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RUNNING HEAD: MEDIATORS OF PSYCHOSOCIAL INTERVENTIONS FOR PERINATAL DEPRESSION

A multiple mediation analysis of the peer delivered Thinking Healthy Program for perinatal depression: Findings from two parallel randomized controlled trials

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ABSTRACT

Background. Low-intensity psychosocial interventions have been effective in targeting perinatal depression but relevant mechanisms of change remain unknown.

Aims. To examine three theoretically-informed mediators of the peer-delivered Thinking Healthy Program Peer-delivered (THPP), an evidence based psychosocial intervention for perinatal depression, on symptom severity in two parallel randomized controlled trials in Goa, India and Rawalpindi, Pakistan.

Methods. Participants included pregnant women aged ≥18 years with moderate to severe depression, as defined by a PHQ-9 score≥10 and were randomized to either THPP or Enhanced Usual Care. We examine whether three pre-specified variables—patient activation, social support, and mother-child attachment— at 3 months post-childbirth mediated the effects of the THPP interventions of perinatal depressive symptom severity (PHQ-9) at the primary endpoint of 6 months post childbirth. We first examined individual mediation within each trial (n=280 in India and n=570 in Pakistan) and then as a pooled analysis across both trials (N=850).

Results. In both site-specific and pooled analyses, patient activation and support at 3 months independently mediated the intervention effects on depressive symptom severity at 6 months, accounting for 23.6% and 18.2% respectively of the total effect of THPP. The intervention had no impact on mother-child attachment scores and thus there was no evidence that this factor mediated the intervention effect.

Conclusion. The effects of the psychosocial intervention on depression outcomes in mothers were mediated by the same two factors in both contexts suggesting that such interventions seeking to alleviate perinatal depression should target both social support and patient activation levels.

Trial Registration. ClinicalTrials.gov Identifier: NCT02104232 in THPP-India and NCT02111915 in THPP-Pakistan.

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INTRODUCTION

Depression is the leading cause of disability among women worldwide[1]. Psychosocial interventions, including cognitive, behavioral and interpersonal therapies, have been effective in targeting perinatal depression[2-3]. However, the growing field of treatment evaluation, including those delivered by non-specialist providers (NSPs)[4], has rarely evaluated how these treatments work which may affect their replication and scale-up. This is particularly true for the field of perinatal mental health, where effective psychosocial interventions exist, are recommended as first-line interventions by international guidelines (mhGAP)[5], and have been successfully implemented by NSPs, including peers. Mediation analysis is a technique to evaluate the theoretical basis of interventions to shed more light into this so-called 'black box'[6] of relevant treatment factors[7]. Investigation of the theoretically-informed mediators of treatments may illuminate how these treatments operate, guide clinicians to predict individual patient trajectories, and guide researchers to develop more effective interventions[7-8].

The current study examined the role of three potential and theoretically-informed mediators within the SHARE trials[9-10]. The goal of SHARE—the **S**outh Asian **H**ub for **A**dvocacy, **R**esearch and **E**ducation on Mental Health supported by the NIMH—was to adapt the Thinking Healthy Program (THP)[11] for delivery by peers (called the Thinking Healthy Program, Peer-Delivered THPP) in India and Pakistan. The THP was originally developed and evaluated in Pakistan[11] and is recommended by the World Health Organization for the treatment of perinatal depression in low-resource settings (http://www.who.int/mental_health/maternal-child/thinking healthy/en/). Unfortunately, the delivery of THP was hampered by the existing demands on community health workers[12]. Two parallel trials examined the effectiveness of peer delivered THPP in Goa, India (hereafter referred to as THPP-India) and Rawalpindi, Pakistan (THPP-Pakistan)[13]. Peers—mothers living in the same community as mothers participating in the intervention—were found to be an acceptable and feasible delivery agent within both of these settings[14].

The theoretical foundation and relevant mediators of THPP

THP was originally designed as an individual, 16-session, cognitive behavioural therapy (CBT) that was delivered by community health workers[15]. Using simplified cognitive and behavioural elements, the intervention primarily focused on three key relationships: the woman's relationships with herself, her family and her infant[11]. While retaining a core emphasis on these three areas, the content of THPP was modified to include a stronger emphasis on behavioural activation (BA) as this was found to be more feasible for delivery by peers[16]. BA is a parsimonious approach that is easy to understand and implement[17]; it has been successfully implemented by other NSPs, including lay counsellors, nurses, midwives, and undergraduate students, to effectively reduce depressive symptoms in general and perinatal populations[18-21]. THPP conceptualizes behavioral activation as the degree to which women (pregnant and postpartum) reportedly engagedment in a variety of activities—including those pertaining to the mother's personal well-being, eliciting social support from spouse, family and friends, and her perceived attachment to her developing infant—and their sense of accomplishment in completing these activities.

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Consequently, and in line with the theoretical emphasis on relationships with self, other, and baby, we selected three potential mediators to explain the pathways of change underlying THPP. These were: patient activation; perceived support (hereon referred to as social support) from one's spouse, family and community, and mother-child attachment. These three variables have been found to significantly influence depression outcomes in perinatal populations[20,22-24], and both patient activation[25-26] and social support[27- 28] have been found to mediate the effects of BA-oriented treatments on depression outcomes.

Analysis of mediation effects is important whether or not there is an overall treatment effect because it sheds light on different aspects of the intervention, such as whether the intervention affected the mediator and whether the mediator is related to the outcome. It is also possible that the test of mediation can have more statistical power than the test of the overall intervention effect. Because mediation analyses do not require a direct effect of the intervention on long-term outcomes (see Methods section below), the examination of potential mediators is key in illuminating causal pathways irrespective whether an intervention is effective[29].

In the current study, we aimed to test the theory of THPP by conducting a rigorous mediation analysis within two parallel, randomized controlled trials (RCTs). Specifically, we examined whether three theoretically-informed variables—patient-reported activation, social support, and mother-child attachment— at 3 months post childbirth mediated the effects of the THPP intervention on perinatal depressive symptoms at 6 months post childbirth.

METHODS

Setting, Participants and Design. The study was conducted in two locations: the semi-urban, North District of the state of Goa, India and Kallar Syeddan, a rural sub-district of Rawalpindi in the province of Punjab, Pakistan. Participants included pregnant women in the second or third trimester, aged ≥18 years with moderate to severe depressive symptoms, as defined by a Patient Health Questionnaire 9 (PHQ-9) score≥10[30]. Potentially eligible participants were screened for depression with a locally-validated version of the PHQ-9[11,31] after providing written informed consent for screening (or witnessed informed consent/audio-recordings for illiterate participants).

In THPP-India, an individual RCT with 1:1 allocation, stratified by place of residence (rural vs. urban) was conducted for a total sample of N=280 participants. In Pakistan, a cluster RCT with 1:1 allocation, 40 village clusters and stratified by 11 union councils, was conducted, with a total sample of N=570 participants ~~were recruited from these 40 village clusters~~. Participants were recruited from routine healthcare settings including two antenatal clinics and two primary health centers in Goa, and from the registers of the community-based Lady Health Workers across the rural sub-district of Kallar Syeddan in Pakistan.

Mothers were randomized to either the THPP interventions or Enhanced Usual Care (EUC). Ethical approval was obtained from the Institutional Review Boards at the University of Liverpool, the London School of Hygiene and Tropical Medicine, the Human Development Research Foundation and Sangath Center (the implementing institutions of each trial in Pakistan and India, respectively) and the India Council of Medical Research. Both trials were

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registered on ClinicalTrials.gov: NCT02104232 in THPP-India and NCT02111915 in THPP-Pakistan. The trials protocols and results been described in full elsewhere[9-10, 13].

Treatment arms.

Thinking Healthy Program Peer-delivered. The intervention for moderate-to-severe perinatal depressive symptoms being assessed in these trials was the Thinking Healthy Program Peer-delivered (THPP). As mentioned, THPP is the adapted (peer-delivered) version of the Thinking Healthy Program (THP) which was originally developed and evaluated (based on delivery by government-employed LHWs) in Pakistan[11]. In both sites, THPP comprised up to 14 sessions of BA, each lasting up to 45 minutes. The intervention began in the antenatal phase and lasted up to 6-months postnatally, with the most active phase of treatment concluding by the end of the first trimester. The core strategies used by the peers, focusing on the 3 areas of personal well-being, relationship with the infant and relationship with significant others, were: active listening, collaboration with the family, guided discovery using pictures and stories, homework, and behavioral activation (identifying and replacing unhealthy behaviours with healthy ones and practicing them)[16]. THPP-India was implemented primarily in participants' homes and individually-randomised and, THPP-Pakistan was conducted in a community setting with woman randomised in village clusters to avoid contamination.

In both sites, THPP was delivered by peers—women with children, a similar socio-demographic background as participants, and good communication skills[14,16]—who were recruited from the local community through word-of-mouth, particularly from key informants such as community health workers, women's self-help groups and community elders. Recruited peers underwent one week of classroom-based training including learning the THPP content, general counseling skills, confidentiality issues and interactive learning involving role plays. This was followed by competency assessments which determined the selection of peers for the trial. Peers were initially supervised by expert trainers, followed by a cascade model of training using peer-led supervision. In THPP-India, 37 peers were trained and 26 were selected for the trial; in THPP-Pakistan, 66 peers were recruited and selected for the trial. Their mean age and education levels were 37.85 years (range 27 to 50 years) and 11.85 years (9 to 15 years) respectively in India and 28.0 years (21 to 45 years) and 6.6 years (0 to 14 years) respectively in Pakistan[16].

Enhanced usual care. Participants received EUC in both the intervention and control arms. In both arms, EUC comprised the following: 1) Informing participants about their diagnosis of depression; 2) In Pakistan, informing depressed participants about ways to seek appropriate health care (i.e. by going for assistance to their LHWs, to the primary health centre or to the tertiary health centre, which is the Institute of Psychiatry, Rawalpindi, Pakistan); 3) In India, providing gynaecologists with the findings of the screening results for perinatal depression; 4) Providing the primary health-care centres and the gynaecologists with the adapted WHO mhGAP treatment guidelines for perinatal depression[32]; and 5) Providing an information sheet about how and where to seek health care from including local Community Health Workers (CHWs), primary health facilities and tertiary care facilities, both during pregnancy and beyond.

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Measures.

Outcome. The outcome of the current study was depressive symptom severity scores on the PHQ-9 at 6 months post-childbirth, as assessed by independent evaluators who were blind to treatment status. Similar to other mediation analyses[33], this variable was selected over the trials' other primary outcome of remission status because depressive symptoms offered a continuous score which provides more variability in our regression analyses[34].

Potential Mediators. Three separate scales are used to assess the three *a priori* mediators at the 3 month post-childbirth outcome assessment.

