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

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

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eTable 1 | PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE	I	F	
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	1	r	
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 re- view, 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 in- tervention 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 de- tails 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 pro- cess.	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 meth- ods	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 assess- ment	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 + eFig- ure 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 character- istics	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 indi- vidual 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 synthe- ses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among con- tributing 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 + Ta- ble 1 + eFig- ure 2-6
	20c	Present results of all investigations of possible causes of heterogeneity among study re- sults.	p. 3-9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the syn- thesized results.	p. 3-8
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting bi- ases) for each synthesis assessed.	p. 8 + eFig- ure 12
Certainty of evi- dence	22	Present assessments of certainty (or confidence) in the body of evidence for each out- come assessed.	p. 3-8 + Ta- ble 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 INFORM	IATIO	N	
Registration and protocol	24a	Provide registration information for the review, including register name and registra- tion 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 inter- ests	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

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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

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

Item No	Recommendation	Reported on Page No
Reporting of	f 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	f 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	f 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 appropri- ate)	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	Supplemen- tary
Reporting of	f 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

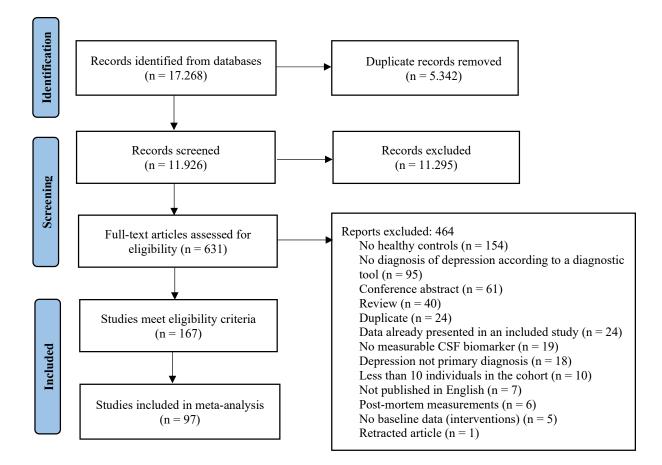
Item No	Recommendation	Reported on Page No				
Reporting of discussion should include						
29	Quantitative assessment of bias (eg, publication bias)	p. 8-9				
30	Justification for exclusion (eg, exclusion of non-English language citations)	p. 8-9				
31	Assessment of quality of included studies	p. 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").



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
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Included in Study		Case subjects			Cont	rol subjects	Markers in-	CSF assay
Study		N, diagnosis (di- agnostic tool)	% of males / mean (SD)	Psychotropic medication status	N	% of males / mean (SD)	cluded in metaanalysis	method
å . 1 1	1004		age		((age		NIA
Åsberg ¹	1984	60 ^a , unipolar en- dogenous MDD (Newcastle In- ventory and RDC)	37/52.5 (13.6) ^b	No medication for ≥ 10 days	66	59/37.8 (11.4)	HVA, 5-HIAA, MHPG	NA
Bar- baccia 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 (diaze- pam-binding inhibitor)	Radioimmuno- assay
Bissette ³	1986	17, major depres- sion (DSM-III- R)	69/49.1 (3.5), SEM	No medication for ≥ 2 weeks	10	50/34.2 (3.2), SEM	Somatostatin	Radioimmuno- assay
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	Radioimmuno- assay
Brundin ⁶	2016	31, MDD and de- pression NOS (DSM-III-R)	NA/62.27 (NA)	No medication for 14.6 (9) days, mean (SD)	36	NA/30 (NA)	PIC	Gas chroma- tography–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	· ·	43/33.0 (9.7)	100% of patients on medication	27°	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 ¹		18, MDD (DSM- IV)	50/38.3 (13.4)	No medication for \geq 3 weeks	26	46/32.7 (10.0)	IL-6	'Quantikine' highsensitivity immunoassay
Carpenter, Tyrka ¹²	2004 b	27, MDD (DSM- IV)	41/37.4 (13)	No medication for ≥ 2 weeks	25	48/34.0 (11.5)	CRH	Radioimmuno- assay
DeBellis ¹³	1993	9, MDD (RDC and DSM-III-R)	56/42.8 (11.1)	No medication for \geq 3 weeks	46	50/37.2 (10.4)	HVA, 5-HIAA, MHPG	High-perfor- mance liquid chromatog- raphy
De- uschle ¹⁴	2005	11, MDE (DSM- IV)	36/56.5 (15)	No medication for ≥ 6 days	11	100/51.4 (23.3)	Substance P	Enzyme immu- noassay

^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.

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Diniz ¹⁵	2014	16, major depres- sion (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 In- ventory 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	Ultrahighper- formance liquid chromatog- raphy
Frye ¹⁹	2007	8, unipolar de- pression (DSM- IV)	NA	No medication for ≥ 1 week	14	NA/38.31(12. 56)	Aspartate ^h	High-perfor- mance liquid chromatog- raphy
Gara- kani ²⁰	2013	18 ⁱ , MDD (DSM-IV)	44/40.4 (20)	No medication for ≥ 2 weeks	24 ⁱ	52/29.9 (6.7)	CRH, gluta- mate, gluta- mine	NA
George ²¹	1994	43, recurrent uni- polar (RDC)	53/37.2 (12.6)	No medication for ≥ 2 weeks	59	37/30.5 (12.5)	Magnesium	Atomic absorp- tion technique
Geraci- oti ²²	2006	40, MDD (DSM- IV)	50/36.7 (13.8)	No medication for ≥ 2 weeks	47	45/32.7 (10.9)	Substance P	Radioimmuno- assay (solid phase)
Gerner ²³	1981	19, unipolar de- pression (RDC)	46/42.6 (NA) ^j	No medication for ≥ 1 week	29	48/32 (NA)	GABA	Ionexchange flurometric procedure
Gerner ²⁴	1982	19, MDD unipo- lar (RDC)	NA	No medication for ≥ 1 week	9	44/NA	B-endorphin	Radioimmuno- assay
Gerner ²⁵	1983	22, MDD unipo- lar (RDC)	NA	No medication for ≥ 1 week	22	NA	Cortisol	Radioimmuno- assay
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
Gudmun- dsson 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	ELISA
Gudmun- dsson ²⁸	2010	11, MDD (DSM-III-R)	0/73.9 (3.2) ^k	NA	65	0/73.9 (3.2) ^k	ratio 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	Immunonephe- lometric method
Hampel ³⁰	1999	29, major depression (DSM-III-R and ICD-10)		NA	11	55/72.8 (6.9)	IgG Index	Immunonephe- lometric 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.

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Hashi- moto ³¹	2016	28, MDD (DSM- IV)	64/66.5 (5.4)	79% of patients on medication	19	37/68.1/7.3	Glutamate, glu- tamine, gly- cine, L-serine, D-serine	High-perfor- mance liquid chromatog- raphy
Hashi- moto 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 chroma- tography–mass spectrometry
Hattori ³³	2015	66 ^l , 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, somato- statin, HVA, 5- HIAA, MHPG	Radioimmuno- assay
Hertze ³⁵	2010	28, depression (DSM-IV)	50/58.0 (8.4)	NA	38	29/77 (8.2)	Amyloid-B-42 xMAP, amy- loid-B-42, am- yloid-B-40, amyloid-B-38, t-tau, p-tau 181, sABPP-alfa, sABPP-beta	xMAP technol- ogy (obs, com- ment)
Heuser ³⁶	1998	37, MDE (DSM- III-R)	30/46.8(17.2)	No medication for \geq 5 days	25	68/65.5 (15.4)	CRH, somato- statin, vaso- pressin	Radioimmuno- assay
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, neuro- pilin-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/TNFSF 13, BAFF/TNFSF1 3B, Soluble CD30/TNFSF8 , Soluble CD163, IFN- $\alpha 2$, IFN- β , sol- uble IL-6 re- ceptor, IL-8, IL-10, IL-11, IL-12 (p40), IL-19, IL-26, IL-29/IFN- $\lambda 1$, MMP-3, Oste- ocalcin, Solu- ble TNF-recep- tor 1 and 2, TSLP	Multiplex im- munoassay

 $^{^1}$ SL000022, SL000424, SL003341 measured in a subsample of 30 cases and 30 controls. © 2022 American Medical Association. All rights reserved.

Ishii ⁴⁰	2018	89, MDD (DSM-	48/43.8(10.4)	NA	117	56/42.5	C5	ELISA
Ishiwata ⁴¹	2018	IV) 26 ^m , MDD (DSM-IV)	50/41.4(7.3)	85% of patients on medication	27	(15.3) 52/41.6 (9.1)	D-serine, L-ser- ine	High-perfor- mance liquid chromatog- raphy
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 (auto- taxin)	ELISA
Janeli- dze ⁴⁴	2015	52, MDD and de- pression NOS (DSM-III-R)	NA	No medication for 15 (8) days, mean (SD)	48	81/38 (22)	IL-8	Electrochemi- luminescence- based immuno- assay
Janeli- dze ⁴⁵	2013	51, MDD and de- pression 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 elec- trochemilumi- nescence-based immunoassay
Jensen ⁴⁶	1999	15, MDD (DSM- IV)	40/65(9)	NA	24	42/69 (8)	Amyloid-B-42, amyloid-B-40	ELISA
Kaddu- rah- Daouk ⁴⁷	2012	14 with current MDD, 14 remit- ted (DSM-IV)	57/38(13)	No medication for ≥ 3 weeks, mean (SD): 122.5 (147.5)	18	44/40 (11)	5-HIAA, tryp- tophan, tryp- tophol, kynurenine, HVA, L- DOPA, tyro- sine, MHPG, tyramine, 4HPAC, 4HPLA, 4HBAC, HX, xanthine, xan- thosine, gr, 7MXAN, uric, X7MG, methi- onine, GLNTRP, glu- tathione, ascor- bic acid, HHASC	Liquid chroma- tography elec- trochemical ar- ray
Kage- yama 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 de- pression (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.

 $^{^{\}rm o}$ 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.

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Kling ⁵¹	1991	21, major depres- sion (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 unipo- lar (RDC)	0/49.3(13.6)	No medication for ≥ 2 weeks	80	0/43.83 (14.38)	HVA, 5-HIAA, MHPG	Gas chroma- tography–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-perfor- mance liquid chromatog- raphy
Lind- qvist ⁵⁴	2009	32, MDD and de- pression 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-ser- ine, 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, glu- tamine	High-perfor- mance liquid chromatog- raphy
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 chroma- tography–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 depres- sion (DSM-IV)	34/47.6(12.9)	No medication for ≥ 15 days	19	79/63.8 (6.4)	Calcitonin, CGRP	Radioimmuno- assay
Mizui ⁶⁰	2019	18, MDD (DSM- IV)	56/42.0, me- dian	78% of patients on medication	27	52/42.0, me- dian	BDNF propep- tide, total pro- tein	ELISA
Molchan ⁶¹	1991	18, major depres- sion (DSM-III- R)	33/64.6(9.9)	No medication for ≥ 3 weeks	12	67/65.8 (10.7)	HVA, 5-HIAA, MHPG, soma- tostatin	High-perfor- mance liquid chromatog- raphy
Molchan ⁶²	1993	18, major depres- sion (DSM-III- R)	33/64.6(9.9)	No medication for \geq 3 weeks	13 ^w	77/63.5 (10.0)	CRH	Radioimmuno- assay
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)	Phosphoethan- olamine, threo- nine, serine, as- paragine, gluta- mine, glycine, alanine, alfa- aminobutyrate, valine, methio- nine,	High-perfor- mance liquid chromatog- raphy

^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.

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							isoleucine, leu- cine, tyrosine, phenylalanine, ethanolamine, lysine, histidin + 1-methylhis- tidin, arginine, aspartate, gluta- mate, cystine, tryptophan, or- nithine, carno- sine, 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, to- tal protein, glu- cose, WCC ^y	NA
Oreland ⁶⁵	1981	20 ^z current de- pression and 11 recovered (New- castle Inventory)	100/NA	No medication for ≥ 1 week	28	100/NA	HVA, 5-HIAA, MHPG	Mass fragmen- tography
Pillai ⁶⁶	2019	• /	65/66.9(5.3)	NA	20	40/68.4 (7.2)	C3	ELISA
Pitts ⁶⁷	1995	,	53/37.3(13.8)	100% of patients on medication	18	50/30.7 (10.6)	CRH, vasopres- sin, oxytocin	RIA/high-per- formance liquid chromatog- raphy
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	Electrochemi- luminescence 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; Immu- noassay; Elec- trochemilomi- nesce immuno- assay
Post ⁷⁰	1982	2, unipolar de- pression (RDC)	100/29(2), SEM	No medication for ≥ 2 weeks	41	NA	Cyclic AMP, cyclic GMP	Radioimmuno- assay
Pålha- gen 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, corti- costerone, orexin	Mass fragmen- tography
Re- genold ⁷²	2000	10, unipolar de- pression (RDC)	40/42.1(14.5)	20% of patients on medication, the remaining had no medica- tion for ≥ 2 weeks	10	60/41.1 (8.2)	Glucose, sorbi- tol	Gas chroma- tography–mass spectrometry
Reis ⁷³	2012	20, MDD (DSM- IV)	5/71.3(6.10)	No actual medi- cation	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

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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	Radioimmuno- assay
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 chromatog- raphy
Rubi- now ⁷⁶	1983	7, unipolar de- pression (RDC)	NA	No medication for ≥ 2 weeks	39	NA	Somatostatin	Radioimmuno- assay
Rymo ⁷⁷	2017	19 major and mi- nor depression (DSM-IV)	0/70.8(1.7)	NA	67	0/72.4 (3.1)	YKL-40, GAP- 43, MBP	ELISA
Sanfil- ippo ⁷⁸	2016	6, MDD (DSM- IV)	50/73(NA)	NA	44	30/71 (NA)	Amyloid-B-42, t-tau, p-tau 181, neurogranin	ELISA
Sa- sayama ⁷⁹	2012	17, MDD (DSM- IV)	100/39.5(8.0)	71% of patients on medication	21	100/38.3 (15.3)	Oxytocin	ELISA
Sa- sayama ⁸⁰	2013	30, MDD (DSM- IV)	63/42.7(8.2)	NA	35	60/41.3 (16.4)	IL-6, WCC, to- tal 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-perfor- mance liquid chromatog- raphy
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-perfor- mance liquid chromatog- raphy
So- leimani 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	Radioimmuno- assay
Stokes ⁸⁵	1984	85 ^{ee} , unipolar depression (RDC)	46/49(14)	No medication for ≥ 9 days	80 ^{ee}	48/46 (15)	cortisol	Radioimmuno- assay
Sullivan ⁸⁶	1999	· /	25/41.5(12.0)	No medication for ≥ 2 weeks	24	62/34.8 (12.3)	TTR (transthy- retin)	Dot-blot immu- noassay
Sullivan, Oquendo ⁸ 7	2006 a	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-perfor- mance liquid chromatog- raphy
Sullivan, Mann ⁸⁸	2006 b	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-perfor- mance liquid chromatog- raphy
Sunder- land ⁸⁹	1991	9, major affec- tive disorder, de- pressed type (DSM-III-R)	NA/66.9(9.8)	No medication for \geq 3 weeks	9	NA/67.2 (9.2)	VIP, NPY, dy- norphin A 1-8, galanin	Radioimmuno- assay

 $^{^{\}rm cc}$ CSF data only on 18 cases and 83 controls. $^{\rm dd}$ 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.

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Swann ⁹⁰	1999	85 ^{ff} , unipolar de- pression (RDC)	NA/49.4 (13.6)	No medication for ≥ 2 weeks	85 ^{ff}	NA	MHPG, HVA	Gas chroma- tography–mass spectrometry
Vawter ⁹¹	2000	17, unipolar af- fective disorder (DSM-III-R and DSM-IV)	35/40.5(5.4) SEM	No actual medi- cation	37	65/33.4 (1.9), SEM	Total protein ^{gg}	SDS-PAGE an- alyse
Ventorp ⁹²	2016	39 ^{hh} , MDD and depression NOS (DSM-III-R and DSM-IV)	52/40.70(13.2 86)	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	1988 a	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	Radioimmuno- assay
Widerlöv, Lindström	1988 b	33, MDD (DSM- III-R)	58/46(NA)	No medication for ≥ 2 weeks	20	45/31 (NA)	NPY, PYY	Radioimmuno- assay
Wong ⁹⁵	2000	10, MDE unipo- lar (DSM-III-R and RDC)	20/40.9(2.7)	No medication for ≥ 2 weeks	14	57/37.7 (2.2)	CRH, NE	Radioimmuno- assay
Yoon ⁹⁶	2017	75, MDD (DSM- IV)	49/44.6(10.8)	NA	87	55/42.0 (15.6)	MHPG, HVA, 5-HIAA	High-perfor- mance liquid chromatog- raphy
Yoon ⁹⁷	2018	24, MDD (DSM- IV)	50/42.8(9.8)	NA	25	48/41.6 (14.0)	CART	ELISA

Not include	ed in me	eta-analysis							
Study		Case subjects			Con subj	trol jects	Markers examined	CSF assay method	Reason not included in
		N, diagnosis (diagnostic tool)	% of males / mean (SD) age	Psychotropic medication status	Ν	% of males / mean (SD) age			meta-analysis
Ågren ⁹⁸	1983	NA, MDD (RDC)	NA	No medication for ≥ 10 days	11	NA	Hypoxanthi ne, xanthine	High- performance liquid chromatography	Data mixed of UP and BP. No data on healthy controls.
Anderson ⁹	1984	28, unipolar depression (RDC)	NA	No medication for ≥ 1 week	36	47/31.1 (11.3)	ΙΑΑ	High- performance liquid chromatography	Data mixed of UP and BP.
Bendix ¹⁰⁰	2017	NA, unipolar major depres- sion (DSM-III- R)	NA	No medica- tion for a mean of 8.6 days	19	63/30 (NA)	Insulin, glucagon	Radioimmunoass ay	Suicide study: no data only for MDD.
Berger ¹⁰¹	1980	13 ⁱⁱ , Depres- sion (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 chromatog- raphy–mass spectrometry	No clear ex- clusion of bi- polar patients.

 $^{^{\}rm ff}$ Sample sizes on the various markers differ due to missing data.

 $^{^{\}mathrm{gg}}$ 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.

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Berrettini ¹ ₀₂	1987	34, major de- pression (DSM-III-R)	29/NA ^{jj}	No medication for ≥ 2 weeks	33	64/NA	NPY	High- performance liquid	Data mixed of UP and BP.
Berrettini ¹	1988	6, MDD (DSM-III-R)	NA	No medication for ≥ 3 weeks	6	NA/67.2 (9.4)	Galanin	chromatography 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 do- sis of medica- tion.	19	42/43.3 (9.0)	Substance P	Radioimmunoass ay	Data mixed of UP and BP.
Catlin ¹⁰⁷	1982	19, unipolar depression (DSM-III-R)	NA	No medication for \geq 4 days	9	NA	B- endorphin	Radioimmunoass ay	Data mixed of UP and BP.
Casper ¹⁰⁸	1988	53, MDD (RDC)	28/NA	No medication for ≥ 2 weeks	60	42/NA	cortisol	Radioimmunoass ay	Data mixed of UP and BP.
Chatzittof is ¹⁰⁹	2013	NA, MDD (DSM-III-R)	NA	No current medication	19	63/30 (NA)	Cortisol, DHEAS, 5- HIAA	Radioimmunoass ay; mass fragmentography	Suicide study: no data only for MDD.
Davis ¹¹⁰	1988	8, major de- pression (RDC)	NA/53.3(7.5)	No medication for ≥ 2 weeks	8	NA/64.5 (8.5)	Somatosta- tin	NA	No clear ex- clusion of bi- polar 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 ex- clusion of bi- polar patients.
Ditzen ¹¹²	2012	12, MDE (ICD- 10)	17/54 (16.01)	NA	12	33/53 (18.08)	Proteomics	Electrophoresis; In-gel protein di- gest/Mass Spec- trometry; West- ern Blot; LCMS	Not sufficient data pre- sented.
Ehnvall ¹¹³	2003	NA, MDD (DSM-IV)	49/46.9 (12.4)	No medica- tion for ≥ 2 weeks	27	44/37.6 (11.1)	HVA, 5- HIAA, MHPG	High-perfor- mance 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.
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Eng- ström ¹¹⁴	1999	36, MDD (DSM-III-R)	NA	No medica- tion for a mean (SD) of 14.8 (7.4) days	29	55/33.5 (9.2)	HVA, 5- HIAA, MHPG	Gas chromatog- raphy–mass spectrometry; high-perfor- mance liquid chromatography	No data on healthy con- trols.
Facchi- netti ¹¹⁵	1986	10, MDD (DSM-III-R)	20/NA	No medica- tion for ≥ 10 days	13	38/NA	B-lipopro- tein, B-en- dorphin, ACTH	Radioimmunoas- say	No data stated, only graphs.
Franzen ¹¹⁶	2020	7, MDD (DSM-IV)	43/NA	No medica- tion for ≥ 2 weeks	8	38/NA	Proteomics	Mass spectrome- try detection	Not sufficient data pre- sented.
Frye ¹¹⁷	1999	28, MDD (DSM-III-R and DSM-IV)	NA/39.8 (12.7) ^{ll}	No medica- tion for ≥ 2 weeks	34	65/32.5 (10)	TRH	Radioimmunoas- say	No standard deviation stated.
Frye ¹¹⁸	2003	6, depression (DSM-III-R and DSM-IV)	43/39.2 (10.4) ^{mm}	No medica- tion for ≥ 2 weeks	25	56/32.9 (11.5)	Somatosta- tin	Radioimmunoas- say	Data mixed of UP and BP.
George ¹¹⁹	1994	5, recurrent unipolar (RDC)	40/39.8 (12.8)	No medica- tion for ≥ 2 weeks	10	50/25.3 (4.8)	Pregne- nolone, pro- gesterone, DBI	High-perfor- mance liquid chromatography; radioimmunoas- say	No data stated, only graphs.
Geraci- oti ¹²⁰	1993	7, MDD (DSM-III-R)	50/37(9) ⁿⁿ	20% of cases medicated. The remain- ing had no medication for ≥ 2 weeks	10	60/33(11)	CCK fast- ing and post prandial, glucose	Radioimmunoass ay	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 remain- ing had no medication for ≥ 2 weeks	10	60/33(11)	CRH	Radioimmunoass ay	Data mixed of UP and BP.
Geracioti, Ekhator ¹²²		7, MDD (DSM-III-R)	50/37(9) ^{kk}	20% of pa- tients medi- cated, the re- maing 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) ⁰⁰	No medication for ≥ 1 week	37	47/31 (NA)	HVA, MHPG, 5- HIAA, tryp- tophan, ty- rosine, GABA, choline, cal- cium	Atomic absorption spectrophotometr y	Data mixed of UP and BP.

