Supplemental Online Content

Mousten IV, Sørensen NV, Christensen RHB, Benros ME. Cerebrospinal fluid biomarkers in patients with unipolar depression compared with healthy control individuals: a systematic review and meta-analysis. *JAMA Psychiatry*. Published online April 20, 2022. doi:10.1001/jamapsychiatry.2022.0645

eTable 1. PRISMA 2020 Checklist

eTable 2. MOOSE Checklist for Meta-analyses of Observational Studies

eTable 3. Search string

eFigure 1. PRISMA 2020 flow diagram

eTable 4. Baseline characteristics from CSF studies

eFigure 2. Neurotransmitters and their metabolites

eFigure 3. Hormones, neuropeptides and metabolites

eFigure 4. Inflammation and BBB permeability

eFigure 5. Neurodegeneration and synaptic plasticity

eFigure 6. Forest plots of biomarkers quantified in only one study

eTable 5. Presentation of all biomarkers identified for the meta-analysis and a brief description of their function

eFigure 7. Meta-regression analyses of mean biomarker levels in relation to mean HAM-D scores for patients. Performed on biomarkers with data for ≧10 studies

eFigure 8. Hospitalized patients compared to not hospitalized patients for biomarkers with data on ≧5 studies

eFigure 9. Patients off antidepressant treatment for ≦14 days compared to >14 days for biomarkers with data on ≧5 studies

eFigure 10. Studies with a total score of ≧4 compared to <4 on the Newcastle Ottawa Scale (NOS) for biomarkers quantified in ≧5 studies

eFigure 11. Studies published before year 2000 compared to studies published in or after 2000 for biomarkers quantified in ≧5 studies

eFigure 12. Funnel plots of biomarkers examined in ≧10 studies

eFigure 13. Meta-regression analyses of mean group size in relation to standard mean difference (SMD) on biomarkers examined in ≧10 studies

eFigure 14. Meta-regression analyses of publication year in relation to standard mean difference (SMD) on biomarkers examined in ≧10 studies

eTable 6. Definition of terms for bias assessment according to the Newcastle-Ottawa criteria for case-control studies

eTable 7. Bias assessment according to the Newcastle-Ottawa criteria for case-control studies

eTable 8. Studies contacted for data request

eTable 9. Studies that had been included in previous meta-analyses but were excluded due to neurological or surgical controls

eTable 10. GRADE evidence profile for biomarkers quantified in ≧2 studies

This supplemental material has been provided by the authors to give readers additional information about their work.

Online-Only Supplemental Material

eTable 1 | PRISMA 2020 Checklist **4**

eTable 2 | MOOSE Checklist for Meta-analyses of Observational Studies **7**

eTable 3 | Search string **9**

eFigure 1 | PRISMA 2020 flow diagram **10**

eTable 4 | Baseline characteristics from CSF studies **11**

Included in meta-analysis *11*

Not included in meta-analysis *18*

Forrest plots of biomarkers quantified in ≧2 studies with both random and fixed effects models **34**

eFigure 2 | Neurotransmitters and their metabolites *34*

eFigure 3 | Hormones, neuropeptides and metabolites *35*

eFigure 4 | Inflammation and BBB permeability *38*

eFigure 5 | Neurodegeneration and synaptic plasticity *39*

eFigure 6 | Forest plots of biomarkers quantified in only one study **40**

eTable 5 | Presentation of all biomarkers identified for the meta-analysis and a brief description of their function **43**

Subgroup analyses **55**

eFigure 7 | Meta-regression analyses of mean biomarker levels in relation to mean HAM-D scores for patients. Performed on biomarkers with data for ≧10 studies *55*

eFigure 8 | Hospitalized patients compared to not hospitalized patients for biomarkers with data on ≧5 studies *58*

eFigure 9 | Patients off antidepressant treatment for ≦14 days compared to >14 days for biomarkers with data on ≧5 studies *59*

Sensitivity analyses **62**

eFigure 10 | Studies with a total score of ≧4 compared to <4 on the Newcastle Ottawa Scale (NOS) for biomarkers quantified in ≧5 studies *62*

eFigure 11 | Studies published before year 2000 compared to studies published in or after 2000 for biomarkers quantified in ≧5 studies *67*

Bias assessment analyses **72**

eFigure 12 | Funnel plots of biomarkers examined in ≧10 studies *72*

eFigure 13 | Meta-regression analyses of mean group size in relation to standard mean difference (SMD) on biomarkers examined in ≧10 studies *75*

eFigure 14 | Meta-regression analyses of publication year in relation to standard mean difference (SMD) on biomarkers examined in ≧10 studies *78*

eTable 6 | Definition of terms for bias assessment according to the Newcastle-Ottawa criteria for case-control studies **81**

eTable 7 | Bias assessment according to the Newcastle-Ottawa criteria for case-control studies **82**

eTable 8 | Studies contacted for data request **85**

eTable 9 | Studies that had been included in previous meta-analyses but were excluded due to neurological or surgical controls **87**

eTable 10 | GRADE evidence profile for biomarkers quantified in ≧2 studies **90**

eTable 1 | PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	p. 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	p. 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	p. 2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	p. 2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	p. 2
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p. 2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	p. eTable 3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	p. 2
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	p. 2
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	p. 2-3
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	p. 2-3
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	p. 3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	p. 3
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	p. 2-3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	p. 3
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	p. 3
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	p. 3
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	p. 3
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized	p. 3

Section and Topic	Item #	Checklist item	Location where item is reported
		results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	p. 3
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	p. 3
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	p. 3 + eFigure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	eTable 4
Study characteristics	17	Cite each included study and present its characteristics.	eTable 4
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	p. 3 + eTable 6-7
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	eTable 4
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	eTable 10
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	p. 3-8 + Table 1 + eFigure 2-6
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	p. 3-9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	p. 3-8
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	p. 8 + eFigure 12
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	p. 3-8 + Table 1
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	p. 8-9
	23b	Discuss any limitations of the evidence included in the review.	p. 8-9
	23c	Discuss any limitations of the review processes used.	p. 8-9
	23d	Discuss implications of the results for practice, policy, and future research.	p. 8-9
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	p. 2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	p. 2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	p. 2
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	p. 9
Competing interests	26	Declare any competing interests of review authors.	p. 9
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	p. 9

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

eTable 2 | MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	p. 2
2	Hypothesis statement	p. 2
3	Description of study outcome(s)	p. 2
4	Type of exposure or intervention used	p. 2
5	Type of study designs used	p. 2
6	Study population	p. 2
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	p. 2-3
8	Search strategy, including time period included in the synthesis and key words	p. 2
9	Effort to include all available studies, including contact with authors	p. 2
10	Databases and registries searched	p. 2
11	Search software used, name and version, including special features used (eg, explosion)	p. 2-3
12	Use of hand searching (eg, reference lists of obtained articles)	p. 2
13	List of citations located and those excluded, including justification	eTable 4
14	Method of addressing articles published in languages other than English	p. 2
15	Method of handling abstracts and unpublished studies	p. 2
16	Description of any contact with authors	p. 2 + eTable 8
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	p. 2-3
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	p. 2-3
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	p. 2-3
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	p. 3
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	p. 2-3
22	Assessment of heterogeneity	p. 3
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	p. 3
24	Provision of appropriate tables and graphics	Supplementary
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figure 1-3 + eFigure 2-6
26	Table giving descriptive information for each study included	eTable 4
27	Results of sensitivity testing (eg, subgroup analysis)	p. 3-8 + eFigure 7-14
28	Indication of statistical uncertainty of findings	All figures

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	p. 8-9
30	Justification for exclusion (eg, exclusion of non-English language citations)	p. 8-9
31	Assessment of quality of included studies	p. 8-9
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	p. 8-9
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	p. 8-9
34	Guidelines for future research	p. 8-9
35	Disclosure of funding source	p. 9

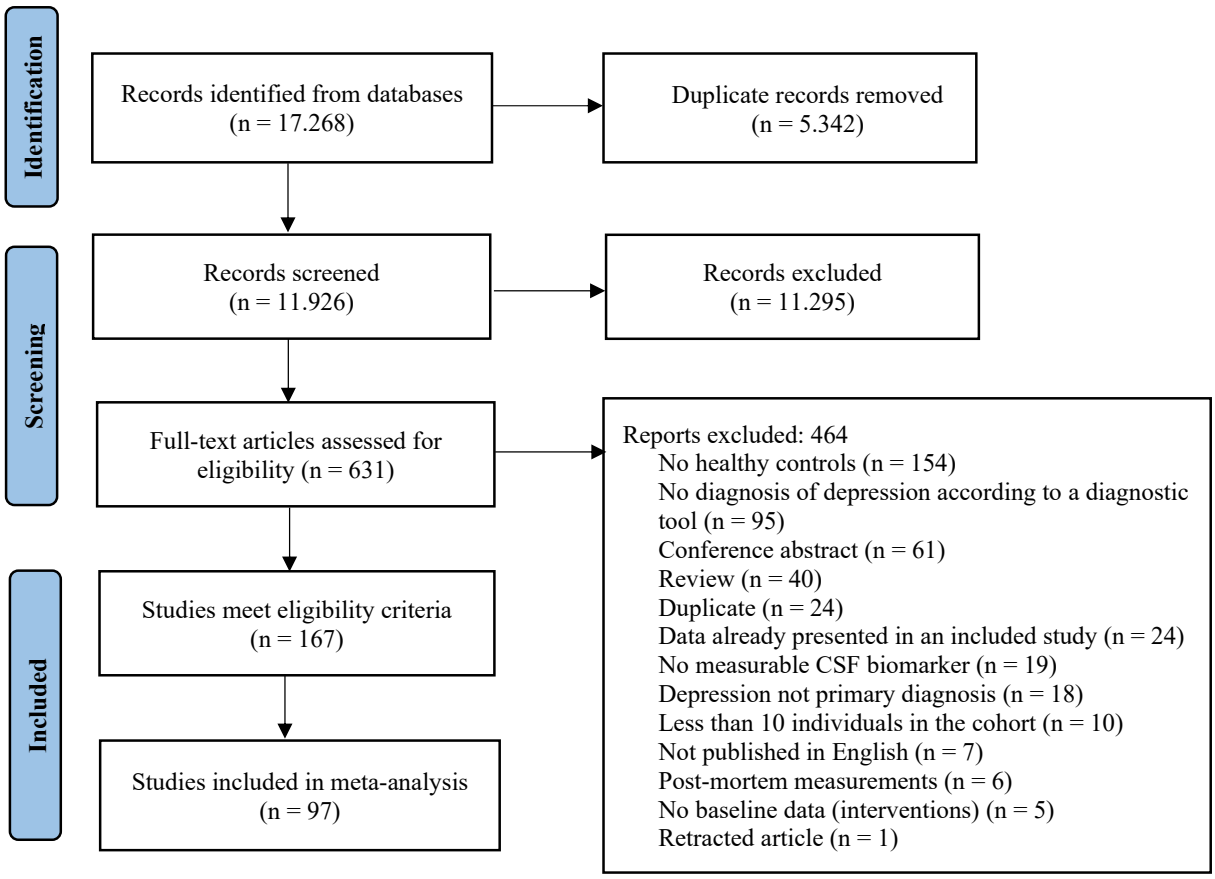
From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

eTable 3 | Search string

We used the following search strategy including the applicable medical subject headings (MeSH) or similar:

("Depression" OR "Depressive" OR "Depressed" OR "Depressive disorder" OR "Major depressive disorder") AND ("CSF" OR "Cerebrospinal Fluid" OR "Biomarkers/cerebrospinal fluid" OR "Spinal puncture" OR "Spinal tap" OR "Lumbar puncture").

eFigure 1 | PRISMA 2020 flow diagram



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

eTable 4 | Baseline characteristics from CSF studies

Included in meta-analysis

Study		Case subjects			Control subjects		Markers included in metaanalysis	CSF assay method
		N, diagnosis (diagnostic tool)	% of males / mean (SD) age	Psychotropic medication status	N	% of males / mean (SD) age		
Åsberg[1]	1984	60[a], unipolar endogenous MDD (Newcastle Inventory and RDC)	37/52.5 (13.6)[b]	No medication for ≥ 10 days	66	59/37.8 (11.4)	HVA, 5-HIAA, MHPG	NA
Barbaccia[2]	1986	10[b], MDE (DSM-III-R)	40/36.2 (2.7), SEM	No medication for ≥ 2 weeks	10[b]	40/35.8 (2.5), SEM	DBI (diazepam-binding inhibitor)	Radioimmunoassay
Bissette[3]	1986	17, major depression (DSM-III-R)	69/49.1 (3.5), SEM	No medication for ≥ 2 weeks	10	50/34.2 (3.2), SEM	Somatostatin	Radioimmunoassay
Blennow[4]	1995	10, MDD (DSM-III-R)	50/54.8 (8.4)	NA	31	61/64.7 (6.4)	T-tau, PHFtau	ELISA
Brundin[5]	2008	45, MDD and depression NOS (DSM-III-R)	NA	No medication for 14 (7) days, mean (SD)	5	NA	CART	Radioimmunoassay
Brundin[6]	2016	31, MDD and depression NOS (DSM-III-R)	NA/62.27 (NA)	No medication for 14.6 (9) days, mean (SD)	36	NA/30 (NA)	PIC	Gas chromatography–mass spectrometry
Bruno[7]	2020	28, MDD (DSM-IV)	64/66.5 (5.4)	79% on current medication	19	37/68.1/7.4	Neurogranin, alfa-synuclein	ELISA
Buerger[8]	2003	34, MDD (DSM-IV)	29/65.4 (12.1)	NA	21	62/57.7 (14.2)	P-tau 231	ELISA
Bumb[9]	2016	44[c], MDD (DSM-IV)	43/33.0 (9.7)	100% of patients on medication	27[c]	41/29.1 (8.2)	Melatonin	ELISA
Bürger née Buch[10]	1999	19, major depression (DSM-III-R and ICD-10)	37/71.1 (6.2)	NA	28	64/69.0 (8.8)	T-tau	ELISA
Carpenter, Heninger[11]	2004a	18, MDD (DSM-IV)	50/38.3 (13.4)	No medication for ≥ 3 weeks	26	46/32.7 (10.0)	IL-6	'Quantikine' highsensitivity immunoassay
Carpenter, Tyrka[12]	2004b	27, MDD (DSM-IV)	41/37.4 (13)	No medication for ≥ 2 weeks	25	48/34.0 (11.5)	CRH	Radioimmunoassay
DeBellis[13]	1993	9, MDD (RDC and DSM-III-R)	56/42.8 (11.1)	No medication for ≥ 3 weeks	46	50/37.2 (10.4)	HVA, 5-HIAA, MHPG	High-performance liquid chromatography
Deuschle[14]	2005	11, MDE (DSM-IV)	36/56.5 (15)	No medication for ≥ 6 days	11	100/51.4 (23.3)	Substance P	Enzyme immunoassay

[a] Sample sizes on the various markers differ due to missing data. Demographic data on cases calculated by IM.

[b] This is a subset of matched cases and controls.

[c] CSF data only available on 25 cases and 13 controls.

Diniz[15]	2014	16, major depression (DSM-IV)	40/69.5 (5.4)[d]	No medication for ≥ 1 month	25	32/71 (3.7)	T-tau, p-tau 181, amyloid-B-42, BDNF	Multiplex
Edman[16]	1986	19, depression (Newcastle Inventory and DSM-III-R)	37/42.5 (11.5)[e]	No medication for ≥ 10 days	32	41/40.3 (12.4)	5-HIAA[f]	NA
Eratne[17]	2021[g]	16, MDD (DSM-IV and DSM-V)	56/54.25 (10.823)	NA	20	25/66.20 (2.38)	Amyloid-B-42, t-tau, p-tau 181, NfL	ELISA
Erhardt[18]	2013	31, MDD and depression NOS (DSM-III-R)	NA	No medication for 14.6 (9) days, mean (SD)	36	81/30 (NA)	KYNA, QUIN	Ultrahighperformance liquid chromatography
Frye[19]	2007	8, unipolar depression (DSM-IV)	NA	No medication for ≥ 1 week	14	NA/38.31(12.56)	Aspartate[h]	High-performance liquid chromatography
Garakani[20]	2013	18[i], MDD (DSM-IV)	44/40.4 (20)	No medication for ≥ 2 weeks	24[i]	52/29.9 (6.7)	CRH, glutamate, glutamine	NA
George[21]	1994	43, recurrent unipolar (RDC)	53/37.2 (12.6)	No medication for ≥ 2 weeks	59	37/30.5 (12.5)	Magnesium	Atomic absorption technique
Geracioti[22]	2006	40, MDD (DSM-IV)	50/36.7 (13.8)	No medication for ≥ 2 weeks	47	45/32.7 (10.9)	Substance P	Radioimmunoassay (solid phase)
Gerner[23]	1981	19, unipolar depression (RDC)	46/42.6 (NA)[j]	No medication for ≥ 1 week	29	48/32 (NA)	GABA	Ionexchange flurometric procedure
Gerner[24]	1982	19, MDD unipolar (RDC)	NA	No medication for ≥ 1 week	9	44/NA	B-endorphin	Radioimmunoassay
Gerner[25]	1983	22, MDD unipolar (RDC)	NA	No medication for ≥ 1 week	22	NA	Cortisol	Radioimmunoassay
Gotoh[26]	2019	52, MDD (DSM-IV)	54/41.9 (8.8)	77% of patients on medication	49	51/41.5 (11.6)	LPA	ELISA
Gudmundsson[27]	2007	11, MDD (DSM-III-R)	0/72.6 (3.1)[k]	NA	70	0/72.6/3.1[k]	Amyloid-B-42, t-tau, albumin ratio	ELISA
Gudmundsson[28]	2010	11, MDD (DSM-III-R)	0/73.9 (3.2)[k]	NA	65	0/73.9 (3.2)[k]	GFAp, NfL	ELISA
Hampel[29]	1997	29, major depression (DSM-III-R and ICD-10)	31/71.6 (10.3)	NA	11	55/72.8 (6.9)	Albumin, IgG, albumin ratio, IgG ratio	Immunonephelometric method
Hampel[30]	1999	29, major depression (DSM-III-R and ICD-10)	31/71.6 (10.3)	NA	11	55/72.8 (6.9)	IgG Index	Immunonephelometric method

[d] Demographic data only on 15 cases.
[e] Demographic data on cases calculated by IM.
[f] Data on HVA and MHPG not available for the control group.
[g] Including updated unpublished data received directly from author.
[h] CSF data on glutamate and glycine mixed for BP and UP and thus not included.
[i] Sample sizes on the various markers differ due to missing data.
[j] Demographic data on the total group of cases with both unipolar (n=19) and bipolar (n=5) depression.
[k] Demographic data on the total group of cases and controls.

Hashimoto[31]	2016	28, MDD (DSM-IV)	64/66.5 (5.4)	79% of patients on medication	19	37/68.1/7.3	Glutamate, glutamine, glycine, L-serine, D-serine	High-performance liquid chromatography
Hashimoto[32]	2017	28, MDD (DSM-IV)	64/66.5 (5.4)	79% of patients on medication	18	39/67.3 (6.7)	Ascorbic acid	Gas chromatography–mass spectrometry
Hattori[33]	2015	66[1], MDD (DSM-IV)	50/44.2 (12.3)	33% of patients on medication	60[1]	50/41.9 (14.3)	WCC, total protein, fibrinogen, SL000022, SL000424, SL003341	Proteomics, SOMAscan
Heilig[34]	2004	51, MDD (DSM-IV)	43/45.5 (11.1)	No medication for ≥ 2 weeks	27	44/37.3 (11.3)	NPY, somatostatin, HVA, 5-HIAA, MHPG	Radioimmunoassay
Hertze[35]	2010	28, depression (DSM-IV)	50/58.0 (8.4)	NA	38	29/77 (8.2)	Amyloid-B-42 xMAP, amyloid-B-42, amyloid-B-40, amyloid-B-38, t-tau, p-tau 181, sABPP-alfa, sABPP-beta	xMAP technology (obs, comment)
Heuser[36]	1998	37, MDE (DSM-III-R)	30/46.8(17.2)	No medication for ≥ 5 days	25	68/65.5 (15.4)	CRH, somatostatin, vasopressin	Radioimmunoassay
Hidese[37]	2017	83, MDD (DSM-IV)	52/42.4(10.1)	75% of patients on medication	111	58/42.5 (15.4)	NCAM	ELISA
Hidese[38]	2020	104, MDD (DSM-IV)	47/43.4(11.0)	75% of patients on medication	118	56/42.4 (15.3)	APP, contactin-1, Erb83, GDNF, HGF, HGF receptor, NCAM, neuropilin-1, S100B, VEGF receptor 1 and 2	MAGPIX CCD imaging system
Hidese[39]	2021	104, MDD (DSM-IV)	47/43.4(11.0)	75% of patients on medication	118	56/42.4 (15.3)	APRIL/TNFSF13, BAFF/TNFSF13B, Soluble CD30/TNFSF8, Soluble CD163, IFN-α2, IFN-β, soluble IL-6 receptor, IL-8, IL-10, IL-11, IL-12 (p40), IL-19, IL-26, IL-29/IFN-λ1, MMP-3, Osteocalcin, Soluble TNF-receptor 1 and 2, TSLP	Multiplex immunoassay

[1] SL000022, SL000424, SL003341 measured in a subsample of 30 cases and 30 controls.

Ishii[40]	2018	89, MDD (DSM-IV)	48/43.8(10.4)	NA	117	56/42.5 (15.3)	C5	ELISA
Ishiwata[41]	2018	26[m], MDD (DSM-IV)	50/41.4(7.3)	85% of patients on medication	27	52/41.6 (9.1)	D-serine, L-serine	High-performance liquid chromatography
Ishiwata[42]	2017	26[m], MDD (DSM-IV)	50/41.4(7.3)	85% of patients on medication	27[n]	52/41.6 (9.1)	G72 (D-amino acid oxidase activator: DAOA)	ELISA
Itagaki[43]	2019	26, MDD (DSM-IV)	50/41.2(7.3)	31% of patients on medication	27	52/41.9 (9.1)	ATX (autotaxin)	ELISA
Janelidze[44]	2015	52, MDD and depression NOS (DSM-III-R)	NA	No medication for 15 (8) days, mean (SD)	48	81/38 (22)	IL-8	Electrochemiluminescence-based immunoassay
Janelidze[45]	2013	51, MDD and depression NOS (DSM-III-R and DSM-IV)	NA	No medication for 14.7 (7.7) days, mean (SD)	NA	NA	Eotaxin-1, IP-10, MIP-1B, MCP-1, MCP-4, TARC	Multiplex electrochemiluminescence-based immunoassay
Jensen[46]	1999	15, MDD (DSM-IV)	40/65(9)	NA	24	42/69 (8)	Amyloid-B-42, amyloid-B-40	ELISA
Kaddurah-Daouk[47]	2012	14 with current MDD, 14 remitted (DSM-IV)	57/38(13)	No medication for ≥ 3 weeks, mean (SD): 122.5 (147.5)	18	44/40 (11)	5-HIAA, tryptophan, tryptophol, kynurenine, HVA, L-DOPA, tyrosine, MHPG, tyramine, 4HPAC, 4HPLA, 4HBAC, HX, xanthine, xanthosine, gr, 7MXAN, uric, X7MG, methionine, GLNTRP, glutathione, ascorbic acid, HHASC	Liquid chromatography electrochemical array
Kageyama[48]	2021	29, MDD (DSM-IV)	50/43.8(14.2)	83.3% of patients on medication	30	50/43.1 (11.7)	Nervonic acid	GC-TOFMS analysis
Kasa[49]	1982	10, unipolar depression (ICD-9)	85/42(NA)[o]	No medication for ≥ 1 weeks	16	69/23 (NA)	HVA[p]	Fluorometric method
Kern[50]	2014	19, major and minor depression (DSM-IV)	NA	5.8% of patients on medication	67	NA	IL-6, IL-8	ELISA

[m] CSF data only available on 18 cases. Data received from author.

[n] CSF data only available on 25 controls. Data received from author.

[o] Demographic data on the total group of cases with both unipolar (n=10) and bipolar (n=3) depression.

[p] CSF data on GABA mixed for BP and UP and thus not included.

Kling[51]	1991	21, major depression (DSM-III-R)	31/40.8(11.4)[q]	No medication for ≥ 2 weeks	62	47/35.9 (18.1)	ACTH[r]	Immunoassay
Koslow[52]	1983	85[s], MDD unipolar (RDC)	0/49.3(13.6)	No medication for ≥ 2 weeks	80	0/43.83 (14.38)	HVA, 5-HIAA, MHPG	Gas chromatography–mass spectrometry
Lewine[53]	1991	19, MDD (DSM-III-R)	NA/41.6(10.2)[t]	No medication for ≥ 1 week	91	NA/32.8 (8.9)	HVA, 5-HIAA	High-performance liquid chromatography
Lindqvist[54]	2009	32, MDD and depression NOS (DSM-III-R)	NA	No medication for 16 (7) days, mean (SD)	47	85/37 (20)	IL-6, IL-8, TNF-alfa, IL-1B	ELISA
Madeira[55]	2015	9, MDD (DSM-IV)	0/69.8(5.8)	89% of patients on medication	10	20/70.7 (6.3)	D-serine, L-serine, total serine, glycine	NA
Madeira[56]	2018	9, MDD (DSM-IV)	0/69.8(5.8)	89% of patients on medication	10	30/70.7 (6.3)	Glutamate, glutamine	High-performance liquid chromatography
Mann[57]	2014	130, MDD (DSM-IV)	49/36.3(11.4)[u]	No medication for ≥ 2 weeks	38	58/34.8 (13.3)	GABA	Gas chromatography–mass spectrometry
Martinez[58]	2012	18[v], MDD (DSM-III-R)	44/40.4(10.0)	No medication for ≥ 2 weeks	25[v]	52/29.9 (6.7)	IL-1, IL-6, TNF-alfa, NPY, BDNF	ELISA
Mathé[59]	2002	29, major depression (DSM-IV)	34/47.6(12.9)	No medication for ≥ 15 days	19	79/63.8 (6.4)	Calcitonin, CGRP	Radioimmunoassay
Mizui[60]	2019	18, MDD (DSM-IV)	56/42.0, median	78% of patients on medication	27	52/42.0, median	BDNF propeptide, total protein	ELISA
Molchan[61]	1991	18, major depression (DSM-III-R)	33/64.6(9.9)	No medication for ≥ 3 weeks	12	67/65.8 (10.7)	HVA, 5-HIAA, MHPG, somatostatin	High-performance liquid chromatography
Molchan[62]	1993	18, major depression (DSM-III-R)	33/64.6(9.9)	No medication for ≥ 3 weeks	13[w]	77/63.5 (10.0)	CRH	Radioimmunoassay
Ogawa[63]	2015	42[x] currently depressed and 10 remitted, MDD (DSM-IV)	45/45.5(12.2)	74% of patients on medication	54[x]	52/43.6(15.3)	Phosphoethanolamine, threonine, serine, asparagine, glutamine, glycine, alanine, alfa-aminobutyrate, valine, methionine,	High-performance liquid chromatography

[q] Demographic data on the total group of cases with both unipolar (n=21) and bipolar (n=15) depression.
[r] Data on CRH only given for both unipolar and bipolar cases and thus not included.
[s] CSF data only on a subset of 61 cases and 61 controls. Sample sizes on the various markers differ due to missing data.
[t] Demographic data on the total group of cases with both unipolar (n=19) and bipolar (n=9) depression.
[u] Demographic data on the total group of cases with both unipolar (n=130) and bipolar (n=37) depression.
[v] Sample sizes on the various markers differ due to missing data.
[w] Sample sizes on the various markers differ due to missing data.
[x] Sample sizes on the various markers differ due to missing data.

							isoleucine, leucine, tyrosine, phenylalanine, ethanolamine, lysine, histidin + 1-methylhistidin, arginine, aspartate, glutamate, cystine, tryptophan, ornithine, carnosine, GABA	
Omori[64]	2020	90, MDD (DSM-IV)	48/43.7(11.0)	NA	106	55/42.6 (15.4)	MMP-2, MMP-7, MMP-10, total protein, glucose, WCC[y]	NA
Oreland[65]	1981	20[z] current depression and 11 recovered (Newcastle Inventory)	100/NA	No medication for ≥ 1 week	28	100/NA	HVA, 5-HIAA, MHPG	Mass fragmentography
Pillai[66]	2019	30, MDD (DSM-IV)	65/66.9(5.3)	NA	20	40/68.4 (7.2)	C3	ELISA
Pitts[67]	1995	19, MDD (DSM-III-R)	53/37.3(13.8)	100% of patients on medication	18	50/30.7 (10.6)	CRH, vasopressin, oxytocin	RIA/high-performance liquid chromatography
Pomara[68]	2012	28[aa], MDD (DSM-IV)	64/66.5(5.4)	79% of patients on medication	19	37/68.1 (7.3)	Amyloid-B-42, amyloid-B-40, t-tau, p-tau 181	Electrochemiluminescence technology
Pomara[69]	2021	27, MDD (DSM-IV)	67/66.67(5.36)	NA	17	41/67.65 (6.74)	AChE, BChE, IL-6, IL-8, sTREM[bb]	Ellman method; Immunoassay; Electrochemilominesce immunoassay
Post[70]	1982	2, unipolar depression (RDC)	100/29(2), SEM	No medication for ≥ 2 weeks	41	NA	Cyclic AMP, cyclic GMP	Radioimmunoassay
Pålhagen[71]	2010	12, major depression (DSM-III-R and DSM-IV)	58/62.7(9.3)	No medication for ≥ 180 days	12	100/29.4 (1.2)	HVA, 5-HIAA, MHPG, BDNF, IL-6, corticosterone, orexin	Mass fragmentography
Regenold[72]	2000	10, unipolar depression (RDC)	40/42.1(14.5)	20% of patients on medication, the remaining had no medication for ≥ 2 weeks	10	60/41.1 (8.2)	Glucose, sorbitol	Gas chromatography–mass spectrometry
Reis[73]	2012	20, MDD (DSM-IV)	5/71.3(6.10)	No actual medication	8	25/70.7 (6.34)	Amyloid-B-42, t-tau, p-tau 181	ELISA

[y] No data provided on MMP-1 and MMP-8.

[z] MHPG only measured in 18 cases.

[aa] Total tau protein only measured in 27 cases.

[bb] C3 included in the study Pillai et al. 2019

Risch[74]	1992	19[cc], unipolar major depression (RDC)	NA/43.0(10.9)	No medication for ≥ 1 week	94[cc]	NA/32.8 (8.9)	CRH, ACTH	Radioimmunoassay
Roy[75]	1991	13, unipolar MDE (DSM-III-R)	19/42.7(11.6)[dd]	No medication for ≥ 2.5 weeks	20	60/31.9 (8.5)	GABA	Ionexchange chromatography
Rubinow[76]	1983	7, unipolar depression (RDC)	NA	No medication for ≥ 2 weeks	39	NA	Somatostatin	Radioimmunoassay
Rymo[77]	2017	19 major and minor depression (DSM-IV)	0/70.8(1.7)	NA	67	0/72.4 (3.1)	YKL-40, GAP-43, MBP	ELISA
Sanfilippo[78]	2016	6, MDD (DSM-IV)	50/73(NA)	NA	44	30/71 (NA)	Amyloid-B-42, t-tau, p-tau 181, neurogranin	ELISA
Sasayama[79]	2012	17, MDD (DSM-IV)	100/39.5(8.0)	71% of patients on medication	21	100/38.3 (15.3)	Oxytocin	ELISA
Sasayama[80]	2013	30, MDD (DSM-IV)	63/42.7(8.2)	NA	35	60/41.3 (16.4)	IL-6, WCC, total protein	ELISA
Schmidt[81]	2011	17, MDD (DSM-IV)	59/51.3(16.3)	100% of patients on medication	10	40/36.4 (11.8)	Orexin / hypocretin-1	Fluorescence immunoassay
Sher[82]	2005	125, unipolar MDE (DSM-IV); hereof 12 with PTSD	45/36.4(12.4)	No medication for ≥ 2 weeks	27	48/36.6 (12.9)	HVA, 5-HIAA, MHPG	High-performance liquid chromatography
Sher[83]	2006	58, MDD (DSM-III-R); hereof 31 with a history of suicide attempt	48/43.5(15.4)	NA	50	50/38.2 (18.3)	HVA	High-performance liquid chromatography
Soleimani[84]	2014	61, MDD (DSM-IV); hereof 24 with childhood abuse.	NA/39.2(NA)	No medication for ≥ 2 weeks	20	NA/34 (NA)	NPY	Radioimmunoassay
Stokes[85]	1984	85[ee], unipolar depression (RDC)	46/49(14)	No medication for ≥ 9 days	80[ee]	48/46 (15)	cortisol	Radioimmunoassay
Sullivan[86]	1999	8, unipolar MDE (DSM-III-R)	25/41.5(12.0)	No medication for ≥ 2 weeks	24	62/34.8 (12.3)	TTR (transthyretin)	Dot-blot immunoassay
Sullivan, Oquendo[87]	2006a	48, MDD (DSM-IV); hereof 13 with comorbid panic disorder	0/35.9(12.1)	No medication for ≥ 2 weeks	15	0/33.3 (11.5)	HVA, 5-HIAA, MHPG	High-performance liquid chromatography
Sullivan, Mann[88]	2006b	17, MDD (DSM-IV)	23/39.7(13.4)	No medication for ≥ 2 weeks	15	40/41.3 (16.1)	HVA, 5-HIAA, MHPG, TTR	High-performance liquid chromatography
Sunderland[89]	1991	9, major affective disorder, depressed type (DSM-III-R)	NA/66.9(9.8)	No medication for ≥ 3 weeks	9	NA/67.2 (9.2)	VIP, NPY, dynorphin A 1-8, galanin	Radioimmunoassay

[cc] CSF data only on 18 cases and 83 controls.

[dd] Demographic data on the total group of cases with both unipolar (n=13) and bipolar (n=12) depression.

[ee] CSF data only on 55 cases and 59 controls.

Swann[90]	1999	85[ff], unipolar depression (RDC)	NA/49.4 (13.6)	No medication for ≥ 2 weeks	85[ff]	NA	MHPG, HVA	Gas chromatography–mass spectrometry
Vawter[91]	2000	17, unipolar affective disorder (DSM-III-R and DSM-IV)	35/40.5(5.4) SEM	No actual medication	37	65/33.4 (1.9), SEM	Total protein[gg]	SDS-PAGE analyse
Ventorp[92]	2016	39[hh], MDD and depression NOS (DSM-III-R and DSM-IV)	52/40.70(13.286)	No medication for 14 (6) days, mean (SD)	45[hh]	82/30.56 (12.28)	HA, sCD44, OPN, MMP-9, MMP-3, MMP-1	ELISA
Widerlöv, Bisette[93]	1988a	22, MDD (DSM-III-R)	59/47.7(3.0), SEM	No medication for ≥ 2 weeks	10	50/34.2 (3.2), SEM	HVA, 5-HIAA, MHPG, CRH	Radioimmunoassay
Widerlöv, Lindström[94]	1988b	33, MDD (DSM-III-R)	58/46(NA)	No medication for ≥ 2 weeks	20	45/31 (NA)	NPY, PYY	Radioimmunoassay
Wong[95]	2000	10, MDE unipolar (DSM-III-R and RDC)	20/40.9(2.7)	No medication for ≥ 2 weeks	14	57/37.7 (2.2)	CRH, NE	Radioimmunoassay
Yoon[96]	2017	75, MDD (DSM-IV)	49/44.6(10.8)	NA	87	55/42.0 (15.6)	MHPG, HVA, 5-HIAA	High-performance liquid chromatography
Yoon[97]	2018	24, MDD (DSM-IV)	50/42.8(9.8)	NA	25	48/41.6 (14.0)	CART	ELISA

Not included in meta-analysis

Study		Case subjects			Control subjects		Markers examined	CSF assay method	Reason not included in meta-analysis
		N, diagnosis (diagnostic tool)	% of males / mean (SD) age	Psychotropic medication status	N	% of males / mean (SD) age			
Ågren[98]	1983	NA, MDD (RDC)	NA	No medication for ≥ 10 days	11	NA	Hypoxanthine, xanthine	High-performance liquid chromatography	Data mixed of UP and BP. No data on healthy controls.
Anderson[99]	1984	28, unipolar depression (RDC)	NA	No medication for ≥ 1 week	36	47/31.1 (11.3)	IAA	High-performance liquid chromatography	Data mixed of UP and BP.
Bendix[100]	2017	NA, unipolar major depression (DSM-III-R)	NA	No medication for a mean of 8.6 days	19	63/30 (NA)	Insulin, glucagon	Radioimmunoassay	Suicide study: no data only for MDD.
Berger[101]	1980	13[ii], Depression (Feighner et al.)	100/50.7 (2.6)[ii]	No medication for ≥ 2 weeks	23[ii]	100/31.6 (3.0), SEM[ii]	HVA, 5-HIAA, MHPG, DOPAC	Gas chromatography–mass spectrometry	No clear exclusion of bipolar patients.

[ff] Sample sizes on the various markers differ due to missing data.

[gg] No data was presented for N-CAM VASE and thus excluded.

[hh] Sample sizes on the various markers differ due to missing data. Data received from author.

[ii] Sample size for DOPAC only 12 cases and 19 controls. Age, mean (SEM), only calculated from 11 cases and 14 controls.

Berrettini[102]	1987	34, major depression (DSM-III-R)	29/NA[jj]	No medication for ≥ 2 weeks	33	64/NA	NPY	High-performance liquid chromatography	Data mixed of UP and BP.
Berrettini[103]	1988	6, MDD (DSM-III-R)	NA	No medication for ≥ 3 weeks	6	NA/67.2 (9.4)	Galanin	Immunoassay	No data stated, only graphs.
Bertilsson, Åsberg[104]	1982	10, depression (Newcastle Inventory)	NA	No medication for ≥ 9 days	11	NA	5-HIAA, HVA, MHPG, cortisol	Mass fragmentography	No baseline data stated.
Bertilsson, Tybring[105]	1982	7, MDD (RDC)	NA	No medication for ≥ 9 days	11	NA	5-HIAA	Mass fragmentography	No baseline data stated.
Carpenter[106]	2008	NA, MDD (DSM-IV)	42/47.9 (8.8)[kk]	All patients on stable dosis of medication.	19	42/43.3 (9.0)	Substance P	Radioimmunoassay	Data mixed of UP and BP.
Catlin[107]	1982	19, unipolar depression (DSM-III-R)	NA	No medication for ≥ 4 days	9	NA	B-endorphin	Radioimmunoassay	Data mixed of UP and BP.
Casper[108]	1988	53, MDD (RDC)	28/NA	No medication for ≥ 2 weeks	60	42/NA	cortisol	Radioimmunoassay	Data mixed of UP and BP.
Chatzittofis[109]	2013	NA, MDD (DSM-III-R)	NA	No current medication	19	63/30 (NA)	Cortisol, DHEAS, 5-HIAA	Radioimmunoassay; mass fragmentography	Suicide study: no data only for MDD.
Davis[110]	1988	8, major depression (RDC)	NA/53.3(7.5)	No medication for ≥ 2 weeks	8	NA/64.5 (8.5)	Somatostatin	NA	No clear exclusion of bipolar patients.
Derkow[111]	2018	8, MDE (DSM-V)	38/58.0 (10.2)	NA	10	70/58.3 (11)	Amyloid-B-42, t-tau, microRNAs (let-7a, let-7b, let-7c, let-7d, let-7e, let-7f, let-7g, let-7i, miR-124)	NA	No clear exclusion of bipolar patients.
Ditzen[112]	2012	12, MDE (ICD-10)	17/54 (16.01)	NA	12	33/53 (18.08)	Proteomics	Electrophoresis; In-gel protein digest/Mass Spectrometry; Western Blot; LCMS	Not sufficient data presented.
Ehnvall[113]	2003	NA, MDD (DSM-IV)	49/46.9 (12.4)	No medication for ≥ 2 weeks	27	44/37.6 (11.1)	HVA, 5-HIAA, MHPG	High-performance liquid chromatography	Data mixed of UP and BP.

[jj] Demographic data on both unipolar (n=34) and bipolar (n=4) patients.

[kk] CSF data and demographic data available only for a total of 19 patients, including patients both unipolar and bipolar patients.

