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Hormones of the hypothalamic-pituitary-gonadal (HPG) axis in male depressive disorders – A systematic review and meta-analysis

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ABSTRACT

Sexual dysfunctions are common in men with depression. As the hypothalamic-pituitary-gonadal (HPG) axis is a crucial regulator of sexual function, and also affects mood and cognition, the following question arises: Is the HPG axis altered in depressed men when compared to healthy controls?

To answer this question, PubMed and PsycINFO were searched. Inclusion criteria for the systematic review and meta-analysis were: (1) case-control study including male patients with a depressive disorder and (2) assessment of follicle-stimulating hormone (FSH), luteinising hormone (LH), oestradiol, or testosterone.

Seventeen studies were identified. Follicle-stimulating hormone and LH did not differ between patients and controls. By contrast, in patients, oestradiol was marginally increased ($g = 0.52$, 95% CI [−0.01, 1.04]; $Z = 1.92$, $p = .055$) and testosterone was significantly decreased ($g = -0.45$, 95% CI [−0.80, −0.10]; $Z = -2.53$, $p = .012$).

Depressed men may be characterised by diminished testosterone and potentially elevated oestradiol, which beyond contributing to sexual dysfunction, could impact mood and cognition.

1. Introduction

Sexual dysfunctions such as diminished sexual desire or erectile dysfunction are present in around 20–50% of male patients with untreated depressive disorders, and are linked to greater severity, longer duration, and recurrence of depressive episodes (Kennedy and Rizvi, 2009; Williams and Reynolds, 2006). The hypothalamic-pituitary-gonadal (HPG) axis governs the release of the gonadal steroids testosterone and oestradiol in the testes via a cascade of hormones, including gonadotropin-releasing hormone, follicle-stimulating hormone (FSH), and luteinising hormone (LH). Given that gonadal steroids influence sexual function, hormonal deviations of the HPG axis may be a possible cause for the diminished sexual desire and erectile dysfunction found in some depressed men.

Indeed, sexual dysfunctions are highly prevalent in hypogonadal men, whose total testosterone levels are, by definition, below 9.7–10.4 nmol/L (Basaria, 2014; Huhtaniemi and Forti, 2011). Interestingly, the same men often present with depressed mood, fatigue, and cognitive problems, which aligns well with the fact that testosterone is neuroactive and may thus contribute to symptoms of depressive disorders above and beyond sexual dysfunctions (McEwen and Milner, 2017; Mueller et al., 2014; Hamson et al., 2016). The same is true of oestradiol, with oestrogen receptors present in numerous extra-hypothalamic areas relevant to mood and cognition, such as the hippocampus and the amygdala. Together, these findings suggest that dysfunctions of the HPG axis may be involved in core symptoms of depressive disorders such as sexual dysfunctions, depressed mood, and impaired concentration.

There are thus several indications of altered HPG axis functioning in male depressive disorders, including the role of gonadal steroids in sexual function, mood, and cognition. The question arising from these indications is: Do men with depressive disorders show altered HPG axis functioning when compared to healthy controls? To answer this question, the present study aimed at systematically reviewing the literature on HPG axis functioning in male depressive disorder for the first time, integrating findings by means of meta-analysis, and using meta-regression to investigate which methodological characteristics are linked to effect sizes within this body of research.

2. Methods

2.1. Search process

A literature search for studies assessing HPG axis functioning in

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male depressive disorders was undertaken from September to November 2018. No time limits were set within the literature search parameters. All search methods followed a systematic approach in line with the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P), a guideline which improves accuracy and transparency in systematic reviews and meta-analyses (Shamseer et al., 2015). Studies were eligible if they (a) included adult men fulfilling diagnostic criteria for a depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM), the International Classification of Diseases (ICD), or Research Diagnostic Criteria (RDC), (b) assessed FSH, LH, oestradiol, or testosterone, and (c) used a case-control design. Only original studies published in German, English, Dutch, Italian, Spanish, Portuguese, or French were included. Studies including patients with bipolar disorder were excluded, unless results were reported separately for unipolar and bipolar patients, thus allowing for data selection; the same applied to studies including women. Studies assessing patients with comorbid illnesses or patients on medication were included, but these factors were recorded.

2.2. Source of literature

The systematic data search was conducted using the electronic bibliographic databases *PubMed* and *PsycINFO*, and was complemented by manual searches of reference lists of all papers included in the systematic review and meta-analysis. A broad search strategy for probable articles was employed in order to include as many potentially relevant studies as possible. The search string was composed of the terms “depression”, “follicle-stimulating hormone”, “luteinizing hormone”, “estradiol”, and “testosterone”, as well as synonyms and related terms, which were additionally broadened through exploded subject headings.

2.3. Study selection

First, titles and abstracts were screened and all duplicates as well as studies that did not meet our eligibility criteria were discarded. Next, full-text articles were screened to select eligible studies. For studies in which a full text or abstract were not available, the corresponding authors were contacted to request access to the publication. The same applied if insufficient data were reported. All studies meeting our eligibility criteria were included in the systematic review, and those providing sufficient statistical data were also included in meta-analyses and meta-regressions. Study selection was performed by two of the authors (SF, RAC).

