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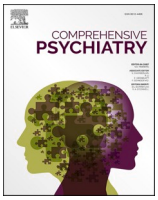

Meta-analysis of cognitive behaviour therapy and selective serotonin reuptake inhibitors for the treatment of hypochondriasis: Implications for trial design

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ABSTRACT

Background: Classification of hypochondriasis as an obsessive-compulsive and related disorder in the International Classification of Diseases 11th Revision (ICD-11) has generated new heuristics for treatment of this common, chronic and disabling disorder. Standard treatment involves cognitive behaviour therapy (CBT) or selective serotonin reuptake inhibitors (SSRIs), but no meta-analysis has so far considered hypochondriasis as a structured diagnosis or assessed the role of medication. A clearer understanding of the relative effectiveness of these interventions and identification of clinically relevant factors moderating the treatment response is needed for clinical guideline development.

Methods: The current systematic review and meta-analysis of interventions for hypochondriasis was preregistered on PROSPERO (CRD42020185768) and follows PRISMA guidelines. We searched MEDLINE, PsycINFO, and Cochrane Library databases until July 2021 for randomized controlled trials (RCTs) of interventions for patients diagnosed with hypochondriasis (or historical diagnostic equivalents). We assessed aspects of study quality using: the CONSORT Checklist for evaluation of RCTs, the Cochrane Risk of Bias 2 tool, researcher allegiance and treatment fidelity. The primary outcome was improvement in hypochondriasis symptoms, comparing intervention and control groups at trial endpoint. Moderator variables were assessed using subgroup and meta-regression analyses.

Results: Searches identified 13 randomised controlled trials (RCTs) ($N = 1405$); 12 included CBT ($N = 1212$) and three included SSRI ($N = 193$) arms as the experimental intervention. Random effects meta-analysis yielded a moderate-to-large effect size for CBT versus all controls ($g = -0.70$ [95% CI -0.99 to −0.41], k = 18, $I^2 = 81.1\%$). Funnel plot asymmetry indicated possible publication bias and two potentially missing trials, reducing the effect size ($g = -0.60$ [95% CI -0.88 to −0.32]). Subgroup analysis showed that choice of control significantly moderated effect size, with those in CBT vs. wait-list ($g = -1.32$ [95% CI -1.75 to −0.90], k = 7, $I^2 = 0\%$) being double those of CBT vs. psychological or pharmacological placebo controls ($g = -0.58$ [95% CI -0.95 to −0.22], k = 7, $I^2 = 82\%$). Analysis of studies directly comparing CBT and SSRIs found a numerical, but not statistical advantage for SSRIs ($g = 0.21$ [95% CI -0.46 to 0.87], k = 2, $I^2 = 58.34\%$) and a modest effect size emerged for SSRIs vs. pill placebo ($g = -0.29$ [95% CI -0.57 to −0.01], k = 3, $I^2 = 0\%$). Most studies (11/13) were rated as high on potential researcher allegiance bias in favour of CBT. Meta-regressions revealed that effect sizes were larger in younger participants, and smaller in better quality and more recent RCTs and those with greater CBT fidelity.

Conclusion: CBT and SSRIs are effective in the acute treatment of hypochondriasis, with some indication that intervention at a younger age produces better outcomes for CBT. In the case of CBT, effect sizes appear to have been significantly inflated by the use of wait list controls, and researcher allegiance bias. We recommend that a

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definitive, adequately controlled trial, designed with respect to the methodological issues raised in this meta-analysis, is needed to determine the magnitude effects for CBT and SSRIs with confidence and the long-term effect of treatments, to inform mental health service provision for this overlooked patient group.

1. Introduction

Hypochondriasis is characterized by an obsessive preoccupation with the possibility of having one or more serious progressive or life-threatening diseases associated with the irresistible urge to repeatedly check physical status or to seek reassurance from physicians or other medical information sources. Emphasis on the intrusive and distressing nature of the health-related preoccupations and associated compulsive checking and reassurance-seeking behaviours led to the classification of hypochondriasis with the Obsessive Compulsive and Related Disorders (OCRDs) in the International Classification of Diseases, 11th revision (ICD-11) [58]. Hypochondriasis is thought to be common, with rates ranging from 0.04–4.5% in the general population to higher percentages in medical settings such as 0.3–8.5% in GP surgeries (locations where a general practitioner regularly sees patients) and 12–20% in specialty hospital clinics [53]. Affecting males and females in roughly equal rates [36], the disorder usually starts in adolescence or in young adulthood. Early in its course, hypochondriasis tends to present as a mild, self-limited problem, and in some people the course remains episodic with infrequent and brief symptomatic periods, often triggered by life stressors. However, for many, the course of the disorder is chronic and relapsing, with around 5% of cases, more often females, experiencing a lifelong unremitting course [38].

Hypochondriasis is a distressing condition and is associated with an increased risk of suicide [52]. It has a profoundly negative effect on health-related quality of life and social and occupational functioning [1,34]. The direct and indirect health-related costs of hypochondriasis include the burden of unnecessary diagnostic interventions, disturbance in the patient-doctor relationship, lost occupational or educational productivity and misuse of disability benefits. For example, according to a recent study [46], at least one patient out of five attending medical clinics in the UK has some form of "health-related anxiety", and the health-care costs of individuals with health anxiety (in terms of outpatient medical care utilization) are 20–30% higher than the adjusted mean cost.

The "treatment-seeking phenotype" is not however the only clinical manifestation of hypochondriasis. Anxiety-related healthcare avoidance and treatment delay in case of actual disease can also lead to increased direct and indirect healthcare cost and health and social burden including lost occupational productivity [26]. In financial terms, the costs of hypochondriasis have been estimated to reach around £56 million per year in the UK, and they represent a large proportion of the €21 billion attributed to the cost of all somatoform disorders combined in the EU [23]. It is therefore relevant to note that an increase in health concerns has recently been reported as a major contributor to mental health difficulties in general population samples during the COVID-19 pandemic [6,27]). Thus, a clear and unmet need exists for timely, effective clinical interventions that produce lasting benefit for patients with hypochondriasis.

Nonetheless, hypochondriasis often goes unrecognized for years and clinicians tend not to identify it as a diagnosis requiring intervention in its own right [39]. The failure to diagnose rests on various physician-related factors, including fears of missing an occult physical disorder, or concerns that giving such a diagnosis is pejorative, or could complicate communication among medical professionals, or cause conflict with the patient. To some extent, these issues reflect the ongoing social stigma associated with being thought to have a mental disorder, as opposed to a physical one [3]. Delay in diagnosis contributes to a longer duration of untreated illness and has proven to be an unfavourable prognostic factor for other OCRDs, such as obsessive-compulsive disorder (OCD), where earlier treatment produces better outcomes [19,53]. Furthermore, without a positive diagnosis of hypochondriasis, medical professionals may be more likely to perform unnecessary clinical investigations 'just in case', thereby at risk of further perpetuating the disorder.

Hypochondriasis was previously classified under somatoform disorders in ICD-10 and DSM-IV and was kept under the family of somatic symptoms and related disorders in the DSM-5. By re-classifying hypochondriasis as an OCRD it was expected that the new ICD-11 definition would help physicians arrive at a more accurate and effective diagnosis. Some preliminary evidence does suggest that this is the case [31]. In this context, understanding the relative effectiveness of the available clinical treatments for hypochondriasis and the factors determining treatment outcome that can be used to select treatments at an individual level is extremely relevant.

Given increased the interest afforded to hypochondriasis in the psychiatric nosology, an expected rise in incidence during the COVID-19 pandemic and the likely damaging effects of untreated or poorly treated illness, alongside uncertainties regarding the effectiveness of existing treatments, the current meta-analysis provides a timely evidence-based assessment of the treatment of hypochondriasis.

1.1. Previous meta-analyses

Three meta-analyses have assessed the use of CBT for hypochondriasis symptoms [2,10,39], and a fourth [48] assessed psychotherapies generally (including for example, psychoeducation). These reviews combined clinical samples diagnosed with hypochondriasis and studies of sub-clinical samples experiencing the broader 'health anxiety'. To date, no meta-analysis has focused exclusively on hypochondriasis as a structured diagnosis or assessed the impact of medications for hypochondriasis. Nonetheless, the previous meta-analyses consistently indicate that CBT (or psychotherapies generally) reduces symptomatology with a large effect size [2,10,48]. The meta-analysis by Olatunji et al. [39] identified a greater effect in those with a greater severity of baseline symptoms, those who larger number of CBT sessions, and had fewer depressive symptoms [39].

Nonetheless, as most of these meta-analyses included studies with open-label designs, inconsistently analysed the rating instruments, or included non-structured diagnosis (e.g., health anxiety) and subclinical samples, considerable uncertainty remains about these findings as any of these factors are likely to impact findings [42]. For example, in the most recent meta-analysis published by Axelsson and Hedman-Lagerlof [2], we showed that the choice of control condition was a significant moderator of effect size [42].

