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Biological markers evaluated in randomized trials of psychological treatments for depression: a systematic review and meta-analysis

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ABSTRACT

Though it is widely believed that psychotherapy changes biology, this contention is largely based on observational data, subject to confounding. We report the first systematic review and meta-analysis of biological variables assessed, as outcomes or predictors of response, in randomized controlled trials of psychotherapy for adult depression. Fifty-one trials (5123 participants) and a pooled analysis were included. Biological markers were outcomes in 43 studies and predictors of treatment response in 9. At post-treatment, psychotherapy could not be distinguished from control conditions for glycaemic control (Hb1AC), 7 trials, Hedges' $g = -.01$, 95% CI -0.30 to 0.29, $I^2 = 65\%$ and cortisol concentration after-wake, 5 trials, Hedges' $g = -.19$, 95% CI -0.45 to 0.06, $I^2 = 0\%$. Follow-up results were similar. For the other biological domains (immunological, neurobiological, inflammatory, weight, blood pressure), overall findings were mixed and often inconsistent. Few trials investigated prediction of response, with only neuroimaging markers showing promise. Across domains, we found limited evidence that benefits of psychological treatments for depression translate to biological outcomes.

1. Introduction

Psychological interventions are effective treatments for depression, on both short and long-term (Cuijpers et al., 2016; Karyotaki et al., 2016). Their effects are usually gauged with self-report or clinician-rated scales, assessing symptoms or other subjective outcomes (e.g., quality of life). Though subjective experience is central to understanding mental disorders, these measures might be unreliable or overly correlated (Cristea et al., 2015; Moore et al., 2014). Biological variables could potentially represent more objective alternatives, with some, such as brain activity, already employed in studying pharmacotherapy (Crettol et al., 2014; Frieing and Tadic, 2013).

Understanding how psychological interventions impact or are impacted by biological variables has distinct implications. Many patients with somatic disorders experience comorbid depression. For instance, effective psychological interventions were conjectured to not only change mood, but also normalize the functioning of autonomic nervous system, with a therapeutic effect in ischemic coronary disease (Howells et al., 2014; Nolan et al., 2008). High comorbidity is also present in other somatic conditions including cancer, diabetes, immune system

and neurological disorders, though the mechanisms linking somatic and psychological disorders are seldom straightforward (Fiest et al., 2016; Uchendu and Blake, 2016). Conversely, biological markers might predict response to treatment in general (predictors) or permit distinguishing between treatments (moderators) (Papakostas and Fava, 2008).

Despite widespread claims that psychological interventions distinctly impact biological outcomes (Boccia et al., 2016), most of the available empirical evidence is observational and limited by confounding. Biological variables are usually not studied in randomized controlled trials (RCT), but in case-control designs, comparing depressed patients pre- and post-treatment, or with a healthy control group (e.g., Fu et al. (2008)), often in small samples. Within these designs, specific biological changes induced by psychotherapy cannot be disentangled from non-specific placebo effects, regression to the mean, or spontaneous recovery.

We conducted a systematic review of all randomized trials examining psychological treatments for depression that included an assessment of a biological variable, as either predictor (including moderator) or outcome.

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2. Methods

This systematic review and meta-analysis is reported using the PRISMA statement (Moher et al., 2009). The search process, data extraction and risk of bias ratings followed the procedures delineated in the Cochrane Handbook (Higgins and Green, 2011).

2.1. Identification and selection of studies

Studies were identified from a complete database of trials of psychological treatment for depression. For this database (Cuijpers et al., Under review), PubMed, PsycINFO, Embase and the Cochrane Central Register of Controlled Trials were systematically searched from inception until January 1st 2018. Search strings combined dictionary (e.g., MeSH) and free terms indicative of psychological treatment and depression (see Appendix 1 for the complete search string for PubMed). Earlier meta-analyses of psychological treatments for depression were also checked.

In total, 15,598 abstracts were examined by two researchers (PC and EK), independently from each other. After abstract screening, 2323 papers were retrieved for full-text selection. These were also consulted independently by the two reviewers (PC and EK). Any disagreements on inclusion between the reviewers were solved through discussion. The final database includes 619 reports, and a range of excluded full-texts with reasons for exclusion (and Appendix Fig. 1 for the PRISMA diagram of this process).

For the present study, we used the database of depression trials as a starting point. We were mindful that biological measures are often reported in secondary reports (i.e., other reports using the same data as the primary paper, but which usually present secondary outcomes or ancillary analyses). Therefore, we used the complete database to screen the full-texts of included reports (619), along with those excluded for being secondary reports (521), not having enough data for effect size (ES) calculation (58) or other reasons (154). The screening took place between June and August 2018. We also checked existing systematic reviews on the biological effects of psychotherapy (Boccia et al., 2016; Brooks and Stein, 2015; Fonseka et al., 2018; Franklin et al., 2016; Messina et al., 2013).

The protocol for the full database of depression trials used to select the studies assessing biological variables has been submitted for publication (Cuijpers et al., Under review). As our study relied on identifying papers from the already developed database, there was not separate protocol registration.

2.2. Inclusion and exclusion criteria

Included studies were: a) RCTs for b) adults with c) depression symptoms or a depressive disorder, assessed using a diagnostic interview or a validated symptom scale, comparing d) a psychological intervention, alone or in combination with another intervention (e.g., psychological, pharmacological, exercise, educational, lifestyle) to e) a control (e.g., waitlist/WL, treatment as usual/TAU, attention control/AC), or another active intervention (e.g., pharmacotherapy), and f) including the assessment of a biological variable, either as an outcome or as a predictor of treatment response. Depression could be either the primary complaint or comorbid to a somatic disorder. We excluded treatment arms consisting exclusively of exercise (e.g., massage) due to the uncertainty of considering them control or active comparisons. Combination trials were included provided both groups received an identical add-on intervention.

Biological measures were eligible if obtained a) by an instrumental technique or procedure (e.g., glucose metabolism as assessed by Positron Emission Tomography/PET), or b) with a reproducible and standard methodology (e.g., blood sample analyzed with a standardized procedure), or c) referring to a well-established molecular, metabolic or physiological domain (e.g., ECG as a measure of cardiac activity).

Two researchers (IC and CG) working independently screened all full-texts and selected papers with biological measures. Ambiguous cases were discussed with a third author (EK).