2.4. Data extraction

For each study, information about the first author, the year of publication, the number of patients and healthy controls, eligibility criteria, HPG axis assessment, and results was extracted. Risk of bias was assessed using a modified version of a study quality assessment scale that was used in one previous systematic review and one previous meta-analysis on the role of cortisol in functional somatic syndromes and on hypothalamic-pituitary-thyroid axis functioning in anxiety disorders (Tak et al., 2011; Fischer and Ehlert, 2018; see Supplement 1). The instrument contained five items in total, which were rated on a 3-point scale from 0 to 2. The items referred to: number of eligibility criteria used, recruitment of the control group, adequacy of HPG axis assessment, blinding procedures, and use of relevant confounders in statistical analyses. The maximum attainable score was 10. Data extraction was conducted by one of the authors (SF) and a research assistant.

2.5. Data analysis

Standardised mean differences between depressed patients and healthy controls were calculated based on means and standard deviations or standard errors (Lipsey and Wilson, 2001; Borenstein et al., 2009). In order to adjust the meta-analyses for small-sample bias, Hedges’ g was calculated. Studies were subsequently weighted based on their inverse variance. Random-effects meta-analyses were conducted using macros for SPSS 22 (https://mason.gmu.edu/~dwilsonb/ma.html). Separate analyses were implemented for FSH, LH, oestradiol, and testosterone, and for basal and stimulated parameters (gonadotropin-releasing hormone challenge). Forest plots were created using an excel sheet from Meta-Essentials: Workbooks for meta-analysis, version 1.4 (ERASMUS Research Institute Rotterdam, The Netherlands). Heterogeneity was assessed by means of Q and I^2 statistics. In the case of homogenous effects, publication bias was examined by visual inspection of funnel plots and a trim-and-fill procedure (Duval and Tweedie, 2000). In the case of heterogeneous effects, meta-regression was undertaken, testing each item of the quality assessment scale as well as the mean age of the sample, patients’ diagnostic status (persistent vs. major depressive disorder), severity of depressive symptoms (Hamilton Rating Scale for Depression score), sampling tissue (blood vs. saliva), and measurement time point (morning vs. afternoon/evening) as potential effect modifiers.

3. Results

3.1. Search results

The study selection process is summarised in Fig. 1. The literature search retrieved 9720 unique references, of which 9534 were considered irrelevant following title and abstract screening. Of the remaining 186, a further 169 were excluded because of sample characteristics (e.g., only depressive symptoms measured) or lack of relevant data (e.g., results not separately reported for men and women). Therefore, in total, 17 studies on HPG axis functioning and male depressive disorder were eligible for data extraction and were included in the systematic review and meta-analysis.

3.2. Characteristics of the included studies

Characteristics of the included studies are provided in Tables 1–3. Studies dated back to 1979, with the most recent study being published in 2017. Sample sizes from which relevant data were available for extraction varied from 15 to 441. Participants’ age ranged from 18 to 97 years. The majority of studies (82%) used the DSM for the diagnostic assessment of depression and nearly all of them included patients with a major depressive disorder (94%). In terms of HPG assessment, 18% of the studies measured hormones in saliva, 18% measured hormones in blood (not specified further), 18% measured hormones in plasma, and 46% measured hormones in serum.

3.3. Follicle-stimulating and luteinising hormone

Seven studies, which are listed in Table 1, investigated FSH or LH in depressed patients and healthy controls. Notably, two of these were likely to have some patient overlap, although the mean ages of the samples were slightly different (Amsterdam et al., 1981; Winokur et al., 1982). The average score for the quality assessments was 3 out of a maximum of 10, suggesting a high risk of bias. All studies included patients with major depressive disorder (rather than persistent depressive disorder) and the majority excluded major physical diseases or medication that could interfere with hormonal assessments. By contrast, comorbidity with other mental disorders (e.g., psychotic disorders) was mostly not accounted for. Most studies recruited healthy controls who were matched to patients in terms of age; however, information about the source of recruitment (e.g., community, students) was often missing. Six studies determined basal FSH and LH concentrations and three determined stimulated levels by challenging the axis with exogenous gonadotropin-releasing hormone. The quality of the HPG measures was mixed, as only half of the studies employed standardised test times, repeated sampling schedules, and reported that assays had coefficients of variation below 10%. None of the studies reported whether lab personnel involved in hormonal analyses were