 $^{^{\}rm ll}$ 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.
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Gerner, Yamada ¹² 4	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	1983 a	11, depression (RDC)	33/36.3 (4.3) ^{pp} , SEM	No medication for ≥ 1 week	18	33/32.4 (2.6), SEM	Prostagland in E	Radioimmunoass ay	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, phosphoseri ne, tyrosine, phenylalani ne, methionine, phosphoeth anolamine, urea, aspartate, threonine, serine, asparagine, alanine, citrulline, alfa- aminobutyr ate, valine, cystathionin e, isoleucine, leucine, ethanolamin e, creatinine, ornithine, lysine, histidine, arginine, alfa- aminoguani dinopropion ic acid, homocystat hionine, B- aminoisobut yrate, B- alanine, hydroxyprol ine	NA	No standard deviation pre- sented.
Hoff- man ¹²⁷	1989	11, MDE (DSM-III-R)	73/36(12)	No actual medication	6	83/26 (6)	Endothelin	Radioimmunoas- say	No clear ex- clusion of bi- polar 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 pre- sented.

 ^{pp} Demographic data on both unipolar (n=11) and bipolar (n=3) patients.
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Isung ¹²⁹	2012	NA, MDD (DSM-III-R)	NA	No medica- tion 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 ¹³	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	Radioimmunoass ay	Suicide study: no data only for MDD.
Jokinen ¹³²	2009	NA, MDD (DSM-III-R)	NA	No current medication	8	100/24(N A)	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 de- pression (DSM-III-R and RDC)	25/41.2 (2.2) ^{qq}	No medication for ≥ 2 weeks	41	37/27.7 (1.2)	Somatostati n	Radioimmunoass ay	Data mixed of UP and BP.
Lindström 135	1985	10, MDD (RDC)	40/53(NA), median	No medica- tion for ≥ 2 weeks	20	45/22.5, median	DSIP	Radioimmunoas- say	No clear ex- clusion of bi- polar 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		N A	NA	5-HIAA, HVA, MHPG	High- performance liquid chromatography	No data on MDD and controls sepa- rately pre- sented.
Mathe ¹³⁸	1994	51, MDD pri- mary unipolar (DSM-III-R)	41/40.37 (12.15) ^{rr}	NA	20	NA	CGRP	Radioimmunoass ay	No data on healthy con- trols.
Naber ¹³⁹	1981	28, MDD (RDC)	43/41(14)	No medica- tion for ≥ 2 weeks	33	64/31 (13)	B-endor- phin	Radioimmunoas- say	No clear ex- clusion of bi- polar patients.
Nemeroff ¹ 40	1984	23, MDD (DSM-III-R)	NA/47.7(3), SEM	No medication for ≥ 2 weeks	10	NA/34.2 (3.2), SEM	CRF	Radioimmunoass ay	No data stated, only graphs.
Nemeroff ¹ ⁴¹	1989	NA, major depression (RDC)	NA	No medication for ≥ 1 week	N A	NA	Neurotensin	Radioimmunoass ay	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.

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Newport ¹⁴	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	Radioimmunoass ay	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 chroma- tography-tandem mass spectrome- try	No data stated, only graphs.
Paz- zaglia 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 con- trols.
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.	Spectrophotomet ry; protein electrophoresis	Data mixed of UP and BP.
Poltorak ¹⁴	1996	8, MDD (DSM-III-R)	44 ^{uu} /39.7 5 (11.99)	$47\%^{uu}$ of patients medicated, the remaing had no medication for ≥ 2 weeks	13	77/30.85 (9.07)	N-CAM, to- tal protein, IgG, IgM, albumin	Radial immuno- diusion; western blot	No data stated, only graphs.
Rich- ards ¹⁴⁷	2018	14, MDD (DSM-IV)	NA	4 unmedi- cated cases, 10 medicated	6	NA	IL-2, IL-5, IL-6, IL-8, VEGF, IFN- gamma, amyloid- A1, adi- ponectin	NA	Not sufficient data stated in article.
Roos ¹⁴⁸	1985	7, depression (RDC)	NA	No medica- tion for ≥ 2 weeks	31	NA	IgG, albu- min, albu- min-ratio	Electroimmuno- diffusion	No clear ex- clusion of bi- polar 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-perfor- mance 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-perfor- mance 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)	HVA CRH	radioimmunoas- say	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.

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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	radioimmunoas- say	Data mixed of UP and BP.
Rubi- now ¹⁵³	1981	8, MDD (RDC)	50/39.14 (2.87) ^{xx}	No medication for ≥ 2 weeks	31	64.5/32.5 2 (2.56)	B-endor- phin, opioid activity (RRA)	radioreceptor method	Data mixed of UP and BP.
Salo- mon ¹⁵⁴	2003	8, MDE (DSM- IV)	33/39(3) ^{yy}	No medication for ≥ 2 months	14	43/41(4)	hypocretin- 1	radioimmunoas- say	Data mixed of UP and BP.
Sharma ¹⁵⁵	1995	19, depression (RDC)	58/38.4(1 3.4)	No medica- tion for 17.7 (4.9) days, mean (SD)	30	100/42.1 (9.6)	fri, conju- gated and total PAA	Gas chromatog- raphy–mass spectrometry	No clear ex- clusion of bi- polar patients.
Sher ¹⁵⁶	2003	135, MDE (DSM-IV); hereof 63 with a history of al- coholism	56/35.8(1 1.1)	No medica- tion for ≥ 2 weeks	22	45/39.1(1 3.9)	HVA, 5- HIAA, MHPG	High-perfor- mance liquid chromatography	No clear ex- clusion of bi- polar 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 pa- tients medi- cated, the re- maing had no medication for ≥ 2 weeks	7	100/NA	HVA	gas chromatog- raphy–mass spectrometry	Mix of pa- tient groups.
Stefans- son ¹⁵⁹	2016	NA, major de- pression (DSM-III-R)	NA	No current medication	19	63/NA	Testosteron	radioimmunoassa y	Suicide study: no data only for MDD.
Stübner ¹⁶⁰	1999	20, major de- pression (DSM-III-R and ICD 10)	35/67.3 (8.4)	95% of patients on medication	20	60/65.8 (9.1)	IL-6, so- luble IL-6 receptor,	ELISA	No standard deviation pre- sented.
Sunderlan d ¹⁶¹	1987	and ICD-10) 20, major de- pression (DSM-III-R)	NA/58.7 (11.4)	No medication for ≥ 3 weeks	15	NA/59.5 (7.9)	sgp130 somatostati n	radioimmunoassa y	No standard deviation pre- sented.
Träsk- man ¹⁶²	1980	19, depression (Feighner et al. and Newcastle Inventory)	47/49(12)	No medication for ≥ 5 days	30	NA/39 (11)	cortisol	Radioimmunoas- say	No clear ex- clusion of bi- polar patients.
Träsk- man ¹⁶³	1981	8, depression (Newcastle In- ventory)	38/48.1(1 1.8)	No medica- tion for ≥ 2 days, 6 (11) days, mean (SD)	45	62/40 (10)	HVA, 5- HIAA, MHPG	Mass fragmen- tography	No clear ex- clusion of bi- polar patients.
Träsk- man- Bendz ¹⁶⁴	1984	7 ^{zz} recurrent depression; 11 ^{zz} recovered	29/45(NA)	(SD) No medica- tion for ≥ 3 weeks	16 ^z	50/34.9 (NA)	5-HIAA, HVA	Mass fragmen- tography	No clear ex- clusion of bi- polar patients.

 $^{^{\}rm ww}$ Demographic data are from both unipolar (n=14) and bipolar (n=3) patients.

 $^{^{\}rm XX}$ 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.

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		(Newcastle In- ventory)							
Verbanck ¹	1984	18, depression (Feighner et al.)	43/44(NA) ^{aaa}	No medica- tion for ≥ 2 weeks	51	57/52 (NA)	CCK (chol- ecystokinin)	Radioimmunoas- say	No clear ex- clusion of bi- polar patients.
Yesavage ¹	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 pre- sented.
Zalsman ¹⁶ Z	2008	NA, MDD (DSM-IV)	NA	No medication for ≥ 2 weeks	N A	NA	HVA, MHPG, 5- HIAA	high- performance liquid chromatography	No data pre- sented.

^{aaa} Demographic data on the total group of cases with both unipolar (n=18) and bipolar (n=12) depression. © 2022 American Medical Association. All rights reserved.

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

eFigure 2 | Neurotransmitters and their metabolites

Study	Experir Total Mean		Total Mean	Control SD	Standardised Mean Difference	SMD	95%-CI	Weight (fixed)	
Homovanillic acid (HVA) Oreland 1981	20 211.95	66.91	42 230.57				[-0.74; 0.33]	4.6%	6.0
Kasa 1982 Koslow 1983	10 19.60 58 194.86	13.20 73.96	16 41.80 62 230.32	16.80 75.59			[-2.27; -0.49] [-0.83; -0.11]	1.7% 10.0%	3.7 7.4
Asberg 1984	43 201.70	92.40	66 245.90				[-0.80; -0.02]	8.8%	7.2
Viderlöv, Bisette 1988a	22 151.20	66.13		63.56		-0.23	[-0.98; 0.52]	2.3%	4.4
₋ewine 1991 Molchan 1991	19 159.30 18 190.20	72.30 83.50	91 160.60 12 201.60	69.70 66.40			[-0.51; 0.48] [-0.88; 0.59]	5.4% 2.5%	6.3 4.6
DeBellis 1993	9 182.90	49.70	46 219.50				[-0.00, 0.09]	2.6%	4.6
Swann 1999	85 195.00	74.00	85 230.00	76.00			[-0.77; -0.16]	14.2%	7.9
Heilig 2004 Sher 2005	51 206.40 125 198.45	86.60 76.50	27 228.80 27 197.20	97.50 69.50			[-0.71; 0.22] [-0.40; 0.43]	6.0% 7.6%	6.5 7.0
Sher 2006	58 169.38	79.11	50 196.90	76.30			[-0.73; 0.03]	9.1%	7.3
Sullivan, Mann 2006b	17 198.10	64.30	15 201.10	79.30			[-0.74; 0.65]	2.7%	4.8
Sullivan, Oquendo 2006a Pålhagen 2010	48 220.83 12 173.20	79.47	15 200.60 12 159.20	76.60 72.40			[-0.33; 0.84] [-0.65; 0.96]	3.9% 2.1%	5.6 4.1
Kaddurah-Daouk 2012	14 23.83	14.88	18 29.06	7.56			[-1.16; 0.26]	2.6%	4.7
Yoon 2017	75 26.32	16.10	87 28.44	12.45				13.8%	7.9
Fixed effect model Random effects model Heterogeneity: $I^2 = 11\%$, $\tau^2 =$ Test of effect (fixed) $z = -4.54$	4 (p < 0.01)	3	681		\$ \$		[-0.38; -0.15] [-0.39; -0.14]	100.0% 	100.0
Test of effect (random) z = -4									
5-hydroxyindole-acetic a Oreland 1981	cid (5-HIAA) 20 99.92	34.17	42 99.63	35.21	_	0.01	[-0.52; 0.54]	5.9%	6.9
Koslow 1983	57 119.32	33.73	58 111.00	30.56			[-0.52, 0.54] [-0.11; 0.62]	12.3%	8.5
Asberg 1984	60 92.10	38.60	66 104.10	38.30		-0.31	[-0.66; 0.04]	13.4%	8.7
Edman 1986 Widerlöv, Bisette 1988a	19 84.40 22 70.30	21.00 23.45	32 119.00 10 72.20	42.00 18.02			[-1.55; -0.35] [-0.83; 0.66]	4.6% 3.0%	6.3 5.1
ewine 1991	19 97.40	42.20	91 90.90	36.00			[-0.32; 0.67]	6.8%	7.3
Aolchan 1991	18 112.10	37.00	12 94.50	34.30		0.48	[-0.27; 1.22]	3.0%	5.2
DeBellis 1993 Heilig 2004	9 95.90 51 127.30	24.60 49.10	46 111.20 27 114.20	44.50 37.40			[-1.08; 0.36] [-0.18; 0.75]	3.2% 7.6%	5.4
Sher 2005	125 100.31	35.10	27 92.90	33.00		0.21	[-0.20; 0.63]	9.6%	8.0
Sullivan, Mann 2006b	17 99.90	34.60	15 105.70	36.40		-0.16	[-0.86; 0.54]	3.4%	5.5
Sullivan, Oquendo 2006a Pålhagen 2010	48 106.57 12 87.00	34.46 38.45	15 93.30 12 67.20	33.60 33.95			[-0.20; 0.97] [-0.29; 1.34]	4.9% 2.5%	6.5 4.7
addurah-Daouk 2012	14 11.20	6.22	18 12.31	10.67		-0.12	[-0.82; 0.58]	3.4%	5.5
(oon 2017	75 8.25	4.70	87 10.72	1.67			[-1.04; -0.40]	16.4%	9.0
Fixed effect model Random effects model	566		558				[-0.22; 0.03] [·] [-0.28; 0.19]	100.0%	100.0
Heterogeneity: $I^2 = 66\%$, $\tau^2 =$ Fest of effect (fixed) $z = -1.44$ Fest of effect (random) $z = -0$	4 (p = 0.15)	1					[0.20, 0.10]		
-methoxy-4-hydroxyphe									
Dreland 1981 Koslow 1983	18 51.27 61 48.50	9.67 11.50	42 49.50 61 43.30	9.60 8.40			[-0.37; 0.73] [0.15; 0.87]	5.4% 12.7%	7.1
Asberg 1984	26 50.80	7.40	60 51.20	10.10			[-0.50; 0.42]	7.8%	8.1
Viderlöv, Bisette 1988a	22 51.70	12.20	10 51.70	7.59		0.00	[-0.75; 0.75]	3.0%	5.5
Molchan 1991	18 60.80	20.90	12 51.10	14.70	+		[-0.24; 1.25]	3.0%	5.5
DeBellis 1993 Swann 1999	9 46.70 85 48.50	14.20 11.50	46 48.00 85 43.30	9.50 8.30			[-0.84; 0.59] [0.21; 0.82]	3.2% 17.6%	5.7
Heilig 2004	51 40.30	9.80	27 38.50	8.20		0.19	[-0.28; 0.66]	7.5%	8.0
Sher 2005	125 42.98	16.26	27 47.40	26.50			[-0.66; 0.18]	9.5%	8.5
Sullivan, Mann 2006b Sullivan, Oquendo 2006a	17 46.00 48 46.33	17.80 18.05	15 42.80 15 50.00	25.50 22.10			[-0.55; 0.84] [-0.77; 0.39]	3.4% 4.9%	5.9
Pålhagen 2010	12 41.80	11.09	12 30.70	9.35			[0.18; 1.91]	2.2%	4.6
Kaddurah-Daouk 2012	14 11.78	2.05	18 11.57	1.72			[-0.59; 0.81]	3.4%	5.8
Yoon 2017 Fixed effect model	75 7.81 581	1.77	87 8.92 517	1.67			[-0.96; -0.33] [-0.05; 0.21]	16.4%	9.6
Random effects model leterogeneity: $I^2 = 70\%$, $\tau^2 =$ rest of effect (fixed) $z = 1.26$	0.1462, <i>p</i> < 0.0	1					[-0.14; 0.36]	-	100.0
Test of effect (random) $z = 0$.									
GABA Gerner 1981	19 134.00	21.32	29 183.20	62 47		-0.06	[-1.57; -0.35]	18 1%	23.7
Roy 1991	13 106.10	21.32	29 183.20	41.20			[-1.57; -0.35] [-1.63; -0.16]	12.5%	19.9
Mann 2014	130 15.10	7.10	38 17.40	7.60		-0.32	[-0.68; 0.05]	51.3%	32.6
Ogawa 2015 Fi xed effect model	18 0.30 180	0.10	24 0.30 111	0.10			[-0.61; 0.61] [-0.71; -0.19]		23.7
Random effects model					$\langle \rangle$		[-0.71; -0.19] [-0.92; -0.08]		100.0
leterogeneity: $I^2 = 55\%$, $\tau^2 =$ est of effect (fixed) $z = -3.38$ est of effect (random) $z = -2$	3 (p < 0.01)	8							
Blutamate	,								
Garakani 2013	13 0.03	0.01	11 0.04	0.01			[-1.82; -0.11]		20.8
Dgawa 2015	40 9.10	5.40	53 8.30	5.20	_ +-		[-0.26; 0.56]	55.3%	38.0
lashimoto 2016 Madeira 2018	28 0.38 9 16.31	0.11 3.81	19 0.65 10 6.16	0.82 3.19			[-1.09; 0.10] [1.43; 4.11]	26.7% 5.2%	30.0 11.2
ixed effect model	90		93		\Leftrightarrow	-0.03	[-0.33; 0.28]		
Random effects model	0.9600 0.0	4				0.21	[-0.79; 1.21]		100.
Heterogeneity: $I^2 = 88\%$, $\tau^2 = $ Test of effect (fixed) $z = -0.18$ Test of effect (random) $z = 0$.	3 (p = 0.86)								
Slutamine		100						1.1200000000000000000000000000000000000	
Garakani 2013	11 33.71	5.60	11 36.23	3.70			[-1.36; 0.34]		19.
Dgawa 2015 Hashimoto 2016	42 711.30 28 591.04		54 644.30 19 568.17				[0.12; 0.94] [-0.32; 0.85]	52.5% 25.9%	35.8 28.3
Madeira 2018	9 493.70		10 359.30			- 1.00	[0.03; 1.97]	9.4%	16.6
Fixed effect model Random effects model Heterogeneity: $I^2 = 54\%$, $\tau^2 =$	90 0.1264, <i>p</i> = 0.0		94			0.38	[0.08; 0.68] [-0.15; 0.82]		100.0
Test of effect (fixed) $z = 2.51$ Test of effect (random) $z = 1$.	(p = 0.01)								
				1		7			
				-2	2 -1 0 1	2			

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eFigure 3 | Hormones, neuropeptides and metabolites

Hormones

Study	Experimental Total Mean SD	Control Total Mean SD	Standardised Mean Difference	SMD	95%-CI	Weight (fixed)	Weight (random)
Cortisol Gerner 1983 Stokes 1984 Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%$, r^2 : Test of effect (fixed) $z = 7$. Test of effect (random) $z = 7$	06 (p < 0.01)	22 6.62 1.97 59 7.10 2.30 81	†+\$\$	1.16 1.23	[0.75; 2.09] [0.77; 1.56] [0.89; 1.57] [0.89; 1.57]		45.4% 54.6% 100.0%
Transthyretin Sullivan 1999 Sullivan, Mann 2006b Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%$, r^2 = Test of effect (fixed) $z = -2$. Test of effect (random) $z =$	93 (p < 0.01)	24 7.28 4.68 15 21.80 2.20 - 39	*	-1.08 -0.82	[-1.34; 0.29] [-1.82; -0.33] [-1.37; -0.27] [-1.37; -0.27]	54.0%	48.7% 51.3% 100.0%
Corticotropin releasing Widerlöv, Bisette 1988a Risch 1992 Molchan 1993 Pitts 1995 Heuser 1998 Wong 2000 Carpenter, Tyrka 2004b Garakani 2013 Fixed effect model Random effects model Heterogeneity: $l^2 = c3\%$, l^2 Test of effect (fixed) $z = 0.2$	22 71.90 19.70 18 83.70 35.40 18 78.60 24.60 19 38.60 10.00 37 49.60 18.40 10 48.90 9.80 27 29.00 9.40 18 78.00 41.80 169 = 0.1661, p = 0.01 27 (p = 0.79)	10 57.30 12.02 83 69.40 38.20 11 87.10 15.80 18 43.30 8.10 25 49.60 13.30 14 57.10 4.10 ← 25 24.90 8.50 24 82.66 30.40 210		0.38 -0.38 -0.50 0.00 -1.13 0.45 -0.13 0.03	[0.03; 1.58] [-0.14; 0.89] [-1.14; 0.38] [-1.16; 0.15] [-0.51; 0.51] [-2.01; -0.25] [-0.74; 0.48] [-0.79; 0.34]	8.0% 18.4% 8.4% 11.2% 18.8% 6.2% 15.9% 12.9% 100.0%	11.3% 13.9% 11.5% 12.5% 13.9% 10.4% 13.5% 12.9%
Adrenocorticotropic ho Kling 1991 Risch 1992 Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, $T^2 = 0\%$ Test of effect (fixed) $z = 0.$ Test of effect (fixed) $z = 0.$	21 27.40 10.54 18 66.70 35.40 39 = 0, p = 0.75 36 (p = 0.72)	56 26.30 8.23 83 66.50 24.60 139	+++	0.01 0.07	[-0.38; 0.62] [-0.50; 0.52] [-0.29; 0.42] [-0.29; 0.42]	49.2%	50.1% 49.9% 100.0%
Oxytocin Pitts 1995 Sasayama 2012 Fixed effect model Random effects model Heterogeneity. $I^2 = 06$, I^2 Test of effect (fixed) $z = -1$. Test of effect (random) $z =$	44 (p = 0.15)	18 8.10 3.50 21 27.42 13.37 39	\$ \$ \$	-0.38 -0.34	[-0.94; 0.36] [-1.02; 0.27] [-0.79; 0.12] [-0.79; 0.12]	49.8% 50.2% 100.0% 	49.9% 50.1% 100.0%
Vasopressin Pitts 1995 Heuser 1998 Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%$, r^2 Test of effect (fixed) $z = -0$. Test of effect (random) $z =$	33 (p = 0.74)	18 22.50 9.10 25 3.70 0.70 43	-1 0 1	0.00 -0.07	[-0.82; 0.47] [-0.51; 0.51] [-0.47; 0.33] [-0.47; 0.33]	61.9%	47.5% 52.5% 100.0%

