

An integrated parenting intervention for maternal depression and child development in a low-resource setting: cluster randomized controlled trial

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An integrated parenting intervention for maternal depression and child development in a low-resource setting: cluster randomized controlled trial

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Abstract

Background: Rates of depression among Pakistani mothers are high, leading to poor developmental outcomes in their children. This study tested the effectiveness of a manualized integrated parenting program; Learning through Play Plus (LTP+) for maternal depression in Karachi, Pakistan. **Methods:** A cluster randomized control trial conducted from January 2014 to December 2015 across 120 villages in Karachi. A total of 774 depressed mothers aged 18 to 44 years with children aged 0-30 months old, were included. Villages were randomized to receive LTP+ added to treatment as usual (TAU) or TAU alone. Primary outcomes were severity of maternal depression at 3 and 6-months measured by the Edinburgh Postnatal Depression Scale (EPDS) and child socio-emotional development at 6-months measured by the Ages and Stages Questionnaire (ASQ). Secondary outcomes included maternal anxiety, quality of life, social support, parenting competence, and knowledge about child development. **Results:** Mothers in the LTP+ group reported significantly lower depression scores compared to those in the TAU group (6.6 vs. 13.8, effect size -7.2, 95 % CI -8.2, -6.1) at 3-months and 6-months (7.2 vs. 12.00, ES -4.6, 95% CI -5.9, -3.4). Child socio-emotional development at 6-months was significantly better in the LTP+ group on all domains of the ASQ. There were also statistically significant improvements on all secondary outcomes at 3-month and 6-month follow up. **Conclusion:** In low-resource settings like Pakistan, low-cost integrated parenting interventions delivered by lay health workers can provide effective treatment for depressed mothers, leading to improvements in child development.

Trial registration: [Clinicaltrials.gov \(NCT02047357\)](https://clinicaltrials.gov/ct2/show/study/NCT02047357).

Key Words: Maternal depression, child development, psychosocial development, low and middle-income countries, Pakistan

Introduction

Poor maternal mental health and inadequate child stimulation (Yousafzai, Rasheed, Rizvi, Armstrong, & Bhutta, 2014) have been identified as the most common causes of compromised mental health and development in children (Goodman et al., 2011; Stein et al., 2014). According to the 2017-18 Pakistan Demographic and Health Survey, 23% of children below five years of age are underweight, 37% stunted and 7% are wasted. Such failure to thrive is associated with poor child socio-emotional development (NIPS, 2019). Meta-analyses suggest that perinatal depression and anxiety in mothers are adversely associated with child development and hence represent important targets for prevention and early intervention to support mothers and the health and well-being of their children (Rogers et al., 2020). Maternal depression is a huge global public health concern with enormous economic costs. Postnatal depression costs the UK approximately £8.1 billion per year (Bauer, Parsonage, Knapp, Iemmi, & Adelaja, 2014). The condition is not only detrimental to mothers (including increased risk of suicide), it also negatively impacts on mother-child attachment and child care during the first three years of life, a critical period for child development (Bauer et al., 2014; Shah & Lonergan, 2017). The prevalence of maternal depression in Pakistan is amongst the highest in the world (28-36%) (Rahman et al., 2013). There is evidence for high risk of stunting, being underweight and more diarrheal episodes in children of depressed mothers as compared to non-depressed mothers in Pakistan (Saeed & Saeed, 2017).

Child stimulation, healthy parent-child interactions and positive parenting are essential elements of child development (Tsivos, Calam, Sanders, & Wittkowski, 2015). Recent studies on parenting interventions in LMICs across diverse settings

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2
3 such as Uganda found significant improvement in children's cognitive and language
4 development (Singla, Kumbakumba, & Aboud, 2015). However most interventions
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6 had no impact on maternal mental health or did so under specific conditions such as
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8 when sessions are delivered during home visits or in group settings (Baker-
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10 Henningham, Powell, Walker, & Grantham-McGregor, 2005; Singla et al., 2015).
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12 There has been a need to integrate parenting interventions with interventions targeting
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14 parents' psychological wellbeing, particularly depression. Such integrated
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16 interventions when delivered by community health workers (CHWs), may minimize
17
18 the need for involvement of already overstretched mental health professionals (Singla
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20 et al., 2015; Stein et al., 2018). CHWs or lay healthcare workers are typically
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22 community members who are trusted and respected, and able to provide a link
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24 between people's homes and formal government primary health care clinics
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26 (Olaniran, Smith, Unkels, Bar-Zeev, & van den Broek, 2017). Clinical trials and
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28 longitudinal observational studies of visits by CHWs have shown to improve maternal
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30 well-being (including symptoms of maternal depression) and child development in
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32 low-resource settings (Katzen et al., 2020; le Roux et al., 2020).
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42 The National Institute for Health and Clinical Excellence guidelines for England
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44 (NICE CG901, 2017) as well as the Scottish Intercollegiate Guidelines Network
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46 (2012) and the South Australian Perinatal Practice (2014) guidelines recommend
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48 Cognitive Behavior Therapy (CBT) as a first line treatment for postnatal depression.
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50 To our knowledge, there have been three previous studies that have used a CBT based
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52 intervention called the Thinking Healthy Program (THP) (Sikander et al., 2019) for
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54 maternal depression in Pakistan, two of which have integrated a parenting
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56 intervention called Learning Through Play with THP (Husain et al., 2020; Husain et
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3 al., 2017; Rahman, Malik, Sikander, Roberts, & Creed, 2008). The combined
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5 intervention, referred to as LTP Plus (LTP+), is a scalable innovation delivered by
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7 trained CHWs. LTP+ has led to a significant reduction in maternal depression, along
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9 with improvement in mothers' Knowledge, Attitude and Practices (KAP) scores as
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11 well as an improved nutritional status in malnourished children (Husain et al., 2020;
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13 Husain et al., 2017). As far as we are aware, no study has yet assessed the impact of
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15 LTP+ on measures of child socio-emotional development. The aim of the present
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17 study was to test the efficacy of LTP+ on improvement of maternal depression and
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19 child socio-emotional development in low resource settings in Karachi, Pakistan.
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26 **Methods**