Engström[114]	1999	36, MDD (DSM-III-R)	NA	No medication for a mean (SD) of 14.8 (7.4) days	29	55/33.5 (9.2)	HVA, 5-HIAA, MHPG	Gas chromatography–mass spectrometry; high-performance liquid chromatography	No data on healthy controls.
Facchinetti[115]	1986	10, MDD (DSM-III-R)	20/NA	No medication for ≥ 10 days	13	38/NA	B-lipoprotein, B-endorphin, ACTH	Radioimmunoassay	No data stated, only graphs.
Franzen[116]	2020	7, MDD (DSM-IV)	43/NA	No medication for ≥ 2 weeks	8	38/NA	Proteomics	Mass spectrometry detection	Not sufficient data presented.
Frye[117]	1999	28, MDD (DSM-III-R and DSM-IV)	NA/39.8 (12.7)[ll]	No medication for ≥ 2 weeks	34	65/32.5 (10)	TRH	Radioimmunoassay	No standard deviation stated.
Frye[118]	2003	6, depression (DSM-III-R and DSM-IV)	43/39.2 (10.4)[mm]	No medication for ≥ 2 weeks	25	56/32.9 (11.5)	Somatostatin	Radioimmunoassay	Data mixed of UP and BP.
George[119]	1994	5, recurrent unipolar (RDC)	40/39.8 (12.8)	No medication for ≥ 2 weeks	10	50/25.3 (4.8)	Pregnenolone, progesterone, DBI	High-performance liquid chromatography; radioimmunoassay	No data stated, only graphs.
Geracioti[120]	1993	7, MDD (DSM-III-R)	50/37(9)[nn]	20% of cases medicated. The remaining had no medication for ≥ 2 weeks	10	60/33(11)	CCK fasting and post prandial, glucose	Radioimmunoassay	Data mixed of UP and BP.
Geracioti, Orth[121]	1997 a	7, MDD (DSM-III-R)	50/37(9)[kk]	20% of cases medicated. The remaining had no medication for ≥ 2 weeks	10	60/33(11)	CRH	Radioimmunoassay	Data mixed of UP and BP.
Geracioti, Ekhator[122]	1997 b	7, MDD (DSM-III-R)	50/37(9)[kk]	20% of patients medicated, the remaing had no medication for ≥ 2 weeks	10	60/33(11)	5-HIAA, MHPG, tryptophan	HLPC (electrochemical detection)	Data mixed of UP and BP.
Gerner[123]	1984	NA, depression (RDC)	44/40 (NA)[oo]	No medication for ≥ 1 week	37	47/31 (NA)	HVA, MHPG, 5-HIAA, tryptophan, tyrosine, GABA, choline, calcium	Atomic absorption spectrophotometry	Data mixed of UP and BP.

[ll] Demographic data on both unipolar (n=28) and bipolar (n=28) patients.
[mm] Demographic data on both unipolar (n=34) and bipolar (n=4) patients.
[nn] Demographic data on both unipolar (n=7) and bipolar (n=3) patients.
[oo] Demographic data on both unipolar (n=30) and bipolar (n=10) patients.

Gerner, Yamada[124]	1982	NA, depression (RDC)	NA	No medication for ≥ 1 week	29	NA	SLI, BLI, CCK-LI	NA	Data mixed of UP and BP.
Gerner, Merrill[125]	1983a	11, depression (RDC)	33/36.3 (4.3)[pp], SEM	No medication for ≥ 1 week	18	33/32.4 (2.6), SEM	Prostaglandin E	Radioimmunoassay	Data mixed of UP and BP.
Goodnick[126]	1980	8, unipolar depression (Feigner et al.)	13/38.8 (11.9)	No medication for ≥ 10 days	2	100/24.0 (NA)	Taurin, glycine, glutamate, glutamine, phosphoserine, tyrosine, phenylalanine, methionine, phosphoethanolamine, urea, aspartate, threonine, serine, asparagine, alanine, citrulline, alfa-aminobutyrate, valine, cystathionine, isoleucine, leucine, ethanolamine, creatinine, ornithine, lysine, histidine, arginine, alfa-aminoguanidinopropionic acid, homocystathionine, B-aminoisobutyrate, B-alanine, hydroxyproline	NA	No standard deviation presented.
Hoffman[127]	1989	11, MDE (DSM-III-R)	73/36(12)	No actual medication	6	83/26 (6)	Endothelin	Radioimmunoassay	No clear exclusion of bipolar patients.
Hou[128]	2006	40, MDD (DSM-IV)	43/42.48 (13.96)	No medication for ≥ 28 days	40	43/42.03 (14.41)	5-HIAA, 5-HT, NPY	ELISA	Not sufficient data presented.

[pp] Demographic data on both unipolar (n=11) and bipolar (n=3) patients.

Isung[129]	2012	NA, MDD (DSM-III-R)	NA	No medication for a mean (SD) of 21 (13.6) days	20	100/29 (5.0)	VEGF, IL-6, IL-8	ELISA	Suicide study: no data only for MDD.
Jimerson[130]	1983	NA, MDD (RDC)	NA	No medication for ≥ 2 weeks	41	55/NA	MHPG	Gas chromatography–mass spectrometry	Data mixed of UP and BP.
Jokinen[131]	2012	NA, MDD (DSM-III-R)	NA	No current medication	18	63/30 (NA)	oxytocin	Radioimmunoassay	Suicide study: no data only for MDD.
Jokinen[132]	2009	NA, MDD (DSM-III-R)	NA	No current medication	8	100/24(NA)	5-HIAA, HVA	Gas chromatography–mass spectrometry	Suicide study: no data only for MDD.
Jones[133]	1990	15, unipolar depression (RDC)	NA/63.2 (6.8)	No medication for ≥ 2 weeks	7	NA/71.3 (6.7)	5-HIAA, HVA	High-performance liquid chromatography	Data mixed of UP and BP.
Kling[134]	1993	18, major depression (DSM-III-R and RDC)	25/41.2 (2.2)[qq]	No medication for ≥ 2 weeks	41	37/27.7 (1.2)	Somatostatin	Radioimmunoassay	Data mixed of UP and BP.
Lindström[135]	1985	10, MDD (RDC)	40/53(NA), median	No medication for ≥ 2 weeks	20	45/22.5, median	DSIP	Radioimmunoassay	No clear exclusion of bipolar patients.
Little[136]	1999	13, unipolar depression (DSM-IV)	50/46(4), SEM	No medication for ≥ 2 weeks	10	50/35(3), SEM	5-HIAA, 5-HT, HVA, MHPG, DOPAC	High-performance liquid chromatography	No data stated, only graphs.
Mann[137]	2008	NA, MDD (DSM-IV)	NA		NA	NA	5-HIAA, HVA, MHPG	High-performance liquid chromatography	No data on MDD and controls separately presented.
Mathe[138]	1994	51, MDD primary unipolar (DSM-III-R)	41/40.37 (12.15)[rr]	NA	20	NA	CGRP	Radioimmunoassay	No data on healthy controls.
Naber[139]	1981	28, MDD (RDC)	43/41(14)	No medication for ≥ 2 weeks	33	64/31 (13)	B-endorphin	Radioimmunoassay	No clear exclusion of bipolar patients.
Nemeroff[140]	1984	23, MDD (DSM-III-R)	NA/47.7(3), SEM	No medication for ≥ 2 weeks	10	NA/34.2 (3.2), SEM	CRF	Radioimmunoassay	No data stated, only graphs.
Nemeroff[141]	1989	NA, major depression (RDC)	NA	No medication for ≥ 1 week	NA	NA	Neurotensin	Radioimmunoassay	No data stated, only graphs.

[qq] Demographic data on both unipolar (n=18) and bipolar (n=10) patients.

[rr] Demographic data are from both primary unipolar (n=51), secondary unipolar (n=7) and bipolar (n=5) patients. Calculated by IM.

Newport[142]	2003	10, MDD (DSM-IV)	0/30.9(8.2)[ss]	No medication for ≥ 2 weeks	18	0/30.9 (8.2)[pp]	CRF, AVP	Radioimmunoassay	No data stated for MDD and controls.
Omori[143]	2021	26, MDD (DSM-IV)	50/40.4(8.3)	NA	27	48/40.4 (7.8)	LPA	Liquid chromatography-tandem mass spectrometry	No data stated, only graphs.
Pazzaglia[144]	1995	43, unipolar depression (DSM-III-R)	30/NA	No medication for ≥ 2 weeks	55	62/NA	Total protein	NA	No data on healthy controls.
Pitts[145]	1990	17, MDD (DSM-III-R)	65/37.42 (12.59)[tt]	NA	17	47/30.03 (9.69)[qq]	Total protein, prealbumin, albumin, alpha-1, alpha-2, beta, gamma.	Spectrophotometry; protein electrophoresis	Data mixed of UP and BP.
Poltorak[146]	1996	8, MDD (DSM-III-R)	44[uu]/39.75 (11.99)	47%[uu] of patients medicated, the remaing had no medication for ≥ 2 weeks	13	77/30.85 (9.07)	N-CAM, total protein, IgG, IgM, albumin	Radial immunodiusion; western blot	No data stated, only graphs.
Richards[147]	2018	14, MDD (DSM-IV)	NA	4 unmedicated cases, 10 medicated	6	NA	IL-2, IL-5, IL-6, IL-8, VEGF, IFN-gamma, amyloid-A1, adiponectin	NA	Not sufficient data stated in article.
Roos[148]	1985	7, depression (RDC)	NA	No medication for ≥ 2 weeks	31	NA	IgG, albumin, albumin-ratio	Electroimmunodiffusion	No clear exclusion of bipolar patients.
Roy[149]	1986	22, MDE (DSM-III-R)	NA	No medication for ≥ 2.5 weeks	32	28/44.66 (NA)	5-HIAA, HVA	High-performance liquid chromatography	Data mixed of UP and BP.
Roy[150]	1988	NA, MDE (DSM-III-R)	NA	No medication for ≥ 2.5 weeks	39	NA	NE, MHPG, 5-HIAA, HVA	high-performance liquid chromatography	Data mixed of UP and BP.
Roy[151]	1987	15, MDE (DSM-III-R)	14/40.9 (10.4)[vv]	No medication for ≥ 2.5 weeks	18	61/31.1 (8.4)	CRH	radioimmunoassay	Data mixed of UP and BP.

[ss] Demographic data on the total population (both patients and controls)

[tt] Age for all patients (MDD=17, BP=2, SZA=1, Drug dep=2, Depr.D/O=1) and calculated by IM.

[uu] Male (%) and psychotropic status on both unipolar (n=8) and bipolar (n=28)

[vv] Demographic data are from both unipolar (n=15) and bipolar (n=7) patients.

Roy[152]	1994	14, MDE (DSM-III-R)	39/40.6 (10.7)[ww]	No medication for ≥ 2.5 weeks	19	89/39(5.2)	TRH	radioimmunoassay	Data mixed of UP and BP.
Rubinow[153]	1981	8, MDD (RDC)	50/39.14 (2.87)[xx]	No medication for ≥ 2 weeks	31	64.5/32.52 (2.56)	B-endorphin, opioid activity (RRA)	radioreceptor method	Data mixed of UP and BP.
Salomon[154]	2003	8, MDE (DSM-IV)	33/39(3)[yy]	No medication for ≥ 2 months	14	43/41(4)	hypocretin-1	radioimmunoassay	Data mixed of UP and BP.
Sharma[155]	1995	19, depression (RDC)	58/38.4(13.4)	No medication for 17.7 (4.9) days, mean (SD)	30	100/42.1 (9.6)	fri, conjugated and total PAA	Gas chromatography–mass spectrometry	No clear exclusion of bipolar patients.
Sher[156]	2003	135, MDE (DSM-IV); hereof 63 with a history of alcoholism	56/35.8(11.1)	No medication for ≥ 2 weeks	22	45/39.1(13.9)	HVA, 5-HIAA, MHPG	High-performance liquid chromatography	No clear exclusion of bipolar patients.
Song[157]	2015	36, MDD (DSM-IV)	42/34.78 (8.65)	No current medication	30	43/33.03 (8.73)	miR-16, serotonin	quatitative RT-PCR; ELISA	No data stated, only graphs.
Spiegel[158]	1992	8, MDD (RDC)	100/NA	3% of patients medicated, the remaing had no medication for ≥ 2 weeks	7	100/NA	HVA	gas chromatography–mass spectrometry	Mix of patient groups.
Stefansson[159]	2016	NA, major depression (DSM-III-R)	NA	No current medication	19	63/NA	Testosteron	radioimmunoassay	Suicide study: no data only for MDD.
Stübner[160]	1999	20, major depression (DSM-III-R and ICD-10)	35/67.3 (8.4)	95% of patients on medication	20	60/65.8 (9.1)	IL-6, soluble IL-6 receptor, sgp130	ELISA	No standard deviation presented.
Sunderland[161]	1987	20, major depression (DSM-III-R)	NA/58.7 (11.4)	No medication for ≥ 3 weeks	15	NA/59.5 (7.9)	somatostatin	radioimmunoassay	No standard deviation presented.
Träskman[162]	1980	19, depression (Feighner et al. and Newcastle Inventory)	47/49(12)	No medication for ≥ 5 days	30	NA/39 (11)	cortisol	Radioimmunoassay	No clear exclusion of bipolar patients.
Träskman[163]	1981	8, depression (Newcastle Inventory)	38/48.1(11.8)	No medication for ≥ 2 days, 6 (11) days, mean (SD)	45	62/40 (10)	HVA, 5-HIAA, MHPG	Mass fragmentography	No clear exclusion of bipolar patients.
Träskman-Bendz[164]	1984	7[zz] recurrent depression; 11[zz] recovered	29/45(NA)	No medication for ≥ 3 weeks	16[zz]	50/34.9 (NA)	5-HIAA, HVA	Mass fragmentography	No clear exclusion of bipolar patients.

[ww] Demographic data are from both unipolar (n=14) and bipolar (n=3) patients.

[xx] Demographic data are from both unipolar (n=8) and bipolar (n=14) patients.

[yy] Demographic data are from both unipolar (n=8) and bipolar (n=7) patients.

[zz] Sample sizes on the various markers differ due to missing data.

		(Newcastle Inventory)							
Verbanck[165]	1984	18, depression (Feighner et al.)	43/44(NA)[aaa]	No medication for ≥ 2 weeks	51	57/52 (NA)	CCK (cholecystokinin)	Radioimmunoassay	No clear exclusion of bipolar patients.
Yesavage[166]	1982	20, MDD (DSM-III-R and RDC)	100/45.5 (12)	No medication for ≥ 2 weeks	44	100/45.4 (15.6)	lactate	NA	No data presented.
Zalsman[167]	2008	NA, MDD (DSM-IV)	NA	No medication for ≥ 2 weeks	NA	NA	HVA, MHPG, 5-HIAA	high-performance liquid chromatography	No data presented.

[aaa] Demographic data on the total group of cases with both unipolar (n=18) and bipolar (n=12) depression.

REFERENCES OF STUDIES

1. Åsberg M, Bertilsson L, Mårtensson B, Scalia-Tomba G -P, Thorén P, Träskman-Bendz L. CSF monoamine metabolites in melancholia. *Acta Psychiatr Scand*. 1984;69(3):201-219. doi:10.1111/J.1600-0447.1984.TB02488.X
2. Barbaccia ML, Costa E, Ferrero P, et al. Diazepam-Binding Inhibitor: A Brain Neuropeptide Present in Human Spinal Fluid: Studies in Depression, Schizophrenia, and Alzheimer's Disease. *Arch Gen Psychiatry*. 1986;43(12):1143-1147. doi:10.1001/archpsyc.1986.01800120029007
3. Bissette G, Widerlöv E, Walléus H, et al. Alterations in Cerebrospinal Fluid Concentrations of Somatostatinlike Immunoreactivity in Neuropsychiatric Disorders. *Arch Gen Psychiatry*. 1986;43(12):1148-1151. doi:10.1001/ARCHPSYC.1986.01800120034008
4. Blennow K, Wallin A, Ågren H, Spenger C, Siegfried J, Vanmechelen E. Tau protein in cerebrospinal fluid - A biochemical marker for axonal degeneration in Alzheimer disease? *Mol Chem Neuropathol*. 1995;26(3):231-245. doi:10.1007/BF02815140
5. Brundin L, Björkqvist M, Träskman-Bendz L, Petersén A. Cocaine and amphetamine regulated transcript (CART) in suicide attempters. *Psychiatry Res*. 2008;158(2):117-122. doi:10.1016/j.psychres.2007.06.031
6. Brundin L, Sellgren CM, Lim CK, et al. An enzyme in the kynurenine pathway that governs vulnerability to suicidal behavior by regulating excitotoxicity and neuroinflammation. *Transl Psychiatry*. 2016;6(8):e865. doi:10.1038/tp.2016.133
7. Bruno D, Reichert Plaska C, Clark DPA, et al. CSF α-synuclein correlates with CSF neurogranin in late-life depression. *Int J Neurosci*. 2020. doi:10.1080/00207454.2020.1744596
8. Buerger K, Zinkowski R, Teipel SJ, et al. Differentiation of geriatric major depression from Alzheimer's disease with CSF tau protein phosphorylated at threonine 231. *Am J Psychiatry*. 2003;160(2):376-379. doi:10.1176/APPI.AJP.160.2.376
9. Bumb JM, Enning F, Mueller JK, et al. Differential melatonin alterations in cerebrospinal fluid and serum of patients with major depressive disorder and bipolar disorder. *Compr Psychiatry*. 2016;68:34-39. doi:10.1016/J.COMPPSYCH.2016.03.005
10. Bürger Née Buch K, Padberg F, Nolde T, et al. Cerebrospinal fluid tau protein shows a better discrimination in young old (<70 years) than in old old patients with Alzheimer's disease compared with controls. *Neurosci Lett*. 1999;277(1):21-24. doi:10.1016/S0304-3940(99)00845-9
11. Carpenter LL, Heninger GR, Malison RT, Tyrka AR, Price LH. Cerebrospinal fluid interleukin (IL)-6 in unipolar major depression. *J Affect Disord*. 2004;79(1-3):285-289. doi:10.1016/S0165-0327(02)00460-3
12. Carpenter LL, Tyrka AR, McDougle CJ, et al. Cerebrospinal fluid corticotropin-releasing factor and perceived early-life stress in depressed patients and healthy control subjects. *Neuropsychopharmacology*. 2004;29(4):777-784. doi:10.1038/SJ.NPP.1300375
13. De Bellis MD, Geracioti TDJ, Altemus M, Kling MA. Cerebrospinal fluid monoamine metabolites in fluoxetine-treated patients with major depression and in healthy volunteers. *Biol Psychiatry*. 1993;33(8-9):636-641. doi:10.1016/0006-3223(93)90103-k
14. Deuschle M, Sander P, Herpfer I, Fiebich BL, Heuser I, Lieb K. Substance P in serum and cerebrospinal fluid of depressed patients: No effect of antidepressant treatment. *Psychiatry Res*. 2005;136(1):1-6. doi:10.1016/J.PSYCHRES.2004.12.007
15. Diniz BS, Teixeira AL, Machado-Vieira R, et al. Reduced cerebrospinal fluid levels of brain-derived neurotrophic factor is associated with cognitive impairment in late-life major depression. *Journals Gerontol - Ser B Psychol Sci Soc Sci*. 2014;69(6):845-851. doi:10.1093/GERONB/GBU096
16. Edman G, Åsberg M, Levander S, Schalling D. Skin Conductance Habituation and Cerebrospinal Fluid 5-Hydroxyindoleacetic Acid in Suicidal Patients. *Arch Gen Psychiatry*. 1986;43(6):586-592. doi:10.1001/ARCHPSYC.1986.01800060080010
17. Eratne D, Loi SM, Walia N, et al. A pilot study of the utility of cerebrospinal fluid neurofilament light chain in differentiating neurodegenerative from psychiatric disorders: A 'C-reactive protein' for psychiatrists and neurologists? *Aust N Z J Psychiatry*. 2020;54(1):57-67. doi:10.1177/0004867419857811
18. Erhardt S, Lim CK, Linderholm KR, et al. Connecting inflammation with glutamate agonism in suicidality. *Neuropsychopharmacology*. 2013;38(5):743-752. doi:10.1038/NPP.2012.248
19. Frye MA, Tsai GE, Huggins T, Coyle JT, Post RM. Low Cerebrospinal Fluid Glutamate and Glycine in Refractory Affective Disorder. *Biol Psychiatry*. 2007;61(2):162-166. doi:10.1016/J.BIOPSYCH.2006.01.024
20. Garakani A, Martinez JM, Yehuda R, Gorman JM. Cerebrospinal fluid levels of glutamate and corticotropin releasing hormone in major depression before and after treatment. *J Affect Disord*. 2013;146(2):262-265. doi:10.1016/j.jad.2012.06.037

21. George MS, Rosenstein D, Rubinow DR, Kling MA, Post RM. CSF Magnesium in Affective Disorder: Lack of Correlation With Clinical Course of Treatment. *Psychiatry Res*. 1994;5:139-146.

22. Geracioti T. Elevated Cerebrospinal Fluid Substance P Concentrations in Posttraumatic Stress Disorder and Major Depression. *Am J Psychiatry*. 2006;163(4):637. doi:10.1176/APPI.AJP.163.4.637

23. Gerner RH, Hare TA. CSF GABA in normal subjects and patients with depression, schizophrenia, mania, and anorexia nervosa. *Am J Psychiatry*. 1981;138(8):1098-1101. doi:10.1176/AJP.138.8.1098

24. Gerner RH, Sharp B. CSF β-endorphin-immunoreactivity in normal, schiziphrenic, depressed, manic and anorexic subjects. *Brain Res*. 1982;237(1):244-247. doi:10.1016/0006-8993(82)90574-1

25. Gerner RH, Wilkins JN. CSF cortisol in patients with depression, mania, or anorexia nervosa and in normal subjects. *Am J Psychiatry*. 1983;140(1):92-94. doi:10.1176/ajp.140.1.92

26. Gotoh L, Yamada M, Hattori K, et al. Lysophosphatidic acid levels in cerebrospinal fluid and plasma samples in patients with major depressive disorder. *Heliyon*. 2019;5(5). doi:10.1016/J.HELIYON.2019.E01699

27. Gudmundsson P, Skoog I, Waern M, et al. The relationship between cerebrospinal fluid biomarkers and depression in elderly women. *Am J Geriatr psychiatry Off J Am Assoc Geriatr Psychiatry*. 2007;15(10):832-838. doi:10.1097/JGP.0b013e3180547091

28. Gudmundsson P, Skoog I, Waern M, et al. Is there a CSF biomarker profile related to depression in elderly women? *Psychiatry Res*. 2010;176(2-3):174-178. doi:10.1016/J.PSYCHRES.2008.11.012

29. Hampel H, Kötter HU, Möller HJ. Blood-cerebrospinal fluid barrier dysfunction for high molecular weight proteins in alzheimer disease and major depression: Indication for disease subsets. *Alzheimer Dis Assoc Disord*. 1997;11(2):78-87. doi:10.1097/00002093-199706000-00004

30. Hampel H, Kötter HU, Padberg F, Körschenhausen DA, Möller HJ. Oligoclonal bands and blood-cerebrospinal-fluid barrier dysfunction in a subset of patients with Alzheimer disease: Comparison with vascular dementia, major depression, and multiple sclerosis. *Alzheimer Dis Assoc Disord*. 1999;13(1):9-19. doi:10.1097/00002093-199903000-00002

31. Hashimoto K, Bruno D, Nierenberg J, et al. Abnormality in glutamine-glutamate cycle in the cerebrospinal fluid of cognitively intact elderly individuals with major depressive disorder: A 3-year follow-up study. *Transl Psychiatry*. 2016;6. doi:10.1038/TP.2016.8

32. Hashimoto K, Ishima T, Sato Y, et al. Increased levels of ascorbic acid in the cerebrospinal fluid of cognitively intact elderly patients with major depression: a preliminary study. *Sci Rep*. 2017;7(1):3485. doi:10.1038/s41598-017-03836-0

33. Hattori K, Ota M, Sasayama D, et al. Increased cerebrospinal fluid fibrinogen in major depressive disorder. *Sci Rep*. 2015;5. doi:10.1038/srep11412

34. Heilig M, Zachrisson O, Thorsell A, et al. Decreased cerebrospinal fluid neuropeptide Y (NPY) in patients with treatment refractory unipolar major depression: Preliminary evidence for association with preproNPY gene polymorphism. *J Psychiatr Res*. 2004;38(2):113-121. doi:10.1016/S0022-3956(03)00101-8

35. Hertze J, Minthon L, Zetterberg H, Vanmechelen E, Blennow K, Hansson O. Evaluation of CSF biomarkers as predictors of Alzheimer's disease: A clinical follow-up study of 4.7 years. *J Alzheimer's Dis*. 2010;21(4):1119-1128. doi:10.3233/JAD-2010-100207

36. Heuser I, Bissette G, Dettling M, et al. CEREBROSPINAL FLUID CONCENTRATIONS OF CORTICOTROPIN-RELEASING HORMONE, VASOPRESSIN, AND SOMATOSTATIN IN DEPRESSED PATIENTS AND HEALTHY CONTROLS: RESPONSE TO AMITRIPTYLINE TREATMENT. *Depress Anxiety*. 1998;8:71-79.

37. Hidese S, Hattori K, Sasayama D, et al. Cerebrospinal fluid neural cell adhesion molecule levels and their correlation with clinical variables in patients with schizophrenia, bipolar disorder, and major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2017;76:12-18. doi:10.1016/j.pnpbp.2017.02.016

38. Hidese S, Hattori K, Sasayama D, et al. Cerebrospinal fluid neuroplasticity-associated protein levels in patients with psychiatric disorders: a multiplex immunoassay study. *Transl Psychiatry*. 2020;10(1). doi:10.1038/S41398-020-0843-5

39. Hidese S, Hattori K, Sasayama D, et al. Cerebrospinal Fluid Inflammatory Cytokine Levels in Patients With Major Psychiatric Disorders: A Multiplex Immunoassay Study. *Front Pharmacol*. 2021. doi:10.3389/fphar.2020.594394

40. Ishii T, Hattori K, Miyakawa T, et al. Increased cerebrospinal fluid complement C5 levels in major depressive disorder and schizophrenia. *Biochem Biophys Res Commun*. 2018;497(2):683-688. doi:10.1016/J.BBRC.2018.02.131

41. Ishiwata S, Hattori K, Sasayama D, et al. Cerebrospinal fluid D-serine concentrations in major depressive disorder negatively correlate with depression severity. *J Affect Disord*. 2018;226:155-162. doi:10.1016/J.JAD.2017.09.035

42. Ishiwata S, Hattori K, Sasayama D, et al. Plasma and cerebrospinal fluid G72 protein levels in schizophrenia and major depressive disorder. *Psychiatry Res*. 2017;254:244-250. doi:10.1016/j.psychres.2017.04.060

43. Itagaki K, Takebayashi M, Abe H, et al. Reduced Serum and Cerebrospinal Fluid Levels of Autotaxin in Major Depressive Disorder. *Int J Neuropsychopharmacol*. 2019;22(4):261-269. doi:10.1093/ijnp/pyz005

44. Janelidze S, Suchankova P, Ekman A, et al. Low IL-8 is associated with anxiety in suicidal patients: Genetic variation and decreased protein levels. *Acta Psychiatr Scand*. 2015;131(4):269-278. doi:10.1111/ACPS.12339

45. Janelidze S, Ventorp F, Erhardt S, et al. Altered chemokine levels in the cerebrospinal fluid and plasma of suicide attempters. *Psychoneuroendocrinology*. 2013;38(6):853-862. doi:10.1016/j.psyneuen.2012.09.010

46. Jensen M, Schröder J, Blomberg M, et al. Cerebrospinal Fluid A42 Is Increased Early in Sporadic Alzheimer's Disease and Declines with Disease Progression The initial increase and subsequent decrease of A42 adds a new biochemical tool to follow the progression of AD and might be important in the monitoring of therapeutics. 1999.

47. Kaddurah-Daouk R, Yuan P, Boyle SH, et al. Cerebrospinal fluid metabolome in mood disorders-remission state has a unique metabolic profile. *Sci Rep*. 2012;2:667. doi:10.1038/srep00667

48. Kageyama Y, Deguchi Y, Hattori K, et al. Nervonic acid level in cerebrospinal fluid is a candidate biomarker for depressive and manic symptoms: A pilot study. *Brain Behav*. 2021;11(4):e02075. doi:10.1002/BRB3.2075

49. Kasa K, Otsuki S, Yamamoto M, Sato M, Kuroda H, Ogawa N. Cerebrospinal fluid γ-aminobutyric acid and homovanillic acid in depressive disorders. *Biol Psychiatry*. 1982;17(8):877-883.

50. Kern S, Skoog I, Börjesson-Hanson A, et al. Higher CSF interleukin-6 and CSF interleukin-8 in current depression in older women. Results from a population-based sample. *Brain Behav Immun*. 2014;41(1):55-58. doi:10.1016/J.BBI.2014.05.006

51. Kling MA, Roy A, Doran AR, et al. Cerebrospinal fluid immunoreactive corticotropin-releasing hormone and adrenocorticotropin secretion in Cushing's disease and major depression: potential clinical implications. *J Clin Endocrinol Metab*. 1991;72(2):260-271. doi:10.1210/jcem-72-2-260

52. Koslow SH, Maas JW, Bowden CL, Davis JM, Hanin I, Javaid J. CSF and Urinary Biogenic Amines and Metabolites in Depression and Mania: A Controlled, Univariate Analysis. *Arch Gen Psychiatry*. 1983;40(9):999-1010. doi:10.1001/ARCHPSYC.1983.01790080081011

53. Lewine RRJ, Risch SC, Risby E, et al. Lateral ventricle-brain ratio and balance between CSF HVA and 5-HIAA in schizophrenia. *Am J Psychiatry*. 1991;148(9):1189-1194. doi:10.1176/AJP.148.9.1189

54. Lindqvist D, Janelidze S, Hagell P, et al. Interleukin-6 Is Elevated in the Cerebrospinal Fluid of Suicide Attempters and Related to Symptom Severity. *Biol Psychiatry*. 2009;66(3):287-292. doi:10.1016/J.BIOPSYCH.2009.01.030

55. Madeira C, Lourenco M V., Vargas-Lopes C, et al. D-serine levels in Alzheimer's disease: Implications for novel biomarker development. *Transl Psychiatry*. 2015;5. doi:10.1038/TP.2015.52

56. Madeira C, Vargas-Lopes C, Brandão CO, et al. Elevated Glutamate and Glutamine Levels in the Cerebrospinal Fluid of Patients With Probable Alzheimer's Disease and Depression. *Front psychiatry*. 2018;9:561. doi:10.3389/fpsyt.2018.00561

57. Mann JJ, Oquendo MA, Watson KT, et al. Anxiety in major depression and cerebrospinal fluid free gamma-aminobutyric acid. *Depress Anxiety*. 2014;31(10):814-821. doi:10.1002/DA.22278

58. Martinez JM, Garakani A, Yehuda R, Gorman JM. Proinflammatory and "resiliency" proteins in the CSF of patients with major depression. *Depress Anxiety*. 2012;29(1):32-38. doi:10.1002/DA.20876

59. Mathé AA, Ågren H, Wallin A, Blennow K. Calcitonin gene-related peptide and calcitonin in the CSF of patients with dementia and depression: Possible disease markers. *Prog Neuro-Psychopharmacology Biol Psychiatry*. 2002;26(1):41-48. doi:10.1016/S0278-5846(01)00219-6

60. Mizui T, Hattori K, Ishiwata S, et al. Cerebrospinal fluid BDNF pro-peptide levels in major depressive disorder and schizophrenia. *J Psychiatr Res*. 2019;113:190-198. doi:10.1016/J.JPSYCHIRES.2019.03.024

61. Molchan SE, Lawlor BA, Hill JL, et al. CSF monoamine metabolites and somatostatin in Alzheimer's disease and major depression. *Biol Psychiatry*. 1991;29(11):1110-1118. doi:10.1016/0006-3223(91)90253-I

62. Molchan SE, Hill JL, Martinez RA, et al. CSF somatostatin in Alzheimer's disease and major depression: Relationship to hypothalamic-pituitary-adrenal axis and clinical measures. *Psychoneuroendocrinology*. 1993;18(7):509-519. doi:10.1016/0306-4530(93)90044-L

63. Ogawa S, Hattori K, Sasayama D, et al. Reduced cerebrospinal fluid ethanolamine concentration in major depressive disorder. *Sci Rep*. 2015;5. doi:10.1038/srep07796

64. Omori W, Hattori K, Kajitani N, et al. Increased matrix metalloproteinases in cerebrospinal fluids of patients with major depressive disorder and schizophrenia. *Int J Neuropsychopharmacol*. 2020;23(11):713-720. doi:10.1093/ijnp/pyaa049

65. Oreland L, Wiberg A, Isberg M, et al. Platelet MAO Activity and Monoamine Metabolites in Cerebrospinal Fluid in Depressed and Suicidal Patients and in Healthy Controls. *Psychiatry Res*. 1981;4:21-29.

66. Pillai A, Bruno D, Nierenberg J, et al. Complement component 3 levels in the cerebrospinal fluid of cognitively intact elderly individuals with major depressive disorder. *Biomarkers in neuropsychiatry*. 2019;1. doi:10.1016/j.bionps.2019.100007

67. Pitts AF, Samuelson SD, Meller WH, Bissette G, Nemeroff CB, Kathol RG. Cerebrospinal fluid corticotropin-releasing hormone, vasopressin, and oxytocin concentrations in treated patients with major depression and controls. *Biol Psychiatry*. 1995;38(5):330-335. doi:10.1016/0006-3223(95)00229-A

68. Pomara N, Bruno D, Sarreal AS, et al. Lower CSF amyloid beta peptides and higher F2-isoprostanes in cognitively intact elderly individuals with major depressive disorder. *Am J Psychiatry*. 2012;169(5):523-530. doi:10.1176/APPI.AJP.2011.11081153

69. Pomara N, Bruno D, Plaska CR, et al. Evidence of upregulation of the cholinergic anti-inflammatory pathway in late-life depression. *J Affect Disord*. 2021;286:275-281. doi:10.1016/J.JAD.2021.03.012

70. Post RM, Ballenger JC, Uhde T, Smith C, Rubinow DR, Bunney WE. Effect of carbamazepine on cyclic nucleotides in CSF of patients with affective illness. *Biol Psychiatry*. 1982;17(9):1037-1045.

71. Pålhagen S, Qi H, Mårtensson B, Wålinder J, Granérus AK, Svenningsson P. Monoamines, BDNF, IL-6 and corticosterone in CSF in patients with Parkinson's disease and major depression. *J Neurol*. 2010;257(4):524-532. doi:10.1007/S00415-009-5353-6

72. Regenold WT, A. Kling M, Hauser P. Elevated sorbitol concentration in the cerebrospinal fluid of patients with mood disorders. *Psychoneuroendocrinology*. 2000;25(6):593-606. doi:10.1016/S0306-4530(00)00012-3

73. Reis T, Brandão CO, Freire Coutinho ES, Engelhardt E, Laks J. Cerebrospinal Fluid Biomarkers in Alzheimer's Disease and Geriatric Depression: Preliminary Findings from Brazil. *CNS Neurosci Ther*. 2012;18(7):524-529. doi:10.1111/J.1755-5949.2012.00311.X

74. Risch SC, Lewine RJ, Kalin NH, et al. Limbic-hypothalamic-pituitary-adrenal axis activity and ventricular-to-brain ratio studies in affective illness and schizophrenia. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol*. 1992;6(2):95-100.

75. Roy A, Dejong J, Ferraro T. CSF GABA in depressed patients and normal controls. *Psychol Med*. 1991;21(3):613-618. doi:10.1017/S0033291700022248

76. Rubinow DR, Gold PW, Post RM, et al. CSF Somatostatin in Affective Illness. *Arch Gen Psychiatry*. 1983;40(4):409-412. doi:10.1001/ARCHPSYC.1983.01790040063009

77. Rymo I, Kern S, Bjerke M, et al. CSF YKL-40 and GAP-43 are related to suicidal ideation in older women. *Acta Psychiatr Scand*. 2017;135(4):351-357. doi:10.1111/acps.12701

78. Sanfilippo C, Forlenza O, Zetterberg H, Blennow K. Increased neurogranin concentrations in cerebrospinal fluid of Alzheimer's disease and in mild cognitive impairment due to AD. *J Neural Transm*. 2016;123(12):1443-1447. doi:10.1007/S00702-016-1597-3

79. Sasayama D, Hattori K, Teraishi T, et al. Negative correlation between cerebrospinal fluid oxytocin levels and negative symptoms of male patients with schizophrenia. *Schizophr Res*. 2012;139(1-3):201-206. doi:10.1016/J.SCHRES.2012.06.016

80. Sasayama D, Hattori K, Wakabayashi C, et al. Increased cerebrospinal fluid interleukin-6 levels in patients with schizophrenia and those with major depressive disorder. *J Psychiatr Res*. 2013;47(3):401-406. doi:10.1016/J.JPSYCHIRES.2012.12.001

81. Schmidt FM, Arendt E, Steinmetzer A, et al. CSF-hypocretin-1 levels in patients with major depressive disorder compared to healthy controls. *Psychiatry Res*. 2011;190(2-3):240-243. doi:10.1016/J.PSYCHRES.2011.06.004

82. Sher L, Oquendo MA, Li S, et al. Higher cerebrospinal fluid homovanillic acid levels in depressed patients with comorbid posttraumatic stress disorder. *Eur Neuropsychopharmacol*. 2005;15(2):203-209. doi:10.1016/J.EURONEURO.2004.09.009

83. Sher L, Mann JJ, Traskman-Bendz L, et al. Lower cerebrospinal fluid homovanillic acid levels in depressed suicide attempters. *J Affect Disord*. 2006;90(1):83-89. doi:10.1016/J.JAD.2005.10.002

84. Soleimani L, Oquendo MA, Sullivan GM, Mathé AA, Mann JJ. Cerebrospinal fluid neuropeptide Y levels in major depression and reported childhood trauma. *Int J Neuropsychopharmacol*. 2014;18(1). doi:10.1093/ijnp/pyu023

85. Stokes PE, Stoll PM, Koslow SH, et al. Pretreatment DST and Hypothalamic-Pituitary-Adrenocortical Function in Depressed Patients and Comparison Groups: A Multicenter Study. *Arch Gen Psychiatry*. 1984;41(3):257-267. doi:10.1001/archpsyc.1984.01790140047006

86. Sullivan GM, Hatterer JA, Herbert J, et al. Low levels of transthyretin in the CSF of depressed patients. *Am J Psychiatry*. 1999;156(5):710-715. doi:10.1176/AJP.156.5.710

87. Sullivan GM, Oquendo MA, Huang Y, Mann JJ. Elevated cerebrospinal fluid 5-hydroxyindoleacetic acid levels in women with comorbid depression and panic disorder. *Int J Neuropsychopharmacol*. 2006;9(5):547-556. doi:10.1017/S1461145705006231

88. Sullivan GM, Mann JJ, Oquendo MA, Lo ES, Cooper TB, Gorman JM. Low Cerebrospinal Fluid Transthyretin Levels in Depression: Correlations with Suicidal Ideation and Low Serotonin Function. *Biol psychiatry*. 2006;60(5):500-506.

doi:10.1016/j.biopsych.2005.11.022

89. SUNDERLAND T, BERRETTINI WH, MOLCHAN SE, et al. Reduced cerebrospinal fluid dynorphin A1-8 in Alzheimer's disease. *Biol psychiatry*. 1991;30(1):81-87. doi:10.1016/0006-3223(91)90073-U

90. Swann AC, Katz MM, Bowden CL, Berman NG, Stokes PE. Psychomotor performance and monoamine function in bipolar and unipolar affective disorders. *Biol psychiatry*. 1999;45(8):979-988. doi:10.1016/S0006-3223(98)00172-3

91. Vawter MP, Frye MA, Hemperly JJ, et al. Elevated concentration of N-CAM VASE isoforms in schizophrenia. *J Psychiatr Res*. 2000;34(1):25-34. doi:10.1016/S0022-3956(99)00026-6

92. Ventorp F, Barzilay R, Erhardt S, et al. The CD44 ligand hyaluronic acid is elevated in the cerebrospinal fluid of suicide attempters and is associated with increased blood–brain barrier permeability. *J Affect Disord*. 2016;193:349-354. doi:10.1016/j.jad.2015.12.069

93. Widerlöv E, Bissette G, Nemeroff CB. Monoamine metabolites, corticotropin releasing factor and somatostatin as CSF markers in depressed patients. *J Affect Disord*. 1988;14(2):99-107. doi:10.1016/0165-0327(88)90051-1

94. Widerlöv E, Lindström L., Wahlestedt C, Ekman R. Neuropeptide Y and peptide YY as possible cerebrospinal fluid markers for major depression and schizophrenia, respectively. *J Psychiatr Res*. 1988;22(1):69-79. doi:10.1016/0022-3956(88)90030-1

95. Wong ML, Kling MA, Munson PJ, et al. Pronounced and Sustained Central Hypernoradrenergic Function in Major Depression with Melancholic Features: Relation to Hypercortisolism and Corticotropin-Releasing Hormone. *Proc Natl Acad Sci - PNAS*. 2000;97(1):325-330. doi:10.1073/pnas.97.1.325

96. Yoon HS, Hattori K, Ogawa S, et al. Relationships of Cerebrospinal Fluid Monoamine Metabolite Levels With Clinical Variables in Major Depressive Disorder. *J Clin Psychiatry*. 2017;78(8):e947-e956. doi:10.4088/JCP.16m11144

97. Yoon HS, Hattori K, Sasayama D, Kunugi H. Low cocaine- and amphetamine-regulated transcript (CART) peptide levels in human cerebrospinal fluid of major depressive disorder (MDD) patients. *J Affect Disord*. 2018;232:134-138. doi:10.1016/j.jad.2018.02.039

98. Ågren H, Niklasson F, Hällgren R. Brain purinergic activity linked with depressive symptomatology: Hypoxanthine and xanthine in CSF of patients with major depressive disorders. *Psychiatry Res*. 1983;9(3):179-189. doi:10.1016/0165-1781(83)90042-2

99. Anderson GM, Gerner RH, Cohen DJ, Fairbanks L. Central tryptamine turnover in depression, schizophrenia, and anorexia: Measurement of indoleacetic acid in cerebrospinal fluid. *Biol Psychiatry*. 1984;19(10):1427-1435.