2.3. Data extraction

For each study, we extracted characteristics of the participants (i.e., primary depression, comorbid somatic disorders, others); interventions (e.g., psychotherapy, pharmacotherapy, other); control (e.g., WL, TAU, AC); treatment (duration (weeks); exposure (number of sessions)); clinical (e.g., depression severity) and biological outcomes, whether they were primary and their assessment method. Biological variables were classified as outcomes or predictors/moderators. For outcomes, we noted the nature (i.e., pre-to-post change, between group differences) and direction (i.e., no changes, improvement or worsening) of changes. For predictor/moderators, we also noted the statistical approach used.

2.4. Risk of bias (rob) assessment

We used the five domains of the ‘Risk of bias’ assessment tool, developed by the Cochrane Collaboration (Higgins et al., 2011): (i) adequate sequence generation; (ii) concealment of allocation; (iii) blinding of outcome assessors; (iv) dealing with incomplete data; (v) selective reporting. We rated blinding separately for depression symptoms and biological outcomes. Blinding of assessors was described as self-report, if only such instruments were used, and retrospective, if already existent information was extracted from patient charts. Incomplete outcome data were assessed as low RoB when intention-to-treat (ITT) analyses, including all randomized participants, were conducted for the primary outcome (regardless of whether it was biological). Trials not mentioning dropouts at all were rated as high RoB. For selective outcome reporting, we extracted trial registration numbers and checked (1) if registration was prospective (i.e., predating participant enrollment) and (2) if substantial changes had been made to the primary outcome registered, or if there were discrepancies between the registration and the report. Retrospectively registered trials were rated as unclear, unless there was evidence of the issues described at (2), in which case they were rated high risk.

Two researchers (CG, IC) independently extracted study data and rated RoB. The primary papers and any referenced protocols were also consulted. Disagreements were resolved through discussion. We also computed Krippendorff’s alpha (Zapf et al., 2016) for inter-rater agreement for each RoB domain, prior to resolving disagreements.

2.5. Data synthesis and meta-analysis

We report results separately for biological variables, grouped by type, as outcomes and predictors/moderators of treatment response. As we expected many trials to report on multiple distinct indicators, we also tabulated (1) how many biological parameters had been analyzed and (2) how many of these showed significant differences. For (2), we distinguished between comparisons with a control condition (AC, WL, TAU) versus another active treatment (e.g., pharmacotherapy). If a study reported on multiple biological markers from the same category, only one was chosen to avoid ES dependency (Scammacca et al., 2014). In each case, we chose the marker most frequently used across studies. In the case more follow-up timepoints were available for the same measure, we chose the one most similar to the other included studies. ITT data were preferred where available.

For biological variables consistently evaluated across more trials, we computed and pooled effect sizes, using STATA (v15.1), packages *metan* (Harris et al., 2010), *metaeff* (Kontopantelis and Reeves, 2009) and *heterogi* (Orsini et al., 2006). We computed the standardized mean difference (SMD), corrected for small sample bias, Hedges’ g, between the psychological intervention and control at post-intervention and

Fig. 1. PRISMA flow diagram of the study selection process for the trials included in the present systematic review and meta-analysis.

follow-up. If means and standard deviations were not available, we calculated the SMD from other statistics available in the report, such as *t*-values or exact *p*-values.

Heterogeneity was assessed with the I^2 statistic (Higgins et al., 2003) and its confidence intervals (Ioannidis et al., 2007), with values of 25%, 50% and respectively 75% indicating low, moderate and high heterogeneity. Effects were pooled with a random effects model using the inverse-variance DerSimonian and Laird method (DerSimonian and Laird, 1986).

3. Results

3.1. Selection of studies

As shown in the PRISMA flowchart (Fig. 1), we screened 1353 full-text reports and selected 52, describing 51 distinct trials. An additional report (Harley et al., 2010b) describing a pooled analysis of two trials was included separately, owing to the scarcity of studies on treatment response predictors. The list of included studies is displayed in the Appendix 2.

3.2. Study characteristics (Appendix Table 1)

The 51 RCTs reported data on 2821 participants in the psychological intervention and 2302 in the control or other active comparison arms. The average number of randomized participants per trial was 100, but there was large variability, with 17 trials with over 100 and 16 with under 50 randomized participants.

Most participants were diagnosed with major depressive (MDD) or other depressive mood disorders (34 RCTs), or had depressive symptoms (17). Thirty-five trials were conducted on special populations, mostly somatic diseases: diabetes (13), HIV (5), cardiovascular disorders/risk (4), autoimmune diseases (2) or others (hypertension, stroke, metastatic cancer, age-related macular degeneration). Three trials involved pregnant women, and two, overweight women. Most psychological interventions could be classified as cognitive behavioral therapy/CBT (32), followed by interpersonal therapy/IPT (6), behavioral activation/BA (5), mindfulness (4) and mind-body psychotherapies (4). In 37 trials, a psychological intervention was contrasted to control conditions (WL, TAU, AC) or employed as an add-on to another intervention delivered identically in both groups. In 19

Fig. 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

trials, a psychological intervention was compared to another active psychological or pharmacological intervention. The ancillary pooled analysis (Harley et al., 2010a) combined an RCT of 117 MDD patients receiving psychotherapy (CBT versus IPT) (Luty et al., 2007) with another of 195 participants with depressive disorders receiving antidepressant medication (nortryptiline vs fluoxetine) (Joyce et al., 2002). Additional study characteristics are presented in Appendix Table 1.

3.3. Risk of bias (Fig. 2)

Krippendorff's alpha inter-rater reliability coefficients (and standard errors/SEs) were 0.96 (SE = .04) for sequence generation, 0.94 (SE = .04) for concealment of allocation, 0.97 (SE = .03) for blinding of outcome assessors for psychological outcomes, 0.87 (SE = .06) for blinding of outcome assessors for biological outcomes, 0.96 (SE = .04) for dealing with incomplete data, and 0.77 (SE = .09) for selective outcome reporting. Overall, with the exception of selective outcome reporting, inter-rater reliability was very good or excellent even prior to resolving disagreements. Ratings for each trial are provided in Appendix Table 2. Thirty-three trials reported adequate sequence generation and 25 properly concealed treatment allocation. Twenty-five properly blinded outcome assessors for psychological outcomes, and 21 used self-report measures. Seventeen trials blinded assessment of biological outcomes, and five used retrospective information. Twenty-seven trials employed proper ITT methods, and 25 were rated as high risk for incomplete outcome data. Twenty-six trials were matched with public registries, but one described a different trial from the report (Ahmadpanah et al., 2016). Only 10 trials were prospectively registered, and four of them were rated as low risk of selective reporting. Ten trials were rated as high risk due to *a posteriori* defining or modifying the primary outcome assessment or its time frame, or upgrading a secondary outcome to primary.