27 *Study Design*

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29 A two-arm, community-based, cluster randomized controlled trial (RCT). 120 clusters
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31 (villages) were divided equally in to the LTP+ (intervention) arm and treatment as
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33 usual (TAU) (control) arm.
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40 *Study Setting*

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42 The study was conducted in Gadap town, one of the 18 towns of Karachi, Pakistan.
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44 Gadap town has 8 Union Councils (UCs) and 400 villages, with around 15,000 births
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46 per year.
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50 *Participants*

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52 Inclusion criteria were: Mothers 18 to 44 years of age; having a 0-30 months old
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54 child; Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)
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56 diagnosis of major depressive episode and an Edinburgh Postnatal Depression Scale
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3 (EPDS) score >12 (Husain et al., 2013); residing in the trial catchment area; willing
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5 and able to provide informed consent and complete a baseline assessment.
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10 Exclusion criteria were: Serious physical health condition (e.g. cardiac, hepatic, renal
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12 or respiratory disorders); residing temporarily in the catchment area and unavailable
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14 for follow-up assessments; active suicidal ideation; presence of any other severe
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16 mental disorder (e.g. schizophrenia or bipolar disorder).
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21 The criteria for study withdrawal were: (1) at the participant's request; (2) at the
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23 discretion of the trial investigator (e.g., an adverse event, poor compliance).
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28 The study was conducted in accordance with the principles of the Declaration of
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30 Helsinki. Ethical approval for the study was obtained from the ethics committee of
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32 Karachi Medical and Dental College (KMDC) (Ref #0019/13).
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35 36 37 *Randomisation and masking*

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39 A total of 120 villages (clusters) were selected for the study in consultation with local
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41 community leaders, taking into consideration factors including safety and status of
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43 crime in the villages. Some villages were out of the trial catchment area, and
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45 community leaders of a few others were not prepared to participate in the trial, and as
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47 such were excluded. Each village constituted the unit of randomization. The
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49 randomisation resulted in 60 villages allocated to the intervention (LTP+) and 60 to
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51 the TAU arm. Participants within the clusters were mother-child dyads with the child
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53 being 0-30 months of age at the time of enrolment. The off-site trial statistician and
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55 the researchers carrying out follow up assessments were blinded to group allocation.
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Study Procedures

CHWs approached mothers of young children either in their homes or Basic Health Units (BHUs). Mothers were assessed for eligibility using a screening checklist (with the pre-defined inclusion and exclusion criteria) and the EPDS (Cox, Holden, & Sagovsky, 1987). The EPDS is a 10-item symptom scale for postnatal depression that has been validated in the Pakistani population (Husain et al., 2013).

CHWs were trained in using the screening checklist and EPDS by two researchers (TK, SN). Fortnightly supervision with the same researchers involving discussion on experiences of using the EPDS and any challenges faced were provided. In addition, CHWs received training refreshers including role-play sessions. Potentially eligible mothers were assessed by trained researchers at a screening visit during which a structured diagnostic interview (Clinical Interview Schedule revised, CIS-R) (Lewis & Pelosi, 1990) was used to confirm a diagnosis of DSM-IV current major depressive episode. The Urdu version of the CIS-R has already been used in a previous trial with depressed mothers (Husain et al., 2017). All participants were provided with a Participant Information Leaflet and trained CHWs provided them with information about the study. Handwritten signature or thumbprints were used when obtaining informed consent at the screening visit. Participants were assured that they were free to withdraw at any time without any impact on their routine care, that assessments and interventions were all by interview or questionnaires and thus there were no invasive procedures involved in the study. All information was kept confidential and all participant identifiable data were secured in locked cabinets.