100. Bendix M, Uvnäs-Moberg K, Petersson M, Kaldo V, Åsberg M, Jokinen J. Insulin and glucagon in plasma and cerebrospinal fluid in suicide attempters and healthy controls. *Psychoneuroendocrinology*. 2017;81:1-7. doi:10.1016/J.PSYNEUEN.2017.03.019

101. Berger PA, Faull KF, Kilkowski J, et al. CSF monoamine metabolites in depression and schizophrenia. *Am J Psychiatry*. 1980;137(2):174-180. doi:10.1176/ajp.137.2.174

102. Berrettini WH, Doran AR, Kelsoe J, Roy A, Pickar D. Cerebrospinal fluid neuropeptide Y in depression and schizophrenia. *Neuropsychopharmacology*. 1987;1(1):81-83. doi:10.1016/0893-133X(87)90013-3

103. Berrettini WH, Kaye WH, Sunderland T, et al. Galanin immunoreactivity in human csf: Studies in eating disorders and alzheimer's disease. *Neuropsychobiology*. 1988;19(2):64-68. doi:10.1159/000118436

104. Bertilsson L, Åsberg M, Lantto O, Scalia-Tomba GP, Träskman-Bendz L, Tybring G. Gradients of monoamine metabolites and cortisol in cerebrospinal fluid of psychiatric patients and healthy controls. *Psychiatry Res*. 1982;6(1):77-83. doi:10.1016/0165-1781(82)90040-3

105. Bertilsson L, Tybring G, Braithwaite R, Träskman-Bendz L, ÅSberg M. Urinary excretion of 5-hydroxyindoleacetic acid - no relationship to the level in cerebrospinal fluid. *Acta Psychiatr Scand*. 1982;(3):190-198.

106. Carpenter LL, Bayat L, Moreno F, et al. Decreased cerebrospinal fluid concentrations of substance P in treatment-resistant depression and lack of alteration after acute adjunct vagus nerve stimulation therapy. *Psychiatry Res*. 2008;157(1-3):123-129. doi:10.1016/J.PSYCHRES.2007.04.016

107. Catlin DH, Gorelick DA, Gerner RH. CLINICAL PHARMACOLOGY OF β-ENDORPHIN IN DEPRESSION AND SCHIZOPHRENIA. *Ann N Y Acad Sci*. 1982;398(1):434-447. doi:10.1111/J.1749-6632.1982.TB39515.X

108. Casper RC, Kocsis J, Dysken M, Stokes P, Croughan J, Maas J. Cortisol measures in primary major depressive disorder with hypersomnia or appetite increase. *J Affect Disord*. 1988;15(2):131-140. doi:10.1016/0165-0327(88)90081-X

109. Chatzittofis A, Nordstrom P, Hellstrom C, Arver S, Asberg M, Jokinen J. CSF 5-HIAA, Cortisol and DHEAS Levels in Suicide Attempters and Healthy Volunteers. In: *BIOLOGICAL PSYCHIATRY*. Vol 73. ; 2013:204S.

110. Davis KL, Davidson M, Yang RK, et al. CSF Somatostatin in alzheimer's disease, depressed patients, and control subjects. *Biol Psychiatry*. 1988;24(6):710-712. doi:10.1016/0006-3223(88)90147-3

111. Derkow K, Rössling R, Schipke C, et al. Distinct expression of the neurotoxic microRNA family let-7 in the cerebrospinal

fluid of patients with Alzheimer's disease. *PLoS One*. 2018;13(7). doi:10.1371/JOURNAL.PONE.0200602

112. Ditzen C, Tang N, Jastorff AM, et al. Cerebrospinal fluid biomarkers for major depression confirm relevance of associated pathophysiology. *Neuropsychopharmacology*. 2012;37(4):1013-1025. doi:10.1038/NPP.2011.285

113. Ehnvall A, Sjögren M, Zachrisson OCG, Ågren H. Lifetime burden of mood swings and activation of brain norepinephrine turnover in patients with treatment-refractory depressive illness. *J Affect Disord*. 2003;74(2):185-189. doi:10.1016/S0165-0327(02)00011-3

114. Engström G, Alling C, Blennow K, Regnéll G öran, Träskman-Bendz L. Reduced cerebrospinal HVA concentrations and HVA/5-HIAA ratios in suicide attempters: Monoamine metabolites in 120 suicide attempters and 47 controls. *Eur Neuropsychopharmacol*. 1999;9(5):399-405. doi:10.1016/S0924-977X(99)00016-4

115. Facchinetti F, Petraglia F, Sances G, et al. Dissociation between CSF and plasma B-endorphin in major depressive disorders: evidence for a different regulation. *J Endocrinol Invest*. 1986;9(1):11-14. doi:10.1007/BF03348054

116. Franzen AD, Lam TT, Williams KR, et al. Cerebrospinal fluid proteome evaluation in major depressive disorder by mass spectrometry. *BMC Psychiatry*. 2020;20(1). doi:10.1186/S12888-020-02874-9

117. Frye MA, Gary KA, Marangell LB, et al. CSF thyrotropin-releasing hormone gender difference: Implications for neurobiology and treatment of depression. *J Neuropsychiatry Clin Neurosci*. 1999;11(3):349-353. doi:10.1176/JNP.11.3.349

118. Frye MA, Pazzaglia PJ, George MS, et al. Low CSF somatostatin associated with response to nimodipine in patents with affective illness. *Biol Psychiatry*. 2003;53(2):180-183. doi:10.1016/S0006-3223(02)01343-4

119. George MS, Guidotti A, Rubinow D, Pan B, Mikalauskas K, Post RM. CSF neuroactive steroids in affective disorders: Pregnenolone, progesterone, and DBI. *Biol Psychiatry*. 1994;35(10):775-780. doi:10.1016/0006-3223(94)91139-8

120. Geracioti TD, Nicholson WE, Orth DN, Ekhator NN, Loosen PT. Cholecystokinin in human cerebrospinal fluid: concentrations, dynamics, molecular forms and relationship to fasting and feeding in health, depression and alcoholism. *Brain Res*. 1993;629(2):260-268. doi:10.1016/0006-8993(93)91329-Q

121. Geracioti TD, Loosen PT, Orth DN. Low cerebrospinal fluid corticotropin-releasing hormone concentrations in eucortisolemic depression. *Biol Psychiatry*. 1997;42(3):165-174. doi:10.1016/S0006-3223(96)00312-5

122. Geracioti Jr TD, Loosen PT, Ekhator NN, et al. Uncoupling of serotonergic and noradrenergic systems in depression: Preliminary evidence from continuous cerebrospinal fluid sampling. *Depress Anxiety*. 1997;4(2):89-94. doi:10.1002/(SICI)1520-6394(1997)6:3<89::AID-DA1>3.0.CO;2-0

123. Gerner RH, Fairbanks L, Anderson GM, et al. CSF neurochemistry in depressed, manic and schizophrenic patients compared with that of normal controls. *Am J Psychiatry*. 1984;141(12):1533-1540. doi:10.1176/AJP.141.12.1533

124. Gerner RH, Yamada T. Altered neuropeptide concentrations in cerebrospinal fluid of psychiatric patients. *Brain Res*. 1982;238(1):298-302. doi:10.1016/0006-8993(82)90801-0

125. Gerner RH, Merrill JE. Cerebrospinal fluid prostaglandin E in depression, mania, and schizophrenia compared to normals. *Biol psychiatry*. 1983;18(5):565-569.

126. Goodnick PJ, Evans HE, Dunner DL, Fieve RR. Amino acid concentrations in cerebrospinal fluid: effects of aging, depression, and probenecid. *Biol Psychiatry*. 1980;15(4):557-563.

127. Hoffman A, Keiser HR, Grossman E, Goldstein DS, Gold PW, Kling M. ENDOTHELIN CONCENTRATIONS IN CEREBROSPINAL FLUID IN DEPRESSIVE PATIENTS. *Lancet*. 1989;334(8678-8679):1519. doi:10.1016/S0140-6736(89)92955-3

128. Hou C, Jia F, Liu Y, Li L. CSF serotonin, 5-hydroxyindolacetic acid and neuropeptide Y levels in severe major depressive disorder. *Brain Res*. 2006;1095(1):154-158. doi:10.1016/J.BRAINRES.2006.04.026

129. Isung J, Aeinehband S, Mobarrez F, et al. Low vascular endothelial growth factor and interleukin-8 in cerebrospinal fluid of suicide attempters. *Transl Psychiatry*. 2012;2. doi:10.1038/TP.2012.123

130. Jimerson DC, Rubinow DR, Ballenger JC, Post RM, Kopin IJ. Peripheral contribution to cerebrospinal fluid MHPG: Studies in depressed patients. *Psychopharmacol Bull*. 1983:665-668.

131. Jokinen J, Chatzittofis A, Hellström C, Nordström P, Uvnäs-Moberg K, Åsberg M. Low CSF oxytocin reflects high intent in suicide attempters. *Psychoneuroendocrinology*. 2012;37(4):482-490. doi:10.1016/J.PSYNEUEN.2011.07.016

132. Jokinen J, Nordström AL, Nordström P. Cerebrospinal fluid monoamine metabolites and suicide. *Nord J Psychiatry*. 2009;63(4):276-279. doi:10.1080/08039480802571077

133. Sidney Jones J, Stanley B, John Mann J, et al. CSF 5-HIAA and HVA concentrations in elderly depressed patients who attempted suicide. *Am J Psychiatry*. 1990;147(9):1225-1227. doi:10.1176/AJP.147.9.1225

134. Kling MA, Rubinow DR, Doran AR, et al. Cerebrospinal fluid immunoreactive somatostatin concentrations in patients with Cushing's disease and major depression: relationship to indices of corticotropin-releasing hormone and cortisol secretion. *Neuroendocrinology*. 1993;57(1):79-88. doi:10.1159/000126345

135. Lindström LH, Ekman R, Walleus H, Widerlöv E. Delta-sleep inducing peptide in cerebrospinal fluid from schizophrenics, depressives and healthy volunteers. *Prog Neuropsychopharmacol Biol Psychiatry*. 1985;9(1):83-90. doi:10.1016/0278-5846(85)90182-4

136. Little JT, Ketter TA, Mathé AA, Frye MA, Luckenbaugh D, Post RM. Venlafaxine but not bupropion decreases cerebrospinal fluid 5- hydroxyindoleacetic acid in unipolar depression. *Biol Psychiatry*. 1999;45(3):285-289. doi:10.1016/S0006-3223(98)00078-X

137. Mann JJ, Currier D, Murphy L, et al. No association between a TPH2 promoter polymorphism and mood disorders or monoamine turnover. *J Affect Disord*. 2008;106(1-2):117-121. doi:10.1016/J.JAD.2007.05.031

138. Mathé AA, Ågren H, Lindström L, Theodorsson E. Increased concentration of calcitonin gene-related peptide in cerebrospinal fluid of depressed patients. A possible trait marker of major depressive disorder. *Neurosci Lett*. 1994;182(2):138-142. doi:10.1016/0304-3940(94)90782-X

139. Naber D, Pickar D, Post RM, et al. Endogenous opioid activity and β-endorphin immunoreactivity in CSF of psychiatric patients and normal volunteers. *Am J Psychiatry*. 1981;138(11):1457-1462. doi:10.1176/AJP.138.11.1457

140. Nemeroff CB, Widerlöv E, Bissette G, et al. Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. *Science (80-)*. 1984;226(4680):1342-1344. doi:10.1126/SCIENCE.6334362

141. Nemeroff CB, Bissette G, Widerlov E, et al. Neurotensin-like immunoreactivity in cerebrospinal fluid of patients with schizophrenia, depression, anorexia nervosa-bulimia, and premenstrual syndrome. *J Neuropsychiatry Clin Neurosci*. 1989;1(1):16-20. doi:10.1176/JNP.1.1.16

142. Newport DJ, Heim C, Owens MJ, et al. Cerebrospinal fluid corticotropin-releasing factor (CRF) and vasopressin concentrations predict pituitary response in the CRF stimulation test: A multiple regression analysis. *Neuropsychopharmacology*. 2003;28(3):569-576. doi:10.1038/SJ.NPP.1300071

143. Omori W, Kano K, Hattori K, et al. Reduced Cerebrospinal Fluid Levels of Lysophosphatidic Acid Docosahexaenoic Acid in Patients With Major Depressive Disorder and Schizophrenia. doi:10.1093/ijnp/pyab044

144. Pazzaglia PJ, Post RM, Rubinow D, Kling MA, Huggins TS, Sunderland T. Cerebrospinal fluid total protein in patients with affective disorders. *Psychiatry Res*. 1995;57(3):259-266. doi:10.1016/0165-1781(95)02704-z

145. Pitts AF, Carroll BT, Gehris TL, Kathol RG, Samuelson SD. Elevated CSF protein in male patients with depression. *Biol Psychiatry*. 1990;28(7):629-637. doi:10.1016/0006-3223(90)90401-M

146. Poltorak M, Frye MA, Wright R, et al. Increased neural cell adhesion molecule in the CSF of patients with mood disorder. *J Neurochem*. 1996;66(4):1532-1538. doi:10.1046/J.1471-4159.1996.66041532.X

147. Richards EM, Zanotti-Fregonara P, Fujita M, et al. PET radioligand binding to translocator protein (TSPO) is increased in unmedicated depressed subjects. *EJNMMI Res*. 2018;8. doi:10.1186/S13550-018-0401-9

148. Roos RP, Davis K, Meltzer HY. Immunoglobulin Studies in Patients With Psychiatric Diseases. *Arch Gen Psychiatry*. 1985;42(2):124-128. doi:10.1001/ARCHPSYC.1985.01790250018002

149. Roy A, Agren H, Pickar D, et al. Reduced CSF concentrations of homovanillic acid and homovanillic acid to 5-hydroxyindoleacetic acid ratios in depressed patients: Relationship to suidical behavior and dexamethasone nonsuppression. *Am J Psychiatry*. 1986;143(12):1539-1545. doi:10.1176/AJP.143.12.1539

150. Roy A, Pickar D, Jong J, Karoum F, Linnoila M. Norepinephrine and Its Metabolites in Cerebrospinal Fluid, Plasma, and Urine: Relationship to Hypothalamic-Pituitary-Adrenal Axis Function in Depression. *Arch Gen Psychiatry*. 1988;45(9):849-857. doi:10.1001/ARCHPSYC.1988.01800330081010

151. ROY A, PICKAR D, PAUL S, DORAN A, CHROUSOS GP, GOLD PW. CSF corticotropin-releasing hormone in depressed patients and normal control subjects. *Am J Psychiatry*. 1987;144(5):641-645. doi:10.1176/ajp.144.5.641

152. ROY A, WOLKOWITZ OM, BISSETTE G, NEMEROFF CB. Differences in CSF concentrations of thyrotropin-releasing hormone in depressed patients and normal subjects: negative findings. *Am J Psychiatry*. 1994;151(4):600-602. doi:10.1176/ajp.151.4.600

153. Rubinow DR, Post RM, Pickar D, et al. Relationship between urinary free cortisol and CSF opioid binding activity in depressed patients and normal volunteers. *Psychiatry Res*. 1981;5(1):87-93. doi:10.1016/0165-1781(81)90064-0

154. Salomon RM, Ripley B, Kennedy JS, et al. Diurnal variation of cerebrospinal fluid hypocretin-1 (Orexin-A) levels in control and depressed subjects. *Biol psychiatry*. 2003;54(2):96-104. doi:10.1016/S0006-3223(02)01740-7

155. Sharma RP, Faull K, Javaid JI, Davis JM. Cerebrospinal fluid levels of phenylacetic acid in mental illness: behavioral associations and response to neuroleptic treatment. *Acta Psychiatr Scand*. 1995;91(5):293-298. doi:10.1111/J.1600-0447.1995.TB09785.X

156. Sher L, Oquendo MA, Li S, et al. Lower CSF homovanillic acid levels in depressed patients with a history of alcoholism. *Neuropsychopharmacology*. 2003;28(9):1712-1719. doi:10.1038/SJ.NPP.1300231

157. Song MF, Dong JZ, Wang YW, et al. CSF miR-16 is decreased in major depression patients and its neutralization in rats induces depression-like behaviors via a serotonin transmitter system. *J Affect Disord*. 2015;178:25-31.

doi:10.1016/j.jad.2015.02.022

158. Spiegel D, King R. Hypnotizability and CSF HVA levels among psychiatric patients. *Biol Psychiatry*. 1992;31(1):95-98. doi:10.1016/0006-3223(92)90009-O

159. Stefansson J, Chatzittofis A, Nordström P, Arver S, Åsberg M, Jokinen J. CSF and plasma testosterone in attempted suicide. *Psychoneuroendocrinology*. 2016;74:1-6. doi:10.1016/j.psyneuen.2016.08.009

160. Stübner S, Schön T, Padberg F, et al. Interleukin-6 and the soluble IL-6 receptor are decreased in cerebrospinal fluid of geriatric patients with major depression: no alteration of soluble gp130. *Neurosci Lett*. 1999;259(3):145-148. doi:10.1016/S0304-3940(98)00916-1

161. Sunderland T, Rubinow DR, Tariot PN, et al. CSF somatostatin in patients with Alzheimer's disease, older depressed patients, and age-matched control subjects. *Am J Psychiatry*. 1987;144(10):1313-1316. doi:10.1176/ajp.144.10.1313

162. Träskman L, Tybring G, Åsberg M, Bertilsson L, Lantto O, Schalling D. Cortisol in the CSF of Depressed and Suicidal Patients. *Arch Gen Psychiatry*. 1980;37(7):761-767. doi:10.1001/archpsyc.1980.01780200039004

163. Träskman L, Åsberg M, Bertilsson L, Sjüstrand L. Monoamine Metabolites in CSF and Suicidal Behavior. *Arch Gen Psychiatry*. 1981;38(6):631-636. doi:10.1001/archpsyc.1981.01780310031002

164. Träskman-Bendz L, Åsberg M, Bertilsson L, Thorén P. CSF monoamine metabolites of depressed patients during illness and after recovery. *Acta Psychiatr Scand*. 1984;69(4):333-342. doi:10.1111/j.1600-0447.1984.tb02503.x

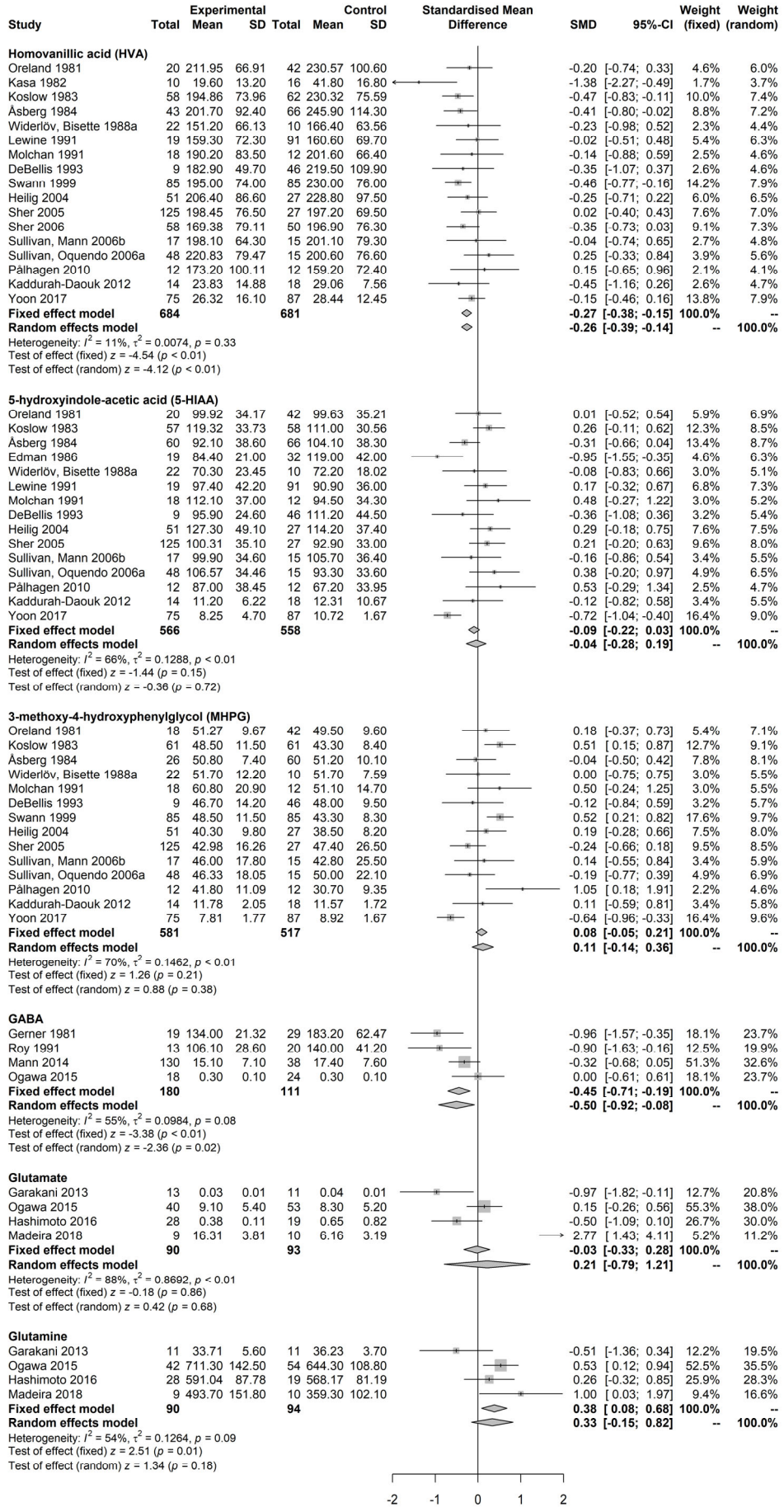
165. Verbanck PM., Lotstra F, Gilles C, Linkowski P, Mendlewicz J, Vanderhaeghen J. Reduced cholecystokinin immunoreactivity in the cerebrospinal fluid of patients with psychiatric disorders. *Life Sci*. 1984;34(1):67-72. doi:10.1016/0024-3205(84)90331-X

166. Yesavage JA, Holman CA, Berger PA. Cerebrospinal Fluid Lactate Levels and Aging: Findings in Normals and Patients with Major Depressive Disorders. *Gerontol*. 1982;28(6):377-380. doi:10.1159/000212559

167. Zalsman G, Huang Y, Oquendo MA, et al. No Association of COMT Val158Met Polymorphism with Suicidal Behavior or CSF Monoamine Metabolites in Mood Disorders. *Arch suicide Res*. 2008;12(4):327-335. doi:10.1080/13811110802324912

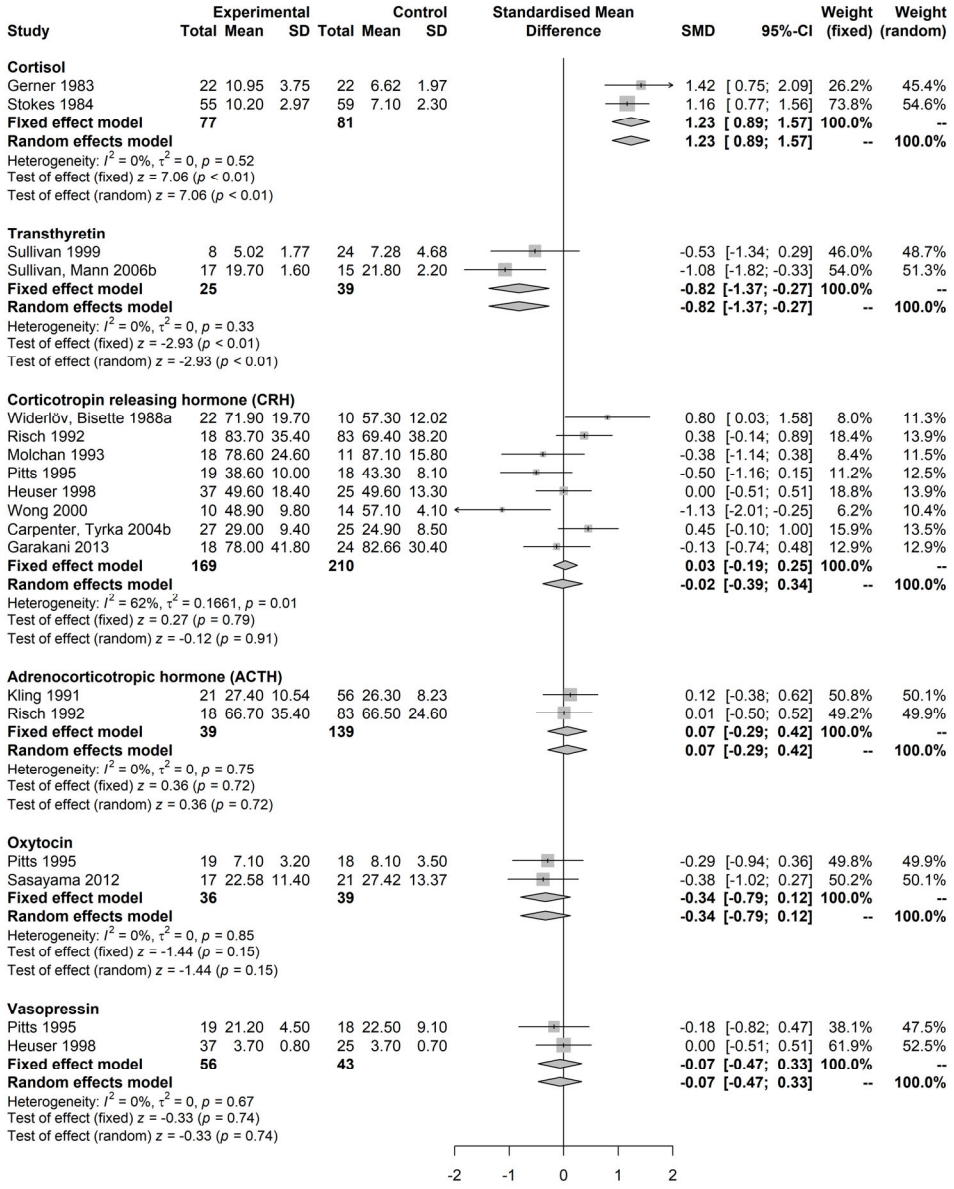
Forrest plots of biomarkers quantified in ≧2 studies with both random and fixed effects models