Neuropeptides

Study	Total	Experi Mean		Total		ontrol SD	Standardised Mean Difference	SMD	95%-CI	Weight (fixed)	Weight (random)
Comotostatin							T				
Somatostatin Rubinow 1983	7	30.40	5.90	39	62.80	6.38		E 04	16 20: 2 701	4.7%	15.9%
Bissette 1986	17	65 40	32 16		116.10				[-6.39; -3.70] [-2.11; -0.39]	4.7%	19.7%
Molchan 1991	18	45.10	15.50	12	60.20				[-1.71; -0.39]	14.2%	20.3%
Heuser 1998	37	31.40	9.90	25	38.60	8.80			[-1.28; -0.22]	30.8%	21.9%
Heilia 2004	51	29.60	9.00	27	32.20	9.40	-		[-0.75; 0.19]	38.7%	22.2%
Fixed effect model	130	20.00	0.00	113	02.20	0.10			[-1.15; -0.56]		
Random effects model						-			[-2.53; -0.45]		100.0%
Heterogeneity: $I^2 = 91\%$, $\tau^2 = $ Test of effect (fixed) $z = -5.74$									[1.00, 0.10]		
Test of effect (random) $z = -2$											
Neuropeptide Y (NPY)											
Widerlöv, Lindström 1988	33	102.20	11.49	20	121.80	13.86	- <u></u>	-1.55	[-2.19; -0.92]	18.1%	20.2%
Sunderland 1991		123.00	21.00		142.00				[-1.69; 0.23]	7.9%	17.9%
Heilig 2004	51	134.10	23.70		161.80				[-1.62; -0.62]	29.1%	20.9%
Martinez 2012	18	176.13	47.26	25	137.66	24.14		1.06	[0.41; 1.71]	17.3%	20.1%
Soleimani 2014	61	7.90	1.50	20	7.00	1.30		0.61	[0.10; 1.13]	27.6%	20.9%
Fixed effect model	172			101			\Leftrightarrow	-0.31	[-0.58; -0.04]	100.0%	
Random effects model								-0.34	[-1.37; 0.69]		100.0%
Heterogeneity: $I^2 = 93\%$, $\tau^2 =$											
Test of effect (fixed) $z = -2.28$											
Test of effect (random) z = -0).65 (p =	0.52)									
Substance P											
Deuschle 2005	11	25.60	7.80	11	24.10				[-0.65; 1.03]	22.6%	47.1%
Geracioti 2006	40	79.10	23.50	47	52.50	25.10			[0.63; 1.53]		52.9%
Fixed effect model	51			58			$\langle \rangle$		[0.48; 1.28]	100.0%	
Random effects model								0.71	[-0.15; 1.57]		100.0%
Heterogeneity: $I^2 = 70\%$, $\tau^2 =$ Test of effect (fixed) $z = 4.33$	0.2773	p = 0.07									
Test of effect (random) $z = 1$											
Cocaine- and amphetami Brundin 2008						70.00		0.04	1001:004	20 00/	47.09/
Yoon 2018	45	832.62 2.05	0.60	5 25	830.00	0.88			[-0.91; 0.94]		47.0% 53.0%
Fixed effect model	69	2.05	0.60	25 30	2.55	0.00			[-1.23; -0.07] [-0.95; 0.02]		53.0%
Random effects model	09			30					[-0.95, 0.02]	100.0%	100.0%
Heterogeneity: $I^2 = 30\%$, $\tau^2 =$	0.0666	n = 0.23						-0.42	[-1.04, 0.20]		100.0 %
Test of effect (fixed) $z = -1.86 (p = 0.06)$											
Test of effect (random) $z = -2$											
Orexin / hypocretin-1											
Pålhagen 2010	12	163.00	45.38	12	167.40	74 13		-0.07	[-0.87; 0.73]	49.4%	49.9%
Schmidt 2011		74.32		10	82.82				[-1.21; 0.37]		50.1%
Fixed effect model	29	17.02	17.01	22	52.02	22.00			[-0.81; 0.31]		50.170
Random effects model	23								[-0.81; 0.31]		100.0%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$	0 = 0	54						0.20	[0.01, 0.01]		100.070
Test of effect (fixed) $z = -0.8$											
Test of effect (random) $z = -0$											
						1		٦			
						÷	2 -1 0 1	2			

Amino acids and derivates

0			imental			Control	Standardised Mean				Weight
Study D-serine	Total	Mean	50	Total	Mean	SD	Difference	SMD	95%-01	(fixed)	(random)
Madeira 2015	9	5.14	3.28	10	2.45	0.65	п	> 1.12	[0.13; 2.10]	15.4%	22.5%
Hashimoto 2016	28	1.75	0.43	19	1.76	0.38		-0.02	[-0.61; 0.56]	44.0%	39.4%
Ishiwata 2018	18	0.57	0.16	27	0.50	0.12			[-0.10; 1.11]		38.1%
Fixed effect model	55			56			\diamond		[-0.02; 0.75]	100.0%	400.0%
Random effects model Heterogeneity: $l^2 = 52\%$, τ^2		51 n = 0.13						0.43	[-0.15; 1.02]		100.0%
Test of effect (fixed) $z = 1.8$											
Test of effect (random) z =											
L-serine											
Madeira 2015	9	35.75	11.68	10	27.52	9.28		0.75	[-0.19; 1.69]	16.9%	23.7%
Hashimoto 2016	28	22.36	5.13	19	25.45	5.58			[-1.17; 0.02]		38.4%
Ishiwata 2018	18	6.60	1.40	27 56	6.00	1.30			[-0.16; 1.04]		37.9%
Fixed effect model Random effects model	55			50					[-0.32; 0.45] [-0.64; 0.96]	100.0%	100.0%
Heterogeneity: $I^2 = 75\%$, τ^2	2 = 0.367	75, p = 0.02							[0.0 ., 0.00]		
Test of effect (fixed) $z = 0.3$ Test of effect (random) $z =$											
		,									
Serine Madeira 2015	9	42.88	11.24	10	29.97	9.02		1 22	[0.22; 2.22]	14.0%	30.7%
Ogawa 2015	42	29.30	7.50	54	27.90	6.10			[-0.20; 0.61]	86.0%	69.3%
Fixed effect model	51			64			\diamond	0.35	[-0.03; 0.72]	100.0%	
Random effects model								0.60	[-0.36; 1.57]		100.0%
Heterogeneity: $I^2 = 70\%$, τ^2 Test of effect (fixed) $z = 1.8$ Test of effect (random) $z =$	82 (p = 0	0.07)									
Glycine											
Madeira 2015	9	322.90	44.95	10	291.60	68.36		0.51	[-0.41; 1.43]	11.6%	21.7%
Ogawa 2015	42	6.40	2.00	54	6.00	1.80			[-0.19; 0.61]	60.0%	43.9%
Hashimoto 2016	28	11.38	2.67	19	12.99	5.95		-0.37	[-0.96; 0.22]	28.4%	34.5%
Fixed effect model	79			83					[-0.23; 0.39]	100.0%	
Random effects model Heterogeneity: $l^2 = 43\%$, τ^2		n = 0.19						0.07	[-0.38; 0.52]		100.0%
Test of effect (fixed) $z = 0.5$											
Test of effect (random) z =	0.31 (p	= 0.76)									
Tryptophan											
Kaddurah-Daouk 2012	14	512.67	127.74	18	508.71	105.74			[-0.67; 0.73]		44.1%
Ogawa 2015 Fixed effect model	23 37	1.80	0.70	36 54	2.00	0.40			[-0.90; 0.16] [-0.64; 0.20]	63.7%	55.9%
Random effects model				54					[-0.64; 0.20]	100.0%	100.0%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0\%$	= 0, p =										
Test of effect (fixed) $z = -1$.											
Test of effect (random) z =	-1.03 (p	b = 0.30)									
Tyrosine											
Kaddurah-Daouk 2012	14	1289.95	202.89	18	1242.21	180.65			[-0.46; 0.95]		40.1%
Ogawa 2015 Fixed effect model	42 56	9.00	1.80	54 72	9.40	2.30			[-0.59; 0.21] [-0.43; 0.27]		59.9%
Random effects model				12			T.		[-0.45; 0.27]		100.0%
Heterogeneity: $I^2 = 9\%$, τ^2		7, p = 0.29							,		
Test of effect (fixed) $z = -0$.											
Test of effect (random) z =	-0.37 (p	b = 0.71									
Aspartate	0	0.00	0.45		4 57	0.40		1.00	10.70.0.071	00.00/	00.40/
Frye 2007 Oqawa 2015	8 25	0.80 0.70	0.45 0.30	14 33	1.57 0.70	0.43 · 0.20			[-2.72; -0.67] [-0.52; 0.52]		33.1% 66.9%
Fixed effect model	33	0.110	0.00	47	0.1.0	0.20	$ \rightarrow $		[-0.81; 0.12]		
Random effects model								-0.79	[-2.44; 0.87]		100.0%
Heterogeneity: $I^2 = 88\%$, τ^2 Test of effect (fixed) $z = -1$.											
Test of effect (random) z =											
Methionine											
Kaddurah-Daouk 2012	14	345.87	35.84	18	344.41	53.25		0.03	[-0.67; 0.73]	25.1%	40.2%
Ogawa 2015	42	3.30	0.90	54	3.50	0.80			[-0.64; 0.17]		59.8%
Fixed effect model	56			72					[-0.52; 0.18]	100.0%	
Random effects model	- 0	0.50					$ \rightarrow $	-0.17	[-0.52; 0.18]		100.0%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0\%$ Test of effect (fixed) $z = -0$.	- 0, p = .94 (p =	0.35)									
Test of effect (random) z =											
Ascorbic acid											
Kaddurah-Daouk 2012		10527.63			11063.17				[-0.86; 0.54]		47.4%
Hashimoto 2017	28	0.30	0.06	18	0.24	0.07			[0.32; 1.57]		52.6%
Fixed effect model	42			36					[-0.01; 0.92]	100.0%	100 0%
Random effects model Heterogeneity: $I^2 = 81\%$, τ^2		p = 0.02						0.40	[-0.67; 1.48]		100.0%
Test of effect (fixed) z = 1.9	91 (p = 0	0.06)									
Test of effect (random) z =						,		1			
						-2	2 -1 0 1	2			
						-		-			

eFigure 4 | Inflammation and BBB permeability

Inflammatory markers

y	markers												
	Study	Total	Experi Mean		Total		ontrol SD		rdised Mean ference	SME	95%-CI		Weight (random)
	IL-6 Carpenter, Heninger 2004a Lindqvist 2009 Pålhagen 2010 Martinez 2012 Sasayama 2013 Kern 2014 Pomara 2021 Fixed effect model Random effects model Heterogeneity: $l^2 = 16\%, \tau^2 = 0$ Test of effect (fixed) z = 3.28 (Test of effect (random) z = 2.9	p < 0.0*	1)	1.00 9.21 8.56 0.01 1.22 4.33 3.08	26 47 12 25 35 67 17 229	2.40 0.64 4.34 0.06 1.54 1.91 4.87	1.90 6.17 6.34 0.01 0.80 1.81 5.27		*** *** *** * * * * * * * * * *	0.3 ⁴ 0.4 ⁴ 0.70 0.58 0.58 -0.08 0.36	 [-0.72; 0.48] [-0.14; 0.76] [-0.40; 1.22] [0.08; 1.33] [0.09; 1.08] [0.06; 1.09] [0.06; 1.09] [0.06; 0.52] [0.14; 0.57] [0.12; 0.59] 	22.0% 6.9% 11.5% 18.1% 16.8% 12.2%	13.1% 19.8% 8.1% 12.3% 17.3% 16.4% 12.9%
	IL-8 Lindqvist 2009 Kern 2014 Janelidze 2015 Hidese 2021 Pomara 2021 Fixed effect model Random effects model Heterogeneity: $l^2 = 66\%$, $\tau^2 = 0$ Test of effect (fixed) $z = 1.32$ (Test of effect (random) $z = 0.7$	p = 0.19	9)	7.24 14.40 9.39 4.40 15.40	47 67 48 118 17 297	23.10 36.40 24.30 22.80 96.46	6.65 9.47 6.50 4.50 32.75		*	0.84 -0.14 0.13 -0.41 0.12	<pre>[-0.28; 0.62] [[0.32; 1.37] [-0.53; 0.25] [-0.13; 0.40] [-1.02; 0.20] [-0.06; 0.30] [-0.21; 0.45]</pre>	11.3% 20.2% 44.8% 8.3% 100.0%	18.6% 15.0% 22.0% 32.6% 11.9%
	TNF-alfa Lindqvist 2009 Martinez 2012 Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, Test of effect (fixed) $z = 1.25$ (Test of effect (random) $z = 1.25$	p = 0.2	1)	0.04 0.11	47 25 72	0.13 0.10	0.07 0.06	_	++ () ()	0.12 0.23	0 [-0.16; 0.75] 2 [-0.49; 0.72] 3 [-0.13; 0.59] 3 [-0.13; 0.59]	35.7%	60.4% 39.6% 100.0%
	White cell count (WCC) Sasayama 2013 Hattori 2015 Omori 2020 Fixed effect model Random effects model Heterogeneity: $l^2 = 42\%$, $r^2 = t^2$ Test of effect (random) $z = 0.35$ (Test of effect (random) $z = 0.35$)	p = 0.72	2)	2.91 2.41 3.00	31 60 104 195	2.97 4.20 4.00	2.32 3.21 3.00	-		-0.18 0.07 0.0 4) [-0.11; 0.91] 3 [-0.53; 0.17] 7 [-0.22; 0.35] 4 [-0.17; 0.24] 5 [-0.23; 0.33]	33.3% 51.0%	21.8% 35.1% 43.1% 100.0%
	MMP-3 Ventorp 2016 Hidese 2021 Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, Test of effect (fixed) $z = 1.23$ (Test of effect (random) $z = 1.2$	37 104 141 <i>p</i> = 0.4 <i>p</i> = 0.22	251.31 732.90 6 2)			252.99 715.80	87.80	2 -1	0 1	0.19 0.1 4	[-0.49; 0.47] [-0.07; 0.46] [-0.09; 0.38] [-0.09; 0.38]	76.9%	34.2% 65.8% 100.0%

Blood-brain-barrier permeability

Study		Experin Mean		Total	C Mean	ontrol SD	Standardised Mean Difference	SMD	95%-CI	Weight (fixed)	Weight (random)
Total protein Vawter 2000 Sasayama 2013 Hattori 2015 Mizui 2019 Omori 2020 Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%, \tau^2$ Test of effect (fixed) $z = 5$. Test of effect (fixed) $z = 5$.	29 66 18 90 220 = 0, <i>p</i> = 68 (<i>p</i> <	39.40 = 0.89 0.01)	13.28 18.01 0.29 17.10	31 60 27	25.20 38.10 36.60 0.86 33.40	9.95 8.50 0.16	* * * * * * * * * *	0.73 0.48 0.63 0.46 0.53	[0.06; 1.24] [0.21; 1.26] [0.13; 0.84] [0.02; 1.24] [0.17; 0.74] [0.35; 0.72]	9.1% 41.9%	13.8% 16.3% 25.7% 13.1% 31.1% 100.0%
Albumin ratio Hampel 1997 Gudmundsson 2007 Fixed effect model Random effects model Heterogeneity: $l^2 = 62\%$, t Test of effect (fixed) $z = 2$. Test of effect (random) $z =$	29 11 40 ² = 0.19 18 (p =	5.90 7.10 918, <i>p</i> = 0.03)	2.80 2.80 0.11	11 70 81	5.60 5.40	2.20 1.70	***	0.90 0.53	[-0.58; 0.81] [0.25; 1.55] [0.05; 1.00] [-0.26; 1.29]	53.2%	47.5% 52.5% 100.0%
Glucose Regenold 2000 Omori 2020 Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%$, r^2 Test of effect (fixed) $z = 0$. Test of effect (random) $z =$	89 99 = 0, p = 27 (p =	0.78)	8.00		58.90 61.00			0.05 0.04 0.04	[-0.98; 0.77] [-0.23; 0.34] [-0.23; 0.31] [-0.23; 0.31]	90.6%	19.0% 81.0% 100.0%

Synaptic plasticity

-	1	Experim	ental		(Control	Star	ndardise	d Mean			Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD		Differen	ce	SMD	95%-C	(fixed)	(random)
Brain-derived neurotro	ophic fa	ctor (BD	NF)					1					
Pålhagen 2010	12	66.50	38.80	12	201.00	190.87				-0.94	[-1.79; -0.09]	21.4%	23.1%
Martinez 2012	18	4.28	1.88	25	4.86	2.22	-			-0.27	[-0.88; 0.34]	41.8%	40.4%
Diniz 2014	16	46.99	37.73	25	98.14	84.00				-0.72	[-1.37; -0.07]	36.9%	36.5%
Fixed effect model	46			62			<	\sim		-0.58	[-0.97; -0.19]	100.0%	
Random effects model							<	\sim		-0.58	[-0.97; -0.19]		100.0%
Heterogeneity: $I^2 = 0\%$, τ^2	= 0, p =	0.40											
Test of effect (fixed) $z = -2$	2.89 (p <	0.01)											
Test of effect (random) z =	= -2.89 (/	o < 0.01)											
Neural cell adhesion n	nolecul	e (NCAM	I)										
Hidese 2017	83	236.00	77.50	111	247.20	78.50				-0.14	[-0.43; 0.14]	46.2%	48.4%
Hidese 2020	104	178.40	59.00	118	184.00	63.50				-0.09	[-0.35; 0.17]	53.8%	51.6%
Fixed effect model	187			229				\diamond		-0.11	[-0.31; 0.08]	100.0%	
Random effects model											[-0.31; 0.08]		100.0%
Heterogeneity: $I^2 = 0\%$, τ^2	= 0, p =	0.79											
Test of effect (fixed) $z = -1$													
Test of effect (random) z =	= -1.16 (/	p = 0.24)											
									1				
						-	-2 -1	0	1	2			

Neurodegeneration

eration											
Study	Total	Exper Mean	rimental SD	Total	Mean	Control SD	Standardised Mean Difference	SMD	95%-CI		Weight (random)
Amyloid-B-40 Jensen 1999 Hertze 2010 Pomara 2012 Fixed effect model Random effects model Heterogeneity: /² = 0%, r² Test of effect (fixed) z = -4 Test of effect (random) z =	28 28 71 = 0, p = 4.64 (p <	0.01)	2535.00		2311.00 11036.00 6518.00	2613.00	* * * * *	-1.07 -0.54 -0.80	[-1.35; -0.02] [-1.60; -0.55] [-1.13; 0.05] [-1.14; -0.46] [-1.14; -0.46]	41.7% 32.4%	31.2% 35.5% 33.3% 100.0%
Total tau Blennow 1995 Bürger née Buch 1999 Gudmundsson 2007 Hertze 2010 Pomara 2012 Reis 2012 Diniz 2014 Sanfilippo 2016 Eratne 2021 Fixed effect model Random effects model Heterogeneity: I ² = 66%, rt Test of effect (fixed) z = -2 Test of effect (random) z =	2 ² = 0.21 3.05 (p <	0.01)	13.00 283.00 114.90 26.00 114.30 101.81 41.62 45.53 82.07	31 28 70 38 19 8 25 44 20 283	185.00 273.00 331.70 91.00 328.70 161.62 68.41 67.65 182.24	50.00 203.00 189.80 49.00 151.70 85.91 54.07 20.18 55.52		0.17 -0.24 -0.89 -0.42 0.36 -0.07 0.24 -0.24 -0.24	[-2.52; -0.89] [-0.42; 0.75] [-0.88; 0.40] [-1.41; -0.38] [-1.01; 0.18] [-0.47; 1.18] [-0.70; 0.56] [-0.61; 1.10] [-0.90; 0.42] [-0.55; -0.12] [-0.70; 0.06]	17.9% 13.4% 6.9% 12.0% 6.5% 10.8%	9.7% 12.1% 11.5% 12.9% 12.0% 9.6% 9.6% 9.3% 11.6% 9.3%
P-tau 181 Hertze 2010 Pomara 2012 Reis 2012 Diniz 2014 Sanfilippo 2016 Eratne 2021 Fixed effect model Random effects model Heterogeneity: $\tilde{f} = 0\%, \tau^2$ Test of effect (fraeld) z = C Test of effect (fraeld) z =	= 0, p = 0.15 (p =	0.88)	11.00 25.90 33.86 41.76 25.12 14.21	38 19 8 25 44 20 154	31.00 51.60 36.22 49.04 35.71 41.09	17.00 20.90 25.46 33.90 14.95 8.80		-0.11 0.07 0.24 0.26 -0.21 -0.02	[-0.62; 0.35] [-0.69; 0.47] [-0.75; 0.89] [-0.39; 0.87] [-0.60; 1.11] [-0.87; 0.45] [-0.28; 0.24]	28.3% 19.9% 10.0% 17.0% 9.2% 15.5% 100.0% 	19.6% 18.1% 14.3% 17.3% 13.8% 16.8%
Amyloid-B-42 Jensen 1999 Gudmundsson 2007 Hertze 2010 Pomara 2012 Reis 2012 Diniz 2014 Sanfilippo 2016 Eratne 2021 Fixed effect model Heterogeneity: / ² = 82%, r Test of effect ((med) = 2 Test of effect ((med) = 2	$p^2 = 0.50$ 0.06 (p =	0.95)		24 70 38 19 8 25 44 20 248	74.00 794.00 1019.00 335.40 834.64 464.97 550.97 857.92	30.00 234.40 435.00 182.70 436.53 166.48 118.09 94.86		0.78 -0.37 -0.72 0.24 0.08 -0.09 -0.86 -0.01	[0.90; 2.40] [0.13; 1.42] [-0.87; 0.12] [-0.58; 0.70] [-0.55; 0.70] [-0.94; 0.76] [-1.55; -0.77] [-0.24; 0.22] [-0.48; 0.62]	9.6% 12.9% 22.3% 14.9% 8.0% 13.7% 7.4% 11.3% 100.0%	11.7% 12.9% 14.9% 13.5% 10.9% 13.2% 10.5% 12.4%
Neurogranin Sanfilippo 2016 Bruno 2020 Fixed effect model Random effects model Heterogeneity: / ² = 0%, t ² Test of effect ((random) z	6 28 34 = 0, p = 0.68 (p =	179.95 100.30 0.33 0.50)	180.53 124.30	44 19 63	256.06 100.80	139.76 91.40		-0.00 -0.17	[-1.38; 0.34] [-0.59; 0.58] [-0.65; 0.32] [-0.65; 0.32]	68.5%	43.2% 56.8% 100.0%
Neurofilament light (Ni Gudmundsson 2010 Eratne 2021 Fixed effect model Random effects model Heterogeneity: I ² = 88%, r Test of effect (fixed) z = 0. Test of effect (random) z =	fL) 11 16 27 I : ² = 0.88 .15 (p =	427.00 432.58 30, <i>p</i> < 0.0 0.88)	101.85	65 20 85	277.00 523.03	186.00 142.29		-0.70 0.04	[0.06; 1.36] [-1.38; -0.02] [-0.43; 0.51] [-1.38; 1.39]	47.7%	50.7% 49.3% 100.0%