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3 Researchers who were blind to treatment assignment and not involved in the baseline
4 assessment or the intervention sessions, completed 3-month follow up assessments.
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7 After the 3-month follow-up, mothers were contacted once a month for a further 3
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9 months to ensure retention for a 6-month follow-up assessment.
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12 13 14 *LTP+ Intervention*

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16 LTP+ is a manualized, 10-session group intervention that integrates parental
17 information about child development and CBT (Husain et al., 2017). The elements of
18 the intervention are derived from two evidence-based interventions: i) the LTP
19 programme, which helps stimulate early child development. It includes a pictorial
20 calendar designed for parents, which is a key feature of this intervention. The pictorial
21 calendar is made up of 8 successive stages of child development from birth to 3 years,
22 with pictures of parent-child play and other activities that promote parental
23 involvement, learning, and attachment. ii) The CBT component is derived from the
24 Thinking Healthy Programme (THP)(Rahman et al., 2008) which has been adapted
25 for a group setting (Husain et al., 2017). The THP adopts a ‘here and now’ problem-
26 solving approach, uses CBT techniques of active listening, changing negative
27 thinking, engagement with the family and regular homework. This integrated
28 intervention, called LTP Plus (LTP+), provides information and strategies to promote
29 child development in the 5 areas (sense of self, physical development, relationships,
30 understanding of world and communication) represented in the LTP calendar and
31 helps participants to identify and change their unhelpful thoughts related to their own
32 health and wellbeing, their child’s growth and development and their relationships.
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3 The intervention has been culturally adapted to the Pakistani context and designed to
4 be delivered in Urdu. A full description of the approach to cultural adaptation has
5 been published previously (Husain et al., 2017). CHWs delivering the intervention
6 attended a three-day training course (totalling 18 hours) on LTP+ involving
7 presentations, discussions and role-play. Thereafter, CHWs attended monthly training
8 refreshers on LTP+ for the duration of the study. The trained local CHWs delivered
9 10 sessions of LTP+ intervention over a three-month period with co-facilitation from
10 Masters level LTP+ trained psychologists. The sessions lasted 60 to 90 minutes,
11 delivered weekly over 8 weeks and then fortnightly during the final 4 weeks. Sessions
12 took place at the home of one of the participants and was mutually agreed by all the
13 group members. CHWs delivering LTP+ did not deliver treatment as usual (TAU) in
14 the villages randomized to the TAU arm.

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17 For evaluation of fidelity of the intervention, the participant observation method was
18 used, in which the rater/observer not just observes, but also takes an active role in that
19 setting (Pope & Mays 1995). Therefore, two senior researchers (raters) attended the
20 LTP+ sessions as delegates. Specific observation checklists were developed by the
21 raters, which included different domains from each age range of LTP and from each
22 area of development from five areas identified in the LTP manual, as well as core
23 components of THP. During the sessions, the two raters independently rated each
24 session. All scores on the observation checklist were then reviewed for assessment of
25 fidelity. The same two raters completed the fidelity assessments to ensure
26 consistency.

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58 *Treatment as Usual (TAU)*
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3 CHWs in Pakistan are called Lady Health Workers (LHWs). All participants in TAU
4 received routine follow-ups by LHWs as well as baseline, 3 and 6-month follow-up
5 assessments with research staff. In Pakistan, each LHW is responsible for 150
6 households (around 1000 people) and they visit each household once a month
7 (visiting 5-7 homes daily). They cover all domains of maternal and child health care
8 along with family planning support and immunization. They are also trained in
9 interpersonal communication and community engagement.
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21 *Outcomes*

22 *Maternal health measures*

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24 The primary outcome measure was severity of maternal depressive symptoms at 3-
25 month follow up assessment (i.e., completion of intervention), assessed using the
26 EPDS (Cox et al., 1987). The Patient Health Questionnaire (PHQ-9) (Kroenke,
27 Spitzer, & Williams, 2001) is a 10-item questionnaire that was also used to assess the
28 severity of depressive symptoms in mothers. Secondary mental health measures
29 included severity of maternal anxiety assessed using the Generalised Anxiety
30 Disorder scale (GAD-7) (Spitzer, Kroenke, Williams, & Löwe, 2006), maternal health
31 related quality of life using the EuroQol Quality of Life Scale – 5 Dimensions (EQ-
32 5D) (Brooks & Group, 1996) and maternal social support using the Multidimensional
33 Scale of Perceived Social Support (MSPSS) (Akhtar et al., 2010). All scales were
34 translated in Urdu and have been used in previous studies in Pakistan (Husain et al.,
35 2020; Husain et al., 2017).
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56 *Parenting measures*

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3 Other secondary measures included the the Home Observation for Measurement of
4 the Environment (HOME)(Bradley & Caldwell, 1977), which is a descriptive profile
5 was used to objectively assess the caring environment in which the child is reared.
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10 There are 45 items and 6 subscales of HOME: responsivity, acceptance, organization,
11 learning materials, involvement and variety. The Learning through Play (LTP)
12 Knowledge, Attitude and Practices (KAP) Questionnaire (Caldwell, 1967) was used to
13 assess change in maternal knowledge, attitude and practices. There are total of 114
14 items on the KAP regarding a child's physical development, sense of self,
15 understanding about the world, relationships and communication for children aged
16 between 0-3 years. Parenting Sense of Competence scale is 17-item scale (Gibaud-
17 Wallston & Wandersman, 1978), each item is rated on 6 point Likert scale. Higher
18 score on this scale indicates a higher parenting sense of competency.
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35 *Child health measures*