eFigure 2 | Neurotransmitters and their metabolites

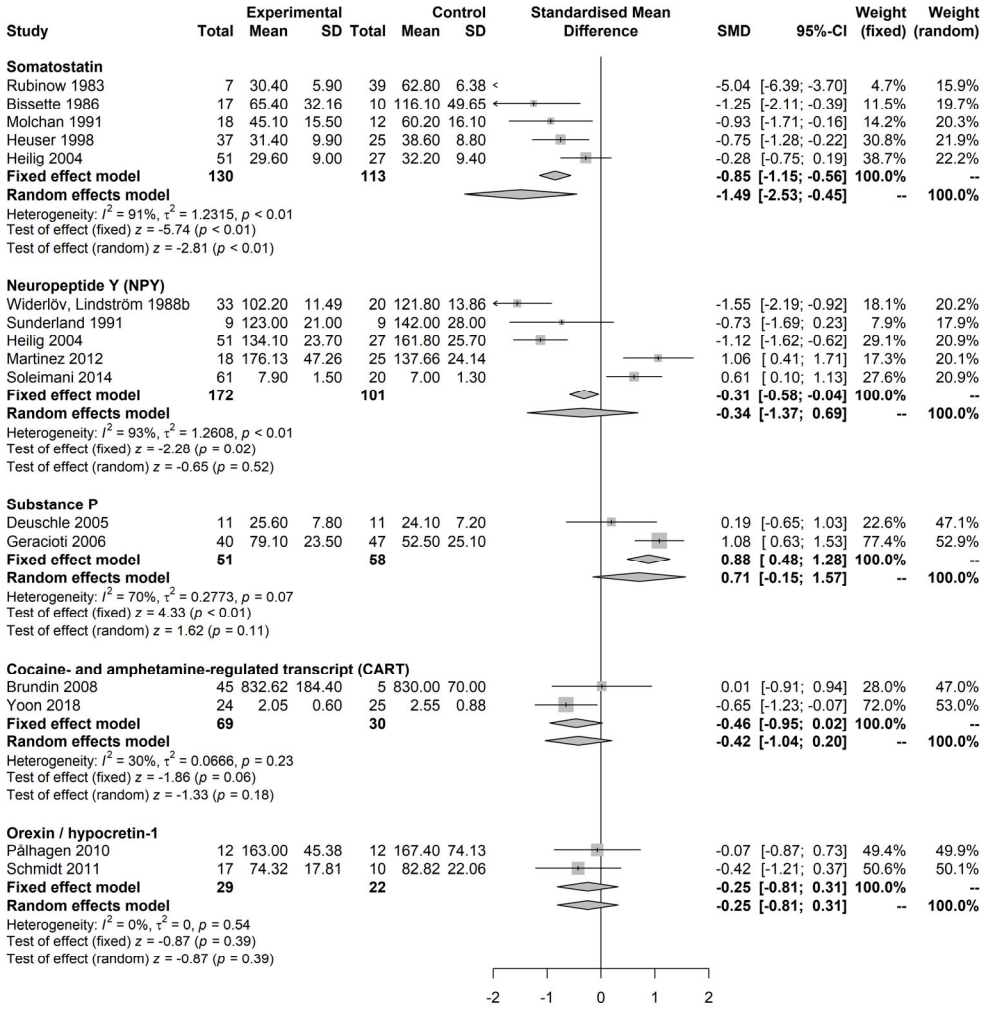


eFigure 3 | Hormones, neuropeptides and metabolites

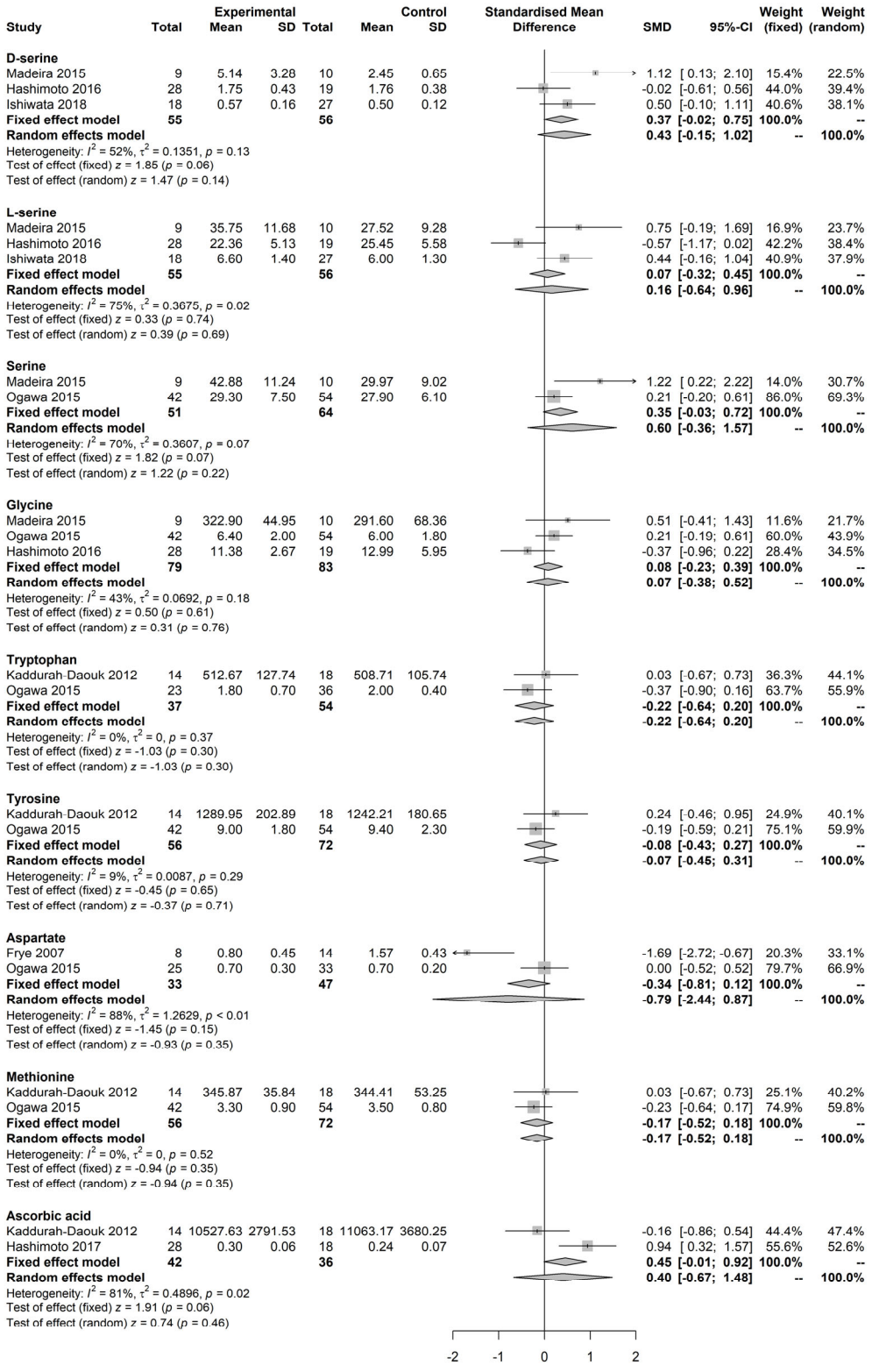
Hormones



Neuropeptides

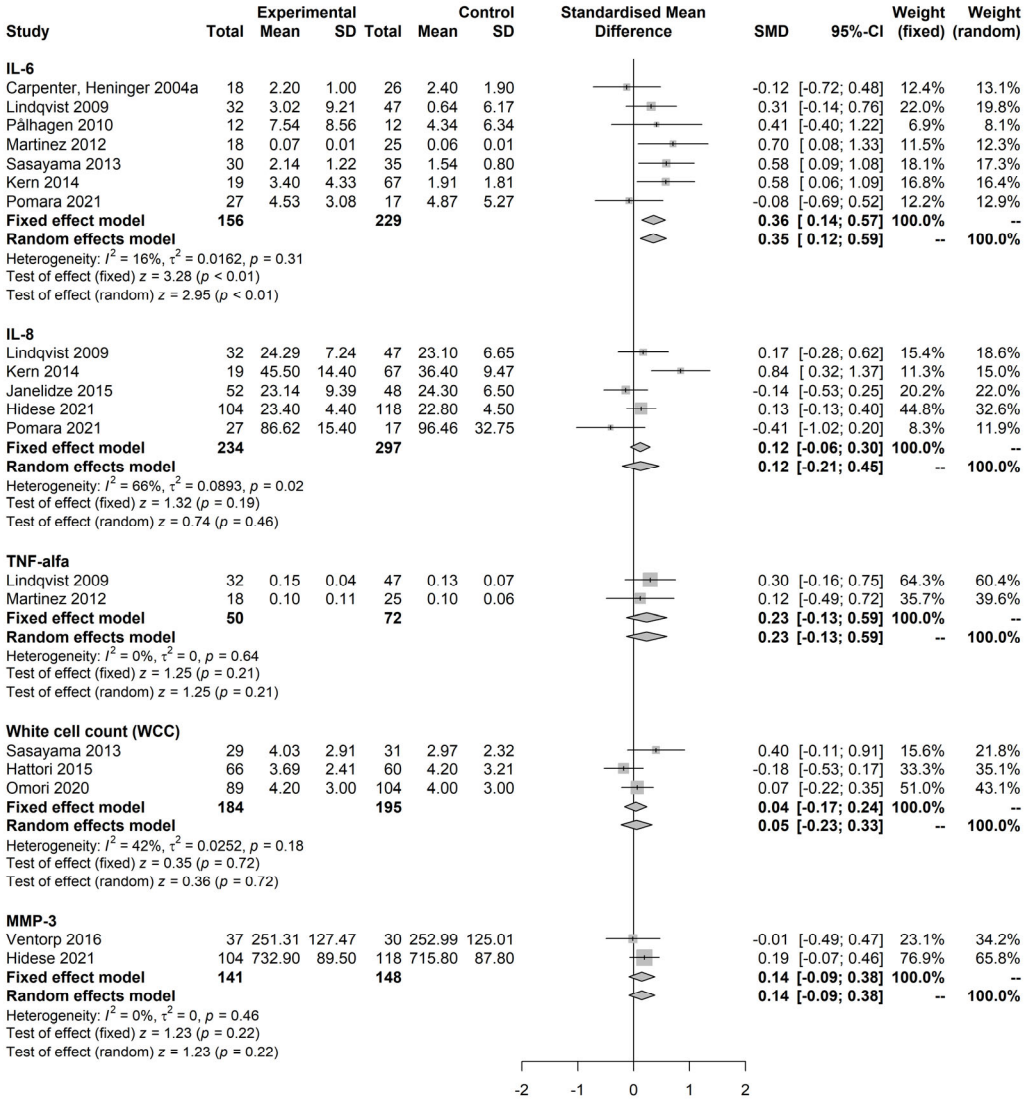


Amino acids and derivates

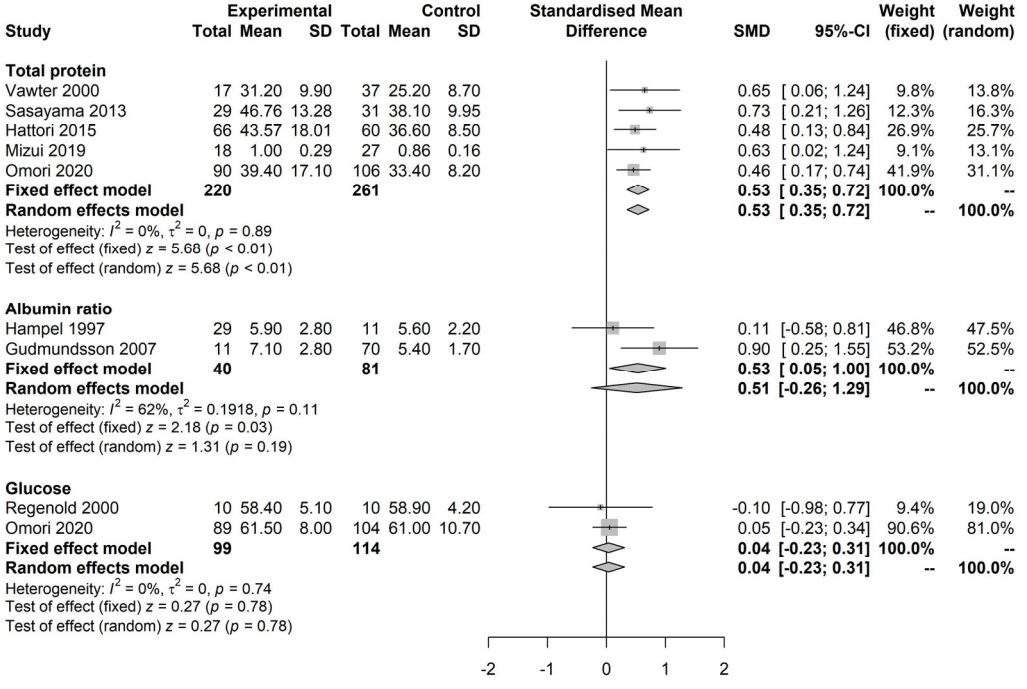


eFigure 4 | Inflammation and BBB permeability

Inflammatory markers

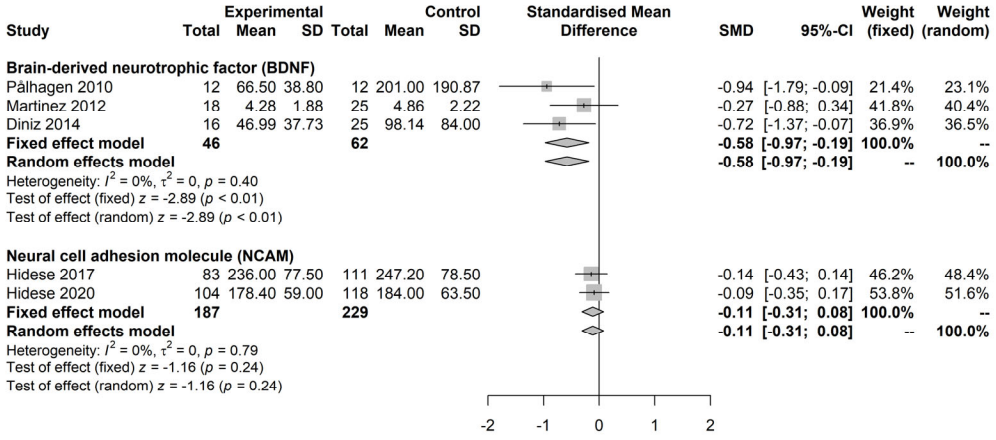


Blood-brain-barrier permeability

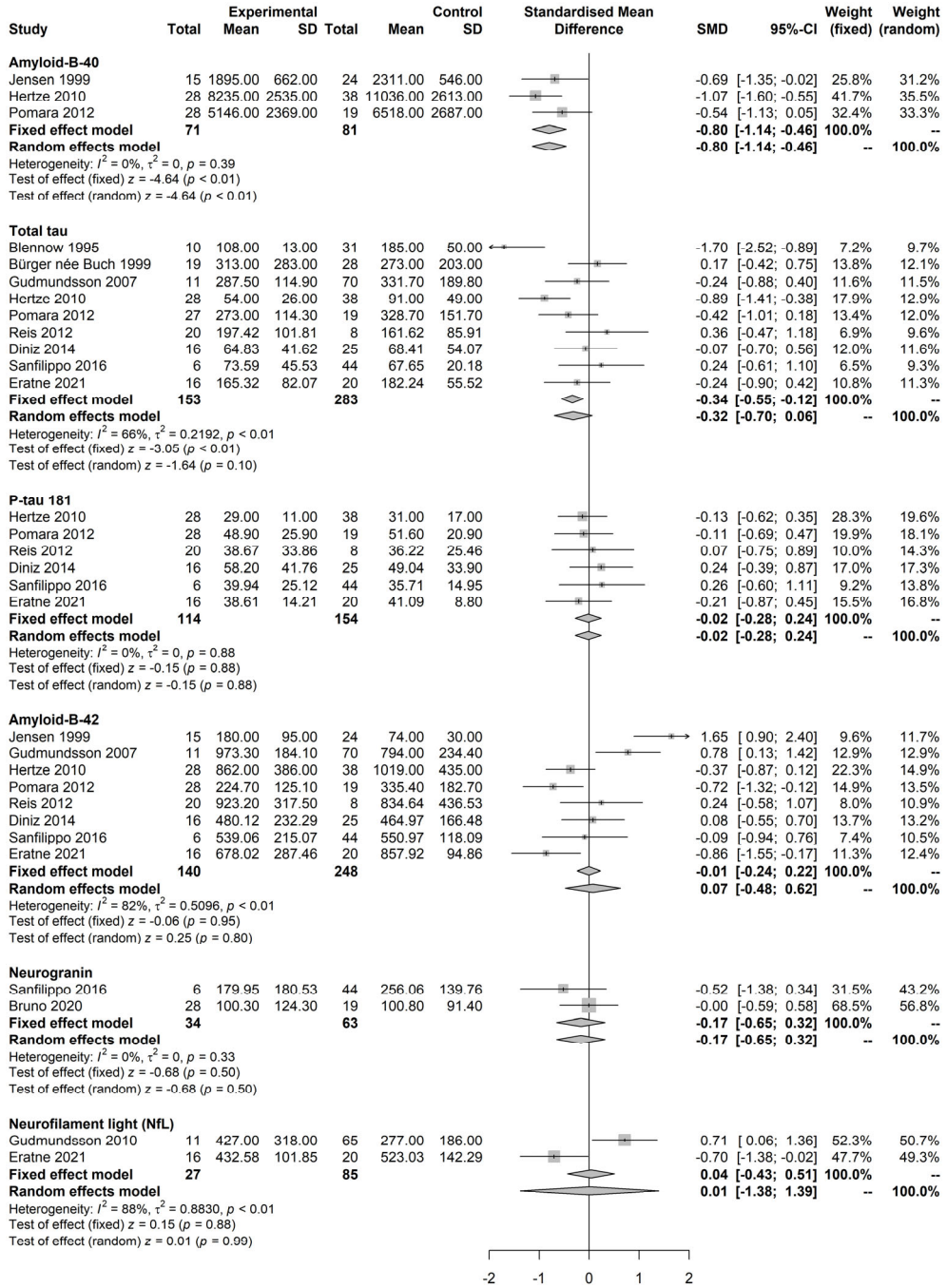


eFigure 5 | Neurodegeneration and synaptic plasticity

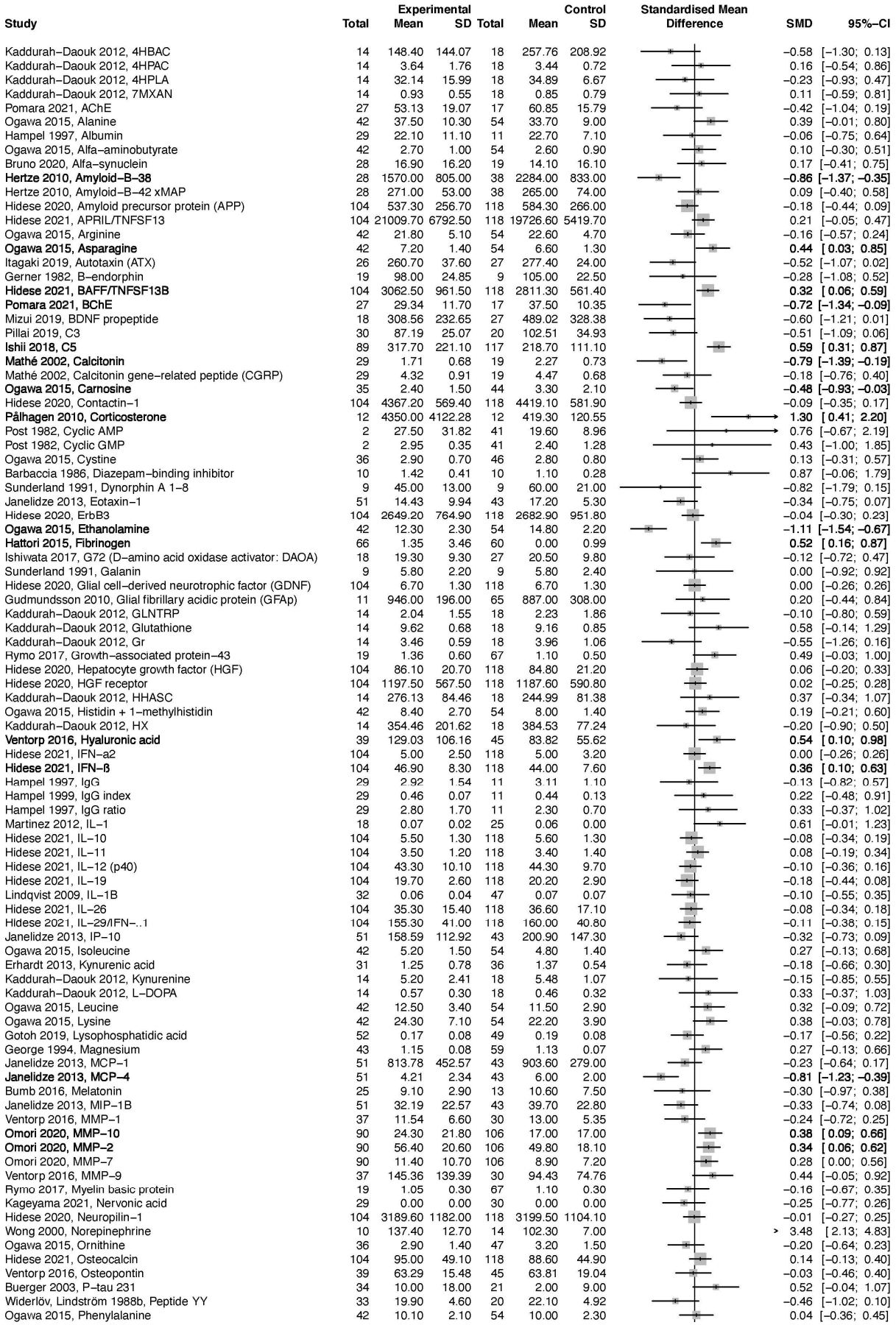
Synaptic plasticity

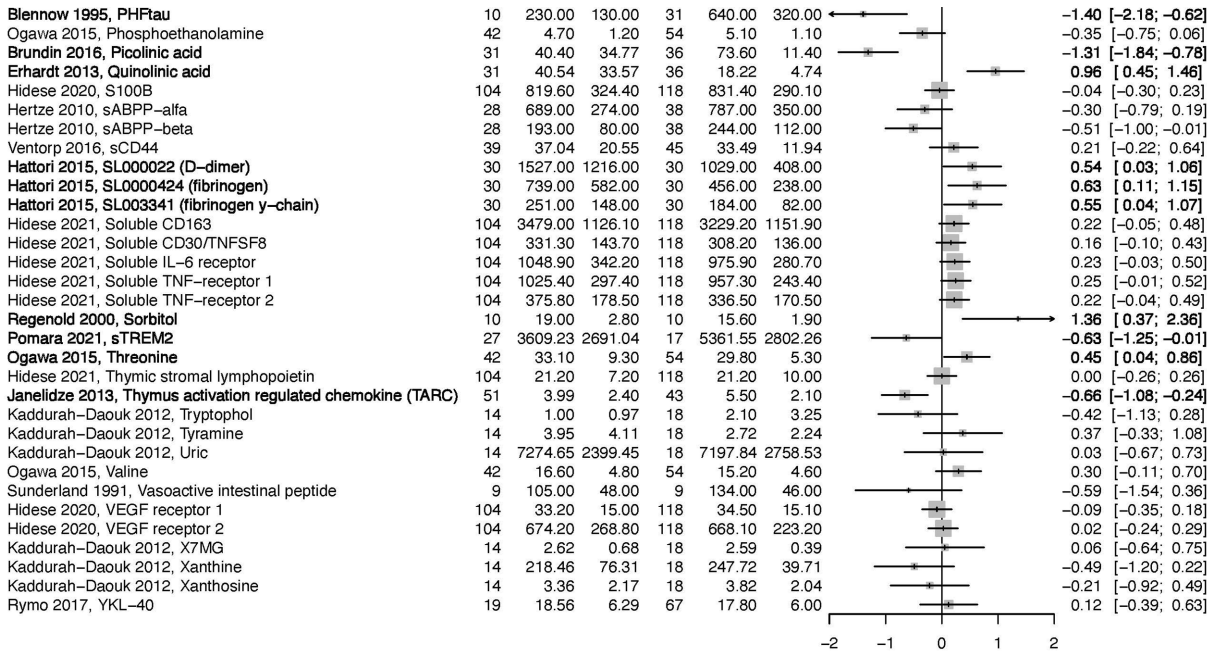


Neurodegeneration



eFigure 6 | Forest plots of biomarkers quantified in only one study





eTable 5 | Presentation of all biomarkers identified for the meta-analysis and a brief description of their function

Neurotransmitters and their metabolites	
5-hydroxytryptamine (5-HT), 5-hydroxyindole-acetic acid (5-HIAA)	5-HT or serotonin[1] is a monoaminergic neurotransmitter regulating a wide range of brain functions including mood, memory, sleep, appetite, aggression and thermoregulation. Serotonin depletion as a cause of depression has been a hypothesis for many years.[2] 5-HIAA is the main metabolite of serotonin and reflects the levels of serotonin in the brain.[1]
Dopamine (DA), Homovanillic acid (HVA), Dihydroxyphenylalanine (L-DOPA)	Dopamine (DA) is a neurotransmitter involved in the experience of pleasure, motivation, and reward. Decreased levels have repeatedly been associated with depression. Homovanillic acid (HVA) is the final excretion product of dopamine and reflects dopamine levels in the brain.[3] L-DOPA is the precursor of dopamine, produced from tyrosine.[4] A decrease in dopamine can be caused by decrease in L-DOPA.
Norepinephrine (NE) / Noradrenaline (NA), 3-Methoxy-4-hydroxyphenylglycol (MHPG)	NA/NE is a neurotransmitter in the central nervous system (CNS) involved in learning, memory, sleep, arousal and adaption.[5] The noradrenergic system is also involved in regulation of the stress response.[6] NA deficiency as a cause of depression has been a hypothesis for many years.[7] MHPG is the primary metabolite of norepinephrine in the brain and reflects NA levels.[8]
γ-aminobutyric acid (GABA)	GABA is the major inhibitory neurotransmitter in the CNS suggested to play a vital role in the control of stress and depression. GABA deficiency has repeatedly been observed in patients with depression. This may result in local hyperexcitability leading to compromised neurogenesis and HPA axis hyperactivity; factors also presumed to be important in depression.[9]
Glutamate, glutamine	Glutamate is the major excitatory neurotransmitter in CNS mediating both cognition and emotion. Elevated levels of extra synaptic glutamate are thought to be excitotoxic and abnormally transmission of glutamate has been suggested to play a role in depression. Glutamine is the metabolite of glutamate.[10,11]
Hormones, neuropeptides and amino acids	
Hormones	
Corticotropin releasing hormone **(**CRH) / Corticotropin releasing factor **(**CRF)	CRH/CRF is a peptide hormone vital in regulation of the hypothalamic-pituitary-adrenal (HPA) axis. CRH is released primarily from the paraventricular nucleus of the hypothalamus in response to stress. CRH stimulates the release of ACTH from the pituitary gland and the release of NA from the autonomic neurons.[12]
Adrenocorticotropic hormone **(**ACTH)	ACTH is released from the anterior pituitary when stimulated by CRH. By binding to MC2 receptors in the adrenal cortex ACTH induces synthesis and secretion of glucocorticoids – primarily cortisol – to the blood. ACTH also stimulates the synthesis of NA in the adrenal medulla.[12,13]
Cortisol, corticosterone	Cortisol and corticosterone are glucocorticoids secreted from the adrenal cortex upon activation of the hypothalamic-pituitary-adrenal (HPA) axis. Prolonged psychological stress can increase levels of cortisol, which repeatedly has been observed in patients with depression. This may affect several systems, including the release of inflammatory markers, increased excitotoxicity and reduced neurogenesis.[14,15]
Arginine-vasopressin **(**AVP) / Vasopressin / Antidiuretic hormone (ADH)	AVP, also known as ADH or vasopressin, is a neuropeptide hormone released from the posterior pituitary. Like CRH, AVP is a potent ACTH secretagogue thought to potentiate the effect of CRH in response to stress.[14]
Oxytocin (OT)	OT is a neuropeptide synthesized in hypothalamus. OT functions as a neurotransmitter in CNS but is also released to the blood from the posterior pituitary. OT is important for uterine contractions during parturition and enhancing of milk ejection during suckling. However, OT also reduces cortisol release during stress/fear and mediates social behaviours and attachment.[16]
Transthyretin (TTR) / prealbumin	TTR or prealbumin is a transport protein synthesized in the choroid plexus. TTR is involved in the transport of T4 across the blood-brain barrier. Lower levels of CSF TTR have been reported in depression, and is thought to reduce T4 levels in the brain and thus induce depressive symptoms similar to those of global hypothyroidism.[17]

Neuropeptides and opioids	
Somatostatin (SS)	SS is a peptide synthesized both in the endocrine pancreas, the GI tract and in the periventricular region of the hypothalamus.[18] In CNS SS acts as an inhibitory and modulatory neuropeptide often co-expressed and co-released with GABA.[19] SS deficiency have been linked to depression, since it affects physiological and behavioural stress responses, induces serotonin release, is associated with BNDF levels, and exhibits general inhibitory effects.[18,19]
β-endorphin	β-endorphin is an endogenous opioid receptor agonist produced in the hypothalamus and pituitary gland while peripherally released by leukocytes in response to inflammation. Alterations in β-endorphin levels are suggested to play a role in depression through effects on HPA axis regulation, stress-induced analgesia and anti-nociception besides mood-enhancing and anxiolytic effects.[20]
Dynorphin A 1-8	Dynorphin A1-8 is an endogenous opioid receptor agonist and part of the dynorphin family. Dynorphin release is triggered by stress. Both dynorphin and opioid receptors are expressed throughout brain areas related to depression, fear and anxiety.[21]
Substance P	Substance P is a neuropeptide from the family of neurokinins. SP is expressed widely in the CNS and is often co-localized with serotonin, noradrenalin and dopamine. The potential role of SP in depression depends on its modulation of serotonergic and noradrenergic systems, as well its immunomodulating role within the CNS.[22]
Neuropeptide tyrosine (NPY), Peptide YY (PYY)	NPY belongs to a family of pancreatic polypeptides also including PYY. NPY is densely expressed in hippocampus and amygdala, and is associated with memory, anxiety and stress responses. Clinical studies have implied NPY to decrease in patients with depression and to increase with antidepressant treatment, but results are ambiguous.[23]
Cocaine- and amphetamine-regulated transcript **(**CART)	CART is a brain-enriched mRNA, but the term CART is also used for the peptide product of CART, which applies here. CART is a neuropeptide expressed in the limbic structures, such as: amygdala, hypothalamus, hippocampus and nucleus accumbens, which are believed to regulate energy homeostasis, anxiety, addiction and mood.[24,25]
Galanin	Galanin is a neuropeptide co-localized with serotonin in the dorsal raphe nucleus and with noradrenalin in the locus coeruleus. Knowledge of the physiological role of galanin is still very limited, but it is suggested a potential target of antidepressant treatment due to interactions with monoaminergic neurotransmitters.[26]
G27 / DAOA	G72 is a D-amino acid oxidase activator (DAOA). The impact of G72 in depression is still unrevealed.[27,28]
Diazepam binding inhibitor (DBI)	DBI is a neuropeptide located in GABA-containing neurons. DBI's role in depression is believed to rely on its inhibition of GABAergic neurotransmission.[29]
Hypocretin-1 / orexin	Hypocretin-1, also known as orexin, is a neuropeptide synthesized in the hypothalamus. It is involved in several brain activities including sleep-wake-regulation, arousal, reward, and emotion. Studies have implied hypocretin-1 to be involved in depression by stimulation of GABAergic neurotransmission affecting stress responses.[30]
Cyclic adenosine monophosphate (cAMP), Cyclic guanosine monophosphate (cGMP)	cAMP and cGMP are second messengers important for signal transduction in many organs. In the CNS they are implied to affect neuroplasticity and thus play a role in the pathophysiology of depression.[31]
Amino acids and derivates	
Tryptophan, Tyrosine, Serine, L-serine, D-serine, Glycine, Alanine, Aspartate, Methionine, Phenylalanine, Asparagine, Arginine, Threonine, Valine, Isoleucine, Leucine, Ornithine, Lysine, Cystine, Histidin + 1-methylhistidin, Tyramine,	Amino acids, derivates and metabolites are small molecules with various functions and suggested relations to depression. The amino acid tryptophan is the precursor of both serotonin and kynurenine,[1] whereas the amino acid tyrosine is the precursor of dopamine[4] and norepinephrine. Reduced CSF levels of these amino acid can result in reduction of the important downstream products. Some amino acids might exert an influence on other transmitter systems, e.g. both glycine[32] and D-serine[33] being functional co-agonists of the anti-N-methyl-D-aspartate receptor (NMDAR). However the final effect hereof remains ambiguous, and D-serine is suggested both to have

Phosphoethanolamine, Ethanolamine, α-amino-butyrate, Carnosine	antidepressant-like effects,[34] but also to cause excitotoxicity and contribute to neurodegeneration.[35] In animal studies L-serine have been indicated to induce antidepressant-like behaviour by activation of GABA-A receptors.[36] However, the impact of most of the amino acids (alanine, aspartate, methionine, phenylalanine, asparagine, arginine, threonine, valine, isoleucine, leucine, ornithine, lysine, cystine, histidine) and derivates (tyramine, α-amino-butyrate**,** 1-methylhistidin, ethanolamine, phosphoethanolamine, carnosine) on depression pathophysiology has still to be elucidated.
Inflammation and blood brain barrier permeability	
Inflammatory markers	
White cell count **(**WCC)	WCC comprises the number of neutrophil granulocytes, monocytes and lymphocytes in the CSF and is an unspecific marker of inflammation in the brain. Normally WCC is under 5 cells/mL, but during neuro-infections numbers can increase, termed pleocytosis.[37]
Pro-inflammatory cytokines (IL-1, IL-1β, IL-6, IL-8, IL-12 (p40), IL-19, IL-26, IL-29/IFN-λ1, TNF-α)	These cytokines primarily possess pro-inflammatory properties, that has been suggested to induce a 'sickness behaviour' in patients with depression and increased levels in blood and CSF are repeatedly associated with depression.[38] Interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α) both activates the HPA axis,[39,40] reduce monoamine availability by up-regulating presynaptic reuptake pumps for 5-HT, NE and DA and reduce levels of BDNF.[38] IL-1β and IL-19[41] stimulates the synthesis of other proinflammatory cytokines such as IL-6 and TNF-α,[39] whereas IL-6 and TNF-α promotes chronic inflammation.[4243] IL-8 enhances chemotaxis and diapedesis of leukocytes,[44] and IL-12 increases activity of natural killer cells.[45] IL-29/ IFN-λ1 is one out of three cytokines summarized as INF-λ[46] and both IL-29 and IL-26 held diverse proinflammatory functions.[46,47]
Anti-inflammatory cytokines (IL-10, IL-11)	IL-10 is an anti-inflammatory cytokine released by Th2 cells. It inhibits both the innate and adaptive immune responses, hereby reducing tissue damage. It has been associated with autoimmune disorders.[48] IL-11 has various functions with primarily anti-inflammatory properties[49] and also promotes neuronal differentiation.[50]
Soluble cytokine receptors (sIL-6 receptor, sTNF-α receptor 1 and 2)	The sIL-6-receptor binds in a complex with IL-6 and the protein gp130 and this complex initiates intracellular signaling mediating the effect of IL-6.[51] The sTNF-receptor 1 and 2 functions depending on their concentration relative to TNF-α; either by blocking TNF-α binding and functioning or by enhancing the action of TNF-α.[52]
IFN-α2, IFN-β	IFN-α2 and IFN-β are both type 1 interferons and major components of the innate immune response. The type 1 IFNs exhibit a broad range of actions on multiple immune cells including stimulation of cytotoxicity, apoptosis and differentiation.[53]
Thymic stromal lymphopoietin **(**TSLP)	TSLP is a cytokine primarily expressed by epithelial cells in the skin, intestines, thymus and lungs, but also by stromal and mast cells. TSLP expression is induced by several factors including infections and pro-inflammatory mediators (e.g. TLR, IL-1β, TNF-α). TSLP functions on different immune cells, but evidence suggest a particularly critical role in Th2 cell differentiation.[54]
sCD163, sCD30/TNFSF8	sCD163 and sCD30 are soluble variants of the membrane proteins CD163 and CD30 expressed by macrophages/monocytes and T-cells, B-cells and natural killer cells respectively. Both the shedding of sCD163 and sCD30 are induced by toll like receptor (TLR) activation similar to the shedding of TNF-α, and the levels of sCD163 and sCD30 increase acutely during inflammation and macrophage activation.[55,56]
A proliferation-inducing ligand (APRIL)/TNFSF13, B-cell activating factor (BAFF)/TNFSF13B	APRIL and BAFF are two members of the tumor necrosis factor superfamily (TNFSF). The overall function is still discussed, but BAFF regulates B-cell homeostasis and autoimmunity, while APRIL is involved in both B- and T-cell responses.[57]
Glial fibrillary acidic protein (GFAp)	GFAp is an intermediate filament protein in astrocytes and important for both motility, mitosis and synaptic plasticity. Traditionally GFAp is a marker of astrocyte destruction associated with neurodegeneration, brain damage and aging. Due to novel findings of several isotypes, the exact functions of such different isoforms are still to be investigated.[58]

Myelin basic protein (MBP)	MBP is expressed in oligodendrocytes and is essential to the formation of myelin sheets in CNS. MBP in the CSF is thus a presumed marker of white matter degeneration[59] and thought to induce neuroinflammation and neuronal damage.[60]
Osteocalcin	Osteocalcin is a bone-derived protein secreted by osteoclasts, but the knowledge of osteocalcin's function in the CNS is sparse. However, it is able to cross the BBB and is suggested to affect the synthesis of both monoamines and GABA[61] and could hereby be involved in depression pathophysiology.
C3, C5	The complement system is an integral feature of the innate immune system and suggested to be involved in synaptic plasticity.[62] Initiation of the cascade includes both the complement factor C3 and C5. By their cleavage anaphylatoxins are split off increasing blood vessel permeability and inducing chemotaxis.[63]
Autotaxin (ATX), Lysophosphatidic acid (LPA)	ATX is an enzyme expressed in both the brain and peripheral tissues converting extracellular lysophosphatidyl choline to LPA. LPA is involved in brain immune responses and in synaptic transmission. Blocking of LPA receptors in mice have caused depressive-like behaviour, and the LPA receptor is suggested a target for antidepressants. Since LPA is unstable, ATX can be used as a proxy of LPA levels.[64]
sCD44, Hyaluronic acid (HA)	sCD44 is the soluble variant of the adhesion molecule CD44 and is primarily expressed by microglia, astrocytes and some neurons. CD44 is assumed to induce inflammation by increasing gene expression in leukocytes and parenchymal cells. CD44 is the primary receptor for HA; a glycosaminoglycan and a central element in the extracellular matrix (ECM) in the CNS.[65]
Osteopontin (OPN)	OPN is a matricellular protein involved in inflammation by acting as a chemical attractant for inflammatory cells as well as regulating macrophage and T-cell activity and thereby OPN modulates both acute and chronic immune responses.[66]
Magnesium	Magnesium is an essential mineral, known to be involved in the cardiovascular, alimentary, endocrine and osteoarticular systems. Magnesium also affect neuronal biochemistry and deficiency can cause both psychiatric and neuromuscular symptoms. Some evidence has linked depression to magnesium deficiency and supplements can reduce depressive symptoms.[67]
Pro-inflammatory chemokines (Eotaxin-1/CCL11, Interferon gamma-induced protein-10 (IP-10)/CXCL10, Macrophage inflammatory protein-1ß (MIP-1ß)/CCL4, Monocyte chemotactic protein 1 (MCP-1)/CCL2 and 4 (MCP-4)/CCL13, Thymus activation regulated chemokine (TARC)/CCL17)	Chemokines are a superfamily consisting of ligands and their receptors and is divided into inflammatory and homeostatic chemokines based on their function.[68] Eotaxin-1/CCL11, IP-10/CXCL-10, MIP-1ß/CCL4, MCP-1/CCL2, MCP-4/CCL13 and TARC/CCL17 are all inflammatory chemokines. They are upregulated during inflammation and known to induce migration of immune cells to inflamed sites. However, for some chemokines the function and thus division is more diffuse.[69] In the CNS chemokines regulates axonal growth, cell migration and neuronal survival, but are also suggested to affect neurotransmission and neuron-glia interaction.[70]
MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-10	Matrix metalloproteinases (MMPs) are proteolytic enzymes. In the CNS they are expressed by astrocytes, microglia and neurons.[71] MMPs are important for both neuronal plasticity and modulation of inflammatory processes.[72] Elevated levels cause neuronal injury.[71]
Acetylcholinesterase (AChE), Butyrylcholinesterase (BChE)	AChE and BChE are both cholinergic enzymes catalysing the breakdown of the neurotransmitter acetylcholine. Increased central cholinergic activity is suggested to have an anti-inflammatory effect, whereas a reduction – due to for example AChE and BChE – may increase both central and peripheral inflammation.[73]
The kynurenic pathway	
Kynurenine	Kynurenine is a metabolite of tryptophan. Chronic stress and inflammation can shunt tryptophan metabolism towards the kynurenine pathway by inducing the enzymes IDO and TDO, and hereby decreasing the availability of this precursor of serotonin.[1,38]
Quinolinic acid (QUIN), Kynurenic acid (KYNA), Picolinic acid (PIC)	QUIN, KYNA and PIC are metabolites of kynurenine.**Error! Bookmark not defined.** QUIN is an NMDA agonist assumed to be neurotoxic through stimulation of glutamate release and simultaneous block of the reuptake, leading to increased extra-synaptic glutamate

	levels.[38] KYNA, mainly produced by astrocytes, is an NMDA antagonist with neuroprotective properties.[1] PIC is likewise neuroprotective by antagonizing the effect of QUIN.[74] Imbalance between these neuroprotective and neurodegenerative metabolites are suggested to be involved in stress coping and depression.[1]
Tryptophol	Tryptophol is another metabolite of tryptophan. It is suggested to play a role in physiological sleep mechanisms.[75]
Blood-brain-barrier permeability	
Total protein, albumin, albumin ratio, IgG, IgG ratio, IgG index	The CSF to serum ratios of both albumin and IgG are commonly accepted indicators of blood-brain-barrier (BBB) function.[76] Increased CSF total protein is normally caused by BBB dysfunction and increased permeability.[77] Increased IgG ratio can also be caused by intrathecal synthesis due to CNS inflammation, and to discriminate BBB dysfunction from intrathecal synthesis the IgG index is used.[78] Increased BBB permeability has been associated with depression.[79]
Fibrinogen, SL000022, SL0000424, SL003341	Fibrinogen is the main coagulation protein in the blood. Besides importance for blood clotting, it is also involved in inflammation and angiogenesis. SL000022, SL0000424 and SL003341 are fibrinogen related molecules representing D-dimer, fibrinogen and fibrinogen y-chain respectively. An increased level of fibrinogen in CSF has been linked to depression as a suggested marker of increased BBB permeability or as a result of local hypercoagulation in the brain; so-called "vascular depression".[80]
Glucose, sorbitol	Glucose is a simple monosaccharide, a subcategory of carbohydrates, and sorbitol is a sugar alcohol made from reduction of glucose. The incidence of glucose intolerance, insulin resistance and diabetes are more frequent in patients with depression, which have led to speculations that an abnormal carbohydrate metabolism and thus a parallel neural neuropathy might be involved in depression.[81]
Neurodegeneration and synaptic plasticity	
Neurodegeneration	
Tau, p-tau 181, p-tau 213	Tau proteins are a group of microtubule-associated proteins that are associated with cytoskeletal functioning in neurons.[82] Specific phosphorylation of tau is important for correct functioning, and abnormal phosphorylation can lead to dysfunction and decreased cell viability.[83] Tau can be phosphorylated on several sites including threonine 181 (p-tau 181) and 231 (p-tau 231). Misfolding of the protein is suggested to play a role in the pathogenesis of Alzheimer's disease (AD),[82] and since depression is a risk factor for future AD and can occur as an early symptom of AD, it has also become a field of interest in depression research.[84]
AβPP	Amyloid-β precursor protein (AβPP) is an integral membrane protein with high expression in the synapses of neurons. It is involved in synaptic formation and repair, as well as anterograde neuronal transport.[85]
Soluble AβPP alfa protein (sAβPPα) and soluble AβPP beta protein (sAβPPβ)	sAβPPα and sAβPPβ are released from the cleavage of APP by α- and β-secretase, respectively. Hence they reflect the turnover from AβPP to Aβ, whereas sAβPPα is also suggested to have proliferative and neuroprotective properties.[86]
Amyloid-β (Aβ), Amyloid-β-42 (Aβ42), Amyloid-β-40 (Aβ40), Amyloid-β-38 (Aβ38)	Aβ is a heterogeneous mix of small peptides (from 36 to 43 amino acids) derived from cleavage of the APP. Aβ is normally secreted from cells and degraded, but in AD an abnormal accumulation in the brain leads to insoluble plaques. Aβ42, Aβ40 and Aβ38 are isotypes of Aβ consisting of 42, 40 and 38 amino acids respectively. Aβ42 is the dominating isotype in the brain.[85]
Neurogranin	Neurogranin is a postsynaptic protein expressed in the CNS. It is a marker of synaptic loss connected to cognitive decline and shown to be increased in AD.[87]
α-synuclein (α-Syn)	α-Syn is a presynaptic protein expressed in CNS. It is aggregated to form Levi bodies that play an important role in Parkinson disease and dementia.[88] α-Syn is also suggested to be implicated in the pathophysiology of depression and higher plasma levels of α-Syn has been reported in patients with MDD compared to controls.[89]

Neurofilament light protein (NfL)	NfL is a cytoskeletal protein only expressed by central and peripheral neurons. In CSF NfL reflects neuroaxonal damage which has shown to be elevated in several neurological diseases such as AD and ALS,[90] and recent evidence implies that axonal damage might also play a role in depression.[91]
Nervonic acid	Nervonic acid is an omega-9 fatty acid central in the composition of sphingomyelin, a key component of myelin. As a part of the metabolic pathway of myelin, increased levels of nervonic acid is suggested to reflect neural degeneration and decreased neurogenesis.[92]
Synaptic plasticity	
Glial cell-derived neurotrophic factor (GDNF)	GDNF supports differentiation, development and protection of neurons, especially the dopaminergic subtype. It has been suggested that chronic stress decrease GDNF expression in hippocampus and reduced plasma levels of GDNF is associated with cognitive dysfunction in patients with depression.[93]
Brain-derived neurotrophic factor (BDNF)	BDNF is a secretory protein primarily expressed by neurons in the CNS. It is involved in neurogenesis, synaptic plasticity, the modulating of neurotransmission, and affects neuronal death and survival. Expression of BDNF can be regulated by stress, diet and physical activity, and lower levels of BNDF in CNS is repeatedly found in patients with major depression.[94]
Neural cell adhesion molecule (NCAM)	NCAM is a synaptic membrane glycoprotein expressed in neurons and astrocytes. It is a member of the immunoglobulin superfamily. NCAM mediates signal transduction, cell-to-cell adhesion and affects synaptic plasticity.[95]
ErbB3	ErbB3 is a tyrosine kinase receptor and part of the growth factor receptor (EGFR) family. ErbB3 is important for neuroplasticity, due to its involvement in oligodendroglia differentiation and myelination. Lower levels have been found in blood? CSF? from patients with depression.[96]
Hepatocyte growth factor (HGF) and HGF receptor	HGF was originally identified as a potent mitogen for hepatocytes, but also contribute substantial to the CNS promoting angiogenesis, survival of neurons, and regeneration and guiding of axons.[97]
S100 calcium-binding protein (S100B)	S100B is a neurotrophic factor synthesized in the astrocytes and involved in neuroplasticity.[98]
Vascular endothelia growth factor (VEGF) receptor 1 and 2	VEGF is a mitogen and survival factor for endothelial cells, and in CNS it affects neurogenesis, cell survival and synaptic plasticity. Antidepressant treatment can induce VEGF expression, implying that VEGF might play a role in depression pathophysiology.[99]
Contactin-1	Contactin-1 is a soluble cell adhesion protein expressed on axons and reported to be involved in myelin formation. Contactin-1 is thus thought to reflect axonal dysfunction.[100]
Neuropilin-1	Neuropilin-1 is a co-receptor for several growth factors including VEGF and HGF and exhibit numerous functions, including angiogenesis, immunity and axonal guiding.[101]
YKL-40 / chitinase-3-like protein 1 (CHI3L1)	YKL-40, also known as CHI3L1, is a glycoprotein suggested to be involved in angiogenetic processes and tissue remodeling during inflammation. In the CNS YKL-40 is primarily expressed by microglia and astrocytes during neuroinflammation.[102]
Growth-associated protein-43 (GAP-43)	GAP-43 plays a role in synaptic plasticity, neuronal morphology and communication. It is implied to be a marker of neurodegeneration and compromised neuronal plasticity.[60]
Soluble triggering receptor expressed on myeloid cells 2 (sTREM2)	TREM2 is expressed on microglia, and when shedded it form sTREM2. TREM2 signaling regulates microglial activity, and dysregulated microglial function have been associated with psychiatric disease.[103]

ABBREVIATIONS

5-HT	5-hydroxytryptamine
5-HIAA	5-hydroxyindole-acetic acid
Aβ	Amyloid-β
AβPP	Amyloid-β precursor protein
ACTH	Adrenocorticotropic hormone
ADH	Antidiuretic hormone
α-Syn	α-synuclein
ATX	Autotaxin
APRIL	A proliferation-inducing ligand
AVP	Arginine-vasopressin
BAFF	B-cell activating factor
BBB	Blood-brain-barrier
BDNF	Brain-derived neurotrophic factor
CART	Cocaine- and amphetamine-regulated transcript
cAMP	Cyclic adenosine monophosphate
cGMP	Cyclic guanosine monophosphate
CHI3L1	Chitinase-3-like protein 1
CRF	Corticotropin releasing factor
CRH	Corticotropin releasing hormone
DA	Dopamine
DBI	Diazepam binding inhibitor
GABA	γ-aminobutyric acid
GAP-43	Growth-associated protein-43
GDNF	Glial cell-derived neurotrophic factor
GFAp	Glial fibrillary acidic protein
HA	Hyaluronic acid
HGF	Hepatocyte growth factor
HPA axis	Hypothalamic-pituitary-adrenal axis
HVA	Homovanillic acid
IFN	Interferon
IP-10	Interferon gamma-induced protein-10
KYNA	Kynurenic acid
L-DOPA	Dihydroxyphenylalanine
LPA	Lysophosphatidic acid
MBP	Myelin basic protein
MCP	Monocyte chemotactic protein
MHPG	Methoxy-4-hydroxyphenylglycol
MIP-1ß	Macrophage inflammatory protein-1ß
MMP	Matrix metalloproteinase
NA	Noradrenaline
NCAM	Neural cell adhesion molecule
NE	Norepinephrine
NfL	Neurofilament light protein
NPY	Neuropeptide tyrosine
OPN	Osteopontin
OT	Oxytocin
PEA	Phosphoethanolamine
PIC	Picolinic acid
PYY	Peptide YY
sAβPPα	Soluble AβPP alfa protein
sAβPPβ	Soluble AβPP beta protein
S100B	S100 calcium-binding protein
SS	Somatostatin
TARC	Thymus activation regulated chemokine
TLR	Toll like receptor
TNF-α	Tumor necrosis factor-alpha
TNFSF	Tumor necrosis factor superfamily
TSLP	Thymic stromal lymphopoietin
TTR	Transthyretin
VEGF	Vascular endothelia growth factor
QUIN	Quinolinic acid