1.2. Aims

We evaluated the evidence-basis supporting available treatments for patients diagnosed with hypochondriasis to determine their effectiveness and the patient related and study related factors moderating the treatment response. In the light of the new ICD-11 classification, we were particularly interested in evidence relating to Exposure and Response Prevention (ERP) as the favored form of CBT for many OCRDs [43] as well as higher dosages of SSRIs [19].

2. Method

2.1. Design and search strategy

The review and meta-analysis was pre-registered at the International Prospective Register of Systematic Reviews: PROSPERO CRD42020185768: Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020185768. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in conducting and reporting our findings [40]. We searched three databases: Pubmed, Cochrane Library, and PsycINFO from the earliest publication until July 2021. The search keywords consisted of: hypochondri* OR "health anxiety" OR "illness anxiety disorder" AND "randomized controlled trial" OR "randomised controlled trial" OR RCT.

2.2. Study selection

Studies were deemed eligible for inclusion if they: a) assessed participants meeting the diagnostic criteria of ICD Hypochondriasis or DSM Illness Anxiety Disorder; b) were randomized controlled trials employing any therapeutic intervention against any control comparator; and c) were written in English.

The first stage of the analysis focused on removing duplicate studies. Once this had been completed, researchers reviewed the title of the selected studies and excluded those that were ineligible. Next, the abstracts of the studies were assessed and based on their summary of contents, those that were inapplicable were excluded. Finally, the remaining studies were subject to a full text review.

The searches and extraction were conducted independently by two researchers (LP and AC). In the occurrence of any disagreements, the reasons were discussed among the research team and a consensus formed.

2.3. Data extraction

Data from the RCTs meeting inclusion criteria were extracted and placed in a Microsoft Excel spreadsheet. The inputting of study data into tabulated spreadsheets was conducted by one researcher and was doublechecked by a second researcher before the data was cleaned. We decided to use as primary outcomes the following scales: the Hypochondriasis Y-BOCS (H-YBOCS), Whiteley Index (WI), the Health Anxiety Inventory (HAI), and the short-form HAI (S-HAI); these scales are the most commonly used in RCTs of Hypochondriasis and the most consistent among the studies. If these questionnaires were not available, the primary outcome measures of the specific studies were used. For two studies [9,56], visual analog scales with multiple items were used to measure hypochondriasis symptoms; in this instance, the most objective items were selected as primary outcomes: in Warwick et al. [56], the global problem item rated objectively by the assessor was used, and similarly in Clark et al. [9] the distress/disability item rated by the assessor (clinician) was used.

Secondary measures were entered into a separate spreadsheet. These included measures of depression, anxiety, and obsessive-compulsive symptoms. Moderator variables such as gender, mean age, duration of illness and treatment, as well as hypochondriasis scores at baseline for both intervention and control groups were also extracted.

The data was cleaned using Data Extraction for Complex Meta-Analysis, DECiMAL [41]. Data cleaning consisted of removing non-numerical information from the extraction spreadsheet and substituting this information with numerical values. To keep track of what information this system of numbers was replacing, a glossary was kept and maintained in a separate spreadsheet. In the instance of the intervention type, CBT was assigned a value of 1, Behavioral stress management 2, Short term psychodynamic psychotherapy 3, and so on according to how many different forms of interventions there were. This was also the case for the type of instrument that was used to measure Hypochondriasis: Health anxiety inventory =1, short version-HAI = 2, Whitely index, = 3, etc. This allowed for transference to a Comprehensive Meta-Analysis file a smoother process.

2.4. Study quality

Overall study quality was assessed using the CONSORT checklist [44], in which a two-point grading system was assigned to each criterion; a value of 0 was given if an item was not present, a value of 1 if the CONSORT item was present but not clear, and a value of 2 if the item was present and clear. From this, a summation of quality was produced.

The Cochrane Risk of Bias tool [47] was used to assess risk of bias in the following domains: selection bias, performance bias, detection bias, attrition bias and reporting bias. Incongruences were discussed amongst the research team.

2.5. Risk of bias

The Cochrane risk of bias tool version 2.0 [47] was used to assess each study. Incongruences were discussed amongst the research team and a conclusion reached.

2.6. Researcher allegiance

Researcher allegiance was assessed for all trials using an adapted version of the 'researcher allegiance assessment tool' from Cuijpers et al. [12], which was originally designed for detecting researcher-bias in studies of psychotherapies for depression and was previously used in meta-analyses examining psychological interventions for psychosis [49] and OCD [43]. In order to be able to apply the assessment to the full range of retrieved studies, in particular those studies comparing a medication with pill placebo or a psychological treatment with a non-active control group such as waiting list (WL), we adapted the version of the tool used by Turner et al. [49], following the principles of Cuijpers et al. [12], and made changes to some of the items. The questions used to evaluate the presence of researcher allegiance are listed in Table 1.

2.7. Treatment fidelity

An assessment was made of CBT treatment fidelity - based on the descriptions given in the studies - by an independent CBT expert (LD). Assessments were made on 10 relevant factors, including the presence of: Psychoeducation; Problem Solving; Cognitive Therapy (identification of Negative Thoughts, Formulation and cognitive reattribution etc); Exposure and ERP; Relaxation; Stress Management; Mindfulness; Acceptance and Commitment Therapy, Homework tasks and experience of therapists working in this area. Each component was given a score of between zero (insufficient information was available to decide) and three (awarded where the component appeared was at a level consistent with recognised 'best practice').

2.8. Statistical analysis

The statistical database package used in this meta-analysis was

Table 1
Researcher allegiance criteria - adapted version of the researcher allegiance tool from [12].

If the answer to any of these questions is yes, the study is deemed at risk of researcher allegiance.
• Is only one of the interventions mentioned in the title? • In the introduction, is one of the experimental interventions explicitly described as being the main experimental intervention? • Does the choice of control intervention favour any of the experimental interventions investigated in the study?

Comprehensive Meta-Analysis V2. Hedge's *g* based on random effects was used to calculate the effect sizes. Following Cohen's convention, an effect size of 0.2 was considered small, 0.5 as moderate, and 0.8 as large. Hedge's *g* was calculated using the mean, standard deviation and sample sizes of the intervention and control groups end of trial. Where insufficient data were presented to calculate effect sizes, we contacted authors for the missing data; and this resulted in one author providing us with raw means (and standard deviations) at post treatment for both intervention and control groups.

When multiple time-points were available in studies, the post-treatment values were favored. Two studies did not lend themselves to this format of data entry [5,51]. For Buwalda et al. [5], the pre vs post treatment improvement scores were given instead of a post treatment mean score. Thus, the Hedge's *g* was calculated using sample sizes and a *t*-value. Similarly, the paper by Tyrer et al. [51] reported mean improvement from baseline. To calculate this effect size, sample sizes and an independent groups *p* value was used. Sample sizes were divided by the number of their involved comparisons so as not to inflate the weighting for effect sizes.

Heterogeneity was assessed using the I^2 statistic, and for interpretation we followed Cochrane guidance [30]: 0%–40% as might not be important; 30–60% as may represent moderate heterogeneity; 50–90% may represent substantial heterogeneity; 75%–100% representing considerable heterogeneity.

The identified interventions, CBT and SSRIs, were analyzed together and separately. The efficacy of CBT was assessed through comparisons of effect sizes with different comparators (other psychological interventions, placebo, treatment as usual, wait list control), as well as CBT against SSRIs. We did not plot active comparators (alternative psychological interventions other than CBT) against control groups as they were too varied in form. For example, in the case of the study by Hedman et al. [28], the control arm was a discussion-forum and this was included as a psychological placebo control. The efficacy of SSRIs was plotted against pill placebo.

Subgroup analyses were conducted for categorical moderator variables including preregistered analyses of researcher allegiance, and risk of bias. Publication bias was assessed by observing funnel plots to test for any asymmetry. Test statistics such as Duval and Tweedie's trim and fill method, Begg's rank test, and Egger's regression test were used to infer the potential of there being publication bias.

Additionally, meta-regression analyses using Method of Moments were planned for continuous moderator variables including: Mean age, proportion of females in sample, depressive and anxious symptoms, obsessive-compulsive symptoms at baseline, hypochondriasis scores at baseline, duration of illness and treatment, study quality (Risk of Bias tool), year of study and treatment fidelity. Although there is no definitive minimum number of studies required for meta-regression, we follow the general recommendations of at least 6 to 10 studies for a continuous variable [21,30], and for a categorical subgroup variable, a minimum of 4 studies per group [21].

