Prospective biomarkers of major depressive disorder: a systematic review and meta-analysis

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Received: 18 January 2019 / Revised: 9 July 2019 / Accepted: 19 August 2019 / Published online: 19 November 2019
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Abstract
Leading biological hypotheses propose that biological changes may underlie major depressive disorder onset and relapse/recurrence. Here, we investigate if there is prospective evidence for biomarkers derived from leading theories. We focus on neuroimaging, gastrointestinal factors, immunology, neurotrophic factors, neurotransmitters, hormones, and oxidative stress. Searches were performed in Pubmed, Embase and PsychInfo for articles published up to 06/2019. References and citations of included articles were screened to identify additional articles. Inclusion criteria were having an MDD diagnosis as outcome, a biomarker as predictor, and prospective design search terms were formulated accordingly. PRISMA guidelines were applied. Meta-analyses were performed using a random effect model when three or more comparable studies were identified, using a random effect model. Our search resulted in 67,464 articles, of which 75 prospective articles were identified on: Neuroimaging (N = 24), Gastrointestinal factors (N = 1), Immunology (N = 8), Neurotrophic (N = 2), Neurotransmitters (N = 1), Hormones (N = 39), Oxidative stress (N = 1). Meta-analyses on brain volumes and immunology markers were not significant. Only cortisol (N = 19, OR = 1.294, p = 0.024) showed a predictive effect on onset/relapse/recurrence of MDD, but not on time until MDD onset/relapse/recurrence. However, this effect disappeared when studies including participants with a baseline clinical diagnosis were removed from the analyses. Other studies were too heterogeneous to compare. Thus, there is a lack of evidence for leading biological theories for onset and maintenance of depression. Only cortisol was identified as potential predictor for MDD, but results are influenced by the disease state. High-quality (prospective) studies on MDD are needed to disentangle the etiology and maintenance of MDD.

Introduction
Major depressive disorder (MDD) is a disabling disorder that is amongst the most prevalent mental health disorders worldwide [1, 2] and is highly recurrent [3–5]. Therapeutic strategies, such as antidepressant medication, are available, although outcomes are suboptimal given roughly 50% of patients do not adequately respond [6, 7]. In order to improve treatment approaches and prevent recurrence, it is important to examine the underlying vulnerabilities that predispose individuals to depression onset and recurrence. By prospectively investigating biological predictors of MDD onset, relapse and recurrence, more insights into the potential causes of MDD can be gained. For these purposes, biomarkers could be particularly informative for understanding the etiology of MDD, and could stimulate development of new clinical approaches in the future.

Numerous studies suggest that MDD is related to alterations in various biological systems [8, 9]. For instance, MDD has been associated with alterations in brain structure
and function, (e.g. [10, 11]), gastrointestinal factors (e.g. [12, 13]), immunology (e.g. [14]), endocrinology (including neurotransmitters, e.g. [15, 16]), neurotrophic factors (e.g. [17, 18]), hormones (e.g. [19]), and oxidative stress (e.g. [20]). Based on these frequently reported biomarker alterations several biological hypotheses for the etiology of MDD have been formulated. Support for these hypotheses have primarily been derived from cross-sectional studies. However, cross-sectional studies cannot provide evidence for causality, and thus cannot distinguish causes from consequences secondarily to the illness [21]. To determine whether an etiological mechanism is potentially causal for the development of MDD, the minimal requirement for a study is that the biomarkers are assessed before the development of MDD or prior to a recurrent episode. Thus, prospective studies investigating biomarkers before the onset or relapse/recurrence of MDD are necessary. Further, there are indications that first onset versus relapse/recurrence of MDD is based on different mechanisms [22, 23]. Therefore, investigating predictive biomarkers for onset and relapse/recurrence separately can improve predictive models. However, to our knowledge, no systematic overview of prospective studies comparing biomarkers of onset and relapse/recurrence of MDD has been conducted.

Therefore, we will provide a systematic overview of prospective studies investigating leading biological hypotheses on the etiology of MDD. The first goal is to determine whether there is prospective evidence that these biomarkers predict onset, and relapse/recurrence of MDD. A systematic search for prospective studies will be performed. We explicitly focus on studies using a clinical interview to determine the onset and re-occurrence of a major depressive episode. The search is subdivided into the following biological areas: neuroimaging, gastrointestinal, immunology, neurotrophic, neurotransmitters, hormones, and oxidative stress (see Supplementary Fig. 1). The second goal will be to establish the robustness of each biomarker and to compare the effect size of different biomarkers. Further, subgroup analyses and meta-regression will be performed to investigate potential moderators.

**Methods**

**Search process and study selection**

The study was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA [24]; see Appendices A and B for search terms and flow charts and Appendix C for PRISMA checklist). This meta-analysis was part of a larger project on evidence for leading theories for MDD onset, and relapse/recurrence and mechanisms of change (for the current study see registration in Prospero CRD42017072990; for psychological predictors of depression see Prospero CRD42017073975; CRD42017073977). Literature searches per biological system were performed between July 2016 and July 2017 in the online databases PubMed, PsychINFO and EMBASE, and a combined search update was performed in June 2019. No start date was included, so all articles that were digitalized until June 2019 were included. The search included terms related to: (1) MDD, (2) longitudinal studies predicting onset, relapse and recurrence, and (3) biological systems of interest (see Appendix A). The articles were independently screened for eligibility based on title and abstract (see criteria below) by two team members, including at least one of the researchers (MK, LG, or MvD), and a member of our screening team (psychology/research Master students; see “Acknowledgements”). The following inclusion criteria were applied: (1) Diagnostic status of MDD for all participants through clinical interview (e.g., SCID, K-SADS from DSM, CIDI from ICD) or report of a clinician-assessed diagnosis (e.g., being hospitalized for MDD treatment, self-report of being diagnosed with MDD by a clinician). (2) The study design is longitudinal. (3) The target variable(s) (e.g., the proposed vulnerability factors) are assessed prospectively, that is before the onset or relapse/recurrence of MDD. (4) The target variable is derived from one of the leading biological models. Exclusion criteria were: diagnosis of mood disorders other than MDD (e.g. bipolar disorder), late-life depression, MDD due to the other (medical) disorders, or studies including a mixed group of diagnoses where less than 75% was diagnosed with MDD. In order to trace studies published after the initial search date, and to add recently published studies, we screened of the included articles the reference list, articles citing, and reference lists of recent reviews. This was done between August and September 2017, and in June 2019 for the new inclusions.

**Data extraction and quality assessment**

Data extraction was performed by two team members independently (but not blind to the data extracted by the first data extractor) including at least one author (MK, LG, and MvD) and a member of our screening team (see “Acknowledgement”). The following data were extracted: number of included participants and group membership (developing MDD or not), age, gender, study country, MDD diagnosis at baseline, assessment tool of diagnosis, diagnostic criteria, biomarker measurement outcome, biomarker type of measurement, assessment tool of diagnosis, diagnostic criteria, biomarker measurement outcome, biomarker type of measurement, biomarker time of measurement, follow-up time, summary of main outcome. The quality of included studies was assessed by two team members according to a minimally adjusted version of the GRADE guidelines on study level [25]. Information was
extracted on selection of cohorts (similar for groups compared), quality of MDD assessment instrument, presence of baseline MDD (symptoms), matching of samples or adjustment for covariates, biomarker assessment, interviewer, description of drop-outs, description of interventions, and other sources of bias. A score for the quality was also given, by counting the number of questions where there was limited risk of bias (max score = 9).