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

Study	Total	Experimental Mean SD	Total	Co Mean	ontrol SD	Standardised Mean Difference	SMD	95%–Cl
Kaddurah–Daouk 2012, 4HBAC Kaddurah–Daouk 2012, 4HPAC	14 14	148.40 144.07 3.64 1.76	18 18	257.76 2 3.44	208.92 0.72			[-1.30; 0.13] [-0.54; 0.86]
Kaddurah-Daouk 2012, 4HPLA	14	32.14 15.99	18	34.89	6.67			[-0.93; 0.47]
Kaddurah–Daouk 2012, 7MXAN	14	0.93 0.55	18	0.85	0.79			[-0.59; 0.81]
Pomara 2021, AChE	27	53.13 19.07	17		15.79			[-1.04; 0.19]
Ogawa 2015, Alanine Hampel 1997, Albumin	42 29	37.50 10.30 22.10 11.10	54 11	33.70 22.70	9.00 7.10			[-0.01; 0.80] [-0.75; 0.64]
Ogawa 2015, Alfa-aminobutyrate	42	2.70 1.00	54	2.60	0.90			[-0.30; 0.51]
Bruno 2020, Alfa-synuclein	28	16.90 16.20	19		16.10			[-0.41; 0.75]
Hertze 2010, Amyloid–B–38 Hertze 2010, Amyloid–B–42 xMAP	28 28	1570.00 805.00 271.00 53.00	38 38		333.00 74.00	<u> </u>		[–1.37; –0.35] [–0.40; 0.58]
Hidese 2020, Amyloid precursor protein (APP)	104	537.30 256.70	118		266.00			[-0.44; 0.09]
Hidese 2021, APRIL/TNFSF13		21009.70 6792.50		19726.60 54				[-0.05; 0.47]
Ogawa 2015, Arginine	42	21.80 5.10	54	22.60	4.70			[-0.57; 0.24]
Ogawa 2015, Asparagine Itagaki 2019, Autotaxin (ATX)	42 26	7.20 1.40 260.70 37.60	54 27	6.60 277.40	1.30 24.00			[0.03; 0.85] [-1.07; 0.02]
Gerner 1982, B-endorphin	19	98.00 24.85	9		22.50			[-1.08; 0.52]
Hidese 2021, BAFF/TNFSF13B	104	3062.50 961.50	118		61.40			[0.06; 0.59]
Pomara 2021, BChE Mizui 2019, BDNF propeptide	27 18	29.34 11.70 308.56 232.65	17 27		10.35 328.38			[–1.34; –0.09] [–1.21; 0.01]
Pillai 2019, C3	30	87.19 25.07	20		34.93			[-1.09; 0.06]
lshii 2018, C5	89	317.70 221.10	117		11.10			[0.31; 0.87]
Mathé 2002, Calcitonin Mathé 2002. Calcitonin gene-related peptide (CGRP)	29 29	1.71 0.68 4.32 0.91	19 19	2.27 4.47	0.73			[–1.39; –0.19] [–0.76; 0.40]
Ogawa 2015, Carnosine	29 35	4.32 0.91 2.40 1.50	44	3.30	0.68 2.10			[-0.93; -0.03]
Hidese 2020, Contactin-1	104	4367.20 569.40	118	4419.10 5	81.90	-	-0.09	[-0.35; 0.17]
Pålhagen 2010, Corticosterone	12	4350.00 4122.28	12		20.55			[0.41; 2.20]
Post 1982, Cyclic AMP Post 1982, Cyclic GMP	2 2	27.50 31.82 2.95 0.35	41 41	19.60 2.40	8.96 1.28			[-0.67; 2.19] [-1.00; 1.85]
Ogawa 2015, Cystine	36	2.90 0.70	46	2.80	0.80			[-0.31; 0.57]
Barbaccia 1986, Diazepam-binding inhibitor	10	1.42 0.41	10	1.10	0.28			[-0.06; 1.79]
Sunderland 1991, Dynorphin A 1–8 Janelidze 2013, Eotaxin–1	9 51	45.00 13.00 14.43 9.94	9 43	60.00 17.20	21.00 - 5.30			[-1.79; 0.15] [-0.75; 0.07]
Hidese 2020, ErbB3	104	2649.20 764.90	118		951.80			[-0.30; 0.23]
Ogawa 2015, Ethanolamine	42	12.30 2.30	54	14.80	2.20	- <u>z</u> -		[-1.54; -0.67]
Hattori 2015, Fibrinogen Ishiwata 2017, G72 (D-amino acid oxidase activator: DAOA)	66 18	1.35 3.46 19.30 9.30	60 27	0.00 20.50	0.99 9.80			[0.16; 0.87] [-0.72; 0.47]
Sunderland 1991, Galanin	9	5.80 2.20	9	5.80	2.40			[-0.92; 0.92]
Hidese 2020, Glial cell-derived neurotrophic factor (GDNF)	104	6.70 1.30	118	6.70	1.30	+		[-0.26; 0.26]
Gudmundsson 2010, Glial fibrillary acidic protein (GFAp) Kaddurah–Daouk 2012, GLNTRP	11 14	946.00 196.00 2.04 1.55	65 18	887.00 3 2.23	308.00 1.86			[-0.44; 0.84] [-0.80; 0.59]
Kaddurah–Daouk 2012, Glutathione	14	9.62 0.68	18	9.16	0.85			[-0.14; 1.29]
Kaddurah–Daouk 2012, Gr	14	3.46 0.59	18	3.96	1.06		-0.55	[-1.26; 0.16]
Rymo 2017, Growth-associated protein-43 Hidese 2020, Hepatocyte growth factor (HGF)	19 104	1.36 0.60 86.10 20.70	67 118	1.10 84.80	0.50 21.20			[-0.03; 1.00] [-0.20; 0.33]
Hidese 2020, HGF receptor	104	1197.50 567.50	118		590.80			[-0.25; 0.28]
Kaddurah–Daouk 2012, HHASC	14	276.13 84.46	18		81.38			[-0.34; 1.07]
Ogawa 2015, Histidin + 1–methylhistidin Kaddurah–Daouk 2012, HX	42 14	8.40 2.70 354.46 201.62	54 18	8.00 384.53	1.40 77.24			[-0.21; 0.60] [-0.90; 0.50]
Ventorp 2016, Hyaluronic acid	39	129.03 106.16	45		55.62			[0.10; 0.98]
Hidese 2021, IFN-a2	104	5.00 2.50	118	5.00	3.20		0.00	[-0.26; 0.26]
Hidese 2021, IFN-B Hampel 1997, IgG	104 29	46.90 8.30 2.92 1.54	118 11	44.00 3.11	7.60 1.10			[0.10; 0.63]
Hampel 1999, IgG index	29	0.46 0.07	11	0.44	0.13			[-0.82; 0.57] [-0.48; 0.91]
Hampel 1997, IgG ratio	29	2.80 1.70	11	2.30	0.70		0.33	[-0.37; 1.02]
Martinez 2012, IL–1 Hidese 2021, IL–10	18 104	0.07 0.02 5.50 1.30	25 118	0.06 5.60	0.00 1.30			[-0.01; 1.23]
Hidese 2021, IL-10 Hidese 2021, IL-11	104	3.50 1.30		3.40	1.30			[-0.34; 0.19] [-0.19; 0.34]
Hidese 2021, IL-12 (p40)	104	43.30 10.10	118	44.30	9.70			[-0.36; 0.16]
Hidese 2021, IL-19	104	19.70 2.60	118	20.20	2.90			[-0.44; 0.08]
Lindqvist 2009, IL-1B Hidese 2021, IL-26	32 104	0.06 0.04 35.30 15.40	47 118	0.07 36.60	0.07 17.10			[-0.55; 0.35] [-0.34; 0.18]
Hidese 2021, IL-29/IFN1	104	155.30 41.00	118	160.00	40.80	- 	-0.11	[-0.38; 0.15]
Janelidze 2013, IP-10	51	158.59 112.92	43		47.30			[-0.73; 0.09]
Ogawa 2015, Isoleucine Erhardt 2013, Kynurenic acid	42 31	5.20 1.50 1.25 0.78	54 36	4.80 1.37	1.40 0.54			[-0.13; 0.68] [-0.66; 0.30]
Kaddurah–Daouk 2012, Kynurenine	14	5.20 2.41	18	5.48	1.07		-0.15	[-0.85; 0.55]
Kaddurah-Daouk 2012, L-DOPA	14	0.57 0.30	18	0.46	0.32			[-0.37; 1.03]
Ogawa 2015, Leucine Ogawa 2015, Lysine	42 42	12.50 3.40 24.30 7.10	54 54	11.50 22.20	2.90 3.90			[-0.09; 0.72] [-0.03; 0.78]
Gotoh 2019, Lysophosphatidic acid	52	0.17 0.08	49	0.19	0.08			[-0.56; 0.22]
George 1994, Magnesium	43	1.15 0.08	59	1.13	0.07			[-0.13; 0.66]
Janelidze 2013, MCP–1 Janelidze 2013, MCP–4	51 51	813.78 452.57 4.21 2.34	43 43	903.60 2 6.00	279.00 2.00			[-0.64; 0.17] [-1.23; -0.39]
Bumb 2016, Melatonin	25	9.10 2.90	13	10.60	7.50			[-0.97; 0.38]
Janelidze 2013, MIP-1B	51	32.19 22.57	43		22.80			[-0.74; 0.08]
Ventorp 2016, MMP–1 Omori 2020, MMP–10	37 90	11.54 6.60 24.30 21.80	30 106	13.00 17.00	5.35 17.00			[-0.72; 0.25] [0.09; 0.66]
Omori 2020, MMP-2	90	56.40 20.60	106		18.10			[0.06; 0.62]
Omori 2020, MMP-7	90	11.40 10.70	106	8.90	7.20		0.28	[0.00; 0.56]
Ventorp 2016, MMP–9 Rymo 2017, Myelin basic protein	37 19	145.36 139.39 1.05 0.30	30 67	94.43 1.10	74.76 0.30			[-0.05; 0.92] [-0.67; 0.35]
Kageyama 2021, Nervonic acid	29	0.00 0.00	30	0.00	0.00			[-0.77; 0.26]
Hidese 2020, Neuropilin-1	104	3189.60 1182.00	118	3199.50 11	04.10	+	-0.01	[-0.27; 0.25]
Wong 2000, Norepinephrine Ogawa 2015, Ornithine	10 36	137.40 12.70 2.90 1.40	14 47	102.30 3.20	7.00 1.50			[2.13; 4.83] [-0.64; 0.23]
Hidese 2021, Osteocalcin	104	95.00 49.10	118		44.90			[-0.13; 0.40]
Ventorp 2016, Osteopontin	39	63.29 15.48	45	63.81	19.04		-0.03	[-0.46; 0.40]
Buerger 2003, P-tau 231 Widerlöv, Lindström 1988b, Peptide YY	34 33	10.00 18.00 19.90 4.60	21 20	2.00 22.10	9.00 4.92			[-0.04; 1.07] [-1.02; 0.10]
Ogawa 2015, Phenylalanine	42	10.10 2.10	54	10.00	2.30	- <u>+</u>		[-0.36; 0.45]

Blennow 1995, PHFtau	10	230.00	130.00	31	640.00	320.00 ←		-1.40 [-2.18; -0.62]
Ogawa 2015, Phosphoethanolamine	42	4.70	1.20	54	5.10	1.10		-0.35 [-0.75; 0.06]
Brundin 2016, Picolinic acid	31	40.40	34.77	36	73.60	11.40 -		-1.31 [-1.84; -0.78]
Erhardt 2013, Quinolinic acid	31	40.54	33.57	36	18.22	4.74		0.96 [0.45; 1.46]
Hidese 2020, S100B	104	819.60	324.40	118	831.40	290.10	-	-0.04 [-0.30; 0.23]
Hertze 2010, sABPP-alfa	28	689.00	274.00	38	787.00	350.00		-0.30 [-0.79; 0.19]
Hertze 2010, sABPP-beta	28	193.00	80.00	38	244.00	112.00		-0.51 [-1.00; -0.01]
Ventorp 2016, sCD44	39	37.04	20.55	45	33.49	11.94		0.21 [-0.22; 0.64]
Hattori 2015, SL000022 (D–dimer)	30	1527.00	1216.00	30	1029.00	408.00		0.54 [0.03; 1.06]
Hattori 2015, SL0000424 (fibrinogen)	30	739.00	582.00	30	456.00	238.00		0.63 [0.11; 1.15]
Hattori 2015, SL003341 (fibrinogen y-chain)	30	251.00	148.00	30	184.00	82.00		0.55 [0.04; 1.07]
Hidese 2021, Soluble CD163	104	3479.00	1126.10	118	3229.20	1151.90		0.22 [-0.05; 0.48]
Hidese 2021, Soluble CD30/TNFSF8	104	331.30	143.70	118	308.20	136.00		0.16 [-0.10; 0.43]
Hidese 2021, Soluble IL-6 receptor	104	1048.90	342.20	118	975.90	280.70		0.23 [-0.03; 0.50]
Hidese 2021, Soluble TNF-receptor 1	104	1025.40	297.40	118	957.30	243.40		0.25 [-0.01; 0.52]
Hidese 2021, Soluble TNF-receptor 2	104	375.80	178.50	118	336.50	170.50		0.22 [-0.04; 0.49]
Regenold 2000, Sorbitol	10	19.00	2.80	10	15.60	1.90		→ 1.36 [0.37; 2.36]
Pomara 2021, sTREM2	27	3609.23	2691.04	17	5361.55	2802.26		-0.63 [-1.25; -0.01]
Ogawa 2015, Threonine	42	33.10	9.30	54	29.80	5.30		0.45 [0.04; 0.86]
Hidese 2021, Thymic stromal lymphopoietin	104	21.20	7.20	118	21.20	10.00		0.00 [-0.26; 0.26]
Janelidze 2013, Thymus activation regulated chemokine (TARC)	51	3.99	2.40	43	5.50	2.10		-0.66 [-1.08; -0.24]
Kaddurah–Daouk 2012, Tryptophol	14	1.00		18	2.10	3.25		-0.42 [-1.13; 0.28]
Kaddurah–Daouk 2012, Tyramine	14	3.95	4.11	18	2.72	2.24		0.37 [-0.33; 1.08]
Kaddurah–Daouk 2012, Uric	14	7274.65	2399.45	18	7197.84	2758.53		0.03 [-0.67; 0.73]
Ogawa 2015, Valine	42	16.60	4.80	54	15.20	4.60		0.30 [-0.11; 0.70]
Sunderland 1991, Vasoactive intestinal peptide	9	105.00	48.00	9	134.00	46.00		-0.59 [-1.54; 0.36]
Hidese 2020, VEGF receptor 1	104	33.20	15.00	118	34.50	15.10	-	-0.09 [-0.35; 0.18]
Hidese 2020, VEGF receptor 2	104	674.20		118	668.10	223.20		0.02 [-0.24; 0.29]
Kaddurah–Daouk 2012, X7MG	14	2.62	0.68	18	2.59	0.39		0.06 [-0.64; 0.75]
Kaddurah–Daouk 2012, Xanthine	14	218.46		18	247.72	39.71		-0.49 [-1.20; 0.22]
Kaddurah–Daouk 2012, Xanthosine	14	3.36		18	3.82	2.04		-0.21 [-0.92; 0.49]
Rymo 2017, YKL-40	19	18.56	6.29	67	17.80	6.00		0.12 [-0.39; 0.63]
						1		1
						-2	-1 0 1	2

eTabl	e 5	Presentatio	on of all b	iomarkers identif	fied for the meta-a	analysis and a bri	ef description o	of their function	
		• • •							

Neurotransmitters and their me	etabolites
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), Dihydroxyphenyl- alanine (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) / Nora- drenaline (NA), 3-Methoxy-4-hydroxyphenyl- glycol (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 a <i>Hormones</i>	imino acids
Cantination in allers' 1	
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
(CRH) / Corticotropin releasing	(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
(CRH) / Corticotropin releasing factor (CRF) Adrenocorticotropic hormone	 (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 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
(CRH) / Corticotropin releasing factor (CRF) Adrenocorticotropic hormone (ACTH)	 (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 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 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
 (CRH) / Corticotropin releasing factor (CRF) Adrenocorticotropic hormone (ACTH) Cortisol, corticosterone Arginine-vasopressin (AVP) / Vasopressin / Antidiuretic hor- 	 (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 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 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} 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 ef-

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 pi- tuitary gland while peripherally released by leukocytes in response to inflammation. Altera- tions 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-reg- ulated 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 be- lieved 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 monophos- phate (cAMP), Cyclic guanosine monophos- phate (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,	Amino acids, derivates and metabolites are small molecules with various functions and sug- gested relations to depression.
Phenylalanine, Asparagine,	The amino acid tryptophan is the precursor of both serotonin and kynurenine, ¹ whereas the
Arginine, Threonine, Valine, Isoleucine, Leucine, Ornithine, Lysine, Cystine, Histidin + 1- methylhistidin, Tyramine,	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-1 β (IL-1 β) and tumor necrosis factor-alpha (TNF- α) both activates the HPA axis, ^{39,40} reduce monoamine availability by upregulating presynaptic reuptake pumps for 5-HT, NE and DA and reduce levels of BDNF. ³⁸ IL-1 β 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- λ 1 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 recep- tor 1 and 2) IFN-α2, IFN-β	The sIL-6-receptor binds in a complex with IL-6 and the protein gp130 and this complex ini- tiates intracellular signaling mediating the effect of IL-6. ⁵¹ The sTNF-receptor 1 and 2 func- tions 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- α 2 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 includ- ing 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-1 β , 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 acti- vating 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 osteocal cin'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 per meability and inducing chemotaxis. ⁶³
Autotaxin (ATX), Lysophos- phatidic acid (LPA)	ATX is an enzyme expressed in both the brain and peripheral tissues converting extracellu- lar 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 be- haviour, and the LPA receptor is suggested a target for antidepressants. Since LPA is unsta- ble, 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 de ficiency 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 pro- tein-10 (IP-10)/CXCL10, Mac- rophage 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-1B/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 neurotrans- mitter acetylcholine. Increased central cholinergic activity is suggested to have an anti-in- flammatory effect, whereas a reduction – due to for example AChE and BChE – may in- crease 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), Pico- linic 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 re- lease and simultaneous block of the reuptake, leading to increased extra-synaptic glutamate

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	levels. ³⁸ KYNA, mainly produced by astrocytes, is an NMDA antagonist with neuroprotec- tive properties. ¹ PIC is likewise neuroprotective by antagonizing the effect of QUIN. ⁷⁴ Im- balance 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 clot- ting, 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 hypercoagula- tion 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 synapti <i>Neurodegeneration</i>	c plasticity
Tau, p-tau 181, p-tau 213	Tau proteins are a group of microtubule-associated proteins that are associated with cyto- skeletal functioning in neurons. ⁸² Specific phosphorylation of tau is important for correct functioning, and abnormal phosphorylation can lead to dysfunction and decreased cell via- bility. 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 oc- cur as an early symptom of AD, it has also become a field of interest in depression re- search. ⁸⁴
ΑβΡΡ	Amyloid- β precursor protein (A β PP) 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)	sA β PP α and sA β PP β are released from the cleavage of APP by α - and β -secretase, respectively. Hence they reflect the turnover from A β PP to A β , whereas sA β PP α is also suggested to have proliferative and neuroprotective properties. ⁸⁶
Amyloid-β (Αβ), Amyloid-β-42 (Αβ42), Amy- loid-β-40 (Αβ40), Amyloid-β- 38 (Αβ38)	A β is a heterogeneous mix of small peptides (from 36 to 43 amino acids) derived from cleavage of the APP. A β is normally secreted from cells and degraded, but in AD an abnormal accumulation in the brain leads to insoluble plaques. A β 42, A β 40 and A β 38 are isotypes of A β consisting of 42, 40 and 38 amino acids respectively. A β 42 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 dopa- minergic 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 fac- tor (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 sub- stantial to the CNS promoting angiogenesis, survival of neurons, and regeneration and guid- ing 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 fac- tor (VEGF) receptor 1 and 2	VEGF is a mitogen and survival factor for endothelial cells, and in CNS it affects neurogen- esis, cell survival and synaptic plasticity. Antidepressant treatment can induce VEGF ex- pression, 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 pro- tein 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 ex- pressed 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	KYNA	Kynurenic acid
5-HIAA	5-hydroxyindole-acetic acid	L-DOPA	Dihydroxyphenylalanine
Αβ	Amyloid-β	LPA	Lysophosphatidic acid
ΑβΡΡ	Amyloid-β precursor protein	MBP	Myelin basic protein
ACTH	Adrenocorticotropic hormone	MCP	Monocyte chemotactic protein
ADH	Antidiuretic hormone	MHPG	Methoxy-4-hydroxyphenylglycol
α-Syn	α-synuclein	MIP-1ß	Macrophage inflammatory protein-1ß
ATX	Autotaxin	MMP	Matrix metalloproteinase
APRIL	A proliferation-inducing ligand	NA	Noradrenaline
AVP	Arginine-vasopressin	NCAM	Neural cell adhesion molecule
BAFF	B-cell activating factor	NE	Norepinephrine
BBB	Blood-brain-barrier	NfL	Neurofilament light protein
BDNF	Brain-derived neurotrophic factor	NPY	Neuropeptide tyrosine
CART	Cocaine- and amphetamine-regulated transcript	OPN	Osteopontin
cAMP	Cyclic adenosine monophosphate	OT	Oxytocin
cGMP	Cyclic guanosine monophosphate	PEA	Phosphoethanolamine
CHI3L1	Chitinase-3-like protein 1	PIC	Picolinic acid
CRF	Corticotropin releasing factor	РҮҮ	Peptide YY
CRH	Corticotropin releasing hormone	sAβPPa	Soluble ABPP alfa protein
DA	Dopamine	sAβPPβ	Soluble ABPP beta protein
DBI	Diazepam binding inhibitor	S100B	S100 calcium-binding protein
GABA	γ-aminobutyric acid	SS	Somatostatin
GAP-43	Growth-associated protein-43	TARC	Thymus activation regulated chemokine
GDNF	Glial cell-derived neurotrophic factor	TLR	Toll like receptor
GFAp	Glial fibrillary acidic protein	TNF-α	Tumor necrosis factor-alpha
HA	Hyaluronic acid	TNFSF	Tumor necrosis factor superfamily
HGF	Hepatocyte growth factor	TSLP	Thymic stromal lymphopoietin
HPA axis	Hypothalamic-pituitary-adrenal axis	TTR	Transthyretin
HVA	Homovanillic acid	VEGF	Vascular endothelia growth factor
IFN	Interferon	QUIN	Quinolinic acid
IP-10	Interferon gamma-induced protein-10		

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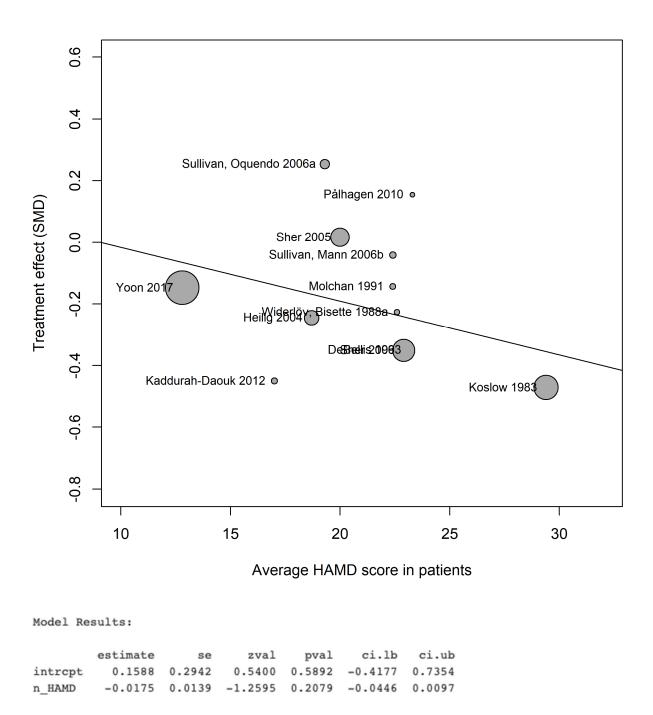
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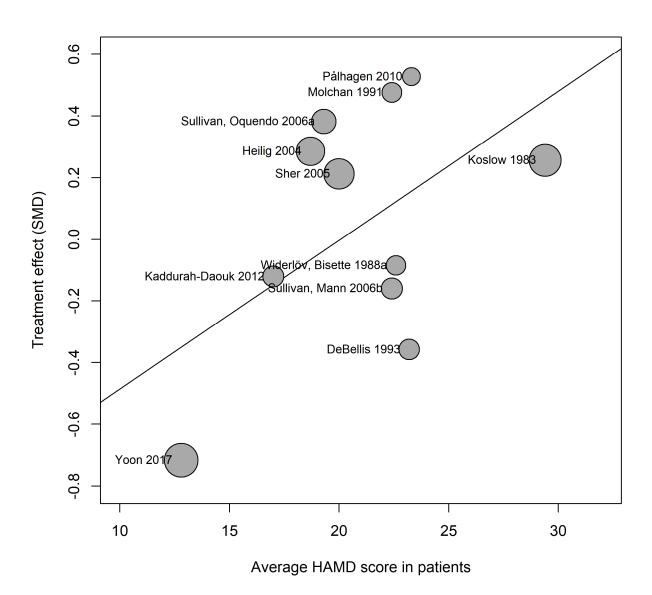
Subgroup analyses

