An individual participant data meta-analysis of psychological interventions for preventing depression relapse

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Major depressive disorder is a leading cause of disability worldwide; identifying effective strategies to prevent depression relapse is crucial. This individual participant data meta-analysis addresses whether and for whom psychological interventions can be recommended for relapse prevention of major depressive disorder. One- and two-stage individual patient data meta-analyses were conducted on 14 randomized controlled trials ($N = 1,720$). The relapse risk over 12 months was substantially lower for those who received a psychological intervention versus treatment as usual, antidepressant medication, or evaluation-only control (hazard ratio, 0.60; 95% confidence interval, 0.48–0.74). The number of previous depression episodes moderated the treatment effect, with psychological interventions demonstrating greater efficacy for patients with three or more previous episodes. Our results suggest that adding psychological interventions to current treatment to prevent depression relapse is recommended. For patients at lower risk of relapse, less-intensive approaches may be indicated.

Major depressive disorder (MDD) is one of the leading causes of disability-adjusted life years worldwide[1] and is characterized by high relapse rates[2,3]. The risk for relapse contributes largely to the overall burden of MDD, making relapse prevention a matter of urgent priority.

Antidepressant medication (ADM), psychological interventions[2,4], or their combination are commonly employed to prevent depression relapse. These interventions can either be the same by which the patient achieved remission (continuation therapy) or altered (sequential)[5]. Recent systematic reviews and meta-analyses have shown that psychological interventions alone or in combination with antidepressants can be viable alternatives to antidepressants with sustained effects[6–8], regardless of clinical risk factors[9].

While a range of approaches for relapse prevention of depression are available, it remains unclear which intervention to offer to whom. A personalized strategy can help to reduce trial and error in determining the most accurate relapse prevention strategy for each patient[10,11]. Advances in personalization for patients with recurrent depression can be achieved by individual participant data meta-analysis (IPDMA). By pooling individual participant data (IPD) in a meta-analysis, moderators and predictors of relapse can be assessed more specifically compared with standard meta-analyses[12,13]. This adds power and precision over standard aggregate meta-analysis[14].

To date, two IPDMAs have been conducted for depression relapse prevention[15,16]. Kuyken et al.[16] compared mindfulness-based cognitive

therapy (MBCT) with antidepressants or treatment as usual (TAU) alone. This study found that MBCT-based interventions (with TAU or tapering) were effective in reducing the risk of relapse versus control (hazard ratio (HR), 0.69; 95% confidence interval (CI), 0.58–0.82). Severity of depressive symptomatology was a moderator; patients with higher depression scores at baseline had a longer time to relapse when receiving MBCT compared with patients in control conditions. A more recent IPDMA has evaluated the effects of a psychological intervention while tapering ADM compared with ADM continuation[9]. No difference in time to relapse was observed between the two treatments, and no variable was identified that moderated outcome.

A broader set of psychological interventions (cognitive behavioral therapy (CBT), continuation cognitive therapy (C-CT), preventive cognitive therapy (PCT), and MBCT) and comparisons (psychological intervention versus active control, psychological intervention versus TAU) remain to be explored.

This study is an IPDMA of randomized controlled trials (RCTs) on psychological interventions for previously depressed patients compared with patients in antidepressant, TAU, or evaluation control. This IPDMA is crucial as it goes beyond previous IPDMAs by including a broader set of moderators and psychological interventions.

Results

Selected studies

After screening 15,792 references and reviewing 236 full-text articles, we included 28 studies ($n = 4,053$) that compared a psychological intervention for relapse prevention versus control. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[17] flow chart is presented in appendix 6 in the Supplementary Information. Of the 28 included studies, authors of 18 (64%) studies agreed to provide IPD ($n = 2,840$). The remaining ten studies were included as aggregate data in a sensitivity analysis. An overview of author-specific reasons for not providing data is provided in appendix 4 in the Supplementary Information. Reasons for not being able to supply data were data lost due to lab closure[18,19], data transfer, ethics regulations[20,21], and unable to provide data either for no reason or in time[22–27].

On receipt of data, two studies did not include time to relapse as an outcome measure[28,29] and were therefore excluded from the analyses. Two studies included an active psychological control group (for example, CBT and psychological placebo); these studies were not included in this analysis[30,31] due to too few studies to allow for comparisons and heterogeneity between control conditions.

An overview of the 14 studies that provided IPD and their intervention characteristics is provided in appendices 7 and 8 in the Supplementary Information. Table 1 provides summary statistics (at baseline) for the psychological intervention versus non-psychological intervention control conditions. The mean age of the participants was 45.1 years (s.d. 11.1, $n = 1,724$). The average number of previous episodes was 4.8 (s.d. 5.0, $n = 1,614$): 5% ($n = 74$ out of 1,614) had one episode, 20% ($n = 327$ out of 1,614) had two episodes, and 75% ($n = 1,213$ out of 1,614) had three or more episodes. The proportion of women was 73% ($n = 1,258$ out of 1,725).

Study and participant characteristics

Seventeen predefined sociodemographic and clinical characteristics were identified in the provided IPD: age, sex, ethnicity, education, employment, marital status, treatment group, number of previous episodes, age of onset, time in remission (months), duration of last episode (months), stable/unstable remission, previous psychological intervention, comorbid mental health condition, comorbid physical health condition, and baseline depression at point of randomization as measured with the Beck Depression Inventory (BDI)[32] and Hamilton Depression Rating Scale (HAM-D)[33] (appendix 9 in the Supplementary Information).