1. *Patient Activation.* The **PREMIUM Abbreviated Activation Scale** (PAAS) is a 5-item scale, originally developed and used in a separate trial of a brief behavioural activation treatment (the Healthy Activity Program) trial[26], and which is based on the Behavioural Activation for Depression Scale[35]. PAAS includes five indicators of behavioural activation — a treatment factor that is explicitly targeted in the THPP trial — such as the mother's self-report of her engagement with a variety of activities ("*did you engage in many different activities?*" and "*were you an active person and accomplished the goals you set out to do?*"), and associated pleasure ("*did you do things that were enjoyable?"* and mastery ("*are you content with the amounts and types of activities you did?*"). The final item included a reverse question: "*Did you spend long periods thinking over and over about your problems?*". All five items are assessed on a scale of 0 (*'not at all'*) to 5 (*'yes, completely'*) for a total continuous score of 25. In both settings, the PAAS at 3 months showed good internal consistency (α=0.801 in THPP-India and α=0.811 in THPP-Pakistan) and good concurrent validity with social support at 3 months (r=0.341, p<0.001 in THPP-India and r=0.367 in THPP-P, p<0.001).
2. *Social Support.* The **Multidimensional Scale of Perceived Social Support** (MSPSS) is a 12-item scale for assessment of mothers' perceived social support from one's spouse, family and community[36]. This scale has been widely used and previously validated in current study contexts[11, 37]. Mothers are asked to rate the availability of social support on a 5-point Likert scale, ranging from 1 ('*strongly disagree'*) to 5 ('*strongly agree'*), for a total continuous score ranging from 1 to 60. Sample items include "*I get the emotional help and support I need from my family*." In the current study, this scale showed excellent internal consistency (α=0.862 in THPP-India and α=0.853 in THPP-Pakistan) excellent predictive validity between social support between baseline and 3 months (r=0.489, p<0.001 in THPP-India and r=0.358, p<0.001 in THPP-Pakistan), and 3 and 6 months (r=0.449, p<0.001 in THPP-India and r=0.359, p<0.001 in THPP-Pakistan).
3. *Mother-Child Attachment.* The **Maternal Postnatal Attachment Scale** (MPAS) assesses mother's reported attachment to the child and satisfaction with parenting[38]. The original scale was reduced to seven culturally-relevant items, as determined by local clinical experts, in order to rate the mother's feelings, thoughts and relationship to her baby after birth. Sample items include rating one's competence or enjoyment when interacting with the baby. For example, '*When I interact with my baby, I feel…'* very incompetent (scored 1) to very competent (scored 5). As in the original scale, all items score from 1 to 5, with a higher score indicating a higher degree of maternal attachment to her baby (total continuous score of 35). The scale has been adapted for the Pakistan setting[39], and shows sound internal consistency (α=0.791 in THPP-India and α=0.793 in THPP-Pakistan) as well as good

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concurrent validity with social support at 3 months in both sites (r=0.225, p<0.001 in THPP-India and r=0.115, p<0.01).

Baseline sample characteristics related to the patient (age, education, marital status, occupation, number of children, chronicity (duration of depressive symptoms), and PHQ-score) were all examined as potential covariates.

Data Collection. Independent interviewers assessed primary outcomes at the 3 and 6 month post childbirth endpoints. These timepoints were selected in the larger trials to estimate the active phase of THPP and to examine its potentially sustained effects, respectively. These data were recorded using tablets that were uploaded in real-time to a server with data being reviewed by independent data managers.

Analyses. The current study was a secondary mediation analysis within the context of two, parallel RCTs. Mediation conditions were met if the regression models (described below) demonstrated that there were significant effects of the independent variable on the proposed mediator (X→M) and of the proposed mediator on outcome scores (M→Y), adjusted for the independent variable[40], where significance was defined as p<0.05. It is possible for mediating effects to be present even if there is no overall effect of the independent variable on the dependent variable (X→Y)[29]. An intention-to-treat (ITT) analysis was conducted and multiple imputation methods were used to account for missing values. Using SAS PROC MI and PROC MIANALYZE, five imputed datasets were created the and the model averaged results across the five iterations. To ensure consistency across trials, data was analyzed at the individual participant level, while controlling for the cluster-level variable in the regression analysis. Mplus version 8.1[41] was used to conduct mediation analyses.

Individual mediation pathways. First, means and 95% confidence intervals were estimated for baseline variables, followed by means, 95% confidence intervals and t-tests for each mediating variable and depression outcomes at 3 and 6 months post-childbirth. Second, because measures of patient activation and mother-child attachment were not collected at baseline, we used baseline social support scores in the model. Baseline social support scores were significantly correlated with patient activation (r=0.248, p<0.001 in THPP-India and r=0.161, p<0.01 in THPP-Pakistan) and mother-child attachment (r=0.195, p<0.01 in THPP- India and r=0.166, p<0.01 THPP- Pakistan) at 3 months post-child birth.

Next, we used multiple linear regression modelling to estimate models whereby the dependent variable was PHQ-depressive symptoms at 6 months post-childbirth. In each trial, we examined three individual pathways to determine whether a) patient activation; b) social support; and c) mother-child attachment mediated the effects of THPP-India or THPP-Pakistan on depressive symptoms. In order to do this, we first examined the effects of treatment arm (THPP vs. EUC) within each trial on the three proposed mediators followed by the examination of effects of the three proposed mediators on depressive symptom outcomes. This resulted in the examination of six pathways, in which we controlled for baseline PHQ-9 and social support scores as well as patient education levels. In THPP-Pakistan, we also controlled for cluster in these regressions. The variance inflation factor (VIF) was assessed for each independent variable within each model to estimate multicollinearity (VIF≥5).

For Peer Review

Finally, if mediation conditions were met, we assessed individual mediating pathways using the Monte Carlo Method for Assessing Mediation (MCMAM)[42]. In this approach, a distribution of the indirect effect was used to estimate a confidence interval (CI) around the observed value of the indirect effect[43]. MCMAM performs better than the Sobel test and comparably with bootstrap approaches[35,44] and no direct effect is required of the independent variable (in this case, THPP-India or THPP-Pakistan) on the dependent variable (depressive symptoms at 6 months)[29,40]. In the current study, we computed a 95% CI with 20,000 repetitions. Following the recommendations of Selig and Preacher[45] for MCMAM, non-standardized betas were used for individual mediation analyses.

Pooled Analysis. After assessing individual mediators within each trial, we conducted a pooled mediation analysis. This approach was used to ensure that the proposed mediators were first being assessed within their respective trials and did not assume that the relations between the proposed mediators and outcomes will be similar across trials. Data were pooled by two independent statisticians and analyzed at the individual participant level. In the pooled analysis and in order to compare results across a variety of measures, standardized betas are presented. We examined the role of all three potential mediators simultaneously on the same PHQ-9 depressive symptom severity score. Similar to the individual mediating pathways, we controlled for baseline PHQ-9 and MSPSS scores, cluster and patient education levels. Finally, and across all participants (N=850), we estimated the contribution of each potential mediator on the total effect by dividing each mediating effect by the total effect. The sample size of the current study is reasonable to conduct this analysis, where a minimum of 500 observations is suggested[46].

RESULTS

Participants included those randomized to THPP (n=140 in THPP-India and n=283 in THPP-Pakistan) compared to Enhanced Usual Care (n=140 in THPP-India and n=287 in THPP-Pakistan). Pooled analyses involved the total sample across the two trials (N=850). On average, participants across the two trials were 26 years of age (95% CI=26.1 to 26.8 years and range of 18 to 45); the majority had up to primary and secondary levels of education (75% in THPP-India vs. 65% in THPP-Pakistan), were married (everyone except one participant in THPP-I) and had more than one child (82% in THPP-Pakistan and 57% in THPP-India). As expected, fewer women in THPP-Pakistan worked outside of the home than in THPP-India (6% vs. 15%). Descriptive scores of variables related to the current analysis are detailed in Table 1. Data were missing at 6 month follow-up among 10.3% of participants in THPP-India (n=29) and 13.7% (n=117) in THPP-Pakistan. No differences were found between participants who remained vs. those who dropped out in both trials; similarly, there were no differences between treatment and control conditions. These and other results of each trial have been published elsewhere[9-10].

[INSERT TABLE 1]

Mediational Pathways. Descriptive frequencies and t-tests of potential mediating variables and clinical outcomes can be found in Table 2. In ~~both sites~~each individual site, there were higher patient activation and support scores at 3 months and lower depressive symptoms at both 3 and 6 months post-childbirth among THPP intervention participants as compared to EUC

For Peer Review

participants; however, these differences were not significant for ~~a significant difference in~~ social support scores ~~were not found~~ in Pakistan ~~nor were differences in~~or for depression outcomes at 6 months in either individual trial. In addition, there was no significant difference in mother-child attachment scores between arms in either trial.

[INSERT TABLE 2]

Individual mediators were analyzed within each trial and detailed in Table 3. In both trials, and once correlates were considered in regression models, we found that improved patient activation and social support at 3 months post-child birth mediated the effects of THPP intervention on reduced depressive symptom severity. This was not the case for mother-child attachment, was which found to have an effect on depressive symptoms but there was no effect of the THPP-intervention on this variable; thus, no indirect effect was calculated because mediation conditions were not met. There was no evidence for multicollinearity (VIF<3).

[INSERT TABLE 3]

In the pooled analysis, a similar pattern emerged (Figure 1). Specifically, we found significant indirect effects of both patient activation (*axb*=0.027, 95% CI=0.016 to 2.210, *p*=0.027) and social support (*axb*=0.035, 95% CI=0.027, 95% CI=0.013 to 2.059, *p*=0.040) at 3 months post-childbirth, suggesting their independent roles in partly mediating the effects of the THPP intervention on depression outcomes at 6 months post- childbirth. This was not the case for the hypothesized mediator of mother-child attachment, which did not result in a significant indirect effect (*axb*=0.015, 95% CI=0.012 to 1.288, *p*=0.198). The total direct effect of THPP on PHQ-9 outcomes was standardized *ϐ*=0.148 (95%=0.033 to 0.269, *p*=0.038), demonstrating a significant effect of the intervention on depression outcomes when pooling the data across the two trials. Furthermore, we observed that social support was found to be the most significant among the two significant mediators across trials. We found that social support and patient activation at 3 months accounted for 23.6% and 18.2% respectively of the total effect of THPP on PHQ-9 depressive symptoms at 6 months.

[INSERT FIGURE 1]

Finally, recent research has suggested the consideration of unmeasured confounders[46-47]. We followed these suggested methods and found that we would require a large correlation (*r*=0.5 or higher) to remove the mediating effects of patient activation or social support on long-term depression outcomes.

DISCUSSION

The current study found that two of the three pre-specified variables—patient activation and social support at 3 months post-childbirth—mediated the effects of THPP on depression outcomes at 6 months post-childbirth. Thus, despite varying contexts, the THPP intervention worked through the same mediators in two diverse contexts. This suggests the generalisability

For Peer Review

of the intervention and emphasizes that low-intensity psychosocial interventions seeking to alleviate perinatal depression should focus on improving social support and patient activation levels.

Our results are consistent with THPP's theoretical emphasis on behavioural activation which suggest that the key to feeling less depressed is to increase enjoyable or fulfilling activities that align with one's values and key relationships[17]. After taking into account relevant correlates, we also found that women who had higher levels of patient activation and social support reported lower depressive symptoms. Furthermore, and in line with previous mediation studies[25-28, 49], these factors were found to independently and concurrently mediate the effects of the THPP intervention on perinatal depressive symptoms. The results add to the interpretation by suggesting that improving patient activation and social support levels within perinatal depression interventions may benefit a reduction in perinatal depressive symptoms. None, however, have examined these mediators simultaneously and when delivered by an NSP in community-based settings, or in diverse global and cultural contexts.