3.4. Main findings- outcomes (Table 1)

Biological variables were employed as efficacy outcomes in 42 trials and as safety in one. They were listed as primary outcomes in 10 trials. Seventeen trials assessed five or more distinct biological indexes, and seven more than 10.

In the 35 trials including a control arm, four did not report results and 21 did not find any additional intervention benefits on the biological outcomes at post-test. In two trials, the control group had superior results (Field et al., 2013; Lesperance et al., 2007). Eight trials found differences favoring the intervention group, but in most (5), these were restricted to a small fraction of the biological variables assessed, with rates of significant findings to total tested ranging from 0.05 to 0.33.

Twenty trials reported follow-up results, 8 of which did not find differences between groups (one did not report them).

From the 13 trials with an active comparator arm, one did not report statistical analysis and five found no changes within the psychological intervention group or between it and a comparator, at post-test or follow-up. The remaining seven trials evidenced some such differences for a small proportion of the biological variables analyzed. In studies with neurobiological outcomes, it was impossible to gauge the total number of tests performed (Hirvonen et al., 2011; Martin et al., 2001).

Glycaemic control was the most common biological outcome, assessed with the hemoglobin A1c test (HbA1c) in 13 trials (Ebert et al., 2017; Gois et al., 2014; Huang et al., 2016; Lamers et al., 2011; Lustman et al., 1998; Newby et al., 2017; Penckofer et al., 2012; Petrak et al., 2015; Pibernik-Okanovic et al., 2009, 2015; Safren et al., 2014; Tovote et al., 2014; van Bastelaar et al., 2011), all on diabetic patients. It was labeled primary in 4 trials (Huang et al., 2016; Newby et al., 2017; Petrak et al., 2015; Pibernik-Okanovic et al., 2009). Two studies additionally measured fasting glucose. Trial findings are narratively synthesized in Appendix 3. The pooled ES for HbA1C from studies with sufficient data was non-significant at post-test (7 trials), Hedges' $g = -.01$, 95% CI -0.30 to 0.29, $I^2 = 65\%$ (95% CI 21% to 84%) (Fig. 3a) and follow-up (7 trials): Hedges' $g = -.08$, 95% CI -0.42 to 0.25, $I^2 = 74\%$ (95% CI 43% to 88%) (Appendix Fig. 2a).

Considering all trials pooled for post-test and follow-up, six of them had low RoB for three or more of the domains rated: sequence generation, allocation concealment and dealing with incomplete outcome data (Appendix Table 2). For two trials, the biological outcome was assessed blindly. We rated two studies as free of selective outcome reporting. Two trials had high risk of bias for incomplete outcome data and three for selective outcome reporting.

For active comparators, one trial (Tovote et al., 2014) contrasted CBT and mindfulness CBT and found no significant HbA1c change over time in either group. Similarly, two trials compared IPT (Gois et al., 2014) and respectively CBT (Petrak et al., 2015) with antidepressant medication (sertraline) and reported no significant within- or between-groups differences at follow-up.

Immunological markers were outcomes in nine trials (Doering et al., 2007; Euteneuer et al., 2017; Markowitz et al., 1998; Mohr et al., 2001b; Safren et al., 2016, 2009; Safren et al., 2012; Savard et al., 2006; Simoni et al., 2013) (primary in 1), five of which recruited HIV patients (Markowitz et al., 1998; Safren et al., 2016, 2009; Safren et al., 2012; Simoni et al., 2013). Other special populations were multiple sclerosis (Mohr et al., 2001a), metastatic breast cancer (Savard et al., 2006) and coronary artery bypass (Doering et al., 2007). The heterogeneity of markers used precluded us from pooling effects. Four HIV trials

Table 1
Summary of findings for depression trials with biological variables as outcomes.