Table 1 | Baseline summary statistics

	N participants	%	Mean	s.d.	Total n	Range
Sex						
Female	1,258	73			1,725	
Male	467	27				
Ethnicity						
White	449	91			496	
Non-white	47	9				
Marital status						
Married/cohabiting	769	45			1,701	
Single/DSW	932	55				
Employment						
Employed	616	64			959	
Non-employed	343	36				
Presence of a comorbid psychiatric condition						
No	481	69			700	
Anxiety disorder	133	19				
Other mental health disorder	58	8				
Comorbid anxiety disorder and other mental health disorder	28	4				
Sessions completed						
Yes	624	27			850	
No	226	73				
Education level						
No higher education	332	20			1,625	
Higher education	1,303	80				
Age			45.1	11	1,724	19–81
Age of onset			25.8	11.9	1,617	3–61
Previous episodes			4.8	5	1,614	1–69
One	74	5			1,614	1–69
Two	327	20			1,614	1–69
Three or more	1,213	75			1,614	1–69
Time in remission since last episode (months)			13	13.1	559	0–168
Duration last episode (months)			21	49	951	0–528
Previous psychological intervention						
Yes	511	54			951	
No	440	46				
Previous medication						
Yes	243	62			395	
No	152	38				
Comorbid physical health condition						
Yes	203	48			388	
No	185	52				
Depressive symptoms—HAM-D			4.6	3.6	1,070	0–15
Depressive symptoms—BDI			10.9	8.7	1,008	0–50

DSW, divorced/separated/widowed; HAM-D[33] measured at study baseline. 'No higher education' indicates completed only high school or equivalent; 'higher education' indicates college or academic qualification.
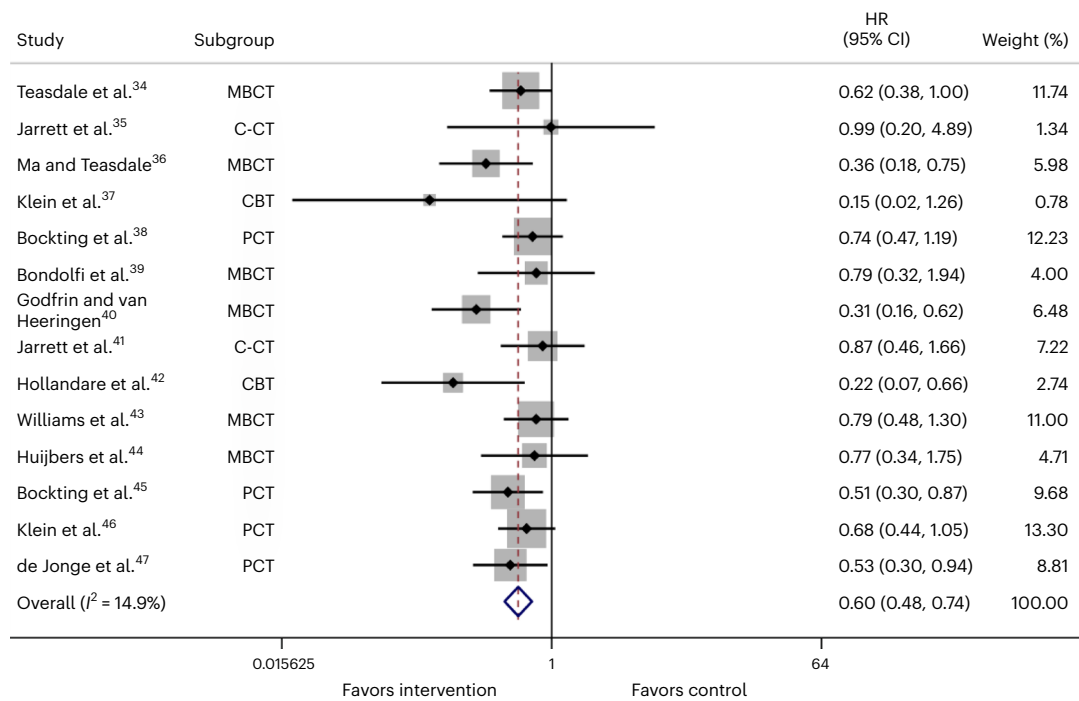
Fig. 1 | Forest plot of the effects of psychological interventions versus non-psychological intervention control on depression relapse. Weights are from random-effects model; $n = 1,720$ participants. Data are presented as HR ± 95% CI. The following studies are cited: refs. 34–47.

Table 2 | Pairwise comparisons of psychological intervention versus control

Comparison	Two-stage random effects: HR (95% confidence interval)	P	N participants (N participants who experienced relapse)	N studies
Psychological intervention versus no psychological intervention control	0.60 (0.48–0.74)	0.000	1,720 (581)	14
Psychological intervention with TAU versus TAU control	0.62 (0.47–0.82)	0.005	1,191 (475)	8

Meta-analysis pooling of main (treatment) effect estimate using the random-effects inverse-variance model with the Hartung–Knapp–Sidik–Jonkman variance estimator based on DerSimonian–Laird estimate of tau².

The 14 studies ($n = 1,725$) tested 4 different psychological interventions (PCT, CBT, MBCT and C-CT) and included 3 different control conditions (ADM, TAU and evaluation only). We were able to make two pairwise comparisons: Psychological interventions alone, with ADM, or TAU versus non-psychological control (TAU, ADM or evaluation only; 14 studies)[34–47] and psychological interventions with TAU versus TAU (8 studies)[34,36,38–40,43,46,47].