We did not, however, find that the THPP intervention influenced mother-child reported attachment. An independent observation of mother-child attachment and interaction, as implemented in other perinatal depression treatment programs (e.g.,[50,51]), may be more reliable than the measure used in the current study. Or this may be due to the intervention content and delivery lacking an explicit emphasis on mother-child attachment and interactions. These results may reflect the widely inconsistent effects of psychosocial interventions for maternal depression on child development outcomes and one reason may be because there is a lack of emphasis on explicitly targeting mother-child interactions[28]. For example, despite robust and persistent effects on reduced maternal and child mental health outcomes, the original THP trial did not show any positive effects on child growth and developmental outcomes[52]. Similarly, there are few mother-child programs that have explicitly targeted maternal mental health symptoms[28]. In order to achieve the integration of mental health services in other services, perhaps a stronger emphasis on mother-child attachment and interactions need to be emphasized in maternal mental health interventions in order to influence both maternal and child development outcomes.

Limitations. We also acknowledge several limitations. First, there may be other potential mediators that may explain the THPP intervention. For example, we did not measure therapeutic alliance between the peer counsellor and participant. Therapeutic alliance is a frequently-studied phenomenon in the psychosocial treatment literature[53] and may be particularly relevant for a peer context. In addition, we did not assess how cognitions may have influenced key patient behaviours and depression outcomes. This has been examined in other trials[54] and the interplay of patient cognitions and behaviours may inform how THPP works. Second, all of our measures were based on self-report. As mentioned above, independent observations of mother-child attachment, including the HOME Inventory[51] or video-recordings[49] have been conducted in other low-resource settings[28] and may offer a more valid assessment of mother-child-attachment, but we know of no other objective measures for activation or social support. Third, we did not assess patient activation levels or were unable to assess mother-child attachment levels at baseline. The latter was not possible because THPP began during the

For Peer Review

antenatal phase. If we had baseline measures of these variables, power to detect mediated effects would have been increased to account for baseline patient variables or potentially explain lack of effects on perceived mother-child attachment. Finally, our results supporting activation and social support as mediators suggest further investigations of these underlying mechanisms of psychosocial interventions for perinatal mental health[55].

In sum, this study contributes to the larger field of psychosocial treatment literature by identifying two key and theoretically-informed mediators for perinatal depression. In two diverse contexts, our findings highlight the importance of one's relationship with self and others is playing a key role in alleviating perinatal depressive symptoms. Additional strengths of our study are following key guidelines for mediation[56,57], including the assessment of multiple, potential mediators, the use of a temporal design with hypothesized mediators being assessed at distinct time-points, with large sample sizes within randomized controlled trial designs and adjusting for key variables at baseline. Our findings suggest the generalisability of the THPP across two diverse contexts and that psychosocial interventions seeking to alleviate perinatal depression should target both social support and patient activation levels. Finally, peer-delivered interventions, have the potential of being more feasible than other interventions and might result in a greater adherence of patients, especially from patients that are more socioeconomically disadvantaged and isolated from the health care system.

For Peer Review

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For Peer Review

REFERENCES

1. Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJ, et al. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. PLoS Med. 2013; 10(11): e1001547.
2. Rahman A, Fisher J, Bower P, Luchters S, Tran T, Yasamy MT, et al. Interventions for common perinatal mental disorders in women in low-and middle-income countries: a systematic review and meta-analysis. Bulletin of the World Health Organization. 2013; 91: 593-601I.
3. Sockol LE, Epperson CN, Barber JP. A meta-analysis of treatments for perinatal depression. Clinical psychology review. 2011; 31(5): 839-49.
4. Singla DR, Kohrt B, Murray LK, Anand A, Chorpita BF, Patel V. Psychological treatments for the world: lessons from low-and middle-income countries. Annual Review of Clinical Psychology. 2017; 13(1).
5. World Health Organization (WHO). Mental Health Global Action Programme Humanitarian Intervention Guide (mhGAP-HIG): Clinical Management of Mental, Neurological, and Substance Use Conditions in Humanitarian Emergencies. World Health Organization, Geneva: 2015.
6. Hafeman DM, Schwartz S. Opening the black box: a motivation for the assessment of mediation. International Journal of Epidemiology. 2009; 38(3): 838-45.
7. Kazdin AE. Mediators and mechanisms of change in psychotherapy research. Annu Rev Clin Psychol. 2007; 3: 1-27.
8. Kraemer HC. Messages for clinicians: moderators and mediators of treatment outcome in randomized clinical trials. American Journal of Psychiatry. 2016; 173(7): 672-9.
9. Fuhr DC, Weobong B, Lazarus A, Vanobberghen F, Weiss HA, Singla DR, et al. Delivering the Thinking Healthy Programme for perinatal depression through peers: an individually-randomised controlled trial in India The Lancet Psychiatry. 2019; 6: 115-27.
10. Sikander S, Ahmad I, Atif N, Zaidi A, Vanobberghen F, Weiss HA, et al. Delivering the Thinking Healthy Programme for perinatal depression through volunteer peers: a cluster randomised controlled trial in Pakistan. The Lancet Psychiatry. 2019; 6: 128-39.
11. Rahman A, Malik A, Sikander S, Roberts C, Creed F. Cognitive behaviour therapy-based intervention by community health workers for mothers with depression and their infants in rural Pakistan: a cluster-randomised controlled trial. The Lancet. 2008; 372(9642): 902-9.
12. Haq Z, Iqbal Z, Rahman A. Job stress among community health workers: a multi-method study from Pakistan. International journal of mental health systems. 2008; 2(1): 15.
13. Sikander S, Lazarus A, Bangash O, Fuhr DC, Weobong B, Krishna RN, et al. The effectiveness and cost-effectiveness of the peer-delivered Thinking Healthy Programme for perinatal depression in Pakistan and India: the SHARE study protocol for randomised controlled trials. Trials. 2015; 16(1): 534.
14. Singla D, Lazarus A, Atif N, Sikander S, Bhatia U, Ahmad I, et al. "Someone like us": Delivering maternal mental health through peers in two South Asian contexts. Journal of affective disorders. 2014; 168: 452-8.

For Peer Review

15. Rahman A. Challenges and opportunities in developing a psychological intervention for perinatal depression in rural Pakistan–a multi-method study. Archives of women's mental health. 2007; 10(5): 211-9.
16. Atif N, Krishna RN, Sikander S, Lazarus A, Nisar A, Ahmad I, et al. Mother-to-mother therapy in India and Pakistan: adaptation and feasibility evaluation of the peer-delivered Thinking Healthy Programme. BMC psychiatry. 2017; 17(1): 79.
17. Dimidjian S, Barrera Jr M, Martell C, Muñoz RF, Lewinsohn PM. The origins and current status of behavioral activation treatments for depression. Annual Review of Clinical Psychology. 2011; 7: 1-38.
18. Dimidjian S, Goodman SH, Sherwood NE, Simon GE, Ludman E, Gallop R, et al. A pragmatic randomized clinical trial of behavioral activation for depressed pregnant women. Journal of Consulting and Clinical Psychology. 2017; 85(1): 26.
19. Patel V, Weobong B, Weiss HA, Anand A, Bhat B, Katti B, et al. The Healthy Activity Program (HAP), a lay counsellor-delivered brief psychological treatment for severe depression, in primary care in India: a randomised controlled trial. The Lancet. 2017; 389(10065): 176-85.
20. O'mahen H, Richards D, Woodford J, Wilkinson E, McGinley J, Taylor RS, et al. Netmums: a phase II randomized controlled trial of a guided Internet behavioural activation treatment for postpartum depression. Psychological medicine. 2014; 44(08): 1675-89.
21. Richards DA, Ekers D, McMillan D, Taylor RS, Byford S, Warren F, et al. Behavioural Therapy for Depression (COBRA): a randomised, controlled, non-inferiority trial. 2016.
22. Stein A, Gath DH, Bucher J, Bond A, Day A, Cooper PJ. The relationship between post-natal depression and mother–child interaction. The British Journal of Psychiatry. 1991; 158(1): 46-52.
23. Stewart RC, Umar E, Tomenson B, Creed F. Validation of the multi-dimensional scale of perceived social support (MSPSS) and the relationship between social support, intimate partner violence and antenatal depression in Malawi. BMC psychiatry. 2014; 14(1): 180.
24. Field T. Prenatal depression effects on early development: a review. Infant behavior & development. 2011; 34(1): 1-14.
25. Gaynor ST, Harris A. Single-participant assessment of treatment mediators: Strategy description and examples from a behavioral activation intervention for depressed adolescents. Behavior Modification. 2008; 32(3): 372-402.
26. Weobong B, Weiss HA, McDaid D, Singla DR, Hollon SD, Nadkarni A, et al. Sustained effectiveness and cost-effectiveness of the Healthy Activity Program, a brief psychological treatment for depression delivered by lay counsellors in primary care: twelve-month follow-up of a randomised controlled trial. PLoS Medicine. 2017; 17(9).
27. Toth SL, Rogosch FA, Oshri A, Gravener-Davis J, Sturm R, Morgan-López AA. The efficacy of interpersonal psychotherapy for depression among economically disadvantaged mothers. Development and Psychopathology. 2013; 25(4pt1): 1065-78.
28. Singla DR, Kumbakumba E, Aboud FE. Effects of a parenting intervention to address maternal psychological wellbeing and child development and growth in rural Uganda: a community-based, cluster-randomised trial. The Lancet Global Health. 2015; 3(8): e458-e69.
29. O'Rourke HP, MacKinnon DP. Reasons for testing mediation in the absence of an intervention effect: A research imperative in prevention and intervention research. Journal of studies on alcohol and drugs. 2018; 79(2): 171-81.