Analysis

Random effects meta-analyses were performed using comprehensive meta-analysis (www.meta-analysis.com). A meta-analysis was conducted when three or more studies were included using a similar modality of biomarker assessment [26]. When multiple studies investigated the same sample, analysis included only the study with the largest sample size. Odds ratio or risk ratio were the summary effects of outcome. Significance was determined with \( p = 0.05 \) for meta-analyses. First, analysis was performed on onset and relapse/recurrence of MDD combined to investigate the predictive effect of all biomarkers on MDD development in general. Differences between biomarker effects was also investigated with a subgroup analysis. If a difference exists, meta-analyses were performed per biomarker. Second, separate analyses were performed on studies including participants without baseline clinical MDD diagnosis and/or first onset only versus studies including participants with baseline clinical MDD diagnosis and/or relapse/recurrence (including mixed groups with onset and relapse/recurrence). Heterogeneity was assessed with the \( Q \)-test and \( I^2 \) statistic [27]. Sensitivity analyses were also performed by re-running analyses after removal of outliers (defined by having no overlap of the 95% CI with the pooled effect 95% CI) and studies with low risk of bias. Baseline age, percentage female participants, biomarker assessment, follow-up time, and quality assessment score were assessed as moderators, when sufficient studies (three per subcategory) were included in the analysis. For analysis of biomarker assessment all effect sizes reported were taken into account. Publication bias was also assessed using Egger’s test for asymmetry [28] of the funnel plot and Duval and Tweedie’s trim and fill procedure [29].

Results

Search results and quality assessment

The PRISMA flow chart provides an overview of the number of articles screened, included and excluded for all biomarkers combined (see Fig. 1; flow charts per biological system can be found in Appendix B). In total, 67,464 articles were screened for eligibility across all biomarkers. After initial screening, eligibility of 707 articles was assessed based on the full text. In total, only 75 unique prospective studies were identified (see Table 1; [30–104]). Overall, 75 prospective articles were identified on: Neuroimaging (\( N = 24 \)), Gastrointestinal factors (\( N = 1 \)), Immunology/inflammation (\( N = 8 \)), Neurotrophic (\( N = 2 \)), Neurotransmitters (\( N = 1 \)), Hormones (\( N = 39 \)), and Oxidative stress (\( N = 1 \)). In total 39,028,432 participants (median 85, range [9–9275]) were included (Table 1), of which 3267 developed MDD over the follow-up period (median 22, range [3–608]). The median age of study participants was 39 [range 9–66] and the median percentage of females included was 64% [29–100%]. Follow-up time ranged from 4 months to 22 years, which is adequate for detecting onset, relapse or recurrence (median 3 years). The SCID (\( N = 23 \)) and versions of the (K)SADS (\( N = 19 \)) were the most frequently administered clinical interviews to assess MDD using DSM criteria (DSM \( N = 54 \)) over ICD criteria. Studies describing a clinical diagnosis made by two independent psychiatrist or self-report of hospitalization or diagnosis for MDD were also included incidentally (\( N = 7 \)).

Most studies were performed in Western countries (e.g. USA, UK, and Germany, see Table 1). Only 38 studies were identified that excluded participants with baseline clinical MDD diagnosis. First onset of MDD was investigated in 31 studies, relapse/recurrence in 35 studies, and 9 studies included mixed onset and relapse/recurrence samples. Overall, the mean quality score of studies was good (average quality score = 6.3, median 6, range (3–9)), 19 studies had a very low risk of bias (>6 quality score), 26 studies had some risk of bias (5–6 quality score), and 8 studies had high risk of bias (4 or lower quality score). Below, meta-analyses will be described and incidental findings will be discussed narratively (see tables in Supplementary material).

Neuroimaging

Out of the 4210 articles screened for neuroimaging, 21 prospective biomarker studies fulfilled eligibility criteria and the update revealed 3 additional articles (total \( N = 1952 \), median \( N = 83 \), MDD development \( N = 420 \), median \( N = 18 \), range for age [6–63], % female [29–100], follow-up time [1–10], QA score (4–9)). However, due to overlap in study samples and heterogeneity in methods applied (e.g. tasks, regions of interest), meta-analysis could only be performed on some hippocampus, amygdala and frontal brain area volumes (see Table 1 and Supplementary Fig. 2). No significant odds ratios were observed for volume of the

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1 Note that this number may include duplicates since articles may be screened two times for different classes of biomarkers.
Fig. 1 Flow Diagram of systematic search for prospective studies of MDD overall biological searches combined [24]. See Supplementary material for flow charts per search.

hippocampus \((N = 3, \ OR = 0.660 \ [0.426 \ 1.022], \ p = 0.063 [54, 73, 91])\), frontal brain regions \((N = 3, \ OR = 0.869 \ [0.480 \ 1.673], \ p = 0.730 [51, 74, 95])\), nor the amygdala \((N = 3, \ OR = 6.108 \ [0.143 \ 261.388], \ p = 0.345 [54, 74, 81])\). Due to the small number of studies, no further analyses were performed.

Incidental structural MRI studies reported that both smaller and larger insula volume was significantly related to MDD development in two studies [51, 91]. No significant predictive value of the amygdala volume was found in three studies investigating two unique samples [53, 54, 74]. Two studies investigated cortical thickness in the same sample. MDD was predicted by a thinner right para-hippocampus and right fusiform gyrus but not by subcortical thickness [85, 86]. One study reported that higher ACC gray matter volume predicting MDD onset but did not report enough data for analysis [77].

Ten studies investigated if baseline brain activation predicted MDD onset, of which seven used fMRI [49, 50, 76, 82, 99–101] and three used EEG [31, 39, 83]. Studies were too heterogeneous to compare. These studies showed that MDD development was predicted by: lower activity in the frontal lobe in various contexts ([39] reward task loss-gain contrast [83]; rest [71, 82]; go/no-go task, errors; [31] pre- vs posttryptophan depletion), higher activity in the insula ([99] sentence completion increasing in difficulty), higher subgenual anterior cingulate cortex (ACC) temporal and striatal connectivity ([76] self-blame vs other-blame situations) and higher mPFC activity ([50] viewing sad vs neutral movie clips). One study reported no group differences during rest [49]. Differences in subgenual ACC and MFG connectivity were also found in various regions of these networks during rest [71, 101].

**Immunology**

Out of the 5603 articles screened for immunology, seven met inclusion criteria [43, 46, 61, 69, 87, 88, 94], and one additional study was identified in the update (total \(N = 27,009\), median \(N = 2514\), MDD development \(N = 1682\), median \(N = 160\), range for age (9–66), % female (43–100), follow-up time (3–12), QA score (4–9)). These studies investigated several markers for immunology: C-Reactive Protein, Interleukin-6 (IL-6), IL-1β, Tumor Necrosis Factor-α (TNFα), Soluble Urokinase Plasminogen Activator Receptor (suPAR), 3-nitrotyrosine, and heat-shock protein 70 (HSP70) in blood or serum.

CRP was the investigated in five studies with compatible measures for odds ratio [43, 46, 55, 69, 88, 94], IL (1 and or 6) in four studies, of which two studies investigated the same sample. No significant predictive effects for CRP \((N = 4, \ OR = 1.557, \ 95\% \ CI [0.870 \ 2.788], \ p = 0.136)\) IL
Table 1: Study details on all prospective studies (N = 75), subdivided by the following biological sublevels: Neuroimaging, Gastrointestinal factors, Immunology, Neurotransmitters, Neurotrophic factors, Hormones: HPA axis, HPG axis, HPS axis, and HPT axis