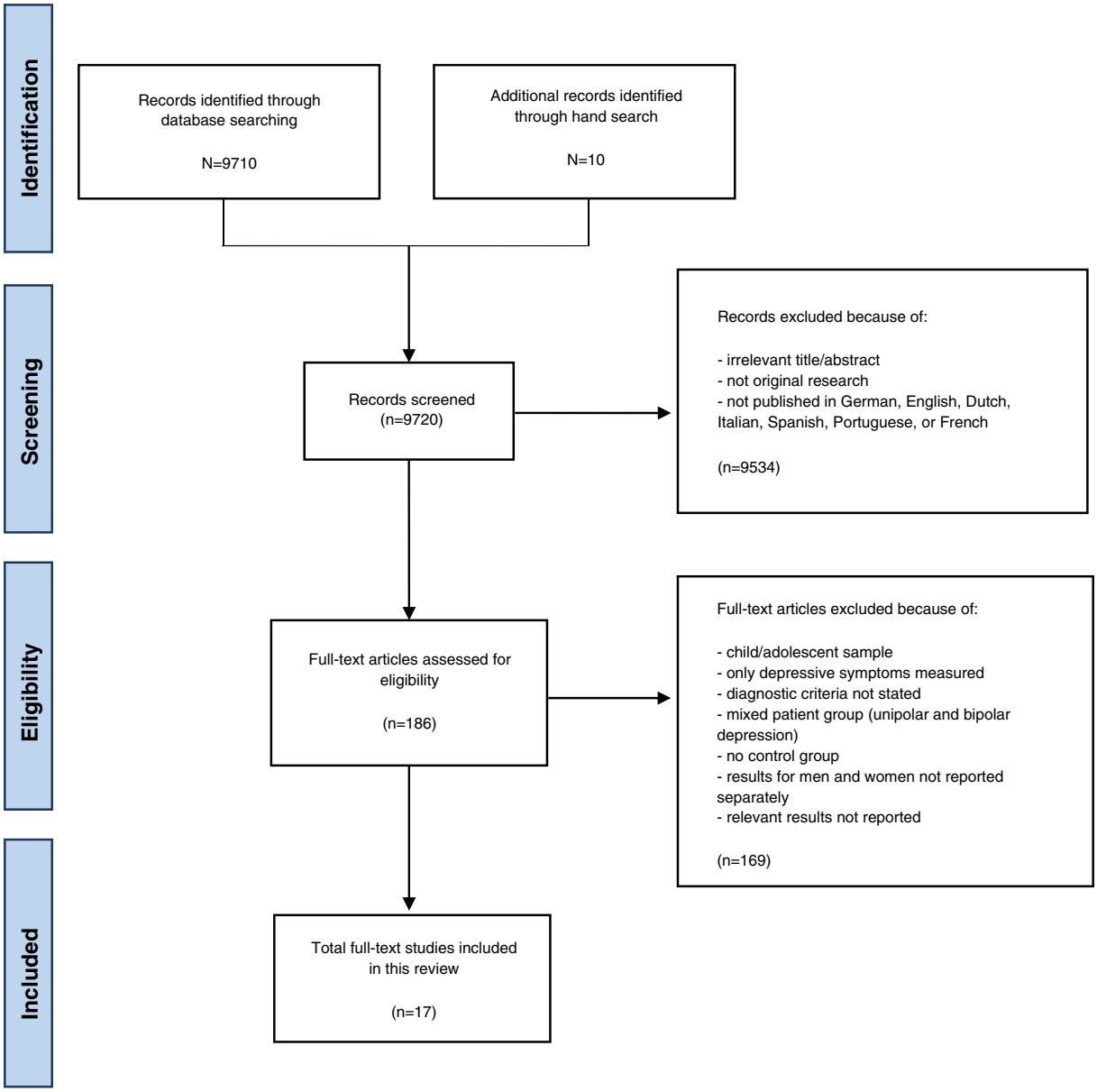

Fig. 1. Study screening and selection process.

blind to the diagnostic status of participants. Whereas most studies controlled for age, none adjusted their statistical analyses for potential group differences in socioeconomic status, physical activity levels, or smoking.

The systematic review did not yield any evidence of differences in basal or stimulated FSH between patients and controls. For basal FSH, this null finding was confirmed by meta-analysis (k = 2, g = 0.13, 95% CI [−0.38, 0.64]; Z = 0.51, p = .614). The results were slightly more ambiguous in terms of LH, with two studies showing lower absolute LH levels or pulse frequencies in depressed patients as compared to controls, and one showing higher stimulated levels in patients with secondary depression. However, meta-analysis, which, again, was only possible for basal LH, did not yield any evidence of a significant group difference (k = 2, g = −0.11, 95% CI [−0.81, 0.58]; Z = −0.32, p = .751).

3.4. Oestradiol

Four studies investigated basal oestradiol (see Table 2). The quality ratings yielded an average score of 4 out of 10, suggesting a moderate risk of bias. All studies included patients with major depressive disorder and all were careful to exclude medicated patients, whereas comorbidity with physical or other mental illnesses was mostly tolerated. Quality in terms of recruiting controls (representative vs. selected sample) and with respect to HPG assessments (standardisation of time, repeated sampling schedules, storage conditions, assay variation) was mixed. Again, no study reported whether the lab personnel involved in hormonal analyses were blind to whether a sample belonged to a patient or a healthy control. Adjustment of statistical analysis for socioeconomic status, physical activity or smoking was lacking, while some studies did at least consider age and BMI as covariates.