The risk of bias was low (appendix 10 in the Supplementary Information). Blinding participants and personnel was the only category with a consistently high risk of bias because it is impossible to blind respondents to condition in psychotherapy study designs. Domains that were well adhered to were complete outcome data, lack of selective outcome reporting, intention to treat analysis, blinding of outcome assessors, and identical post-timing. Areas that were less well adhered to (or where it was difficult to ascertain) were similar groups at baseline (no baseline differences) and compliance to intervention protocol, sequence generation, and allocation concealment.

Effects of psychological interventions versus control

Two-stage random-effects analysis found that psychological interventions were significantly better than control conditions in delaying the time to relapse: HR 0.60 (0.48–0.74), $P \le 0.000$, $I^2 = 14.9\%$ ($n = 1,720$, 14 studies). Adding psychological interventions to TAU also significantly reduced the risk of relapse compared with TAU only: HR 0.62 (0.47–0.82), $P = 0.005$, $I^2 = 28.3\%$ ($n = 1,191$, 8 studies). Subgroup analysis within the two-stage random-effects analysis found no difference in efficacy of psychological intervention type. Forest plots of subgroup analyses can be found in appendices 11–13 in the Supplementary Information.

Table 2 shows the results from the pairwise IPDMA, using two-stage approach on the IPD available. Forest plots of pairwise meta-analyses are shown in Fig. 1 and appendix 14 in the Supplementary Information. Fixed-effects analysis results were comparable (appendix 15 in the Supplementary Information). The I^2 statistic was considered low across comparisons.

Predictors of depression relapse

Fixed-effects one-stage models were used for predictor analysis of the control group as I^2 was low between studies. Among the predefined sociodemographic and clinical covariates, age, sex, marital status, previous episodes, age of onset, and residual depression symptoms (HAM-D[33]) had 60% availability in the dataset. Among these, bivariable fixed-effects models found that being married versus single, divorced, or widowed decreased the risk of relapse for patients randomized to control (Table 3). Furthermore, we found that more previous episodes; being single, divorced, separated, or widowed (marital status); a lower age of onset; and increased depressive symptoms individually significantly increased the risk of relapse at $P < 0.10$ in the control group. On incorporating all predictors in a multivariable model, marital status and age of onset were no longer significant at $P < 0.10$. Thus, the identified predictors for relapse (independent of therapy) were number of previous depressive episodes and residual depressive symptoms at baseline as measured with HAM-D. After adding the non-significant variables back into the model, we found none of them to be significant.

Table 3 | Predictors of relapse in control group

Predictors	Predictors in control at 12 months bivariable model (HR (95% CI))	N total (N relapse)	Final predictors in control at 12 months multivariable model (HR (95% CI))	N total (N relapse)
Age	1.01 (1.00–1.02)	841 (338)	n.s.	n.s.
Sex (male)	0.84 (0.65–1.07)	841 (338)	n.s	n.s.
Marital status	0.82 (0.66–1.03), P=0.09	831 (334)	n.s.	n.s.
Previous episodes	1.02 (1.00–1.04), P=0.07	783 (299)	1.03 (1.00–1.06), P=0.04	533 (182)
Age onset	0.99 (0.98–1.00), P=0.07	786 (312)	n.s.	n.s.
Depressive symptoms HAM-D	1.08 (1.05–1.14), P=0.00	533 (182)	1.08 (1.04–1.13), P=0.00	533 (182)

Stratified Cox regression–Breslow method for ties. HAM-D[33] measured at study baseline; n.s., not specified/variable not included in final model; marital status, divorced/separated/widowed versus married/cohabiting.

Moderators of intervention outcome

Table 4 provides an overview of the moderator analyses. No significant interaction effects were observed for our first pairwise comparison (psychological interventions versus non-psychological interventions). For the second pairwise comparison (psychological interventions added to TAU versus TAU only), we found a significant interaction effect for previous depressive episodes. Participants with three or more previous episodes had a lower risk of relapse when receiving a psychological intervention compared with participants with two or fewer previous episodes who received a psychological intervention (HR 0.55 (0.37–0.79), P = 0.006).

When evaluating the moderator effect of previous episodes in more detail, we note that psychological interventions were not more effective in reducing relapse for those with two episodes or fewer for psychological interventions versus TAU (two episodes, five studies, HR 0.85 (0.37–1.92), P = 0.613; one episode, one study, HR 1.48 (0.40–5.53), P = 0.556).

Sensitivity analyses

We conducted a sensitivity analysis to compare studies that provided IPD and where co-authors were named authors on this manuscript versus studies that did not provide IPD (and authors were not listed on this manuscript). We found no difference in effect (appendix 16 in the Supplementary Information). The funnel plot comparing all psychological interventions versus control conditions at 12 and 14 months showed little evidence for small study effects at 12 months (Egger's test P value = 0.34), but there was evidence of such effects at 14 months (Egger's test P value = 0.01), although the associated funnel plot did not show extreme asymmetry (appendices 17 and 18 in the Supplementary Information). Given that Klein et al.[37] included participants with chronic depression, we also conducted a sensitivity analysis excluding this study. No differential results compared with the original analysis were observed.