| Study | Country | Gender | Age | Follow-up | Biomarker of interest | Measure | Technical details | Direction result of biomarker | Quality score |
|-------|---------|--------|-----|-----------|-----------------------|---------|------------------|-------------------------------|--------------|
| Bees et al. [39] | USA | male | 25 | 2 years | Frontal brain areas (ERP) | DISC; ICD-10 | Activity: EEG | During mood task, comparing loss-gain | 7 |
| Davey et al. [49] | Australia | female | 20 | 2 years | Amygdala→ACC connectivity | K-SADS-PL; DSM-IV | Resting state | Amygdala→ACC connectivity | 4 |
| Foland-Ross et al. [51] | USA | female | 25 | 2 years | Hippocampus, amygdala, OFC and ACC | K-SADS-PL and SCID; DSM-IV | Volumes | Most important classifiers for MDD were: mOFC, PFC, ACC, and insula | 7 |
| Little et al. [73] | Australia | male | 20 | 2 years | Hippocampus | K-SADS-PL, MINE, DSM-IV | Volumes | Hippocampus, OFC and ACC | 6 |
| Little et al. [74] | Australia | female | 20 | 2 years | Hippocampus | K-SADS-PL; DSM-IV | Volumes | hippocampus | 5 |
| Neudock et al. [83] | USA | female | 20 | 2 years | Left frontal brain areas (Alpha power) | SADSC; DSM-IV | Activity: EEG | Rest. eyes-open and eyes-closed | 6 |
| Papmeyer et al. [85] | UK | female | 20 | 2 years | Frontal brain regions | Clinical interview; DSM-IV | Volumes | Right parahippocampal and fusiform gyrus | 9 |
| Papmeyer et al. [86] | UK | female | 20 | 2 years | Subcortical brain regions | Clinical interview; DSM-IV | Volumes | NS | 9 |
| Whalley et al. [99] | UK | male | 20 | 2 years | Brain regions activated by the task | SCID; DSM-IV | Activity: fMRI | Insula activity | 7 |
| Whalley et al. [100] | UK | male | 20 | 2 years | Amygdala, insula, hippocampus, ACC, thalamus | SCID; DSM-IV | Volumes | Thalamus, insula, ACC | 7 |
| Nickson et al. [81] | Denmark | female | 20 | 2 years | VBM | SCID; DSM-IV | Volumes | Whole brain VBM | 7 |
| Macoveanu et al. [77] | USA | female | 20 | 2 years | VBM | SCAN 2.1; (CD-10) | VBM | Whole brain | 7 |
| Belden et al. [36] | USA | male | 20 | 2 years | Anterior insula | Clinician and TRD; DSM-5 | Volumes | Insula volume | 6 |
| Rao et al. [91] | USA | female | 20 | 2 years | Hippocampus | LIFE, PBR; DSM-IV | Volumes | Hippocampus | 5 |
| Serri-Blasso et al. [95] | Spain | male | 20 | 2 years | Whole brain (Freesurfer) | LIFE-Chart Manual for Recurrent Affective Illness, Unclear | Volumes | PREF, ACC, mPFC volumes | 8 |
| Allen et al. [31] | USA | female | 20 | 2 years | Frontal asymmetry | SCID; DSM-II-R | Activity: EEG | Right frontal activity after vs below TD predict lower change of recurrence at follow-up | 6 |
| Farb et al. [50] | Canada | male | 20 | 2 years | ROI mPFC | SCID; DSM-IV | Activity: fMRI | Viewing sad vs neutral movie clips | 7 |
| Fridl et al. [53] | Germany | female | 20 | 2 years | Hippocampus and amygdala | Clinical interview, 2 psychiatrists; DSM-IV | Volumes | Hippocampus | 6 |
| Fridl et al. [54] | Germany | female | 20 | 2 years | Hippocampus and amygdala | SCID; DSM-IV | Volumes | Hippocampus, OFC, and ACC | 6 |
| Krommüller et al. [70] | Germany | male | 20 | 2 years | Hippocampus | SCID / LIFE; DSM-IV | Volumes | Hippocampus | 5 |
| Lythe et al. [76] | UK | male | 20 | 2 years | ROI based on previous studies: ACC, temporal, striatal | LIFE; DSM-IV | Activity: fMRI | Activity during self-blame versus other-blame emotions | 9 |
| Neuroimaging | Baseline MDD excl. Y = yes, N = No | Baseline symptoms a = above cut-off, b = below cut-off, ? = unclear | Country and cohort information (or indicates similar cohorts) | Total N | Onset (O) or relapse/recurrence (R) of MDD (N) | Baseline age (mean or range) | Follow-up time (years; mean or max) | MDD diagnostic interview; Diagnostic criteria | Biomarker of interest | Measure | Technical details | Direction result of biomarker predicting onset, relapse/recurrence of MDD | Quality score |
|--------------|----------------------------------|---------------------------------------------------------------|----------------------------------------------------------|--------|----------------------------------|--------------------------|-------------------------------|--------------------------------|------------------|--------|----------------|-------------------------------------------------|-------------|
| Nixon et al. [117] | Y | b | UK | 38 | 7R | [24–63] | 33 | 1 | SCID; DSM-IV | ROI based on previous studies | Activity: fMRI | GoNoGo task | Right dmPFC activity following errors and negative feedback compared to correct hits in recurrence vs other groups | 6 |
| Workman et al. [100] | Y | ? | UK | 85 | 17R | 37 | 64 | 1.2 | SCID; DSM-IV | sgACC | RSFC: fMRI | Rest. Left sgACC to right sgACC connectivity | Successful regulation sgACC > MFG hyperactivation. Failed regulation: MFG hypoactivation. RSFC: altered successful vs unsuccessful inhibition | 9 |
| Langenecker et al. [71] | Y | b | USA | 94 | 21R | 21 | 63 | 4–6 | DIGS and longitudinal interval follow evaluation | MRI | Activity: fMRI & RSFC (MRI) | Go/No-Go task: task unsuccessful vs unsuccessful inhibition | | 8 |
| Gastrointestinal factors | Baseline MDD excl. Y = yes, N = No | Baseline symptoms a = above cut-off, b = below cut-off, ? = unclear | Country and cohort information (or indicates similar cohorts) | Total N | Onset (O) or relapse/recurrence (R) of MDD (N) | Baseline age (mean or range) | Follow-up time (years; mean or max) | MDD diagnostic interview; Diagnostic criteria | Biomarker of interest | Measure | Technical details | Direction result of biomarker predicting onset, relapse/ recurrence of MDD | QA score |
| Campo et al. [40] | Y | ? | USA | 119 | 14O | [8–12] | ? | 7.5 | K-SADS-E; DSM-IV (nm) | L-5-hydroxytryptophan injection at baseline | Abdominal discomfort, nausea, or vomiting in response to L-5HTP infusion; GI distress | L-5HTP infusion; Survival curve (groups high vs. low sensitive) | GI distress after serotonin challenge | 6 |
| Immunology | Baseline MDD excl. Y = yes, N = No | Baseline symptoms a = above cut-off, b = below cut-off, ? = unclear | Country and cohort information (or indicates similar cohorts) | Total N | Onset (O) or relapse/recurrence (R) of MDD (N) | Baseline age (mean or range) | Follow-up time (years; mean or max) | MDD diagnostic interview; Diagnostic criteria | Biomarker of interest | Measure | Technical details | Direction result of biomarker predicting onset, relapse/ recurrence of MDD | QA score |
| Chocano-Bedoya et al. [43] | N | ? | USA | 4403 | 81O | 56 | 100 | 12 | Self-report of diagnosis; Unclear prescriptions for antidepressant medication or had a hospital discharge diagnosis with the codes F33.3 or F33.3; ICD-10 | CRP, IL-6, TNFα-R2 | Blood, 1 time point | hs-CRP IA, EIA | NS | 4 |
| Haastrup et al. [61] | N | ? | Denmark | 9275 | 22O | [18–47] | 48 | 5 | CRP, IL-6, TNFα-R2 | CRP, IL-6, TNFα-R2 | Blood plasma, 1 time point | suPAR | ELISA | Increased risk (shorter time) to onset of depression with higher SuPAR | 6 |
| Rudaz et al. [84] | Y | ? | Switzerland | 1524 | 192O | 51 | 43 | 5.5 | Diagnostic Interview for Genetic Studies (DIGS); DSM-IV | CRP, IL-10, IL-6, TNFα | Blood serum, 1 time point | hs-CRP IA, multiplex bead particle-based flow cytometric cytokine assay | TNFα, NS for CRP, IL-10, IL-6 | 8 |
| Copeland et al. [46] | Y | b | USA | 5810 | 169O + R | 34 | 49 | 12 | CAPA, YAPA; DSM-IV | CRP | Blood spot, 1 time point | hs-CRP IA | NS | 9 |
| Glass et al. [55] | Y/N | ? | Switzerland | 2580 | 608O + R | [35–60] | 54 | 5.5 | DIGS | CRP | Blood serum, 1 time point | hs-CRP IA | IA and Latex HS | O = R; TNFα | 7 |
| Khandaker et al. [69] | N | ? | UK | 2447 | 422O + R | 9 | 51 | 9 | CIB-R, ICD-10 | CRP | Blood serum, 1 time point | hs-CRP IA | ELISA | TNFα | 5 |
| Pasco et al. [87] | Y | ? | Australia | 822 | 151O + R | 49 | 100 | 10 | SCID, DSM-IV-TR | CRP | Blood serum, 1 time point | hs-CRP IA | CRP reduced time to depression (HR) | 7 |
Table 1 (continued)