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



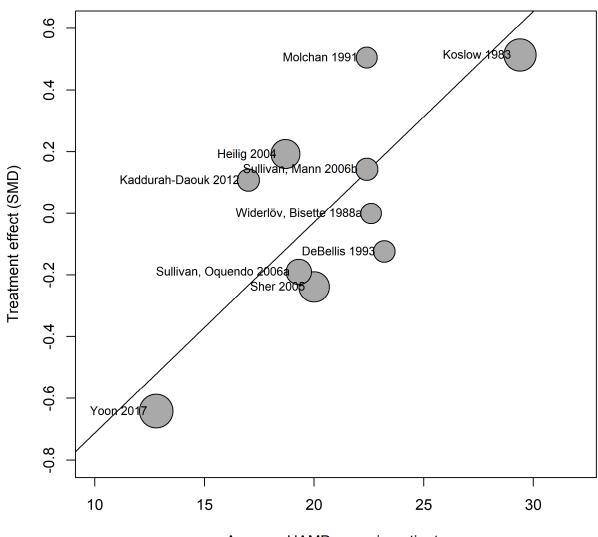
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Model Results:

	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



Average HAMD score in patients

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

		Exper	imental		(Control	Standardised Mean			
Study	Total	Mean	SD	Total	Mean	SD	Difference	SMD	95%-CI	Weight
Hospitalized: no										
Pålhagen 2010	12	173.20	100.11	12	159.20	72.40		0.15 [-	0.65; 0.96]	5.7%
Heilig 2004	51	206.40	86.60	27	228.80	97.50	- <u></u> -	-0.25 [-	0.71; 0.22]	14.6%
Random effects model	63			39				-0.14 [-	0.55; 0.26]	20.4%
Heterogeneity: $I^2 = 0\%$, τ^2	= 0, p =	= 0.40						_	_	
Hospitalized: yes										
Swann 1999	85	195.00	74.00	85	230.00	76.00		-0.46 [-	0.77; -0.16]	27.3%
Widerlöv, Bisette 1988a	22	151.20	66.13	10	166.40	63.56		-0.23 [-	0.98; 0.52]	6.5%
Åsberg 1984	43	201.70	92.40	66	245.90	114.30		-0.41 [-	0.80; -0.02]	19.6%
Koslow 1983	58	194.86	73.96	62	230.32	75.59		-0.47 [-	0.83; -0.11]	21.6%
Kasa 1982	10	19.60	13.20	16	41.80	16.80	<	-1.38 [-	2.27; -0.49]	4.7%
Random effects model	218			239			\diamond	-0.48 [-	0.69; -0.28]	79.6%
Heterogeneity: $I^2 = 12\%$, τ	$^{2} = 0.00$	068, p = 0	0.34					-		
Random effects model				278			🔶	0.42 [-	0.62; -0.22]	100.0%
Heterogeneity: $I^2 = 19\%$, τ								1		
Test for subgroup differen	ces: χ_1^2	= 2.17, d	f = 1 (p =	0.14)		-	2 -1 0 1	2		

5-HIAA

		Experin	nental		с	ontrol	Sta	ndardised N	lean				
Study	Total			Total	Mean	SD	ota	Difference		SMD	9	5%-CI	Weight
Hospitalized: no													
Pålhagen 2010	12	87.00	38.45	12	67.20	33.95				0.53	[-0.29;	1.34]	11.9%
Heilig 2004	51	127.30	49.10	27	114.20	37.40			-	0.29	[-0.18;	0.751	18.3%
Random effects model	63			39				\sim			[-0.06;		30.2%
Heterogeneity: $I^2 = 0\%$, τ^2		0.61									,		
Hospitalized: yes													
Widerlöv, Bisette 1988a	22	70.30	23.45	10	72.20	18.02				-0.08	[-0.83;	0.661	13.0%
Edman 1986	19	84.40	21.00	32	119.00	42.00				-0.95	[-1.55;	-0.351	15.7%
Åsberg 1984	60	92.10	38.60	66	104.10	38.30					[-0.66;		20.7%
Koslow 1983		119.32			111.00						[-0.11;		20.4%
Random effects model				166							[-0.74;		69.8%
Heterogeneity: $I^2 = 76\%$, τ^2		10, p < 0	0.01							0.20	,		
Random effects model	221			205				\rightarrow		-0.06	[-0.45:	0.331	100.0%
Heterogeneity: $I^2 = 71\%$, τ		96 n < (0.01			1	- T		1	1	L,	0.001	
Test for subgroup difference	ces: χ_1^2	= 3.36, di	f = 1 (p	= 0.07)		-3	2 -1	0	1 :	2			

MHPG

	Experiment	al	С	ontrol	Standardised Mean			
Study	Total Mean S	D Total	Mean	SD	Difference	SMD	95%-CI	Weight
Hospitalized: no								
Pålhagen 2010	12 41.80 11.0	09 12	30.70	9.35		- 1.05 [0	0.18; 1.91]	7.0%
Heilig 2004	51 40.30 9.8	30 27	38.50	8.20		0.19 [-(0.28; 0.66]	17.3%
Random effects model	63	39				0.54 [-0	0.28; 1.36]	24.3%
Heterogeneity: $I^2 = 66\%$, τ^2	² = 0.2384, <i>p</i> = 0.09)				-		
Hospitalized: yes								
Swann 1999	85 48.50 11.	50 85	43.30	8.30		0.52 [(0.21; 0.82]	26.3%
Widerlöv, Bisette 1988a	22 51.70 12.2	20 10	51.70	7.59		0.00 [-0	0.75; 0.75]	8.9%
Åsberg 1984	26 50.80 7.4	40 60	51.20	10.10		-0.04 [-0	0.50; 0.42]	17.6%
Koslow 1983	61 48.50 11.	50 61	43.30	8.40		0.51 [(0.15; 0.87]	22.8%
Random effects model Heterogeneity: $I^2 = 46\%$, τ^2		216			\diamond	0.32 [0	0.03; 0.61]	75.7%
Heterogeneity: $I = 46\%$, τ	= 0.0386, p = 0.14							
Random effects model		255		Г		0.35 [0	0.10; 0.60]	100.0%
Heterogeneity: $I^2 = 41\%$, τ^2					1 1 1			
Test for subgroup difference	ces: χ ₁ ² = 0.23, df = 1	1 (p = 0.6	3)	-2	2 -1 0 1	2		

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

HVA

Study	Total	Experi Mean		Total	Mean	Control SD		dardised I Difference		SMD	95%-CI	Weight
Treatment stop: <= 14 d	ays											
Yoon 2017	75	26.32	16.10	87	28.44	12.45				-0.15	[-0.46; 0.16]	13.2%
Sullivan, Mann 2006b	17	198.10	64.30	15	201.10	79.30	-			-0.04	[-0.74; 0.65]	3.5%
Sullivan, Oquendo 2006a	48	220.83	79.47	15	200.60	76.60		- 		0.25	[-0.33; 0.84]	4.8%
Sher 2005	125	198.45	76.50	27	197.20	69.50				0.02	[-0.40; 0.43]	8.5%
Heilig 2004	51	206.40	86.60	27	228.80	97.50	-	- <u>-</u>		-0.25	[-0.71; 0.22]	7.0%
Swann 1999	85	195.00	74.00	85	230.00	76.00	-			-0.46	[-0.77; -0.16]	13.4%
Lewine 1991	19	159.30	72.30	91	160.60	69.70				-0.02	[-0.51; 0.48]	6.4%
Widerlöv, Bisette 1988a	22	151.20	66.13	10	166.40	63.56				-0.23	[-0.98; 0.52]	3.0%
Åsberg 1984	43	201.70	92.40	66	245.90	114.30	-			-0.41	[-0.80; -0.02]	9.4%
Koslow 1983	58	194.86	73.96	62	230.32	75.59	-			-0.47	[-0.83; -0.11]	10.5%
Kasa 1982	10	19.60	13.20	16	41.80	16.80	< 1			-1.38	[-2.27; -0.49]	2.2%
Oreland 1981	20	211.95	66.91	42	230.57	100.60	-			-0.20	[-0.74; 0.33]	5.6%
Random effects model	573			543				\diamond		-0.25	[-0.42; -0.09]	87.5%
Heterogeneity: $I^2 = 33\%$, $\tau^2 =$	= 0.025	3, p = 0.1	3									
Treatment stop: > 14 da	vs											
Kaddurah-Daouk 2012	14	23.83	14.88	18	29.06	7.56		-		-0.45	[-1.16; 0.26]	3.4%
Pålhagen 2010	12	173.20	100.11	12	159.20	72.40					[-0.65; 0.96]	2.7%
DeBellis 1993	9	182.90	49.70	46	219.50	109.90		-		-0.35	[-1.07: 0.37]	3.3%
Molchan 1991	18	190.20	83.50	12	201.60	66.40		-		-0.14	[-0.88; 0.59]	3.2%
Random effects model	53			88				\rightarrow		-0.22	[-0.59; 0.15]	12.5%
Heterogeneity: $I^2 = 0\%$, $\tau^2 =$	0, p = 0	0.70									• • •	
Random effects model	626			631				\diamond		-0.25	[-0.39; -0.12]	100.0%
Heterogeneity: $I^2 = 16\%$, $\tau^2 = 16\%$	= 0.011	5, p = 0.2	28									
Test for subgroup difference				0.86)			-2 -1	0	1	2		

5-HIAA

		Experin	nental		С	ontrol	Standardised Mean			
Study	Total	Mean	SD	Total	Mean	SD	Difference	SMD	95%-CI	Weight
Treatment stop: <= 14 d	ays									
Yoon 2017	75	8.25	4.70	87	10.72	1.67		-0.72	[-1.04; -0.40]	9.0%
Sullivan, Mann 2006b	17	99.90	34.60	15	105.70	36.40		-0.16	[-0.86; 0.54]	5.5%
Sullivan, Oquendo 2006a	48	106.57	34.46	15	93.30	33.60		0.38	[-0.20; 0.97]	6.4%
Sher 2005	125	100.31	35.10	27	92.90	33.00		0.21	[-0.20; 0.63]	8.1%
Heilig 2004	51	127.30	49.10	27	114.20	37.40		0.29	[-0.18; 0.75]	7.5%
Lewine 1991	19	97.40	42.20	91	90.90	36.00		0.17	[-0.32; 0.67]	7.3%
Widerlöv, Bisette 1988a	22	70.30	23.45	10	72.20	18.02		-0.08	[-0.83; 0.66]	5.1%
Edman 1986	19	84.40	21.00	32	119.00	42.00		-0.95	[-1.55; -0.35]	6.3%
Åsberg 1984	60	92.10	38.60	66	104.10	38.30		-0.31	[-0.66; 0.04]	8.7%
Koslow 1983	57	119.32	33.73	58	111.00	30.56	÷ • -	0.26	[-0.11; 0.62]	8.6%
Oreland 1981	20	99.92	34.17	42	99.63	35.21		0.01	[-0.52; 0.54]	6.9%
Random effects model	513			470			\Leftrightarrow	-0.08	[-0.35; 0.19]	79.4%
Heterogeneity: $I^2 = 72\%$, $\tau^2 =$	= 0.143	9, p < 0.0	01							
Treatment stop: > 14 da	ys									
Kaddurah-Daouk 2012	14	11.20	6.22	18	12.31	10.67		-0.12	[-0.82; 0.58]	5.5%
Pålhagen 2010	12	87.00	38.45	12	67.20	33.95		0.53	[-0.29; 1.34]	4.6%
DeBellis 1993	9	95.90	24.60	46	111.20	44.50		-0.36	[-1.08; 0.36]	5.3%
Molchan 1991	18	112.10	37.00	12	94.50	34.30		0.48	[-0.27; 1.22]	5.2%
Random effects model	53			88			<u> </u>	0.11	[-0.32; 0.53]	20.6%
Heterogeneity: $I^2 = 25\%$, $\tau^2 =$	= 0.047	1, p = 0.2	26							
Random effects model	566			558				-0.04	[-0.28; 0.19]	100.0%
Heterogeneity: $I^2 = 66\%$, $\tau^2 =$	= 0.128	8, p < 0.0	01						· · ·	
Test for subgroup difference	s: χ ₁ ² =	0.54, df =	= 1 (p =	0.46)		-3	2 -1 0 1	2		

Study		Experin Mean		Total	-	ontrol SD		dardised M Difference	ean	SMD	9	5%-CI	Weight
Treatment stop: <= 14 c	ave							L:					
Yoon 2017	75	7.81	1.77	87	8.92	1.67	_			0.64	[-0.96;	0 221	9.4%
Sullivan, Mann 2006b		46.00			42.80						[-0.55;	-	9.4 % 6.0%
Sullivan, Oquendo 2006a		46.33			42.00						[-0.55,		6.9%
Sher 2005		40.33			47.40								8.5%
					38.50	26.50					[-0.66;		
Heilig 2004		40.30									[-0.28;		8.0%
Swann 1999		48.50			43.30	8.30					[0.21;		9.5%
Widerlöv, Bisette 1988a		51.70			51.70	7.59		1			[-0.75;		5.6%
Åsberg 1984		50.80			51.20						[-0.50;	-	8.0%
Koslow 1983		48.50			43.30	8.40			-		[0.15;	-	9.0%
Oreland 1981		51.27	9.67		49.50	9.60					[-0.37;		7.2%
Random effects model	528			429				\rightarrow		0.04	[-0.24;	0.33]	77.9%
Heterogeneity: $I^2 = 76\%$, τ^2	= 0.156	i3, p < 0	0.01										
T													
Treatment stop: > 14 da				10		1 70				~		0.047	
Kaddurah-Daouk 2012		11.78			11.57	1.72			_		[-0.59;		5.9%
Pålhagen 2010		41.80			30.70	9.35					[0.18;	-	4.8%
DeBellis 1993		46.70			48.00		-				[-0.84;		5.8%
Molchan 1991		60.80	20.90		51.10	14.70					[-0.24;		5.6%
Random effects model	53			88						0.34	[-0.13;	0.82]	22.1%
Heterogeneity: $I^2 = 37\%$, τ^2	= 0.087	(1, p = 0)	.19										
Random effects model	581			517		r		\rightarrow		0.11	[-0.14;	0.36]	100.0%
Heterogeneity: $I^2 = 70\%$, τ^2						1		L.	1 1				
Test for subgroup difference	es: $\chi_1^2 =$	1.10, df	f = 1 (p	= 0.29)		-2	2 -1	0	1 2				

CRH

Study	Ex Total M	operim Mean		Total	C Mean	ontrol SD	Sta	ndardised I Difference		SMD	95	%-CI	Weight
Treatment stop: <= 14	days							1					
Garakani 2013	18 7	78.00	41.80	24	82.66	30.40				-0.13	[-0.74;	0.48]	13.1%
Carpenter, Tyrka 2004b	27 2	29.00	9.40	25	24.90	8.50		+ +		0.45	[-0.10;	1.00]	14.1%
Wong 2000	10 4	18.90	9.80	14	57.10	4.10	< +	I		-1.13	[-2.01; -	0.25]	9.3%
Heuser 1998	37 4	19.60	18.40	25	49.60	13.30					[-0.51;		14.8%
Pitts 1995	19 3	38.60	10.00	18	43.30	8.10				-0.50	[-1.16;	0.15]	12.4%
Risch 1992		33.70			69.40						[-0.14;	-	14.7%
Widerlöv, Bisette 1988a		71.90	19.70	10	57.30	12.02			1		[0.03;	-	10.7%
Random effects model				199				\rightarrow		0.02	[-0.38;	0.42]	89.1%
Heterogeneity: $I^2 = 65\%$, τ^2		7, p < 1	0.01										
Treatment stop: > 14 d					07.40	4 5 00		_				0.001	10.00/
Molchan 1993		78.60	24.60		87.10	15.80		•			[-1.14;	-	10.9%
Random effects model Heterogeneity: not applical	18 ble			11						-0.38	[-1.14;	0.38]	10.9%
Random effects model Heterogeneity: $I^2 = 62\%$, τ^2	2 = 0.166			210			г <u>г</u>		1	_ -0.02	[-0.39;	0.34]	100.0%
Test for subgroup difference	ces: $\chi_1^2 = 0$	0.84, d	lf = 1 (µ	0 = 0.36	6)	-	2 -1	0	1	2			

Somatostatin

	E	Experin	nental		С	ontrol	Standar	dised Mean			
Study	Total	Mean	SD	Total	Mean	SD	Diff	erence	SMD	95%-CI	Weight
Treatment stop: <= 14	days							T			
Heilig 2004	51	29.60	9.00	27	32.20	9.40		+-	-0.28 [-0	0.75; 0.19]	21.8%
Heuser 1998	37	31.40	9.90	25	38.60	8.80			-0.75 [-1	1.28; -0.22]	21.6%
Bissette 1986	17	65.40	32.16	10	116.10	49.65	~ 1		-1.25 [-2	2.11; -0.39]	19.8%
Rubinow 1983	7	30.40	5.90	39	62.80	6.38	<		-5.04 [-6	5.39; -3.70]	16.5%
Random effects model	112			101	-				-1.68 [-3	8.00; -0.35]	79.7%
Heterogeneity: $I^2 = 93\%$, τ^2	= 1.63	372, p <	0.01								
Treatment stop: > 14 d	ays										
Molchan 1991	18	45.10	15.50	12	60.20	16.10	•	-	-0.93 [-1	1.71; -0.16]	20.3%
Random effects model	18			12				- 1	-0.93 [-1	.71; -0.16]	20.3%
Heterogeneity: not applicab	le										
Random effects model	130			113					-1.49 [-2	2.53; -0.45]	100.0%
Heterogeneity: $I^2 = 91\%$, τ^2	= 1.23	315, p <	0.01					1 1			
Test for subgroup difference	es: χ_1^2	= 0.90,	df = 1 (p = 0.34	1)	-3	2 -1	0 1	2		

Neuropeptide Y

tide Y									
		Experin				ontrol	Standardised Mean		
Study	Total	Mean	SD	Total	Mean	SD	Difference	SMD	95%-CI Weight
Treatment stop: <= 14 da	vs						:		
Soleimani 2014	6 1	7.90	1.50	20	7.00	1.30	· · · · · ·	0.61 [0	0.10; 1.13] 20.7%
Martinez 2012	18	176.13	47.26	25	137.66	24.14			0.41; 1.71] 20.1%
Heilig 2004	51	134.10	23.70	27	161.80	25.70		-1.12 [-1	1.62, -0.62] 20.8%
Widerlöv, Lindström 1988b	33	102.20	11.49	20	121.80	13.86	~ • • • •	-1.55 [-2	2.19; -0.92] 20.2%
Random effects model	163			92				-0.25 [-1	.46; 0.96] 81.7%
Heterogeneity: $I^2 = 94\%$, $\tau^2 =$	1.4372	, <i>p</i> < 0.01							
Treatment stone > 14 day	-								
Treatment stop: > 14 day Sunderland 1991		123.00	21.00	٩	142.00	28.00		-0.73 [-1	1.69; 0.23] 18.3%
Random effects model	9	125.00	21.00	9	142.00	20.00			.69; 0.23] 18.3%
Heterogeneity: not applicable								-0.70 [-1	1.00, 0.20] 10.0%
· · · · · · · · · · · · · · · · · · ·									
Random effects model	172			101				-0.34 [-1	.37; 0.69] 100.0%
Heterogeneity: I^2 = 93%, τ^2 =									
Test for subgroup differences	$\chi_1^2 = 0$.37, df =	1 (p = 0).54)			2 -1 0 1	2	

IL-6

	E>	perim	ental		Co	ntrol	Standardised Mean			
Study	Total	Mean	SD	Total	Mean	SD	Difference	SMD	95%-CI \	Neight
Treatment stop: <= 14 da	ys									
Pomara 2021	27	4.53	3.08	17	4.87	5.27		-0.08	[-0.69; 0.52]	16.2%
Kern 2014	19	3.40	4.33	67	1.91	1.81		0.58	[0.06; 1.09]	20.2%
Sasayama 2013	30	2.14	1.22	35	1.54	0.80	· · · ·	0.58	[0.09; 1.08]	21.1%
Martinez 2012	18	0.07	0.01	25	0.06	0.01		0.70	[0.08; 1.33]	15.6%
Random effects model	94			144			$\langle \mathbf{x} \rangle$	0.46	[0.14; 0.78]	73.1%
Heterogeneity: $I^2 = 26\%$, $\tau^2 = 10\%$	0.0289,	p = 0.2	5							
Treatment stop: > 14 day	5									
Pålhagen 2010	12	7.54	8.56	12	4.34	6.34		0.41	[-0.40; 1.22]	10.4%
Carpenter, Heninger 2004a	18	2.20	1.00	26	2.40	1.90		-0.12	[-0.72; 0.48]	16.5%
Random effects model	30			38				0.07	[-0.43; 0.58]	26.9%
Heterogeneity: $I^2 = 7\%$, $\tau^2 = 0$.0096, <i>µ</i>	0 = 0.30								
Random effects model Heterogeneity: $I^2 = 30\%$, $\tau^2 = 10^{-10}$	124	p = 0.2	1	182		ſ		0.36	[0.07; 0.65] 1	00.0%
Test for subgroup differences:	$\chi_1^2 = 1.$	62, df =	1 (p =	= 0.20)		-2	2 -1 0 1	2		

