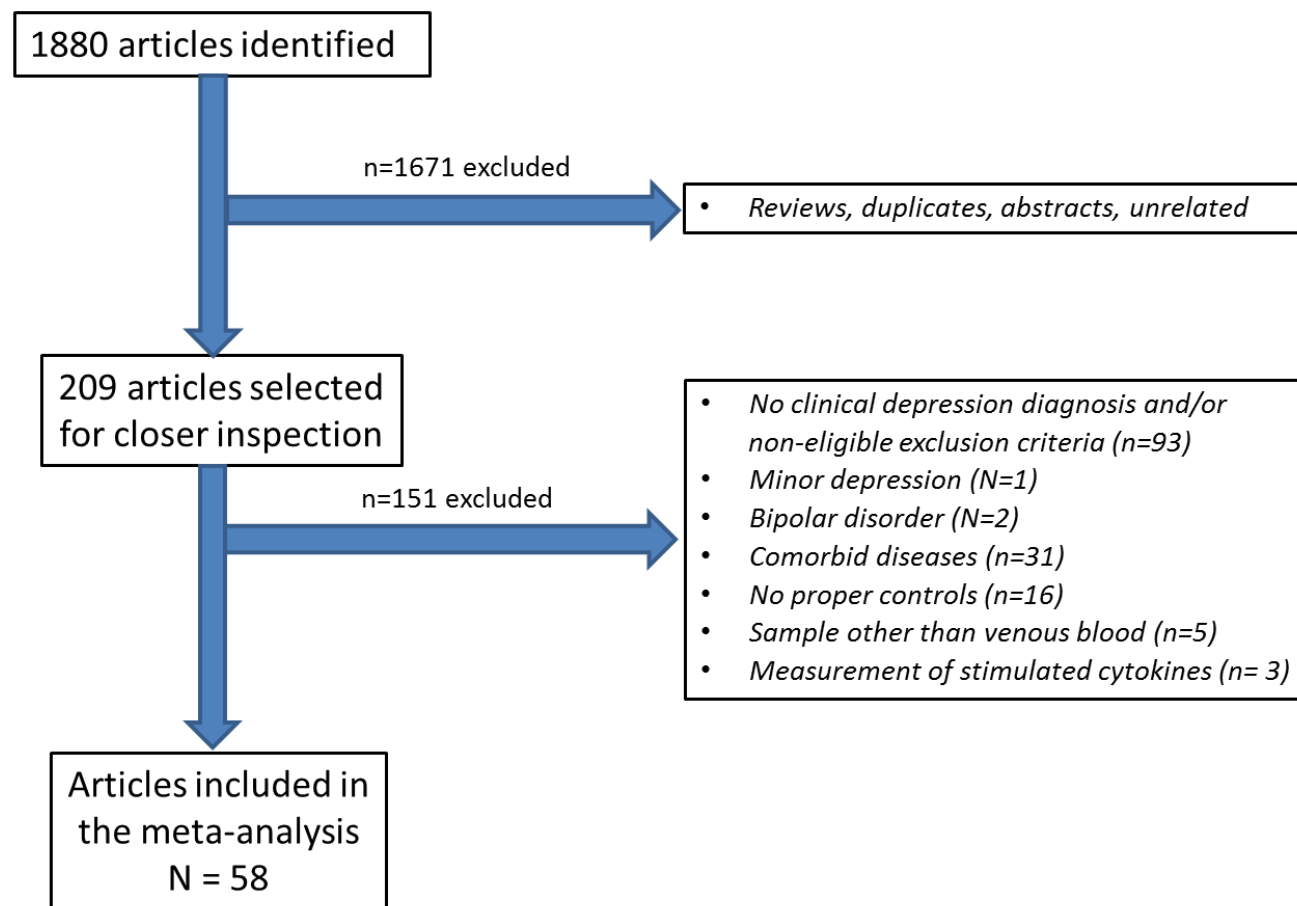
~ 1: smoking, 2: alcohol and/or substance dependence, 3: drug abuse

^b Depression severity (*mean score of all patients*): M = mild/moderate, S = severe (HAMD: mild/moderate: score <19, severe: ≥19; MADR: mild/moderate: <34, severe: >34; IDS: mild/moderate: <39, severe: ≥39; BDI: mild/moderate: <30, severe: ≥30)

[†] 1: SSRIs, 2: other antidepressant or class n/a, 3: mood stabilizers, 4: anxiolytics, 5: antipsychotics, 6: anti-inflammatory, 7: contraceptives, 8: antibiotics, 9: corticosteroids, 10: antihypertensive, 11: other

[^] 1: SSRIs, 2: other antidepressants or class n/a, 3: mood stabilizers, 4: anxiolytics, 5: antipsychotics, 6: anti-inflammatory, 7: contraceptives, 8: antibiotics, 9: corticosteroids, 10: antihypertensive, 11: other