| Neuroimaging | Baseline symptoms a = above cut-off, b = below cut-off, ? = unclear | Country and cohort information (or indicates similar cohorts) | Total N | Onset (O) or relapse/ recurrence (R) of MDD (N) | Baseline age (mean or range) | % female | Follow-up time (years; mean or max) | MDD diagnostic interview; Diagnostic criteria | Biomarker of interest | Measure | Technical details | Direction result of biomarker predicting onset, relapse/ recurrence of MDD | Quality score |
|--------------|--------------------------------------------------------------------|-------------------------------------------------|---------|-----------------------------------------------|----------------------------|---------|-----------------------------------|-----------------------------------------------|------------------|--------|----------------|------------------------------------------------|---------------|
| Johnston et al. [68] | N a UK 31 20 R 47 71 8 | SCID I/P; DSM-III-R | Plasma Norepinephrine, cortisol | Blood plasma, 1 time point | Chromatography, RIA | ↓ Norepinephrine, shorter time to first recurrence. | 6 |
| Pasquali et al. [88] | N b USA 148 37 O 40 100 3 | SCID; DSM-IV | Neurotrophic: BDNF Immunology: HSP70, 3-Nitrotyrosine, Oxidative stress: Protein carbonyl, Lipid peroxidation, Thiol content | Blood serum, 1 time point | ELISA, quantitative sandwich enzyme immunoassay, colorimetric assay (thiol) | ↑ BDNF, ↓ Oxidative stress | 6 |
| Vinberg et al. [97] | Y ? Denmark 234 24 O 44 65 7.5 | SCAN, ICD 8/ICD-10 BDNF | Blood, 1 time point | Two-site sandwich ELISA | NS | 5 |
| Hormones: HPA | Baseline symptoms a = above cut-off, b = below cut-off, ? = unclear | Country and cohort information (or indicates similar cohorts) | Total N | Onset (O) or relapse/ recurrence (R) of MDD (N) | Baseline age (mean or range) | % female | Follow-up time (years; mean or max) | MDD diagnostic interview; Diagnostic criteria | Biomarker of interest | Measure | Technical details | Direction result of biomarker predicting onset, relapse/ recurrence of MDD | Quality score |
| Adam et al. [30] | N ? USA 230 18 O 17 75 1 | SCID; DSM-IV | AUC, CAR, diurnal, slope cortisol pre- post- trier stress test | Saliva, 3 days, 6 times a day | DELFIA | ↑ cortisol reactivity in early puberty & cortisol reactivity in late puberty | 9 |
| Colich et al. [45] | Y b USA1 89 31 O 12 100 6 | K-SADS, SCID; DSM-IV | Cortisol pro- post- trier social stress test | Saliva, 4 time points | LIA | ↑ cortisol reactivity in early puberty & cortisol reactivity in late puberty | 9 |
| Goodyer et al. [56] | ? ? UK2 171 30 O 14 59 1 | K-SADS, DSM-IV | Peaks 8:00, cortisol and DHEA | Saliva 4 days, 2 time points | ELISA | ↑ cortisol & DHEA | 6 |
| Goodyer et al. [57] | ? ? UK2 234 31 O 14 53 1 | K-SADS, DSM-IV | Morning and evening cortisol, DHEA | Saliva 4 days, 2 time points | ELISA | ↑ DHEA, NS cortisol | 7 |
| Goodyer et al. [58] | ? b UK2 367 32 O 14 46 1 | K-SADS, DSM-IV | Morning cortisol | Saliva 4 days, 1 time point | ELISA | ↑ cortisol | 6 |
| Goodyer et al. [59] | ? b UK2 357 40 O 14 47 1 | K-SADS, DSM-IV | Morning cortisol | Saliva 4 days, 1 time point | ELISA | ↑ cortisol | 6 |
| Grynderup et al. [60] | Y ? Denmark 2920 62 O 56 78 2 | SCAN, ICD-10-DSR | Morning, diurnal, evening, morning to evening slope in cortisol | Saliva, 2 hours after awakening, and between 5PM and 4AM | RIA | ↑ difference in morning to evening cortisol | 9 |
| Harris et al. [63] | ? ? UK 116 28 O 39 100 1 | SCAN, DSM-IV | DHEA and cortisol | Saliva, 4 days, 2 time points | ELISA | ↑ cortisol predicts MDD | 8 |
| Herbert et al. [65] | Y ? UK 279 53 O 37 100 1 | SCAN, DSM-IV | Morning cortisol | Saliva, 4 days, 1 time point | ELISA | ↑ cortisol predicts MDD | 8 |
### Table 1 (continued)