Discussion

In this study, we conducted an IPDMA on psychological-relapse prevention interventions on relapse of depression. We aimed to identify predictors and moderators of treatment outcome to inform personalized treatment decisions. We found that psychological interventions combined with TAU or alone were superior to TAU and other control conditions. Consistent with previous meta-analyses, we observed no difference in efficacy between psychological intervention types (PCT, MBCT, C-CT and CBT)[15,48–51]. Patients with three or more previous episodes appear to benefit more from psychological interventions added to TAU compared with TAU or any other control.

The results of this IPDMA offer evidence for the effectiveness of psychological interventions for preventing depression relapse. Adding a psychological intervention to TAU during recovery or remission significantly reduces the risk of relapse. Moreover, assuming equal access to options for preventing depression relapse, patients have the option to choose among different psychological interventions to add to TAU as we did not find evidence for a difference in effect among the studied psychological interventions (MBCT, PCT, CBT and C-CT). However, this finding may be attributable to power issues as well given low sample sizes in certain treatments and needs to be interpreted with caution. Nevertheless, our finding is consistent with findings in previous meta-analyses[15,48–51].

It is interesting that in our study we found a moderating effect for previous episodes in our psychological intervention with TAU versus TAU comparison. There was a greater effect of psychological interventions after three or more previous episodes. The previous literature on this has been mixed. While one previous aggregate data meta-analysis by Zhang et al.[50] found this effect for patients taking part in MBCT compared with TAU, this was not observed for the Kuyken et al.[16] IPDMA. This might be because some studies in this IPDMA included only participants with three or more previous episodes[39,40,43,44]. In addition, an aggregate data meta-analysis by Biesheuvel-Leliefeld et al.[49] did not observe a moderating effect for previous episodes, and other previous analyses did not explore the potential moderating effect of previous episodes[8,48,52], something we were able to achieve in this study. Note that our subgroup size was relatively small for two or fewer episodes (two episodes, n = 182 out of 1,191) and those with one previous episode (n = 32 out of 1,191). Therefore we must be careful to conclude that psychological interventions are not effective for those with two or fewer previous episodes. Still, the most convincing evidence is that psychological interventions can be more effective for those with three or more previous episodes.

It may also be surprising that residual symptoms did not help predict which preventive intervention would work best for whom. In contrast to prior meta-analyses and meta-reviews, we suggest our well-powered IPDMA offers a more reliable picture.

Our finding that age of onset was not significant when pooled in a model with depressive episodes and residual depressive symptoms does not mean that age of onset is not a meaningful variable to evaluate for risk of relapse. Age of onset may still be relevant if there is not yet a high number of previous episodes. Still, future research is needed to further disentangle the relationship between age of onset and depression relapse[53]. Further, it is possible that age of onset interacts with psychological treatment primarily when examined in 'at risk' populations. For example, early intervention in at-risk younger populations can mitigate the suffering in depression[54]. Such early intervention has the potential to reduce risk and number and duration of episodes.

There is a widely held assumption that demographic factors have little influence on depression relapse[53,55]. In our study, we observed that marital status did predict relapse when entered individually in a model, with those being married or in a partnership having a significantly lower risk of relapse. This is consistent with a larger literature showing that poor social support and poor social ties are related to a poorer course of depression[56]. Given our results, the assumption that demographic factors do not matter in predicting relapse may not be adequate. Perhaps there is a complex interplay of factors (for example, additive and/or synergistic) that increase the risk of relapse at any given time, or marital status (and potentially other demographic predictors) may be predictive for certain groups with recurrent depression[57]. For example, sex and marital status have been considered risk factors for relapse when they are present in those with multiple previous episodes of depression[53]. Further research regarding when and how marital status interacts with other predictors is warranted. This would include a

Table 4 | Moderators of depression relapse after (partial) remission

Moderators	Psychological intervention versus non-psychological intervention control at 12 months (HR for interaction effect (95% CI))	N total (N relapse)	Psychological intervention versus treatment as usual at 12 months (HR for interaction effect (95% CI))	N total (N relapse)
Age	0.99 (0.97–1.00)	1,719 (581)	0.99 (0.97–1.00), P=0.092	1,190 (475)
Male	0.78 (0.52–1.17)	1,720 (581)	0.74 (0.46–1.19)	1,191 (475)
Education level	1.32 (0.65–2.67)	1,620 (565)	1.38 (0.63–3.04)	1,171 (464)
Marital status	1.11 (0.79–1.56)	1,696 (572)	1.16 (0.79–1.70)	1,171 (467)
Previous episodes	1.00 (0.97–1.02)	1,609 (526)	0.98 (0.95–1.01)	1,069 (418)
Previous episodes—three or more	0.77 (0.48–1.22)	1,609 (526)	0.58 (0.34–0.99), P=0.047	1,069 (418)
Age onset	1.01 (0.99–1.02)	1,612 (548)	1.01 (0.99–1.03)	1,173 (464)
Depressive symptoms BDI	0.99 (0.97–1.01)	1,003 (358)	0.99 (0.97–1.02)	773 (341)
Depressive symptoms HAM-D	0.99 (0.93–1.06)	1,065 (310)	0.96 (0.88–1.04)	585 (202)

Stratified Cox regression–Breslow method for ties. HAM-D[33] measured at study baseline.

more granular approach looking at clusters of risk factors for specific patient groups (those with more or fewer than two previous episodes or environmental and life stressors; both of these characteristics are not reported consistently and hence were not included).