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37 The primary outcome for child development was the Ages and Stages Questionnaire
38 (ASQ) (Squires, Bricker, & Twombly, 2009). The ASQ consists of 21 intervals, each
39 with 30 items in five areas: (i) personal-social, (ii) gross motor, (iii) fine motor, (iv)
40 problem solving, and (v) communication for children ages 2-66 months. It has
41 excellent psychometric properties, a test-retest reliability of 92%, sensitivity of 87.4%
42 and specificity of 95.7% (Singh, Yeh, & Blanchard, 2017). The Ages and Stages
43 Social - Emotional Questionnaire (Squires, Bricker, & Twombly, 2002) was used to
44 obtain the maternal report on their child's social and emotional development. These
45 questionnaires have previously been used in Pakistan (Turner et al., 2016).
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3 All measures were assessed at baseline, 3 and 6 months by trained researchers
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5 (Masters level psychologists) who were blinded to group allocation.
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10 *Sample Size*

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12 Results from a previous cluster RCT from Pakistan (Rahman et al., 2008) were used
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14 to calculate the sample size in the present study. In the earlier study the attrition rate
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16 at 6-month follow-up was 10%, the effect size was approximately 0.2, and the intra-
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18 cluster correlation coefficient (ICC) was 0.09. We randomized 120 villages with 60
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20 villages allocated to the LTP+ arm and 60 to the TAU arm. We proposed
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22 to recruit 294 new mothers in each group. Assuming the same rate of attrition, we
23
24 expected to have 6-month data on 265 mothers per group. Using a 25% one-sided
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26 significance level, the trial has a power of 90% to detect an effect of 0.2 under the
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28 same assumptions.
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40 *Statistical analysis*

41 The trial design was a cluster RCT with randomisation performed at the village level.
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43 Multiple participants were recruited from each village. It is likely that outcomes from
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45 participants within the same village will be more similar than outcomes from
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47 participants from differing villages. As a result, the analysis was performed using
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49 multilevel regression methods. Analyses were performed for the outcomes at 3 and 6-
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51 months in a single combined model. Therefore three-level models were used with
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53 measurements at individual timepoints nested within study participants, contained
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55 within villages. Baseline summary statistics were calculated for the two randomized
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57 arms.
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6 The majority of outcomes were continuous in nature, so the treatment effect was
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8 estimated using multilevel linear models. The outcome value at baseline was used as a
9
10 covariate in the analysis. In addition, three other pre-specified covariates were also
11
12 included in the analysis: age of the infant at baseline, education level and housing
13
14 type. The numbers of diarrhoea and chest infection days were found to have highly
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16 positively skewed distributions. These were considered as counts and were analysed
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18 using multilevel negative binomial regression, as the level of over dispersion meant
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20 that Poisson regression was inappropriate. The occurrence of other illness was a
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22 binary measure and was analysed using multilevel logistic regression.
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28 To investigate the mediating effects of the infant/toddler scores and MSPSS scores,
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30 these variables were added in the primary analyses as covariates. The treatment
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32 groups would be expected to be balanced for the scores at baseline. To examine the
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34 mediating effects, the changes in infant/toddler scores and MSPSS from baseline to 6-
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36 months were added to the analyses.
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40 The following models were run:

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- 42 • Model 1: Adjustments as per the primary study analysis. Adjusting for
- 43 outcome at baseline, age of infant at baseline, education and housing type
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- 45 • Model 2: Adjustments as per Model 1, plus further adjustment for change in
- 46 infant/toddler total score/MSPSS score
- 47
- 48 • Model 3: Adjustments as per Model 1, plus further adjustment for change in
- 49 all infant/toddler subscores/MSPSS score
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3 The total infant/toddler score and infant/toddler components were considered
4 separately, as the total score would be strongly associated/dependent on all the
5 individual subscores. Hence it is not appropriate to include all in the same analysis.
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7 Similarly, the total MSPSS score and MSPSS components were considered in
8 separate analyses, as the total score would be strongly associated/dependent on all the
9 individual subscores. Therefore it would not be appropriate to include all in the same
10 analysis.
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21 **Results**