For Peer Review

30. Spitzer RL, Kroenke K, Williams JB, Group PHQPCS. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Jama. 1999; 282(18): 1737-44.
31. Patel V, Araya R, Chowdhary N, King M, Kirkwood B, Nayak S, et al. Detecting common mental disorders in primary care in India: a comparison of five screening questionnaires. Psychol Med. 2008; 38(2): 221-8.
32. World Health Organization. mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings. World Health Organization, Geneva: 2010.
33. Lemmens LH, Galindo-Garre F, Arntz A, Peeters F, Hollon SD, DeRubeis RJ, et al. Exploring mechanisms of change in cognitive therapy and interpersonal psychotherapy for adult depression. Behaviour Research and Therapy. 2017; 94: 81-92.
34. MacKinnon DP, Pirlott AG. Statistical approaches for enhancing causal interpretation of the M to Y relation in mediation analysis. Personality and Social Psychology Review. 2015; 19(1): 30-43.
35. Manos RC, Kanter JW, Luo W. The behavioral activation for depression scale–short form: development and validation. Behavior Therapy. 2011; 42(4): 726-39.
36. Zimet GD, Dahlem NW, Zimet SG, Farley GK. The multidimensional scale of perceived social support. Journal of personality assessment. 1988; 52(1): 30-41.
37. Akhtar A, Rahman A, Husain M, Chaudhry IB, Duddu V, Husain N. Multidimensional scale of perceived social support: psychometric properties in a South Asian population. Journal of Obstetrics and Gynaecology Research. 2010; 36(4): 845-51.
38. Condon JT, Corkindale CJ. The assessment of parent-to-infant attachment: Development of a self-report questionnaire instrument. Journal of Reproductive and Infant Psychology. 1998; 16(1): 57-76.
39. Sikander S, Ahmad I, Lisa B GJ, Hagaman A, Elizabeth T, Ahmed Z, et al. Cohort Profile: Perinatal depression and child socioemotional development: A pregnancy-birth cohort study in rural Pakistan. BMJ Open. under review.
40. MacKinnon DP, Fairchild AJ, Fritz MS. Mediation analysis. Annu Rev Psychol. 2007; 58: 593-614.
41. Muthén L, Muthén B. Mplus. The comprehensive modelling program for applied researchers: user's guide. 2015; 5.
42. Selig JP, Preacher KJ. Monte Carlo method for assessing mediation: An interactive tool for creating confidence intervals for indirect effects [Computer software]. 2008.
43. MacKinnon DP, Lockwood CM, Williams J. Confidence limits for the indirect effect: Distribution of the product and resampling methods. Multivariate behavioral research. 2004; 39(1): 99-128.
44. MacKinnon DP, Lockwood CM, Hoffman JM, West SG, Sheets V. A comparison of methods to test mediation and other intervening variable effects. Psychological methods. 2002; 7(1): 83.
45. Selig JP, Preacher KJ. Mediation models for longitudinal data in developmental research. Research in Human Development. 2009; 6(2-3): 144-64.
46. MacKinnon DP, Warsi G, Dwyer JH. A simulation study of mediated effect measures. Multivariate behavioral research. 1995; 30(1): 41-62.

For Peer Review

47. Cox MG, Kisbu-Sakarya Y, Miočević M, MacKinnon DP. Sensitivity plots for confounder bias in the single mediator model. Evaluation review. 2013; 37(5): 405-31.
48. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Annals of internal medicine. 2017; 167(4): 268-74.
49. Reyes-Portillo JA, McGlinchey EL, Yanes-Lukin PK, Turner JB, Mufson L. Mediators of interpersonal psychotherapy for depressed adolescents on outcomes in Latinos: The role of peer and family interpersonal functioning. Journal of Latina/o Psychology. 2017; 5(4): 248.
50. Murray L, Fiori-Cowley A, Hooper R, Cooper P. The impact of postnatal depression and associated adversity on early mother-infant interactions and later infant outcome. Child development. 1996; 67(5): 2512-26.
51. Bradley RH, Caldwell BM. The HOME Inventory and family demographics. Developmental Psychology. 1984; 20(2): 315.52. Maselko J, Sikander S, Bhalotra S, Bangash O, Ganga N, Mukherjee S, et al. Effect of an early perinatal depression intervention on long-term child development outcomes: follow-up of the Thinking Healthy Programme randomised controlled trial. The Lancet Psychiatry. 2015; 2(7): 609-17.
53. Ackerman SJ, Hilsenroth MJ. A review of therapist characteristics and techniques positively impacting the therapeutic alliance. Clinical psychology review. 2003; 23(1): 1-33.

54. Murray L, Cooper PJ, Wilson A, Romaniuk H. Controlled trial of the short-and long-term effect of psychological treatment of post-partum depression: 2. Impact on the mother-child relationship and child outcome. The British Journal of Psychiatry. 2003; 182(5): 420-7.
55. Holmes EA, Ghaderi A, Harmer CJ, Ramchandani PG, Cuijpers P, Morrison AP, et al. The Lancet Psychiatry Commission on psychological treatments research in tomorrow's science. The Lancet Psychiatry. 2018; 5(3): 237-86.
56. Lemmens LH, Muller VN, Arntz A, Huibers MJ. Mechanisms of change in psychotherapy for depression: An empirical update and evaluation of research aimed at identifying psychological mediators. Clin Psychol Rev. 2016; 50: 95-107.
57. VanderWeele T, Vansteelandt S. Conceptual issues concerning mediation, interventions and composition. Statistics and its Interface. 2009; 2(4): 457-68.

For Peer Review

Table 1. Baseline Characteristics of Participants.

Variable, mean (95% CI) unless otherwise indicated	**THPP-India (N=280)**	**THPP-Pakistan (N=570)**	**Pooled (N=850)**
Age	25.18 (24.63 to 25.71)	27.05 (26.65 to 27.44)	26.43 (26.11 to 26.75)
Education Level (n, %)			
No formal education	34 (12%)	107 (19%)	141 (17%)
Up to primary	120 (43%)	39 (7%)	159 (19%)
Up to secondary	90 (32%)	333 (58%)	423 (50%)
Beyond secondary	36 (13%)	91 (16%)	127 (15%)
Marital Status (% Married)	100%	99.6%	99.9%
Parity (n (%))			
Primiparous	119 (43%)	102 (18%)	221 (26%)
Multiparous	161 (57%)	468 (82%)	629 (74%)
Occupation (%)			
Does not work outside of home	237 (85%)	533 (94%)	770 (91%)
Works outside of home	43 (15%)	37 (6%)	80 (9%)
PHQ-9 Score (0 to 27)	13.38 (12.98 to 13.77)	14.69 (14.38 to 14.99)	14.26 (14.01 to 14.50)
MSPSS Score (0 to 7)	5.29 (5.16 to 5.42)	3.93 (3.82 to 4.05)	4.38 (4.28 to 4.48)

Note. MSPSS = Multidimensional Scale of Perceived Social Support; PHQ-9 = Patient Health Questionnaire-9.

For Peer Review

Table 2. Raw mean scores (95% CI) of Potential Intervention Mediators and Depression Outcomes by Arm and Trial

Variables	THPP-India (N=140)	EUC (N=140)	T-test¶	THPP-Pakistan (N=283)	EUC (N=287)	T-test¶	Pooled THPP (N=423)	Pooled EUC (N=427)	T-test¶ (Effect Size)
Potential Mediators									
Patient Activation (0-25)	12.54 (11.86 to 13.23)	11.09 (10.33 to 11.85)	2.78**	17.59 (17.15 to 18.03)	16.83 (16.34 to 17.32)	2.56**	15.81 (15.35 to 16.26)	14.72 (14.20 to 15.23)	3.13**
Social Support (0-7)	5.65 (5.45 to 5.83)	5.30 (5.10 to 5.50)	2.31*	4.53 (4.37 to 4.68)	4.41 (4.23 to 4.57)	1.04(ns)	4.92 (4.79 to 5.05)	4.73 (4.59 to 4.87)	1.94*
Mother-Child Interaction (0-35)	21.14 (20.87 to 21.41)	20.90 (20.62 to 21.18)	1.23 (ns)	19.21 (19.0 to 19.4)	19.19 (18.9 to 19.4)	0.10(ns)	17.68 (16.84 to 18.52)	16.77 (15.89 to 17.65)	1.47(ns)
Depression Scores									
PHQ-9 at 3 months (0-27)	4.26 (3.51 to 5.02)	5.81 (4.78 to 6.83)	-2.44**	6.16 (5.41 to 6.90)	7.82 (6.88 to 8.75)	-2.75**	5.48 (4.92 to 6.04)	7.08 (6.37 to 7.79)	-3.51***
PHQ-9 at 6 months (0-27)	3.47 (2.66 to 4.27)	4.45 (3.56 to 5.33)	-1.61(ns)	6.07 (5.30 to 6.85)	6.78 (5.97 to 7.59)	-1.25(ns)	5.17 (4.57 to 5.76)	5.93 (5.31 to 6.55)	-1.75¥

¶Note. ¥p<0.10; *p<0.05; **p<0.01; ***p<0.001; ns=not significant

For Peer Review

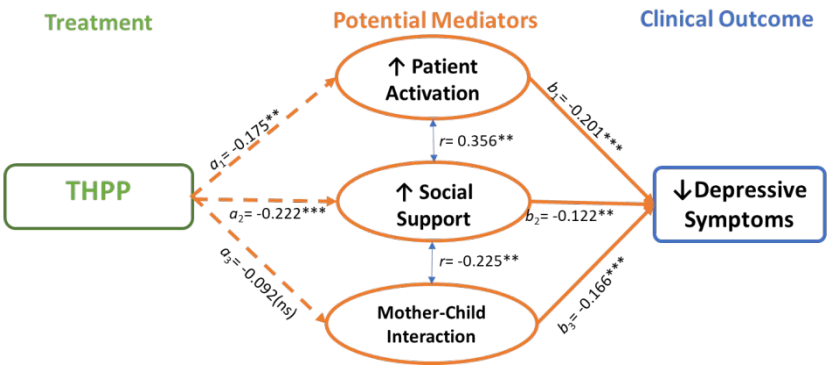
Table 3. Individual mediating pathways within THPP-India and THPP-Pakistan[¥]

	THPP-India (N=280)			THPP-Pakistan (N=570)		
Mediating Pathways	**β[£]**	**S.E.**	**F-value**	**β**	**S.E.**	**F-value**
1. *Patient Activation*						
a (THPP → Patient Activation)	-1.36**	0.50	7.68***	-1.91***	0.54	5.64***
b (Patient Activation→ PHQ-9)	-0.28***	0.08	5.65***	-0.34***	0.08	5.17***
a x *b* [95% CI]	0.38 [0.08 to 0.78]			0.64 [0.23 to 1.18]		
2. *Social Support*						
a (THPP → Social Support)	-0.33**	0.13	15.74***	-0.285*	0.143	8.17***
b (Social Support→PHQ-9)	-1.32***	0.32	5.39***	-1.144***	0.295	4.90***
a x *b* [95% CI]	0.43 [0.09 to 0.88]			0.33 [0.01 to 0.74]		
3. *Mother-Child Interaction*						
a (THPP → Mother-Child Interaction)	-0.22(ns)	0.19	2.31*	-0.05(ns)	0.16	3.85**
b (Mother-Child Interaction→PHQ-9)	-0.06(ns)	0.21	2.72*	-0.46*	0.18	5.73***
a x *b* [95% CI][¶]	—			—		

Note. *p<0.05; **p<0.01; ***p<0.001; ns=not significant; [¶]did not meet conditions of mediation (X→M or M→Y where p<0.05) and therefore indirect effect was not calculated; [£]non-standardized betas are presented. Individual pathways controlled for baseline depressive (PHQ-9) and social support (MSPSS) scores, patient education and cluster (for THPP-Pakistan).

For Peer Review

Figure 1. Multiple mediation analyses across sites (N=850) ¥£



¥Note. *p<0.05; **p<0.01; ***p<0.001; ns=not significant; £standardized betas presented. All mediation analyses controlled for baseline depressive (PHQ-9) and social support (MSPSS) scores and patient education and cluster (for THPP-Pakistan). *r*= refers to Pearson Correlation.