Strengths and limitations

In this study, we employed an IPDMA to study the effects of psychological interventions versus control conditions for relapse prevention of depression. While we did not receive IPD from all the datasets that we requested (64% of included studies provided data), a sensitivity analysis suggested no evidence of data availability bias for this IPD meta-analysis. The included studies were of high quality, all including independent (blinded) outcome assessors.

The strength of our study lies in our IPDMA approach, which can add power and precision compared with standard meta-analytic approaches[12,13]. For this reason, IPDMAs are called the 'gold standard' of evidence synthesis. By using an IPDMA, we were able to estimate the relative efficacies of psychological interventions, predictors, and moderators of effect, improving our ability to suggest more personalized treatment strategies in the future. Moreover, compared with previous literature, our review aimed to evaluate all psychological intervention types versus control, offering an additional contribution to previous IPDMAs for recurrent depression focusing on MBCT or tapering studies alone[9,16].

This study has several important limitations. First, the time to follow-up was censored at 12 months for consistency; it is unknown whether the performance of predictors and moderators may differ in the longer term. We recommend that future research include even longer follow-ups to explore this further.

Second, we included only study designs that randomized after remission (sequential or continuation study designs) and not studies that evaluated long-term effects of active interventions or the therapy patients received previously (via naturalistic follow-up), which can also offer certain long-term effects[58]. Moreover, we did not search gray-literature databases for potentially relevant trials.

Third, we included the largest number of predictors to date but were not able to include all the predictors we requested. Therefore, moderators such as childhood trauma, socioeconomic status, employment, and cognitive processing styles were not considered. It is recommended that future RCTs include these constructs. Moreover, we included only moderators with at least 60% of data available across studies. Capturing (more) baseline characteristics consistently would be important for future research.

Fourth, few studies were available for certain subgroup analyses, which meant that we were unable to conduct them. Multifactorial trials can help to identify which particular intervention element is most

effective in reducing the risk of relapse[58]. This information can aid further personalization of relapse prevention interventions so that intervention components can be tailored to an individual's profile. Moreover, IPD network meta-analysis could allow comparison of multiple treatment groups at the same time[59].

Fifth, we did not find a significant difference in effect for psychological interventions versus TAU control for respondents with two or fewer episodes. This might be due to small sample size: 32 out of 1,191 had 1 episode, and 182 out of 1,191 had 2 episodes. In addition, rates of relapse are lower for those with fewer previous episodes, so we may have had reduced power to identify a significant difference[60]. Hence, it remains poignant to conduct more research into what works for patients with two or fewer previous episodes. We recommend future high-powered trials with longer follow-ups to assess whether and which psychological interventions can reduce the risk of depression relapse for patients with two or fewer episodes.

Furthermore, it would be relevant to identify whether there are different mechanisms of change at play for patients with two or fewer episodes. It would be relevant to study specific (potentially differential) mechanisms of change that can be targeted with intervention. Prospective ecological momentary assessment studies within trials may help to identify such mechanisms[61].

Sixth, not all studies provided IPD. While our sensitivity analysis found no significant difference in effect, this result does raise important questions regarding data availability and data sharing and for prospective studies to adhere to the findability, accessibility, interoperability, and reuse principles of data access[62].

Seventh, while we were able to include most frequently studied psychological interventions in this IPD (CBT, MBCT, PCT, and C-CT), we were not able to assess the effects of interpersonal psychotherapy (IPT) (as no study provided data) or other intervention types. Therefore, it is not possible for us to make any conclusions about what works for whom for this treatment type. Further research on IPT may be needed, as to the best of our knowledge only two trials are available on this treatment type[18,63].

Finally, there is a potential of allegiance bias given that the individual trial authors who developed the interventions were invited as co-authors as part of the IPDMA. To minimize the potential of allegiance bias, we invited all authors of different relapse intervention treatments. Moreover, the study was led by a researcher (J.J.F.B.) with no conflict of interest. The analyses were overseen by an independent statistician (F.C.W.).

Conclusions

In summary, the results of this IPDMA show that psychological interventions are effective in reducing the risk of relapse for adults with

depression, especially for those who need them the most. Our findings provide support for residual depression symptoms and number of depression episodes being the primary predictors of relapse in recurrent depression.

These results raise important implications for clinical practice. Psychological interventions (PCT, MBCT, CBT and C-CT) can be especially effective in preventing depression relapse for those with three or more previous episodes. Moreover, depression symptoms and previous depression episodes appear to be important parameters for risk stratification in clinical practice. Future research will need to explore the effects of interventions after a first and second episode using a wider range of predictors and estimate indirect associations via an individual participant data network meta-analysis.

Methods

Eligibility criteria

A full protocol of the study has been published[64], and the protocol was registered on PROSPERO: CRD42019127844. The PRISMA-IPD statement was followed[65]. Studies that met our eligibility criteria (1) were RCTs; (2) compared a psychological intervention with any type of control condition (TAU, wait-list, antidepressants, psychological placebo, or psychological intervention; for example, study designs comparing MBCT with CBT);[31] (3) were in adults (the mean age of participants had to be between 18– and 65 years) in remission from MDD, with remission being defined as either no or subthreshold depression symptoms for at least eight weeks or as defined by the authors of the study; and (4) were where the primary outcome of time to relapse was established by a clinical diagnostic interview. With regards to TAU, TAU often consists of no care at all or antidepressant continuation in primary care[47,66,67]. Only studies published in English were included.