According to the systematic review, only one study found that patients and controls differed in basal oestradiol levels. Sufficient data for meta-analysis were available for two of the four studies. A trend for a group effect was found, insofar as patients had marginally higher oestradiol levels compared to controls (k = 2, g = 0.52, 95% CI [−0.01, 1.04]; Z = 1.92, p = .055).

Table 1
Characteristics of studies comparing follicle-stimulating hormone (FSH) and luteinising hormone (LH) between male patients with depressive disorders and healthy controls.

Study	Patients	Controls	Endocrine assessment	Results	Quality rating
Ettigi et al. (1979)	N = 9 Mean age 36 ± 5 Inclusion: unipolar depression according to RDC Exclusion: drugs within 7 days	N = 6 Mean age 34 ± 4	Challenge: GnRH (100 μg) Time point: 9 am Tissue: serum Assay: radioimmunoassay	No group differences in basal LH levels (controlling for BMI) Patients with secondary depression had higher LH levels after GnRH infusion (controlling for BMI)	2
Amsterdam et al. (1981)	N = 12 Mean age 37 ± 4 Inclusion: unipolar depression according to RDC, HRSD-17 score ≥ 16 Exclusion: physical disease, history of endocrinopathy, varicocele, vasectomy, or sexual surgery, drugs within 7 days, ECT within 2 years, history of slow-release antipsychotic intake	N = 18 Mean age 33 ± 3	Challenge: GnRH (250 μg) Time points: −15, 0, +30, +60, +90, +120 min Tissue: serum Assay: radioimmunoassay	No group differences in basal FSH or LH levels No group differences in either parameter after GnRH infusion	2
Winokur et al. (1982)	N = 12 Mean age 34 ± 3 Inclusion: unipolar depression according to RDC Exclusion: physical disease, history of endocrinopathy, vasectomy, drugs within 2 weeks, ECT within 2 years, history of intake of slow-release antipsychotic drugs	N = 12 Mean age 34 ± 3	Challenge: GnRH (250 mg) Time points: −15, 0, +30, +60, +90, +120 min Tissue: blood Assay: radioimmunoassay	No group differences in FSH or LH levels after GnRH infusion	3
Rupprecht et al. (1988)	N = 6 Mean age 42 ± 15 Inclusion: major depressive disorder according to the DSM-III Exclusion: medication	N = 20 Mean age 37 ± 10	Time points: 7 am and 4 pm Tissue: serum Assay: radioimmunoassay	No group differences in basal FSH levels Patients had lower basal LH levels when compared to healthy controls	3
Schweiger et al. (1999)	N = 15 Mean age 48 ± 15 Inclusion: major depressive disorder according to the DSM-III-R, HRSD-21 score ≥ 18 Exclusion: major physical disease, history of substance abuse or dependence, psychotropic medication within 7 days	N = 22 Mean age 53 ± 18	Time points: 10-min intervals from 6 pm to 12 am Tissue: blood Assay: immunoradiometric assay	No group differences in basal FSH levels (controlling for BMI) Trend for lower LH pulse frequency in patients when compared to controls (controlling for BMI)	6
Kaneda and Fujii (2002)	N = 11 Mean age 62 ± 9 Inclusion: major depressive disorder according to the DSM-IV Exclusion: organic central nervous system disorder, substance abuse, mental retardation, medication	N = 11 Mean age 62 ± 8	Time point: between 11 am and 12 pm Tissue: serum Assay: radioimmunoassay	No group difference in basal FSH or LH levels	2
Eskelinen et al. (2007)	N = 74Mean age 72 (total sample) Inclusion: depressive disorder according to the DSM-IV Exclusion: sex steroids or medication for prostate cancer or benign prostatic hyperplasia	N = 367 Mean age 72 (total sample)	Time point: between 8 am and 10 am Tissue: blood Assay: fluorescence immunoassay	No group difference in basal FSH or LH levels (controlling for BMI)	3

BMI = Body Mass Index, DSM = Diagnostic and Statistical Manual of Mental Disorders, ECT = electroconvulsive therapy, FSH = follicle-stimulating hormone, GnRH = gonadotropin-releasing hormone, HRSD = Hamilton Rating Scale for Depression, LH = luteinising hormone, RDC = Research Diagnostic Criteria.

Table 2
Characteristics of studies comparing oestradiol between male patients with depressive disorders and healthy controls.