For Peer Review

RUNNING HEAD: MEDIATORS OF PSYCHOSOCIAL INTERVENTIONS FOR PERINATAL DEPRESSION

A multiple mediation analysis of the peer delivered Thinking Healthy Program for perinatal depression: Findings from two parallel randomized controlled trials

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ABSTRACT

Background. Low-intensity psychosocial interventions have been effective in targeting perinatal depression but relevant mechanisms of change remain unknown.

Aims. To examine three theoretically-informed mediators of the peer-delivered Thinking Healthy Program Peer-delivered (THPP), an evidence based psychosocial intervention for perinatal depression, on symptom severity in two parallel randomized controlled trials in Goa, India and Rawalpindi, Pakistan.

Methods. Participants included pregnant women aged ≥18 years with moderate to severe depression, as defined by a PHQ-9 score≥10 and were randomized to either THPP or Enhanced Usual Care. We examine whether three pre-specified variables—patient activation, social support, and mother-child attachment— at 3 months post-childbirth mediated the effects of the THPP interventions of perinatal depressive symptom severity (PHQ-9) at the primary endpoint of 6 months post childbirth. We first examined individual mediation within each trial (n=280 in India and n=570 in Pakistan) and then as a pooled analysis across both trials (N=850).

Results. In both site-specific and pooled analyses, patient activation and support at 3 months independently mediated the intervention effects on depressive symptom severity at 6 months, accounting for 23.6% and 18.2% respectively of the total effect of THPP. The intervention had no impact on mother-child attachment scores and thus there was no evidence that this factor mediated the intervention effect.

Conclusion. The effects of the psychosocial intervention on depression outcomes in mothers were mediated by the same two factors in both contexts suggesting that such interventions seeking to alleviate perinatal depression should target both social support and patient activation levels.

Trial Registration. ClinicalTrials.gov Identifier: NCT02104232 in THPP-India and NCT02111915 in THPP-Pakistan.

For Peer Review

INTRODUCTION

Depression is the leading cause of disability among women worldwide[1]. Psychosocial interventions, including cognitive, behavioral and interpersonal therapies, have been effective in targeting perinatal depression[2-3]. However, the growing field of treatment evaluation, including interventions delivered by non-specialist providers (NSPs)[4], has rarely evaluated how these treatments work which may affect their replication and scale-up. This is particularly true for the field of perinatal mental health, where effective psychosocial interventions exist, are recommended as first-line interventions by international guidelines (mhGAP)[5], and have been successfully implemented by NSPs, including peers. Mediation analysis is a technique to evaluate the theoretical basis of interventions to shed more light into this so-called 'black box'[6] of relevant treatment factors[7]. Investigation of the theoretically-informed mediators of treatments may illuminate how these treatments operate, guide clinicians to predict individual patient trajectories, and guide researchers to develop more effective interventions[7-8].

The current study examined the role of three potential and theoretically-informed mediators within the SHARE trials[9-10]. The goal of SHARE—the **S**outh Asian **H**ub for **A**dvocacy, **R**esearch and **E**ducation on Mental Health supported by the NIMH—was to adapt the Thinking Healthy Program (THP)[11] for delivery by peers (called the Thinking Healthy Program, Peer-Delivered THPP) in India and Pakistan. The THP was originally developed and evaluated in Pakistan[11] and is recommended by the World Health Organization for the treatment of perinatal depression in low-resource settings (http://www.who.int/mental_health/maternal-child/thinking healthy/en/). Unfortunately, the delivery of THP was hampered by the existing demands on community health workers[12]. Two parallel trials examined the effectiveness of peer delivered THPP in Goa, India (hereafter referred to as THPP-India) and Rawalpindi, Pakistan (THPP-Pakistan)[13]. Peers—mothers living in the same community as mothers participating in the intervention—were found to be an acceptable and feasible delivery agent within both of these settings[14].

The theoretical foundation and relevant mediators of THPP

THP was originally designed as an individual, 16-session, cognitive behavioural therapy (CBT) that was delivered by community health workers[15]. Using simplified cognitive and behavioural elements, the intervention primarily focused on three key relationships: the woman's relationships with herself, her family and her infant[11]. While retaining a core emphasis on these three areas, the content of THPP was modified to include a stronger emphasis on behavioural activation (BA) as this was found to be more feasible for delivery by peers[16]. BA is a parsimonious approach that is easy to understand and implement[17]; it has been successfully implemented by other NSPs, including lay counsellors, nurses, midwives, and undergraduate students, to effectively reduce depressive symptoms in general and perinatal populations[18-21]. THPP conceptualizes behavioral activation as the degree to which women (pregnant and postpartum) reportedly engaged in a variety of activities—including those pertaining to the mother's personal well-being, eliciting social support from spouse, family and friends, and her perceived attachment to her developing infant—and their sense of accomplishment in completing these activities.

For Peer Review

Consequently, and in line with the theoretical emphasis on relationships with self, other, and baby, we selected three potential mediators to explain the pathways of change underlying THPP. These were: patient activation; perceived support (hereon referred to as social support) from one's spouse, family and community, and mother-child attachment. These three variables have been found to significantly influence depression outcomes in perinatal populations[20,22-24], and both patient activation[25-26] and social support[27- 28] have been found to mediate the effects of BA-oriented treatments on depression outcomes.

Analysis of mediation effects is important whether or not there is an overall treatment effect because it sheds light on different aspects of the intervention, such as whether the intervention affected the mediator and whether the mediator is related to the outcome. It is also possible that the test of mediation can have more statistical power than the test of the overall intervention effect. Because mediation analyses do not require a direct effect of the intervention on long-term outcomes (see Methods section below), the examination of potential mediators is key in illuminating causal pathways irrespective whether an intervention is effective[29].

In the current study, we aimed to test the theory of THPP by conducting a rigorous mediation analysis within two parallel, randomized controlled trials (RCTs). Specifically, we examined whether three theoretically-informed variables—patient-reported activation, social support, and mother-child attachment— at 3 months post childbirth mediated the effects of the THPP intervention on perinatal depressive symptoms at 6 months post childbirth.

METHODS

Setting, Participants and Design. The study was conducted in two locations: the semi-urban, North District of the state of Goa, India and Kallar Syeddan, a rural sub-district of Rawalpindi in the province of Punjab, Pakistan. Participants included pregnant women in the second or third trimester, aged ≥18 years with moderate to severe depressive symptoms, as defined by a Patient Health Questionnaire 9 (PHQ-9) score≥10[30]. Potentially eligible participants were screened for depression with a locally-validated version of the PHQ-9[11,31] after providing written informed consent for screening (or witnessed informed consent/audio-recordings for illiterate participants).

In THPP-India, an individual RCT with 1:1 allocation, stratified by place of residence (rural vs. urban) was conducted for a total sample of N=280 participants. In Pakistan, a cluster RCT with 1:1 allocation, 40 village clusters and stratified by 11 union councils, was conducted, with a total sample of N=570 participants. Participants were recruited from routine healthcare settings including two antenatal clinics and two primary health centers in Goa, and from the registers of the community-based Lady Health Workers across the rural sub-district of Kallar Syeddan in Pakistan.

Mothers were randomized to either the THPP interventions or Enhanced Usual Care (EUC). Ethical approval was obtained from the Institutional Review Boards at the University of Liverpool, the London School of Hygiene and Tropical Medicine, the Human Development Research Foundation and Sangath Center (the implementing institutions of each trial in Pakistan and India, respectively) and the India Council of Medical Research. Both trials were

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registered on ClinicalTrials.gov: NCT02104232 in THPP-India and NCT02111915 in THPP-Pakistan. The trials protocols and results been described in full elsewhere[9-10, 13].

Treatment arms.

Thinking Healthy Program Peer-delivered. The intervention for moderate-to-severe perinatal depressive symptoms being assessed in these trials was the Thinking Healthy Program Peer-delivered (THPP). As mentioned, THPP is the adapted (peer-delivered) version of the Thinking Healthy Program (THP) which was originally developed and evaluated (based on delivery by government-employed LHWs) in Pakistan[11]. In both sites, THPP comprised up to 14 sessions of BA, each lasting up to 45 minutes. The intervention began in the antenatal phase and lasted up to 6-months postnatally, with the most active phase of treatment concluding by the end of the first trimester. The core strategies used by the peers, focusing on the 3 areas of personal well-being, relationship with the infant and relationship with significant others, were: active listening, collaboration with the family, guided discovery using pictures and stories, homework, and behavioral activation (identifying and replacing unhealthy behaviours with healthy ones and practicing them)[16]. THPP-India was implemented primarily in participants' homes and individually-randomised and, THPP-Pakistan was conducted in a community setting with woman randomised in village clusters to avoid contamination.

In both sites, THPP was delivered by peers—women with children, a similar socio-demographic background as participants, and good communication skills[14,16]—who were recruited from the local community through word-of-mouth, particularly from key informants such as community health workers, women's self-help groups and community elders. Recruited peers underwent one week of classroom-based training including learning the THPP content, general counseling skills, confidentiality issues and interactive learning involving role plays. This was followed by competency assessments which determined the selection of peers for the trial. Peers were initially supervised by expert trainers, followed by a cascade model of training using peer-led supervision. In THPP-India, 37 peers were trained and 26 were selected for the trial; in THPP-Pakistan, 66 peers were recruited and selected for the trial. Their mean age and education levels were 37.85 years (range 27 to 50 years) and 11.85 years (9 to 15 years) respectively in India and 28.0 years (21 to 45 years) and 6.6 years (0 to 14 years) respectively in Pakistan[16].

Enhanced usual care. Participants received EUC in both the intervention and control arms. In both arms, EUC comprised the following: 1) Informing participants about their diagnosis of depression; 2) In Pakistan, informing depressed participants about ways to seek appropriate health care (i.e. by going for assistance to their LHWs, to the primary health centre or to the tertiary health centre, which is the Institute of Psychiatry, Rawalpindi, Pakistan); 3) In India, providing gynaecologists with the findings of the screening results for perinatal depression; 4) Providing the primary health-care centres and the gynaecologists with the adapted WHO mhGAP treatment guidelines for perinatal depression[32]; and 5) Providing an information sheet about how and where to seek health care from including local Community Health Workers (CHWs), primary health facilities and tertiary care facilities, both during pregnancy and beyond.

For Peer Review

Measures.

Outcome. The outcome of the current study was depressive symptom severity scores on the PHQ-9 at 6 months post-childbirth, as assessed by independent evaluators who were blind to treatment status. Similar to other mediation analyses[33], this variable was selected over the trials' other primary outcome of remission status because depressive symptoms offered a continuous score which provides more variability in our regression analyses[34].

Potential Mediators. Three separate scales are used to assess the three *a priori* mediators at the 3 month post-childbirth outcome assessment.