3. Results

3.1. Description of studies

The PRISMA flowchart (Fig. 1) details the search and screening process. 463 studies were retrieved through the database search. Of these, 44 were removed as duplicates. 381 were excluded based on screening the titles and abstracts. Of the 38 studies whose full text was assessed for eligibility, 25 failed to meet our inclusion criteria (see Fig. 1).

The main characteristics of the studies are presented in Table 2. A total of 13 studies were identified (12 RCTs contained at least one arm that was CBT; 3 contained at least one arm that was SSRI). The total number of participants in the 13 trials was $N = 1405$. (See Table 3.)

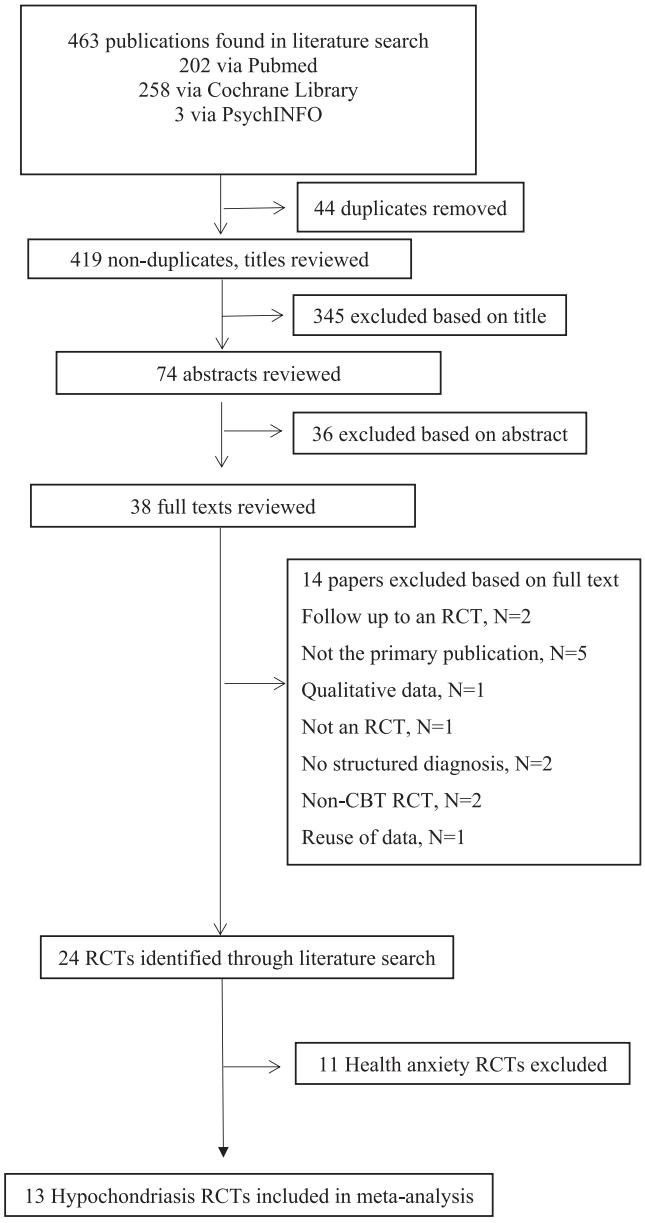

Fig. 1. Prisma flow-chart of the studies.

3.2. Randomised controlled trials of CBT

Twelve eligible RCTs involving 18 independent comparisons were identified. The form and mode of delivery of CBT intervention differed from study to study (six CBT, three CBT with ERP, one mindfulness-based CBT, two online CBT). Similarly, the choice of control differed largely across the comparisons – five studies included wait list (WL) as the principal control, five a placebo (either psychological placebo or pharmacological/pill placebo) and two, treatment as usual (TAU). The duration of the studies ranged from 8 weeks to 16 weeks, apart from the study by [51]; see below) that lasted for 24 months. A few studies included an uncontrolled follow-up phase. Two studies [17,25] investigated both CBT and SSRI head-to-head. Seven of the 12 studies used an intent-to-treat (ITT) analysis [17,25,28,29,35,45,57].

Eleven of the 12 studies investigating CBT found a significant advantage for CBT versus control on the primary analysis. CBT with ERP is the recommended psychological treatment for OCD, and therefore of particular interest for hypochondriasis. All three ERP studies found the intervention to be effective (Visser et al., 2001) [29,57]. In the largest

Table 2
Features of the included studies.

Study name	Structured diagnosis	Mean Age	Female %	Intervention (n)	Control (n)	Treatment duration	Outcome measures
Warwick et al. [56]	SCID for DSM-111-R	37.00	45.00	CBT (14)	WL (15)	16 weeks	Visual analogue scale
Clark et al. [9]	SCID for DSM-111-R	34.00	67.00	Cognitive therapy (21)	BSM (23) & WL (14)	28 weeks	Visual analogue scale
Visser & Bouman [55]	ADIS-R	36.20	50.00	CBT (20)	ET (22) & WL (14)	12 weeks	IAS-HA
[5]	ADIS	41.50	72.70	CBT (24)	PS (24)	6 weeks	GIAS
Greeven et al. [25]	SCID for Axis-1	41.30	58.00	CBT (37) & Paroxetine (37)	Placebo (35)	16 weeks	WI
Fallon et al. [16]	SCID for DSM-111-R	37.80	50.00	Fluoxetine (18)	Placebo (14)	12 weeks	HAI**
Hedman et al. [28]	HAI*	39.30	74.07	iCBT (40)	Discussion forum (41)	12 weeks	HAI**
Sorensen et al. [45]	ICD & SCAN	37.00	63.00	CBT (20)	STPP (20) & WL (36)	16 weeks	HAI**
McManus et al. [35]	SCID for Axis-1	41.28	75.00	MBCT (36)	TAU (38)	8 weeks	SHAI
Hedman et al. [29]	ADIS	41.70	79.11	iCBT (79)	iBSM (79)	12 weeks	HAI**
[51]	SCID for DSM-IV	50.30	52.00	CBT-HA (190)	TAU (183)	12 weeks	HAI**
Weck et al. [57]	SCID for DSM-IV	40.05	59.52	CBT (19) & ET (19)	WL (35)	12 weeks	H-YBICS
[17])	SDIH	39.70	43.58	CBT (43) & Fluoxetine (45)	Placebo (44)	24 weeks	WI

Foot note: ADIS = Anxiety Disorders Interview Schedule, ADIS-R = Anxiety disorders Interview Schedule-Revised, SCID for DSM-111-R = Structured Clinical Interview for DSM-III-R, HAI* = Health Anxiety Interview, SCID for Axis-1 = Structured Clinical Interview for DSM-IV-TR Axis 1 disorders, SCID for DSM-IV = Structured Clinical Interview for DSM-IV, SCAN = Schedule for Clinical Assessment in Neuropsychiatry, SDIH = Structured Diagnostic Interview for Hypochondriasis, CBT = Cognitive Behavioural Therapy, WL = Waiting List, BSM = Behavioural Stress Management, ET = Exposure Therapy, PS = Problem Solving, iCBT = internet based-CBT, STPP = Short Term Psychodynamic Psychotherapy, MBCT = Mindfulness Based Cognitive Therapy, TAU = Treatment as usual, iBSM = internet based-BSM, CBT-HA = CBT-Health Anxiety, IAS-HA = Illness Anxiety Scale-Health Anxiety, GIAS = Groningen Illness Attitude Scale, WI = Whitely Inventory, HAI** = Health Anxiety Inventory, SHAI = Short-HAI, H-YBOCS = Yale-Brown Obsessive-Compulsive Scale for Hypochondriasis.

Table 3
Meta-regression analyses.

	Mean (SD)	Range	Z-test
Age (k = 17)	39.31 (3.73)	34–50	Z = 2.01, df = 1,16, $p = 0.04$*
Proportion of females (k = 17)	60 (11.12)	43% - 79%	Z = -0.96, df = 1,16, $p = 0.33$
Study Quality (k = 17)	44.78 (11.46)	27–61	Z = -2.27, df = 1,16, $p = 0.02$*
Treatment Fidelity (k = 17)	10.22 (3.29)	5–20	Z = -2.17, df = 1,16, $p = 0.03$*
Year of Publication (k = 17)	2008. 46 (6.65)	1996–2017	Z = -2.29, df = 1,16, $p = 0.02$*
Duration of Illness (k = 13)	29.71 (32.21)	5.80–103.10	Z = -0.69, df = 1,12, $p = 0.49$
Duration of Treatment (k = 13)	14.62 (6.60)	6–28	Z = -0.72, df = 1,12, $p = 0.47$
Depression BDI (k = 7)	8.59 (3.14)	3.27–13.06	Z = 0.30, df = 1,6, $p = 0.77$

RCT by Hedman et al. [29] which randomized 158 patients, internet-delivered exposure-based CBT ($n = 79$) produced statistically greater improvement than behavioral stress management (n = 79). In the two other ERP studies (Visser et al., 2001) [57], patients (respectively $n = 78$ or $n = 84$) were randomly allocated to ERP, Cognitive Therapy (CT) or waiting list (WL). In both studies, ERP and CT were more effective than WL and no different from one another, but the studies were probably not powered to show a between-active-arm difference. In the study by Visser et al. (2001), 52 patients were followed up under uncontrolled conditions for an additional 7 months, at which point gains in both ERP and CT arms were maintained.