| Neuroimaging | Baseline MDD excl. Y = yes, N = No | Baseline symptoms a = above cut-off, b = below cut-off, ? = unclear | Country and cohort information (or indicates similar cohorts) | Total N | Onset (O) or relapse/recurrence (R) of MDD N | Baseline age (mean or range) | Follow-up time (years; mean or max) | MDD diagnostic interview; Diagnostic criteria | Biomarker of interest Measure Technical details | Direction result of biomarker predicting onset, relapse/recurrence of MDD | Quality score |
|--------------|-----------------------------------|------------------------------------------------------------------|-------------------------------------------------------------|---------|---------------------------------------------|-----------------------------|------------------------------------------|---------------------------------------------|-------------------------------------------------|------------------------------------------------|-------------|
| LeMoult et al. [72]† | Y b | USA1 | 62 | 26 O | 12 | 100 | 6.5 | K-SADS, SCID, DSM-IV | Morning cortisol | Saliva, 2 days, 4 time points | ELISA | † cortisol predicts MDD | 9 |
| Rao et al. [93]† | Y b | USA2 | 89 | 14 O | 15 | 58 | 5 | K-SADS, DSM-IV | Saliva, NUC | Saliva, 3 time points before sleep and Urine 1 time point before sleep | RIA | † cortisol predicts MDD | 6 |
| Canegie et al. [41]† | N ? | UK | 841 | 46 O + R | 15 | 49 | 3 | CIS-R, ICD-10 | AUC, CAR, DD, bedtime (mm), waking (mm), TEC | Urine, over 24 h | EIA | NS | 5 |
| Vehse-Schullhorn et al. [98]† | Y ? | USA | 270 | 42 O + R | 17 | 72 | 4 | SCID, DSM-IV | AUC, CAR, diurnal slope | Saliva, 3 days, multiple time points | Time-resolved fluorescent-detection IA | † cortisol recurrence | 9 |
| Appelhof et al. [32]† | N a | Spain | 45 | 52 R | 30 | 44 | 22 | At baseline; SCID, Relapse: HRSD, MADRS, and BD; DSM-IV | Post dexamethasone cortisol, Max ACTH, Delta ACTH, Max cortisol, delta cortisol, discharge, difference cortisol | Blood, 2 days, multiple time points before and after DEX/CRH combined with TRH | Immulite 2000 analyser | † AUC and delta in relapse | 8 |
| Aubry et al. [34]† | Y a | Switzerland | 34 | 12 R | 44 | 56 | 1 | MNI, DSM-III-R/IV, ICD-10 | Cortisol after DEX/CRH test | Blood, 2 days, multiple points before and after DEX/CRH | RIA | † cortisol related to relapse | 7 |
| Banki et al. [35]† | N a | Hungary | 24 | 9 R | 51 | 100 | 0.5 | Hospital diagnosis; DSM-III-R | CRH, SHF | RIA | NS | 6 |
| Bockting et al. [37]† | Y b | Netherlands1 | 55 | 43 R | 44 | 73 | 5.5 | SCID, DSM-IV | Morning and evening cortisol | Saliva, 2 days, 1–2 time points a day | EIA | † cortisol related to relapse | 7 |
| Bouhuys et al. [38]† | N b | Netherlands | 77 | 21 R | 44 | 66 | 2 | CIDI, DSM-IV | 24 h urine | RIA | NS | 6 |
| Charles et al. [42]† | N ? | Belgium | 13 | 7 R | [33–67] | 77 | 1.5 | SADS-L, DSM-III and RDC | Morning after DST | Blood plasma, 2 time points after taking DEX | EIA | † cortisol (non suppression at recovery) higher rates of MDD readmission | 4 |
| Chopra et al. [44]† | Y b | Canada | 55 | 28 R | 39 | 64 | 1.5 | SCID, DSM-IV | Morning/evening (before mood induction) | Saliva, 4 time points | EIA | † cortisol | 4 |
| Cosgriff et al. [48]† | N b | New Zealand | 13 | 4 R | 51 | 54 | 0.25 | Clinical readmission; Unclear | Mean cortisol, Delta TSH | Blood, 10–12 time points | EIA/RIA | † cortisol | 5 |
| Hardeveld et al. [62]† | Y a | Netherlands | 549 | 193 R | 45 | 71 | 4 | CIDI, DSM-IV | Salivary CAR, evening, DST | Saliva, 2 days, 6 times day 1, 1 time day 2 after DEX | EIA | † AUC increase differ; related to time to recurrence. Other measures, mean evening, DST and AUC were not predictive | 7 |
| Hauser et al. [64]† | N a | Switzerland | 20 | 12 R | 52 | 70 | 1 | SCID, ICD-10 | Cortisol after DEX/CRH | Blood plasma, 1 time point after DEX/CRH | RIA | † DHEAS diurnal course, † cortisol/DHEAS ratio diurnal course | 6 |
| Lok et al. [75]† | Y b | Netherlands1 | 187 | 102 R | 44 | 68 | 2 | SCID, DSM-IV | Morning and evening cortisol | Saliva, 2 days, 3 time points | RIA | NS | 8 |
| Mander et al. [78]† | N ? | UK | 70 | 32 R | Unclear | Unclear | 3 | SCID, DSM-III | DEX suppression | Saliva, 1 day, 3 time points after DEX | RIA | NS | 5 |
| Mocking et al. [110]† | Y b | Netherlands1 | 187 | 154 R | 44 | 68 | 10 | SCID, DSM-IV | Cortisol/DHEAS ratio | Saliva, 2 days, 2 time points a day | EIA | † cortisol(DHEAS ratio) diurnal course | 6 |
| Morris et al. [80]† | Y ab | USA | 32 | 9 R | 23 | 63 | 0.75 | SCID, DSM-IV | Cortisol pre-post- TSST | Saliva, 6 time points | ELISA | NS | 8 |
| Pittor et al. [89]† | N a | Spain1 | 43 | 18 R | 51 | 53 | 2 | SCID, DSM-IV | Cortisol and ACTH after CRF injection | Blood plasma, 6 time points around CRF injection | ELISA | NS | 8 |
| Table 1 (continued) |
|---------------------|
| Neuroimaging        | Baseline MDD excl. | Y = yes, N = No | Baseline symptoms a = above cut-off, b = below cut-off, ? = unclear | Country and cohort information (or indicates similar cohorts) | Total N | Onset (O) or relapse/recurrence (R) of MDD N | Baseline age (mean or range) | % female | Follow-up time (years; mean or max) | MDD diagnostic interview; Diagnostic criteria | Biomarker of interest | Measure | Technical details | Direction result of biomarker predicting onset, relapse/recurrence of MDD | Quality score |
|---------------------|--------------------|----------------|-------------------------------------------------|-------------------------------------------------|---------|-----------------------------------|--------------------------|----------|-----------------------------------|---------------------------------------------|-----------------|---------|----------------|-------------------------------------------------------------------|--------------|
| Piantor et al. [90] | N                  | a               | Spain1                                          | 43                                              | 18 R    | 51                                | 46                       | 2        | SCID, DSM-IV                      | Cortisol and ACTH after CRF injection         | Blood plasma, 6 time points around CRF injection | EIA/RIA | 1 cortisol (NAUCC) after CRF, LACTH after CRF                  | 5              |
| Rao et al. [92]    | N                  | b               | USA2                                            | 47                                              | 20 R    | 15                                | 64                       | 3.5      | K-SADS-PL, DSM-IV                 | NuCC            | ACTH, cortisol, CSF, ACTH after CRF injection | RIA            | 1 cortisol                         | 5              |
| Tsun et al. [96]   | N                  | a               | Japan                                           | 25                                              | 9 R     | 41                                | 64                       | 10       | SCID, DSM-IV                      | ACTH and cortisol, TSH                         | Blood, 2 days, day 1 TRH test 5 time points, day 2 DEX/CRH test, 60 time points | IRMA     | NS cortisol and ACTH/TSH after TRH test in recurrence | 5              |
| Zimmerman et al.   | N                  | ?               | USA1                                            | 165                                             | 47 R    | 40                                | 73                       | 2        | DEX suppression                   | DEX suppression | Blood, 2 time points around DEX injection | RIA            | 1 cortisol after DEXCRH at discharge predicts MDD relapse         | 3              |
| Zobel et al. [103] | N                  | a               | Germany2                                        | 40                                              | 10 R    | 30                                | 65                       | 2        | DEXCRH test                       | DEXCRH test | Blood, 9 time points                | RIA            | 1 cortisol predicts MDD, ACTH NS                                | 5              |
| Zobel et al. [104] | N                  | a               | Germany2                                        | 74                                              | 13 R    | 50                                | 59                       | 0.5      | DEXCRH test, cortisol and ACTH    | DEXCRH test, cortisol and ACTH                | Blood, 5 time points DEX/CRH test            | RIA            | 1 cortisol predicts MDD, ACTH NS                                | 5              |
| Asselm et al. [33] | N                  | ?               | Germany                                        | 1760                                            | 165 O   | 45                                | 50                       | 9        | DIA-XM-CIDI                       | Testosterone, Androstenedione, sex hormone-binding globuline | Blood serum 8AM-7PM Liquid chromatography-tandem mass spectrometry and RIA | NS            | 6 | Testosterone, Androstenedione, sex hormone-binding globuline | 6              |
| Hormones: HPG axis | Baseline MDD excl. | Y = yes, N = No | Baseline symptoms a = above cut-off, b = below cut-off, ? = unclear | Country and cohort information (or indicates similar cohorts) | Total N | Onset (O) or relapse/recurrence (R) of MDD N | Baseline age (mean or range) | % female | Follow-up time (years; mean or max) | MDD diagnostic interview; Diagnostic criteria | Biomarker of interest | Measure | Technical details | Direction result of biomarker predicting onset, relapse/recurrence of MDD | Quality score |
|---------------------|--------------------|----------------|-------------------------------------------------|-------------------------------------------------|---------|-----------------------------------|--------------------------|----------|-----------------------------------|---------------------------------------------|-----------------|---------|----------------|-------------------------------------------------------------------|--------------|
| Coplan et al. [47] | Y                  | ?               | USA1                                            | 34                                              | 13 O    | 15                                | 52                       | 9.6      | K-SADS & K-SADS-E & SADS-LA, RDC | Growth hormone (sleep)                        | Blood over 2 nights, 72 time points         | RIA            | 1 GH secretion                  | 8              |
| Franz et al. [52]  | N                  | a               | USA3                                            | 29                                              | 22 R    | 40                                | 10                      | 3        | SADS, RDC                         | Growth hormone (sleep)                       | Blood before onset of and during sleep, every 20 min | RIA            | 1 GH secretion                  | 5              |
| Jarrett et al. [86] | N                  | a               | USA3                                            | 29                                              | 22 R    | 40                                | 10                      | 3        | SADS, RDC                         | Growth hormone (sleep)                       | Blood before onset of and during sleep, every 20 min | NS            | NS                               | 6              |
| Owashi et al. [84] | N                  | b               | Japan                                           | 26                                              | 6 R     | 57                                | 76                       | 0.5      | Unclear, DSM-IV                   | Growth hormone, ACTH, cortisol                | Blood after DEX/CRH and GHRH test, 5 time points | RIA            | 1 GH after GHRH at time of discharge. Control and ACTH around DEX/CRH NS | 4              |
| Hormones: HPT axis | Baseline MDD excl. | Y = yes, N = No | Baseline symptoms a = above cut-off, b = below cut-off, ? = unclear | Country and cohort information (or indicates similar cohorts) | Total N | Onset (O) or relapse/recurrence (R) of MDD N | Baseline age (mean or range) | % female | Follow-up time (years; mean or max) | MDD diagnostic interview; Diagnostic criteria | Biomarker of interest | Measure | Technical details | Direction result of biomarker predicting onset, relapse/recurrence of MDD | Quality score |
|---------------------|--------------------|----------------|-------------------------------------------------|-------------------------------------------------|---------|-----------------------------------|--------------------------|----------|-----------------------------------|---------------------------------------------|-----------------|---------|----------------|-------------------------------------------------------------------|--------------|
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Table 1 (continued)