Study	Patients	Controls	Endocrine assessment	Results	Quality rating
Rupprecht et al. (1988)	N = 6 Mean age 42 ± 15 Inclusion: major depressive disorder according to the DSM-III Exclusion: medication	N = 20 Mean age 37 ± 10	Time points: 7 am and 4 pm Tissue: serum Assay: radioimmunoassay	No group differences in basal oestradiol levels	3
Rubin et al. (1999)	N = 8 Mean age 45 ± 7 Inclusion: major depressive disorder according to the DSM-III-R, HRSD-21 score ≥ 17 Exclusion: major medical illness, comorbid major mental disorder, medication interfering with endocrine functioning, psychotropic medication within 3 years	N = 8 Mean age 42 ± 8	Time points: at 6 pm on four consecutive days Tissue: plasma Assay: radioimmunoassay	No group differences in basal oestradiol levels (controlling for BMI)	7
Eskelinen et al. (2007)	N = 74Mean age 72 (total sample) Inclusion: depressive disorder according to the DSM-IV Exclusion: sex steroids or medication for prostate cancer or benign prostatic hyperplasia	N = 367Mean age 72 (total sample)	Time point: between 8 am and 10 am Tissue: blood Assay: fluorescence immunoassay	Patients had lower basal oestradiol levels when compared to controls	2
Findikli et al. (2017)	N = 22 Mean age 34 ± 11 (total sample) Inclusion: major depressive disorder according to the DSM-IV Exclusion: physical disease, comorbid mental disorder, drugs influencing prolactin levels, psychotropic medication	N = 18 Mean age 37 ± 10	Time point: between 8 am and 11 am Tissue: serum Assay: radioimmunoassay	No group differences in basal oestradiol levels	3

BMI = Body Mass Index, DSM = Diagnostic and Statistical Manual of Mental Disorders, HRSD = Hamilton Rating Scale for Depression

3.5. Testosterone

Thirteen studies investigated basal testosterone (see Table 3). The average score from the quality assessments was 4 out of 10, suggesting a moderate risk of bias. All but one study included patients with major depressive disorder, whereas three used mixed samples of patients with major depression or persistent depressive disorder. The majority of studies employed liberal eligibility criteria, which meant that patients with comorbid physical or mental illnesses and those on medication were not excluded from participation. Around half of the studies recruited community controls rather than students or hospital employees, and around half used standardised time points and repeated sampling schedules to obtain a measure of testosterone. Sample storage conditions and assay variation were adequate in most studies, although again, no study stated whether lab personnel were blind to the diagnostic status of each analysed participant. Nearly all studies adjusted their analyses for age, and a third of the studies considered socioeconomic status and BMI as potential covariates. Physical activity and smoking, on the other hand, were rarely ever accounted for.

The systematic review indicated lower basal testosterone levels in men with a depressive disorder as compared to healthy controls (seven out of 13 studies found evidence in favour of this). All but two studies, for which original data were not available, were included in the meta-analysis. The findings of the systematic review were confirmed: Patients had significantly lower testosterone than did controls ($k = 11$, $g = -0.45$, 95% CI $[-0.80, -0.10]$; $Z = -2.53$, $p = .012$; see also Fig. 2). Heterogeneity of this analysis was high ($Q = 57.36$, $p < .001$, $I^2 = 83\%$). Meta-regression revealed that, by trend, studies measuring testosterone in blood ($\beta = 0.50$, $p = .062$) and studies controlling for BMI ($\beta = -0.48$, $p = .093$) had a greater likelihood of reporting lower testosterone levels in patients than in controls. No other effect modifiers were identified.

4. Discussion

This systematic review and meta-analysis investigated the extent to which the HPG axis may be altered in male depressive disorders. We report two main findings: First, overall, FSH and LH did not differ between depressed patients and healthy controls. Second, oestradiol was marginally increased in patients (statistical trend), whereas testosterone was decreased.

With regard to the first finding, a closer look at the data reveals that while studies examining FSH unequivocally yielded null findings, this was not quite true of studies measuring LH: Here, some studies also reported lower basal levels (Rupprecht et al., 1988) and a trend for lower LH pulse frequency (Schweiger et al., 1999), and one study found elevated stimulated LH in patients fulfilling criteria for the now obsolete diagnostic subcategory of secondary depressive disorder (Ettigi et al., 1979). Given that only a third of the identified studies provided sufficient data for meta-analysis, and as it was not possible to retrieve data sets from the missing studies because they were mostly published in the 1970s and 80s, further research on LH in male depressive disorders is clearly warranted. This is particularly important as the time span between the FSH and LH studies ranged from 1979 to 2007, with great advances in assay development occurring during this period (i.e., enhanced sensitivity and improved intra- and inter-assay variation).

A similar conclusion must be drawn regarding the role of oestradiol in male depressive disorders: Although a trend for higher basal oestradiol in patients was shown, this finding is tentative as only half of the studies were eligible for meta-analysis. This is particularly noteworthy given that one of the studies for which data were unavailable for meta-analysis reported diminished oestradiol in patients. However, this study did not control for comorbid illnesses or for BMI, and it had the lowest overall quality score. Either way, the tentative oestradiol findings are interesting in the light of more recent evidence of higher levels of the G protein-coupled oestrogen receptor 1 (GPER) (Findikli et al., 2017) and

Table 3
Characteristics of studies comparing testosterone between male patients with depressive disorders and healthy controls.