Study	Comp (ctrl) ^{a)}	Comp (active) ^{a)}	Biological variables ^{b)}	Time-point ^{c)}	Main findings (biological) ^{c)}	Type of total & sign comp (biological) ^{d)}
Ahmadpanah et al., 2016	Psy vs AC	Psy1 vs Psy2	BP-S; BP-D	8, 16 wks	BP decreased at post & FU in both MDM & SMT vs AC	Post/FU (Psy vs AC): Bw gr diff 2/2 var
Barr Taylor et al., 2009	Psy vs WL		Cortisol conc & slope (saliva), RSA, HR, BP-S, BP-D, BMI, CRP, TG, HDL-C, LDL-C, TC	6 mths	HR, TG & TG/HDL-C reduced at post in CBT vs WL	Post/FU (Psy1 vs Psy 2): Within gr diff in both 2/2 var; No bw gr diff
Beevers et al., 2015	Psy vs AC		Brain activity (Resting state fMRI)	4 wks	dACC-rMFG connectivity increased at post in CBM vs AC	Post: Bw gr diff 3/18 var (none primary)
Beutler et al., 1987	Psy + ADM vs ADM		Sleep efficiency (polysomnography)	17–19 wks	Sign time*CBT. Pre-post improvement across CBT gr	Post: Bw gr diff in 2/21 resting state nodes connections
Chan et al., 2011		Psy1 vs Psy2	EEG analysis (alpha power prefrontal asymmetry)	1 mth	Pre-post prefrontal asymmetry increased within DMBI, not CBT gr	Post: Within gr diff in psy gr 1/1 var
Doering et al., 2007	Psy + TAU vs TAU		Immunological (NKCC, IL-6), CRP	3 mths	No sign diff at post	Post: Post: Within gr diff in psy1 2/2 var; Bw gr diff NR
Ebert et al., 2017	Psy vs AC + TAU		HbA1c	6 mths	No sign diff at FU	Post: No bw gr diff for 3 var
Euteneuer et al., 2017	Psy vs WL	Psy1 vs Psy2	Immunological (IL-6, IL-10, IL-6/IL-10, LPS-stimulated IL-6 prod, leukocytes, lymphocytes, neutrophils, monocytes; T, T helper, cytotoxic T, regulatory T, B & NK cells), CRP	16 wks	IL-10 increased in CBT-E vs CBT & WL at post	Post: NR
Field et al., 2004	Psy vs TAU		Cortisol, serotonin (5-HIAA), epinephrine, norepinephrine, dopamine (urine)	16 wks	No sign diff at post	FU: No bw or within gr diff for 1 var
Field et al., 2013	Psy vs AC		Cortisol conc (saliva)	12 wks	Cortisol reduction in both gr, higher in PSG at post	Post (both comp): Bw gr diff 1/15 var
Fissler et al., 2017	Psy vs AC		EEG analysis (ERN, CRN)	3 wks	Sign time*group in Fz electrode for ERN & AERN; sign increase in MT vs AC	Post: Bw gr diff NR & no within gr diff 5 var
Freedland et al., 2015	Psy + TAU vs TAU		Average daily activity (actigraphy); 6-min walk distance test	6 mths	No sign diff at post	Post: Bw gr diff fav ctrl 1/3 var
Gois et al., 2014		Psy vs ADM	HbA1c	24 wks	No sign diff at FU	Post: Bw gr diff 2/6 var
Hirvonen et al., 2011		Psy vs ADM	D2/3 receptor binding as binding potential in striatal & thalamic brain areas (11C/raclopride PET)	4 mths	Sign time*group in lateral thalamus (ns in striatum): increase in fluoxetine not PDT gr	Post: No bw gr diff 2 var
Hsiao et al., 2011	Psy + ADM vs ADM		Cortisol conc & slope (saliva)	2, 5, 8 mths	No sign diff (authors suggest steeper diurnal cortisol slope in BMSP) at post & FU	FU: No within gr & no bw gr diff for 1 var
Hsiao et al., 2014	Psy + ADM vs AC + ADM		Cortisol conc & slope (saliva)	2, 5, 8, 14 mths	Sign Time*Group; steeper cortisol slope for BMSP at FU, not post	Post: Within gr diff for ADM, not Psy (total comp incalculable)
Huang et al., 2016	Psy + TAU vs TAU		HbA1c, fasting glucose, BMI	3, 6 mths	No sign diff at post; Fasting glucose and HbA1c reduced at FU in MET + CBT	Post/FU: No bw gr diff in baseline
Lamers et al., 2011	Psy + TAU vs TAU		HbA1c	3, 9 mths	No sign diff at post; HbA1c reduced in MET + CBT gr at FU	-21 h slope on 2 nd order polynomial (planned comparison) for 5 var
Lesperance et al., 2007 ³⁾	Psy + ADM/PLA vs AC + ADM/PLA		BP-S, BP-D, ECG	12 wks	BP increased in IPT vs. clinical management at post	Post: No bw gr diff 7 var
Linde et al., 2011	Psy 1 + Psy 2 vs Psy 2		Weight	12 mths	No sign diff at post	FU: Bw gr diff 1/3 timepoints & 1/7 var

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Table 1 (continued)

Study	Comp (ctrl) ^{a)}	Comp (active) ^{a)}	Biological variables ^{b)}	Time-point ^{c)}	Main findings (biological) ^{c)}	Type of total & sign comp (biological) ^{d)}
Lustman et al., 1998	Psy + Ed vs Ed		HbA1c	10 wks, 6 mths	No sign diff at post; HbA1c reduced in CBT vs ctrl at FU	Post: No bw gr diff (adjusted analysis) 1 var FU: Bw gr diff 1/1 var
Markowitz et al., 1998		Psy1 vs Psy2	CD4 count	15 wks	No sign diff at post	Post: No within gr & no bw gr diff 1 var
Martin et al., 2001		Psy vs ADM	Brain metabolism (SPECT)	6 wks ^{e)}	Increased metabolism in right basal ganglia & posterior cingulate in IPT vs ADM at post	Post: Within & bw gr diff in some brain areas (total comp incalculable)
Mohr et al., 2001a, 2001b		Psy1 vs Psy2; Psy vs ADM	Immunological (OKT3-, MOG-, MBP-stimulated IFN- γ ; IL-4; T-cell proliferative response) HbA1c	16 wks 11 wks	Decreased nonspecific & increased OKT3-stimulated IFN- γ production across gr at post No sign diff at post	Post: Within gr diff 2/11 var; no bw gr diff 11 var Post: No within gr & no bw gr diff 1 var
Newby et al., 2017	Psy vs TAU		Weight, BP-S, BP-D, TC, HDL-C, LDL-C	6, 12 mths	No sign diff at post; HDL-C improved & TC/HDL-C reduced in BBT vs ctrl at FU	Post: No Bw gr diff 7 var FU: Bw gr diff 2/7 var
Parker et al., 2003	Psy + ADM vs ADM; Psy + ADM vs AC + ADM		Inflammatory (ESR, PIP), grip strength, 50-feet walking speed	10 wks, 6, 15 mths	No sign diff at post & FU	Post/FU (both comp): No within gr & no bw gr diff 5 var
Penckofer et al., 2012	Psy vs TAU		HbA1c, fasting glucose	3, 6 mths	No sign diff at post & FU	Post/FU: No within gr & no bw gr diff 2 var
Pentecost et al., 2015		Psy1 vs Psy2 Psy vs ADM	BP, BMI, accelerometer	4 mths	NR	NR
Petrak et al., 2015			HbA1c	15 mths	No sign diff	FU: No within gr & no bw gr diff (adjusted analysis) 1 var
Pibernik-Okanovic et al., 2009	Psy vs TAU		HbA1c	6, 12 mths	HbA1c improved in both gr at post-tx & FU, with no sign diff	Post/FU: Within gr diff in both gr & no bw gr diff 1 var
Pibernik-Okanovic et al., 2015	Psy vs TAU		Hb1Ac, BMI, TC, HDL-C, LDL-C, TG, leukocyte, CRP, sialic acid, u-8-OxodG, uric acid, adiponectin	8 wks, 6, 12 mths	Sign Time*Group for sialic acid (Bonferroni ns); Reduced TC, LDL-C, TG, leukocytes, u-8-OxodG, sialic acid, & increased uric acid in both gr at FU	FU: Bw gr diff 1/13 var (only uncorrected analysis) Post: NR
Safren et al., 2009	Psy vs TAU		HIV VL (plasma RNA)	3, 6, 12 mths	No sign diff	Post: No bw gr diff FU: Bw gr diff NR
Safren et al., 2012	Psy vs TAU		CD4 + count, HIV VL (plasma RNA)	3, 6, 12 mths	No sign diff at post; Higher CD4+ count for CBT vs ctrl at FU	Post: No bw gr diff 2 var FU: Bw gr diff 1/2 var (adjusted analysis)
Safren et al., 2014	Psy + TAU vs TAU		HbA1c	4, 8, 12 mths	Reduced HbA1c for CBT at post & FU	Post/FU: Bw gr diff 1/1 var
Safren et al., 2016	Psy + TAU vs TAU	Psy1 + TAU vs Psy2 + TAU	CD4 + count, HIV VL (plasma RNA)	4, 8, 12 mths	No sign diff	Post/FU (both comp): No within gr & no bw gr diff 2 var
Savard et al., 2006	Psy vs WL		Immunological (CD3+, CD4+, CD8+, CD16+/CD56+ cells; WBC, lymphocytes, monocytes, IFN- γ , IL-1 β ; NKCA)	8 wks, 5, 8 mths	Sign Time* Group for CD3+, CD4+, CD8+ regression to the mean	Post: Bw gr diff 3/10 var (possible)
Schramm et al., 2016	Psy vs TAU	Psy1 vs Psy2	Sleep quality (stable & unstable sleep -cardiopulmonary coupling), sleep efficiency (total sleep & wake time), VLFC	5, 6 nights	Lower wake time for CBASP vs MBCT (nights averaged)	Post (Psy vs TAU): No bw gr diff 7 var Post (Psy1 vs Psy2): Bw gr diff 1/7 var
Simoni et al., 2013	Psy vs TAU		CD4 count, HIV VL	6, 9 mths	No sign diff at post & FU	Post/FU: No bw gr diff 2 var
Tovote et al., 2014	Psy vs WL	Psy1 vs Psy2	HbA1c	3 mths	No sign diff at post	Post (Psy vs WL): NR Post (Psy1 vs Psy2): No within gr diff 1 var