1. *Patient Activation.* The **PREMIUM Abbreviated Activation Scale** (PAAS) is a 5-item scale, originally developed and used in a separate trial of a brief behavioural activation treatment (the Healthy Activity Program) trial[26], and which is based on the Behavioural Activation for Depression Scale[35]. PAAS includes five indicators of behavioural activation — a treatment factor that is explicitly targeted in the THPP trial — such as the mother's self-report of her engagement with a variety of activities ("*did you engage in many different activities?*" and "*were you an active person and accomplished the goals you set out to do?*"), and associated pleasure ("*did you do things that were enjoyable?"* and mastery ("*are you content with the amounts and types of activities you did?*"). The final item included a reverse question: "*Did you spend long periods thinking over and over about your problems?*". All five items are assessed on a scale of 0 (*'not at all'*) to 5 (*'yes, completely'*) for a total continuous score of 25. In both settings, the PAAS at 3 months showed good internal consistency (α=0.801 in THPP-India and α=0.811 in THPP-Pakistan) and good concurrent validity with social support at 3 months (r=0.341, p<0.001 in THPP-India and r=0.367 in THPP-P, p<0.001).
2. *Social Support.* The **Multidimensional Scale of Perceived Social Support** (MSPSS) is a 12-item scale for assessment of mothers' perceived social support from one's spouse, family and community[36]. This scale has been widely used and previously validated in current study contexts[11, 37]. Mothers are asked to rate the availability of social support on a 5-point Likert scale, ranging from 1 ('*strongly disagree'*) to 5 ('*strongly agree'*), for a total continuous score ranging from 1 to 60. Sample items include "*I get the emotional help and support I need from my family*." In the current study, this scale showed excellent internal consistency (α=0.862 in THPP-India and α=0.853 in THPP-Pakistan) excellent predictive validity between social support between baseline and 3 months (r=0.489, p<0.001 in THPP-India and r=0.358, p<0.001 in THPP-Pakistan), and 3 and 6 months (r=0.449, p<0.001 in THPP-India and r=0.359, p<0.001 in THPP-Pakistan).
3. *Mother-Child Attachment.* The **Maternal Postnatal Attachment Scale** (MPAS) assesses mother's reported attachment to the child and satisfaction with parenting[38]. The original scale was reduced to seven culturally-relevant items, as determined by local clinical experts, in order to rate the mother's feelings, thoughts and relationship to her baby after birth. Sample items include rating one's competence or enjoyment when interacting with the baby. For example, '*When I interact with my baby, I feel…'* very incompetent (scored 1) to very competent (scored 5). As in the original scale, all items score from 1 to 5, with a higher score indicating a higher degree of maternal attachment to her baby (total continuous score of 35). The scale has been adapted for the Pakistan setting[39], and shows sound internal consistency (α=0.791 in THPP-India and α=0.793 in THPP-Pakistan) as well as good

For Peer Review

concurrent validity with social support at 3 months in both sites (r=0.225, p<0.001 in THPP-India and r=0.115, p<0.01).

Baseline sample characteristics related to the patient (age, education, marital status, occupation, number of children, chronicity (duration of depressive symptoms), and PHQ-score) were all examined as potential covariates.

Data Collection. Independent interviewers assessed primary outcomes at the 3 and 6 month post childbirth endpoints. These timepoints were selected in the larger trials to estimate the active phase of THPP and to examine its potentially sustained effects, respectively. These data were recorded using tablets that were uploaded in real-time to a server with data being reviewed by independent data managers.

Analyses. The current study was a secondary mediation analysis within the context of two, parallel RCTs. Mediation conditions were met if the regression models (described below) demonstrated that there were significant effects of the independent variable on the proposed mediator (X→M) and of the proposed mediator on outcome scores (M→Y), adjusted for the independent variable[40], where significance was defined as p<0.05. It is possible for mediating effects to be present even if there is no overall effect of the independent variable on the dependent variable (X→Y)[29]. An intention-to-treat (ITT) analysis was conducted and multiple imputation methods were used to account for missing values. Using SAS PROC MI and PROC MIANALYZE, five imputed datasets were created the and the model averaged results across the five iterations. To ensure consistency across trials, data was analyzed at the individual participant level, while controlling for the cluster-level variable in the regression analysis. Mplus version 8.1[41] was used to conduct mediation analyses.

Individual mediation pathways. First, means and 95% confidence intervals were estimated for baseline variables, followed by means, 95% confidence intervals and t-tests for each mediating variable and depression outcomes at 3 and 6 months post-childbirth. Second, because measures of patient activation and mother-child attachment were not collected at baseline, we used baseline social support scores in the model. Baseline social support scores were significantly correlated with patient activation (r=0.248, p<0.001 in THPP-India and r=0.161, p<0.01 in THPP-Pakistan) and mother-child attachment (r=0.195, p<0.01 in THPP- India and r=0.166, p<0.01 THPP- Pakistan) at 3 months post-child birth.

Next, we used multiple linear regression modelling to estimate models whereby the dependent variable was PHQ-depressive symptoms at 6 months post-childbirth. In each trial, we examined three individual pathways to determine whether a) patient activation; b) social support; and c) mother-child attachment mediated the effects of THPP-India or THPP-Pakistan on depressive symptoms. In order to do this, we first examined the effects of treatment arm (THPP vs. EUC) within each trial on the three proposed mediators followed by the examination of effects of the three proposed mediators on depressive symptom outcomes. This resulted in the examination of six pathways, in which we controlled for baseline PHQ-9 and social support scores as well as patient education levels. In THPP-Pakistan, we also controlled for cluster in these regressions. The variance inflation factor (VIF) was assessed for each independent variable within each model to estimate multicollinearity (VIF≥5).

For Peer Review

Finally, if mediation conditions were met, we assessed individual mediating pathways using the Monte Carlo Method for Assessing Mediation (MCMAM)[42]. In this approach, a distribution of the indirect effect was used to estimate a confidence interval (CI) around the observed value of the indirect effect[43]. MCMAM performs better than the Sobel test and comparably with bootstrap approaches[35,44] and no direct effect is required of the independent variable (in this case, THPP-India or THPP-Pakistan) on the dependent variable (depressive symptoms at 6 months)[29,40]. In the current study, we computed a 95% CI with 20,000 repetitions. Following the recommendations of Selig and Preacher[45] for MCMAM, non-standardized betas were used for individual mediation analyses.

Pooled Analysis. After assessing individual mediators within each trial, we conducted a pooled mediation analysis. This approach was used to ensure that the proposed mediators were first being assessed within their respective trials and did not assume that the relations between the proposed mediators and outcomes will be similar across trials. Data were pooled by two independent statisticians and analyzed at the individual participant level. In the pooled analysis and in order to compare results across a variety of measures, standardized betas are presented. We examined the role of all three potential mediators simultaneously on the same PHQ-9 depressive symptom severity score. Similar to the individual mediating pathways, we controlled for baseline PHQ-9 and MSPSS scores, cluster and patient education levels. Finally, and across all participants (N=850), we estimated the contribution of each potential mediator on the total effect by dividing each mediating effect by the total effect. The sample size of the current study is reasonable to conduct this analysis, where a minimum of 500 observations is suggested[46].

RESULTS

Participants included those randomized to THPP (n=140 in THPP-India and n=283 in THPP-Pakistan) compared to Enhanced Usual Care (n=140 in THPP-India and n=287 in THPP-Pakistan). Pooled analyses involved the total sample across the two trials (N=850). On average, participants across the two trials were 26 years of age (95% CI=26.1 to 26.8 years and range of 18 to 45); the majority had up to primary and secondary levels of education (75% in THPP-India vs. 65% in THPP-Pakistan), were married (everyone except one participant in THPP-I) and had more than one child (82% in THPP-Pakistan and 57% in THPP-India). As expected, fewer women in THPP-Pakistan worked outside of the home than in THPP-India (6% vs. 15%). Descriptive scores of variables related to the current analysis are detailed in Table 1. Data were missing at 6 month follow-up among 10.3% of participants in THPP-India (n=29) and 13.7% (n=117) in THPP-Pakistan. No differences were found between participants who remained vs. those who dropped out in both trials; similarly, there were no differences between treatment and control conditions. These and other results of each trial have been published elsewhere[9-10].

[INSERT TABLE 1]

Mediational Pathways. Descriptive frequencies and t-tests of potential mediating variables and clinical outcomes can be found in Table 2. In each individual site, there were higher patient activation and support scores at 3 months and lower depressive symptoms at both 3 and 6 months post-childbirth among THPP intervention participants as compared to EUC participants;

For Peer Review

however, these differences were not significant for social support scores in Pakistan or for depression outcomes at 6 months in either individual trial. In addition, there was no significant difference in mother-child attachment scores between arms in either trial.

[INSERT TABLE 2]

Individual mediators were analyzed within each trial and detailed in Table 3. In both trials, and once correlates were considered in regression models, we found that improved patient activation and social support at 3 months post-child birth mediated the effects of THPP intervention on reduced depressive symptom severity. This was not the case for mother-child attachment, was which found to have an effect on depressive symptoms but there was no effect of the THPP-intervention on this variable; thus, no indirect effect was calculated because mediation conditions were not met. There was no evidence for multicollinearity (VIF<3).

[INSERT TABLE 3]

In the pooled analysis, a similar pattern emerged (Figure 1). Specifically, we found significant indirect effects of both patient activation (*axb*=0.027, 95% CI=0.016 to 2.210, *p*=0.027) and social support (*axb*=0.035, 95% CI=0.027, 95% CI=0.013 to 2.059, *p*=0.040) at 3 months post-childbirth, suggesting their independent roles in partly mediating the effects of the THPP intervention on depression outcomes at 6 months post- childbirth. This was not the case for the hypothesized mediator of mother-child attachment, which did not result in a significant indirect effect (*axb*=0.015, 95% CI=0.012 to 1.288, *p*=0.198). The total direct effect of THPP on PHQ-9 outcomes was standardized *β*=0.148 (95%=0.033 to 0.269, *p*=0.038), demonstrating a significant effect of the intervention on depression outcomes when pooling the data across the two trials. Furthermore, we observed that social support was found to be the most significant among the two significant mediators across trials. We found that social support and patient activation at 3 months accounted for 23.6% and 18.2% respectively of the total effect of THPP on PHQ-9 depressive symptoms at 6 months.

[INSERT FIGURE 1]

Finally, recent research has suggested the consideration of unmeasured confounders[46-47]. We followed these suggested methods and found that we would require a large correlation (*r*=0.5 or higher) to remove the mediating effects of patient activation or social support on long-term depression outcomes.

DISCUSSION

The current study found that two of the three pre-specified variables—patient activation and social support at 3 months post-childbirth—mediated the effects of THPP on depression outcomes at 6 months post-childbirth. Thus, despite varying contexts, the THPP intervention worked through the same mediators in two diverse contexts. This suggests the generalisability of the intervention and emphasizes that low-intensity psychosocial interventions seeking to

For Peer Review

alleviate perinatal depression should focus on improving social support and patient activation levels.

Our results are consistent with THPP's theoretical emphasis on behavioural activation which suggest that the key to feeling less depressed is to increase enjoyable or fulfilling activities that align with one's values and key relationships[17]. After taking into account relevant correlates, we also found that women who had higher levels of patient activation and social support reported lower depressive symptoms. Furthermore, and in line with previous mediation studies[25-28, 49], these factors were found to independently and concurrently mediate the effects of the THPP intervention on perinatal depressive symptoms. The results add to the interpretation by suggesting that improving patient activation and social support levels within perinatal depression interventions may benefit a reduction in perinatal depressive symptoms. None, however, have examined these mediators simultaneously and when delivered by an NSP in community-based settings, or in diverse global and cultural contexts.