REFERENCES

1. Höglund E, Øverli Ø, Winberg S. Tryptophan Metabolic Pathways and Brain Serotonergic Activity: A Comparative Review. Front Endocrinol (Lausanne). 2019;10:158. doi:10.3389/fendo.2019.00158
2. Haase J, Brown E. Integrating the monoamine, neurotrophin and cytokine hypotheses of depression--a central role for the serotonin transporter? Pharmacol Ther. 2015;147:1-11. doi:10.1016/j.pharmthera.2014.10.002
3. Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. Arch Gen Psychiatry. 2007;64(3):327-337. doi:10.1001/archpsyc.64.3.327
4. Bressan RA, Crippa JA. The role of dopamine in reward and pleasure behaviour--review of data from preclinical research. Acta Psychiatr Scand Suppl. 2005;(427):14-21. doi:10.1111/j.1600-0447.2005.00540.x
5. Moret C, Briley M. The importance of norepinephrine in depression. Neuropsychiatr Dis Treat. 2011;7(SUPPL.):9-13. doi:10.2147/NDT.S19619
6. Leonard BE. Stress, Norepinephrine and Depression. Vol 26.; 2001.
7. Brunello N, Mendlewicz J, Kasper S, et al. The role of noradrenaline and selective noradrenaline reuptake inhibition in depression. Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol. 2002;12(5):461-475. doi:10.1016/s0924-977x(02)00057-3
8. Goddard AW, Ball SG, Martinez J, et al. Current perspectives of the roles of the central norepinephrine system in anxiety and depression. Depress Anxiety. 2010;27(4):339-350. doi:10.1002/da.20642
9. Luscher B, Shen Q, Sahir N. The GABAergic deficit hypothesis of major depressive disorder. Mol Psychiatry. 2011;16(4):383-406. doi:10.1038/mp.2010.120
10. Madeira C, Vargas-Lopes C, Brandão CO, et al. Elevated Glutamate and Glutamine Levels in the Cerebrospinal Fluid of Patients With Probable Alzheimer's Disease and Depression. Front psychiatry. 2018;9:561. doi:10.3389/fpsyt.2018.00561
11. Sanacora G, Treccani G, Popoli M. Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. Neuropharmacology. 2012;62(1):63-77. doi:10.1016/j.neuropharm.2011.07.036
12. Arborelius L, Owens MJ, Plotsky PM, Nemeroff CB. The role of corticotropin-releasing factor in depression and anxiety disorders. J Endocrinol. 1999;160(1):1-12. doi:10.1677/joe.0.1600001
13. Boron WF, Boulpaep EL. Medical Physiology. Third.; 2017.
14. Yang L, Zhao Y, Wang Y, et al. The Effects of Psychological Stress on Depression. Curr Neuropharmacol. 2015;13(4):494-504. doi:10.2174/1570159x1304150831150507
15. Won E, Kim Y-K. Stress, the Autonomic Nervous System, and the Immune-kynurenine Pathway in the Etiology of Depression. Curr Neuropharmacol. 2016;14(7):665-673. doi:10.2174/1570159x14666151208113006
16. Cochran DM, Fallon D, Hill M, Frazier JA. The role of oxytocin in psychiatric disorders: A review of biological and therapeutic research findings. Harv Rev Psychiatry. 2013;21(5):219-247. doi:10.1097/HRP.0b013e3182a75b7d
17. Sullivan GM, Mann JJ, Oquendo MA, Lo ES, Cooper TB, Gorman JM. Low cerebrospinal fluid transthyretin levels in depression: correlations with suicidal ideation and low serotonin function. Biol Psychiatry. 2006;60(5):500-506. doi:10.1016/j.biopsych.2005.11.022
18. Faron-Górecka A, Kuśmider M, Solich J, et al. Involvement of prolactin and somatostatin in depression and the mechanism of action of antidepressant drugs. Pharmacol Rep. 2013;65(6):1640-1646. doi:10.1016/s1734-1140(13)71525-1
19. Lin LC, Sibille E. Reduced brain somatostatin in mood disorders: A common pathophysiological substrate and drug target? Front Pharmacol. 2013;4 SEP. doi:10.3389/fphar.2013.00110
20. Hegadoren KM, O'Donnell T, Lanius R, Coupland NJ, Lacaze-Masmonteil N. The role of beta-endorphin in the pathophysiology of major depression. Neuropeptides. 2009;43(5):341-353. doi:10.1016/j.npep.2009.06.004
21. Knoll AT, Carlezon WAJ. Dynorphin, stress, and depression. Brain Res. 2010;1314:56-73. doi:10.1016/j.brainres.2009.09.074
22. Schwarz MJ, Ackenheil M. The role of substance P in depression: Therapeutic implications. Dialogues Clin Neurosci. 2002;4(1):21-29. doi:10.31887/dcns.2002.4.1/mschwarz
23. Morales-Medina JC, Dumont Y, Quirion R. A possible role of neuropeptide Y in depression and stress. Brain Res. 2010;1314:194-205. doi:10.1016/j.brainres.2009.09.077
24. Pae C-U, Lee C, Paik I-H. Therapeutic implication of cocaine- and amphetamine-regulated transcript (CART) in the treatment of depression. Med Hypotheses. 2007;69(1):132-135. doi:10.1016/j.mehy.2006.11.009
25. Brundin L, Björkqvist M, Träskman-Bendz L, Petersén A. Cocaine and amphetamine regulated transcript (CART) in

suicide attempters. Psychiatry Res. 2008;158(2):117-122. doi:10.1016/j.psychres.2007.06.031

26. Ögren SO, Kuteeva E, Ḧokfelt T, Kehr J. Galanin receptor antagonists: A potential novel pharmacological treatment for mood disorders. CNS Drugs. 2006;20(8):633-654. doi:10.2165/00023210-200620080-00003

27. Ishiwata S, Hattori K, Sasayama D, et al. Plasma and cerebrospinal fluid G72 protein levels in schizophrenia and major depressive disorder. Psychiatry Res. 2017;254:244-250. doi:10.1016/j.psychres.2017.04.060

28. Rietschel M, Beckmann L, Strohmaier J, et al. G72 and Its Association With Major Depression and Neuroticism in Large Population-Based Groups From Germany. Am J Psychiatry. 2008;165(6):753-762. doi:10.1176/appi.ajp.2008.07060883

29. Barbaccia ML, Costa E, Ferrero P, et al. Diazepam-Binding Inhibitor: A Brain Neuropeptide Present in Human Spinal Fluid: Studies in Depression, Schizophrenia, and Alzheimer's Disease. Arch Gen Psychiatry. 1986;43(12):1143-1147. doi:10.1001/archpsyc.1986.01800120029007

30. Ji MJ, Zhang XY, Chen Z, Wang JJ, Zhu JN. Orexin prevents depressive-like behavior by promoting stress resilience. Mol Psychiatry. 2019;24(2):282-293. doi:10.1038/s41380-018-0127-0

31. W. Reierson G, Guo S, Mastronardi C, Licinio J, Wong M-L. cGMP Signaling, Phosphodiesterases and Major Depressive Disorder. Curr Neuropharmacol. 2011;9(4):715-727. doi:10.2174/157015911798376271

32. Johnson JW, Ascher P. Glycine potentiates the NMDA response in cultured mouse brain neurons. Nature. 1987;325(6104):529-531. doi:10.1038/325529a0

33. Wolosker H, Radzishevsky I. The serine shuttle between glia and neurons: Implications for neurotransmission and neurodegeneration. Biochem Soc Trans. 2013;41(6):1546-1550. doi:10.1042/BST20130220

34. Malkesman O, Austin DR, Tragon T, et al. Acute d-serine treatment produces antidepressant-like effects in rodents. Int J Neuropsychopharmacol. 2012;15(8):1135-1148. doi:10.1017/S1461145711001386

35. Wolosker H, Radzishevsky I. The serine shuttle between glia and neurons: implications for neurotransmission and neurodegeneration. Biochem Soc Trans. 2013;41(6):1546-1550. doi:10.1042/BST20130220

36. Nagasawa M, Otsuka T, Togo Y, et al. Single and chronic l-serine treatments exert antidepressant-like effects in rats possibly by different means. Amino Acids. 2017;49(9):1561-1570. doi:10.1007/s00726-017-2448-8

37. Martínez-Girón R, Pantanowitz L. Cerebrospinal fluid cytology in nonmalignant aseptic meningeal disorders. Diagn Cytopathol. 2017;45(11):1020-1029. doi:10.1002/dc.23797

38. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat Rev Immunol. 2016;16(1):22-34. doi:10.1038/nri.2015.5

39. Iwata M, Ota KT, Duman RS. The inflammasome: pathways linking psychological stress, depression, and systemic illnesses. Brain Behav Immun. 2013;31:105-114. doi:10.1016/j.bbi.2012.12.008

40. Dunn AJ. Cytokine activation of the HPA axis. In: Annals of the New York Academy of Sciences. Vol 917. New York Academy of Sciences; 2000:608-617. doi:10.1111/j.1749-6632.2000.tb05426.x

41. Liao Y-C, Liang W-G, Chen F-W, Hsu J-H, Yang J-J, Chang M-S. IL-19 induces production of IL-6 and TNF-alpha and results in cell apoptosis through TNF-alpha. J Immunol. 2002;169(8):4288-4297. doi:10.4049/jimmunol.169.8.4288

42. Gabay C. Interleukin-6 and chronic inflammation. Arthritis Res Ther. 2006;8 Suppl 2(Suppl 2):S3. doi:10.1186/ar1917

43. Landskron G, De La Fuente M, Thuwajit P, Thuwajit C, Hermoso MA. Chronic inflammation and cytokines in the tumor microenvironment. J Immunol Res. 2014;2014. doi:10.1155/2014/149185

44. Baggiolini M, Walz A, Kunkel SL. Neutrophil-activating peptide-1/interleukin 8, a novel cytokine that activates neutrophils. J Clin Invest. 1989;84(4):1045-1049. doi:10.1172/JCI114265

45. Trinchieri G. Interleukin-12: A proinflammatory cytokine with immunoregulatory functions that bridge innate resistance and antigen-specific adaptive immunity. Annu Rev Immunol. 1995;13:251-276. doi:10.1146/annurev.iy.13.040195.001343

46. Kelm NE, Zhu Z, Ding VA, et al. The role of IL-29 in immunity and cancer. Crit Rev Oncol Hematol. 2016;106:91-98. doi:10.1016/j.critrevonc.2016.08.002

47. Stephen-Victor E, Fickenscher H, Bayry J. IL-26: An Emerging Proinflammatory Member of the IL-10 Cytokine Family with Multifaceted Actions in Antiviral, Antimicrobial, and Autoimmune Responses. PLoS Pathog. 2016;12(6):e1005624. doi:10.1371/journal.ppat.1005624

48. Ouyang W, Rutz S, Crellin NK, Valdez PA, Hymowitz SG. Regulation and functions of the IL-10 family of cytokines in inflammation and disease. Annu Rev Immunol. 2011;29:71-109. doi:10.1146/annurev-immunol-031210-101312

49. Janssens K, Slaets H, Hellings N. Immunomodulatory properties of the IL-6 cytokine family in multiple sclerosis. Ann N Y Acad Sci. 2015;1351:52-60. doi:10.1111/nyas.12821

50. Gurfein BT, Zhang Y, López CB, et al. IL-11 regulates autoimmune demyelination. J Immunol. 2009;183(7):4229-4240. doi:10.4049/jimmunol.0900622

51. Rose-John S. IL-6 trans-signaling via the soluble IL-6 receptor: importance for the pro-inflammatory activities of IL-6. Int J Biol Sci. 2012;8(9):1237-1247. doi:10.7150/ijbs.4989

52. Waetzig GH, Rosenstiel P, Arlt A, et al. Soluble tumor necrosis factor (TNF) receptor-1 induces apoptosis via reverse TNF signaling and autocrine transforming growth factor-beta1. FASEB J Off Publ Fed Am Soc Exp Biol. 2005;19(1):91-93. doi:10.1096/fj.04-2073fje

53. Pestka S, Krause CD, Walter MR. Interferons, interferon-like cytokines, and their receptors. Immunol Rev. 2004;202:8-32. doi:10.1111/j.0105-2896.2004.00204.x

54. He R, Geha RS. Thymic stromal lymphopoietin. Ann N Y Acad Sci. 2010;1183:13-24. doi:10.1111/j.1749-6632.2009.05128.x

55. Møller HJ. Soluble CD163. Scand J Clin Lab Invest. 2012;72(1):1-13. doi:10.3109/00365513.2011.626868

56. Velásquez SY, García LF, Opelz G, Alvarez CM, Süsal C. Release of soluble CD30 after allogeneic stimulation is mediated by memory T cells and regulated by IFN-γ and IL-2. Transplantation. 2013;96(2):154-161. doi:10.1097/TP.0b013e318296fd69

57. Stein J V, López-Fraga M, Elustondo FA, et al. APRIL modulates B and T cell immunity. J Clin Invest. 2002;109(12):1587-1598. doi:10.1172/JCI15034

58. Middeldorp J, Hol EM. GFAP in health and disease. Prog Neurobiol. 2011;93(3):421-443. doi:10.1016/j.pneurobio.2011.01.005

59. Bjerke M, Zetterberg H, Edman Å, Blennow K, Wallin A, Andreasson U. Cerebrospinal fluid matrix metalloproteinases and tissue inhibitor of metalloproteinases in combination with subcortical and cortical biomarkers in vascular dementia and Alzheimer's disease. J Alzheimers Dis. 2011;27(3):665-676. doi:10.3233/JAD-2011-110566

60. Rymo I, Kern S, Bjerke M, et al. CSF YKL-40 and GAP-43 are related to suicidal ideation in older women. Acta Psychiatr Scand. 2017;135(4):351-357. doi:10.1111/acps.12701

61. Oury F, Khrimian L, Denny CA, et al. Maternal and Offspring Pools of Osteocalcin Influence Brain Development and Functions. Cell. 2013;155:228-241. doi:10.1016/j.cell.2013.08.042

62. Pillai A, Bruno D, Nierenberg J, et al. Complement component 3 levels in the cerebrospinal fluid of cognitively intact elderly individuals with major depressive disorder. Biomarkers in neuropsychiatry. 2019;1. doi:10.1016/j.bionps.2019.100007

63. Holm CK. Immunologi. First edit.; 2017.

64. Itagaki K, Takebayashi M, Abe H, et al. Reduced Serum and Cerebrospinal Fluid Levels of Autotaxin in Major Depressive Disorder. Int J Neuropsychopharmacol. 2019;22(4):261-269. doi:10.1093/ijnp/pyz005

65. Ventorp F, Barzilay R, Erhardt S, et al. The CD44 ligand hyaluronic acid is elevated in the cerebrospinal fluid of suicide attempters and is associated with increased blood-brain barrier permeability. J Affect Disord. 2016;193:349-354. doi:10.1016/j.jad.2015.12.069

66. Lund SA, Giachelli CM, Scatena M. The role of osteopontin in inflammatory processes. J Cell Commun Signal. 2009;3(3-4):311-322. doi:10.1007/s12079-009-0068-0

67. Serefko A, Szopa A, Wlaź P, et al. Magnesium in depression. Pharmacol Reports. 2013;65(3):547-554. doi:10.1016/S1734-1140(13)71032-6

68. Zlotnik A, Burkhardt AM, Homey B. Homeostatic chemokine receptors and organ-specific metastasis. Nat Rev Immunol. 2011;11(9):597-606. doi:10.1038/nri3049

69. Zlotnik A, Yoshie O. The Chemokine Superfamily Revisited. Immunity. 2012;36(5):705-716. doi:10.1016/j.immuni.2012.05.008

70. Janelidze S, Ventorp F, Erhardt S, et al. Altered chemokine levels in the cerebrospinal fluid and plasma of suicide attempters. Psychoneuroendocrinology. 2013;38(6):853-862. doi:10.1016/j.psyneuen.2012.09.010

71. Alaiyed S, Conant K. A role for matrix metalloproteases in antidepressant efficacy. Front Mol Neurosci. 2019;12:117. doi:10.3389/fnmol.2019.00117

72. Bobińska K, Szemraj J, Czarny P, Gałecki P. Expression and activity of metalloproteinases in depression. Med Sci Monit. 2016;22:1334-1341. doi:10.12659/MSM.895978

73. Pomara N, Bruno D, Plaska CR, et al. Evidence of upregulation of the cholinergic anti-inflammatory pathway in late-life depression. J Affect Disord. 2021;286:275-281. doi:10.1016/J.JAD.2021.03.012

74. Brundin L, Sellgren CM, Lim CK, et al. An enzyme in the kynurenine pathway that governs vulnerability to suicidal behavior by regulating excitotoxicity and neuroinflammation. Transl Psychiatry. 2016;6(8):e865. doi:10.1038/tp.2016.133

75. Feldstein A, Chang FH, Kucharski JM. Tryptophol, 5-hydroxytryptophol and 5-methoxytryptophol induced sleep in mice. Life Sci. 1970;9(6):323-329. doi:10.1016/0024-3205(70)90220-1

76. Reiber H, Peter JB. Cerebrospinal fluid analysis: disease-related data patterns and evaluation programs. J Neurol Sci. 2001;184(2):101-122. doi:10.1016/s0022-510x(00)00501-3

77. Breiner A, Moher D, Brooks J, et al. Adult CSF total protein upper reference limits should be age-partitioned and significantly higher than 0.45 g/L: a systematic review. J Neurol. 2019;266(3):616-624. doi:10.1007/s00415-018-09174-z

78. Simonsen CS, Flemmen HØ, Lauritzen T, Berg-Hansen P, Moen SM, Celius EG. The diagnostic value of IgG index versus oligoclonal bands in cerebrospinal fluid of patients with multiple sclerosis. Mult Scler J - Exp Transl Clin. 2020;6(1):2055217319901291. doi:10.1177/2055217319901291

79. Orlovska-waast S, Köhler-forsberg O, Wiben S, et al. Cerebrospinal fluid markers of inflammation and infections in schizophrenia and affective disorders: a systematic review and meta-analysis. Mol Psychiatry. 2019;24:869-887. doi:10.1038/s41380-018-0220-4

80. Hattori K, Ota M, Sasayama D, et al. Increased cerebrospinal fluid fibrinogen in major depressive disorder. Sci Rep. 2015;5. doi:10.1038/srep11412

81. Regenold WT, A. Kling M, Hauser P. Elevated sorbitol concentration in the cerebrospinal fluid of patients with mood disorders. Psychoneuroendocrinology. 2000;25(6):593-606. doi:10.1016/S0306-4530(00)00012-3

82. Cárdenas AM, Ardiles AO, Barraza N, Baéz-Matus X, Caviedes P. Role of tau protein in neuronal damage in Alzheimer's disease and Down syndrome. Arch Med Res. 2012;43(8):645-654. doi:10.1016/j.arcmed.2012.10.012

83. Johnson GVW, Stoothoff WH. Tau phosphorylation in neuronal cell function and dysfunction. J Cell Sci. 2004;117(Pt 24):5721-5729. doi:10.1242/jcs.01558

84. Brown EE, Iwata Y, Chung JK, Gerretsen P, Graff-Guerrero A. Tau in Late-Life Depression: A Systematic Review and Meta-Analysis. J Alzheimer's Dis. 2016;54(2):615-633. doi:10.3233/JAD-160401

85. Chen G-F, Xu T-H, Yan Y, et al. Amyloid beta: structure, biology and structure-based therapeutic development. Acta Pharmacol Sin. 2017;38(9):1205-1235. doi:10.1038/aps.2017.28

86. Chasseigneaux S, Allinquant B. Functions of Aβ, sAPPα and sAPPβ : similarities and differences. J Neurochem. 2012;120 Suppl:99-108. doi:10.1111/j.1471-4159.2011.07584.x

87. Mattsson N, Insel PS, Palmqvist S, et al. Cerebrospinal fluid tau, neurogranin, and neurofilament light in Alzheimer's disease. EMBO Mol Med. 2016;8(10):1184-1196. doi:10.15252/emmm.201606540

88. Bruno D, Reichert Plaska C, Clark DPA, et al. CSF α-synuclein correlates with CSF neurogranin in late-life depression. Int J Neurosci. 2021;131(4):357-361. doi:10.1080/00207454.2020.1744596

89. Ishiguro M, Baba H, Maeshima H, et al. Increased Serum Levels of α-Synuclein in Patients With Major Depressive Disorder. Am J Geriatr psychiatry Off J Am Assoc Geriatr Psychiatry. 2019;27(3):280-286. doi:10.1016/j.jagp.2018.10.015

90. Bridel C, van Wieringen WN, Zetterberg H, et al. Diagnostic Value of Cerebrospinal Fluid Neurofilament Light Protein in Neurology: A Systematic Review and Meta-analysis. JAMA Neurol. 2019;76(9):1035-1048. doi:10.1001/jamaneurol.2019.1534

91. Spanier S, Kilian HM, Meyer DM, Schlaepfer TE. Treatment resistance in major depression is correlated with increased plasma levels of neurofilament light protein reflecting axonal damage. Med Hypotheses. 2019;127:159-161. doi:10.1016/j.mehy.2019.03.022

92. Kageyama Y, Deguchi Y, Hattori K, et al. Nervonic acid level in cerebrospinal fluid is a candidate biomarker for depressive and manic symptoms: A pilot study. Brain Behav. 2021;11(4):e02075. doi:10.1002/BRB3.2075

93. Tsybko AS, Ilchibaeva T V, Popova NK. Role of glial cell line-derived neurotrophic factor in the pathogenesis and treatment of mood disorders. Rev Neurosci. 2017;28(3):219-233. doi:10.1515/revneuro-2016-0063

94. Lima Giacobbo B, Doorduin J, Klein HC, Dierckx RAJO, Bromberg E, de Vries EFJ. Brain-Derived Neurotrophic Factor in Brain Disorders: Focus on Neuroinflammation. Mol Neurobiol. 2019;56(5):3295-3312. doi:10.1007/s12035-018-1283-6

95. Hidese S, Hattori K, Sasayama D, et al. Cerebrospinal fluid neural cell adhesion molecule levels and their correlation with clinical variables in patients with schizophrenia, bipolar disorder, and major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2017;76:12-18. doi:10.1016/j.pnpbp.2017.02.016

96. Milanesi E, Minelli A, Cattane N, et al. ErbB3 mRNA leukocyte levels as a biomarker for major depressive disorder. BMC Psychiatry. 2012;12:145. doi:10.1186/1471-244X-12-145

97. Russo AJ. Decreased serum hepatocyte growth factor (HGF) in individuals with depression correlates with severity of disease. Biomark Insights. 2010;2010(5):63-67. doi:10.4137/bmi.s5183

98. Arolt V, Peters M, Erfurth A, et al. S100B and response to treatment in major depression: A pilot study. Eur Neuropsychopharmacol. 2003;13(4):235-239. doi:10.1016/S0924-977X(03)00016-6

99. Warner-Schmidt JL, Duman RS. VEGF as a Potential Target for Therapeutic Intervention in Depression. http://www.cdc.gov/nchs/pressroom/04news/hus04.htm. Accessed June 11, 2021.

100. Chatterjee M, Koel-Simmelink MJ, Verberk IM, et al. Contactin-1 and contactin-2 in cerebrospinal fluid as potential biomarkers for axonal domain dysfunction in multiple sclerosis. Mult Scler J - Exp Transl Clin. 2018;4(4):2055217318819535. doi:10.1177/2055217318819535

101. Prud'homme GJ, Glinka Y, Lichner Z, Yousef GM. Neuropilin-1 is a receptor for extracellular miRNA and AGO2/miRNA complexes and mediates the internalization of miRNAs that modulate cell function. Oncotarget. 2016;7(42):68057-68071. doi:10.18632/ONCOTARGET.10929

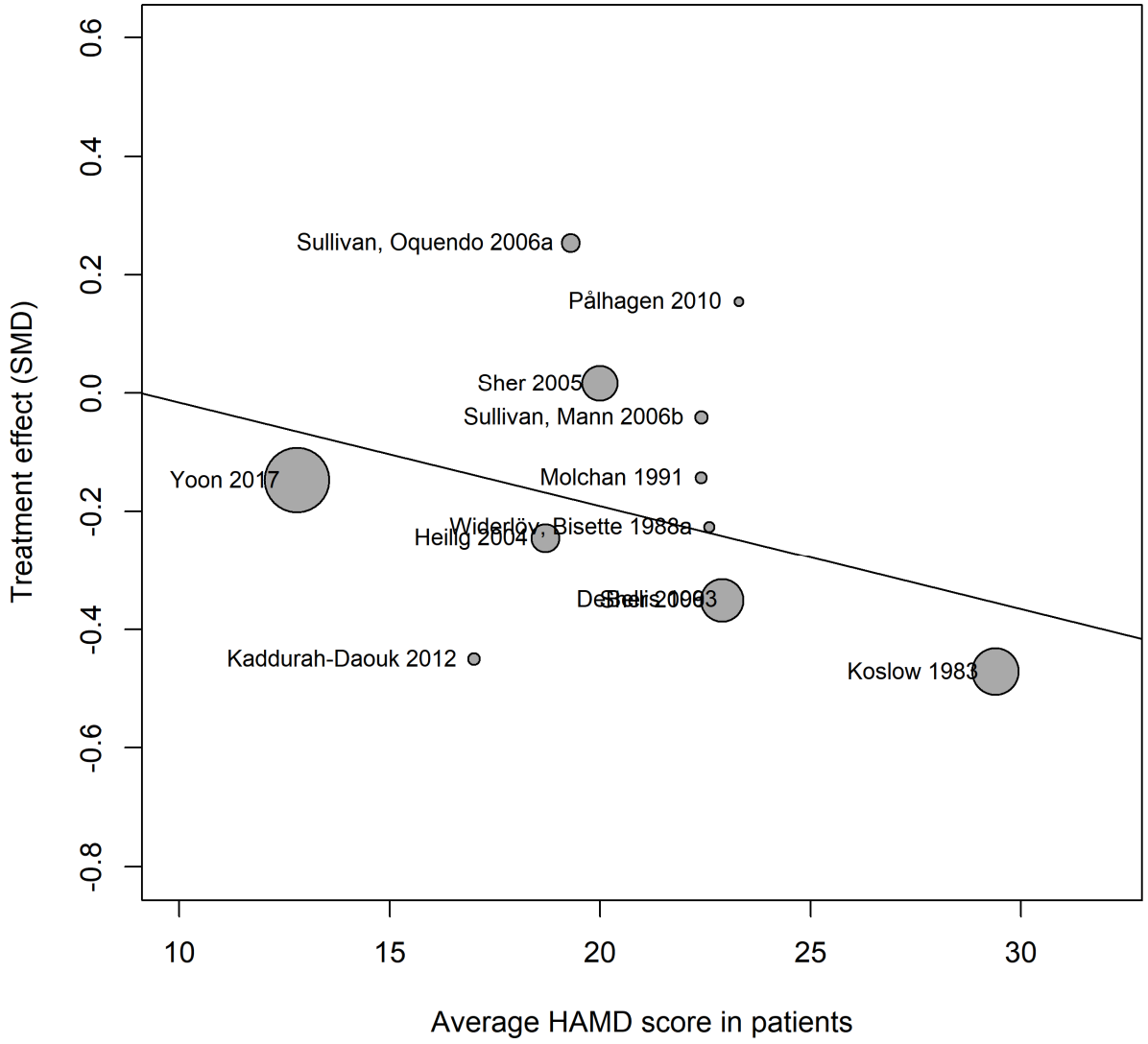
102. Llorens F, Thüne K, Tahir W, et al. YKL-40 in the brain and cerebrospinal fluid of neurodegenerative dementias. Mol Neurodegener. 2017;12(1):83. doi:10.1186/s13024-017-0226-4

103. Konishi H, Kiyama H. Non-pathological roles of microglial TREM2/DAP12: TREM2/DAP12 regulates the physiological functions of microglia from development to aging. Neurochem Int. 2020;141:104878. doi:10.1016/J.NEUINT.2020.104878

Subgroup analyses

eFigure 7 | Meta-regression analyses of mean biomarker levels in relation to mean HAM-D scores for patients. Performed on biomarkers with data for ≧10 studies

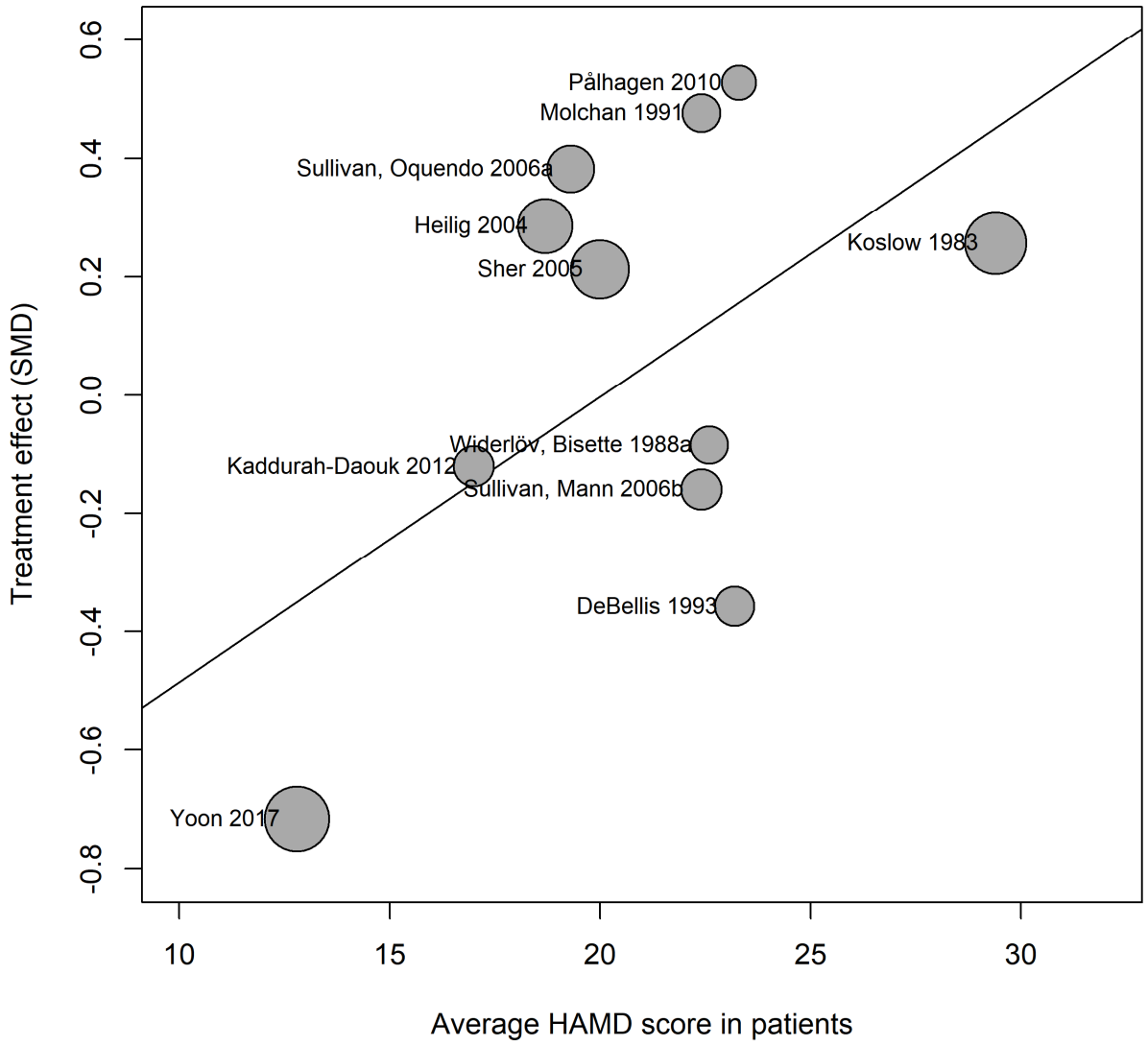
HVA



Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub
intrcpt	0.1588	0.2942	0.5400	0.5892	-0.4177	0.7354
n_HAMD	-0.0175	0.0139	-1.2595	0.2079	-0.0446	0.0097

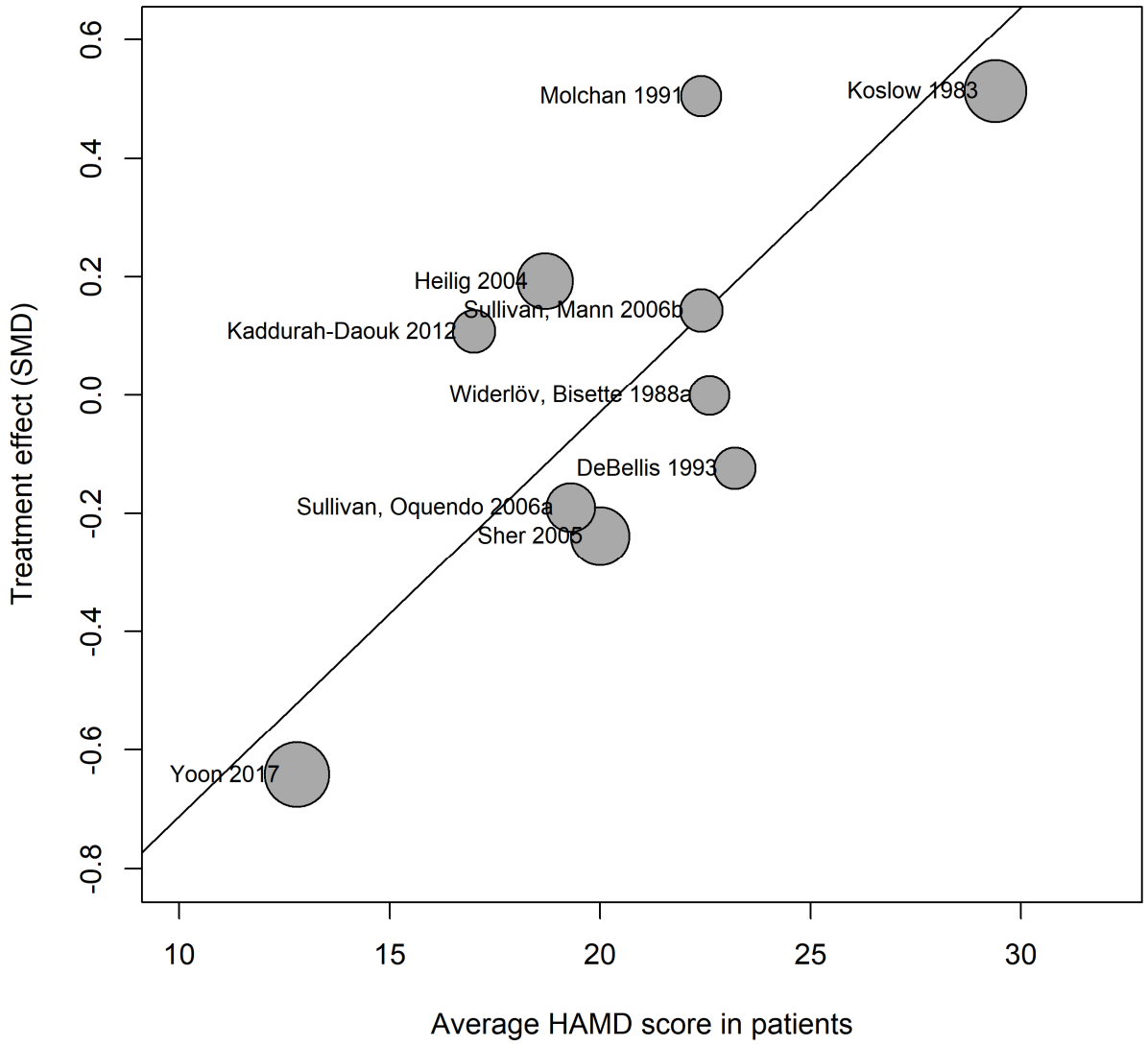
5-HIAA



Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub	
intrcpt	-0.9684	0.5066	-1.9116	0.0559	-1.9613	0.0245	.
n_HAMD	0.0483	0.0239	2.0220	0.0432	0.0015	0.0951	*

MHPG

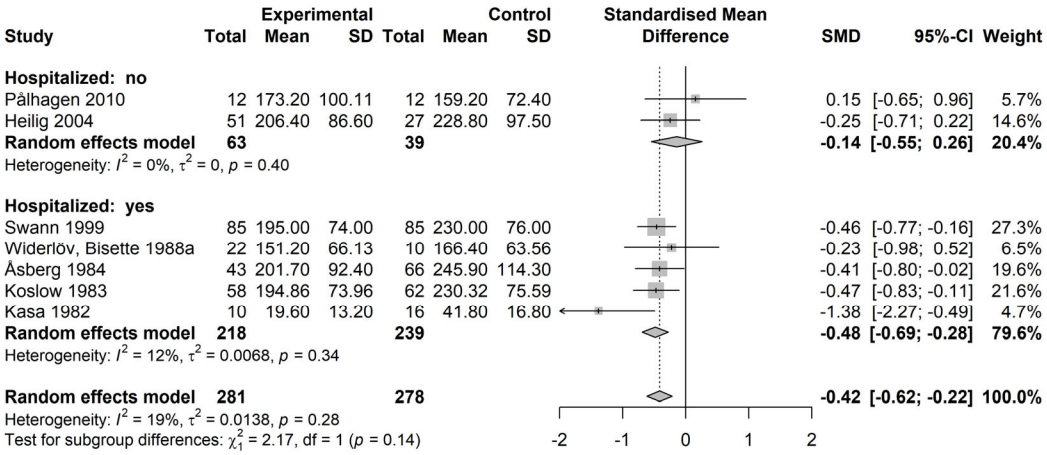


Model Results:

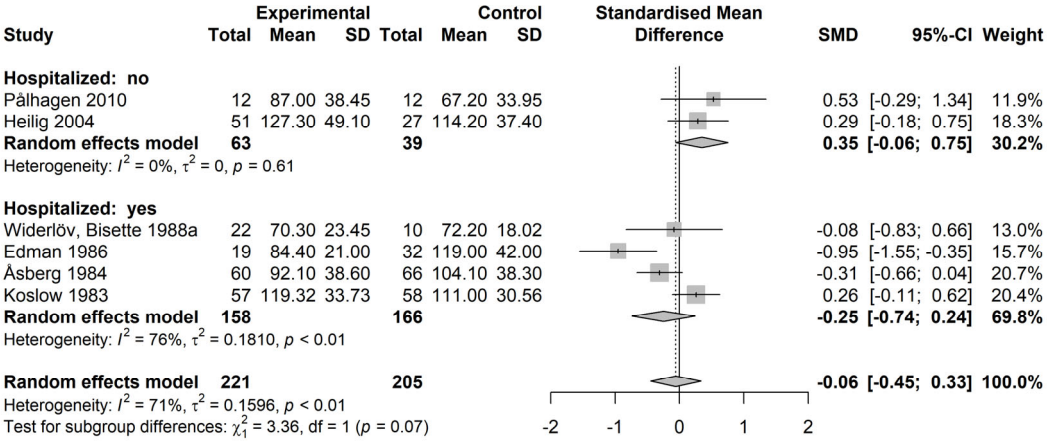
	estimate	se	zval	pval	ci.lb	ci.ub	
intrcpt	-1.3954	0.3452	-4.0428	<.0001	-2.0720	-0.7189	***
n_HAMD	0.0683	0.0164	4.1773	<.0001	0.0363	0.1004	***

eFigure 8 | Hospitalized patients compared to not hospitalized patients for biomarkers with data on ≧5 studies