Study identification and selection of studies

PubMed, PsychINFO, Embase, and Cochrane Central Register of Controlled Trials were searched on 23 January 2021. To identify eligible studies, index and free terms, jointly with Boolean operators, were used on four tiers: (1) depression disorder, (2) recurrence and relapse, (3) preventive interventions, and (4) RCTs (see appendix 1 in the Supplementary Information for search strings). We also reviewed the reference lists from previous meta-analyses and contacted members of the international task-force group to ask whether they knew any other studies on psychological-relapse prevention intervention for depression. Once the references were imported into Covidence (covidence.org), they were independently screened by J.J.F.B. and one other reviewer (M.E.B., C.L.B., or a research assistant). Full texts were screened independently by J.J.F.B., and a research assistant. A senior author (C.L.B.) was consulted about any conflict.

Data collection and data items

The first and last authors of the study were contacted, and if they did not respond we contacted the corresponding authors. The authors of included studies received a variable collection sheet that included the variables of interest to this IPDMA (appendix 2 in the Supplementary Information). Variables were selected on the basis of previous reviews (for example, refs. 53,68). Upon receipt of data, two independent reviewers led by J.J.F.B. checked the received data for accuracy in a two-stage process that assessed (1) whether the variables of interest were present in the provided dataset and (2) whether the received data reflected the data in the published article by calculating participant numbers, means, and standard deviations for selected variables and relapse rate for each of the provided datasets (see appendix 3 in the Supplementary Information for an overview).

Risk-of-bias assessment

The risk-of-bias assessments were conducted independently by three researchers, J.J.F.B., J. Gulpen, and M.E.B., using the updated Cochrane

Risk of Bias tool by Furlan et al.[69] including six items for risk of bias: (1) random sequence generation, (2) allocation concealment, (3) blinding of outcome assessors, (4) incomplete outcome data, (5) selective outcome reporting, and (6) other threats to validity (similar groups, cointerventions, compliance, and similar timing of outcome assessment). Studies were rated on each criterion as 'low risk,' 'high risk,' or 'unclear risk.' A minimum of five criteria with a low-risk rating qualified as the overall low risk of bias.

Statistical analysis

This IPDMA focused on the differential effects of psychological interventions and control on time to relapse (in weeks), with relapse being assessed via a diagnostic interview such as the Structured Clinical Interview for Depression (SCID)[70]. Studies were excluded from the analysis where the time to relapse was not measured or where the follow-up period post randomization was less than 12 months. The primary analyses used follow-up data to 12 months, with participants who had data beyond 12 months being censored at 12 months (see appendix 4 in the Supplementary Information for an overview of follow-up timings and censoring).

Analyses were conducted in Stata (v.15.1 and v.17). Two or more studies were required to conduct one pairwise comparison analysis[71]. This resulted in two pairwise comparisons: (1) psychological interventions (alone, with TAU, or with ADM) versus any non-psychological control group and (2) psychological interventions with TAU versus TAU only. One- and two-stage random-effects and fixed-effects analyses were conducted for the identified pairwise comparisons. We report on the two-stage random-effects meta-analysis as we expected and observed clinical heterogeneity in the primary studies (including different types of psychological interventions delivered in different settings). The Hartung–Knapp–Sidik–Jonkman method for random-effects meta-analysis was used[72]. Our effect size was the hazard ratio, which quantifies the relative risk of an event occurring between two groups or conditions over time.

Heterogeneity was assessed using the I^2 statistic, based on two-stage meta-analyses; the I^2 represents the proportion of variation across studies that is due to heterogeneity rather than sampling error, with 0% indicating no heterogeneity, 25% low heterogeneity, 50% moderate heterogeneity, and 75% high heterogeneity[73].

One-stage meta-analyses were performed using a series of Cox proportional hazards models, with a fixed effect on study. The analysis consisted of two stages. First, predictors of relapse in the control group were identified to ascertain predictors of relapse independently of treatment or active intervention. Second, a series of interaction terms were created on the basis of the predictors identified in the control group to identify which treatment would work best for whom. The interaction terms were created between the binarized treatment group variable and a single predictor variable.

With regard to predictors, we previously set out to include predictors that had at least 40% of data available in at least three studies[64]. This resulted in very low sample sizes, especially when covariates were combined. We therefore set the minimum number of observations for each covariate in a comparison with 60%. This means that we expected no more than 40% of data in each covariate to be missing. This allowed for more highly powered and representative estimates of predictor and moderator effects.

Predictors of relapse were identified by entering each of the individual predictors into a multivariable time-to-event model using control-group data only. The independent variable was the predictor of interest, and time to relapse was the dependent variable. Study was included in the model to account for the clustering of patients in studies. All relapse predictors that predicted time to relapse at $P < 0.10$ were included in a Cox proportional hazards regression model. This regression model also included intervention allocation.

To identify the final list of predictors, those significant at $P < 0.05$ were selected. To study interaction effects, a series of models were performed that added the interaction term for each predictor and treatment allocation (only one interaction term per model was included), thus allowing investigation of whether the predictor also acted as a moderator. An interaction term was deemed significant if it had a P value < 0.05.

Predictors were all centered to facilitate interpretation and improve model estimation. To avoid ecological bias[74,75], which refers to the potential discrepancy between group-level associations (across trial) and individual-level associations (within trial), we added a fixed effect on study level in the one-stage IPDMA. The two-stage IPDMA already accounts for ecological bias by estimating within-study analysis first and then across-study (meta-analysis) in the second step[74,75].