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23 In January 2014, 120 villages from Gadap town were randomly assigned to either
24 LTP+ arm (n = 60) or TAU arm (n = 60). Within the villages assigned to the
25 intervention arm, 564 mother-child dyads were recruited from January 2014 to June
26 2015. Of those, 408 met eligibility criteria and 402 (98.5%) completed baseline
27 assessment, 399 (97.8%) completed 3 month follow-up (FU) and 396 (97%)
28 completed 6 month FU (Figure 1). Within the villages assigned to the TAU arm, we
29 screened 510 mother-child dyads, 403 of who met eligibility criteria. Out of those,
30 372 (92.3%) completed baseline assessment, 370 (91.8%) completed 3 month FU and
31 368 (91.3%) completed 6 month FU.
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47 On average, mothers in the intervention arm attended 7.89 (SD 2.035) group sessions,
48 with 89.48% of mothers attending six sessions or more and 66.92% mothers attending
49 8 or more sessions. There were no significant differences in any of the child, mother
50 and family related variables in the two groups at baseline (Table 1). The results
51 indicate significant improvements in maternal health outcomes at 3 and 6 months
52 (Table 2) in the intervention arm as compared to TAU arm ($p < 0.001$). The analysis
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3 suggests that mothers in the intervention arm showed significantly more
4 improvements in their depression and anxiety symptoms, health related quality of life,
5 and perceived social support at the end of the intervention than those in the TAU arm.
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10 The differences between groups were maintained at 6 months (Table 2). The effect of
11 the intervention on maternal depression symptoms was partly mediated by mother's
12 perceived positive support and active ways of coping (Supplementary Table 1). The
13 results suggest that LTP+ improves parenting at 3 and 6 months (Table 3), with
14 mothers in the intervention arm reporting feeling better in their roles as mothers, as
15 compared to those in the TAU arm (Table 3). The results suggest improvements in
16 parenting competence and KAP scores in the intervention arm, both at 3 and 6 months
17 (Table 3).
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31 Regarding the primary outcome for child development, the ASQ, scores were
32 significantly better in the LTP+ arm for all of domains ($p < 0.001$) including
33 development of social, motor, problem solving and communication skills (Table 4).
34 However, there were no significant differences found in infants' weight or height
35 between the two groups (Table 4). Measures of child health outcomes in the
36 intervention arm also showed significant improvements as compared to the TAU arm
37 (Table 5). The number of days children suffered from diarrhoea or chest infection
38 were found to be significantly less in the intervention arm as compared to the TAU
39 arm (40% lower in intervention arm) (Table 5). In addition, children in the
40 intervention arm were significantly less likely to experience illness with the odds of
41 other illness being only half as great in the intervention arm compared to the TAU
42 arm. The improved child health outcomes with regards to the number of diarrhoea
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3 days and number of chest infection days, was maintained at 6-month follow up (Table
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10 Analyses were also performed to compare the outcomes of the two groups at 6
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12 months, adjusted for potential mediators such as infant/toddler HOME scores and
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14 MSPSS scores. The results of these analyses are summarised in Supplementary
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16 Tables 1 and 2. The results for all the ASQ scores suggest that the differences
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18 between treatments were almost unchanged after adjusting for the infant/toddler
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20 HOME scores (Supplementary Table 1). There was a slight reduction in treatment
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22 difference for PHQ-9 after the adjustments. However, this was relatively marginal,
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24 and a highly significant treatment difference remained. Supplementary Table 2 shows
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26 that the differences between groups showed only minimal reduction after adjusting for
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28 MSPSS scores.
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35 **Discussion**

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37 This cluster RCT investigated the effect of a novel manual assisted psychosocial
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39 intervention (LTP+) in reducing maternal depression and improving the social and
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41 emotional development and physical health of children aged 0-3 years. Mothers in the
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43 intervention arm showed significant improvement in depression, anxiety, health-
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45 related quality of life (QoL) and perceived social support following participation.
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47 More specifically, LTP+ effectively improved parenting knowledge and practices
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49 indicated by improvement in their scores on KAP scale and all domains of the HOME
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51 inventory. Mothers in the intervention arm had significant improvement in parenting
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53 sense of competence as compared to the TAU arm. Along with the improvement in
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55 mothers' psychological wellbeing, their children had improved scores on
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3 communication, gross and fine motor movements, problem solving skills and social
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5 development.
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10 Consistent with findings from our previous LTP+ trial, the current study showed a
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12 beneficial effect of the intervention on maternal depression and anxiety. There is
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14 strong evidence on the effectiveness of group CBT (Sockol, 2015) in reducing
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16 maternal depression but not of improving the child outcomes (Rahman et al., 2008).
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18 There is mixed evidence in the literature on the role of integrated interventions in
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20 improving both mother and child health outcomes. One previous study showed
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22 improved maternal and child outcomes (Singla et al., 2015), however, another study
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24 did not show improvement in child outcomes with an integrated intervention (Stein et
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26 al., 2018). More recently, our group led an RCT of LTP+ for mothers of malnourished
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28 children in Pakistan and showed that mothers engaged with LTP+ significantly
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30 showed improvements in depression ($p < 0.001$), social support ($p = 0.02$) and quality
31
32 of life ($p < 0.001$) at the end of the intervention (3 months) as compared to those in the
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34 TAU group. In addition, at both 3 and 6 months after baseline, the times which a child
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36 suffered from diarrhoea and chest infections was significantly lower in the
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38 intervention group ($p < 0.001$ for both outcomes at both time points). The number of
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40 diarrhoea days was approximately 50% lower in the intervention group at both time
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42 points, whilst the number of chest infection days was reduced by almost three-fold at
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44 6 months in the intervention group compared to control group (Husain et al., 2020).
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54 Improvement in both depression and anxiety scores in the intervention arm of the
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56 present study sustained at 6-month follow up indicates that LTP+ may help in
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58 preventing worsening of these symptoms in mothers. However future studies should
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3 include longer-term follow-up as evidence suggests that depressive symptoms may
4 worsen as the child grows (Evans et al., 2012). A recent cluster RCT of a peer-
5 delivered psychosocial intervention (The Thinking Healthy Program, Peer-delivered
6 Plus, THPP+) in rural Pakistan showed no significant differences between the
7 intervention group and enhanced usual care with regards to maternal depression
8 symptoms and child socio-emotional skills (strengths and difficulties questionnaire
9 [SDQ-TD]) at 36-months postnatal follow up (Maselko et al., 2020). However, LTP+
10 distinguishes itself from THPP+ by integrating a parental training program with CBT
11 principles, and hence may have different long-term benefits when compared to
12 THPP+ alone.
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Maternal depression is known to be associated with marked psychosocial difficulties (Husain et al., 2011). Social support has been shown as a significant protective factor for maternal depression, and the variety of support providers in a mothers' social network is important (Ongeri et al., 2018). There is evidence that Pakistani mothers with perceived positive support from spouses report fewer depressive symptoms (Qadir, Khalid, Haqqani, & Medhin, 2013). In the present study LTP+ improved perceived social support in all three areas of the MSPSS; significant other, family and friends. A parenting intervention trial from Uganda highlighted that perceived positive support mediates the effect of the intervention on maternal wellbeing (Singla et al., 2015), however our mediation analysis suggests that this measure had little effect on the treatment differences observed.