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Table 1 (continued)

Study	Comp (ctrl) ^{a)}	Comp (active) ^{a)}	Biological variables ^{b)}	Time-point ^{c)}	Main findings (biological) ^{c)}	Type of total & sign comp (biological) ^{d)}
Urizar and Munoz, 2011	Psy vs TAU		Cortisol conc & slope (saliva)	6, 18 mths (ppar)	Lower mean cortisol for CBSM vs ctrl at FU but not post	Post: No bw gr diff 4 var (adjusted analysis) FU: Bw gr diff 1/4 var (adjusted analysis)
Van Bastelaar et al., 2011	Psy vs WL		HbA1c	8–12 wks	No sign diff	Post: No bw gr diff 1 var
Yang et al., 2009	Psy + ADM vs ADM		Cortisol conc & slope (saliva)	4, 6 mths	Sign Time*Group; Lower 21 h conc & increased dev from wake for BMSP vs ctrl at FU not post	Post: No bw gr diff 8 var FU: Bw gr diff 2/8 var

Note.

^{a)} Biological outcomes are reported as cardiac safety data. Cardiovascular events were also considered, but not statistically analysed.

^{b)} AC, Attention control; ADM, Antidepressant medication; Ctrl, Control; Comp, Comparison; Ed, Psychoeducation; LI, Lifestyle intervention; PLA, Placebo; Psy, Psychotherapy; TAU, Treatment as usual; WL, Waitlist.

^{c)} BMI, Body mass index; BP, Blood pressure (S, systolic; D, diastolic); CRN, Correct response negativity; Conc, Concentration; CRP, C-Reactive Protein; ECG, Electrocardiography; EEG, Electroencephalography; ERN, Error related negativity; ESR, Erythrocyte sedimentation rate; 5-HIAA, 5-hydroxyindoleacetic acid; HR, Heart rate; Hb1AC, hemoglobin A1c; IFN- γ , Interferon- γ ; IL, Interleukin; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; LPS, Lipopolysaccharide; MBP, Myelin basic protein; MOG, Human myelin oligodendrocyte glycoprotein; NKCA, Natural killer cells activity; NKCC, Natural killer cells cytotoxicity; OKT3, Muromonab-CD3; PET, Positron emission tomography; PIP, Proximal interphalangeal joints; Prod, Production; RSA, Respiratory Sinus Arrhythmia; SPECT, Single-photon emission computed tomography; u-8-oxodG, Urinary 8-oxo-deoxyguanosine; TC, Total cholesterol; TG, Triglyceride; VL, Viral load; VLFC, Very-low-frequency coupling band; WBC, White blood count.

^{d)} Timepoint (post-randomization) for the measurement of biological outcome. ^{e)} Only mid-treatment evaluation available. Mth, Month; Ppar, post-partum; Wk, week.

^{e)} BBT, Brief Behavioral Therapy; BMSP, Body-mind-spirit psychotherapy; CBASP, Cognitive behavioral analysis system of psychotherapy; CBM, Cognitive bias modification; CBT, Cognitive behavioral therapy; dACC, Dorsal anterior cingulate; Dev, deviation; Diff, difference; DMBI, Defiant Mind Body Intervention; FU, Follow-up; Gr, Group; IPT, Interpersonal psychotherapy; MBCT, Mindfulness based cognitive therapy; MDM, Metacognitive detached mindfulness; NR, Not reported; Ns, Non-significant; Post, Post-treatment; rMFG, right middle frontal gyrus; Sign, Significant; SMT, Stress management training; Time* Group, Interaction between Time and Group.

^{e)} Unless otherwise specified, in comparisons with control differences favor the experimental intervention. Biol, Biological; Bw, Between; Sign, Significant; Var, variable.

Fig. 3. Forest plot of standardized mean differences at post-treatment for psychological interventions (psy) versus control conditions (ctrl) for (a) glycaemic control and (b) cortisol concentration.

compared CBT integrated with adherence counselling with TAU and generally reported no benefits for CD4 counts and HIV viral load at post-intervention and follow-up (with one exception- Safren et al., 2012) for CD4 at follow-up). Another HIV trial (Markowitz et al., 1998) compared CBT, IPT, supportive therapy and its combination with imipramine and reported no changes over time in CD4 counts by group. The remaining trials found nonexistent (Doering et al., 2007) or very limited (Euteneuer et al., 2017; Mohr et al., 2001a; Savard et al., 2006) effects on immunological variables. In all cases where some changes were found, these were restricted to very few immunological markers from an array measured (over 10) or there were suspicions of methodological confounding (Savard et al., 2006).