3.2.1. *Effectiveness of CBT in hypochondriasis*

We performed a random effects meta-analysis of the 12 available RCTs involving CBT (18 independent samples, see Fig. 2). The results yielded a significant improvement in hypochondriasis symptoms ($g = -0.70$ [95% CI -0.99 to −0.41]; k = 18; $p < 0.001$), however considerable heterogeneity emerged across study effect sizes ($I^2 = 81.1\%$; $p < 0.001$). Nine of the 18 individual comparisons gave non-significant effect sizes as the confidence intervals crossed the zero-line and CBT and pill placebo did not differ in efficacy ($g = -0.065$ [95% CI: −0.04 - 0.43]).

Begg and Mazumadar rank correlation identified a significant tau (−0.41, $p < 0.01$), Egger's regression intercept was also significant (intercept = −2.12, $p = 0.05$). The funnel plot showed visible asymmetry and Trim and Fill analysis indicated possible publication bias with two potentially missing trials, reducing the effect size ($g = -0.60$ [95% CI -0.88 to −0.32]). (See Fig. 3.)

3.2.2. *Subgroup analyses*

Subgroup analyses were used to compare CBT against the various classes of control implemented across the studies. CBT was significantly superior to WL controls ($g = -1.32$ [−1.75 to −0.9], k = 7, $p < 0.001$; $I^2 = 0\%$) and a form of psychological or pill placebo control ($g = -0.58$ [−0.95 to −0.22], k = 7, $p = 0.002$; $I^2 = 82\%$), was superior to TAU ($g = -0.29$ [−0.89 to 0.31], k = 2, $p = 0.54$; $I^2 = 0\%$) without statistically significance, but was not superior against SSRI ($g = 0.21$ [−0.46 to 0.87], k = 2, $p = 0.35$; $I^2 = 58.34\%$). The effect size for CBT compared to WL was significantly larger than the effect size for CBT vs a psychological or pill placebo control ($p < 0.001$); the other controls groups had too few studies for comparison (see Fig. 4).

In the subgroup analysis for intention to treat (ITT) approach, we found that the 11 studies with ITT have a smaller effect size ($g = -0.61$ [−1.0 to −0.21], k = 11, $p = 0.003$; $I^2 = 84.6\%$, $p < 0.001$) compared to the 7 studies without ITT approach ($g = -0.9$ [−1.42 to −0.38], k = 7, $p = 0.001$; $I^2 = 76.3\%$, $p < 0.001$); however there was not a statistically significant difference between groups ($p = 0.39$).

We also ran a subgroup analysis for blinding to intervention (no-blinding vs single-blinding) and we found that the effect size was numerically greater for the unblinded studies ($g = -0.77$ [−1.3 to −0.22], k = 6, $p = 0.006$; $I^2 = 63.6\%$, $p = 0.01$), compared to studies with single-blinding ($g = -0.68$ [−1.05 to −0.31], k = 12, $p < 0.001$; $I^2 = 85.5\%$, $p < 0.001$), without statistical significance between the two groups ($p = 0.78$).

3.2.3. *Meta-regressions*

Effect sizes were significantly larger in younger participants, and smaller in better quality trials and in more recent trials (the two are likely to be related). Study quality was measured through the CONSORT checklist and proved to be a significant moderator of the overall effect size. Finally, we found that effect sizes were significantly larger in trials rated as having greater CBT fidelity (see Table 3).

3.2.4. *Treatment fidelity*

The generally recognised CBT interventions for Hypochondriasis involve psychoeducation combined with cognitive therapy and exposure with response prevention (such as described by [15,50]). Sometimes

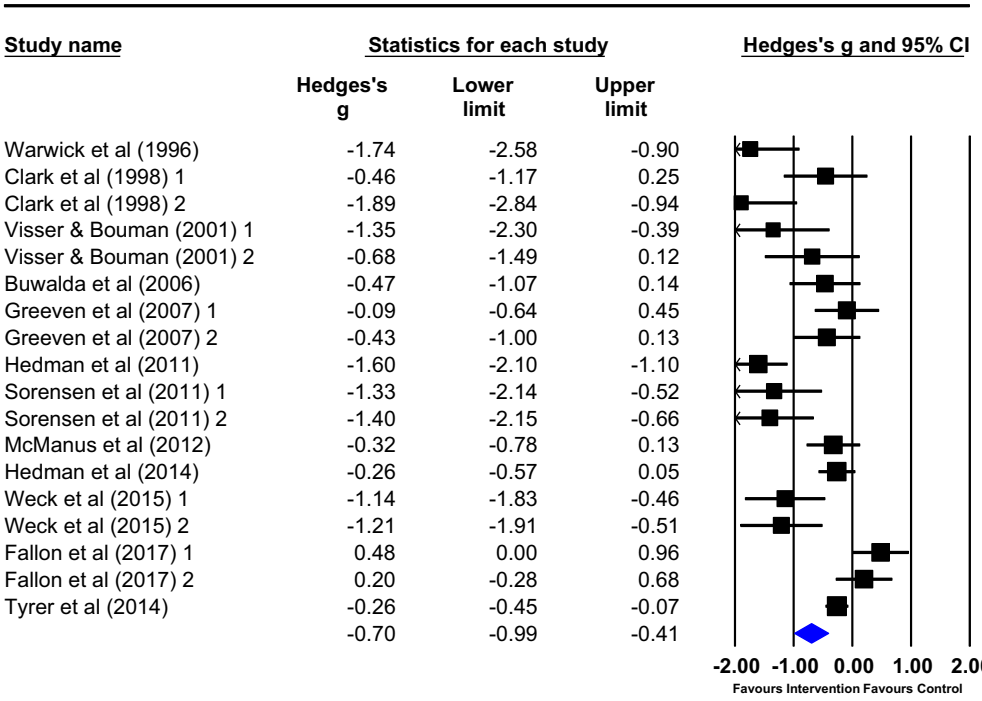

Fig. 2. Hypochondriasis symptom scores at end of treatment for the 12 CBT studies (k = 18).

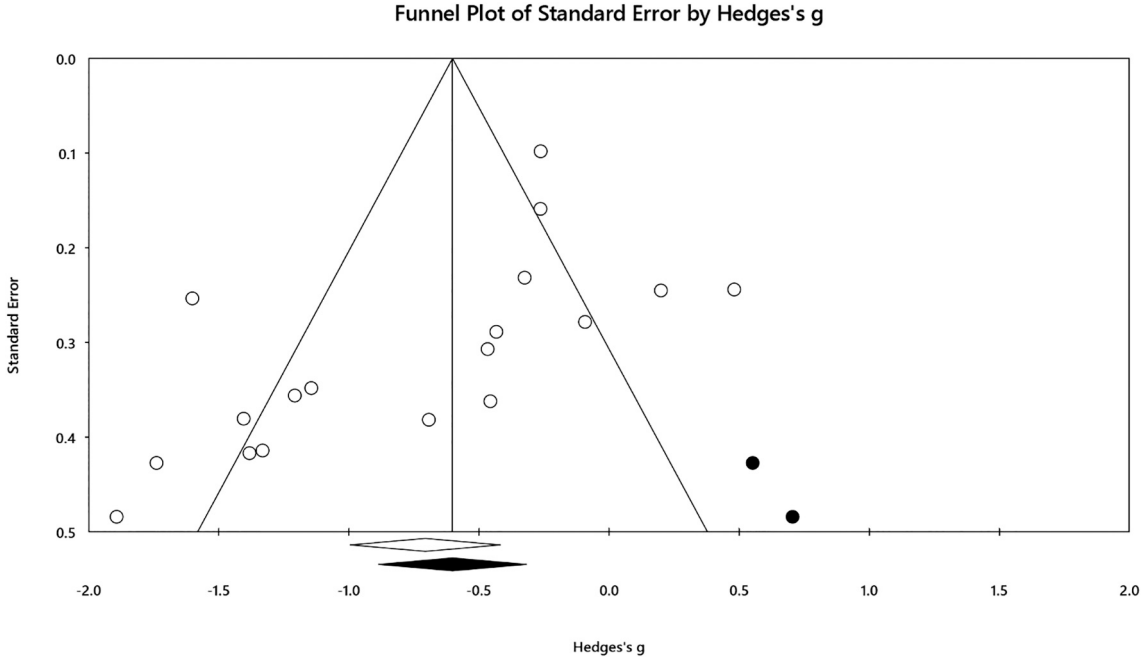

Fig. 3. Funnel Plot indicating potential publication bias.

additional interventions have been proposed including the addition of mindfulness to the CBT model [35,48].