Sensitivity analyses

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

HVA

Study	Total		imental SD	Total		Control SD	Standardised Mean Difference	SMD	95%-CI	Weight
Bias score: <4							1			-
Kaddurah-Daouk 2012	14	23.83	14.88	18	29.06	7.56		0.45	[-1.16; 0.26]	2.9%
		173.20			159.20	72.40			[-0.65; 0.96]	2.3%
Pålhagen 2010		220.83	79.47		200.60	76.60				4.2%
Sullivan, Oquendo 2006a									[-0.33; 0.84]	
Sher 2006		169.38	79.11		196.90	76.30			[-0.73; 0.03]	8.9%
Sher 2005		198.45	76.50		197.20	69.50			[-0.40; 0.43]	7.7%
DeBellis 1993		182.90	49.70		219.50				[-1.07; 0.37]	2.9%
Widerlöv, Bisette 1988a		151.20	66.13		166.40	63.56			[-0.98; 0.52]	2.6%
Kasa 1982	10		13.20	16		16.80	< <u>■</u>		[-2.27; -0.49]	1.9%
Oreland 1981		211.95	66.91		230.57	100.60			[-0.74; 0.33]	5.0%
Random effects model	318			236			\sim	-0.22	[-0.47; 0.02]	38.5%
Heterogeneity: $I^2 = 34\%$, $\tau^2 = 34\%$	= 0.046	3, p = 0.	14							
Bias score: >= 4										
Yoon 2017	75		16.10	87		12.45			[-0.46; 0.16]	12.5%
Sullivan, Mann 2006b	17	198.10	64.30	15	201.10	79.30		-0.04	[-0.74; 0.65]	3.0%
Heilig 2004	51	206.40	86.60	27	228.80	97.50		-0.25	[-0.71; 0.22]	6.3%
Swann 1999	85	195.00	74.00	85	230.00	76.00		-0.46	[-0.77; -0.16]	12.8%
Lewine 1991	19	159.30	72.30	91	160.60	69.70		-0.02	[-0.51; 0.48]	5.7%
Molchan 1991	18	190.20	83.50	12	201.60	66.40		-0.14	[-0.88; 0.59]	2.8%
Åsberg 1984	43	201.70	92.40	66	245.90	114.30		-0.41	[-0.80; -0.02]	8.7%
Koslow 1983	58	194.86	73.96	62	230.32	75.59			[-0.83; -0.11]	9.7%
Random effects model	366			445			\$		[-0.44: -0.16]	61.5%
Heterogeneity: $I^2 = 0\%$, $\tau^2 =$	0 n = 1	0.63							,	
	-, 12									
Random effects model	684			681			\$	-0.26	[-0.39; -0.14]	100.0%
Heterogeneity: $l^2 = 11\%$, τ^2		4 n = 0	33						,	
Test for subgroup difference				0.60)		1	2 -1 0 1	2		
rest isi susgioup unerence	. 11 -	0.20, ul ·	· (p = 0)				-		

5-HIAA

Study	Total	Experin Mean		Total		ontrol SD	Standardised Mean Difference	SMD	95%-CI	Weight
Bias score: < 4										
Kaddurah-Daouk 2012	14	11.20	6.22	18	12.31	10.67		-0.12 [-0	0.82; 0.58]	5.5%
Pålhagen 2010	12	87.00	38.45	12	67.20	33.95		0.53 [-0	0.29; 1.34]	4.6%
Sullivan, Oquendo 2006a	48	106.57	34.46	15	93.30	33.60		0.38 [-0	0.20; 0.97]	6.4%
Sher 2005	125	100.31	35.10	27	92.90	33.00		0.21 [-0	0.20; 0.63]	8.1%
DeBellis 1993	9	95.90	24.60	46	111.20	44.50		-0.36 [-1	.08; 0.36]	5.3%
Widerlöv, Bisette 1988a	22	70.30	23.45	10	72.20	18.02		-0.08 [-0	.83; 0.66]	5.1%
Oreland 1981	20	99.92	34.17	42	99.63	35.21		0.01 [-0	0.52; 0.54]	6.9%
Random effects model	250			170			\Rightarrow	0.11 [-0	.12; 0.33]	42.0%
Heterogeneity: $I^2 = 0\%$, $\tau^2 =$	0, <i>p</i> =	0.61								
Bias score: >= 4										
Yoon 2017	75	8.25	4.70	87	10.72	1.67		-0.72 [-1	.04; -0.40]	9.0%
Sullivan, Mann 2006b	17	99.90	34.60	15	105.70	36.40		-0.16 [-0	0.86; 0.54]	5.5%
Heilig 2004	51	127.30	49.10	27	114.20	37.40			0.18; 0.75]	7.5%
Lewine 1991	19	97.40	42.20	91	90.90	36.00		0.17 [-0	0.32; 0.67]	7.3%
Molchan 1991	18	112.10	37.00	12	94.50	34.30		0.48 [-0	0.27; 1.22]	5.2%
Edman 1986	19	84.40	21.00	32	119.00	42.00			.55; -0.35]	6.3%
Åsberg 1984	60	92.10	38.60	66	104.10	38.30		-0.31 [-0	0.66; 0.04]	8.7%
Koslow 1983	57	119.32	33.73	58	111.00	30.56		0.26 [-0	0.11; 0.62]	8.6%
Random effects model	316			388			\sim	-0.13 [-0	.48; 0.22]	58.0%
Heterogeneity: I^2 = 78%, τ^2 =	= 0.191	3, <i>p</i> < 0.	01							
Random effects model	566			558			4	-0.04 [-0	.28; 0.19]	100.0%
Heterogeneity: $I^2 = 66\%$, τ^2		8. p < 0.	01			٢	I			
Test for subgroup difference				0.26)		-2	2 -1 0 1	2		
								_		

	Experimental		Standardised Mean	
Study	Total Mean SD	Total Mean SD	Difference	SMD 95%-CI Weight
Bias score: < 4				
Kaddurah-Daouk 2012	14 11.78 2.05	18 11.57 1.72		0.11 [-0.59; 0.81] 5.9%
Pålhagen 2010	12 41.80 11.09	12 30.70 9.35		— 1.05 [0.18; 1.91] 4.8%
Sullivan, Oquendo 2006a	48 46.33 18.05	15 50.00 22.10		-0.19 [-0.77; 0.39] 6.9%
Sher 2005	125 42.98 16.26	27 47.40 26.50		-0.24 [-0.66; 0.18] 8.5%
DeBellis 1993	9 46.70 14.20	46 48.00 9.50		-0.12 [-0.84; 0.59] 5.8%
Widerlöv, Bisette 1988a	22 51.70 12.20	10 51.70 7.59		0.00 [-0.75; 0.75] 5.6%
Oreland 1981	18 51.27 9.67	42 49.50 9.60		0.18 [-0.37; 0.73] 7.2%
Random effects model	248	170	\Leftrightarrow	0.03 [-0.24; 0.30] 44.6%
Heterogeneity: $I^2 = 24\%$, τ^2	= 0.0319, <i>p</i> = 0.24			
Bias score: >= 4			_	
Yoon 2017	75 7.81 1.77			-0.64 [-0.96; -0.33] 9.4%
Sullivan, Mann 2006b	17 46.00 17.80			0.14 [-0.55; 0.84] 6.0%
Heilig 2004	51 40.30 9.80			0.19 [-0.28; 0.66] 8.0%
Swann 1999	85 48.50 11.50			0.52 [0.21; 0.82] 9.5%
Molchan 1991	18 60.80 20.90			0.50 [-0.24; 1.25] 5.6%
Åsberg 1984	26 50.80 7.40			-0.04 [-0.50; 0.42] 8.0%
Koslow 1983	61 48.50 11.50			0.51 [0.15; 0.87] 9.0%
Random effects model	333	347		0.15 [-0.24; 0.55] 55.4%
Heterogeneity: I^2 = 83%, τ^2	= 0.2225, <i>p</i> < 0.01			
Random effects model	581	517		0.11 [-0.14; 0.36] 100.0%
Heterogeneity: $I^2 = 70\%$, τ^2				
Test for subgroup difference	es: χ ₁ ² = 0.27, df = 1 (<i>p</i>	= 0.60) -2	-1 0 1	2

CRH

Study	Experimenta Total Mean SE	l Control) Total Mean SD	Standardised Mean Difference	SMD 95%-CI Weight
Bias score: < 4 Garakani 2013 Wong 2000 Heuser 1998 Widerlöv, Bisette 1988a		 14 57.10 4.10 ← 25 49.60 13.30 10 57.30 12.02 		-0.13 [-0.74; 0.48] 13.1% -1.13 [-2.01; -0.25] 9.3% 0.00 [-0.51; 0.51] 14.8% 0.80 [0.03; 1.58] 10.7%
Random effects mode Heterogeneity: $I^2 = 71\%$, 1		73		-0.09 [-0.72; 0.55] 47.9%
Bias score: >= 4 Carpenter, Tyrka 2004b Pitts 1995 Molchan 1993 Risch 1992 Random effects mode Heterogeneity: J ² = 60%, 1	19 38.60 10.00 18 78.60 24.60 18 83.70 35.40 82) 18 43.30 8.10) 11 87.10 15.80		0.45[-0.10; 1.00]14.1%-0.50[-1.16; 0.15]12.4%-0.38[-1.14; 0.38]10.9%0.38[-0.14; 0.89]14.7%0.03[-0.45; 0.51]52.1%
Random effects mode Heterogeneity: $I^2 = 62\%$, a Test for subgroup differen	$^{2} = 0.1661, p = 0.01$	210 (<i>p</i> = 0.77) -2	-1 0 1	- 0.02 [-0.39; 0.34] 100.0%

Somatostatin

	Experin	nental		C	ontrol	Standardi	ised Mean			
Study	Total Mean	SD	Total	Mean	SD	Diffe	rence	SMD	95%-CI	Weight
Bias score: < 4							1			
Heuser 1998	37 31.40	9.90	25	38.60	8.80			-0.75	-1.28; -0.22]	21.6%
Bissette 1986	17 65.40	32.16	10	116.10	49.65 ←				-2.11; -0.39]	19.8%
Rubinow 1983	7 30.40	5.90	39	62.80	6.38 <	_			-6.39; -3.70]	16.5%
Random effects model	61		74					-2.25	4.29; -0.21]	57.9%
Heterogeneity: $I^2 = 94\%$, τ^2	² = 3.0070, <i>p</i> <	0.01						-	-	
Bias score: >= 4										
Heilig 2004	51 29.60	9.00	27	32.20	9.40			-0.28 [-0.75; 0.19]	21.8%
Molchan 1991	18 45.10		12	60.20					-1.71; -0.16]	20.3%
Random effects model		10.00	39	00.20	10.10		-		-1.15; 0.09]	42.1%
Heterogeneity: $I^2 = 50\%$, τ^2		0.16						0.00 [1110, 0.00]	42.170
	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,									
Random effects model	130		113					-1.49 [-2.53; -0.45]	100.0%
Heterogeneity: $I^2 = 91\%$, τ^2						1				
Test for subgroup difference	ces: $\chi_1^2 = 2.51$,	df = 1 (/	0 = 0.11)	-2	-1 (D 1	2		

Neuropeptide Y

	Expe	rimental	C	ontrol	Standardised Mean		
Study	Total Mea	n SD To	tal Mean	SD	Difference	SMD	95%-CI Weight
Bias score: < 4 Martinez 2012 Widerlöv, Lindström 1988b Random effects model	18 176. ⁻ 33 102.2 51	0 11.49	25 137.66 20 121.80 45		<u> </u>	-1.55 [-2	0.41; 1.71] 20.1% 2.19; -0.92] 20.2% 2.81; 2.31] 40.2%
Heterogeneity: $l^2 = 97\%$, $\tau^2 =$ Bias score: >= 4	3.3109, <i>p</i> < 0	01					
Soleimani 2014 Heilig 2004 Sunderland 1991 Random effects model Heterogeneity: $l^2 = 91\%$, $\tau^2 =$	121	0 23.70 00 21.00	20 7.00 27 161.80 9 142.00 56			-1.12 [-1 -0.73 [-1	0.10; 1.13] 20.7% .62; -0.62] 20.8% .69; 0.23] 18.3% .62; 0.82] 59.8%
Random effects model Heterogeneity: $I^2 = 93\%$, $\tau^2 =$ Test for subgroup differences	172 1.2608, <i>p</i> < 0 : χ ₁ ² = 0.01, df	01	01	-	2 -1 0 1	-0.34 [-1 2	.37; 0.69] 100.0%

IL-6

	E	perime	ental		Co	ntrol	Standar	dised Mean			
Study	Total	Mean	SD	Total	Mean	SD	Diff	ference	SMD	95%-CI	Weight
Bias score: < 4											
Martinez 2012	18	0.07	0.01	25	0.06	0.01			0.70	[0.08; 1.33]	12.1%
Pålhagen 2010	12	7.54	8.56	12	4.34	6.34	-		0.41	[-0.40; 1.22]	7.6%
Lindqvist 2009	32	3.02	9.21	47	0.64	6.17			0.31	[-0.14; 0.76]	20.5%
Random effects model	62			84				\langle	0.44	[0.11; 0.77]	40.2%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$,	p = 0.6	61									
Bias score: >= 4											
Pomara 2021	27	4.53	3.08	17	4.87	5.27			-0.08	[-0.69; 0.52]	12.7%
Kern 2014	19	3.40	4.33	67	1.91	1.81			0.58	[0.06; 1.09]	16.6%
Sasayama 2013	30	2.14	1.22	35	1.54	0.80			0.58	[0.09; 1.08]	17.6%
Carpenter, Heninger 2004a	18	2.20	1.00	26	2.40	1.90			-0.12	[-0.72; 0.48]	12.9%
Random effects model	94			145				$\langle \rangle$	0.27	[-0.11; 0.65]	59.8%
Heterogeneity: $I^2 = 48\%$, $\tau^2 = 0$	0.0730,	p = 0.1	2								
Random effects model	156			229					0.25	0 42. 0 501	100.0%
Heterogeneity: $I^2 = 16\%$, $\tau^2 = 0$		n = 0.2	1	229		ſ			0.35	[0.12; 0.59]	100.0%
Test for subgroup differences:				- 0 51)		-2	2 -1	0 1	2		
rescior subgroup differences.	$\chi_1 = 0.$	43, di -	т (р -	- 0.51)		-2	<u>د</u> -۱	0 1	2		

IL-8

	Experin	nental	C	ontrol	Standardised Mean		
Study	Total Mean	SD Tot	al Mean	SD	Difference	SMD	95%-CI Weight
Bias score: < 4							
Lindqvist 2009	32 24.29	7.24	7 23.10	6.65		0.17 [-(0.28; 0.62] 19.8%
Random effects model	32		17		\rightarrow	0.17 [-0	0.28; 0.62] 19.8%
Heterogeneity: not applicat	ble						
Bias score: >= 4							
Hidese 2021	104 23.40	4.40 1	8 22.80	4.50		0.13 [-(0.13; 0.40] 26.1%
Pomara 2021	27 86.62	15.40	17 96.46	32.75		-0.41 [-1	1.02; 0.20] 15.0%
Janelidze 2015	52 23.14	9.39 4	18 24.30	6.50		-0.14 [-(0.53; 0.25] 21.7%
Kern 2014	19 45.50	14.40 6	67 36.40	9.47		0.84 [0	0.32; 1.37] 17.4%
Random effects model	202	2	50		\checkmark	0.11 [-0	0.31; 0.53] 80.2%
Heterogeneity: $I^2 = 75\%$, τ^2	² = 0.1331, <i>p</i> <	0.01				_	-
Random effects model	234	29	97			0.12 [-0	0.21; 0.45] 100.0%
Heterogeneity: $I^2 = 66\%$, τ^2	$^{2} = 0.0893, p =$	0.02		Ľ			
Test for subgroup difference			.85)	-2	2 -1 0 1	2	

Total protein

	Experimental	Control	Standardised Mean	
Study	Total Mean SD	Total Mean SD	Difference	SMD 95%-CI Weight
Bias score: < 4				
Vawter 2000	17 31.20 9.90	37 25.20 8.70		0.65 [0.06; 1.24] 9.8%
Random effects model Heterogeneity: not applica		37		0.65 [0.06; 1.24] 9.8%
Bias score: >= 4				
	00 00 40 47 40	100 00 10 0 00		0 40 50 47 0 741 44 00/
Omori 2020	90 39.40 17.10			0.46 [0.17; 0.74] 41.9%
Mizui 2019	18 1.00 0.29			0.63 [0.02; 1.24] 9.1%
Hattori 2015	66 43.57 18.01	60 36.60 8.50		0.48 [0.13; 0.84] 26.9%
Sasayama 2013	29 46.76 13.28	31 38.10 9.95		0.73 [0.21; 1.26] 12.3%
Random effects model	203	224	\diamond	0.52 [0.33; 0.71] 90.2%
Heterogeneity: $I^2 = 0\%$, τ^2	= 0, <i>p</i> = 0.81			
Random effects model		261		0.53 [0.35; 0.72] 100.0%
Heterogeneity: $I^2 = 0\%$, τ^2				
Test for subgroup differen	ces: $\chi_1^2 = 0.17$, df = 1 ((p = 0.68) -2	-1 0 1	2

Total tau

Study	Total	Experi Mean	imental SD	Total		Control SD	Standardised Mean Difference	SMD	95%-CI	Weight
Bias score: < 4										
Sanfilippo 2016	6	73.59	45.53	44	67.65	20.18		0.24	[-0.61; 1.10]	9.2%
Reis 2012	20	197.42	101.81	8	161.62	85.91			[-0.47; 1.18]	9.5%
Bürger née Buch 1999	19	313.00	283.00	28	273.00	203.00	÷	0.17	[-0.42; 0.75]	12.2%
Blennow 1995	10	108.00	13.00	31	185.00	50.00	< · · · · · · · · · · · · · · · · · · ·	-1.70	[-2.52; -0.89]	9.6%
Random effects model	55			111			i	-0.23	[-1.14; 0.69]	40.4%
Heterogeneity: $I^2 = 83\%$, τ	2 = 0.718	B2, p < 0	0.01							
0, 1										
Bias score: >= 4										
Eratne 2021	16	165.32	82.07	20	182.24	55.52		-0.24	[-0.90; 0.42]	11.3%
Diniz 2014	16	64.83	41.62	25	68.41	54.07		-0.07	[-0.70; 0.56]	11.7%
Pomara 2012	27	273.00	114.30	19	328.70	151.70		-0.42	[-1.01; 0.18]	12.1%
Hertze 2010	28	54.00	26.00	38	91.00	49.00		-0.89	[-1.41; -0.38]	13.0%
Gudmundsson 2007	11	287.50	114.90	70	331.70	189.80		-0.24	[-0.88; 0.40]	11.6%
Random effects model	98			172			\sim	-0.41	[-0.71; -0.11]	59.6%
Heterogeneity: $I^2 = 21\%$, τ	² = 0.024	49, p = 0	.28							
		0.00								
Random effects model				283			\diamond	-0.32	[-0.70; 0.06]	100.0%
Heterogeneity: $I^2 = 66\%$, τ						I		1		
Test for subgroup differen	ces: χ ₁ ² =	0.14, df	f = 1 (p =	0.71)		-2	2 -1 0 1	2		

P-tau 181

	Experin	nental		Co	ontrol	Standardised Me	an		
Study	Total Mean	SD	Total M	ean	SD	Difference	SMD	95%-CI	Weight
Bias score: < 4						1			
Sanfilippo 2016	6 39.94	25.12	44 3	5.71	14.95		- 0.26	[-0.60; 1.11]	9.2%
Reis 2012	20 38.67	33.86	8 36	6.22	25.46		0.07	[-0.75; 0.89]	10.0%
Random effects model			52				0.16	[-0.43; 0.75]	19.3%
Heterogeneity: $I^2 = 0\%$, τ^2	= 0, <i>p</i> = 0.76								
Bias score: >= 4									
Eratne 2021	16 38.61	14.21	20 4	1.09	8.80		-0.21	[-0.87; 0.45]	15.5%
Diniz 2014	16 58.20	41.76	25 49	9.04	33.90		0.24	[-0.39; 0.87]	17.0%
Pomara 2012	28 48.90	25.90	19 5	1.60	20.90		-0.11	[-0.69; 0.47]	19.9%
Hertze 2010	28 29.00	11.00	38 3	1.00	17.00		-0.13	[-0.62; 0.35]	28.3%
Random effects model			102			\Leftrightarrow	-0.06	[-0.35; 0.23]	80.7%
Heterogeneity: $I^2 = 0\%$, τ^2	= 0, <i>p</i> = 0.75								
Random effects model Heterogeneity: $I^2 = 0\%$, τ^2			154		Г		-0.02	[-0.28; 0.24]	100.0%
Test for subgroup difference	ces: $\chi_1^2 = 0.45$, c	df = 1 (µ	o = 0.50)		-2	2 -1 0	1 2		

Study	Experimenta Total Mean Sl	l D Total Mea	Control n SD	Standardised Mean Difference	SMD	95%-Cl Weight
Bias score: < 4 Sanfilippo 2016 Reis 2012 Random effects mode Heterogeneity: $l^2 = 0\%$, τ'			97 118.09 94 436.53		0.24 [-	0.94; 0.76] 11.3% 0.58; 1.07] 11.5% 0.51; 0.68] 22.9%
Bias score: >= 4 Erathe 2021 Diniz 2014 Pomara 2012 Hertze 2010 Gudmundsson 2007 Jensen 1999 Random effects mode		9 25 464.9 0 19 335.4 0 38 1019.0 0 70 794.0	2 94.86 17 166.48 0 182.70 10 435.00 10 234.40 10 30.00		0.08 [- -0.72 [- -0.37 [- 0.78 [→ 1.65 [1.55; -0.17] 12.5% 0.55; 0.70] 12.9% 1.32; -0.12] 13.1% 0.87; 0.12] 13.8% 0.13; 1.42] 12.8% 0.90; 2.40] 12.0% 0.63; 0.78] 77.1%
Heterogeneity: $l^2 = 87\%$, Random effects mode Heterogeneity: $l^2 = 82\%$, Test for subgroup differen	140 ² = 0.5096, <i>p</i> < 0.01	248 = 0.98)	۲ -2	-1 0 1	0.07 [-	0.48; 0.62] 100.0%