We did not, however, find that the THPP intervention influenced mother-child reported attachment. An independent observation of mother-child attachment and interaction, as implemented in other perinatal depression treatment programs (e.g.,[50,51]), may be more reliable than the measure used in the current study. Or this may be due to the intervention content and delivery lacking an explicit emphasis on mother-child attachment and interactions. These results may reflect the widely inconsistent effects of psychosocial interventions for maternal depression on child development outcomes and one reason may be because there is a lack of emphasis on explicitly targeting mother-child interactions[28]. For example, despite robust and persistent effects on reduced maternal and child mental health outcomes, the original THP trial did not show any positive effects on child growth and developmental outcomes[52]. Similarly, there are few mother-child programs that have explicitly targeted maternal mental health symptoms[28]. In order to achieve the integration of mental health services in other services, perhaps a stronger emphasis on mother-child attachment and interactions need to be emphasized in maternal mental health interventions in order to influence both maternal and child development outcomes.

Limitations. We also acknowledge several limitations. First, there may be other potential mediators that may explain the THPP intervention. For example, we did not measure therapeutic alliance between the peer counsellor and participant. Therapeutic alliance is a frequently-studied phenomenon in the psychosocial treatment literature[53] and may be particularly relevant for a peer context. In addition, we did not assess how cognitions may have influenced key patient behaviours and depression outcomes. This has been examined in other trials[54] and the interplay of patient cognitions and behaviours may inform how THPP works. Second, all of our measures were based on self-report. As mentioned above, independent observations of mother-child attachment, including the HOME Inventory[51] or video-recordings[49] have been conducted in other low-resource settings[28] and may offer a more valid assessment of mother-child-attachment, but we know of no other objective measures for activation or social support. Third, we did not assess patient activation levels or were unable to assess mother-child attachment levels at baseline. The latter was not possible because THPP began during the antenatal phase. If we had baseline measures of these variables, power to detect mediated

For Peer Review

effects would have been increased to account for baseline patient variables or potentially explain lack of effects on perceived mother-child attachment. Finally, our results supporting activation and social support as mediators suggest further investigations of these underlying mechanisms of psychosocial interventions for perinatal mental health[55].

In sum, this study contributes to the larger field of psychosocial treatment literature by identifying two key and theoretically-informed mediators for perinatal depression. In two diverse contexts, our findings highlight the importance of one's relationship with self and others is playing a key role in alleviating perinatal depressive symptoms. Additional strengths of our study are following key guidelines for mediation[56,57], including the assessment of multiple, potential mediators, the use of a temporal design with hypothesized mediators being assessed at distinct time-points, with large sample sizes within randomized controlled trial designs and adjusting for key variables at baseline. Our findings suggest the generalisability of the THPP across two diverse contexts and that psychosocial interventions seeking to alleviate perinatal depression should target both social support and patient activation levels. Finally, peer-delivered interventions, have the potential of being more feasible than other interventions and might result in a greater adherence of patients, especially from patients that are more socioeconomically disadvantaged and isolated from the health care system.

For Peer Review

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For Peer Review

REFERENCES

1. Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJ, et al. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. PLoS Med. 2013; 10(11): e1001547.
2. Rahman A, Fisher J, Bower P, Luchters S, Tran T, Yasamy MT, et al. Interventions for common perinatal mental disorders in women in low-and middle-income countries: a systematic review and meta-analysis. Bulletin of the World Health Organization. 2013; 91: 593-601I.
3. Sockol LE, Epperson CN, Barber JP. A meta-analysis of treatments for perinatal depression. Clinical psychology review. 2011; 31(5): 839-49.
4. Singla DR, Kohrt B, Murray LK, Anand A, Chorpita BF, Patel V. Psychological treatments for the world: lessons from low-and middle-income countries. Annual Review of Clinical Psychology. 2017; 13(1).
5. World Health Organization (WHO). Mental Health Global Action Programme Humanitarian Intervention Guide (mhGAP-HIG): Clinical Management of Mental, Neurological, and Substance Use Conditions in Humanitarian Emergencies. World Health Organization, Geneva: 2015.
6. Hafeman DM, Schwartz S. Opening the black box: a motivation for the assessment of mediation. International Journal of Epidemiology. 2009; 38(3): 838-45.
7. Kazdin AE. Mediators and mechanisms of change in psychotherapy research. Annu Rev Clin Psychol. 2007; 3: 1-27.
8. Kraemer HC. Messages for clinicians: moderators and mediators of treatment outcome in randomized clinical trials. American Journal of Psychiatry. 2016; 173(7): 672-9.
9. Fuhr DC, Weobong B, Lazarus A, Vanobberghen F, Weiss HA, Singla DR, et al. Delivering the Thinking Healthy Programme for perinatal depression through peers: an individually-randomised controlled trial in India The Lancet Psychiatry. 2019; 6: 115-27.
10. Sikander S, Ahmad I, Atif N, Zaidi A, Vanobberghen F, Weiss HA, et al. Delivering the Thinking Healthy Programme for perinatal depression through volunteer peers: a cluster randomised controlled trial in Pakistan. The Lancet Psychiatry. 2019; 6: 128-39.
11. Rahman A, Malik A, Sikander S, Roberts C, Creed F. Cognitive behaviour therapy-based intervention by community health workers for mothers with depression and their infants in rural Pakistan: a cluster-randomised controlled trial. The Lancet. 2008; 372(9642): 902-9.
12. Haq Z, Iqbal Z, Rahman A. Job stress among community health workers: a multi-method study from Pakistan. International journal of mental health systems. 2008; 2(1): 15.
13. Sikander S, Lazarus A, Bangash O, Fuhr DC, Weobong B, Krishna RN, et al. The effectiveness and cost-effectiveness of the peer-delivered Thinking Healthy Programme for perinatal depression in Pakistan and India: the SHARE study protocol for randomised controlled trials. Trials. 2015; 16(1): 534.
14. Singla D, Lazarus A, Atif N, Sikander S, Bhatia U, Ahmad I, et al. “Someone like us”: Delivering maternal mental health through peers in two South Asian contexts. Journal of affective disorders. 2014; 168: 452-8.

For Peer Review

15. Rahman A. Challenges and opportunities in developing a psychological intervention for perinatal depression in rural Pakistan–a multi-method study. Archives of women's mental health. 2007; 10(5): 211-9.
16. Atif N, Krishna RN, Sikander S, Lazarus A, Nisar A, Ahmad I, et al. Mother-to-mother therapy in India and Pakistan: adaptation and feasibility evaluation of the peer-delivered Thinking Healthy Programme. BMC psychiatry. 2017; 17(1): 79.
17. Dimidjian S, Barrera Jr M, Martell C, Muñoz RF, Lewinsohn PM. The origins and current status of behavioral activation treatments for depression. Annual Review of Clinical Psychology. 2011; 7: 1-38.
18. Dimidjian S, Goodman SH, Sherwood NE, Simon GE, Ludman E, Gallop R, et al. A pragmatic randomized clinical trial of behavioral activation for depressed pregnant women. Journal of Consulting and Clinical Psychology. 2017; 85(1): 26.
19. Patel V, Weobong B, Weiss HA, Anand A, Bhat B, Katti B, et al. The Healthy Activity Program (HAP), a lay counsellor-delivered brief psychological treatment for severe depression, in primary care in India: a randomised controlled trial. The Lancet. 2017; 389(10065): 176-85.
20. O'mahen H, Richards D, Woodford J, Wilkinson E, McGinley J, Taylor RS, et al. Netmums: a phase II randomized controlled trial of a guided Internet behavioural activation treatment for postpartum depression. Psychological medicine. 2014; 44(08): 1675-89.
21. Richards DA, Ekers D, McMillan D, Taylor RS, Byford S, Warren F, et al. Behavioural Therapy for Depression (COBRA): a randomised, controlled, non-inferiority trial. 2016.
22. Stein A, Gath DH, Bucher J, Bond A, Day A, Cooper PJ. The relationship between post-natal depression and mother–child interaction. The British Journal of Psychiatry. 1991; 158(1): 46-52.
23. Stewart RC, Umar E, Tomenson B, Creed F. Validation of the multi-dimensional scale of perceived social support (MSPSS) and the relationship between social support, intimate partner violence and antenatal depression in Malawi. BMC psychiatry. 2014; 14(1): 180.
24. Field T. Prenatal depression effects on early development: a review. Infant behavior & development. 2011; 34(1): 1-14.
25. Gaynor ST, Harris A. Single-participant assessment of treatment mediators: Strategy description and examples from a behavioral activation intervention for depressed adolescents. Behavior Modification. 2008; 32(3): 372-402.
26. Weobong B, Weiss HA, McDaid D, Singla DR, Hollon SD, Nadkarni A, et al. Sustained effectiveness and cost-effectiveness of the Healthy Activity Program, a brief psychological treatment for depression delivered by lay counsellors in primary care: twelve-month follow-up of a randomised controlled trial. PLoS Medicine. 2017; 17(9).
27. Toth SL, Rogosch FA, Oshri A, Gravener-Davis J, Sturm R, Morgan-López AA. The efficacy of interpersonal psychotherapy for depression among economically disadvantaged mothers. Development and Psychopathology. 2013; 25(4pt1): 1065-78.
28. Singla DR, Kumbakumba E, Aboud FE. Effects of a parenting intervention to address maternal psychological wellbeing and child development and growth in rural Uganda: a community-based, cluster-randomised trial. The Lancet Global Health. 2015; 3(8): e458-e69.
29. O'Rourke HP, MacKinnon DP. Reasons for testing mediation in the absence of an intervention effect: A research imperative in prevention and intervention research. Journal of studies on alcohol and drugs. 2018; 79(2): 171-81.