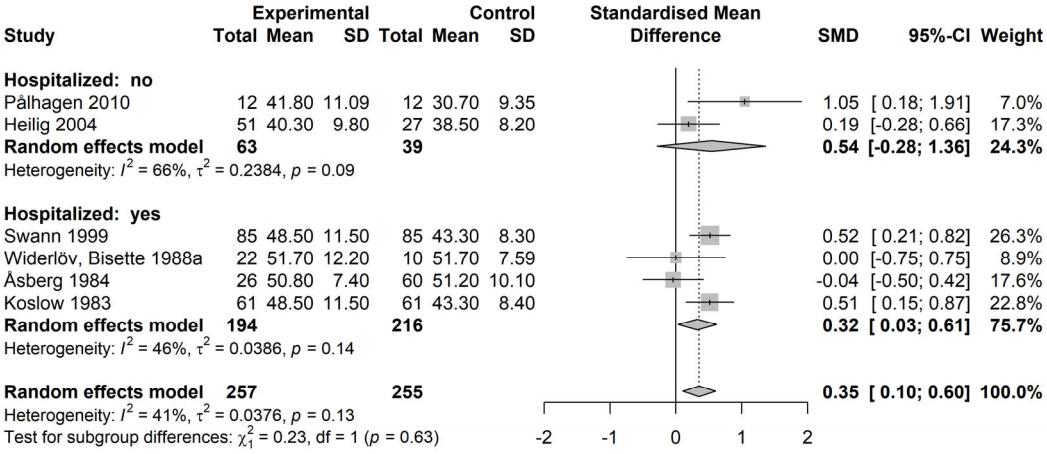
HVA



5-HIAA

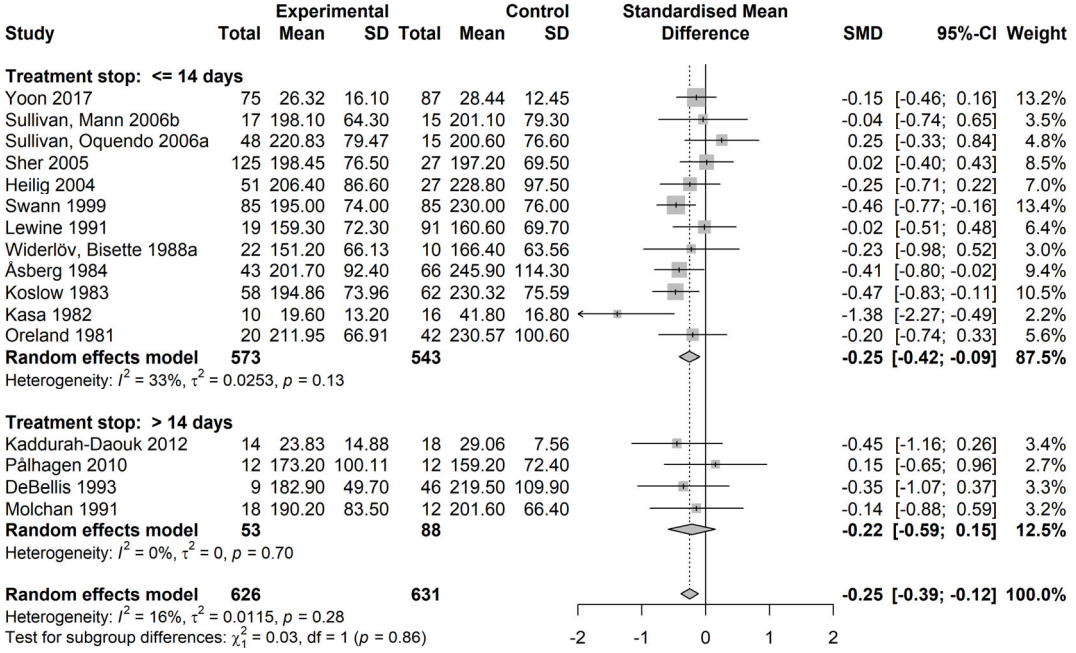


MHPG

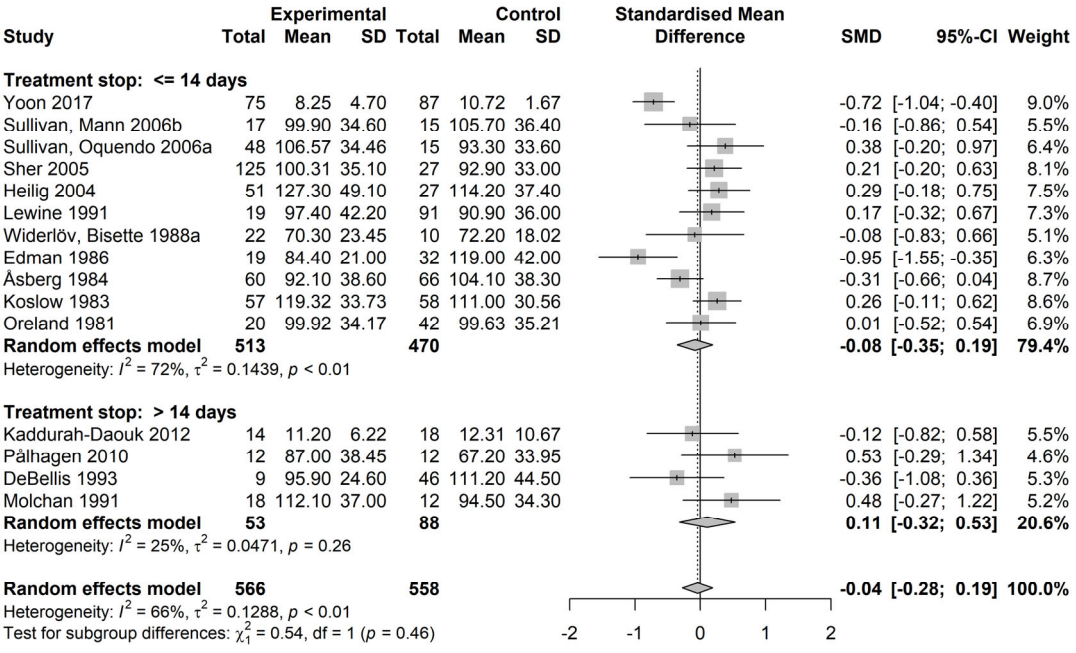


eFigure 9 | Patients off antidepressant treatment for ≦14 days compared to >14 days for biomarkers with data on ≧5 studies

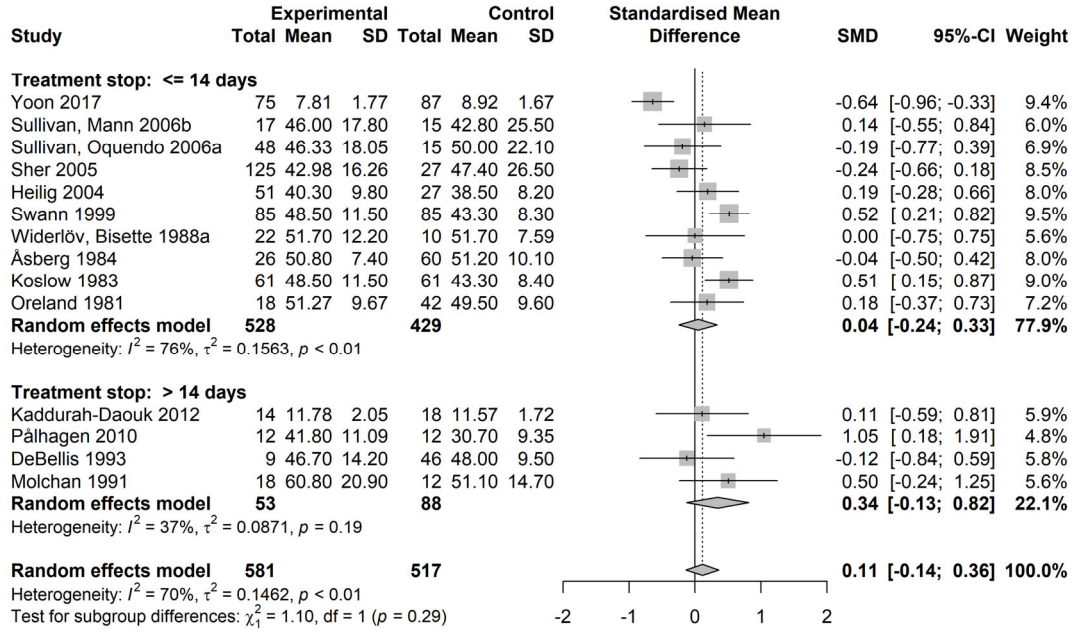
HVA



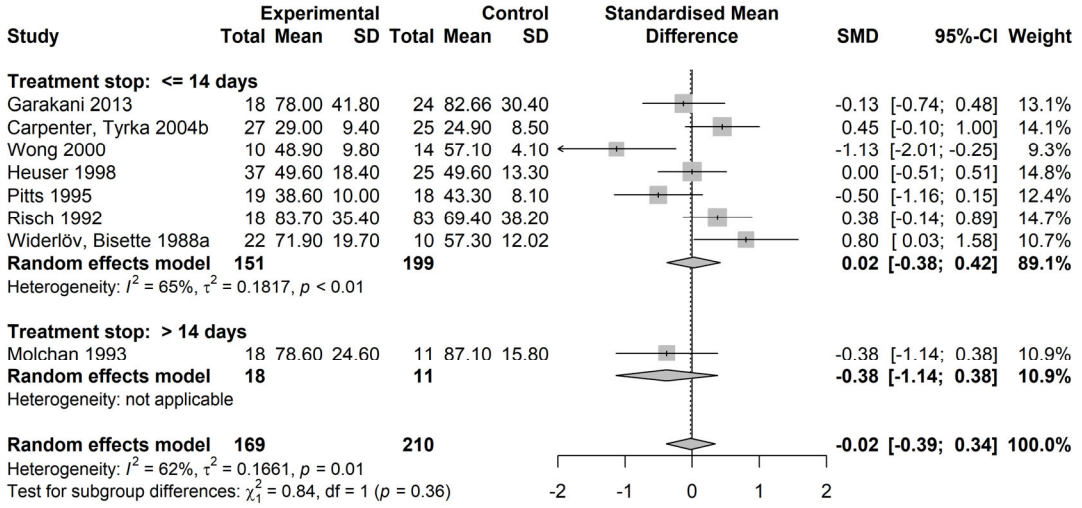
5-HIAA



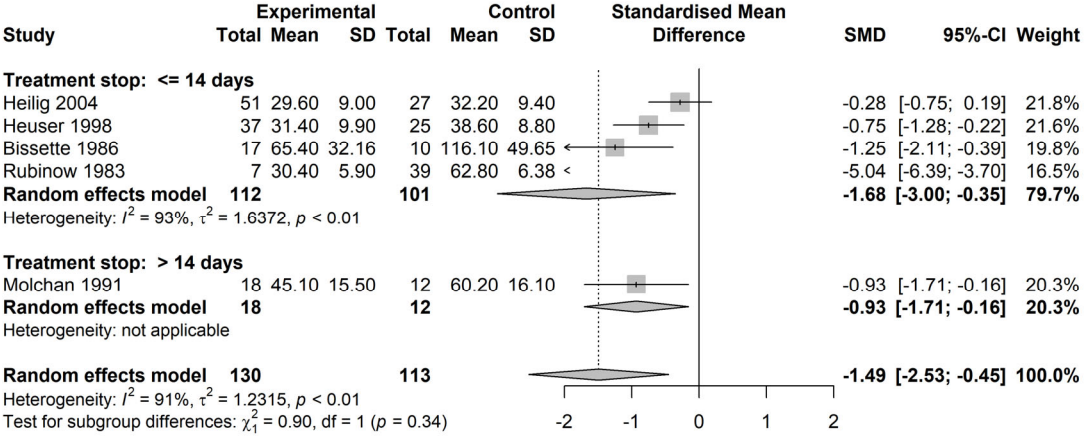
MHPG



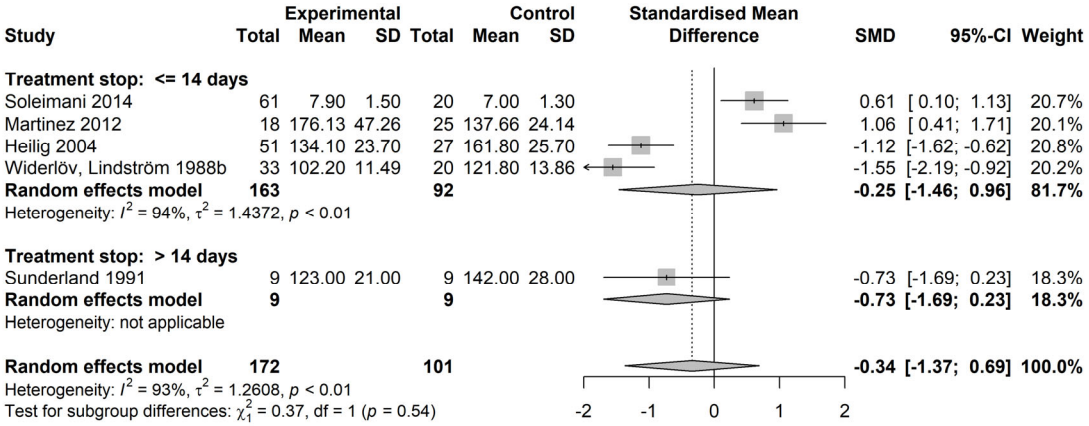
CRH



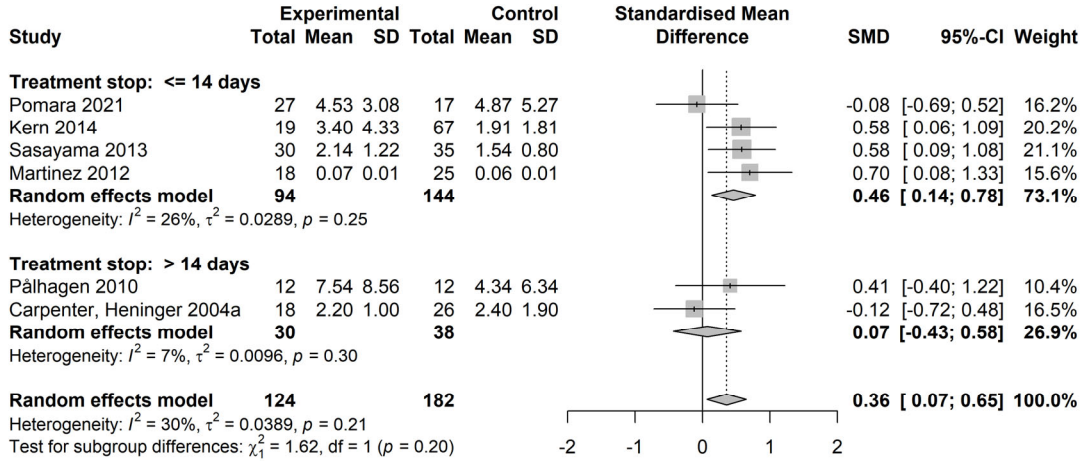
Somatostatin



Neuropeptide Y



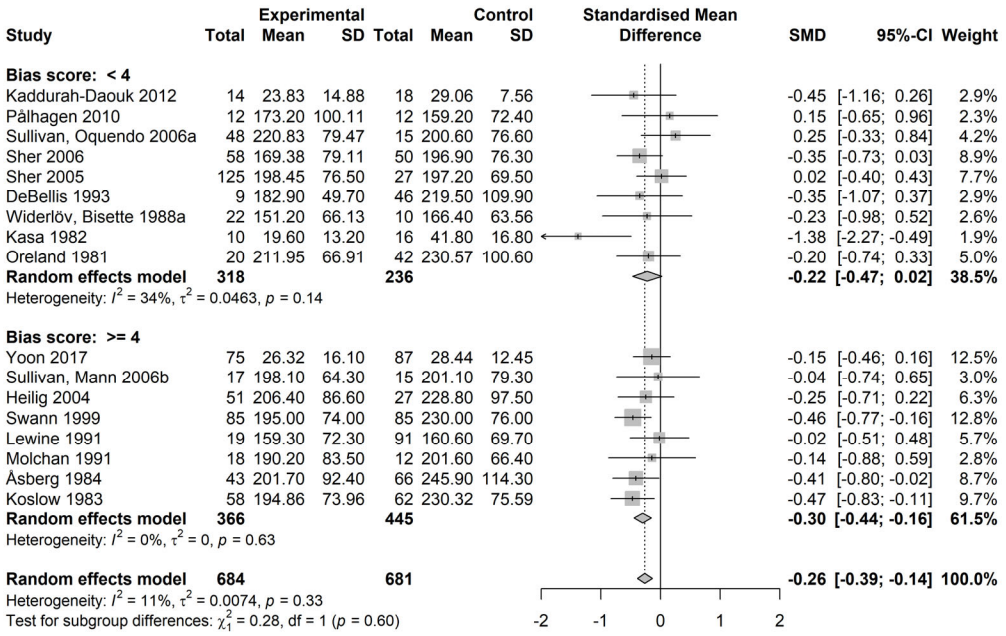
IL-6



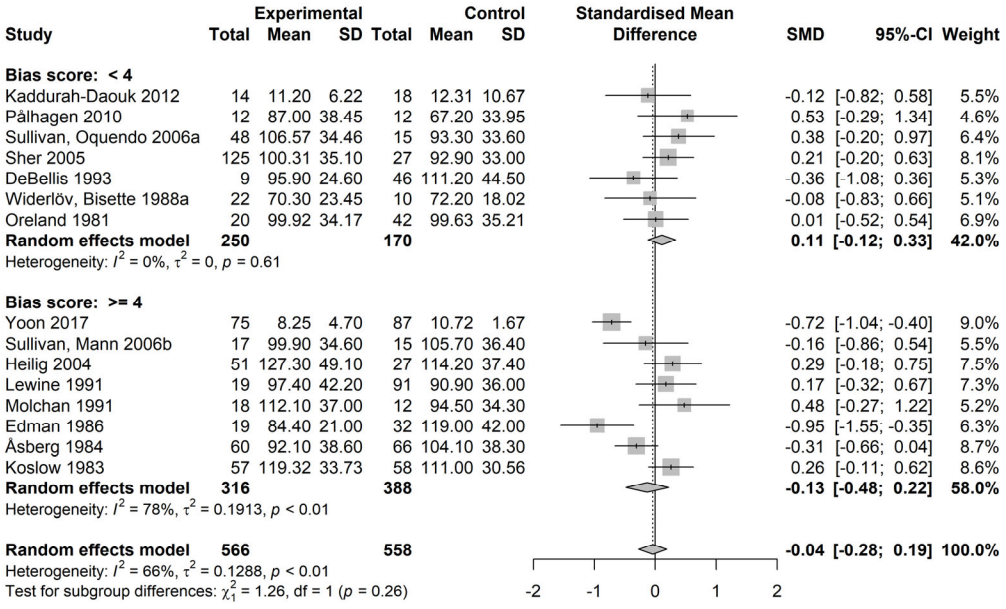
Sensitivity analyses

eFigure 10 | Studies with a total score of ≧4 compared to <4 on the Newcastle Ottawa Scale (NOS) for biomarkers quantified in ≧5 studies

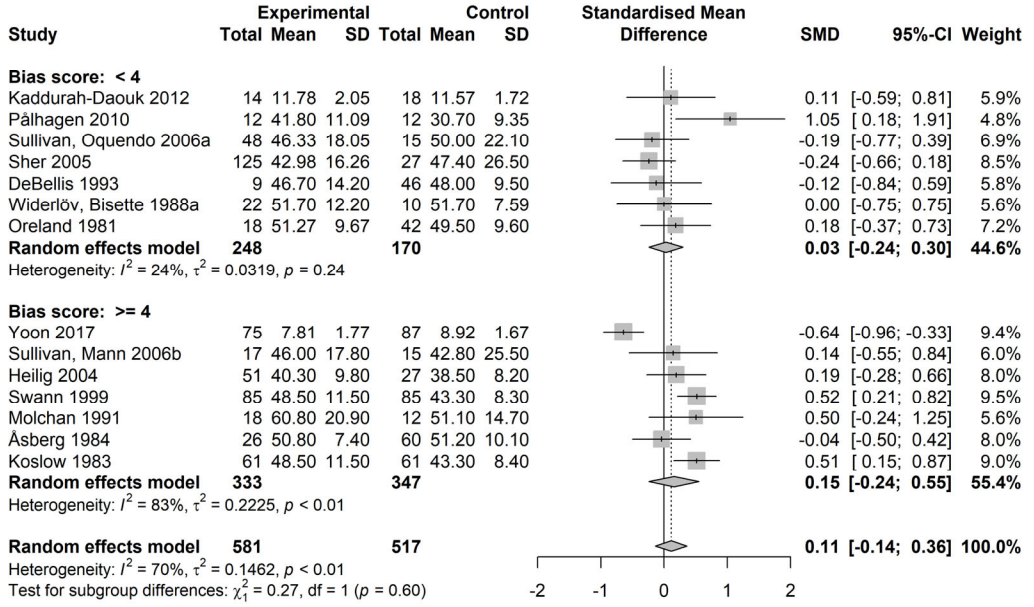
HVA



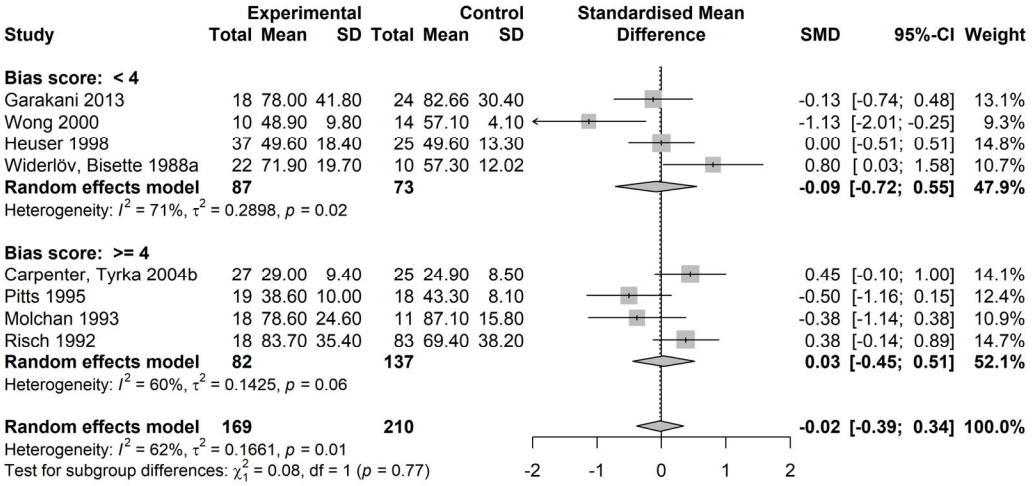
5-HIAA



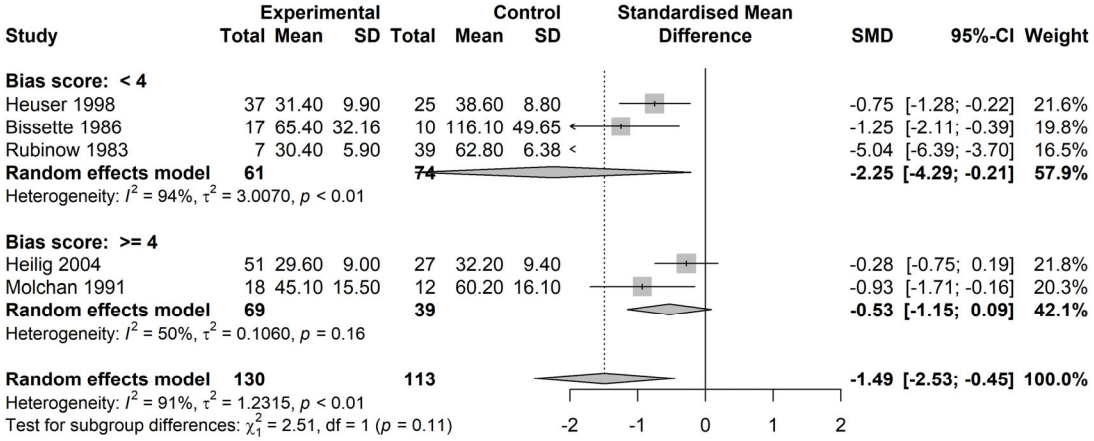
MHPG



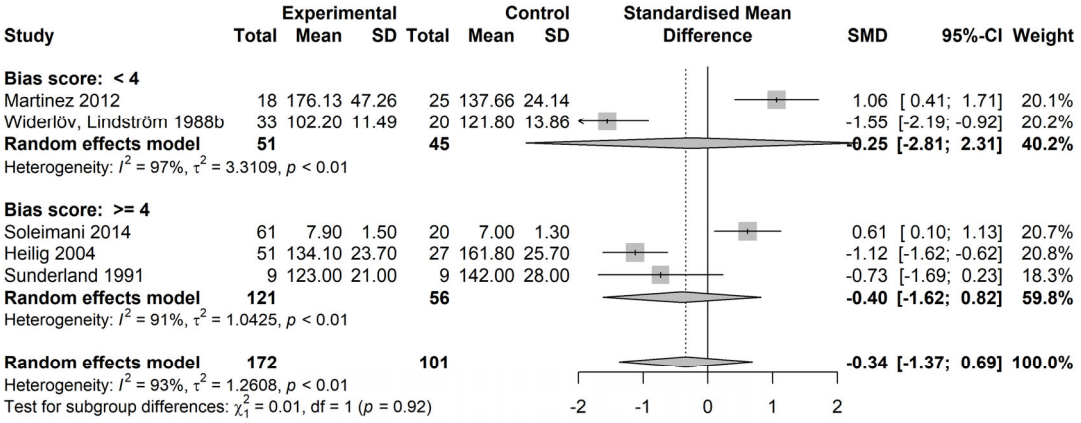
CRH



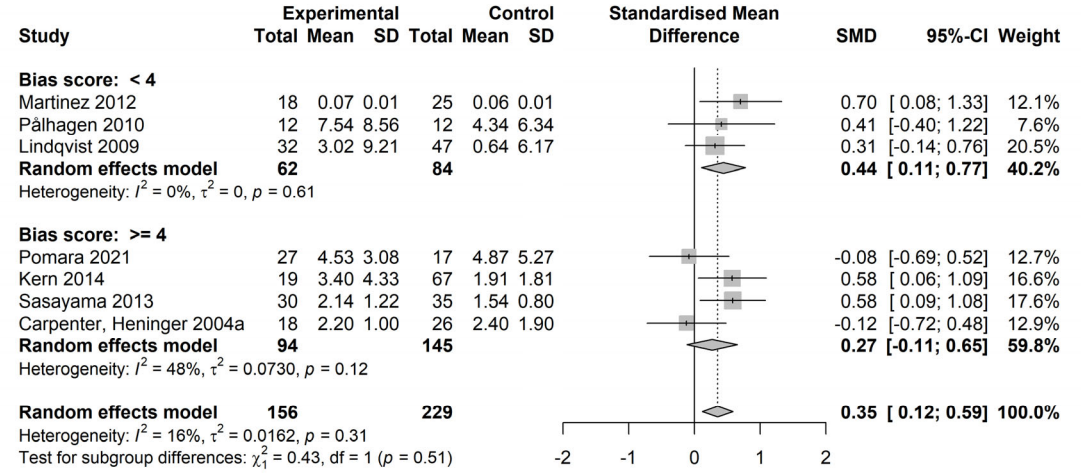
Somatostatin



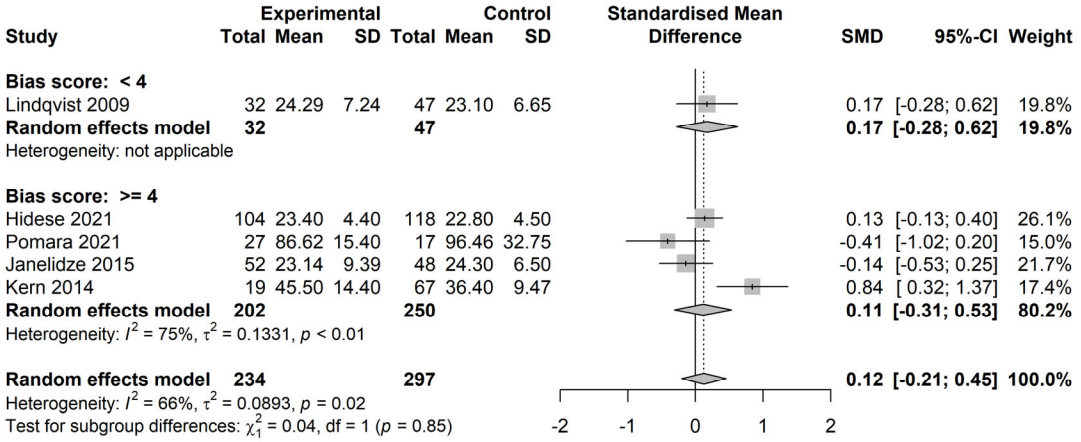
Neuropeptide Y



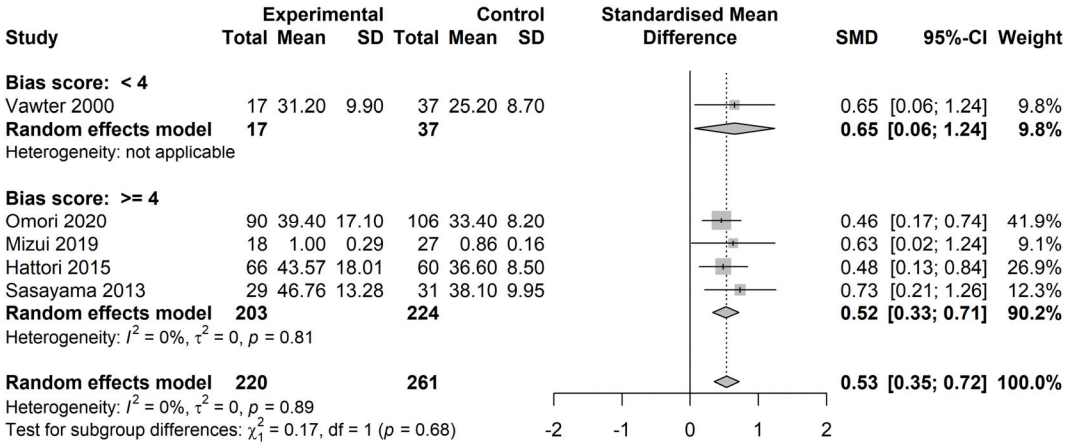
IL-6



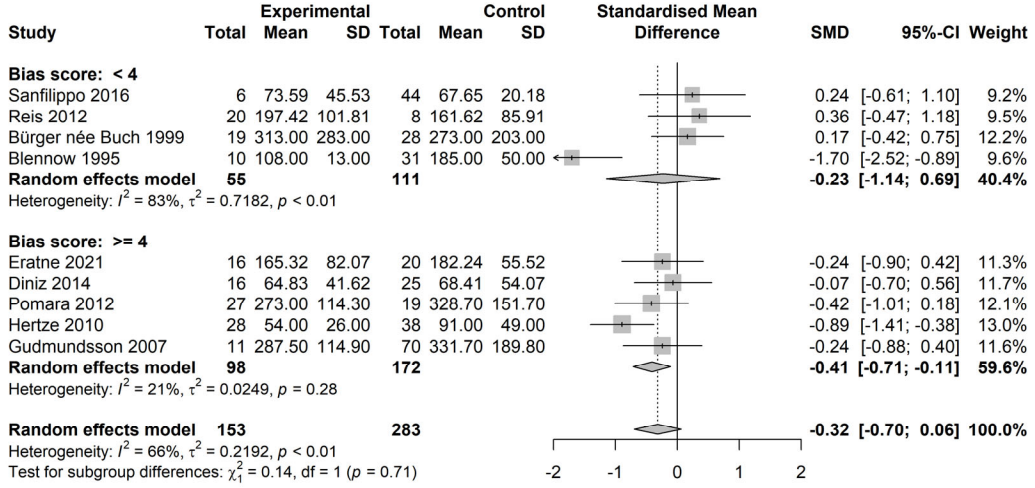
IL-8



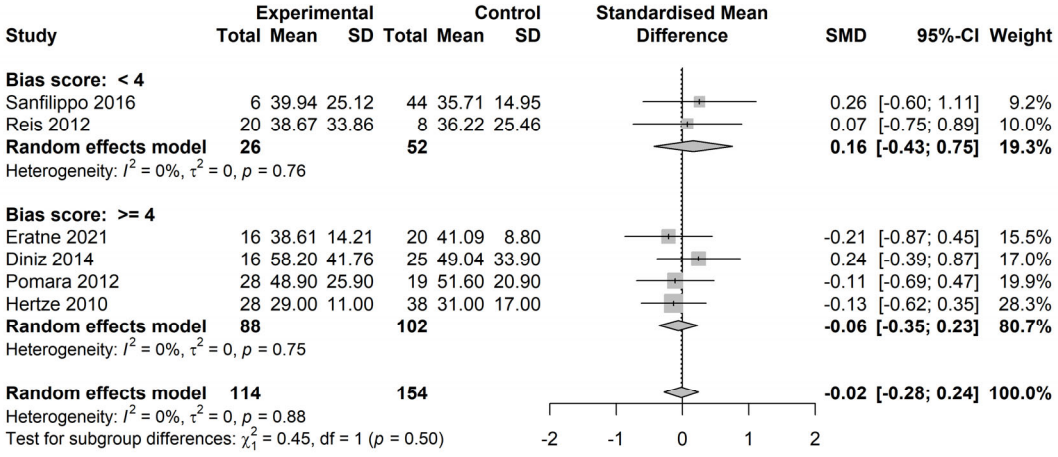
Total protein



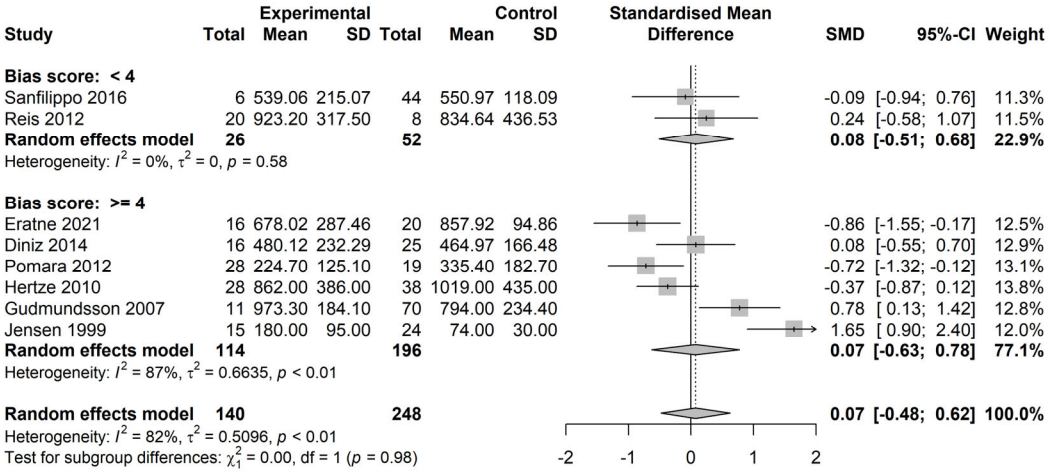
Total tau



P-tau 181

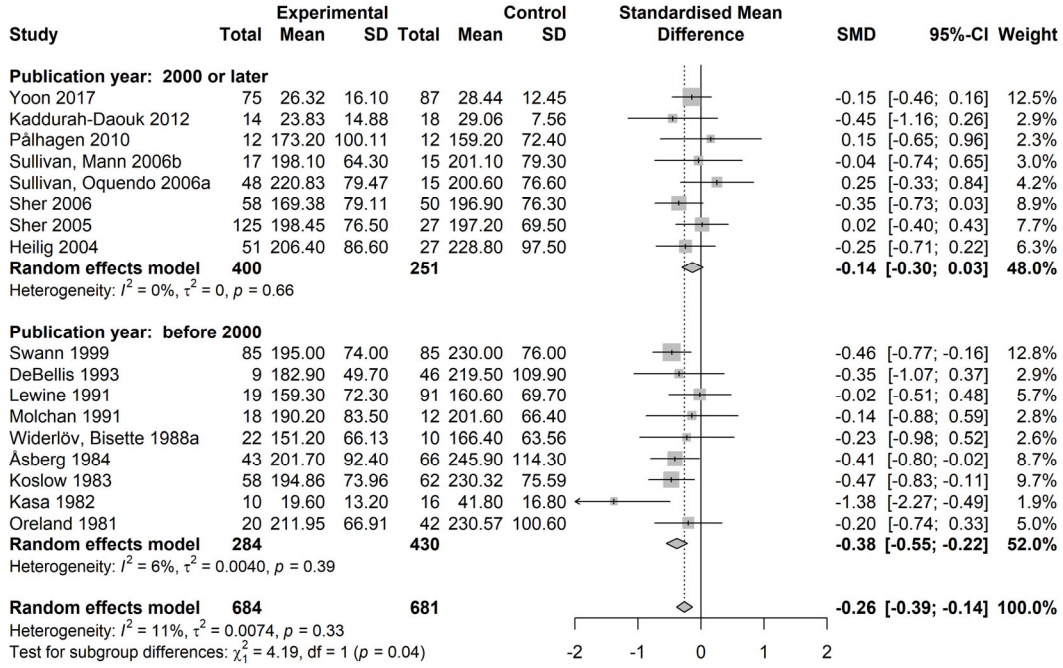


Amyloid-B-42

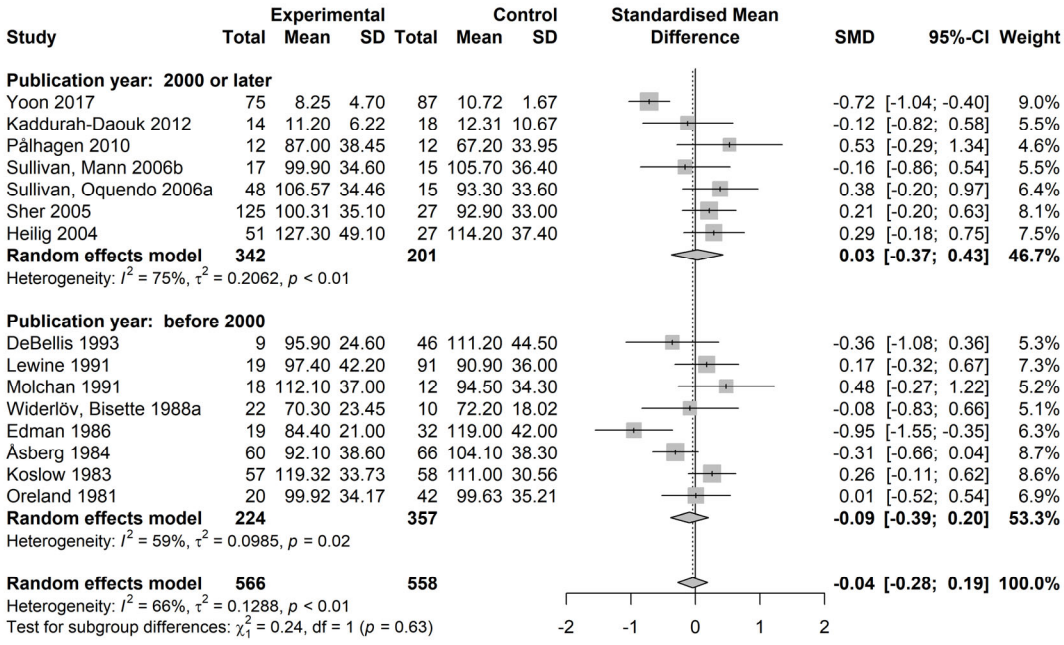


eFigure 11 | Studies published before year 2000 compared to studies published in or after 2000 for biomarkers quantified in ≧5 studies