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

HVA

Experimental Contr							Standardised Mean			
Study	Total	Mean	SD	Total	Mean	SD	Difference	SMD	95%-CI	Weight
Publication year: 2000 of	r later									
Yoon 2017	75	26.32	16.10	87	28.44	12.45		-0.15	[-0.46; 0.16]	12.5%
Kaddurah-Daouk 2012	14	23.83	14.88	18	29.06	7.56		-0.45	[-1.16; 0.26]	2.9%
Pålhagen 2010	12	173.20	100.11	12	159.20	72.40		0.15	[-0.65; 0.96]	2.3%
Sullivan, Mann 2006b	17	198.10	64.30	15	201.10	79.30		-0.04	[-0.74; 0.65]	3.0%
Sullivan, Oquendo 2006a	48	220.83	79.47	15	200.60	76.60	÷ - •	0.25	[-0.33; 0.84]	4.2%
Sher 2006	58	169.38	79.11	50	196.90	76.30		-0.35	[-0.73; 0.03]	8.9%
Sher 2005	125	198.45	76.50	27	197.20	69.50		0.02	[-0.40; 0.43]	7.7%
Heilig 2004	51	206.40	86.60	27	228.80	97.50		-0.25	[-0.71; 0.22]	6.3%
Random effects model	400			251				-0.14	[-0.30; 0.03]	48.0%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$	p, p = 0	0.66								
Publication year: before										
Swann 1999		195.00	74.00		230.00	76.00			[-0.77; -0.16]	12.8%
DeBellis 1993	-	182.90	49.70		219.50				[-1.07; 0.37]	2.9%
Lewine 1991		159.30	72.30		160.60	69.70			[-0.51; 0.48]	
Molchan 1991		190.20	83.50		201.60	66.40			[-0.88; 0.59]	2.8%
Widerlöv, Bisette 1988a		151.20	66.13		166.40				[-0.98; 0.52]	
Åsberg 1984		201.70	92.40		245.90				[-0.80; -0.02]	8.7%
Koslow 1983		194.86	73.96		230.32				[-0.83; -0.11]	9.7%
Kasa 1982	10		13.20	16			< <u></u>		[-2.27; -0.49]	
Oreland 1981		211.95	66.91		230.57	100.60			[-0.74; 0.33]	5.0%
Random effects model	284			430				-0.38	[-0.55; -0.22]	52.0%
Heterogeneity: $I^2 = 6\%$, $\tau^2 = 0$	0.0040	, p = 0.39	9							
Random effects model	684			681				-0.26	[-0.39; -0.14]	100.0%
Heterogeneity: $I^2 = 11\%$, $\tau^2 =$	0.007	4, p = 0.3	33			1				
Test for subgroup differences				0.04)		-3	2 -1 0 1	2		

5-HIAA

		Experin	nontal		<u> </u>	ontrol	61	tandardised	Moon				
Study		Mean		Total	Mean	SD	31	Differenc		SMD	9	5%-CI	Weight
Publication year: 2000 o	or late	r											
Yoon 2017	75	8.25	4.70	87	10.72	1.67				-0.72	[-1.04;	-0.40]	9.0%
Kaddurah-Daouk 2012	14	11.20	6.22	18	12.31	10.67			-	-0.12	[-0.82;	0.58]	5.5%
Pålhagen 2010	12	87.00	38.45	12	67.20	33.95				0.53	[-0.29;	1.34]	4.6%
Sullivan, Mann 2006b	17	99.90	34.60	15	105.70	36.40				-0.16	[-0.86;	0.54]	5.5%
Sullivan, Oquendo 2006a	48	106.57	34.46	15	93.30	33.60				0.38	[-0.20;	0.97]	6.4%
Sher 2005	125	100.31	35.10	27	92.90	33.00		 ••	-	0.21	[-0.20;	0.63]	8.1%
Heilig 2004	51	127.30	49.10	27	114.20	37.40			_	0.29	[-0.18;	0.75]	7.5%
Random effects model	342			201				\Rightarrow		0.03	[-0.37;	0.43]	46.7%
Heterogeneity: $I^2 = 75\%$, $\tau^2 =$	= 0.206	2, p < 0.0	01										
Publication year: before	2000												
DeBellis 1993	9	95.90	24.60	46	111.20	44.50				-0.36	[-1.08:	0.361	5.3%
Lewine 1991	19	97.40	42.20	91	90.90	36.00			_	0.17	[-0.32;	0.671	7.3%
Molchan 1991	18	112.10	37.00	12	94.50	34.30			<u> </u>		-0.27;		5.2%
Widerlöv, Bisette 1988a	22	70.30	23.45	10	72.20	18.02		i	_		[-0.83;	-	5.1%
Edman 1986	19	84.40	21.00	32	119.00	42.00		•			[-1.55;		6.3%
Åsberg 1984	60		38.60	66	104.10	38.30					[-0.66;	-	8.7%
Koslow 1983	57	119.32	33.73	58	111.00	30.56			-		[-0.11;		8.6%
Oreland 1981	20	99.92	34.17	42	99.63	35.21					[-0.52;		6.9%
Random effects model	224			357				\triangleleft		-0.09	[-0.39;	0.201	53.3%
Heterogeneity: I^2 = 59%, τ^2 =	= 0.098	5, <i>p</i> = 0.0	02								• /	•	
Random effects model	566			558				\diamond		-0.04	[-0.28:	0.191	100.0%
Heterogeneity: $I^2 = 66\%$, $\tau^2 =$		8. p < 0.0	01							7			
Test for subgroup difference				0.63)		_	2 -	·1 0	1	2			
5	1.01		U.	,									

MHPG

	Experimental	Control	Standardised Mean	
Study	Total Mean SD	Total Mean SD	Difference	SMD 95%-CI Weight
Publication year: 2000	or later		1	
Yoon 2017	75 7.81 1.77	87 8.92 1.67		-0.64 [-0.96; -0.33] 9.4%
Kaddurah-Daouk 2012	14 11.78 2.05	18 11.57 1.72		0.11 [-0.59; 0.81] 5.9%
Pålhagen 2010	12 41.80 11.09	12 30.70 9.35		- 1.05 [0.18; 1.91] 4.8%
Sullivan, Mann 2006b	17 46.00 17.80	15 42.80 25.50		0.14 [-0.55; 0.84] 6.0%
Sullivan, Oquendo 2006a	48 46.33 18.05	15 50.00 22.10		-0.19 [-0.77; 0.39] 6.9%
Sher 2005	125 42.98 16.26	27 47.40 26.50		-0.24 [-0.66; 0.18] 8.5%
Heilig 2004	51 40.30 9.80	27 38.50 8.20		0.19 [-0.28; 0.66] 8.0%
Random effects model	342	201	\rightarrow	-0.02 [-0.39; 0.34] 49.4%
Heterogeneity: $I^2 = 70\%$, τ^2				
Publication year: before			_	
Swann 1999	85 48.50 11.50	85 43.30 8.30		0.52 [0.21; 0.82] 9.5%
DeBellis 1993	9 46.70 14.20	46 48.00 9.50		-0.12 [-0.84; 0.59] 5.8%
Molchan 1991	18 60.80 20.90	12 51.10 14.70		0.50 [-0.24; 1.25] 5.6%
Widerlöv, Bisette 1988a	22 51.70 12.20	10 51.70 7.59		0.00 [-0.75; 0.75] 5.6%
Åsberg 1984	26 50.80 7.40	60 51.20 10.10		-0.04 [-0.50; 0.42] 8.0%
Koslow 1983	61 48.50 11.50	61 43.30 8.40		0.51 [0.15; 0.87] 9.0%
Oreland 1981	18 51.27 9.67	42 49.50 9.60		0.18 [-0.37; 0.73] 7.2%
Random effects model	239	316		0.30 [0.09; 0.51] 50.6%
Heterogeneity: $I^2 = 22\%$, τ^2	= 0.0178, p = 0.26			
Random effects model	581	517	\diamond	0.11 [-0.14; 0.36] 100.0%
Heterogeneity: $I^2 = 70\%$, τ^2	= 0.1462, p < 0.01			
Test for subgroup difference	es: $\chi_1^2 = 2.25$, df = 1 (p	= 0.13) -2	-1 0 1	2

CRH

Experim Study Total Mean	ental Control SD Total Mean SD	Standardised Mean Difference	SMD	95%-CI Weight
Publication year: 2000 or later				
Garakani 2013 18 78.00	1.80 24 82.66 30.40		-0.13 [-0.	74; 0.48] 13.1%
Carpenter, Tyrka 2004b 27 29.00	9.40 25 24.90 8.50		0.45 [-0.	10; 1.00] 14.1%
Wong 2000 10 48.90	9.80 14 57.10 4.10 <		-1.13 [-2.	01; -0.25] 9.3%
Random effects model 55	63		-0.21 [-1.	02; 0.61] 36.5%
Heterogeneity: I^2 = 78%, τ^2 = 0.3984, p =	0.01			
Publication year: before 2000				
Heuser 1998 37 49.60	8.40 25 49.60 13.30		0.00 [-0.	51; 0.51] 14.8%
Pitts 1995 19 38.60	0.00 18 43.30 8.10		-0.50 [-1.	16; 0.15] 12.4%
Molchan 1993 18 78.60	24.60 11 87.10 15.80		-0.38 [-1.	14; 0.38] 10.9%
Risch 1992 18 83.70	35.40 83 69.40 38.20		0.38 [-0.	14; 0.89] 14.7%
Widerlöv, Bisette 1988a 22 71.90	9.70 10 57.30 12.02		0.80 [0.	03; 1.58] 10.7%
Random effects model 114	147	\rightarrow	0.06 [-0.	37; 0.48] 63.5%
Heterogeneity: I^2 = 56%, τ^2 = 0.1292, p =	0.06			
Random effects model 169 Heterogeneity: $l^2 = 62\%$, $\tau^2 = 0.1661$, <i>p</i> =	210		0.02 [-0.	39; 0.34] 100.0%
Test for subgroup differences: $\chi_1^2 = 0.32$, c		-1 0 1	2	

Somatostatin

atin	-		0	0		
Study	Experimen Total Mean	SD Total	Control Mean SD	Standardised Mean Difference	SMD	95%-CI Weight
Publication year: 200 Heilig 2004 Random effects mode Heterogeneity: not applica	51 29.60 9 I 51	.00 27 27	32.20 9.40		-	0.75; 0.19] 21.8% . 75; 0.19] 21.8%
Publication year: before Heuser 1998 Molchan 1991 Bissette 1986 Rubinow 1983 Random effects mode Heterogeneity: I ² = 91%,	37 31.40 9 18 45.10 15 17 65.40 32 7 30.40 5 I 79	.16 10 .90 39 86	38.60 8.80 60.20 16.10 - 116.10 49.65 ← 62.80 6.38 <		-0.93 [-1 -1.25 [-2 -5.04 [-6	.28; -0.22] 21.6% .71; -0.16] 20.3% .11; -0.39] 19.8% .39; -3.70] 16.5% .25; -0.50] 78.2%
Random effects mode Heterogeneity: <i>I</i> ² = 91%, Test for subgroup differer	$t^2 = 1.2315, p < 0.0$		3) -2	· · · · · · · · · · · · · · · · · · ·	-1.49 [-2	.53; -0.45] 100.0%

Neuropeptide Y

Experimental Con						ontrol	Standardised Mean			
Study	Total	Mean	SD	Total	Mean	SD	Difference	SMD	95%-CI	Weight
Publication year: 2000 or	later									
Soleimani 2014	61	7.90	1.50	20	7.00	1.30	· · · · · ·	0.61 [(0.10; 1.13]	20.7%
Martinez 2012	18	176.13	47.26	25	137.66	24.14		- 1.06 [(0.41; 1.71]	20.1%
Heilig 2004	51	134.10	23.70	27	161.80	25.70		-1.12 [-1	1.62; -0.62]	20.8%
Random effects model	130			72				0.17 [-1	1.16; 1.50]	61.5%
Heterogeneity: $I^2 = 94\%$, $\tau^2 = 1$.3011	, p < 0.01						-		
Publication year: before 2	000						_			
Sunderland 1991	9	123.00	21.00	9	142.00	28.00		-0.73 [-1	1.69; 0.23]	18.3%
Widerlöv, Lindström 1988b	33	102.20	11.49	20	121.80	13.86	~ •	-1.55 [-2	2.19; -0.92]	20.2%
Random effects model	42			29				-1.23 [-2	2.02; -0.44]	38.5%
Heterogeneity: $I^2 = 49\%$, $\tau^2 = 0$.1654	, p = 0.16	;							
Random effects model	172			101				-0.34 [-1	1.37; 0.69] ·	100.0%
Heterogeneity: $I^2 = 93\%$, $\tau^2 = 1$		n < 0.01							,	
Test for subgroup differences:	$\chi_1^2 = 3$.14, df =	1 (p = 0	.08)		-	2 -1 0 1	2		

IL-6

		Co	ntrol	Standardi	sed Mean						
Study	Total	Mean	SD	Total	Mean	SD	Diffe	rence	SMD	95%-CI	Weight
Publication year: 2000 or	later										
Pomara 2021	27	4.53	3.08	17	4.87	5.27			-0.08	[-0.69; 0.52]	12.7%
Kern 2014	19	3.40	4.33	67	1.91	1.81			0.58	[0.06; 1.09]	16.6%
Sasayama 2013	30	2.14	1.22	35	1.54	0.80			0.58	[0.09; 1.08]	17.6%
Martinez 2012	18	0.07	0.01	25	0.06	0.01			0.70	[0.08; 1.33]	12.1%
Pålhagen 2010	12	7.54	8.56	12	4.34	6.34		-	0.41	[-0.40; 1.22]	7.6%
Lindqvist 2009	32	3.02	9.21	47	0.64	6.17	-	- · · ·	0.31	[-0.14; 0.76]	20.5%
Carpenter, Heninger 2004a	18	2.20	1.00	26	2.40	1.90		<u> </u>	-0.12	[-0.72; 0.48]	12.9%
Random effects model	156			229				\Leftrightarrow	0.35	[0.12; 0.59]	100.0%
Heterogeneity: $I^2 = 16\%$, $\tau^2 = 0$	0.0162,	p = 0.3	1								
Random effects model	156			229				\diamond	0.35	[0.12; 0.59]	100.0%
Heterogeneity: $I^2 = 16\%$, $\tau^2 = 0$	Heterogeneity: $I^2 = 16\%$, $\tau^2 = 0.0162$, $p = 0.31$									-	
Test for subgroup differences:	$\chi_0^2 = 0.$	00, df =	0 (p =	= NA)		-3	2 -1 () 1	2		

IL-8

Study	Experimenta Total Mean SD	l C Total Mean	Control SD	Standardised Mean Difference	SMD	95%-Cl Weight
Publication year: 2000	or later					
Hidese 2021	104 23.40 4.40	118 22.80	4.50		0.13 [-	0.13; 0.40] 26.1%
Pomara 2021	27 86.62 15.40	17 96.46	32.75	——————————————————————————————————————	-0.41 [-	1.02; 0.20] 15.0%
Janelidze 2015	52 23.14 9.39	48 24.30	6.50		-0.14 [-	0.53; 0.25] 21.7%
Kern 2014	19 45.50 14.40	67 36.40	9.47		0.84 [0.32; 1.37] 17.4%
Lindqvist 2009	32 24.29 7.24	47 23.10	6.65		0.17 [-	0.28; 0.62] 19.8%
Random effects model	234	297		A 1	0.12 [-	0.21; 0.45] 100.0%
Heterogeneity: $I^2 = 66\%$, τ^2	² = 0.0893, <i>p</i> = 0.02					
Random effects model	234	297			0.12 [-	0.21; 0.45] 100.0%
Heterogeneity: $I^2 = 66\%$, τ	2 = 0.0893, <i>p</i> = 0.02					
Test for subgroup difference	ces: $\chi_0^2 = 0.00$, df = 0	(p = NA)	-3	2 -1 0 1	2	

Total protein

	Experim	nental	Co	ntrol	Standard	dised Mean			
Study	Total Mean	SD To	otal Mean	SD	Diffe	erence	SMD	95%-CI	Weight
Publication year: 2000	or later								
Omori 2020	90 39.40	17.10 1	06 33.40	8.20			0.46 [0).17; 0.74]	41.9%
Mizui 2019	18 1.00	0.29	27 0.86	0.16			0.63 [0	0.02; 1.24]	9.1%
Hattori 2015	66 43.57	18.01	60 36.60	8.50			0.48 [0	0.13; 0.84]	26.9%
Sasayama 2013	29 46.76	13.28	31 38.10	9.95		<u> </u>	0.73 [0	0.21; 1.26]	12.3%
Vawter 2000	17 31.20	9.90	37 25.20	8.70			0.65 [0	0.06; 1.24]	9.8%
Random effects model	220	2	261			\diamond	0.53 [0	.35; 0.72]	100.0%
Heterogeneity: $I^2 = 0\%$, τ^2	= 0, <i>p</i> = 0.89								
Random effects model Heterogeneity: $I^2 = 0\%$, τ^2		2	261				0.53 [0	.35; 0.72]	100.0%
Test for subgroup difference		df = 0 (p =	NA)	-3	2 -1	0 1	2		

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Total tau

	Exp	erimental			Control	Standardised Mean				
Study	Total Mea	n SD	Total	Mean	SD	Difference	SMD	95%-CI W	eight	
Publication year: 2000 or later										
Eratne 2021	16 165.3	2 82.07	20	182.24	55.52		-0.24 [-0	0.90; 0.42] 1	1.3%	
Sanfilippo 2016	6 73.5				20.18				9.2%	
Diniz 2014	16 64.8		25	68.41	54.07				1.7%	
Pomara 2012	27 273.0	0 114.30	19	328.70	151.70		-0.42 [-1	1.01; 0.18] 1	2.1%	
Reis 2012	20 197.4	2 101.81	8	161.62	85.91		0.36 [-0	0.47; 1.18]	9.5%	
Hertze 2010	28 54.0	0 26.00	38	91.00	49.00		-0.89 [-1	.41; -0.38] 1	3.0%	
Gudmundsson 2007	11 287.5	0 114.90	70	331.70	189.80		-0.24 [-0	0.88; 0.40] 1	1.6%	
Random effects mode			224			\Leftrightarrow	-0.26 [-0	.57; 0.06] 7	8.2%	
Heterogeneity: $I^2 = 39\%$, 1	$r^2 = 0.0709, p$	= 0.13								
Publication year: before 2000										
Bürger née Buch 1999	19 313.0	0 283.00	28	273.00	203.00		0.17 [-0	0.42; 0.75] 1	2.2%	
Blennow 1995	10 108.0	0 13.00	31	185.00	50.00	< • • • • • • • • • • • • • • • • • • •	-1.70 [-2	2.52; -0.89]	9.6%	
Random effects mode	29		59				-0.75 [-2	.58; 1.08] 2	21.8%	
Heterogeneity: $I^2 = 93\%$, $\tau^2 = 1.6180$, $p < 0.01$										
Random effects mode			283			<u> </u>	-0.32 [-0	.70; 0.06] 10	0.0%	
Heterogeneity: $I^2 = 66\%$, f							I			
Test for subgroup differen	ces: $\chi_1^2 = 0.27$	df = 1 (p =	= 0.60)		-	2 -1 0 1	2			

P-tau 181

Study	Experimental Total Mean SD	C Total Mean	control SD	Standardised Mean Difference	SMD	95%-CI Weight
Publication year: 2000	or later			1		
Eratne 2021	16 38.61 14.21	20 41.09	8.80		-0.21 [-(0.87; 0.45] 15.5%
Sanfilippo 2016	6 39.94 25.12	44 35.71	14.95		0.26 [-	0.60; 1.11] 9.2%
Diniz 2014	16 58.20 41.76	25 49.04	33.90		0.24 [-	0.39; 0.87] 17.0%
Pomara 2012	28 48.90 25.90	19 51.60	20.90		-0.11 [-1	0.69; 0.47] 19.9%
Reis 2012	20 38.67 33.86	8 36.22	25.46		0.07 [-(0.75; 0.89] 10.0%
Hertze 2010	28 29.00 11.00	38 31.00	17.00		-0.13 [-	0.62; 0.35] 28.3%
Random effects model	114	154		\Leftrightarrow	-0.02 [-0	0.28; 0.24] 100.0%
Heterogeneity: $I^2 = 0\%$, $\tau^2 =$	= 0, <i>p</i> = 0.88					
Random effects model		154	_		-0.02 [-0	0.28; 0.24] 100.0%
Heterogeneity: $I^2 = 0\%$, $\tau^2 =$			1	1 1 1	1	
Test for subgroup difference	$xes: \chi_0^2 = 0.00, df = 0$ (p = NA)	-2	-1 0 1	2	

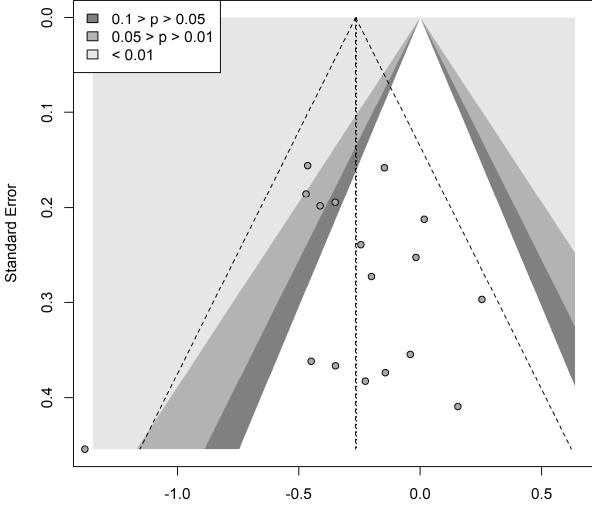
Amyloid-B-42

-D	-42										
	Study	Total		imental	Total	Mean	Control SD	Standardised Mean Difference	SMD	95%-CI Weid	aht
	Study	TOLAT	Weall	30	Total	Weatt	30	Difference	SIND	32 %-CI Weit	gin
	Publication year: 2000 or later										
	Eratne 2021	16	678.02	287.46	20	857.92	94.86	· · · · · ·	-0.86	[-1.55; -0.17] 12.5	5%
	Sanfilippo 2016	6	539.06	215.07	44	550.97	118.09		-0.09	-0.94; 0.76] 11.3	3%
	Diniz 2014	16	480.12	232.29	25	464.97	166.48		0.08	[-0.55; 0.70] 12.9	9%
	Pomara 2012	28	224.70	125.10	19	335.40	182.70		-0.72	-1.32; -0.12] 13.1	1%
	Reis 2012	20	923.20	317.50	8	834.64	436.53		0.24	[-0.58; 1.07] 11.	5%
	Hertze 2010	28	862.00	386.00	38	1019.00	435.00		-0.37	[-0.87; 0.12] 13.8	8%
	Gudmundsson 2007	11	973.30	184.10	70	794.00	234.40	· · · · · ·	0.78	[0.13; 1.42] 12.8	8%
	Random effects model	125			224				-0.15	-0.58; 0.28] 88.0	0%
Heterogeneity: $I^2 = 66\%$, $\tau^2 = 0.2141$, $p < 0.01$											
Publication year: before 2000											
	Jensen 1999	15	180.00	95.00	24	74.00	30.00		+→ 1.65	[0.90; 2.40] 12.0	0%
	Random effects model	15			24				1 .65	0.90; 2.40] 12.0	0%
	Heterogeneity: not applicat	ble									
	Random effects model				248			\rightarrow	0.07	-0.48; 0.62] 100.0	0%
	Heterogeneity: $I^2 = 82\%$, τ^2								1		
	Test for subgroup difference	ces: χ_1^2	= 16.64,	df = 1 (p	< 0.01)		-	2 -1 0 1	2		