Maternal depression can negatively impact quality of life (QoL) in all domains (Kang, Pearlstein, & Sharkey, 2020). A recent study assessed the QoL of mothers in the

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3 postnatal period using the World Health Organization Quality of Life scale
4 (WHOQOL-BREF) and concluded that the QoL decreased as the level of depression
5 and anxiety increased (Daglar, Bilgic, & Aydın Özkan, 2018). Poor health-related
6 QoL can impact mothers from fulfilling their parenting roles and other responsibilities
7 in their daily life activities, thus causing disability (Durukan, Ilhan, Bumin, & Aycan,
8 2011). Our previous LTP+ trials showed that women were supported to engage in
9 interactive activities using the LTP calendar, which offered opportunities for
10 behavioural activation resulting in reduction in depression and reduced disability
11 (Husain et al., 2020; Husain et al., 2017). Similarly, in the current study, LTP+
12 resulted in improvement in health related QoL. In Pakistan, most women are
13 housewives responsible for all domestic chores or work in fields. Our results indicate
14 that mothers' ability to perform work improved significantly after engaging with
15 LTP+.

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35 Maternal self-efficacy can have a significant impact on a mothers' child rearing
36 practices (Leerkes & Crockenberg, 2002). Maternal mood has strong association with
37 parenting confidence and sense of competence (Kwon, Kim, Kim, & Jang, 2006). The
38 present study showed that mothers engaged with LTP+ had significant improvements
39 in their parenting sense of competence. The synergistic effect produced as a result of
40 combining CBT with play activities likely led to the improvement in maternal mood
41 and hence increased motivation for optimal interaction with children.

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54 The LTP+ intervention effectively improved all parenting practices assessed by the
55 HOME inventory and benefited child development as assessed by the ASQ at 6-
56 month follow up. These findings are consistent with the results of another integrated
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3 parenting intervention tested in a community setting in Uganda (Singla et al., 2015).
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5 Similar to the existing evidence on improvement in knowledge, attitude and practices
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7 (KAP) (Husain et al., 2017; Karbhari et al., 2016; Rahman et al., 2008) with parenting
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9 interventions, KAP scores of mothers in the LTP+ arm improved significantly in this
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11 study.
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17 LTP+ is a complex intervention comprising of several components, which make it
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19 challenging to discern the mechanism of its therapeutic action. We propose that the
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21 intervention's effect on perceived social support and coping skills led to
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23 improvements in depressive symptoms in mothers, while the concurrent effect of
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25 increased parenting competencies had positive downstream effects on child socio-
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27 emotional development and physical health (Figure 2). The study was conducted in an
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29 economically deprived urban setting in Pakistan, a LMIC with limited access to
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31 publicly funded healthcare. Given this context, it may be that access to structured
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33 psychosocial treatment in addition to attentive and systematic assessment of mental
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35 health symptoms enhanced treatment differences between groups. It remains unclear
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37 if the intervention would have similar benefits in high-income settings, particularly
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39 those with greater access to healthcare.
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47 The large sample size and excellent retention rate are clear strengths of the current
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49 study. Furthermore, it was conducted in a community setting with the help of CHWs
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51 (also known as lay health workers), who are already engaged with mothers as part of
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53 routine care for mother and child health in Pakistan. Integrating LTP+ in to routine
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55 care could help ensure scale-up and sustainability of this low-cost intervention. One
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57 of the challenges during the study was the conservative environment of the
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3 community, where female participants are often not permitted to leave the home. In
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5 order to overcome this barrier, male CHWs of each village, who are highly respected
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7 in the community, assisted in negotiating with male members of the household to
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9 allow women to attend sessions. As mentioned, certain villages were excluded from
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11 randomization due to concerns about law and order and community reticence to join
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13 the study. The excluded villages may be comprised of families with differing
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15 sociodemographic variables from those included in the present study and as such our
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17 findings may not be generalizable to other settings. The current study is also limited
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19 by a short follow up period that does not allow an assessment on the long-term
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21 benefits of LTP+ for mothers and children. A further limitation is that with the
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23 exception of the HOME inventory, we relied largely on self-report measures for most
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25 outcomes, which can be prone to bias. Finally, our findings cannot be applied to
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27 fathers, who despite playing vital roles in child development, were not included in the
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29 present study. To address this gap in the literature, our group is leading a number of
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31 RCTs of LTP+ for depressed fathers in similar low-resource settings
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33 (Clinicaltrials.gov identifier NCT03564847).
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42 The results of this robust cluster RCT, taken together with existing evidence, indicate
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44 that low-cost integrated parenting interventions such as LTP+ can help improve
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46 symptoms of acute maternal depression and benefit child socio-emotional
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48 development in low-resource settings like Pakistan. Further trials with longer
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50 durations of follow-up are needed to confirm whether such interventions will have
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52 sustainable benefits for both mothers and children. Future studies of LTP+ involving
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54 fathers may add further benefits to maternal well-being and child development. More
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3 studies from LMICs are urgently needed to address the high rates of maternal
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5 depression and compromised child development in these settings.
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10 **Abbreviations:**