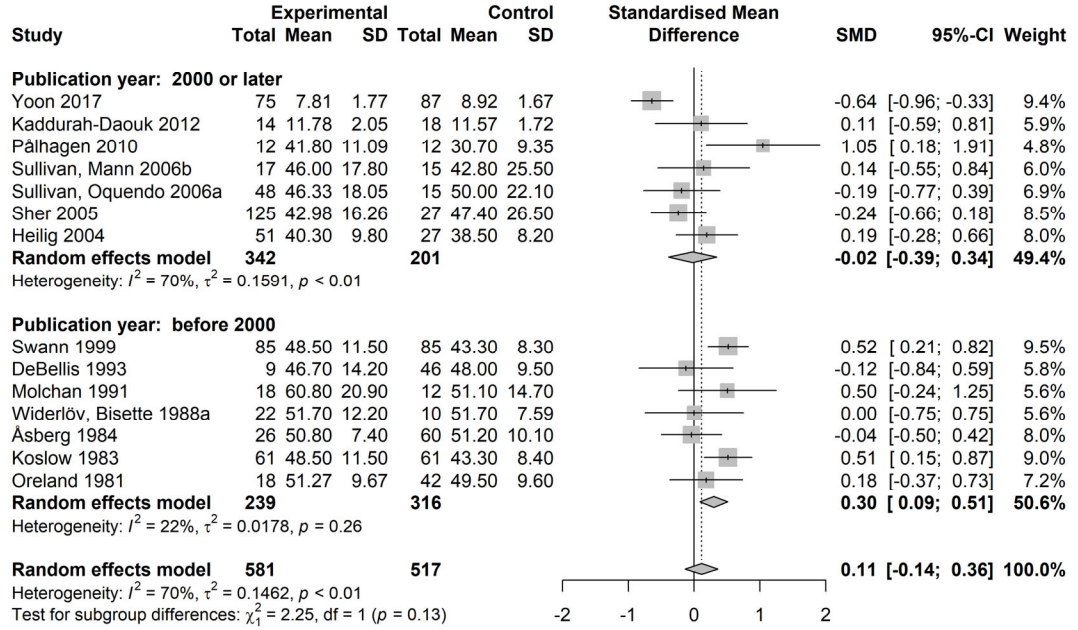
HVA



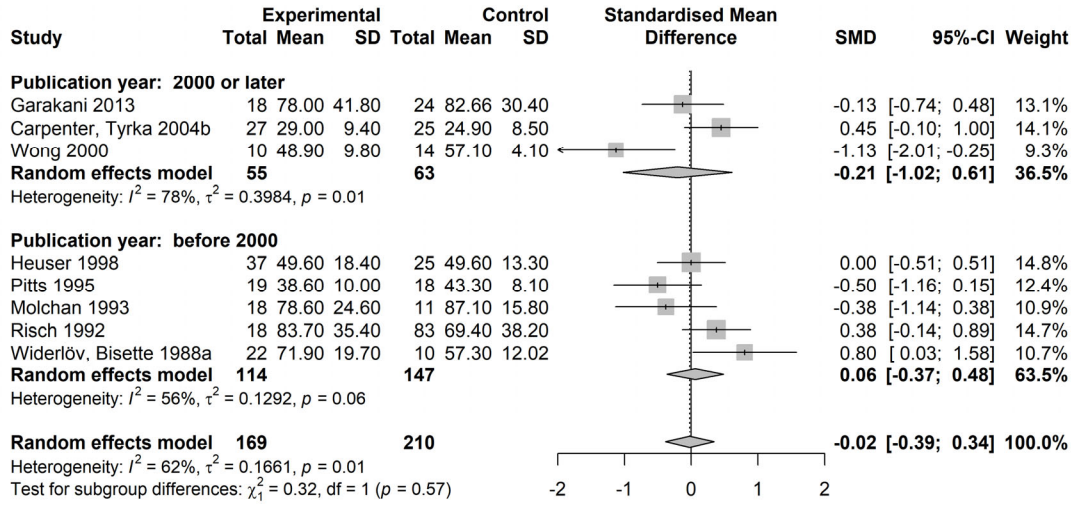
5-HIAA



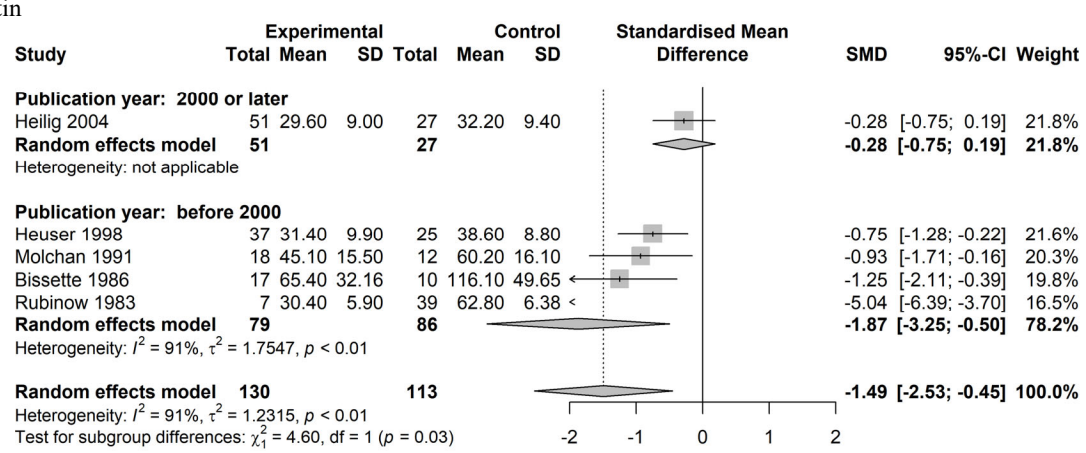
MHPG



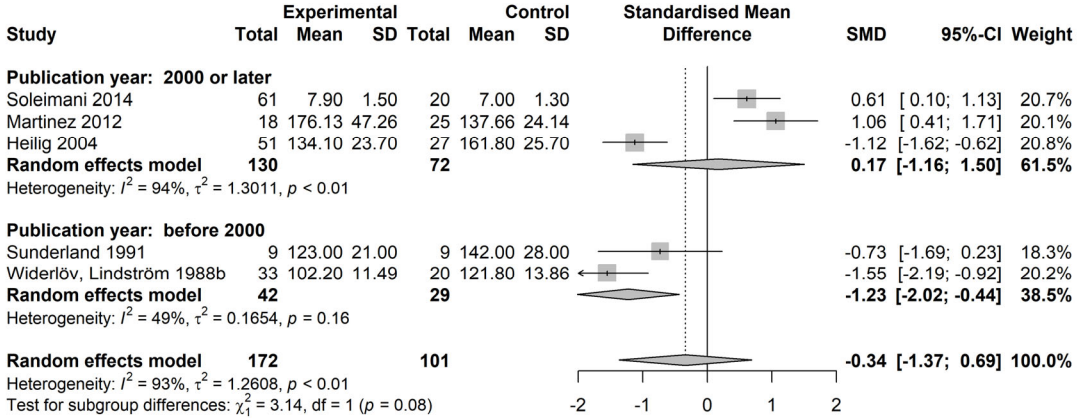
CRH



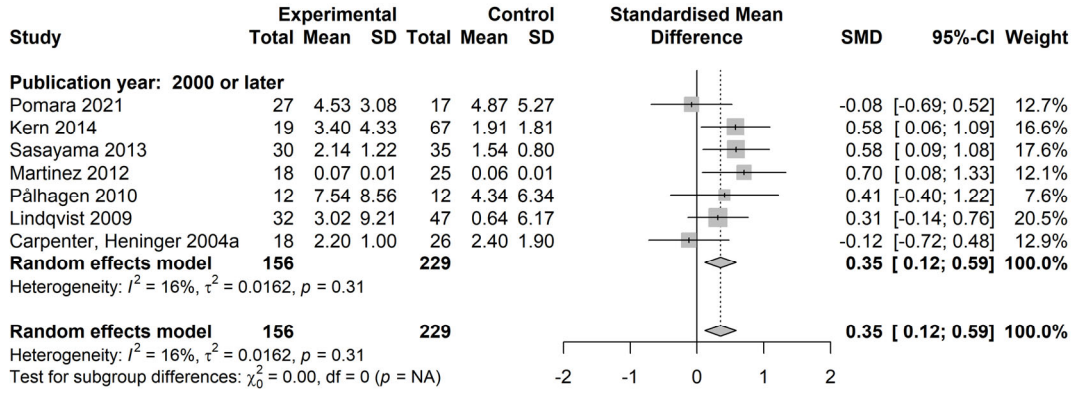
Somatostatin



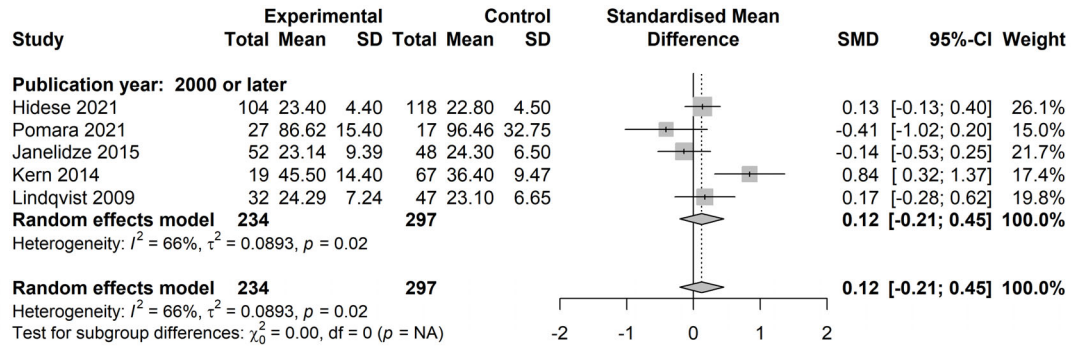
Neuropeptide Y



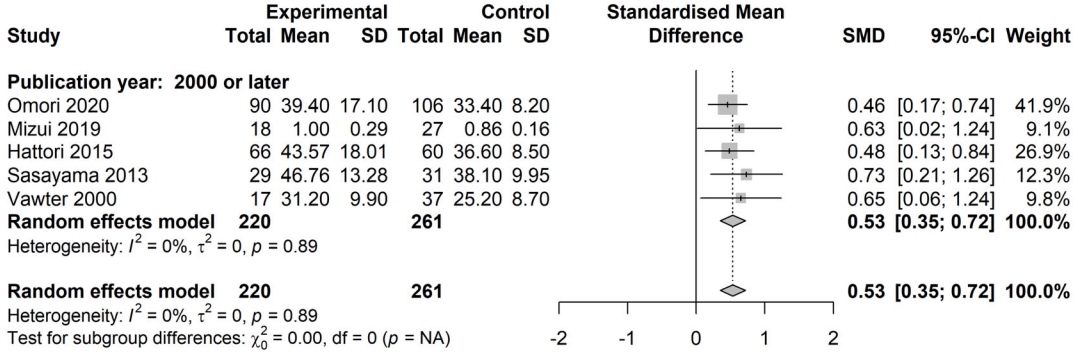
IL-6



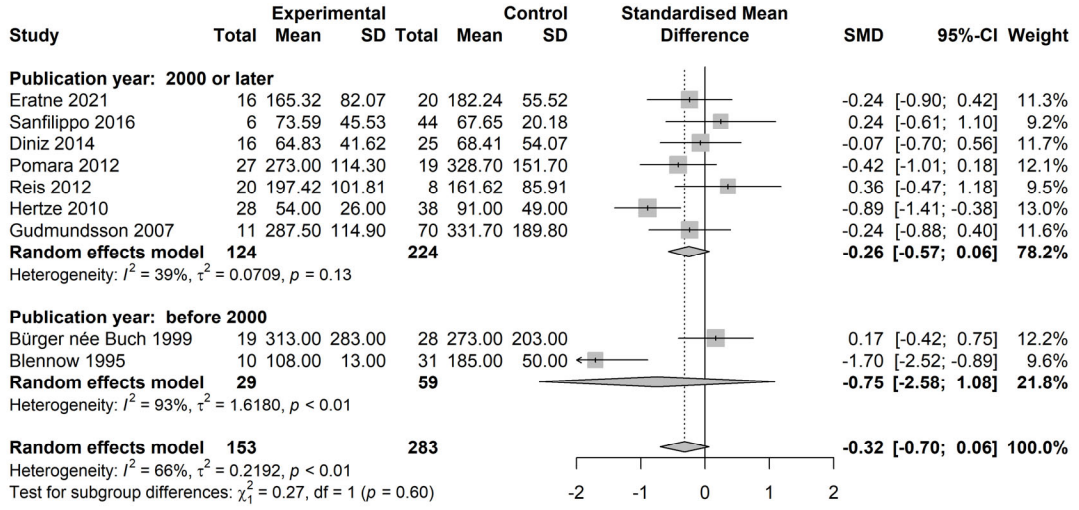
IL-8



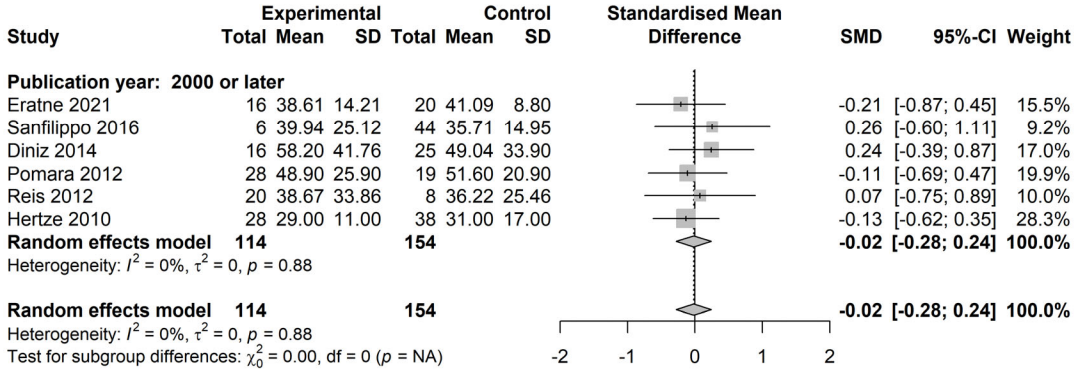
Total protein



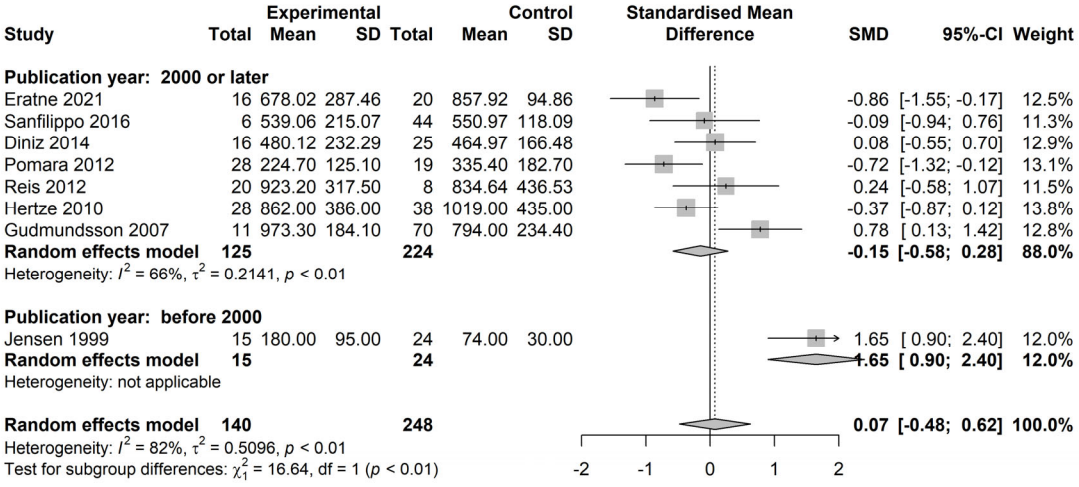
Total tau



P-tau 181



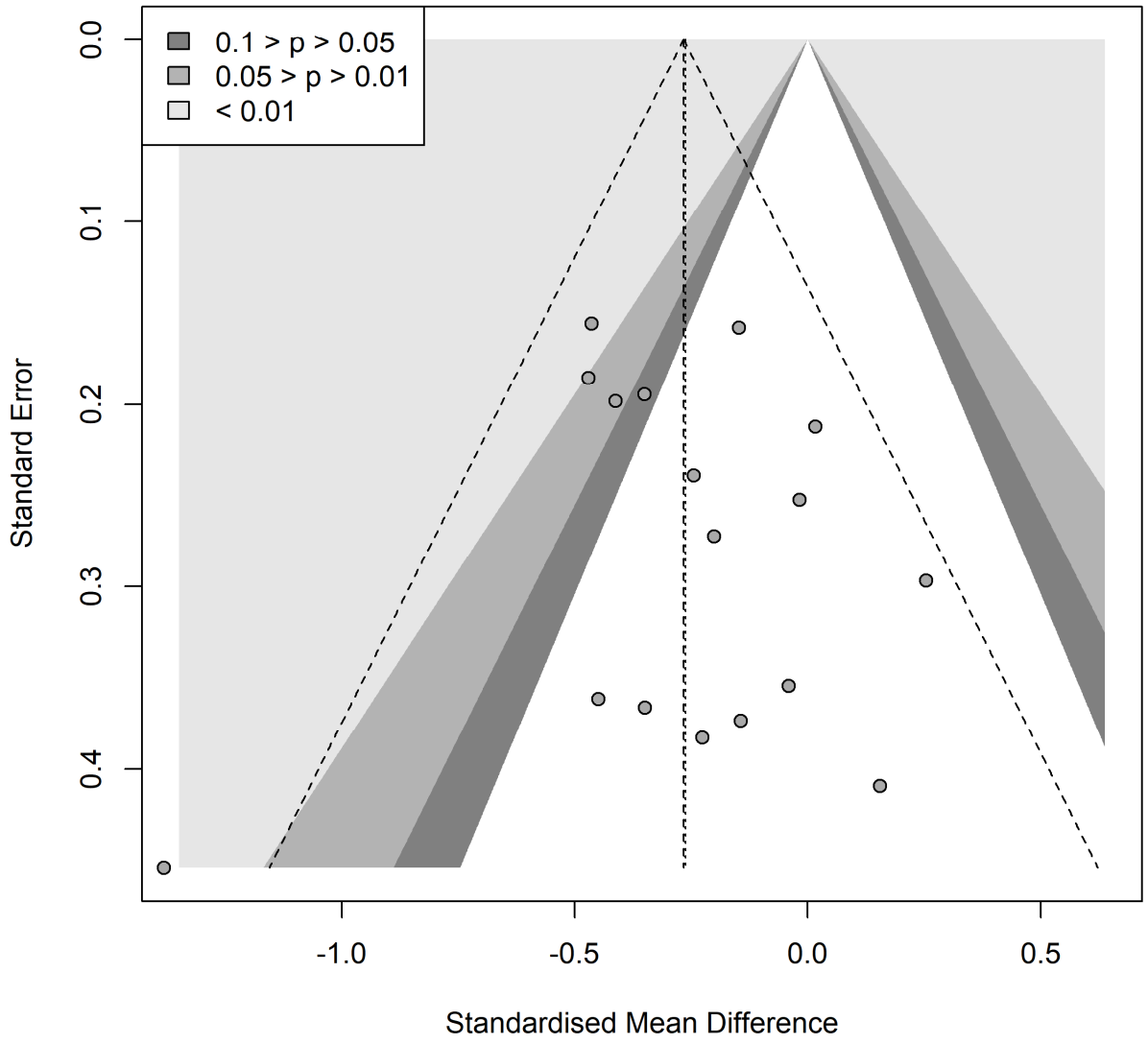
Amyloid-B-42



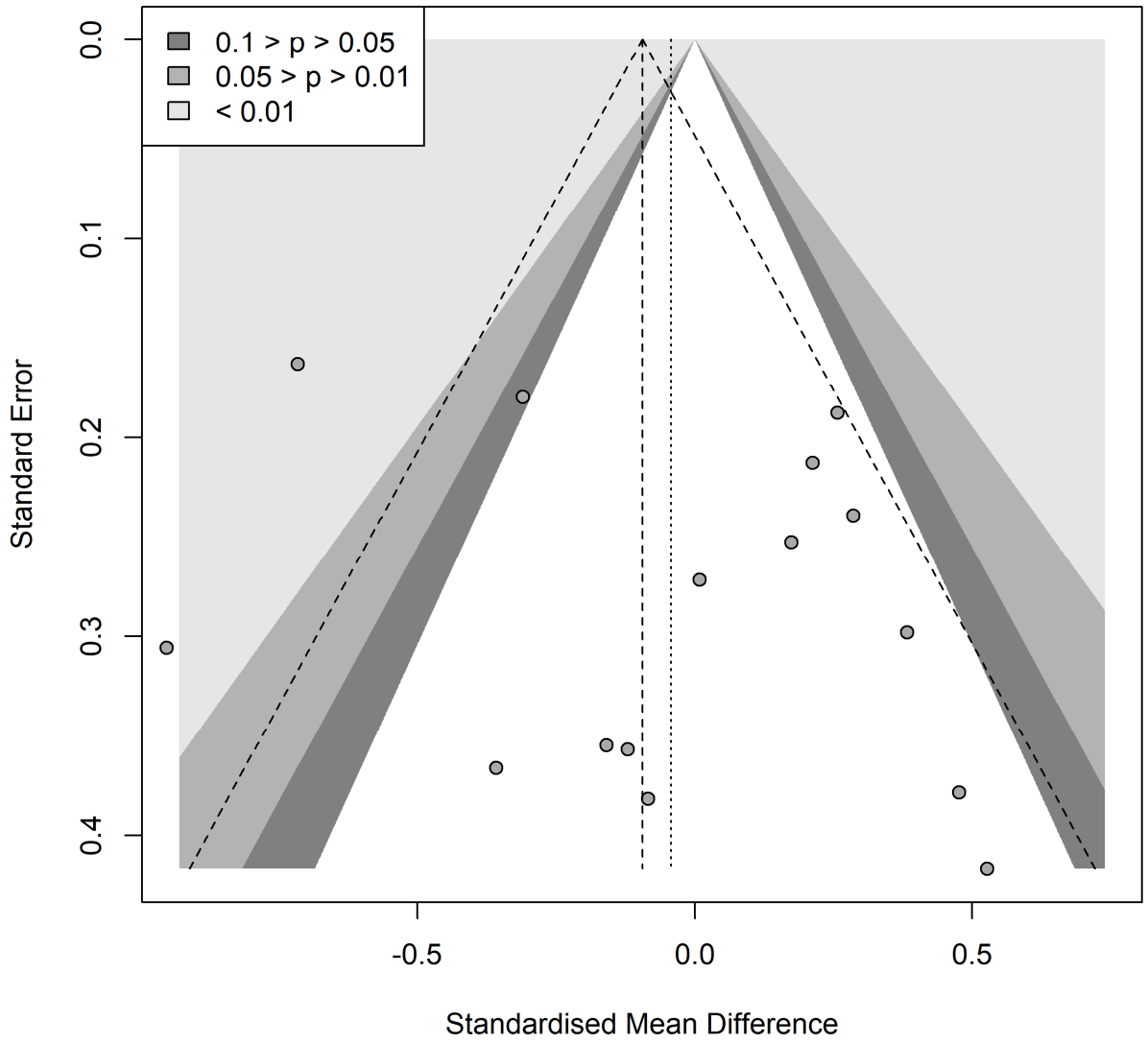
Bias assessment analyses

eFigure 12 | Funnel plots of biomarkers examined in ≧10 studies

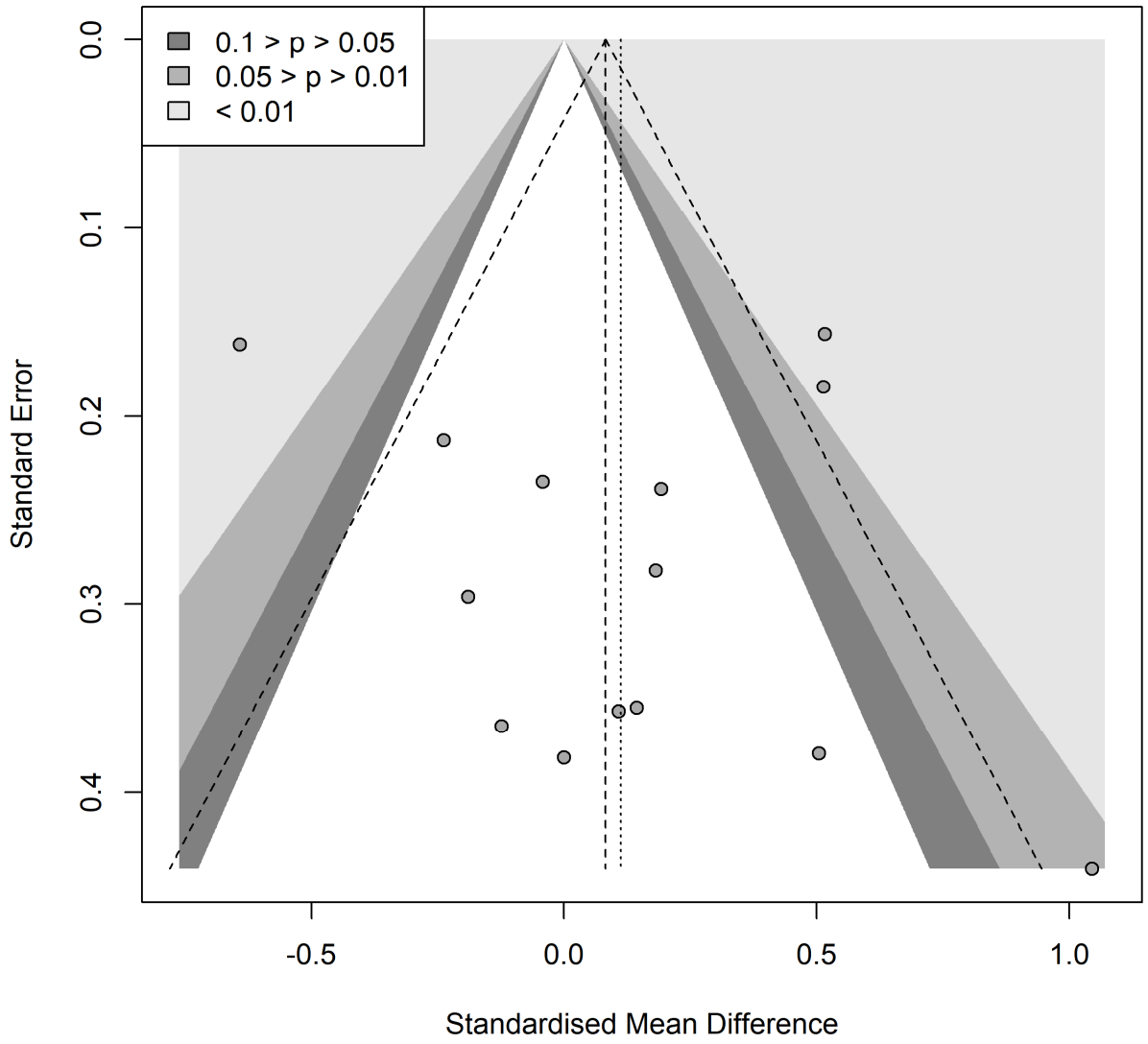
HVA



5-HIAA

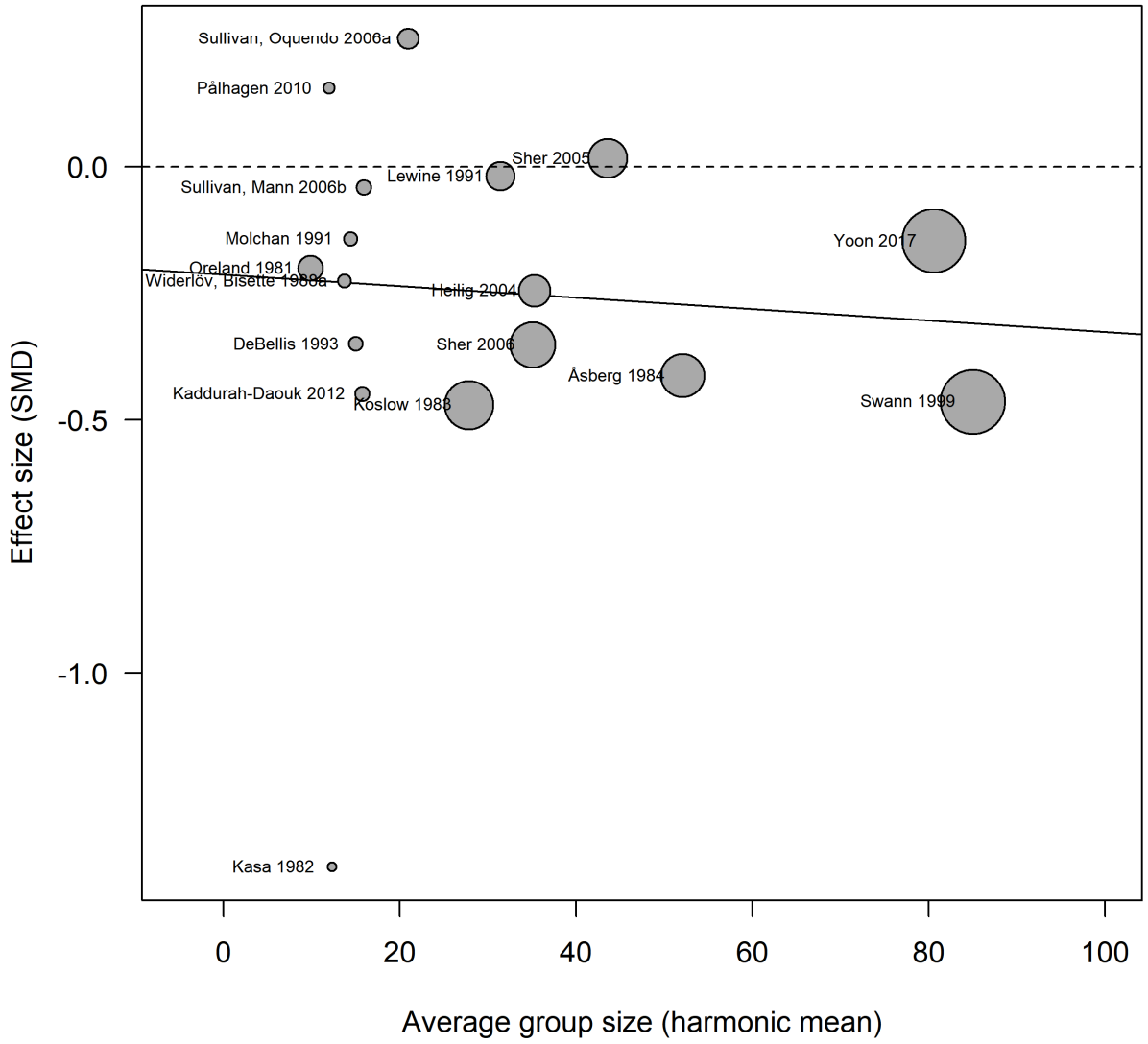


MHPG



eFigure 13 | Meta-regression analyses of mean group size in relation to standard mean difference (SMD) on biomarkers examined in ≧10 studies

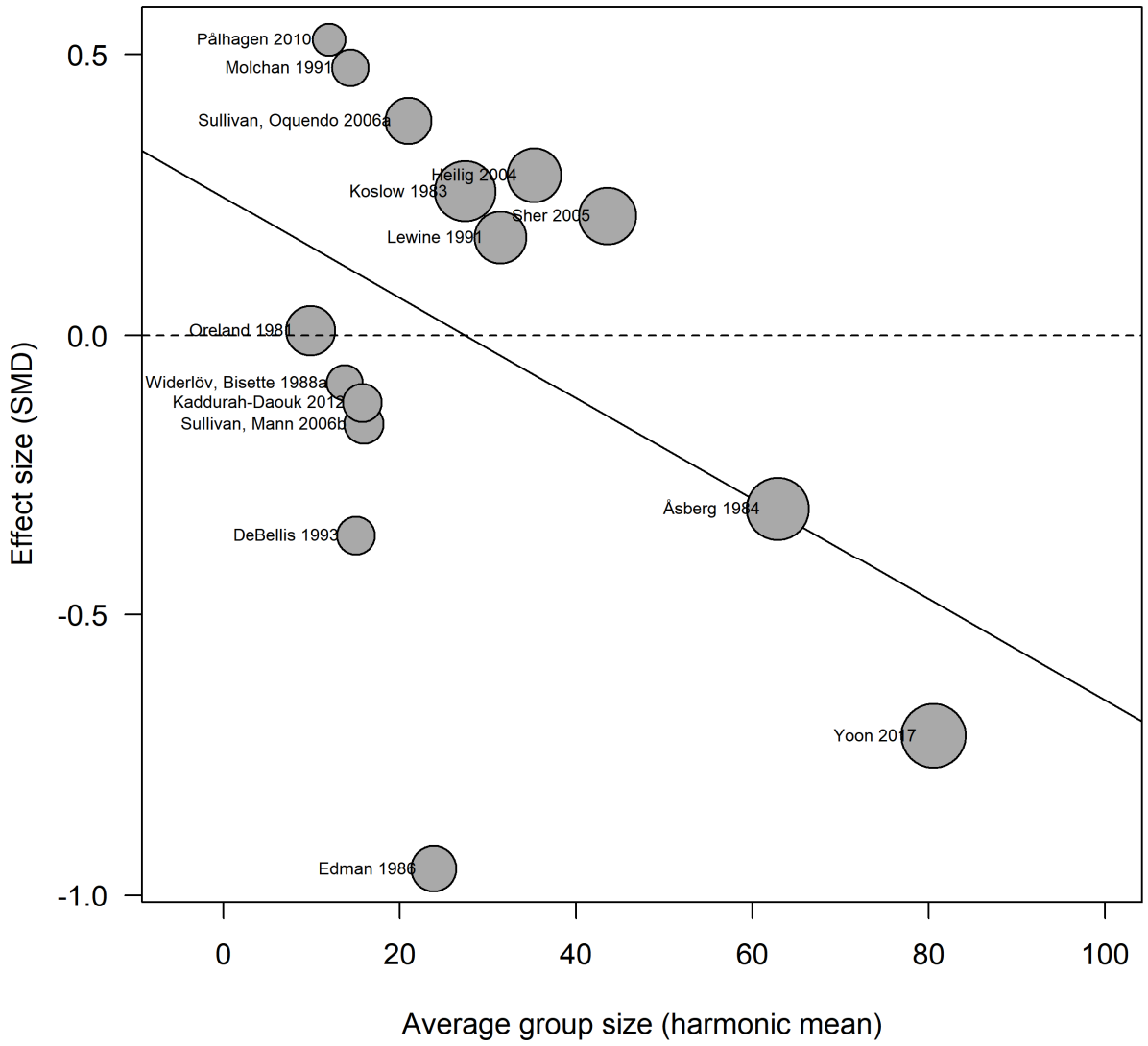
HVA



Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub
intrcpt	-0.2136	0.1261	-1.6947	0.0901	-0.4607	0.0334
n_harmonic	-0.0011	0.0026	-0.4389	0.6608	-0.0061	0.0039

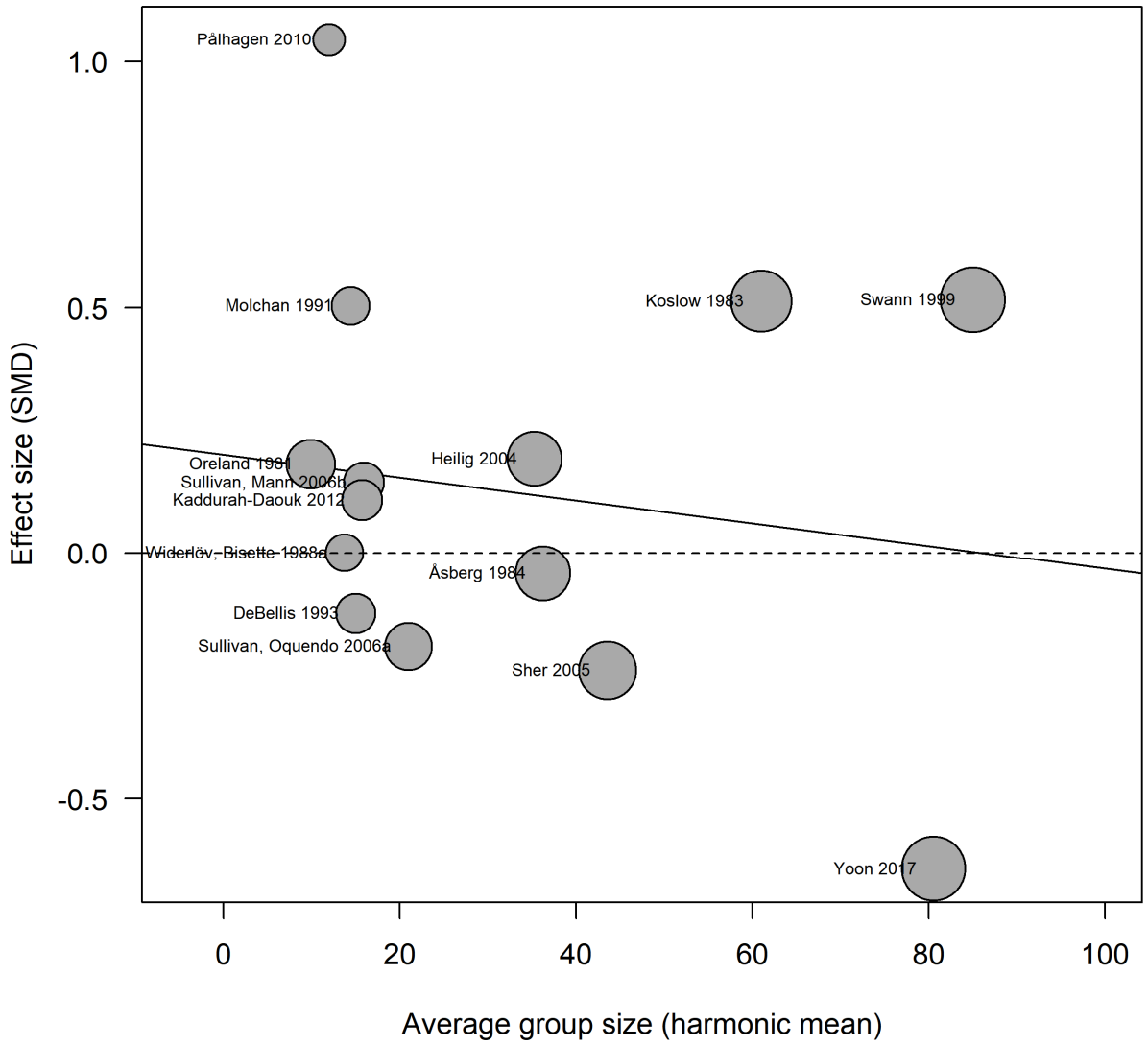
5-HIAA



Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub	
intrcpt	0.2467	0.1807	1.3653	0.1722	-0.1074	0.6007	
n_harmonic	-0.0090	0.0046	-1.9718	0.0486	-0.0179	-0.0001	*

MHPG

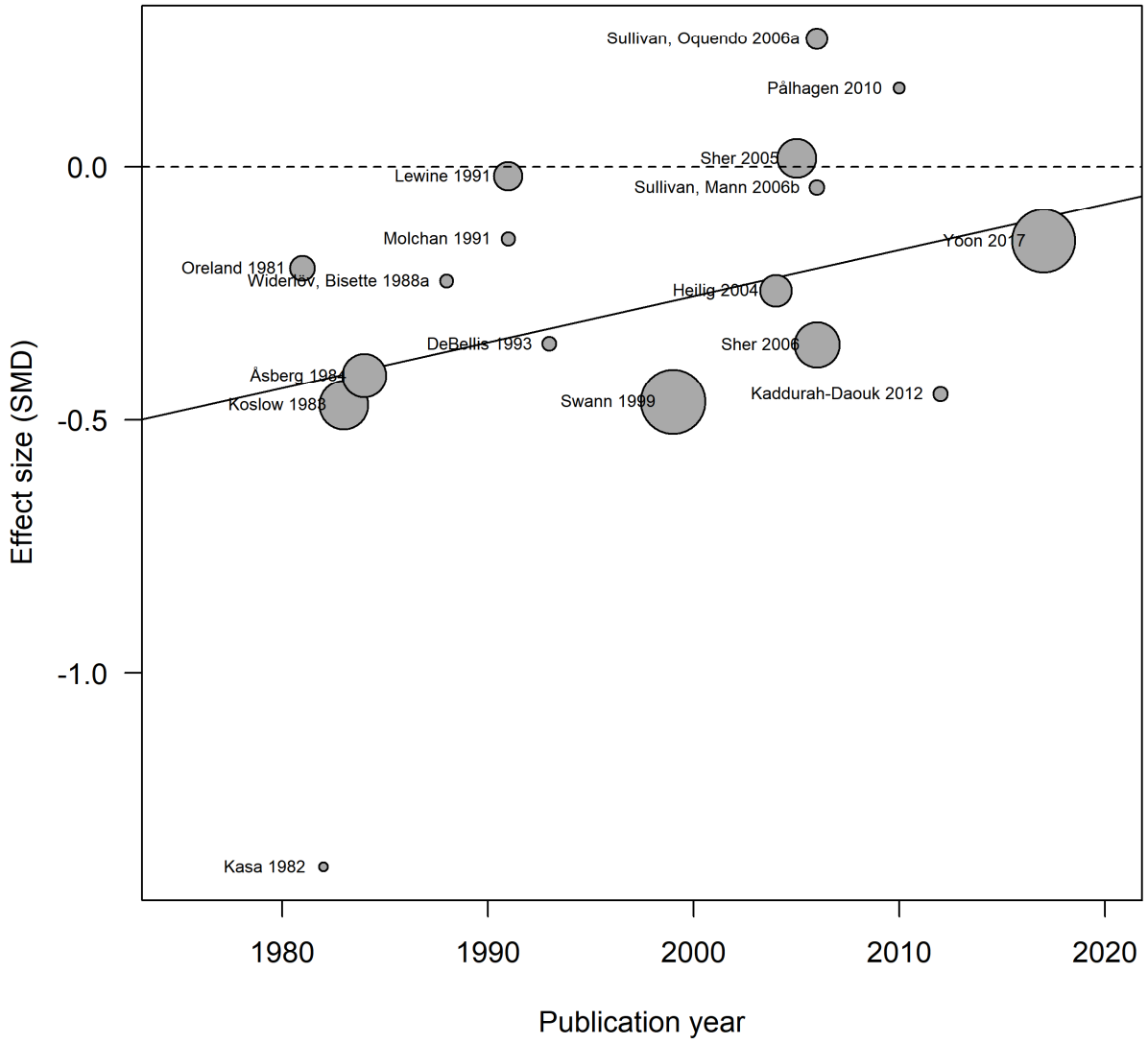


Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub
intrcpt	0.2007	0.2323	0.8637	0.3877	-0.2547	0.6560
n_harmonic	-0.0023	0.0051	-0.4557	0.6486	-0.0124	0.0077