| Neuroimaging | Baseline MDD excl. | Y = yes, N = No | Baseline symptoms a = above cut-off, b = below cut-off, ? = unclear | Country and cohort information (or indicates similar cohorts) | Total N | Onset (O) or relapse/recurrence (R) of MDD N | Baseline age (mean or range) | Follow-up time (years; mean or max) | MDD diagnostic interview; Diagnostic criteria | Biomarker of interest | Technical details | Direction result of biomarker predicting onset, relapse/recurrence of MDD | Quality score |
|--------------|-------------------|----------------|-------------------------------------------------------------------|------------------------------------------------------------|---------|---------------------------------|----------------------|---------------------------------|---------------------------------|-------------------|----------------|---------------------------------------------------------------|-------------|
| Joffe et al. [67] | N | a | Canada 75 71 | R 38 66 10 | SADS-L; RDC | T4, T3, TSH | Unclear | Unclear | ↓T3 was significantly related to time to recurrence. | T4, TSH NS | 4 |

Studies are sorted by the inclusion of participants with onset (O), relapse and recurrence (R) of MDD or both (O + R). The second and third columns represent information on the certainty of including healthy individuals at baseline, where the second column shows if baseline MDD diagnosis was excluded with a clinical interview at baseline, and the third column represents whether symptoms were measured with questionnaires (e.g. Hamilton depression scale, beck depression inventory) and whether participants scored above or below the questionnaires cut-off for clinical symptoms at baseline. Basic information on the demographics of participants and study measures, technical details and outcome are also given. The quality score (range 0–9) represents the overall quality of the studies, where a score > 6 represents good quality, indicative of a low risk of bias and < 4 represents poor quality, a high risk of bias.

Specific abbreviations will be mentioned per subsection

General abbreviations: DIGS Diagnostic Interview for Genetic Studies, DSM diagnostic statistical manual of mental disorders, ICD International Statistical Classification of Diseases and Related Health Problems, MINI mini-international neuropsychiatric interview, nm not mentioned, NS nonsignificant, RDC research diagnostic criteria, SCAN schedules for clinical assessment in neuropsychiatry, SCID Structured Clinical Interview for DSM, K-SADS Kiddie Schedule for Affective Disorders and Schizophrenia.

Neuroimaging abbreviations: ACC anterior cingulate cortex, dmPFC dorsal medial prefrontal cortex, EEG electroencephalography, f functional, IFG inferior frontal gyrus, MFG middle frontal gyrus, mOFC medial orbitofrontal cortex, MRI magnetic resonance imaging, orbitofrontal cortex (OFC), PCG precentral gyrus, ROI region of interest, RSFC resting state functional connectivity, sg subgenual

Gastrointestinal abbreviations: GI gastrointestinal, L-5HTP L-5-Hydroxytryptophan

Immunology abbreviations: CAPA Child and Adolescent Psychiatric Assessment, CRP c-reactive protein, ELISA enzyme-linked immunosorbent assay, HR hazard ratio, IL interleukin, SRIF somatostatin, TNF tumor necrosis factor, YAPA Young Adult Psychiatric Assessment, IA immunoassay

Neurotransmitters abbreviations: RIA radioimmunoassay

Neurotrophic and oxidative stress abbreviations: ELISA enzyme-linked immunosorbent assay, BDNF brain-derived neurotrophic factor

HPA abbreviations: ACTH adrenocorticotropic hormone, AUC area under the curve, CAR Cortisol awakening response, CRH Corticotropin-releasing hormone, DEX/CRH combined dexamethasone-cortisol releasing hormone test, DST dexamethasone suppression test, DHE dehydroepiandosterone, ELISA enzyme-linked immunosorbent assay, HRSD Hamilton Rating Scale for Depression, IA immunoassay, LIA line immunoassay, MADRS Montgomery-Asberg Depression Rating Scale, NUFC nocturnal urinary free cortisol, RIA radioimmunoassay, TSST trier social stress test.

HPG abbreviations: DIA-X/M-CIDI Munich-Composite International Diagnostic Interview, RIA radioimmunoassay

HPS: GH growth hormone, GHRH growth hormone releasing hormone, RIA radioimmunoassay

HPT abbreviations: T3 triiodothyronine, T4 thyroxine, TSH thyroid stimulating hormone

*Not enough studies to meta-analyze

*Not enough data reported in this study to include in meta-analysis

*Included in meta-analysis
(N = 3, OR = 1.025, 95% CI [0.782 1.345], p = 0.856) was found. Due to the small number of studies, no further analyses were conducted.

Incidental findings were also identified. One study investigated hazard ratio and showed that CRP significantly predicted earlier time to onset or relapse/recurrence of depression [87]. In three studies (of which two investigated the same sample) TNFα was not found to predict non-significant were also reported [43, 55, 94]. A protein marker for inflammation SuPAR was found to predict reduced time to MDD [61]. In addition, three-nitrotyrosine and HSP70 were higher at baseline in participants that develop vs that do not develop MDD [88].

**Gastrointestinal biomarkers**

Out of the 760 articles screened for the gut-related biomarkers, only one study met our inclusion criteria [40]. The study showed that children reporting symptoms of abdominal discomfort (e.g. nausea or vomiting) in response to tryptophan (L-5HTP) infusion have a higher risk of developing MDD than children who do not report these symptoms.

**Hormones**

Out of the 17,114 articles screened, 38 articles were included and 1 study was identified with the update. The studies investigated the following hormonal axes: 35 hypothalamic-pituitary axis (HPA axis; the feedback loop regulation stress responses, including ACTH, CRH, CRF, cortisol), 5 hypothalamic-pituitary-gonadal-axis (HPG-axis: regulating the reproductive system e.g. DHEAS), 4 hypothalamic-pituitary-somatic axis (HPS axis: mainly regulating growth and includes growth hormone (GH)), and 3 hypothalamic-pituitary-thymus-axis (HPT axis; mainly regulating metabolism e.g. thyroid hormone). Results will be described below by these biological/hormonal axes.

**HPA axis**

The predictive value of cortisol on subsequent MDD was investigated in 35 prospective studies (total N = 7823, median N = 74, MDD development N = 1236, median N = 26, range for age (12–56), % female (44–100), follow-up time (1–22), QA score (3–9)). Cortisol was primarily measured in saliva, but differed in time of day of measurement (morning, evening, diurnal, nocturnal, reactivity), and both single time point and multiple time point measurements were included. Cortisol was a significant predictor of subsequent MDD with a small effect size (N = 19, OR = 1.294, 95% CI [1.035 1.616], p = 0.024 [30, 32, 37, 41, 42, 45, 48, 58, 60, 63, 65, 78, 80, 84, 90, 92, 96, 102, 104], see Fig. 2) overall comparible studies on unique samples. Heterogeneity was large and significant (76%, p < 0.001). The effect became nonsignificant when outliers were removed (OR = 1.228; p = 0.052) or low quality studies were removed (QA < 4; OR = 1.206, p = 0.094). Inspection of the funnel plot showed indication of publication bias (7 studies were missing on the left side), though the Eggers test was not significant p > 0.05. Correction for publication bias led to a nonsignificant effect. Further, the quality score of the studies moderated the effect (β = −0.176, p = 0.012) indicating a lower study quality is related to an increased effect size.