Study	Patients	Controls	Endocrine assessment	Results	Quality rating
Rupprecht et al. (1988)	N = 6 Mean age 42 ± 15 Inclusion: major depressive disorder according to the DSM-III Exclusion: medication	N = 20 Mean age 37 ± 10	Time points: 7 am and 4 pm Tissue: serum Assay: radioimmunoassay	Patients had lower basal testosterone levels when compared to controls (trend)	3
Davies et al. (1992)	N = 11 Mean age 52 ± 13 Inclusion: major depressive disorder according to the DSM-III Exclusion: not mentioned	N = 10 Mean age 52 ± 11	Time points: 5-min intervals from 5 pm to 5.30 pm Tissue: saliva Assay: radioimmunoassay	No group differences in basal testosterone levels	2
Rubin et al. (1999)	N = 8 Mean age 45 ± 7 Inclusion: major depressive disorder according to the DSM-III-R, HRSD-21 score ≥ 17 Exclusion: major medical illness, comorbid mental disorder, medication interfering with endocrine functioning, psychotropic medication within 2 years	N = 8 Mean age 42 ± 8	Time points: at 6 pm on four consecutive days Tissue: plasma Assay: radioimmunoassay	No group differences in basal testosterone levels (controlling for BMI)	7
Schweiger et al. (1999)	N = 15 Mean age 48 ± 15 Inclusion: major depressive disorder according to the DSM-III-R, HRSD-21 score ≥ 18 Exclusion: major physical disease, history of substance abuse or dependence, psychotropic medication within 7 days	N = 22 Mean age 53 ± 18	Time points: 30-min intervals from 8 am to 6 pm, 10-min intervals from 6 pm to 12 am, 30-min intervals from 12 am to 7.30 am Tissue: blood Assay: radioimmunoassay	Patients had lower basal testosterone levels when compared to controls (controlling for BMI)	6
Kaneda and Fujii (2002)	N = 11 Mean age 62 ± 9 Inclusion: major depressive disorder according to the DSM-IV Exclusion: organic central nervous system disorder, substance abuse, mental retardation, medication	N = 11 Mean age 62 ± 8	Time point: between 11 am and 12 pm Tissue: serum Assay: radioimmunoassay	No group difference in basal testosterone levels	2
Seidman et al. (2002)	N = 45 n = 13 major depressive disorder Mean age 67 ± 6 n = 32 dysthymic disorder Mean age 71 ± 6 Inclusion: major depressive disorder or dysthymic disorder according to the DSM-IV Exclusion: ischemic heart disease	N = 175 Mean age 71 ± 4	Time point: between 9 am and 2 pm (patients) or twice in a 30-min interval within four hours of awakening (controls) Tissue: Serum (controls) Assay: radioimmunoassay (controls)	Patients with dysthymic disorder had lower basal testosterone levels when compared to patients with major depressive disorder and controls	3
McIntyre et al. (2006)	N = 44 Mean age 52 ± 7 Inclusion: major depressive disorder according to the DSM-IV, HRSD-17 score > 16 Exclusion: unstable physical or comorbid mental illness, history of drug or alcohol abuse, uncorrected thyroid disease, psychotropic medication, herbal preparations with antidepressant properties, ECT within 3 months	N = 50 Mean age 51 ± 7	Time point: between 8 am and 11 am Tissue: blood Assay: electrochemiluminescence assay	Patients had lower basal free testosterone levels when compared to controls (controlling for BMI)	2
Eskelinen et al. (2007)	N = 74Mean age 72 (total sample) Inclusion: depressive disorder according to the DSM-IV Exclusion: sex steroids or medication for prostate cancer or benign prostatic hyperplasia	N = 367Mean age 72 (total sample)	Time point: between 8 am and 10 am Tissue: blood Assay: fluorescence immunoassay	Patients had lower basal testosterone levels when compared to controls (controlling for BMI)	3
Markianos et al. (2007)	N = 18 Mean age 47 ± 13 Inclusion: dysthymic disorder according to the DSM-IV Exclusion: chronic psychotic disorder, substance abuse, history of recurrent major depression	N = 36 Mean age 46 ± 12	Time point: between 8 am and 10 am Tissue: plasma Assay: radioimmunoassay	Patients aged below 50 years had lower basal testosterone levels when compared to controls	2
					6

(*continued on next page*)

Table 3 (*continued*)