The scores ranged from a value of 2 (low treatment fidelity) [45] to a value of 13 (high treatment fidelity) [28,29]. Individual scores are shown in Appendix 1.

3.3. Randomised controlled trials of pharmacological therapy

Three studies investigated SSRIs against pill placebo [16,17,25], of which two [17,25] tested both CBT and SSRIs against pill placebo, which choice of control is arguably inadequate for the CBT arms, as pill placebo does not control for non-specific therapist-related effects. All three studies used an ITT analysis and all showed a significant advantage of SSRIs over placebo. In the 16 weeks study by Greeven et al. [25], 112

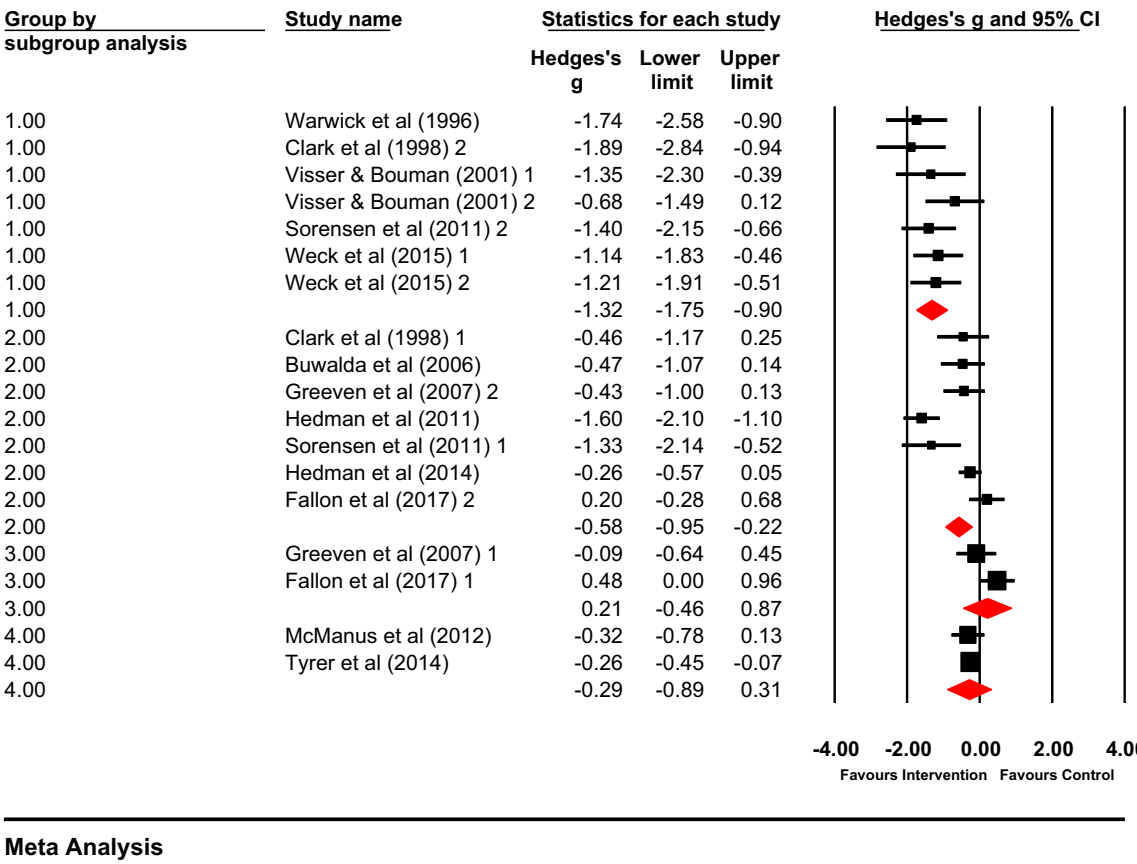

Fig. 4. Subgroup Analysis for type of control.
Note. 1 = CBT vs wait list; 2 = CBT vs psychological control; 3 = CBT vs SSRI; 4 = CBT vs TAU

patients were randomized to paroxetine at a dosage of 40 mg or CBT. Both active interventions were superior to pill placebo with no statistically significant difference between them, though again the study may not have had sufficient power to detect a difference.

In the study by Fallon et al. [16], 45 patients were randomized to an "optimised" dose of fluoxetine (mean dosage = 51 mg) ($N = 24$) or placebo ($N = 21$) for 36 weeks. The primary outcome was the acute treatment response at week 12. Significantly more responders were seen in the fluoxetine group compared with the placebo group, however there was no significant between-group improvement difference on the continuous secondary outcome measure (Whiteley Index).

In the largest RCT involving an SSRI [17], 195 patients were randomized to one of four arms: fluoxetine (mean dose 41 mg) vs CBT vs [fluoxetine (mean dose 31 mg) + CBT] vs pill placebo. The primary analysis assessed categorical outcomes at week 24, with responders defined as having a stringent 25% or greater improvement over baseline on both the Whiteley Index and the H-YBOCS-M. The response rate was greater with combined therapy than either fluoxetine or CBT alone; all three were more effective than placebo. Secondary analyses of the Whiteley Index as a continuous measure revealed that, compared to placebo, fluoxetine (but not CBT) was significantly more effective at week 24 and had a significantly faster rate of improvement. Participants on fluoxetine, but not on CBT, also showed significant improvements in anxiety symptoms and quality of life compared to placebo.

Thus, SSRIs appear an efficacious treatment for hypochondriasis. Whereas patients often received greater than the minimum licensed dosage, in the absence of fixed dose comparator arms it was not possible to infer a dose response relationship.

3.3.1. *Effectivess of SSRIs*

The random effects meta-analysis of the 3 SSRIs studies found a signficanmt effect size of −0.29 ([−0.57 to −0.01], k = 3, $p = 0.04$ ($I^2 = 0\%$, $p = 0.62$)) (see Fig. 5), with the all 3 individual stuides providng non-significant effect sizes (confidence intervals crossing the zero-line).

3.3.2. *Randomized controlled trials of pharmacotherapy versus psychotherapy*

Two studies directly compared CBT against SSRIs [17,25]. CBT did not differentiate from SSRI (paroxetine) in one [25]; in the other, longer (24 week) trial [17], the two treatments did not differ using the primary categorical analysis, but on a secondary continuous outcome analysis utilizing the Whitely Index, CBT was shown to inferior to SSRI (fluoxetine) and equivalent to pill placebo.

3.4. *Long term treatment*

As hypochondriasis follows a chronic course, determining the long-term effectiveness (at least 12 months) of treatments is crucial. Only one RCT, in which patients were randomly assigned to CBT ($n = 205$) or standard care ($n = 212$), analysed long-term outcomes of treatment. Patients were followed-up under controlled conditions for up to two years. The study was unable to demonstrate evidence of cost effectiveness for CBT for hypochondriasis, but symptomatic improvement on CBT was found to be sustained at 24 months, [51].

One other naturalistic study [24] followed up patients completing the acute-phase study treatment [25] for 18 months under open label conditions and found that both CBT (33 patients) and paroxetine (29 patients) continued to be effective. Another uncontrolled naturalistic

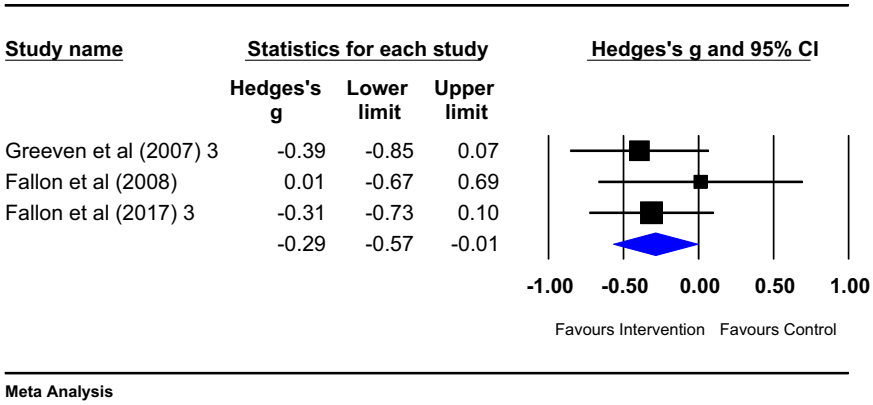

Fig. 5. Hypochondriasis symptom scores at end of treatment with SSRIs against pill placebo.

follow-up study of 58 patients with DSM-IV hypochondriasis who had participated in a trial of SSRI treatment 4 to 16 years earlier (mean ± SD = 8.6 ± 4.5 years), hinted that the gains for SSRIs might persist in the long term [59].