**Table**

| Study name | Odds ratio | Lower limit | Upper limit | p-Value |
|------------|------------|-------------|-------------|---------|
| Adam et al. (2010) | 1.055 | 0.392 | 2.837 | 0.915 |
| Appelhoffer et al. (2005) | 1.970 | 0.669 | 5.800 | 0.218 |
| Bockting et al. (2012) | 0.665 | 0.206 | 2.146 | 0.495 |
| Carnegie et al. (2014) | 1.009 | 0.697 | 1.460 | 0.964 |
| Charles (1989)* | 56.333 | 1.918 | 1654.915 | 0.019 |
| Colich et al. (2015) | 1.332 | 0.634 | 2.799 | 0.450 |
| Cosgriff et al. (1990)* | 32.765 | 2.630 | 408.207 | 0.007 |
| Goodyer et al. (2009) | 2.249 | 1.162 | 4.353 | 0.016 |
| Grynderup et al. (2013) | 0.721 | 0.496 | 1.048 | 0.087 |
| Harris et al. (2000) | 1.978 | 0.910 | 4.301 | 0.085 |
| Herbert et al. (2012) | 1.120 | 1.024 | 1.226 | 0.013 |
| Mander et al. (1989) | 2.225 | 0.834 | 5.935 | 0.110 |
| Moris et al. (2012) | 0.497 | 0.102 | 2.332 | 0.368 |
| Owashi et al. (2008) | 0.915 | 0.175 | 4.787 | 0.916 |
| Pintor et al. (2013) | 8.164 | 2.496 | 26.706 | 0.001 |
| Rao et al. (2009b) | 1.200 | 0.147 | 1.376 | 0.009 |
| Tsuru et al. (2013) | 2.393 | 0.531 | 10.688 | 0.257 |
| Zimmerman 1987 | 0.297 | 0.135 | 0.652 | 0.002 |
| Zobel et al. 2001 | 2.768 | 1.369 | 5.596 | 0.005 |
| Overall effect | 1.294 | 1.035 | 1.616 | 0.024 |

*Outliers: after removal the effect became non-significant

**Fig. 2** Forest plot of a meta-analysis on studies investigating measures of cortisol before MDD onset, relapse or recurrence. Charles et al. [42] and Cosgriff et al. [48] are identified as outliers, and excluding them from analysis resulted in a nonsignificant effect.
Comparing studies including participants with baseline MDD/mixed group versus no baseline MDD showed a significant higher effect size in the first group ($p = 0.027$), confirming the significance of including baseline clinical MDD diagnosis in studies (disease state effect). The pooled odds ratio for studies including baseline diagnosis was medium and significant ($N = 13$, OR $= 1.919$, 95% CI [1.072 1.231], $p = 0.012$), while studies excluding baseline diagnosis had a small nonsignificant pooled odds ratio ($N = 6$, OR $= 1.082$, 95% CI [0.938 1.249], $p = 0.280$). Comparing studies investigating onset, relapse or recurrence, or a mixed groups not significant ($p = 0.107$).

Studies investigating time until MDD onset, relapse or recurrence using Hazard ratios showed no significant predictive effect of cortisol (HR $= 1.011$, 95% CI [0.963 1.040], $p = 0.447$ [32, 38, 62, 79, 98]). Due to the small number of studies, no further analyses were conducted.

Besides cortisol, other HPA-axis markers in relation to relapse or recurrence of MDD were investigated incidentally. Nonsignificant findings were reported for adrenocorticotropic hormone (ACTH) [32, 84, 89, 96, 104], and cortisol releasing hormone (CRH; [35]). One study reported lower ACTH in reaction to a DEX/CHR predicts relapse [90]. Thus, it remains unclear if HPA-axis biomarkers predict MDD development or whether results reflect disease state or quality of studies.

**HPG axis**

HPG biomarkers were investigated in five studies (total $N = 2468$, median $N = 187$, MDD development $N = 408$, median $N = 31$, range for age [14–45], % female [50–100], follow-up time [1–10], QA score (6–7)). Four studies investigated dehydroepiandrosterone (DHEA) or DHEA-sulfate, (DHEAS) in saliva [56, 63, 79], but studies included the same sample and included OR and HR measures, which are not comparable. Both significant predictive effects [56, 57] as well as no significant predictive effects [63] were reported. One study showed that a higher cortisol: DHEAS ratio predicted a shorter time to recurrence [79]. One study investigated serum concentrations of testosterone, androstenedione, and sex hormone-binding globuline (SHBG) and found no predictive effect on first onset nor the combination of onset/recurrence over 17 years [33]. Thus, it remains unclear if androstenediones predict MDD development.

**HPS axis**

Four studies [47, 52, 66, 84] investigated the predictive effect of GH on subsequent MDD (total $N = 118$, median $N = 29$, MDD development $n = 23$, median $N = 22$, range for age [15–57], % female [52–100], follow-up time (0.5–9.6), QA score (4–8)), of which 2 investigated the same sample and one study that did not provide sufficient data for analysis [47]. Three studies investigated GH secretion over night and a steeper increase in GH secretion was found in participants that had later onset [47] and recurrence [52] of MDD, but another study (on the same sample) found no significant predictive value for recurrence [66], and lower GH is also reported in individuals that relapse [84]. No differences were found in somatostatin (GH releasing factor) in CSF between relapsing and not relapsing participants [35]. Thus, it remains unclear if HPS markers predict MDD development.

**HPT axis**

Three studies reported results investigating the HPT axis (total $N = 113$, median $N = 25$, MDD development $n = 84$, median $N = 9$, range for age [38–51], % female [54–66], follow-up time [0.25–10], QA score (4–5); [48, 67, 96]. Higher thyroid stimulating hormone (TSH) was related to recurrence in one study [96], but was also found to not differ between people with and without relapse in another study [48]. One study investigated T4, T3, and TSH using cox regression survival analyses, and reported that lower T3 was related to shorter time until relapse/recurrence [67]. Thus, the relation with HPT axis and subsequent MDD remains unclear and study quality was low.

**Oxidative stress**

Out of the 1336 articles screened, 1 article met inclusion criteria [88]. Pasquali et al. [88] investigated markers for oxidative stress in blood (see Table 1). Lipid peroxidation was higher in participant that develop MDD ($N = 37$) compared to participants who did not develop MDD ($N = 111$). No significant differences between these groups were found for protein carbon and thiol content. Thus, whether oxidative stress predicts subsequent MDD remains unclear.

**Discussion**

A systematic search for prospective studies investigating biomarkers of MDD onset, relapse, and recurrence was performed. Of the 67,464 articles screened, only 75 prospective studies were identified that studied biomarkers before MDD onset or relapse/recurrence. Of those, only 38 studies reported results on participants that were healthy (had no MDD diagnosis) at baseline and are thus unconfounded by disease state. Prospective evidence for the majority of biomarkers predicting onset, and relapse/recurrence of MDD was scarce ($N = 75$) and spread over a wide range of topics: Neuroimaging ($N = 24$), Gastrointestinal
factors \((N = 1)\), Immunology \((N = 8)\), Neurotrophic \((N = 2)\), Neurotransmitters \((N = 1)\), Hormones \((N = 39)\), and Oxidative stress \((N = 1)\). Marked heterogeneity across studies was observed for neuroimaging studies \((N = 24)\). These included assessments based on EEG, task-based functional MRI, and structural MRI that focused on different brain regions, thereby precluding the calculation of an overall effect [105]. This highlights the urgent need for standardized methods in order to be able to compare data from different samples. The only significant biomarkers that increased odds for MDD onset, and relapse/recurrence was cortisol. However, the inclusion of baseline clinical diagnosis was shown to influence this effect. Therefore, the effect of disease state cannot be ruled out. Meta-analyses on CRP, TNF\(\alpha\), IL2&6, GH, hippocampus, amygdala, and frontal brain areas volume were not significant, potentially due to the limited amount of studies included in these analyses [range 3–4]. Only incidental (<3) studies investigated TSH, DHEAS, amygdala volumes, neurotrophic factors, oxidative stress, ACTH, neurotransmitters and gastrointestinal biomarkers. In addition, results on biomarkers were inconsistent.