Sensitivity analyses

A further sensitivity analysis was conducted to investigate the possibility of inclusion bias. Here aggregate risk ratios (extracted from the published article) of included studies that did not provide IPD were combined with risk ratios as calculated from studies that provided IPD. The risk ratios for studies that provided IPD versus those that did not were compared via a one-stage random-effects subgroup analysis in Comprehensive Meta-Analysis (v.3). We identified little variation between study characteristics such as duration of follow-up, country of study, and year of publication and did not perform a further analysis to investigate whether these may have affected our results. To investigate small-sample-size effects, we inspected the funnel plot and conducted Egger's test[76] based on the two-stage IPD analysis. Treatment allocation for the Egger's test was categorized by psychological intervention versus non-psychological intervention.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

This is individual participant data from randomized controlled trials, which cannot be shared publicly due to ethical and consent restrictions that are in place. For data access, please contact the corresponding author. Data access can be provided if these conditions are met: (1) there is approval from all co-authors for the data to be shared, (2) there is a data-sharing agreement in place (which adheres to the requirements for data sharing by the Amsterdam University Medical Centre), (3) individual studies have participant consent and ethics approvals in place to allow for further onward sharing, and (4) there is an analysis plan in place that all co-authors agree with. Upon data sharing, data can be used only for the specified purposes.

Code availability

Analysis code can be found at https://osf.io/fyr7h/.

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Acknowledgments

Author contributions

J.J.F.B., M.E.B., W.F.W., C.P., P.v.O., C.L.B. and E. Karyotaki contributed to the concept and design of this study. Acquisition, analysis and interpretation of data was conducted by J.J.F.B., C.L.B., S.G., E. Karyotaki, F.C.W., M.E.B., F.J., F.H., D.N.K., M.d.J., N.K., Z.S., N.F., K.E.M.B.-L., R.J., J.V., M.T., H.M., W.K., A.J.S., C.v.H., K.H., E. Koster, M.J.H., M.W., A.S., P.C., P.v.O., S.G., M.W., A.J.S. and M.T. Both J.J.F.B. and C.L.B. drafted the manuscript. Thereafter, critical revision of the manuscript was provided by J.J.F.B., C.L.B., S.G., E. Karyotaki, F.C.W., M.E.B., F.J., F.H., D.N.K., M.d.J., N.K., Z.S., N.F., K.E.M.B.-L., R.J., J.V., M.T., H.M., W.K., A.J.S., C.v.H., K.H., E. Koster, M.J.H., M.W., A.S., P.C., P.v.O., S.G. and M.W. The statistical analyses were conducted by J.J.F.B., M.E.B., F.C.W. and C.L.B. Two authors obtained funding, namely J.J.F.B. and C.L.B. J.J.F.B. and C.L.B. had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of analysis.

Ethics statement

Ethical approval was obtained for each of the trials that provided individual patient data. As part of taking part in the original trial, patients provided informed consent that included consent to data sharing for research purposes.

Conflict of interest

F.C.W., E. Karyotaki, E. Koster, M.E.B., J.J.F.B., P.C., P.v.O., D.N.K., K.H., N.F., C.v.H. and S.G. have no conflict of interest to report. All authors with the exception of F.C.W. (independent statistician), E. Karyotaki. (systematic reviewer), M.E.B (systematic reviewer), J.J.F.B. (systematic reviewer), S.G. (systematic reviewer), P.C. (systematic reviewer) and P.v.O. (systematic reviewer) were investigators on one or more of the original randomized clinical trials that contributed data to the individual patient data and secured grant funding for these trials. C.L.B. has presented clinical training workshops, some of which include a fee. C.L.B. receives royalties from her books and co-edited books, and she developed PCT on the basis of the cognitive model of A. T. Beck. M.W. founded the Oxford Mindfulness Centre and was its director until 2013. W.K. is its current director. A.S. is founder and clinical director of the Radboud UMC Centre for Mindfulness and H.M. is director of the Centre for Mindfulness, Hong Kong. M.J.H. is affiliated with the Radboud University-based mindfulness center. M.W. and Z.S. receive royalties for books on mindfulness-based cognitive therapy that they have co-authored. M.W., W.K., A.S., H.M. and Z.S. additionally receive payments for training workshops and presentations related to mindfulness-based cognitive therapy. W.K. donates all such fees to the Oxford Mindfulness Foundation, a charitable trust that supports the work of the Oxford Mindfulness Centre, as does A.S. to the Radboud UMC. Z.S. is a member of the scientific advisory board for Mindful Noggin, which is part of NogginLabs, a private company specializing in customized web-based learning. W.K. was an unpaid director of the Mindfulness Network Community Interest Company until 2015. R.J. is a paid consultant to the NIH, NIMH, and UpToDate. She holds stock equity in Amgen, Procter and Gamble, and Johnson and Johnson. J.V. is a paid reviewer for UpToDate. F.H. licenses a cognitive–behavioral relapse prevention manual for depression to Pear Therapeutics. F.J. receives payments for training workshops and presentations related to mindfulness-based cognitive therapy.

Additional information

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Software and code

Policy information about availability of computer code

Data collection	Stata v.15.1 and v.17 were used to run tests on the dataset received (to assess if paper was similar to manuscript) and append datasets received using the tab, summarize and append commands.
Data analysis	Data were analysed in Stata v.15.1 and v.17 using the ipdmetan and cox regression commands. We have published the code for our analyses on github, accessible here: https://github.com/j-o-s-b/IPDMAdeprelapse.git

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The data that support the findings of this study are not openly available as our data sharing agreements only allow for data sharing with the study team and not any further onward sharing. We have provided a statement on data availability in the data availability section in the manuscript.