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13 LTP+ Learning through Play Plus
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15 TAU Treatment As Usual
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17 EPDS Edinburg Postnatal Depression Scale
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19 ASQ Ages and Stages Questionnaire
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21 LMICs Low and Middle Income Countries
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23 HICs High Income Countries
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25 CHWs Community Health Workers
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27 NICE National Institute for Health and Clinical Excellence guidelines for
28
29 England
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33 CBT Cognitive Behavior Therapy
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35 THP Thinking Healthy Program
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37 KAP Knowledge, Attitude and Practices
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39 RCT Randomized Controlled Trial
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42 UCs Union Councils
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44 KMDC Karachi Medical and Dental College
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46 BHUs Basic Health Units
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48 CIS-R Clinical Interview Schedule revised
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51 LHWs Lady Health Workers
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53 GAD Generalised Anxiety Disorder
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55 EQ-5D EuroQol Quality of Life Scale – 5 Dimensions
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57 MSPSS Multidimensional Scale of Perceived Social Support
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HOME	Home Observation for Measurement of the Environment
ICC	Intra-cluster Correlation Coefficient
FU	Follow up
QoL	Quality of Life
THPP+	Thinking Healthy Program, Peer-delivered Plus
SDQ	Strengths and difficulties questionnaire
WHOQOL	World Health Organization Quality of Life

Declarations

Ethics approval and consent to participate

Ethical approval for the study was obtained from the ethics committee of Karachi Medical and Dental College (KMDC) (Ref #0019/13). All participants were provided with a Participant Information Leaflet and trained CHWs provided them with information about the study. Handwritten signature or thumbprints were used when obtaining informed consent.

Consent for publication

Not applicable

Conflict of Interest:

MIH is a PI for a trial sponsored by COMPASS Pathways Limited. IBC and NH have given lectures and advice to Eli Lilly, Bristol Myers Squibb, Lundbeck, Astra Zeneca and Janssen pharmaceuticals for which they or their employing institution have been reimbursed. MIH, IBC and NH were previously trustees of the Pakistan Institute of Learning and Living (PILL). NC is currently Chief Executive Officer for PILL.

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2
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6 the final responsibility to submit for publication.
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11 ***Authorship***

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13
14 NH and NC had the overall responsibility of the trial. NH, NC, BF and CR were
15 involved in the design of the study. All authors were involved in preparing the
16 manuscript. BF, FN, MIH, MH, ZZ and AR were involved in training and supervision
17 of the research team. TK was involved in screening, recruitment and delivery of the
18 intervention. IBC was leading on data management. PB led the statistical analysis. FJ,
19 SS and SN were responsible for participant and public involvement and engagement.
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28 ***Data sharing and data accessibility:***

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30 Requests for sharing the anonymised trial database should be addressed to the lead
31 author.
32
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Table 1. Baseline characteristics of participants

	TAU (N=372)	LTP+ (N=402)
Family (Mean ± SD)		
Total number of household family member	9.7 (6.0)	9.3 (5.4)
Total Monthly household Income	11729.(9943)	11648.5(13232)
Family Status <i>f</i> (%age)		
Nuclear	190 (51.1%)	184 (45.8%)
Joint	182 (48.9%)	218 (54.2%)
Status of house (Rental or ownership) <i>f</i> (%age)		
Ownership	329 (88.4%)	366 (91.0%)
Rental	43 (11.6%)	36 (9.0%)
Mother Health Related Variables (Mean ± SD)		
GAD-7	12.9 ± 3.3	12.7 ± 3.2
EPDS	18.2 ± 3.1	18.4 ± 3.1
PHQ-9	15.2 ± 3.7	15.4 ± 3.6
Rosenberg self-esteem	12.9 ± 4.1	12.4 ± 4.1
MSPSS-Significant other	16.7 ± 6.6	16.5 ± 6.7
MSPSS Family	16.3 ± 6.0	15.3 ± 6.2
MSPSS Friends	13.8 ± 6.1	12.8 ± 5.9
MSPSS Total score	46.9 ± 15.8	44.5 ± 15.1
EQ-5D Health Index	0.34 ± 0.33	0.32 ± 0.34
EQ-VAS	39 ± 13	39 ± 13
WHO physical health	9.7 ± 1.8	9.8 ± 1.9
WHO psychological health	9.6 ± 1.9	9.4 ± 1.9
WHO social relationship	10.8 ± 3.4	10.9 ± 3.4
WHO environment	8.8 ± 2.0	8.6 ± 1.8
WHO total	38.9 ± 7.1	38.8 ± 6.9
Parenting variables (Mean ± SD)		
Laxness	20.3 ± 5.1	20.5 ± 5.6
Over-activity	21.6 ± 6.4	21.54 ± 6.2
Hostility	10.42 ± 4.8	10.87 ± 4.97
No Factor	71.3 ± 9.0	72.07 ± 9.6
Parenting total	123.7 ± 14.3	125 ± 15.54
HOME Responsibility	7.2 ± 3.1	7.8 ± 2.8
HOME Acceptance	3.6 ± 2.1	3.5 ± 2.1
HOME Organisation	3.6 ± 1.7	3.6 ± 1.5
HOME Learning materials	1.8 ± 2.2	1.9 ± 2.3