Cortisol concentration and slope were measured in 7 RCTs (Barr Taylor et al., 2009; Field et al., 2013, 2004; Hsiao et al., 2014, 2011; Urizar and Munoz, 2011; Yang et al., 2009) (1 primary outcome), generally from saliva (6). Four of these involved special populations: pregnant women (Field et al., 2013, 2004; Urizar and Munoz, 2011) and older adults at risk for coronary heart disease (CHD) (Barr Taylor et al., 2009). Findings are narratively synthesized in Appendix 3.

Cortisol concentration 30–45 min after-wake was used as primary indicator and, if not reported, average cortisol concentration (one trial-Field et al. (2013)). Pooled ESs showed no significant benefits for psychological interventions over control at posttest (5 trials), Hedges' $g = -.19$, 95% CI -0.45 to 0.06, $I^2 = 0\%$ (95% CI 0%–71%) (Fig. 3b), or follow-up (3 trials), Hedges' $g = .04$, 95% CI -0.66 to 0.74, $I^2 = 77\%$ (95% CI 25%–93%) (Appendix Fig. 2b).

Only one trial, which also had the highest weight in the meta-analysis, had low risk of bias on three of the domains considered. Most of

the five trials pooled had uncertain risk of bias across domains. For one trial, blinding was ensured for the biological outcome assessment. For incomplete outcome data, three trials had low RoB, and two others, high RoB.

Weight/body-mass index (BMI) were outcomes in six trials (Barr Taylor et al., 2009; Huang et al., 2016; Linde et al., 2011; Pagoto et al., 2013; Pentecost et al., 2015; Pibernik-Okanovic et al., 2015) (primary in 2), and *physical activity* (measured with actigraphy or an accelerometer) in three (Freedland et al., 2015; Parker et al., 2003; Pentecost et al., 2015). Seven trials included special populations: overweight (BMI > 30) women (Linde et al., 2011; Pagoto et al., 2013), diabetes (Huang et al., 2016; Pibernik-Okanovic et al., 2015), cardiac problems (heart failure, CHD risk) (Barr Taylor et al., 2009; Freedland et al., 2015) and rheumatoid arthritis (Parker et al., 2003). No benefits of psychological interventions over control conditions emerged for either weight or physical activity. Weight data reported (change from baseline, BMI) were too diverse to afford pooling.

Blood pressure (BP) was assessed in five trials (Ahmadpanah et al., 2016; Barr Taylor et al., 2009; Lesperance et al., 2007; Pagoto et al., 2013; Pentecost et al., 2015), four of which included special populations (coronary artery disease (Lesperance et al., 2007), older individuals at risk for CHD (Barr Taylor et al., 2009), women with hypertension (Ahmadpanah et al., 2016) or overweight (Pagoto et al., 2013)). One trial reported benefits versus control for two distinct psychological interventions at post-intervention and follow-up (Ahmadpanah et al., 2016). Two other trials reported no significant differences (Barr Taylor et al., 2009; Pagoto et al., 2013) and another (Lesperance et al., 2007) reporting worsening in the intervention group, though no differences on 6 other cardiac parameters.

Neurobiological markers were evaluated in five trials, as brain activity with functional magnetic resonance imaging/fMRI (Beevers et al., 2015) and EEG (Chan et al., 2011; Fissler et al., 2017), brain metabolism with single-photon emission computed tomography (Martin et al., 2001), and brain neurochemistry with PET (Hirvonen et al., 2011). Two trials comparing psychotherapy (IPT (Martin et al., 2001) or psychodynamic therapy (Hirvonen et al., 2011)) with antidepressants reported specific differences in some brain areas. One study (Chan et al., 2011) suggested mind-body psychotherapy, but not CBT, led to increased prefrontal asymmetry, but whether differences were significant between interventions was unclear. Two other trials reported post-intervention benefits of a psychological intervention versus AC on a minority of the markers analyzed. The total number of distinct neurobiological variables or contrasts evaluated was impossible to establish.

Inflammatory markers were included in 5 trials (Barr Taylor et al., 2009; Doering et al., 2007; Euteneuer et al., 2017; Parker et al., 2003; Pibernik-Okanovic et al., 2015) (C-Reactive Protein/CRP in four), and none of these reported benefits of the intervention versus control. One trial (Parker et al., 2003) on rheumatoid arthritis patients did not evidence any advantage of adding CBT to antidepressant medication versus AC or medication alone on routinely used markers, such as the erythrocyte sedimentation rate or joint swelling.

Regarding *blood lipids*, cholesterol (total, high density and low density) was assessed in three trials (Barr Taylor et al., 2009; Pagoto et al., 2013; Pibernik-Okanovic et al., 2015), two of which also measured triglycerides (Barr Taylor et al., 2009; Pibernik-Okanovic et al., 2015). Findings were mixed, with two trials (Pagoto et al., 2013; Pibernik-Okanovic et al., 2015) reporting no differences between the psychological intervention and control except for high density cholesterol at follow-up (Pagoto et al., 2013), and one trial reporting between group differences for triglycerides (Barr Taylor et al., 2009).

Sleep was assessed in two trials, with mixed results, synthesized narratively in the Appendix 3.

3.5. Main findings- predictors (Table 2)

Eight trials (Dunlop et al., 2017; Kennedy et al., 2007; Kohen et al., 2011; McGrath et al., 2013; McKnight et al., 1992; Rahman et al., 2017; Rovner et al., 2014; Schneider et al., 1986) and a secondary analysis (Harley et al., 2010b) investigated biological markers in relation to treatment response, as potential predictors (2), moderators (4) or both (3). Seven reports focused on the contrast between a psychological intervention and antidepressant medication, and two on the one between two psychological therapies. Most trials (5) analyzed interaction effects between predictor or the dichotomized outcome and treatment type.

Three trials used brain neuroimaging: resting state functional connectivity (Dunlop et al., 2017) and PET glucose (Kennedy et al., 2007; McGrath et al., 2013). One trial (Dunlop et al., 2017) found that functional connectivity between the subgenual cortex and prefrontal, insula and midbrain regions differentially predicted treatment remission and non-response for CBT and antidepressants (duloxetine, escitalopram). Another showed brain metabolism in 6 regions, most notably the right anterior insula, discriminated remission and non-response to CBT and, respectively, escitalopram (McGrath et al., 2013). Finally, the third one (Kennedy et al., 2007) evidenced that CBT compared to venlafaxine responders had increased metabolism from post-treatment to baseline in the inferior temporal cortex, and decreased metabolism in the posterior cingulate.