Study	Patients	Controls	Endocrine assessment	Results	Quality rating
Giltay et al. (2012)	N = 98 Mean age 45 ± 13 (total sample) Inclusion: major depressive disorder according to the DSM-IV Exclusion: primary addiction, psychotic disorder, bipolar disorder, obsessive–compulsive disorder	N = 200 Mean age 45 ± 13 (total sample)	Time points: at awakening, +30, +45, +60 min, at 10 pm, at 11 pm (pooled for analysis) Tissue: saliva Assay: enzyme-linked immunoassay	No group differences in basal testosterone levels (controlling for BMI)	
Matsuzaka et al. (2013)	N = 43Mean age 51 (30–75) Inclusion: major depressive disorder according to the DSM-IV Exclusion: severe or acute physical disease, history of delusions, neurological disorders, use of drugs that may cause depression	N = 50 Mean age 46 (26–74)	Time point: between 7 am and 8 am Tissue: serum Assay: electrochemiluminescence assay	No group difference in basal testosterone levels	3
Sigurdsson et al. (2014)	N = 14 n = 12 major depressive disorder n = 2 dysthymic disorder Mean age 51 ± 16 Inclusion: depressive disorder according to the DSM-IV Exclusion: hypogonadism, prednisolone use	N = 24 Mean age 55 ± 11	Time points: 7 am and 10 pm Tissue: saliva Assay: enzyme immunoassay	No group differences in basal testosterone	5
Giltay et al. (2017)	N = 120 Mean age 70 ± 7 (patients and controls) Inclusion: major depressive disorder according to the DSM-IV Exclusion: dementia, psychotic disorders, bipolar disorder	N = 46 Mean age 70 ± 7 (patients and controls)	Time point: between 8.10 am and 10.45 am Tissue: plasma Assay: second-generation assay without extraction	Patients had lower basal testosterone levels when compared to controls	5

BMI = Body Mass Index, DSM = Diagnostic and Statistical Manual of Mental Disorders, ECT = electroconvulsive therapy, HRSD = Hamilton Rating Scale for Depression.

specific single nucleotide polymorphisms (SNPs) within the oestrogen receptor β gene (Ryan et al., 2011) in male depressive disorders. Together, they point to altered oestrogen signalling in depressed men. Notably, the majority of circulating oestradiol is aromatised from testosterone, and a recent study in obese men found that not only oestradiol per se, but also the imbalance between oestradiol and testosterone, was associated with the level of reported depressive symptoms (Monteagudo et al., 2016). This may suggest a role of increased aromatase activity in male depressive disorders, a subject which seems worthy of further investigation.

The notion of potentially enhanced aromatase activity in depressive disorders fits in well with the main finding of this meta-analysis, namely that of lower testosterone in the same patients. According to meta-regression, effect sizes were not influenced by sample characteristics such as mean age, depression severity, type of depressive disorder, or eligibility criteria. Likewise, most methodological features of a given study (i.e., sampling schedule, storage conditions, assay variation) or confounders used in statistical analyses (i.e., age, socioeconomic status, physical activity, smoking) were found to be irrelevant. Interestingly, however, studies using blood samples and those controlling for BMI had a slightly higher chance of observing significant case-control differences in testosterone (as a trend). The first observation is supported by well-known methodological problems with salivary testosterone (Granger et al., 2004). Specifically, the use of cotton or polyester swabs to collect saliva, issues with blood leakage into the oral mucosa, as well as sub-optimal storage conditions have repeatedly been demonstrated to compromise testosterone values. In line with this, none of the included studies employing saliva sampling yielded positive findings. Regarding the second observation from the meta-regression, it is likely that differences in testosterone between patients and controls may have been masked by group differences in BMI. The BMI is strongly inversely associated with testosterone levels (MacDonald et al., 2010) and related behaviours such as restricted caloric intake can dramatically affect the HPG axis e.g., (Opstad and Aakvaag, 1983; Opstad and Aakvaag, 1982). Hypophagia and weight loss, in turn, are prominent symptoms of major depressive disorders, especially of the melancholic subtype. A higher hypothetical BMI in controls would thus prevent researchers from revealing subtle abnormalities in patients' testosterone levels. However, this remains speculative, especially as barely any studies reported the distribution of melancholic versus atypical subtypes of depression.

Studies inducing hypogonadism in healthy adults have shown that gonadal steroids are directly linked to sexual function: men receiving a GnRH analogue experienced a significant decline in sexual function, which was restored by subsequent testosterone replacement (Schmidt et al., 2009; Bloch et al., 2006; Schmidt et al., 2004). Interestingly, in two of these studies, the authors were also able to show an effect of pharmacologically induced hypogonadism on depression (Bloch et al., 2006; Schmidt et al., 2004). In line with this, congenital endocrine abnormalities presenting with hypogonadism (e.g., Klinefelter syndrome) have repeatedly been linked with depression (Mueller et al., 2014). Gonadal steroid receptors are expressed throughout the entire human brain and – apart from the hypothalamus – particularly in areas such as the amygdala and the hippocampus (McEwen and Milner, 2017). This pattern of distribution may explain the effects of oestrogens and androgens on mood and cognition, and suggests that altered circulating concentrations may be involved in symptoms of depressive disorders beyond sexual dysfunction.