3.5. Quality of the studies

3.5.1. Risk of Bias

Risk of bias was assessed for all the 13 RCTs using the Cochrane Risk of Bias 2 tool (a summary of these assessments is provided in Appendix 2) by two independent raters (AC and LP). In case of disagreement, a third author (KL) was consulted to mediate consensual decisions. Five CBT studies were deemed as having high risk of bias, two studies with some concerns, and three with low risk; two studies involving CBT and SSRI were deemed as low risk, while the one remaining study of SSRI was assessed as having some concerns in terms of bias (see appendix 2).

Two separate independent raters (UA and UP) assessed the studies using the Consort checklist and discrepancies were solved by consulting a third (LP) independent rater (see Appendix 3). In the case of the 10 CBT studies that did not include SSRIs, the overall quality score on the CONSORT checklist was in the range of 27–55. The 3 SSRIs studies had an overall good quality (CONSORT scores ranging from 48 to 50).

3.5.2. Researcher allegiance

Assessments of researcher allegiance resulted in 11 studies assigned to high allegiance to CBT and 2 studies to low allegiance (one study comparing SSRI and placebo [16] and one comparing two forms of CBT [5] (see appendix 4).

4. Discussion

The current systematic review and meta-analysis is the first to investigate treatment outcomes from RCTs assessing samples with a structured diagnosis of hypochondriasis. End-of-trial data from 12 RCTs (18 samples) showed that CBT improved symptoms with a moderate-to-large effect size ($g = -0.71$), though some evidence of publication bias indicated reducing the effect size ($g = -0.60$) and considerable heterogeneity emerged across studies ($I^2 = 81.5\%$). Only three trials assessed SSRIs, indicating a small but significant reduction of symptoms ($g = -0.29$), with no heterogeneity present. We could find little evidence concerning the longer-term effectiveness for either form of intervention – in all but two studies, the interventions were tested under controlled conditions for 16 weeks or less.

The effect size reported here for CBT is comparable if a little smaller those reported in four previous meta-analyses ([48], −0.86 [95% CI: −1.25 to −0.46]; [39], 0.95 [95% CI: 0.66–1.22]; [10], 1.01 [95% CI 0.77–1.25]; [2], 0.79 [95% CI: 0.57–1.01]). Our somewhat smaller effect size might be related to our exclusion of studies not using a structured hypochondriasis diagnosis, while three of the previous meta-analyses included subclinical and/or those identified as having health anxiety [2,10,39]. By contrast, our findings more accurately reflect outcomes for patients with a diagnosis of hypochondriasis and seeking psychiatric care. Thomson and Page looked at psychotherapeutic interventions in general (e.g. psychoeducation) and not specifically CBT.

Our meta-analysis extends previous work by providing insights into the impact of aspects of trial methodology on the confidence that we might assign to the reporting of outcomes. We report that the effect sizes for CBT efficacy strongly depend upon the choice of the control comparator. Indeed, a substantial variety of control conditions were used, with five out of the twelve CBT trials relying upon WL controls. Like others [11,60], we have remarked previously on the inadequacy of using WL as a fair control for a psychological treatment like CBT [42,43]. The effect size for CBT compared to WL reported here was more than twice as large as that for CBT vs psychological control or pill placebo, which is arguably a fairer control comparator than WL. The principal problem lies in the fact that a waiting-list does not control for nonspecific therapeutic ingredients of psychotherapy [12], and may exaggerate the effect size by partly inducing a nocebo effect in the controls. This pattern of findings is consistent with the effect-size inflation often associated with the use of WL controls and their potential for eliciting nocebo effects (e.g. [14,22]). As noted by Leichsenring and Steinert [33] "When examining efficacy, a treatment may be compared with different comparators, that is, with an established treatment, treatment as usual, a placebo, or a waiting list, with *decreasing strictness of the empirical test*." (p.1323, our italics). Within the framework proposed by Chambless and Hollon [8] to determine criteria for empirically-supported treatments, CBT would be identified as *efficacious*, i.e., outperforming no treatment in multiple RCTs conducted by different research teams, but would not be regarded as *specific in mechanisms of action*.

Moreover, as noted above, the other control conditions in CBT studies varied considerably, and included: psychodynamic intervention [45], online self-guided help with information on hypochondriasis [28], behavioral stress management [29], treatment as usual [51], problem-solving [5]. Such variability in controls undoubtedly contributes to the substantial heterogeneity among the CBT results. As hypochondriasis is now considered as an OCRD, relaxation might be considered a fair option in future trials, as this intervention has been shown to be a credible psychological control for CBT with ERP in OCD trials [18].

Indeed, looking at those CBT studies employing a psychological control or pill placebo, and at the SSRI studies, which all used pill-placebo as the control condition, we find treatment produces a small to moderate effect only. This, alongside the large amount of heterogeneity of findings seen among the CBT studies ($I^2 = 79.97\%$), points to the need for better designed definitive trials to be conducted both for CBT and SSRIs. Major limitations included the small sample sizes tested in

most of the trials, meaning that many of the studies were likely to have been underpowered (possibly linked to effect-size inflation-see below) and unable to determine between-intervention differences between active comparators. Additionally, the absence of ITT analyses, affecting five out of the twelve CBT trials, could exposes them to further bias, due to non-random exclusion of patients and potential for false positive results [32].

Our meta-analysis also demonstrates that most studies (11/13), including two studies investigating SSRIs, show researcher allegiance bias in favour of CBT. This finding casts further doubt on the magnitude of the CBT effect size and indicates the need for a high-quality, definitive CBT study to determine the effect size in hypochondriasis. Confirmatory findings emerged in our regression analyses, which found a smaller effect size in better quality trials, though effect sizes were larger in trials rated as having greater CBT fidelity. Based on our analysis, to reduce the risk of bias, a definitive CBT study should employ a fairly-matched control condition, an ITT analysis and strategies to ensure adequate treatment fidelity. As the effect size is used to calculate the sample size needed to provide adequate statistical power, it will be important for researchers to avoid falling into the trap of using inflated effect sizes for designing future hypochondriasis studies.

Inflation of the effect size in published RCTs and meta-analyses is also likely to impact upon clinical guidelines, treatment recommendations and clinical service provision. To date, neither of the two main UK evidence-based clinical guideline providers - the National Institute for Health and Care Excellence (NICE) (https://www.nice.org.uk) and the British Association of Psychopharmacology (https://www.bap.org.uk), nor the American Psychiatric Association Practice Guideline (https://www.psychiatry.org), have produced specific treatment guidelines for hypochondriasis. However, a revision of the 2005 NICE guidance on the OCRDs that currently only covers OCD and body dysmorphic disorder, is planned [37]. As hypochondriasis is now part of the 'OCRD family' and considering our findings supporting the use of both CBT, including CBT with ERP, and SSRIs, there would be strong arguments for including hypochondriasis in such a revision. Based on our findings, forms of CBT and SSRIs would appear effective treatments for hypochondriasis, each with a small to moderate effect size.

We were unable to detect evidence of any advantage of one treatment over the other. Effect sizes were larger in younger participants, suggesting early intervention is likely to be helpful, and emphasising the importance of accurate and timely detection and intervention.

Our findings also suggest that while CBT and SSRIs are modestly effective, newer, more efficacious treatments are needed and that confirmatory research should pay attention to the critical methodological issues outlined by our meta-analysis. The reclassification of hypochondriasis in the ICD-11 family of OCRDs offers exciting new heuristics for future clinical research extending beyond the investigation of generic forms of CBT or SSRIs, for example by 'repurposing', as candidate treatments, interventions already known to be effective for other OCRDs e.g. high dose SSRIs, antipsychotic augmentation, CBT with ERP, other behavioural forms of psychotherapy such as habit reversal therapy, neurostimulation, relapse prevention [20], and service models e.g. early intervention services [4,19], highly specialised services for resistant disorder [7,54]. Therefore, there are grounds to be optimistic that through the benefits that rigorous trial methodology will bring, new forms of effective treatment and service provision will become available for this poorly recognised, costly and burdensome illness.

5. Limitations

Our study has a number of limitations. First, the number of studies including SSRI interventions was very small, therefore the results relating to pharmacotherapy should be interpreted with caution. Additionally, the SSRI trial designs did not allow the differential effect of treatment dosage to be determined. As some of the OCRDs e.g., OCD [20], have been found to respond better at higher dosages of SSRIs, a definitive dose-finding study employing fixed dosages of SSRIs is indicated.

The CBT trials, although giving an overall effect size of 0.70, included few that would be sufficiently powered to detect this effect size (requiring $n = 45$ per group). Those studies that did examine large enough samples include: Hedman et al. [29]; Tyrer et al. [51]; and Fallon et al. [17] – notably, all produced small effect sizes ranging between 0.20 and 0.26.