Genetic polymorphisms were examined in two trials. A serotonin transporter (Kohen et al., 2011) trial found no interaction effect between treatment and predictor, but in exploratory post-hoc comparisons 3 of the 6 markers tested were associated with differential response to psychotherapy. Another trial on the brain-derived neurotrophic factor Val/Met (Rahman et al., 2017) polymorphism reported the Met/Met genotype did not predict treatment response across intervention arms, nor did it differentially predict response compared to Val genotypes or TAU. The authors did find that the interaction of Met genotypes and childhood adversity predicted treatment response across all arms.

Other biomarkers (Dexamethasone Suppression Test/DST, CRP, vision status and orthostatic hypertension) were each examined in one report and are described in the Appendix 3.

4. Discussion

In a systematic review of 51 primary trials and a pooled analysis, we evaluated the impact of psychological treatments for depression on biological variables domains. Most biological variables were examined as efficacy outcomes, though they were rarely designated as primary. There was large variability across the biological domains and markers explored and overall findings were mixed and often inconsistent. Most studies evaluated a stack of biological markers or used multiple indices for measuring the same biological process (e.g., cortisol). Only one fifth of trials reported significant benefits of a psychological intervention versus control at post-intervention, and these were restricted to a tiny fraction of the total variables assessed. Results were slightly better at follow-up with half of the trials reporting some comparative advantage. As the effects of psychotherapy for depression typically wane over time (Karyotaki et al., 2016), these findings are surprising and might be spurious. Follow-up was generally naturalistic and its duration varied among studies, exposing any observed changes to risk of confounding. Trials with an active comparator arm were comparatively fewer and only half reported some differences within one of the active psychological intervention arms, or in contrast with another active intervention. Similarly, differences were confined to a small fraction of the total biological markers tested, indicating that many significant findings were probably spurious and would not have survived multiple

Table 2
Summary of findings for depression trials with biological variables as predictors or moderators.

Study ^{a)}	Comp ^{b)} (ctrl)	Comp ^{b)} (active)	Biol var ^{c)}	P/M ^{d)}	Statistical method ^{e)}	Main finding (biol) ^{f)}
Dunlop et al., 2017		Psy vs ADM	Brain activity (resting state funct conn)	M	Tx*Dichot outcome (remission vs non-response) ANOVA	Sign Tx* Outcome in 6 reg (3 after SMT); SCC Funct conn to left anterior VLPFC/Ins, dorsal midbrain, & left VMPFC: M of tx resp & resist
Kennedy et al., 2007		Psy vs ADM	Brain metabolism (PET glucose)	P & M	Within & bw gr diff separately for responders & non-responders	Decreased OFC, MPFC & increased OTC metab: P of overall tx resp;
Kohen et al., 2011		Psy + ADM vs TAU + ADM	SERT polymorphism	M	Tx*P (polymorphism) ANCOVA	Left ITC and PCC metab: M of tx resp
McGrath et al., 2013		Psy vs ADM	Brain metabolism (PET glucose)	P & M	Tx * Dichot outcome (remission vs non-response) ANOVA	Tx*Predictor ns
McKnight et al., 1992		Psy vs ADM	DST status (DST +, DST-)	M	Tx * Dichot P (DST +, DST-) ANCOVA	Sign Tx*Outcome in right anterior Ins, right ITC, left Amygd, left Premotor, right Motor, Prec;
Rahman et al., 2017	Psy vs TAU		BDNF (VAL66VAL vs. VAL66MET) polymorphism	P & M	Logistic regression of dichot P & Tx response	Pre-tx Ins activity correl % sympt change in CBT
Rovner et al., 2014		Psy1 + LVR vs Psy2 + LVR	Vision status (acuity, contrast sensitivity, scotoma size & location)	P	Visual acuity stratification variable (adjustment covariate) in Poisson regression	Tx*DST status ns;
Schneider et al., 1986		Psy vs ADM	SOP	P	Correl bw P & % outcome change; T test of dichot outcome (> 30% improv vs not) on P	DST- vs DST+ < overall tx resp
Harley et al., 2010a, 2010b (PA Joyce, 2002 & Luty, 2007)		Psy1 vs Psy2 ADM1 vs ADM2	CRP	M	Tx * Dichot P (CRP status) (regression)	Tx*P ns; Sign P*CA: MET + & no CA > overall tx resp, ns in CBT
						> Tx effect in the worst vs best vision stratum (unclear if sign)
						Pre-tx SOP correl with overall sympt improvement
						Sign Tx*P;
						High CRP M of tx resp (> resp to ADM & < resp to CBT)

Note.

Note.

^{a)} PA, Pooled Analysis.

^{b)} ADM, Antidepressant medication; Comp, Comparison; Ctrl, Control; LVR, Low vision rehabilitation; Psy, Psychotherapy.

^{c)} BDNF, Brain-derived neurotrophic factor; Funct conn, Functional connectivity; CRP, C-Reactive Protein; DST, Dexamethasone suppression test (DST-, Non-Suppressors; DST +, Suppressors); SOP, Systolic orthostatic hypotension; SERT, Serotonin Transporter.

^{d)} M, Moderator of treatment; P, Predictor of treatment. The classification refers to how investigators aimed to study the biological variable.

^{e)} Bw, Between; Correl, Correlation; Dichot, Dichotomous; Diff, difference; *, Interaction; Tx, treatment.

^{f)} Amygd, Amygdala; Biol, biological; CA, Childhood Adversity; Ins, Insula; ITC, Inferior temporal cortex; Metab, Metabolism; MET +, carriers of the MET allele; OFC, orbitofrontal cortex; OTC, occipital-temporal cortex; PCC, Posterior cingulate cortex; Prec, Precuneus; Reg, Region; Resist, Resistance; Resp, Response; SCC, Subcallosal cingulate cortex; Sign, Significant; SMT, Subsampling permutation test; Sympt, Symptom; Tx, Treatment

VLPFC, Ventrolateral prefrontal cortex; VMPFC, Ventromedial prefrontal cortex; “<”, Less/Lower; “>”, More/Higher.

comparison corrections.