For Peer Review

528 30. Spitzer RL, Kroenke K, Williams JB, Group PHQPCS. Validation and utility of a self-report
529 version of PRIME-MD: the PHQ primary care study. Jama. 1999; 282(18): 1737-44.
530 31. Patel V, Araya R, Chowdhary N, King M, Kirkwood B, Nayak S, et al. Detecting common
531 mental disorders in primary care in India: a comparison of five screening questionnaires.
532 Psychol Med. 2008; 38(2): 221-8.
533 32. World Health Organization. mhGAP intervention guide for mental, neurological and
534 substance use disorders in non-specialized health settings. World Health Organization, Geneva:
535 2010.
536 33. Lemmens LH, Galindo-Garre F, Arntz A, Peeters F, Hollon SD, DeRubeis RJ, et al.
537 Exploring mechanisms of change in cognitive therapy and interpersonal psychotherapy for adult
538 depression. Behaviour Research and Therapy. 2017; 94: 81-92.
539 34. MacKinnon DP, Pirlott AG. Statistical approaches for enhancing causal interpretation of
540 the M to Y relation in mediation analysis. Personality and Social Psychology Review. 2015;
541 19(1): 30-43.
542 35. Manos RC, Kanter JW, Luo W. The behavioral activation for depression scale–short form:
543 development and validation. Behavior Therapy. 2011; 42(4): 726-39.
544 36. Zimet GD, Dahlem NW, Zimet SG, Farley GK. The multidimensional scale of perceived
545 social support. Journal of personality assessment. 1988; 52(1): 30-41.
546 37. Akhtar A, Rahman A, Husain M, Chaudhry IB, Duddu V, Husain N. Multidimensional scale
547 of perceived social support: psychometric properties in a South Asian population. Journal of
548 Obstetrics and Gynaecology Research. 2010; 36(4): 845-51.
549 38. Condon JT, Corkindale CJ. The assessment of parent-to-infant attachment: Development
550 of a self-report questionnaire instrument. Journal of Reproductive and Infant Psychology. 1998;
551 16(1): 57-76.
552 39. Sikander S, Ahmad I, Lisa B GJ, Hagaman A, Elizabeth T, Ahmed Z, et al. Cohort Profile:
553 Perinatal depression and child socioemotional development: A pregnancy-birth cohort study in
554 rural Pakistan. BMJ Open. under review.
555 40. MacKinnon DP, Fairchild AJ, Fritz MS. Mediation analysis. Annu Rev Psychol. 2007; 58:
556 593-614.
557 41. Muthén L, Muthén B. Mplus. The comprehensive modelling program for applied
558 researchers: user's guide. 2015; 5.
559 42. Selig JP, Preacher KJ. Monte Carlo method for assessing mediation: An interactive tool
560 for creating confidence intervals for indirect effects [Computer software]. 2008.
561 43. MacKinnon DP, Lockwood CM, Williams J. Confidence limits for the indirect effect:
562 Distribution of the product and resampling methods. Multivariate behavioral research. 2004;
563 39(1): 99-128.
564 44. MacKinnon DP, Lockwood CM, Hoffman JM, West SG, Sheets V. A comparison of
565 methods to test mediation and other intervening variable effects. Psychological methods. 2002;
566 7(1): 83.
567 45. Selig JP, Preacher KJ. Mediation models for longitudinal data in developmental research.
568 Research in Human Development. 2009; 6(2-3): 144-64.
569 46. MacKinnon DP, Warsi G, Dwyer JH. A simulation study of mediated effect measures.
570 Multivariate behavioral research. 1995; 30(1): 41-62.

For Peer Review

47. Cox MG, Kisbu-Sakarya Y, Miočević M, MacKinnon DP. Sensitivity plots for confounder bias in the single mediator model. Evaluation review. 2013; 37(5): 405-31.
48. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Annals of internal medicine. 2017; 167(4): 268-74.
49. Reyes-Portillo JA, McGlinchey EL, Yanes-Lukin PK, Turner JB, Mufson L. Mediators of interpersonal psychotherapy for depressed adolescents on outcomes in Latinos: The role of peer and family interpersonal functioning. Journal of Latina/o Psychology. 2017; 5(4): 248.
50. Murray L, Fiori-Cowley A, Hooper R, Cooper P. The impact of postnatal depression and associated adversity on early mother-infant interactions and later infant outcome. Child development. 1996; 67(5): 2512-26.
51. Bradley RH, Caldwell BM. The HOME Inventory and family demographics. Developmental Psychology. 1984; 20(2): 315.52. Maselko J, Sikander S, Bhalotra S, Bangash O, Ganga N, Mukherjee S, et al. Effect of an early perinatal depression intervention on long-term child development outcomes: follow-up of the Thinking Healthy Programme randomised controlled trial. The Lancet Psychiatry. 2015; 2(7): 609-17.
53. Ackerman SJ, Hilsenroth MJ. A review of therapist characteristics and techniques positively impacting the therapeutic alliance. Clinical psychology review. 2003; 23(1): 1-33.

54. Murray L, Cooper PJ, Wilson A, Romaniuk H. Controlled trial of the short-and long-term effect of psychological treatment of post-partum depression: 2. Impact on the mother-child relationship and child outcome. The British Journal of Psychiatry. 2003; 182(5): 420-7.
55. Holmes EA, Ghaderi A, Harmer CJ, Ramchandani PG, Cuijpers P, Morrison AP, et al. The Lancet Psychiatry Commission on psychological treatments research in tomorrow's science. The Lancet Psychiatry. 2018; 5(3): 237-86.
56. Lemmens LH, Muller VN, Arntz A, Huibers MJ. Mechanisms of change in psychotherapy for depression: An empirical update and evaluation of research aimed at identifying psychological mediators. Clin Psychol Rev. 2016; 50: 95-107.
57. VanderWeele T, Vansteelandt S. Conceptual issues concerning mediation, interventions and composition. Statistics and its Interface. 2009; 2(4): 457-68.

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Table 1. Baseline Characteristics of Participants.

Variable, mean (95% CI) unless otherwise indicated	**THPP-India (N=280)**	**THPP-Pakistan (N=570)**	**Pooled (N=850)**
Age	25.18 (24.63 to 25.71)	27.05 (26.65 to 27.44)	26.43 (26.11 to 26.75)
Education Level (n, %)			
No formal education	34 (12%)	107 (19%)	141 (17%)
Up to primary	120 (43%)	39 (7%)	159 (19%)
Up to secondary	90 (32%)	333 (58%)	423 (50%)
Beyond secondary	36 (13%)	91 (16%)	127 (15%)
Marital Status (% Married)	100%	99.6%	99.9%
Parity (n (%))			
Primiparous	119 (43%)	102 (18%)	221 (26%)
Multiparous	161 (57%)	468 (82%)	629 (74%)
Occupation (%)			
Does not work outside of home	237 (85%)	533 (94%)	770 (91%)
Works outside of home	43 (15%)	37 (6%)	80 (9%)
PHQ-9 Score (0 to 27)	13.38 (12.98 to 13.77)	14.69 (14.38 to 14.99)	14.26 (14.01 to 14.50)
MSPSS Score (0 to 7)	5.29 (5.16 to 5.42)	3.93 (3.82 to 4.05)	4.38 (4.28 to 4.48)

Note. MSPSS = Multidimensional Scale of Perceived Social Support; PHQ-9 = Patient Health Questionnaire-9.

For Peer Review

Table 2. Raw mean scores (95% CI) of Potential Intervention Mediators and Depression Outcomes by Arm and Trial

Variables	THPP-India (N=140)	EUC (N=140)	T-test¶	THPP-Pakistan (N=283)	EUC (N=287)	T-test¶	Pooled THPP (N=423)	Pooled EUC (N=427)	T-test¶ (Effect Size)
Potential Mediators									
Patient Activation (0-25)	12.54 (11.86 to 13.23)	11.09 (10.33 to 11.85)	2.78**	17.59 (17.15 to 18.03)	16.83 (16.34 to 17.32)	2.56**	15.81 (15.35 to 16.26)	14.72 (14.20 to 15.23)	3.13**
Social Support (0-7)	5.65 (5.45 to 5.83)	5.30 (5.10 to 5.50)	2.31*	4.53 (4.37 to 4.68)	4.41 (4.23 to 4.57)	1.04(ns)	4.92 (4.79 to 5.05)	4.73 (4.59 to 4.87)	1.94*
Mother-Child Interaction (0-35)	21.14 (20.87 to 21.41)	20.90 (20.62 to 21.18)	1.23 (ns)	19.21 (19.0 to 19.4)	19.19 (18.9 to 19.4)	0.10(ns)	17.68 (16.84 to 18.52)	16.77 (15.89 to 17.65)	1.47(ns)
Depression Scores									
PHQ-9 at 3 months (0-27)	4.26 (3.51 to 5.02)	5.81 (4.78 to 6.83)	-2.44**	6.16 (5.41 to 6.90)	7.82 (6.88 to 8.75)	-2.75**	5.48 (4.92 to 6.04)	7.08 (6.37 to 7.79)	-3.51***
PHQ-9 at 6 months (0-27)	3.47 (2.66 to 4.27)	4.45 (3.56 to 5.33)	-1.61(ns)	6.07 (5.30 to 6.85)	6.78 (5.97 to 7.59)	-1.25(ns)	5.17 (4.57 to 5.76)	5.93 (5.31 to 6.55)	-1.75¥

¶Note. ¥p<0.10; *p<0.05; **p<0.01; ***p<0.001; ns=not significant

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Table 3. Individual mediating pathways within THPP-India and THPP-Pakistan[¥]

	THPP-India (N=280)			THPP-Pakistan (N=570)		
Mediating Pathways	**β[£]**	**S.E.**	**F-value**	**β**	**S.E.**	**F-value**
1. *Patient Activation*						
a (THPP → Patient Activation)	-1.36**	0.50	7.68***	-1.91***	0.54	5.64***
b (Patient Activation→ PHQ-9)	-0.28***	0.08	5.65***	-0.34***	0.08	5.17***
a x *b* [95% CI]	0.38 [0.08 to 0.78]			0.64 [0.23 to 1.18]		
2. *Social Support*						
a (THPP → Social Support)	-0.33**	0.13	15.74***	-0.285*	0.143	8.17***
b (Social Support→PHQ-9)	-1.32***	0.32	5.39***	-1.144***	0.295	4.90***
a x *b* [95% CI]	0.43 [0.09 to 0.88]			0.33 [0.01 to 0.74]		
3. *Mother-Child Interaction*						
a (THPP → Mother-Child Interaction)	-0.22(ns)	0.19	2.31*	-0.05(ns)	0.16	3.85**
b (Mother-Child Interaction→PHQ-9)	-0.06(ns)	0.21	2.72*	-0.46*	0.18	5.73***
a x *b* [95% CI][¶]	—			—		

Note. *p<0.05; **p<0.01; ***p<0.001; ns=not significant; [¶]did not meet conditions of mediation (X→M or M→Y where p<0.05) and therefore indirect effect was not calculated; [£]non-standardized betas are presented. Individual pathways controlled for baseline depressive (PHQ-9) and social support (MSPSS) scores, patient education and cluster (for THPP-Pakistan).

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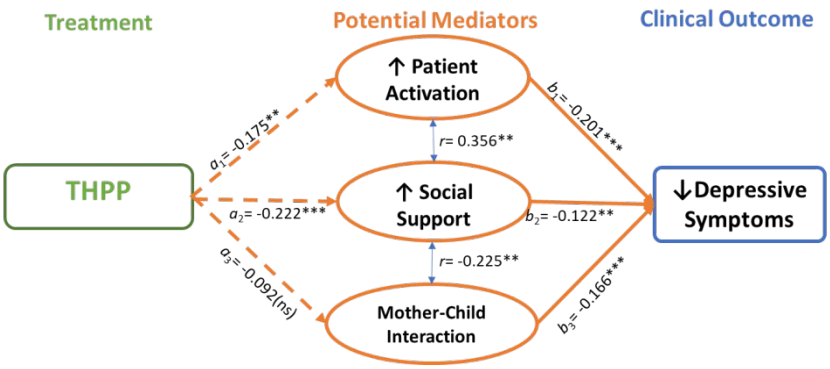
Figure 1. Multiple mediation analyses across sites (N=850) ¥£



¥Note. *p<0.05; **p<0.01; ***p<0.001; ns=not significant; £standardized betas presented. All mediation analyses controlled for baseline depressive (PHQ-9) and social support (MSPSS) scores and patient education and cluster (for THPP-Pakistan). r= refers to Pearson Correlation.

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