Another limitation in comparing the effect sizes of CBT and SSRI interventions is the fact that they involve different control conditions and that trials involving CBT use non-blinded/single-blinded ratings, while SSRI studies adopt double-blinding procedures.

Despite establishing strict criteria for the inclusion of studies, considerable heterogeneity in outcomes was found. By performing subgroup and meta-regression analyses, we identified various factors that explain at least some of this heterogeneity that we were then able to integrate into our interpretation of results. However, the use of different instruments to assess hypochondriasis across the studies represented a source of heterogeneity that was harder to adequately control for. Reaching consensus on the optimal instrument for measuring treatment related outcomes represents another key research goal in this field.

We note that the different standard instruments/tools we used to investigate methodological quality of the included trials (RoB and CONSORT for trial design) do not address all the issues we raise here. In particular, standard measures do not assess the choice of control condition in the assessment of study quality or indeed, researcher allegiance – both of which were extremely influential.

Principally, and somewhat surprisingly, the available instruments do not consider the choice of control condition in the assessment of study quality. The choice of control acts as a well-known mediator of outcomes, such that trials using WL or TAU as the control condition show highly inflated results [13,42]. The implications are that even if a study is designed taking account of CONSORT or ROB2 criteria, it may remain at critical risk of generating effect size inflation. Awareness of this risk should be factored into future study design. Furthermore, researcher allegiance, which could significantly bias outcomes, is not included in any of the standard quality assessment instruments (Risk of bias and CONSORT tools). In sum, we recommend more attention is devoted to standardizing the concept and measurement of researcher allegiance bias, as the existing tools are short and probably incomplete, and their psychometric properties are not fully validated across the whole range of psychiatric interventions.

6. Conclusions

Meta-analysis suggests both CBT and SSRIs are modestly effective for the acute treatment of hypochondriasis, but there remain key gaps in knowledge that undermine confidence in the findings. A definitive and adequately controlled trial, designed with respect to the methodological issues raised in this meta-analysis, is needed to determine the magnitude of the effect of CBT and SSRIs with confidence and the long-term effect of treatment, to meet the needs of this overlooked group of patients and inform mental health service provision.

Role of funding source

None.

Declaration of Competing Interest

Prof. Naomi A. Fineberg declares that in the past 3 years she has held research or networking grants from the UK NIHR, Orchard, COST Action, Wellcome Trust; she has accepted travel and/or hospitality expenses from the BAP, ECNP, RCPsych, CINP, International Forum of Mood and Anxiety Disorders, World Psychiatric Association, Indian Association for Biologi-cal Psychiatry; she has received payment from

the Global Mental Health Academy for delivering lectures and Elsevier for editorial duties. Previously, she has accepted paid speaking engagements in various industry supported symposia and has recruited patients for various industry sponsored studies in the field of OCD treatment. She leads an NHS treat-ment service for OCD. She holds Board membership for various registered charities linked to OCD. She gives expert advice on psychopharmacology to the UK MHRA.

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Appendix 1. Treatment fidelity assessment

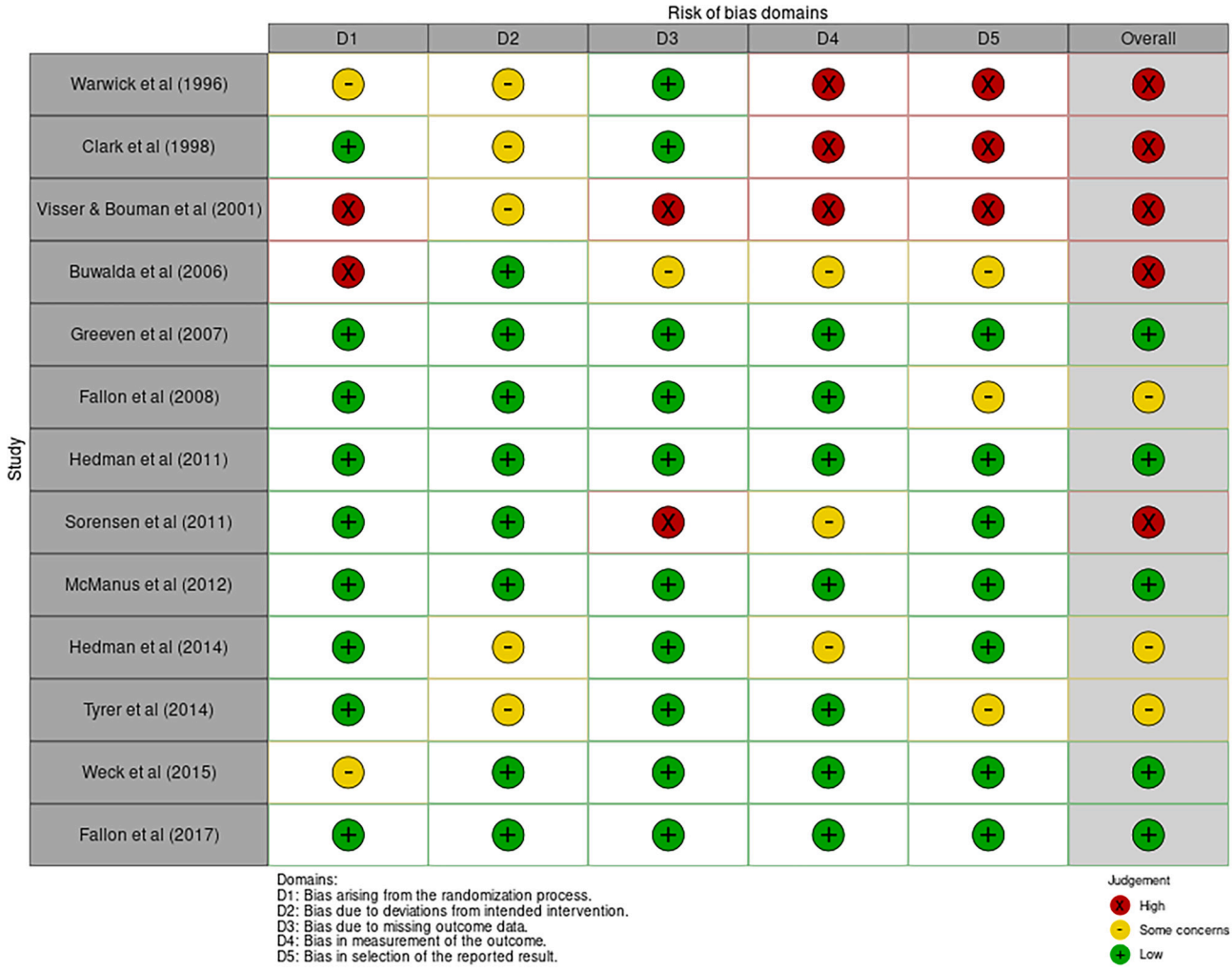
Key:
0 = none; 1 = some; 2 = moderate or medium; 3 = full or high; * = not stated.