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Reporting on sex and gender	Participants self-reported their identified sex upon taking part in the study.
Population characteristics	We requested data from individual trials on the following population characteristics: Age, gender, ethnicity, education, employment, marital status, treatment group, number of previous episodes, age of onset, time in remission (months), duration of last episode (months), stable/unstable remission, previous psychological intervention, co-morbid mental health condition, co-morbid physical health condition, and baseline depression at point of randomisation.
Recruitment	Recruitment methods for the included trials varied from either community recruitment, to referrals from healthcare professionals either in primary, secondary or tertiary mental health care.
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For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	This is an Individual Participant Data Meta-Analysis (IPDMA). In an IPDMA, individual-level participant data from randomised controlled trials is pooled into a larger dataset to analyse predictors, moderators and efficacy of psychological interventions versus control. The data analysed is quantative data.
Research sample	Previously depressed currently (partially) remitted patients were included in this study. Adults (the mean age of participants had to be between 18 – 65 years) in remission from MDD, with remission being defined as either no or subthreshold depressive symptoms for at least 8 weeks or as defined by the authors of the study. As these are respondents taking part in randomised controlled trials that select on a restrictive set of indicators, the sample is not representative of the broader population. The study sample was chosen as it will allow for the development of treatment recommendations for those at risk of relapse of depression.
Sampling strategy	Respondents had to be Randomly Allocated to intervention or control condition.
Data collection	In the original trials, paper-based and online questionnaires were used to collect baseline participant data. Outcome data was collected by a blinded clinical diagnostic interview to establish relapse or recurrence. For the IPDMA, we received data via an encrypted data sharing platform (surfdrive) from the authors. Data collection for the IPDMA took place between 06/2018 and 08/2021
Timing	We requested data for individual randomised controlled trials from 2018 onwards. Studies published between
Data exclusions	Four studies were not included in the analysis. Upon receipt of data, two studies (1,2) did not include time to relapse as an outcome measure and were therefore excluded from the analyses (which was a pre-specified criterion).Two studies (3,4) included an active psychological control group (e.g. CBT and psychological placebo) which were not included in this analysis due to too few studies to allow for comparisons and heterogeneity between control conditions. The studies are detailed below and referenced in the manuscript: 1. Biesheuvel-Leliefeld KEM, Dijkstra-Kersten SMA, Van Schaik DJF, et al. Effectiveness of Supported Self-Help in Recurrent Depression: A Randomized Controlled Trial in Primary Care. Psychother Psychosom. 2017;86(4):220-230. doi:10.1159/000472260 2. Hoorelbeke K, Van den Bergh N, De Raedt R, Wichers M, Koster EHW. Preventing Recurrence of Depression: Long-Term Effects of a Randomized Controlled Trial on Cognitive Control Training for Remitted Depressed Patients. Clin Psychol Sci. 2021;9(4):615-633. doi:10.1177/2167702620979775 3. Shallcross AJ, Willroth EC, Fisher A, et al. Relapse/Recurrence Prevention in Major Depressive Disorder: 26-Month Follow-Up of Mindfulness-Based Cognitive Therapy Versus an Active Control. Behav Ther. 2018;87(6):836-849. doi:10.1016/j.beth.2018.02.001 4. Farb N, Anderson A, Ravindran A, et al. Prevention of relapse/recurrence in major depressive disorder with either mindfulness-based cognitive therapy or cognitive therapy. Beck Bockting, Cherkin, Chiesa, Crane, Devilly, Fava, First, Fresco, Guidi, Hamilton, Jarrett, Kocovski, Pinheiro, Segal, Segal, Teasdale, Therneau, Tovote, Vallis, Weissman B, ed. J Consult Clin Psychol.

<table>
<tr><td></td><td>2018;86(2):200-204. doi:http://dx.doi.org/10.1037/ccp0000266</td></tr>
<tr><td>Non-participation</td><td>Out of the 28 included studies, authors of 18 (64%) studies agreed to provide individual participant data (n = 2840). The remaining studies (k = 10) were included as aggregate data in a sensitivity analysis. An overview of author-specific reasons for not providing data is provided in appendix 3. Reasons for not being able to supply data were: data lost due to lab closure, data transfer, ethics regulations and unable to provide data either for no reason, or in time.</td></tr>
<tr><td>Randomization</td><td>All respondents had to be independently randomised to groups.</td></tr>
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Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	CRD42019127844
Study protocol	doi:10.1136/bmjopen-2019-034158
Data collection	Studies were invited to take part from 2018 onwards after we completed our searches up until January 2021 (last timepoint of searches) we did not exclude studies by location. We included trials conducted in any setting such as primary care, secondary or tertiary care. Trials were conducted in university hospitals, outpatient clinics, in the community, medical centres. Appendix 8 provides some detail on the different settings in which trials were conducted.
Outcomes	Depressive relapse as established by a clinical diagnostic interview by an interviewer blinded to outcome. The outcomes were pre-defined in our PROSPERO and BMJ Open protocols. The measures of interest included the Structured Clinical Interview for DSM-IV Axis 1 Disorders, the Mini-International Neuropsychiatric Interview, the Composite International Diagnostic Interview or the Hamilton Depression Rating Scale. Trials were only included if they specified that they contained a clinical diagnostic interview assessed by blinded assessors.