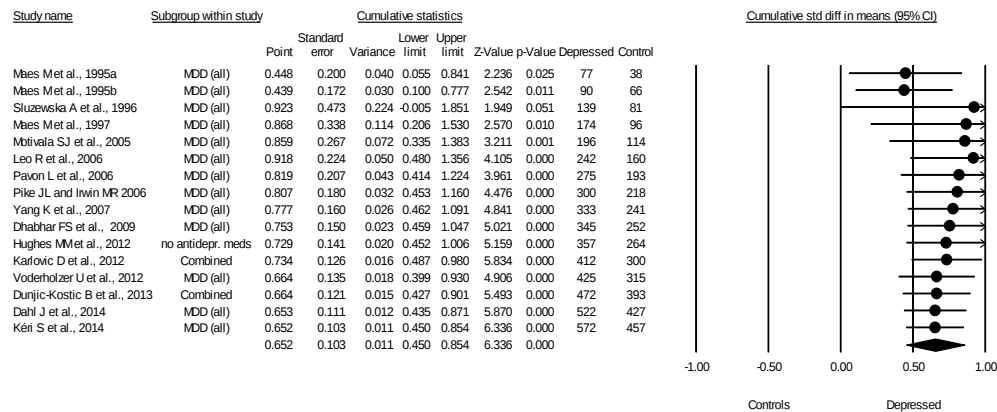
Supplementary Figure 1. Flow diagram on literature search strategy.



Supplementary Figure 2. Sensitivity analysis: cumulative meta-analysis on A) IL-6, B) CRP, C) TNF- α and D) IL1 β including only studies with high quality (score ≥ 6) and subjects not using antidepressants.

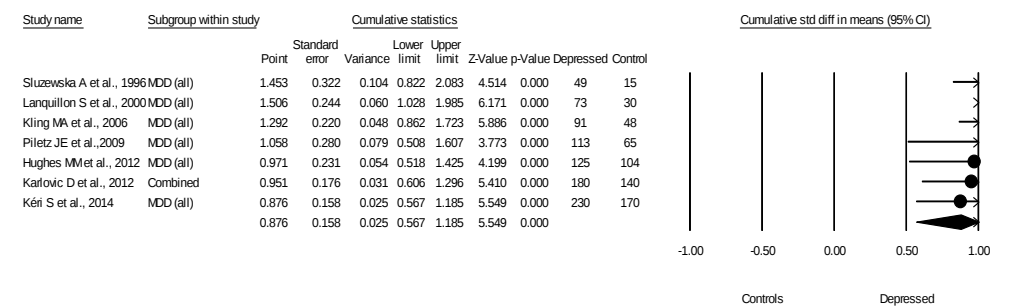
A)

IL-6

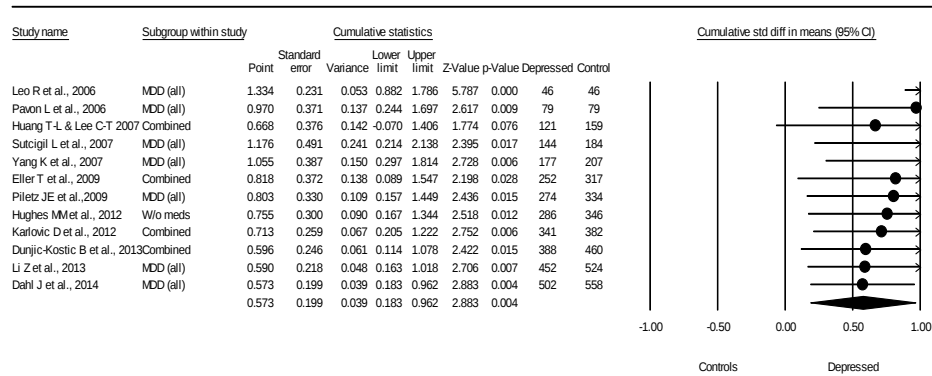


B)

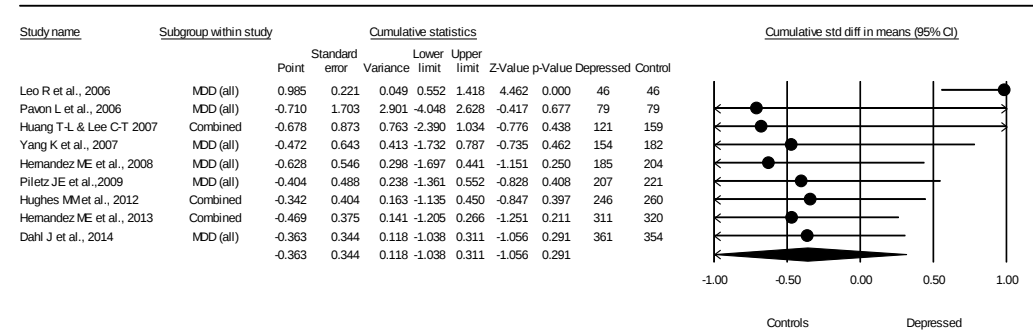
CRP



c)

TNF- α 

D)

IL-1- β 

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