Over half of the trials were conducted on populations with somatic disorders, where psychological interventions are effective treatments for depression, though with smaller effects compared to patients with no comorbidity (SMDs of 0.57 and 0.74 respectively). Nonetheless, for these populations engendering change on key biological markers is arguably as important as reducing depression. However, we could not identify any systematic benefits. Glycaemic control (HbA1c), often employed a surrogate outcome in diabetes trials (Lipska and Krumholz, 2017), was the most common biological outcome, both when examining outcomes in general and when only considering primary ones. Psychological interventions for depression did not show HbA1c benefits over control at post-treatment or follow-up. Similarly, a meta-analysis of CBT for diabetic patients found no significant benefits at short- and long-term for glycaemic control (Uchendu and Blake, 2016). The authors did report a small significant effect on fasting glucose, though it was based on solely 3 trials.

Another group of trials evaluated immunological markers, the largest cluster represented by HIV viral load and CD4 cell counts in patients with HIV, where again no benefits were evidenced for a CBT intervention over control. However, since the primary outcomes in these trials focused on medication adherence, the examination of viral and immunological markers was probably exploratory.

Higher cortisol concentration, altered daily fluctuation (e.g., slope steepness) and alteration of the feedback inhibition system (i.e., dexamethasone inhibition test) were often reported in depressed patients (Furtado and Katzman, 2015). It was suggested cortisol could be involved the development of depression (Zorn et al., 2017), and that remission might be coupled with changes in cortisol rhythm (Herbert, 2013). Our results showed a small and non-significant effect of psychological interventions on cortisol concentration.

Findings for other types of biological outcomes were also negative, mixed or inconsistent. Psychological interventions for depression did not show any benefits on weight or inflammatory markers. Results were mixed and inconsistent for blood pressure. Only one trial reported any benefits, though it was also the one with misleading registration information, which raises doubts about its trustworthiness. Neurobiological variables assessed were heterogeneous, covering brain activity, metabolism and neurochemistry. Though some differences were always evidenced, both versus control or antidepressants, their significance and reliability were difficult to gauge. It was generally impossible to establish how many distinct neurobiological parameters had been tested and judge whether the observed significant differences could be spurious.

Though biological markers, particularly neuroimaging, are regarded as holding great potential in predicting treatment response (Fonseka et al., 2018), few trials (under a fifth) investigated this aspect. Findings were sparse and difficult to integrate. Neuroimaging biomarkers showed promise in distinguishing remission and non-response to CBT and antidepressants, particularly in the light of a larger trial with overall low risk of bias (Dunlop et al., 2017) (PREdict), confirming a role for the subgenual cortex (Dunlop and Mayberg, 2014). Conversely, genetic polymorphisms showed little utility in predicting overall or differential treatment response. The few significant findings observed generally followed non-significant treatment by predictor interaction effects and did not undergo multiple comparison corrections, raising doubts about their stability.

Several limitations should be noted. A considerable proportion of the trials were affected by risk of bias or provided insufficient information to assess it. Only around half could be considered at low RoB for sequence generation, concealed allocation and incomplete outcome data- where the other half was rated as high risk. Only half had been registered and only one fifth prospectively, and, even among them, most were rated as high risk for selective reporting. For the two outcomes where we performed meta-analyses, trials with low RoB for three or more of the domains considered comprised half of the evidence base

for one (glycaemic control) and a fifth for another (cortisol concentration). Following the GRADE guidance for integrating risk of bias ratings in evaluating the quality of the evidence (Guyatt et al., 2011), we would probably rate down for quality for cortisol concentration, but not for glycaemic control. Consequently, we can be satisfactorily confident that psychological treatments for depression do not improve glycaemic control. It is unlikely that these treatments impact cortisol concentration, but this finding remains uncertain.

Moreover, while risk of bias indexes internal validity, establishing external validity is more complex and difficult to formalize (Dekkers et al., 2009). Even for the very basic criterion of deciding whether the study's eligibility criteria are a proper reflection of the study population, one would at the very least need access to a population-based registry with which to compare the selection criteria of the trial. This registry would need to also include measures of the outcomes of interest, which is unlikely for the biological variables considered in this systematic review. Consequently, it is fair to say that both internal and external validity for this cohort of trials remain largely unknown.

Furthermore, several trials had small samples. Small study effects are likely present, though the small number of studies in the outcome categories meta-analyzed precluded us from formally assessing them. One third of the trials assessed more than 5 distinct biological indexes, often in more types of analyses and without employing corrections for multiple comparisons. There were frequent procedural discrepancies across studies even for the assessment of the same biological index. Methodological confounding implies that at least some of the seemingly promising effects showed in single trials could be spurious. Aggregate effect sizes were accompanied by significant heterogeneity and based on few trials, due to fact many trials reported insufficient data on biological variables and did not allow for effect size calculation.

5. Conclusions

To our knowledge, this is the first large scale systematic overview of all biological variables investigated in randomized trials of psychotherapy for depression. Overall, though psychological treatments for depression were repeatedly shown to be effective both generally (Cuijpers et al., 2016; Karyotaki et al., 2016) and for patients with somatic disorders (Cuijpers et al., 2018), we found limited evidence that benefits also translate to biological outcomes. Given the complexity of reliably assessing biological markers, this apparent absence of effects might have been largely influenced by methodological inconsistencies or confounding, often described in research on the biology of mental disorders (Gentili, 2017). Moreover, the choice of biological variables to be investigated excluded biomarkers prevalent in experimental research, such as heart rate variability (Kemp et al., 2010) or hippocampal volume (Cole et al., 2011), scarcely or not at all considered. Our findings suggest that research on biological outcomes of psychotherapy is still inconclusive, despite previously optimistic claims of distinct effects in some areas like brain functioning (Boccia et al., 2016).

Ethics approval and consent to participate

Not applicable as the study used secondary, already published data and no human or animal participants.

Consent for publication

Not applicable as no data from individual persons is contained.

Availability of data and material

The datasets generated during the current study, along with the code underlying the findings are included in the published article and its supplementary material, with additional material in the Figshare repository (doi: <https://doi.org/10.6084/m9.figshare.7496132>).

Competing interests

The authors declare that they have no competing interests.

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Author contributions

Dr. Cristea and Dr. Gentili had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Cristea, Gentili, Cuijpers

Acquisition, analysis, or interpretation of data: Cristea, Karyotaki, Hollon, Gentili

Drafting of the manuscript: Cristea, Gentili

Critical revision of the manuscript for important intellectual content: Cristea, Karyotaki, Hollon, Cuijpers, Gentili

Statistical analysis: Cristea, Gentili

Administrative, technical, or material support: Karyotaki, Cuijpers

Study supervision: Hollon, Cuijpers

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.neubiorev.2019.03.022>.

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