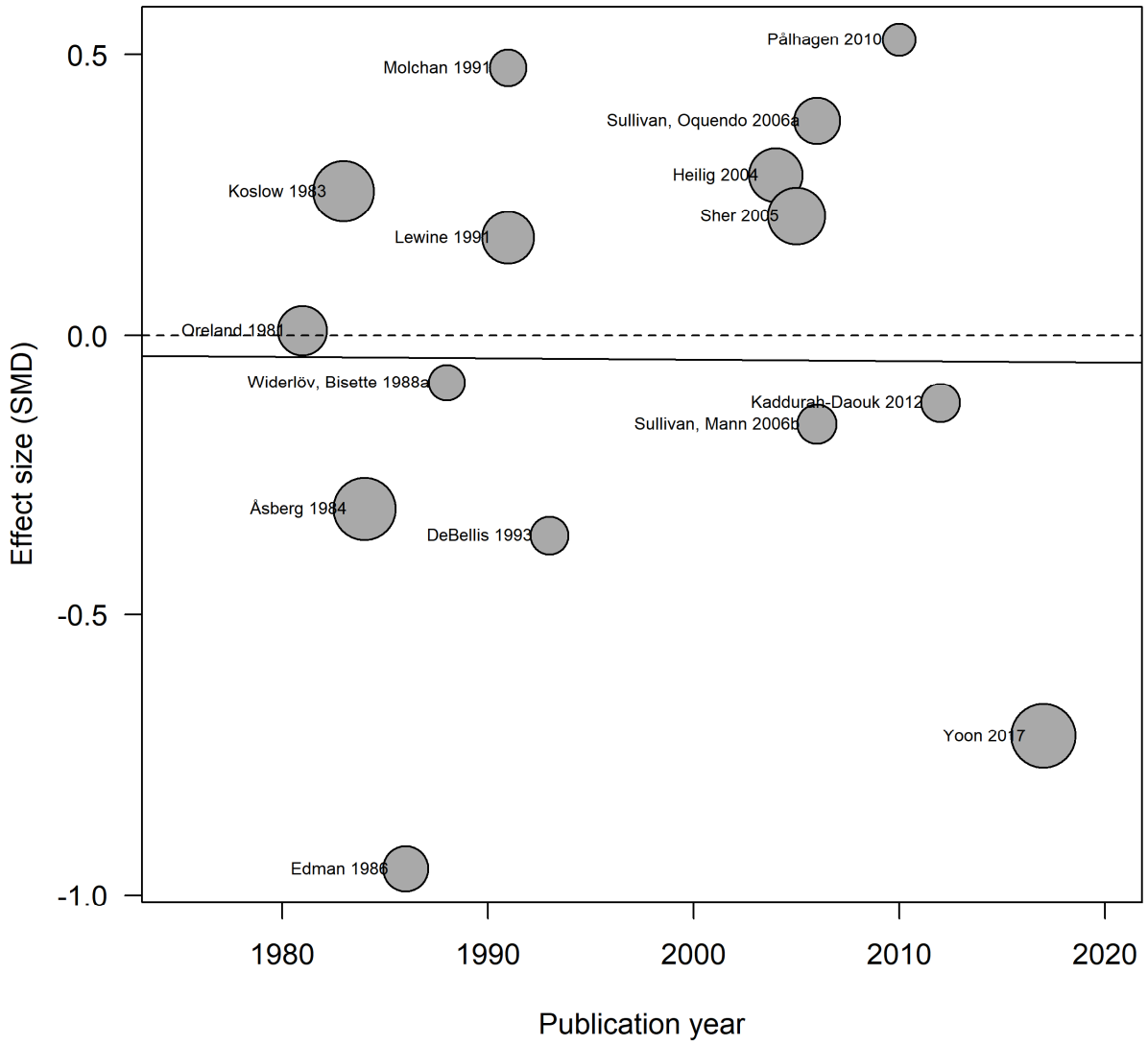
eFigure 14 | Meta-regression analyses of publication year in relation to standard mean difference (SMD) on biomarkers examined in ≧10 studies

HVA



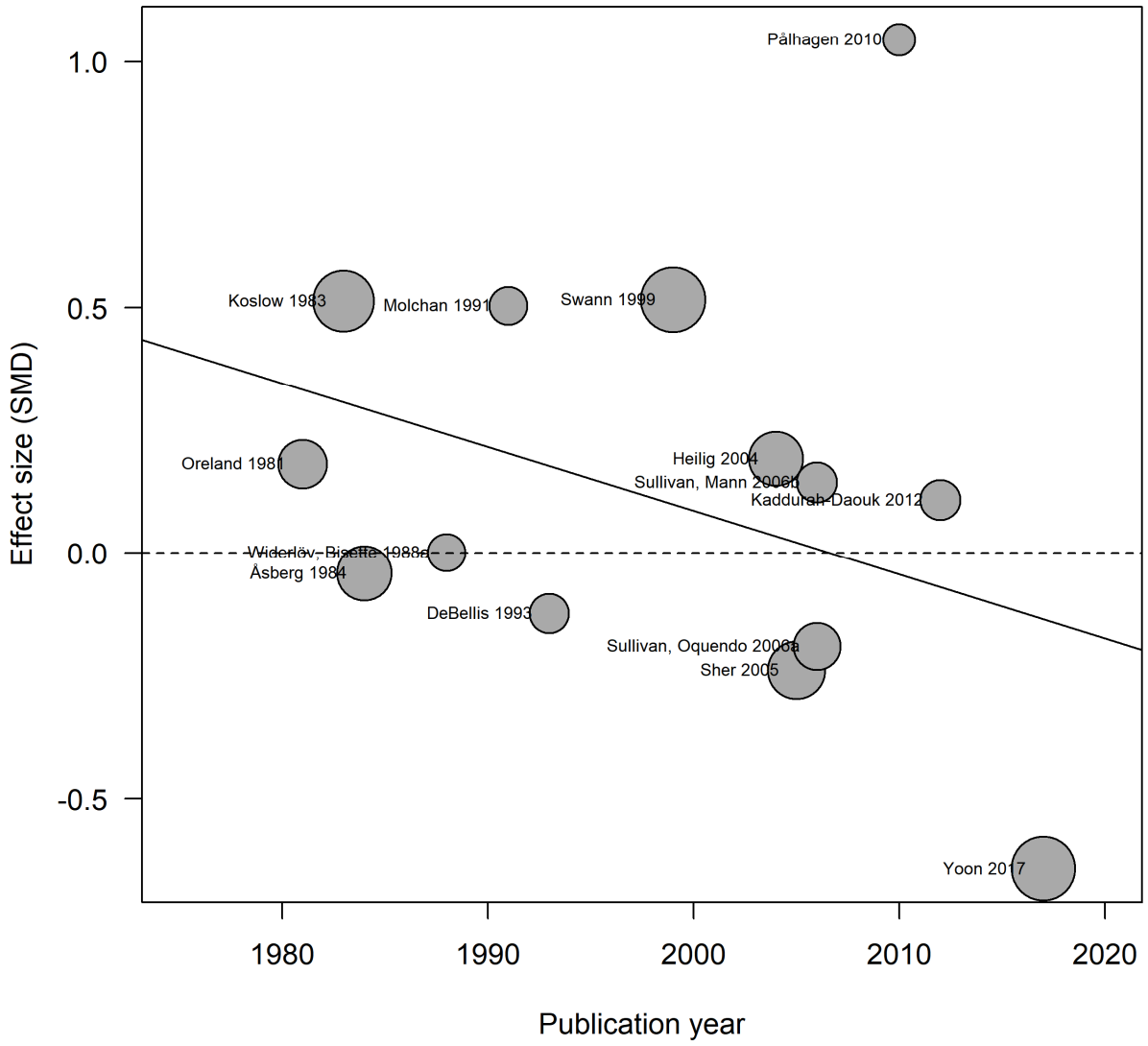
Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub	
intrcpt	-18.4202	9.9904	-1.8438	0.0652	-38.0010	1.1607	.
n_year	0.0091	0.0050	1.8171	0.0692	-0.0007	0.0189	.



Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub
intrcpt	0.4441	20.5279	0.0216	0.9827	-39.7898	40.6780
n_year	-0.0002	0.0103	-0.0237	0.9811	-0.0204	0.0199



Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub
intrcpt	26.1331	19.0148	1.3744	0.1693	-11.1351	63.4014
n_year	-0.0130	0.0095	-1.3688	0.1711	-0.0317	0.0056

eTable 6 | Definition of terms for bias assessment according to the Newcastle-Ottawa criteria for case-control studies

Rating item	Definition
Selection	
1. Adequate case definition	1 star is awarded if subjects are diagnosed separately by at least two doctors/psychologists according to a diagnostic tool (e.g. DSM, RDC, ICD). If patients are referred from a psychiatric ward and the diagnosis is validated independently by an investigator, 1 star will be given.
2. Representativeness of cases	1 star is awarded if it is clearly stated in the article, that all eligible subjects are included over a defined period of time, or in a defined catchment area, and thus are a representative sample of the population of patients from which they are recruited.
3. Selection of controls	1 star will be awarded if it is stated explicit that controls are recruited from the community, hospital staff or similar.
4. Definition of controls	1 star is awarded if it is clearly specified, that the controls have no current or past history of psychiatric illness.
Comparability	
1. Comparability of cases and controls on the basis of the design or analysis	2 stars are awarded if controls and patients are matched on age and sex and/or if these are adjusted for in the analysis. Statements of no significant differences between groups are not sufficient. If only sex or age is matched and/or adjusted for, 1 star is awarded.
Exposure	
1. Ascertainment of exposure	1 star will be awarded if it is specified that the laboratory staff responsible for the biomarker analysis was blinded to the case-control status of the samples.
2. Same method of ascertainment for cases and controls	1 star will be awarded if the exact same assay, quantification method and statistical analysis are used for both patients and controls.
3. Non-response rate	This item is of no relevance and will therefore not be assessed. The maximum number of stars is thus 8.

For details, see http://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf

eTable 7 | Bias assessment according to the Newcastle-Ottawa criteria for case-control studies

Study		Selection				Comparability		Exposure		Total no. of stars	Data source
		1	2	3	4	1		1	2		
Åsberg	1984	1	1	1	1	2	age, sex	0	1	**7**	Article
Barbaccia	1986	0	0	0	1	2	age, sex[bbb]	0	1	**4**	Article
Bissette	1986	0	0	0	0	0		0	1	**1**	Article
Blennow	1995	0	0	0	1	1	age	0	1	**2**	Article
Brundin	2008	1	0	0	0	0		0	1	**2**	Article
Brundin	2016	1	0	0	1	1	age	1	1	**5**	Article
Bruno	2020	0	0	0	0	2	age, sex	0	1	**3**	Article + Pomara[68]
Buerger	2003	0	0	0	0	2	age, sex	0	1	**3**	Article
Bumb	2016	1	0	1	1	2	age, sex	0	1	**6**	Article
Bürger née Buch	1999	0	0	0	0	1	age	0	1	**2**	Article
Carpenter, Heninger	2004	1	0	1	1	2	age, sex	0	1	**6**	Article
Carpenter, Tyrka	2004	0	0	1	1	2	age, sex	0	1	**5**	Article
DeBellis	1993	0	0	0	0	0		0	1	**1**	Article
Deuschle	2005	0	0	0	1	0		0	1	**2**	Article
Diniz	2014	1	0	1	1	1	age	0	1	**5**	Article
Edman	1986	1	0	1	1	2	age, sex	0	1	**6**	Article
Eratne	2020	1	1	1	1	2	age, sex	1	1	**8**	Article
Erhardt	2013	1	1	0	1	1	age	0	1	**5**	Article
Frye	2007	1	0	1	1	2	age, sex	1	1	**7**	Article
Garakani	2013	0	0	0	1	0		0	1	**2**	Article
George	1994	0	1	1	1	2	age, sex	0	1	**6**	Article
Geracioti	2006	1	0	0	1	2	age, sex	1	1	**6**	Article
Gerner	1981	0	0	0	1	0		1	1	**3**	Article
Gerner	1982	0	0	0	0	0		0	1	**1**	Article
Gerner	1983	0	0	0	1	0		1	1	**3**	Article
Gotoh	2019	1	0	1	0	0		0	1	**3**	Article
Gudmundsson	2007	0	1	1	0	2	age, sex	0	1	**5**	Article
Gudmundsson	2010	0	1	1	0	2	age, sex	0	1	**5**	Article
Hampel	1997	0	0	0	0	2	age, sex	0	1	**3**	Article
Hampel	1999	0	0	0	0	2	age, sex	0	1	**3**	Article
Hashimoto	2016	0	0	1	1	2	age, sex	0	1	**3**	Article
Hashimoto	2017	0	0	1	1	2	age, sex	0	1	**3**	Article
Hattori	2015	1	0	1	1	2	age, sex	1	1	**7**	Article
Heilig	2004	1	0	1	1	1	age, sex	0	1	**5**	Article
Hertze	2010	0	0	1	0	2	age, sex	0	1	**4**	Article
Heuser	1998	0	0	0	1	1	age	0	1	**3**	Article
Hidese	2017	1	0	1	1	2	age, sex	0	1	**6**	Article
Hidese	2020	1	0	1	1	2	age, sex	0	1	**6**	Article
Hidese	2021	1	0	1	1	2	age, sex	0	1	**6**	Article
Ishii	2018	1	0	1	1	2	age, sex	0	1	**6**	Article
Ishiwata	2018	1	0	1	1	2	age, sex	1	1	**7**	Article

[bbb] Data from matched subgroup extracted

Ishiwata	2017	1	0	1	1	2	age, sex	0	1	**6**	Article
Itagaki	2019	1	0	1	1	2	age, sex	1	1	**7**	Article
Janelidze	2015	1	1	0	1	2	age, sex	0	1	**6**	Article
Janelidze	2013	1	0	0	1	2	age, sex	0	1	**5**	Article
Jensen	1999	1	0	1	0	2	age, sex	0	1	**5**	Article
Kaddurak-Daouk	2012	0	0	0	1	0		0	1	**2**	Article
Kageyama	2021	0	0	1	0	0		0	1	**2**	Article
Kasa	1982	0	0	0	0	0		0	1	**1**	Article
Kern	2014	1	1	1	1	2	age, sex	0	1	**7**	Article
Kling	1991	0	0	0	1	2	age, sex	0	1	**4**	Article
Koslow	1983	0	0	1	1	2	age, sex	1	1	**6**	Article
Lewine	1991	1	0	1	1	0		0	1	**4**	Article
Lindqvist	2009	0	0	0	1	1	age	0	1	**3**	Article
Madeira	2015	0	0	0	0	1	age	0	1	**2**	Article
Madeira	2018	0	0	0	0	1	age	0	1	**2**	Article
Mann	2014	0	0	1	1	2	age, sex	0	1	**5**	Article
Martinez	2012	0	0	0	1	0		1	1	**3**	Article
Mathé	2002	0	0	0	1	2	age, sex	1	1	**5**	Article
Mizui	2019	1	0	1	1	2	age, sex	0	1	**6**	Article
Molchan	1991	0	0	1	1	1	age	0	1	**4**	Article
Molchan	1993	0	0	1	1	1	age	0	1	**4**	Article
Ogawa	2015	1	0	1	1	2	age, sex	0	1	**6**	Article
Omori	2020	1	0	1	1	2	age, sex	0	2	**7**	Article
Oreland	1981	0	0	1	1	0		0	1	**3**	Article
Pillai	2019	0	0	1	1	0		0	1	**3**	Article
Pitts	1995	1	0	1	1	0		1	1	**5**	Article
Pomara	2012	0	0	1	1	1	age	0	1	**4**	Article
Pomara	2021	0	0	1	1	1	age	0	1	**4**	Article + Pomara[68]
Post	1982	0	0	0	0	0		0	0	**0**	Article
Pålhagen	2010	0	0	1	0	0		0	1	**2**	Article
Regenold	2000	0	0	0	1	1	age	0	0	**2**	Article
Reis	2012	0	0	0	0	0		1	1	**2**	Article
Risch	1992	1	1	1	1	1	age	0	1	**6**	Article
Roy	1991	0	0	1	1	2	age, sex	0	1	**5**	Article
Rubinow	1983	0	0	0	1	0		0	1	**2**	Article
Rymo	2017	0	1	1	1	2	age, sex	1	1	**7**	Article
Sanfilippo	2016	1	0	0	0	0	age, sex	1	1	**3**	Article
Sasayama	2012	1	0	1	1	1	sex	0	1	**5**	Article
Sasayama	2013	1	0	1	1	2	age, sex	0	1	**6**	Article
Schmidt	2011	0	1	0	1	0		0	1	**3**	Article
Sher	2005	0	0	1	0	0	age, sex[ccc]	0	1	**2**	Article
Sher	2006	1	0	0	0	0	age, sex	0	1	**2**	Article
Soleimani	2014	0	0	1	1	2	age, sex	0	1	**5**	Article
Stokes	1984	0	0	1	1	2	age, sex	1	1	**6**	Article
Sullivan	1999	0	0	1	1	2	age, sex	1	1	**6**	Article
Sullivan, Oquendo	2006a	0	0	0	1	1	sex	0	1	**3**	Article

[ccc] The group with comorbid PTSD not matched on sex

Sullivan, Mann	2006b	0	0	1	1	2	age, sex	0	1	**5**	Article
Sunderland	1991	0	0	0	1	2	age, sex	0	1	**4**	Article
Swann	1999	0	0	0	0	2	age, sex	1	1	**4**	Article
Vawter	2000	0	0	0	0	2	age, sex	0	1	**3**	Article
Ventorp	2016	0	0	0	1	2	age, sex	0	1	**4**	Article
Widerlöv, Bisette	1988a	0	0	0	1	0		0	1	**2**	Article
Widerlöv, Lindström	1988b	0	0	0	1	0		0	1	**2**	Article
Wong	2000	0	0	0	1	0		0	1	**2**	Article
Yoon	2017	1	0	1	1	2	age, sex	0	1	**6**	Article
Yoon	2018	1	0	1	1	2	age, sex	1	1	**7**	Article

eTable 8 | Studies contacted for data request

Study		Data requested	Mail sent	Reminder sent	Reply
Ågren	1983	Mean and SD on unipolar subgroup and controls	26.01.2021	16.02.2021	/
Anderson	1984	Mean and SD on unipolar subgroup	18.01.2021	03.02.2021	/
Bendix	2017	Mean and SD on unipolar subgroup	18.01.2021	/	data not available
Bowden	1981	Mean and SD on controls	18.01.2021	03.02.2021	/
Ehnvall	2003	Number of unipolar patients + mean and SD	18.01.21 + 27.01.21	16.02.2021	/
Hou	2006	Mean and SD on patients and controls	18.01.2021	03.02.2021	/
Ishiwata	2017	Mean and SD on patients and controls	09.02.2021	/	data received
Ishiwata	2018	Mean and SD on patients and controls	09.02.2021	/	data received
Yoon	2017	Mean and SD on patients and controls	18.01.2021	03.02.2021	data received
Yoon	2018	Mean and SD on patients and controls	18.01.2021	03.02.2021	data received
Engström	1999	Mean and SD on controls	18.01.2021	03.02.2021	data not available
Fachinetti	1986	Mean and SD on patients and controls	18.01.2021	03.02.2021	/
Isung	2012	Number of patients + mean and SD	19.01.2021	04.03.2021	/
Chatzittofis	2013	Number of patients + mean and SD	19.01.2021	04.03.2021	/
Stefansson	2016	Number of patients + mean and SD	19.01.2021	04.03.2021	/
Janelidze	2015	Demografic data on patients	19.01.2021	03.02.2021	/
Salomon	2003	Mean and SEM on unipolar subgroup	19.01.2021	03.02.2021	data not available
Sasayama	2012	Mean and SD on patients and controls	18.01.2021	/	data received
Sasayama	2013	Mean and SD on patients and controls	18.01.2021	/	data received
Carpenter	2008	Mean and SD on unipolar subgroup	18.01.2021	/	data not available
Bumb	2016	Demografic data on unipolar subgroup	18.01.2021	/	data not available
Ventorp	2016	Mean and SD on patients and controls	19.01.2021	/	data received
Casper	1988	Mean and SD on unipolar subgroup	23.01.2021	/	data not available
Catlin	1982	Mean and SEM on unipolar subgroup	21.01.2021	04.03.2021	data not available
Frye	2003	Mean and SD on unipolar subgroup	21.01.2021	04.03.2021	/
Frye	2007	Mean and SD on unipolar subgroup	21.01.2021	04.03.2021	/
Poltorak	1996	Mean and SD on unipolar subgroup and controls	21.01.2021	04.03.2021	/
Berrettini	1987	Mean and SD on unipolar subgroup	21.01.2021	/	data not available
Berrettini	1988	Mean and SD on patients and controls	21.01.2021	/	data not available
Eratne	2020	Mean and SD on patients and controls	19.01.2021	/	data received
Rubinow	1981	Mean and SD on unipolar subgroup	23.01.2021	/	data not available
Pazzaglia	1995	Mean and SD on controls	23.01.2021	/	data not available
Jimerson	1983	Mean and SD on unipolar subgroup	23.01.2021	/	data not available
Kling	1993	Mean and SEM on unipolar subgroup	23.01.2021	09.02.2021	/
Lewine	1991	Demografic data on unipolar subgroup	23.01.2021	09.02.2021	/
Mann	2008	Number of patients and controls + mean and SD	23.01.2021	09.02.2021	/
Mann	2014	Mean and SD on unipolar subgroup	23.01.2021	09.02.2021	/
Mathe	1994	Mean and SD on controls	25.01.2021	/	data not available
Omori	2020	Mean and SD on MMP-8 in patients and controls	23.01.2021	/	data not available

Pitts	1990	Mean and SD on patients	25.01.2021	09.02.2021	/
Vawter	2000	Mean and SD on patients and controls	25.01.2021	09.02.2021	/
Stübner	1999	Mean and SD on patients and controls	25.01.2021	09.02.2021	/
Song	2015	Mean and SD on patients and controls	25.01.2021	09.02.2021	/
Spiegel	1992	Mean and SD on patients and controls	25.01.2021	09.02.2021	/
Yesavage	1982	Mean and SD on patients and controls	25.01.2021	09.02.2021	/
Bertilsson	1982a	Baseline mean and SD for patients and controls	25.01.2021	/	data not available
Bertilsson	1982b	Baseline mean and SD for patients and controls	25.01.2021	/	data not available
Little 1999	1999	Mean and SD on patients and controls	26.01.2021	09.02.2021	/
Stokes 1987	1987	Number of patients and controls + mean and SD	25.01.2021	16.02.2021	/
Träskman	1980	Info on unipolar / bipolar + mean and SD on patients and controls	25.01.2021	/	data not available
Träskman	1981	Info on unipolar / bipolar + mean and SD on patients and controls	25.01.2021	/	data not available
Träskman-Bendz	1984	Info on unipolar / bipolar + mean and SD on patients	25.01.2021	/	data not available
Richards	2018	Mean and SD on patients and controls	25.01.2021	09.02.2021	/
Roy	1986	Mean and SD on unipolar subgroup and controls	26.01.2021	/	data not available
Roy	1987	Mean and SD on unipolar subgroup	27.01.2021	/	data not available
Roy	1988	Number of unipolar patients + mean and SD	28.01.2021	/	data not available
Roy	1994	Mean and SD on unipolar subgroup	29.01.2021	/	data not available
Geracioti	1993	Mean and SD on unipolar subgroup	02.02.2021	15.07.2021	/
Geracioti	1997a	Mean and SD on unipolar subgroup	02.02.2021	15.07.2021	/
Geracioti	1997b	Mean and SD on unipolar subgroup	02.02.2021	15.07.2021	/
Nemeroff	1984	Mean and SD on patients and controls	29.01.2021	/	data not available
Nemeroff	1989	Mean and SD on patients and controls	29.01.2021	/	data not available
Newport	2003	Mean and SD on patients and controls	29.01.2021	/	data not available
Nappi	1985	Mean and SD on patients	28.01.2021	16.02.2021	/
Jones	1990	Number of unipolar patients + mean and SD	01.02.2021	16.02.2021	/
Kern	2014	Mean and SD on patients with depression	01.02.2021	/	data received
Sanfilippo	2016	Mean and SD on patients and controls	01.02.2021	16.02.2021	/
Sunderland	1987	Mean and SD on patients and controls	04.02.2021	16.02.2021	/
Sunderland	1991	Mean and SD on patients and controls	04.02.2021	16.02.2021	/
Zalsman	2008	Number of patients and controls + mean and SD	19.04.2021	15.07.2021	/
Wong	1999	Info on unipolar / bipolar	26.06.2021	/	data received
Derkow	2018	Info on unipolar / bipolar	18.06.2021	15.07.2021	/
Sher	2003	Info on unipolar / bipolar	17.06.2021	15.07.2021	/
Berger	1980	Info on unipolar / bipolar	21.06.2021	15.07.2021	/
Davis	1988	Info on unipolar / bipolar	21.06.2021	15.07.2021	/
Sharma	1995	Info on unipolar / bipolar	21.06.2021	15.07.2021	/

eTable 9 | Studies that had been included in previous meta-analyses but were excluded due to neurological or surgical controls

First author	Year	Cases	Controls	Biomarkers	Results
Reddy[1]	1992	30 depression ptt	30 spinal anesthesia controls	HVA 5-HIAA	Lower in ptt. No difference
Engström[2]	1999	120 suicide attempters (36 MDD)	47 controls (18 surgical controls, 29 healthy controls)	HVA 5-HIAA MHPG	No difference No difference No difference
Palaniappun[3]	1991	39 depression ptt	17 surgical controls	5-HIAA	Lower in ptt.
Johri[4]	1990	30 depression ptt	10 spinal anesthesia controls	DOPEG, NE	Higher in ptt.
Gjerris[5]	1992	24 depression ptt (ICD-9)	12 neurological controls	NPY	Reduced in ptt.
Sørensen[6]	1985	32 depression ptt	52 neurological controls	Vasopressin	No difference
Kramberger[7]	2012	92 subj. cognitive impairment ppt. (41 depressed, 51 not depressed) 91 Alzheimer ptt. (31 depressed, 60 not depressed)		Aβ42 T-tau P-tau181	No difference Lower in all ptt Lower in SCI ptt
Blasko[8]	2006	76 dementia ptt 11 MDD	77 spinal anesthesia controls	Aβ42 Total tau P-tau 181 MCP-1 MIP-1α TNF-α TGF-β_1 NGF HGF GDNF VEGF BDNF FGF-2	No difference No difference No difference No difference No difference No difference No difference No difference No difference No difference No difference No difference No difference
Schönknecht[9]	2007	80 mild cognitive impairment (MDI) 54 MDD	24 spinal anesthesia controls	T-tau P-tau	No difference No difference
Levine[10]	1999	13 depression ptt	10 neurological controls	sIL-2R	Lower in ptt.
Hestad[11]	2016	44 depression ptt.	21 neurological controls	IL-1Rα IL-1β IL-2 IL-4 IL-5 IL-6 IL-7 IL-8 IL-9 IL-10 IL-12 p70 IL-13 IL-15 IL-17A Eotaxin FGF-basic G-CSF	Lower in ptt. No difference No difference No difference No difference No difference No difference No difference No difference No difference No difference No difference No difference No difference No difference No difference No difference

GM-CSF	No difference
IFN-γ	No difference
IP-10	No difference
MCP-1	No difference
MIP-1α	No difference
MIP-1β	No difference
PDGF-BB	No difference
RANTES	No difference
TNFα	No difference
VEGF	No difference

[1] Reddy, P. L., Khanna, S., Subhash, M. N., Channabasavanna, S. M., & Sridhara Rama Rao, B. S. (1992). CSF amine metabolites in depression. *Biological Psychiatry*, *31*(2), 112–118. https://doi.org/10.1016/0006-3223(92)90198-9

[2] Engström, G., Alling, C., Blennow, K., Regnéll, G. öran, & Träskman-Bendz, L. (1999). Reduced cerebrospinal HVA concentrations and HVA/5-HIAA ratios in suicide attempters: Monoamine metabolites in 120 suicide attempters and 47 controls. *European Neuropsychopharmacology*, *9*(5), 399–405. https://doi.org/10.1016/S0924-977X(99)00016-4

[3] Palaniappun, V., Ramachandran, V., & Somasundaram, O. (1991). Norepinephrine And Serotonin Metabolism And Clinical Response To Combind Imipramine And Amitriptyline Theraphy In Depression. *Indian Journal of Psychiatry*, *33*, 224–231.

[4] Johri MS, Misra NP, Gaur KJ, Trivedi HH. Value of DOPEG estimation in CSF in depression. Indian J Med Res. 1990 Dec;92:417-9. PMID: 2079356.

[5] Gjerris, A., Widerlöv, E., Werdelin, L., & Ekman, R. (1992). Cerebrospinal fluid concentrations of neuropeptide Y in depressed patients and in controls. *Journal of Psychiatry & Neuroscience : JPN*, *17*(1), 23–27.

[6] Sorensen, P.S., Gjerris, A., Hammer, M., 1985. Cerebrospinal-fluid vasopressin in neurological and psychiatric-disorders. J. Neurol. Neurosurg. Psychiatry 48 (1), 50–57.

[7] Kramberger, M. G., Jelic, V., Kåreholt, I., Enache, D., Eriksdotter Jönhagen, M., Winblad, B., & Aarsland, D. (2012). Cerebrospinal Fluid Alzheimer Markers in Depressed Elderly Subjects with and without Alzheimer's Disease. *Dementia and Geriatric Cognitive Disorders Extra*, *2*(1), 48–56. https://doi.org/10.1159/000334644

[8] Blasko, I., Lederer, W., Oberbauer, H., Walch, T., Kemmler, G., Hinterhuber, H., … Humpel, C. (2005). Measurement of thirteen biological markers in CSF of patients with Alzheimer's disease and other dementias. *Dementia and Geriatric Cognitive Disorders*, *21*(1), 9–15. https://doi.org/10.1159/000089137

[9] Schönknecht, P., Pantel, J., Kaiser, E., Thomann, P., & Schröder, J. (2007). Increased tau protein differentiates mild cognitive impairment from geriatric depression and predicts conversion to dementia. *Neuroscience Letters*, *416*(1), 39–42. https://doi.org/10.1016/j.neulet.2007.01.070

[10] Levine, Barak, Y., Chengappa, K. R. N., Rapoport, A., Antelman, S. M., & Barak, V. (1999). Low CSF soluble interleukin 2 receptor levels in acute depression. Journal of Neural Transmission, 106(9), 1011–1015. https://doi.org/10.1007/s007020050219

[11] Hestad, K. A., Engedal, K., Whist, J. E., Aukrust, P., Farup, P. G., Mollnes, T. E., & Ueland, T. (2016). Patients with depression display cytokine levels in serum and cerebrospinal fluid similar to patients with diffuse neurological symptoms without a defined diagnosis. *Neuropsychiatric Disease and Treatment*, *12*, 817–822. https://doi.org/10.2147/NDT.S101925

The latest meta-analyses on this field, which have been searched to identify the studies above:

[a] Ogawa, Hattori, K., Sasayama, D., Yokota, Y., Matsumura, R., Matsuo, J., Ota, M., Hori, H., Teraishi, T., Yoshida, S., Noda, T., Ohashi, Y., Sato, H., Higuchi, T., Motohashi, N., & Kunugi, H. (2015). Reduced cerebrospinal fluid ethanolamine concentration in major depressive disorder. Scientific Reports, 5(1), 7796–7796. https://doi.org/10.1038/srep07796

[b] Pech, Forman, J., Kessing, L. V., & Knorr, U. (2018). Poor evidence for putative abnormalities in cerebrospinal fluid neurotransmitters in patients with depression versus healthy non-psychiatric individuals: A systematic review and meta-analyses of 23 studies. Journal of Affective Disorders, 240, 6–16. https://doi.org/10.1016/j.jad.2018.07.031

[c] Romeo, Choucha, W., Fossati, P., & Rotge, J.-Y. (2018). Meta-analysis of central and peripheral γ-aminobutyric acid levels in patients with unipolar and bipolar depression. Journal of Psychiatry & Neuroscience, 43(1), 58–66. https://doi.org/10.1503/jpn.160228

[d] Tural, & Iosifescu, D. V. (2020). Neuropeptide Y in PTSD, MDD, and chronic stress: A systematic review and meta-analysis. Journal of Neuroscience Research, 98(5), 950–963. https://doi.org/10.1002/jnr.24589

[e] Leighton, Nerurkar, L., Krishnadas, R., Johnman, C., Graham, G. J., & Cavanagh, J. (2018). Chemokines in depression in health and in inflammatory illness: a systematic review and meta-analysis. Molecular Psychiatry, 23(1), 48–58. https://doi.org/10.1038/mp.2017.205

[f] Rutigliano, G, Rocchetti, M., Paloyelis, Y., Gilleen, J., Sardella, A., Cappucciati, M., Palombini, E., Dell'Osso, L., Caverzasi, E., Politi, P., McGuire, P., & Fusar-Poli, P. (2016). Peripheral oxytocin and vasopressin: Biomarkers of psychiatric disorders? A comprehensive systematic review and preliminary meta-analysis. Psychiatry Research, 241, 207–220. https://doi.org/10.1016/j.psychres.2016.04.117

[g] Nascimento, Silva, K. P., Malloy-Diniz, L. F., Butters, M. A., & Diniz, B. S. (2015). Plasma and cerebrospinal fluid amyloid-β levels in late-life depression: A systematic review and meta-analysis. Journal of Psychiatric Research, 69, 35–41. https://doi.org/10.1016/j.jpsychires.2015.07.024

[h] Brown, Iwata, Y., Chung, J. K., Gerretsen, P., & Graff-Guerrero, A. (2016). Tau in Late-Life Depression: A Systematic Review and Meta-Analysis. Journal of Alzheimer's Disease, 54(2), 615–633. https://doi.org/10.3233/JAD-160401

[i] Wang, & Miller, B. J. (2018). Meta-analysis of Cerebrospinal Fluid Cytokine and Tryptophan Catabolite Alterations in Psychiatric Patients: Comparisons Between Schizophrenia, Bipolar Disorder, and Depression. Schizophrenia Bulletin, 44(1), 75–83. https://doi.org/10.1093/schbul/sbx035

[j] Enache, Pariante, C. M., & Mondelli, V. (2019). Markers of central inflammation in major depressive disorder: A systematic review and meta-analysis of studies examining cerebrospinal fluid, positron emission tomography and post-mortem brain tissue. Brain, Behavior, and Immunity, 81, 24–40. https://doi.org/10.1016/j.bbi.2019.06.015

[k] Orlovska-Waast, Köhler-Forsberg, O., Brix, S. W., Nordentoft, M., Kondziella, D., Krogh, J., & Benros, M. E. (2019). Cerebrospinal fluid markers of inflammation and infections in schizophrenia and affective disorders: a systematic review and meta-analysis. Molecular Psychiatry, 24(6), 869–887. https://doi.org/10.1038/s41380-018-0220-4

eTable 10 | GRADE evidence profile for biomarkers quantified in ≧2 studies

Quality assessment						
Biomarker No. of studies, Study design	Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	**Overall quality**
HVA 17, Case control	Serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊕◯ **Moderate**
5-HIAA 15, Case control	No serious limitations	Very serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⊕⊕◯◯ **Low**
MHPG 14, Case control	Serious limitations	Very serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⊕◯◯◯ **Very low**
GABA 4, Case control	No serious limitations	Very serious inconsistency	No serious indirectness	Serious imprecision	Undetected	⊕◯◯◯ **Very low**
Glutamate 4, Case control	Serious limitations	Very serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	⊕◯◯◯ **Very low**
Glutamine 4, Case control	Serious limitations	Very serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	⊕◯◯◯ **Very low**
Cortisol 2, Case control	No serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	⊕⊕◯◯ **Low**
Transthyretin 2, Case control	No serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	⊕⊕◯◯ **Low**
CRH 8, Case control	Serious limitations	Very serious inconsistency	No serious indirectness	Serious imprecision	Undetected	⊕◯◯◯ **Very low**
ACTH 2, Case control	No serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	⊕⊕◯◯ **Low**
Oxytocin 2, Case control	No serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	⊕⊕◯◯ **Low**
Vasopressin 2, Case control	Serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	⊕◯◯◯ **Very low**
Somatostatin 5, Case control	Serious limitations	Very serious inconsistency	No serious indirectness	Serious imprecision	Undetected	⊕◯◯◯ **Very low**
NPY 5, Case control	Serious limitations	Very serious inconsistency	No serious indirectness	Serious imprecision	Undetected	⊕◯◯◯ **Very low**
Substance P 2, Case control	No serious limitations	Very serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	⊕◯◯◯ **Very low**
CART 2, Case control	No serious limitations	Serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	⊕◯◯◯ **Very low**
Orexin 2, Case control	Serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	⊕◯◯◯ **Very low**
D-serine	No serious limitations	Very serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	⊕◯◯◯ **Very low**

3, Case control						
L-serine 3, Case control	No serious limitations	Very serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	⨁◯◯◯ **Very low**
Serine 2, Case control	No serious limitations	Very serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	⨁◯◯◯ **Very low**
Glycine 3, Case control	No serious limitations	Very serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	⨁◯◯◯ **Very low**
Tryptophan 2, Case control	No serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	⨁⨁◯◯ **Low**
Tyrosine 2, Case control	No serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	⨁⨁◯◯ **Low**
Aspartate 2, Case control	No serious limitations	Very serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	⨁◯◯◯ **Very low**
Methionine 2, Case control	No serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	⨁⨁◯◯ **Low**
Ascorbic acid 2, Case control	Serious limitations	Very serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	⨁◯◯◯ **Very low**
IL-6 7, Case control	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected	⨁⨁⨁◯ **Moderate**
IL-8 5, Case control	No serious limitations	Very serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⨁⨁◯◯ **Low**
TNF-alfa 2, Case control	Serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	⨁◯◯◯ **Very low**
WCC 3, Case control	No serious limitations	Very serious inconsistency	No serious indirectness	Serious imprecision	Undetected	⨁◯◯◯ **Very low**
MMP-3 2, Case control	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected	⨁⨁⨁◯ **Moderate**
Total protein 5, Case control	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⨁⨁⨁⨁ **High**
Albumin ratio 2, Case control	No serious limitations	Very serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	⨁◯◯◯ **Very low**
Glucose 2, Case control	No serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	⨁⨁◯◯ **Low**
Amyloid-B-40 3, Case control	No serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	⨁⨁◯◯ **Low**
Total tau 9, Case control	Serious limitations	Very serious inconsistency	No serious indirectness	Serious imprecision	Undetected	⨁◯◯◯ **Very low**
P-tau 181 6, Case control	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected	⨁⨁⨁◯ **Moderate**

Amyloid-B-42 8, Case control	No serious limitations	Very serious inconsistency	No serious indirectness	Serious imprecision	Undetected	⊕◯◯◯ **Very low**
Neurogranin 2, Case control	Serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	⊕◯◯◯ **Very low**
NfL 2, Case control	No serious limitations	Very serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	⊕◯◯◯ **Very low**
BDNF 3, Case control	Serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision	Undetected	⊕◯◯◯ **Very low**
NCAM 2, Case control	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected	⊕⊕⊕◯ **Moderate**

As all included studies are case control studies with both well-defined patient- and control groups, and as this is state-of-the-art within this field, we chose the starting point "high quality" for all analyses. From here the quality was rated downwards based on the following items.
Study limitations: based on the mean Newcastle-Ottawa criteria for case-control studies (eTable 7) total scores for the included studies; rating -1 when <4 and -2 when <2.
Inconsistency: based on point estimate variation, CI overlap, I^2 and *p*-value for I^2; rating -1 if $I^2 > 20\%$ or $p < 0.05$ and -2 if $I^2 > 40\%$ or $p < 0.0$.
Indirectness: based on differences in patients, interventions, outcomes and head-to-head comparison. As this is addressed in inclusion and exclusion criteria all analyses are rated as "no serious indirectness".
Imprecision: based on sample size requirements for effect sizes of SMD = 0.4 and 0.2 ; rating -1 if the total number of cases or total number of controls were < 200 and -2 if < 100.
Publication bias: assessed with funnel plots for biomarkers with > 10 studies included.