One potential cause of alterations in HPG axis hormones may be dysregulations of the stress-responsive HPA axis. Hyperactivity of the hypothalamic-pituitaryadrenal (HPA) axis has been demonstrated to inhibit the synthesis and secretion of gonadotropin-releasing hormone in the hypothalamus, of FSH and LH in the pituitary, and of testosterone and oestradiol in the gonads (Acevedo-Rodriguez et al., 2018; Viau, 2002). This resonates well with the fact that a meta-analysis found elevated cortisol to be one of the most robust pathophysiological findings in depressive disorders (Stetler and Miller, 2011). In addition,

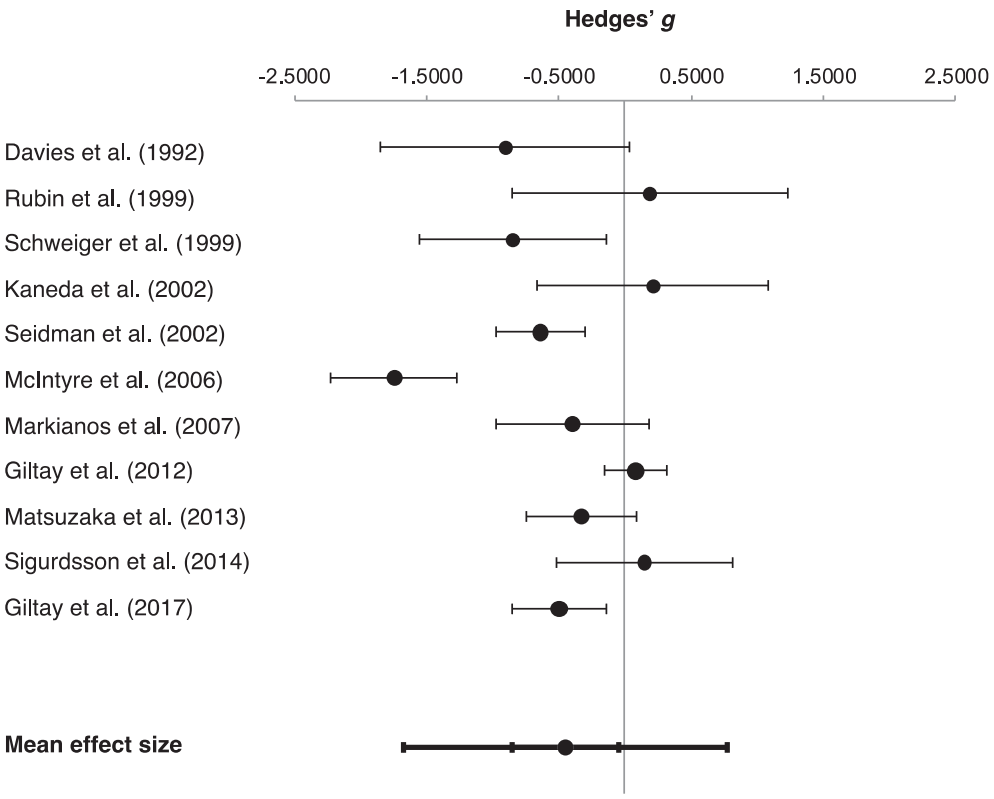

Fig. 2. Forest plot of studies comparing testosterone between male patients with depressive disorders and healthy controls; negative effect sizes indicate that patients had lower testosterone levels when compared to controls; bars indicate confidence intervals; for the mean effect size, both the confidence interval (i.e., the range of expected average effects) and the (larger) prediction interval (i.e., the range of expected individual effects) are indicated.

stress is well-known to act as a predisposing, precipitating, and perpetuating factor in depressive disorders (Hammen, 2005). Taken together, stress may therefore contribute to alterations along the HPG axis, which in turn may facilitate the onset of depressive disorders. Notably, findings on HPA axis activity in depressive disorders are far from being unequivocal see e.g., (Zorn et al., 2017) and case-control studies do not enable the temporal order of these axial disturbances to be established. However, large-scale longitudinal studies suggest that attenuated testosterone is an antecedent rather than a consequence of depressive disorders (Shores et al., 2005; Shores et al., 2004), at least in older men.

The present review constitutes the first attempt at summarising the literature on the HPG axis in male depressive disorders in a quantitative manner, that is, by means of meta-analysis. Additional strengths are the extensive literature search and the rigorous risk-of-bias assessment. However, a number of limitations are equally worthy of mention. First, this meta-analysis was confined to men, although the high incidence of perimenstrual, perinatal, and perimenopausal depressive disorders suggest that the HPG axis is of equal importance in female depression e.g., (Studd and Nappi, 2012; Soares and Zitek, 2008). However, the sheer amount of published studies rendered it impossible to include this line of work in the present meta-analysis, and further meta-analyses focusing on this issue are thus required. Second, the total number of retrieved studies was low. This limits the meaningfulness of the meta-analyses regarding FSH and LH, and prevented us from undertaking meta-regression. Third, it was not possible to gain access to a number of older data sets, even after contacting the authors of the published articles. Finally, heterogeneity between studies was high and the risk-of-bias assessment exposed a number of methodological problems pertaining to this body of research, such as failure to recruit an adequate control group and failure to adjust statistical analyses for relevant confounders (e.g., BMI, physical activity).

In sum, the present systematic review and meta-analysis suggests attenuated testosterone levels in men with depressive disorders. However, further research adhering to rigorous methodological standards is warranted in order to elucidate the role of the HPG axis in male depressive disorders, which could ultimately inform the development of augmentative or alternative treatments for these debilitating illnesses.

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Declaration of Competing Interest

None.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yfrne.2019.100792.

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