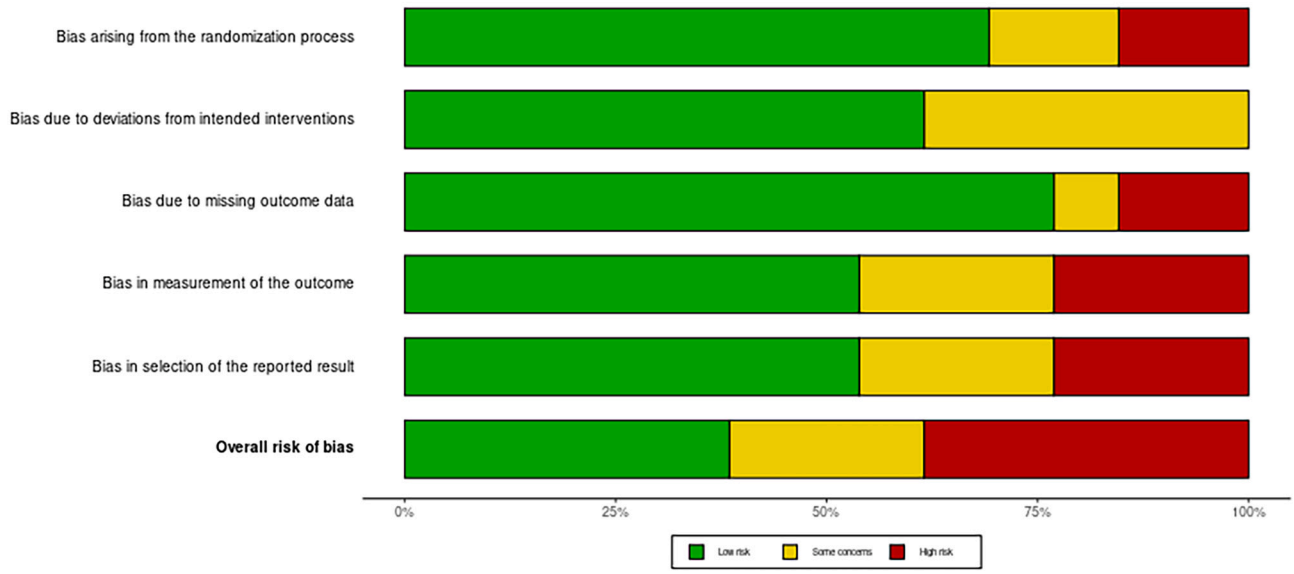
Paper	Comment	PsychoEd	Prob solve	Cog Therapy	Exp and ERP	Relax	Stress Man	Mindful	ACT	HW	Experience of Ther
[5]	Compares CBT with	*	*	3	1	0	0	0	0	3	1
	Problem solving	2	3	0	0	0	0	0	0	3	0
[9] (16 × 1 h)	Cog Therapy	2	0	3	2	0	0	0	0	3	2
	Behav Stress Management	2	3	0	0	0	3	0	0	0	2
[28] (Internet delivered therapy)	CBT versus Control	1	0	3	3	0	0	3	0	3	Internet
[29]	Exposure based CBT via Internet	1	0	3	3	0	0	3	0	3	Internet
	Behavioural Stress management	0	3	0	0	3	3	0	0	0	Internet
[35] (Individual psychotherapy)	Mindfulness versus "usual therapy"	*	*	*	*	*	*	3	0	*	3
[45] (16 sessions over 6/12)	Individual + Gp CBT versus Psychodynamic	1	0	3	1	0	0	3	0	*	2
[51] (5–10 individual sessions)	No details except based on Salkovskis and Warwick	*	*	3	*	0	0	0	0	*	1–2
Visser & Bouman 2001 (6–16 individual sessions)	ERP	2	0	0	3	0	0	0	0	3	1–2
	CT	2	0	3	1	0	0	0	0	3	1–2
[57] (12 weekly individual)	Exposure	2	0	0	3	0	0	0	0	*	2
	CT	2	0	3	1	0	0	0	0	*	2
[17] (6× plus 6 booster)	CBT v SSRI v Combo	3	0	3	0	0	0	0	0	0	2
[25] (6–16 indiv sessions)	CBT v SSRI v Placebo	*	0	3	3	0	0	0	0	3	2
[56]	CBT v WL control (CBT included ERP)	3	*	3	3	0	0	0	0	3	3

Headings above (in order)

- PsychoEducation
- Problem Solving
- Cognitive Therapy (identification of Negative Thoughts, Formulation and cognitive reattribution etc.
- Exposure and ERP
- Relaxation
- Stress Management
- Mindfulness
- Acceptance and Commitment Therapy
- Homework tasks
- Experience of the Therapists in this area

Appendix 2. Risk of bias assessment of the RCTs using the Cochrane risk of bias v2 tool





Appendix 3. CONSORT evaluation of the studies

Study				[28]	[29]	[45]	[57]	[51]	[17]	[25]	[16]	[35]	[56]	[9]	Visser & Bouman 2001	[5]
Treatment				CBT	CBT	CBT	CBT	CBT	CBT/ SSRI	CBT/ SSRI	SSRI	MBCT	CBT	CBT/ BSM	CBT/ Exp + RP	CB vs PS
Title and abstract	**Title and abstract**	1a	Identification	●	●	●	●	●	●	●	○	◒	●	●	○	○
		1b	Structured Summary	◒	●	◒	◒	●	●	●	●	◒	◒	●	◒	●
Introduction	**Background and Objectives**	2a	Background and explanation of rationale	●	●	●	●	●	●	●	●	●	●	●	●	●
		2b	Objectives/ Hypotheses	●	●	◒	●	●	●	●	●	●	◒	◒	◒	●
Methods	**Trial Design**	3a	Trial Design	●	◒	◒	◒	●	◒	◒	◒	●	◒	●	◒	◒
		3b	Changes to method	○	○	○	○	○	○	○	○	○	○	○	○	○
	Participants	4a	Eligibility	●	●	●	●	●	●	●	●	●	●	●	●	●
		4b	Settings and locations	●	◒	●	●	◒	◒	◒	●	◒	◒	◒	●	●
	Interventions	5	Interventions	◒	●	◒	●	◒	◒	◒	●	◒	●	●	●	●
	Outcomes	6a	Outcome measures	◒	◒	◒	◒	◒	●	◒	●	●	◒	◒	◒	●
		6b	Changes to trial outcomes	○	○	○	○	○	○	○	○	○	○	○	○	○
	Sample Size	7a	Sample Size Determined	◒	○	●	●	●	●	○	●	●	○	○	○	◒
		7b	Interim analyses and stopping guidelines	○	○	○	○	○	○	○	○	○	○	○	○	○
Methods (Randomisation)	**Sequence Generation**	8a	Method for randomisation	●	●	●	○	●	●	●	●	●	○	○	○	○
		8b	Type of randomisation	●	◒	●	○	●	◒	●	●	●	○	○	○	○
	Allocation concealment mechanism	9	Mechanism for randomisation	○	●	●	○	●	○	●	◒	●	○	○	○	○
	Implementation	10	Who implemented	◒	○	◒	○	◒	○	●	●	●	○	○	○	◒
	Blinding	11a	Who blinded	●	○	◒	○	◒	◒	◒	●	●	◒	○	○	○
		11b	Similarities in intervention	○	◒	○	◒	○	○	○	●	◒	◒	●	●	●
	Statistical Methods	12a	Stats for primary and secondary	●	◒	●	●	●	●	●	●	●	●	●	●	●
		12b	Additional analyses	●	○	●	●	●	●	●	●	○	○	○	○	○
Results	**Participant Flow**	13a	No. assigned, received, and analysed	●	●	●	●	●	●	●	●	●	◒	◒	◒	◒
		13b	Attrition	●	●	●	◒	●	◒	●	●	●	●	●	◒	◒
	Recruitment	14a	Dates of recruitment and follow up	○	○	◒	●	●	◒	○	◒	●	○	●	○	●
		14b	Why trial ended or stopped	○	○	○	○	○	○	○	○	○	○	○	○	○
	Baseline Data	15	Baseline demographic and clinical characteristics table	●	●	○	○	●	●	●	●	●	○	○	●	○
	Numbers Analysed	16	No. in each analysis	●	●	●	●	●	●	●	●	●	●	●	◒	◒
	Outcomes and Estimation	17a	Results for each group, estimated effect size and precision	●	●	●	◒	●	○	◒	◒	●	◒	◒	◒	◒
		17b	Binary outcomes absolute and relative ES recommended	○	○	○	○	◒	○	○	○	◒	○	○	○	○
	Ancillary Analyses	18	Other analyses	○	○	●	●	●	●	●	●	◒	○	○	○	○
	Harms	19	Harms and unintended effects	○	◒	○	○	◒	●	●	○	○	○	○	○	○
Discussion	**Limitations**	20	Trial limitations	●	●	●	●	●	●	●	●	◒	●	●	●	◒
	Generalisability	21	Generalisability	◒	◒	◒	●	◒	◒	●	◒	◒	●	●	●	●
	Interpretation	22	Interpretation consistency	◒	●	◒	●	◒	●	●	◒	◒	◒	◒	◒	◒
Other Information	**Registration**	23	Registration no and name of trial registry	●	●	●	●	●	●	○	○	○	○	○	○	○
	Protocol	24	Where full protocol can be accessed	●	●	●	●	●	●	○	○	○	○	○	○	○
	Funding	25	Sources of funding and other support	○	○	●	●	●	●	●	●	◒	◒	◒	○	○
total				45	42	48	44	55	48	48	50	47	29	33	27	31

Table 3
CONSORT evaluation of reporting of RCTs investigating treatments for Hypochondriasis.

Key	
○	0
◒	1
●	2

Appendix 4. Researcher allegiance for the studies based on the above assessment instrument

Authors	Research allegiance	Items present
Buwalda et al. [5]	NO	/
Clark et al. [9]	YES	Item 2
[28])	YES	Item 1, 2, 3
Hedman et al. [29]	YES	Item 2, 3
McManus et al. [35]	YES	Item 3, 4
Sorensen et al. [45]	YES	Item 2, 3
Tyrer et al. [51]	YES	Item 1, 2, 3
Visser & Bouman (2001)	YES	Item 1 and 3
Warwick et al. [56]	YES	Item 1, 2, 3
Weck et al. [57]	YES	Item 1 and 3
Fallon et al. [17]	YES	Item 3
Greeven et al. [25]	YES	Item 3
Fallon et al. [16]	NO	/

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