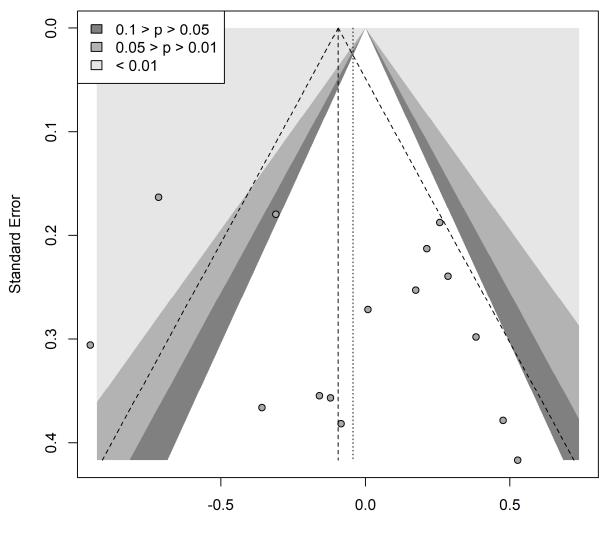
Bias assessment analyses

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

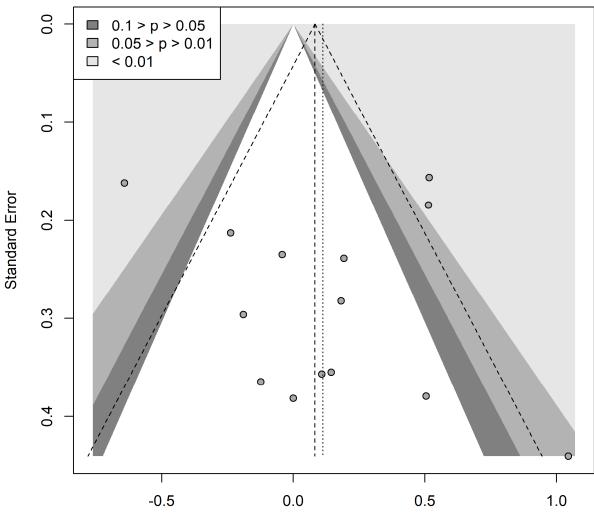
HVA



Standardised Mean Difference



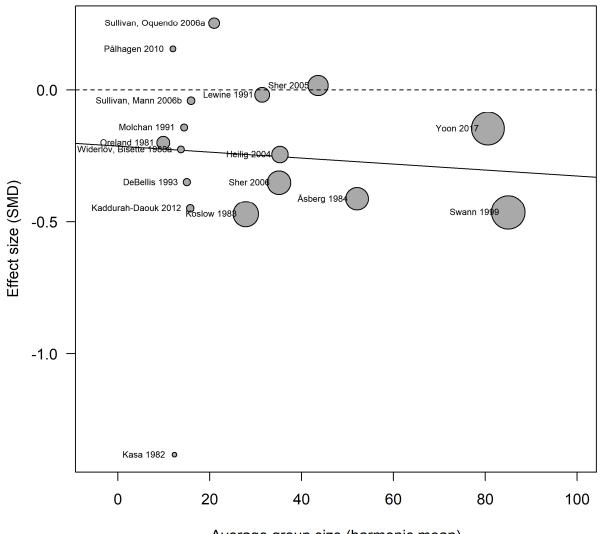
Standardised Mean Difference



Standardised Mean Difference

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

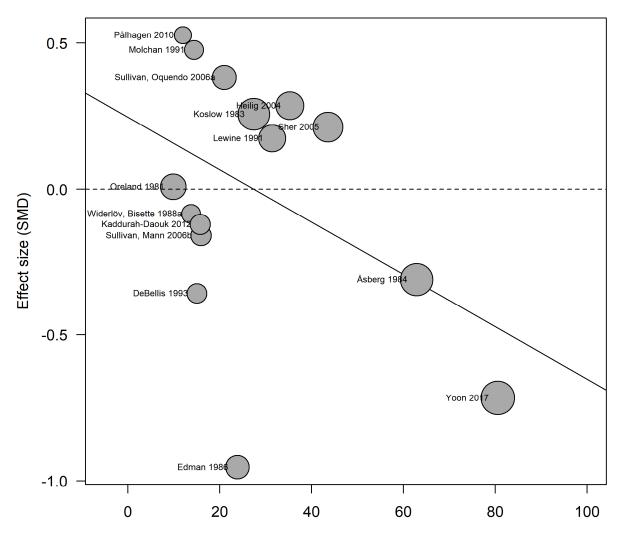
HVA



Average group size (harmonic mean)

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

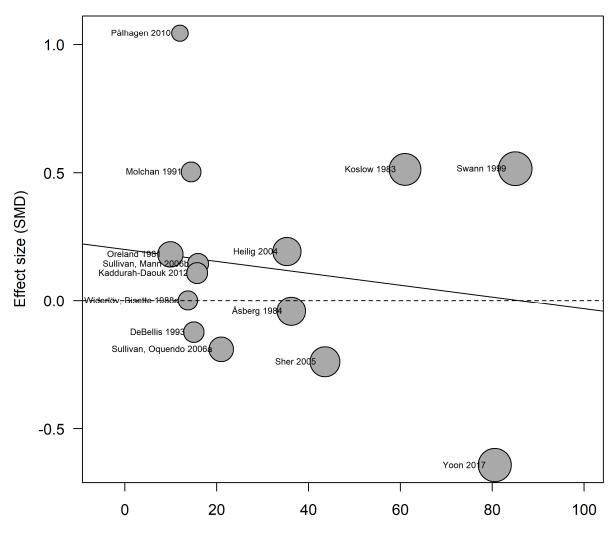


Average group size (harmonic mean)

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



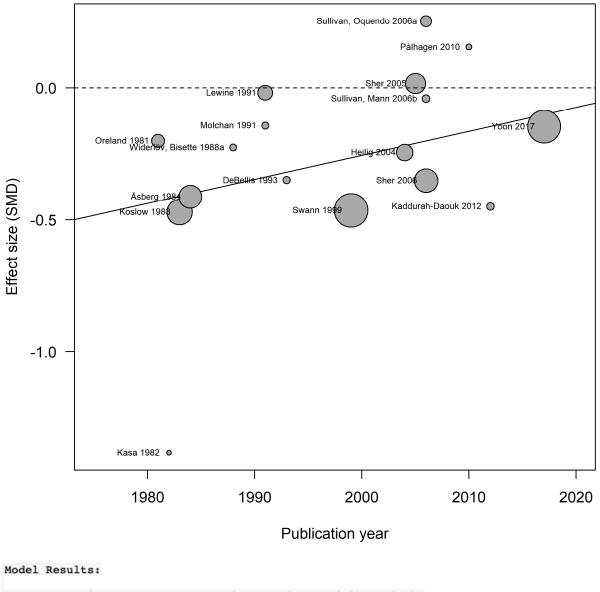
Average group size (harmonic mean)

Model Resu	Its:
------------	------

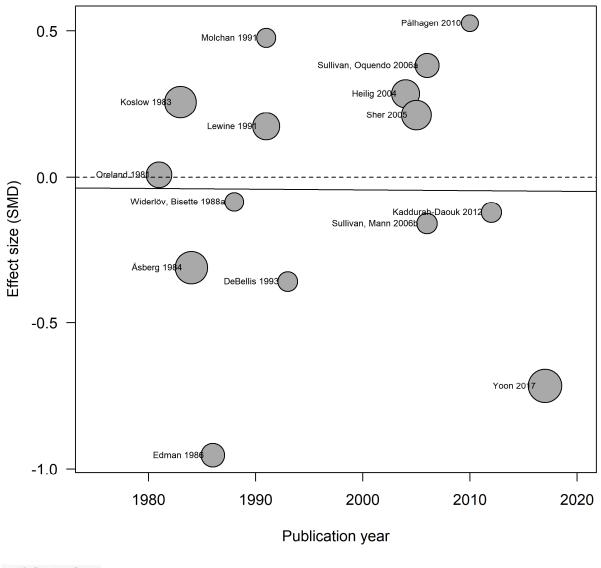
	estimate	se	zval	pval	ci.lb	ci.ub
intrcpt	0.2007	0.2323	0.8637	0.3877	-0.2547	0.6560
n_harmonic	-0.0023	0.0051	-0.4557	0.6486	-0.0124	0.0077

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

HVA



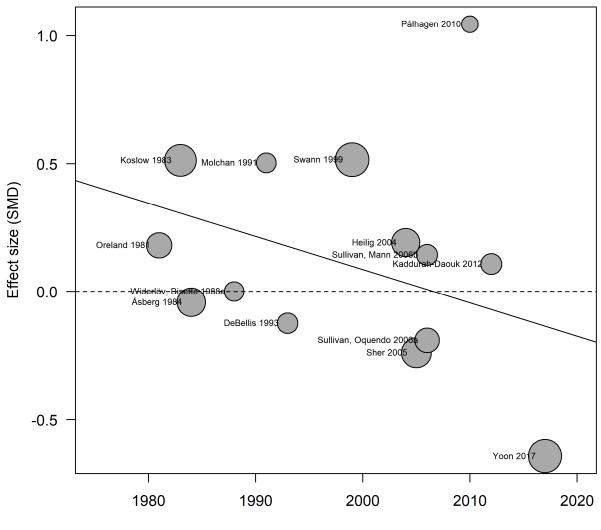
	estimate	se	zval	pval	ci.lb	ci.ub	
intrcpt	-18.4202	9.9904	-1.8438	0.0652	-38.0010	1.1607	
n_year	0.0091	0.0050	1.8171	0.0692	-0.0007	0.0189	



Model F	desults:
---------	----------

	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	

MHPG



Publication year

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	

Rating item	Definition						
Selection							
1. Adequate case definition	1 star is awarded if subjects are diagnosed separately by at least two doctors/psy- chologists according to a diagnostic tool (e.g. DSM, RDC, ICD). If patients are re- ferred from a psychiatric ward and the diagnosis is validated independently by an in vestigator, 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 in- cluded 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 com- munity, 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 his- tory 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 bi- omarker 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 num- ber of stars is thus 8.						

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

eTable 7 Bias asses Study		Selec					parability	Expc		T . 1	D :
Study		1	2	3	4	1	paraonity	1 1	2	Total no. of stars	Data source
Å als and	1094	1	1	1	1	2		0			
Åsberg	1984	1	1	1	1	Z	age, sex age,	0	1	7	Article
Barbaccia	1986	0	0	0	1	2	sex ^{bbb}	0	1	4	Article
Bissette	1986	0	0	0	0	0	ben	0	1	1	Article
Blennow	1995	0	0	0	1	1	age	0	1	2	Article
Brundin	2008	1	0	0	0	0	uge	0	1	2	Article
Brundin	2000	1	0	0	1	1	age	1	1	5	Article
Drunum	2010	1	0	0	1	1	uge	1	1	5	Article +
Bruno	2020	0	0	0	0	2	age, sex	0	1	3	Pomara ⁶
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

eTable 7 | Big stle-Otta ntrol studie rding to the Ne riteria fo nt e

^{bbb} Data from matched subgroup extracted © 2022 American Medical Association. All rights reserved.

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
D	2021	0	0					0			Article +
Pomara	2021	0	0	1	1	1	age	0	1	4	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	2005	1	0	0	0	0		0	1	2	Article
Soleimani	2008	0	0	1	1	2	age, sex age, sex	0	1	2 5	Article
Stokes	2014 1984	0	0	1	1	2	age, sex age, sex	1	1	5 6	Article
Sullivan	1984 1999	0	0	1	1	2	-	1	1	6	Article
Sullivan, Oquendo	1999 2006a	0	0	0	1	2 1	age, sex sex	0	1	0 3	Article
Sunivan, Oquendo	2000d	U	0	0	1	1	30A	U	1	5	AILUU

^{cec} The group with comorbid PTSD not matched on sex © 2022 American Medical Association. All rights reserved.

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

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 availabl
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 availabl
Bumb	2016	Demografic data on unipolar subgroup	18.01.2021	/	data not availabl
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 availabl
Catlin	1982	Mean and SEM on unipolar subgroup	21.01.2021	04.03.2021	data not availabl
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 availabl
Berrettini	1988	Mean and SD on patients and controls	21.01.2021	/	data not availabl
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 availabl
Pazzaglia	1995	Mean and SD on controls	23.01.2021	/	data not availabl
Jimerson	1983	Mean and SD on unipolar subgroup	23.01.2021	/	data not availabl
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 availabl
Omori	2020	Mean and SD on MMP-8 in patients and con- trols	23.01.2021	/	data not availabl

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 pa- tients and controls	25.01.2021	/	data not available
Träskman	1981	Info on unipolar / bipolar + mean and SD on pa- tients 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	/

1992 1999 1991	30 depression ptt 120 suicide attempters (36 MDD)	30 spinal anesthesia controls47 controls (18 surgical	HVA 5-HIAA	Lower in ptt. No difference
				No difference
		47 controls (18 surgical	TTX / A	
		4 / controls (18 surgical		NT 1100
1991	(36 MDD)		HVA	No difference
1991		controls, 29 healthy con-	5-HIAA	No difference
1991		trols)	MHPG	No difference
	39 depression ptt	17 surgical controls	5-HIAA	Lower in ptt.
1990	30 depression ptt	10 spinal anesthesia con- trols	DOPEG, NE	Higher in ptt.
1992	24 depression ptt (ICD- 9)	12 neurological controls	NPY	Reduced in ptt.
1985	32 depression ptt	52 neurological controls	Vasopressin	No difference
2012	02 subi cognitive impair		A B/12	No difference
2012				
				Lower in all ptt
	91 Alzheimer ptt. (31 de- pressed, 60 not de- pressed)		P-tau 181	Lower in SCI ptt
2006	76 dementia ptt	77 spinal anesthesia con-	Αβ42	No difference
			Total tau	No difference
			P-tau 181	No difference
				No difference
				No difference
			HGF	No difference
			GDNF	No difference
			VEGF	No difference
				No difference
			FGF-2	No difference
2007	80 mild cognitive impair	24 spinal anesthesia con	T tou	No difference
2007	ment (MDI)	trols	P-tau	No difference
1999		10 neurological controls	sIL-2R	Lower in ptt.
		-		•
2016	44 depression ptt.	21 neurological controls		Lower in ptt.
			IL-1β	No difference
			IL-2	No difference
			IL-4	No difference
			IL-5	No difference
				No difference
				No difference
			IL-13	No difference
			IL-15	No difference
			IL-17A	No difference
				No difference
			FGF-basic	No difference
			G-CSF	No difference
	1985 2012 2006 2007 1999 2016	 1985 32 depression ptt 2012 92 subj. cognitive impairment ppt. (41 depressed, 51 not depressed) 91 Alzheimer ptt. (31 depressed, 60 not depressed) 2006 76 dementia ptt 11 MDD 2007 80 mild cognitive impairment (MDI) 54 MDD 1999 13 depression ptt 	 1985 32 depression ptt 2012 92 subj. cognitive impairment ppt. (41 depressed, 51 not depressed) 91 Alzheimer ptt. (31 depressed) 91 Alzheimer ptt. (31 depressed) 2006 76 dementia ptt 177 spinal anesthesia controls 2006 76 dementia ptt 11 MDD 2007 80 mild cognitive impairment (MDI) 54 MDD 1999 13 depression ptt 52 neurological controls 52 neurological controls 52 neurological controls 52 neurological controls 	198532 depression ptt52 neurological controlsVasopressin201292 subj. cognitive impairment ppt. (41 depressed, 51 not depressed) $A\beta42$ T-tauT-tau P-tau181200676 dementia ptt 11 MDD77 spinal anesthesia controls $A\beta42$ Total tau P-tau 181 MCP-1 MIP-1 α TNF- α TGF- β_1 , NGF HGF GDNF FGF-2 $A\beta42$ Total tau P-tau 181 MCP-1 MIP-1 α TNF- α TGF- β_1 , NGF HGF GDNF FGF-2200780 mild cognitive impairment (MDI) 54 MDD24 spinal anesthesia controlsT-tau P-tau199913 depression ptt10 neurological controlssIL-2R201644 depression ptt.21 neurological controlsIL-1R α IL-7 IL-4 IL-5 IL-6 IL-7 IL-8 IL-9 IL-10100L-12 p70 IL-13 IL-17A EotaxinL-17A Eotaxin

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

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

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⁸Blasko, 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 Dis orders*, 21(1), 9–15. <u>https://doi.org/10.1159/000089137</u>

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

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

^aOgawa, 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. <u>https://doi.org/10.1038/srep07796</u>

^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. <u>https://doi.org/10.1002/jnr.24589</u>

^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. <u>https://doi.org/10.1016/j.psy-chres.2016.04.117</u>

^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. <u>https://doi.org/10.3233/JAD-160401</u>

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. <u>https://doi.org/10.1016/j.bbi.2019.06.015</u>

^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 \geq 2 studies

Quality assessment						
Biomarker No. of studies, Study design	Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality
HVA 17, Case control	Serious limita- tions	No serious in- consistency	No serious in- directness	No serious im- precision	Undetected	⊕⊕⊕⊖ Moderate
5-HIAA 15, Case control	No serious lim- itations	Very serious in- consistency	No serious in- directness	No serious im- precision	Undetected	
MHPG 14, Case control	Serious limita- tions	Very serious in- consistency	No serious in- directness	No serious im- precision	Undetected	⊕○○○ Very low
GABA 4, Case control	No serious lim- itations	Very serious in- consistency	No serious in- directness	Serious impre- cision	Undetected	⊕○○○ Very low
Glutamate 4, Case control	Serious limita- tions	Very serious in- consistency	No serious in- directness	Very serious imprecision	Undetected	⊕○○○ Very low
Glutamine 4, Case control	Serious limita- tions	Very serious in- consistency	No serious in- directness	Very serious imprecision	Undetected	⊕○○○ Very low
Cortisol 2, Case control	No serious lim- itations	No serious in- consistency	No serious in- directness	Very serious imprecision	Undetected	
Transthyretin 2, Case control	No serious lim- itations	No serious in- consistency	No serious in- directness	Very serious imprecision	Undetected	
CRH 8, Case control	Serious limita- tions	Very serious in- consistency	No serious in- directness	Serious impre- cision	Undetected	⊕○○○ Very low
ACTH 2, Case control	No serious lim- itations	No serious in- consistency	No serious in- directness	Very serious imprecision	Undetected	
Oxytocin 2, Case control	No serious lim- itations	No serious in- consistency	No serious in- directness	Very serious imprecision	Undetected	
Vasopressin 2, Case control	Serious limita- tions	No serious in- consistency	No serious in- directness	Very serious imprecision	Undetected	⊕○○○ Very low
Somatostatin 5, Case control	Serious limita- tions	Very serious in- consistency	No serious in- directness	Serious impre- cision	Undetected	⊕○○○ Very low
NPY 5, Case control	Serious limita- tions	Very serious in- consistency	No serious in- directness	Serious impre- cision	Undetected	⊕○○○ Very low
Substance P 2, Case control	No serious lim- itations	Very serious in- consistency	No serious in- directness	Very serious imprecision	Undetected	⊕○○○ Very low
CART 2, Case control	No serious lim- itations	Serious incon- sistency	No serious in- directness	Very serious imprecision	Undetected	⊕○○○ Very low
Orexin 2, Case control D-serine	Serious limita- tions No serious lim- itations	No serious in- consistency Very serious in- consistency	No serious in- directness No serious in- directness	Very serious imprecision Very serious imprecision	Undetected Undetected	⊕○○○Very low⊕○○○Very low

L-serine 3, Case control	No serious lim- itations	Very serious in- consistency	No serious in- directness	Very serious imprecision	Undetected	⊕○○○ Very low
Serine 2, Case control	No serious lim- itations	Very serious in- consistency	No serious in- directness	Very serious imprecision	Undetected	⊕○○○ Very low
Glycine 3, Case control	No serious lim- itations	Very serious in- consistency	No serious in- directness	Very serious imprecision	Undetected	⊕○○○ Very low
Tryptophan 2, Case control	No serious lim- itations	No serious in- consistency	No serious in- directness	Very serious imprecision	Undetected	
Tyrosine 2, Case control	No serious lim- itations	No serious in- consistency	No serious in- directness	Very serious imprecision	Undetected	
Aspartate 2, Case control	No serious lim- itations	Very serious in- consistency	No serious in- directness	Very serious imprecision	Undetected	⊕○○○ Very low
Methionine 2, Case control	No serious lim- itations	No serious in- consistency	No serious in- directness	Very serious imprecision	Undetected	
Ascorbic acid 2, Case control	Serious limita- tions	Very serious in- consistency	No serious in- directness	Very serious imprecision	Undetected	⊕○○○ Very low
IL-6 7, Case control	No serious lim- itations	No serious in- consistency	No serious in- directness	Serious impre- cision	Undetected	⊕⊕⊕⊖ Moderate
IL-8 5, Case control	No serious lim- itations	Very serious in- consistency	No serious in- directness	No serious im- precision	Undetected	
TNF-alfa 2, Case control	Serious limita- tions	No serious in- consistency	No serious in- directness	Very serious imprecision	Undetected	⊕○○○ Very low
WCC 3, Case control	No serious lim- itations	Very serious in- consistency	No serious in- directness	Serious impre- cision	Undetected	⊕○○○ Very low
MMP-3 2, Case control	No serious lim- itations		No serious in- directness	Serious impre- cision	Undetected	⊕⊕⊕⊖ Moderate
Total protein 5, Case control	No serious lim- itations	No serious in- consistency	No serious in- directness	No serious im- precision	Undetected	$\oplus \oplus \oplus \oplus$ High
Albumin ratio 2, Case control	No serious lim- itations	Very serious in- consistency	No serious in- directness	Very serious imprecision	Undetected	⊕○○○ Very low
Glucose 2, Case control	No serious lim- itations	No serious in- consistency	No serious in- directness	Very serious imprecision	Undetected	
Amyloid-B-40 3, Case control	No serious lim- itations	No serious in- consistency	No serious in- directness	Very serious imprecision	Undetected	
Total tau 9, Case control	Serious limita- tions	Very serious in- consistency	No serious in- directness	Serious impre- cision	Undetected	⊕○○○ Very low
P-tau 181 6, Case control	No serious lim- itations	No serious in- consistency	No serious in- directness	Serious impre- cision	Undetected	⊕⊕⊕⊖ Moderate

Amyloid-B-42 8, Case control	No serious lim- itations	Very serious in- consistency	No serious in- directness	Serious impre- cision	Undetected	⊕○○○ Very low
Neurogranin 2, Case control	Serious limita- tions	No serious in- consistency	No serious in- directness	Very serious imprecision	Undetected	⊕○○○ Very low
NfL 2, Case control	No serious lim- itations	Very serious in- consistency	No serious in- directness	Very serious imprecision	Undetected	⊕○○○ Very low
BDNF 3, Case control	Serious limita- tions	No serious in- consistency	No serious in- directness	Very serious imprecision	Undetected	⊕○○○ Very low
NCAM 2, Case control	No serious lim- itations	No serious in- consistency	No serious in- directness	Serious impre- cision	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.