Our meta-analysis showed increased cortisol had a small predictive effect on onset or relapse and recurrence of MDD, which is in line with literature showing increased cortisol levels in MDD cross-sectionally [106, 107]. Yet, this effect disappeared when studies including baseline clinical diagnoses were excluded. Since increased cortisol is also a marker of stress [108], increased cortisol may be an indirect marker of previous stressful life events or stress induced by being ill. This underlines the importance of future research following healthy samples without subclinical depression longitudinally until a MDD diagnosis is established. Further, cortisol results were influenced by publication bias and study quality and the effect disappeared when outliers were removed or poor quality studies were removed. This underlines the need for high-quality prospective research on biomarkers for MDD.

Some limitations of the studies included and of the meta-analyses are noted. On a study level, poor quality studies were identified and small samples that develop MDD at follow-up were investigated. Neuroimaging studies use smaller samples than immunology and hormones studies. This limits the interpretation and generalization of findings for sample size topics. Further, we did not correct for multiple testing by applying \(p = 0.05\) as threshold for significance. A correction would result in disappearance of the cortisol effect, indicating this may be a false positive. Based on our narrative synthesis heterogeneity of studies was visible and studies reporting no significant results were prominent, yet tend to not report sufficient data for inclusion in meta-analysis, resulting in a bias in the meta-analyses on significant effects. These limitations may have resulted in inflated odds ratios in our meta-analysis, and results should thus be interpreted with caution.

Overall, the findings of the current systematic review highlight the lack of prospective evidence for biomarkers as predictors of onset of MDD and relapse/recurrence. Our systematic search uncovers the causality gap that is present in biomarker research. It is striking not to find strong prospective evidence for any of the postulated biological theories. Thus, most of the leading hypotheses are based on results from cross-sectional research, treatment studies, symptomatology studies, or animal studies (e.g. [8, 12, 16, 18, 20]), which cannot determine causality [21]. Whether the observed changes in putative biomarker systems in MDD is a potential cause or consequence of depression thus remains unclear.

Our results, of course, do not indicate that there are no causal biomarkers, but highlight the dearth of prospective evidence that biomarkers explain onset, and relapse/recurrence of MDD. In addition, prospective evidence would suggest causality, yet it is only the minimum requirement for detecting causal relations. Manipulation studies should also be performed in order to demonstrate that alteration of one variable (biomarker) leads to the expected outcome (MDD). Indeed, experimental challenges including depletion studies, such as tryptophan depletion are available and have been shown to predict depressive relapse in certain circumstances [109]. Yet, a limitation of these studies is the temporary nature of the measured outcome (e.g., brief symptom reduction) and that common higher order biological (e.g. neuromodulatory) changes may also account for the differences in depletion responses [31, 109]. Combining different techniques from different biological levels may disentangle which factors are most directly causally linked to depression etiology. Future studies applying transcranial magnetic stimulation or other brain stimulation approaches to simulate symptoms/relapse may provide more insights into causal neuroimaging biomarkers [110]. It must be noted that we did not search for relatively newly identified biomarkers, such as fatty acids [111], which are not yet part of an established etiological theory. Thus, future research is necessary to investigate if novel biomarkers can predict MDD and replicate the current incidental findings.

Notwithstanding the overall lack of prospective evidence for leading biological models for onset, relapse and recurrence of MDD, future research may be directed to focus on potential predictive biomarkers identified in a small number of studies or showing inconsistent results. These were insula volume [36], thickness [51], and activity [99, 100] frontal brain activity [31, 39, 50, 76, 82], gastrointestinal sensitivity [40], norepinephrine [68], immunology markers [61, 87], androsterones [33], and oxidative stress markers [88]. Prospective research on these biomarkers investigating development of MDD from healthy samples is needed to
replicate these incidental finding and further investigate if predictive effects exist irrespectively of disease state. Indeed, there are indications that biomarkers may be causally involved, for example based on genetics research. Recent large consortium results (e.g. depression PGC [112]) have been successful in identifying genetic loci associated with depression. More importantly, depression is not a single gene disease but rather seems to be related to multiple genes in interaction with environmental factors, which lead to a spectrum of aversive outcomes, ranging from depressive symptoms to full-blown MDD [112]. The genetic loci identified explain only limited variance of depression (e.g. 2% genetic risk score [112] and mendelian randomization studies <1% [113]), whereas the heritability of MDD has been estimated at ~40% [114]. This suggests that MDD may be a more heterogeneous disorder both in etiology and pathophysiology. To unravel the biological mechanisms of MDD we therefore suggest to investigate interactions between biomarkers instead of investigating biomarkers separately for example in pathway or network approach.

In order to falsify biological theories for MDD better comparisons between or integration of studies is necessary. Open science initiatives could play a role in these efforts by enabling researchers to combine datasets over multiple cohorts ( Consortia studies). However, it is noteworthy that there are large cohort samples available that allow prospective analysis on the clinical diagnosis MDD, yet clinical symptoms are more frequently investigated. In addition, baseline measurements where participants are healthy (before the development of MDD onset or relapse/recurrence) are frequently lacking in cohort studies. Further, investigating differential effects of onset versus relapse/recurrence is not common practice in biology research, whilst different mechanisms may underlie MDD onset versus maintenance. Future studies should separate samples with first onset from samples with previous episodes in order to investigate the differential mechanisms. Finally, given most theories on depression etiology include biological, psychological and social factors [115, 116], it is noteworthy that few studies have investigated combinations of these factors in a single study. Viewing depression from a more holistic perspective may help capture important interactions and improve prediction models.

**Conclusion**

This systematic search for prospective evidence for biomarkers of MDD revealed scarce prospective evidence for leading biological models. Prospective evidence for etiological involvement of gastrointestinal factors, neuroimaging, neurotrophic factors, neurotransmitters, hormones (other than cortisol), immunology and oxidative stress in MDD is lacking. Cortisol was found to be a predictor for onset/relapse/recurrence of MDD, but this effect was confounded by baseline clinical depression and quality of studies. Therefore, there is a need for high quality, prospective studies on the relative contribution of biomarkers (in combination with psychosocial factors) in order to disentangle the etiology of MDD and to better understand its clinical course.

**Acknowledgements** We would like to thank M. Brouwer, Z. Fu, A. Cramer, J. H. Orlmel, P. Spinoven, G. Siegle, S. D. Hollon, E. Holmes, C. Harmer, and M. van Hout for their input on the search process. In addition, we would like to thank the Clinical Psychology (Research) Master students from Utrecht University that worked on the project for their help with screening and data extraction on different biomarkers: I. Baltrusaityte, A. Mastora, A. Mroz, M. Barmounis, J. Janssen, and B. Markovitch.

**Funding** Funding was partly received from the Netherlands Institute for Advanced Study in the Humanities and Social Sciences (NIAS), entitled “My Optimism Wears Heavy Boots: So much research, so few implications, towards ‘patient-proof’ empirical models and more effective interventions in mental health” (awarded to CB February–June 2017). This meta-analysis has been pre registered (PROSPERO 2017 CRD42017072990) and preliminary results were presented at the European congress of Psychology (2017 Amsterdam) and Society of Biological Psychiatry annual meeting (2018 New York). All authors have approved the content of the present form of the paper.

**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

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