HOME Involvement	2.7 ± 1.8	2.9 ± 1.7
HOME Variety	2.7 ± 1.1	2.8 ± 1.1
HOME Infant/toddler total	21.7 ± 8.2	22.5 ± 7.4
Parenting confidence	53.4 ± 6.0	54.6 ± 6.7
MAI	80 ± 15	80 ± 16
KAP	80 ± 15	80 ± 17
Child health variables		
Child's age, months Mean (SD)	13.7 (7.9)	14.1 (8.5)
Child's (Female) – <i>f</i> (%age)	186 (50.0%)	196 (48.8%)
Total Number of children	3.38 (1.82)	3.31 (2.06)
ASQ Communication – Mean (SD)	37.6 (11.5)	39.4 (10.9)
ASQ Gross motor - Mean (SD)	37.2 (13.0)	36.7 (12.8)
ASQ Fine motor - Mean (SD)	35.1 (13.3)	36.1 (12.9)
ASQ Problem solving - Mean (SD)	35.1 (13.8)	36.1 (13.5)
ASQ Personal-social - Mean (SD)	36.5 (12.3)	36.5 (11.8)
Ages/stages (month) - Mean (SD)	13.9 (7.8)	14.5 (8.4)
Height (cm) - Mean (SD)	70.0 ± 9.1	70.2 ± 9.4
Weight (kg)	8.1 ± 2.0	8.1 ± 2.1
Diarrhea days - Median [IQR]	3 [0, 5]	2 [0, 5]
Chest infection days - Median [IQR]	4 [0, 7]	4 [0, 7]
Other illnesses – <i>f</i> (%age)	113 (35%)	129 (37%)

Table 2: Maternal health outcomes at 3 and 6-month follow up

Measures	N	LTP+ Mean ± SD	N	TAU Mean ± SD	Treatment effect (*) (95% CI)	P-value
PHQ-9						
3 rd month	399	6.6 ± 4.5	370	13.8 ± 5.3	-7.1 (-8.1, -6.1)	<0.001
6 th month	396	7.2 ± 5.0	368	12.0 ± 6.3	-4.7 (-5.7, -3.6)	<0.001
GAD-7						
3 rd month	399	6.1 ± 3.9	370	11.2 ± 4.1	-5.1 (-5.8, -4.3)	<0.001
6 th month	396	6.3 ± 4.0	368	10.0 ± 4.7	-3.6 (-4.4, -2.8)	<0.001
EPDS						
3 rd month	399	8.2 ± 5.1	370	15.6 ± 5.2	-7.4 (-8.4, -6.3)	<0.001
6 th month	395	9.1 ± 5.1	368	13.6 ± 6.3	-4.5 (-5.5, -3.5)	<0.001
Rosenberg self-esteem						
3 rd month	399	19.4 ± 3.9	370	13.5 ± 4.8	5.8 (4.9, 6.7)	<0.001
6 th month	396	19.2 ± 4.1	368	15.0 ± 5.7	4.1 (3.2, 5.0)	<0.001
MSPSS-Significant other						
3 rd month	398	21.1 ± 4.7	370	18.1 ± 6.0	3.0 (2.0, 3.9)	<0.001
6 th month	396	21.3 ± 4.7	368	17.7 ± 6.5	3.6 (2.7, 4.6)	<0.001
MSPSS Family						
3 rd month	398	20.1 ± 5.2	370	16.2 ± 6.2	3.9 (3.0, 4.8)	<0.001
6 th month	396	19.8 ± 5.7	368	16.7 ± 6.6	3.1 (2.2, 4.0)	<0.001
MSPSS Friends						
3 rd month	398	19.1 ± 5.7	370	15.0 ± 6.1	4.1 (3.2, 5.1)	<0.001
6 th month	396	18.9 ± 6.1	368	15.8 ± 6.9	3.1 (2.1, 4.0)	<0.001
MSPSS Total score						
3 rd month	398	60.3 ± 12.5	370	49.3 ± 15.4	11.0 (8.5, 13.5)	<0.001
6 th month	396	60.0 ± 13.5	368	50.2 ± 17.6	9.8 (7.3, 12.3)	<0.001
EQ5D health index						
3 rd month	399	0.69 ± 0.26	370	0.39 ± 0.36	0.30 (0.25, 0.36)	<0.001
6 th month	396	0.69 ± 0.23	368	0.45 ± 0.36	0.24 (0.19, 0.29)	<0.001
EQVAS						
3 rd month	399	58 ± 14	370	43 ± 13	15 (12, 17)	<0.001
6 th month	396	60 ± 13	368	47 ± 16	12 (10, 15)	<0.001
WHO physical health						
3 rd month	399	13.6 ± 2.2	370	10.9 ± 2.2	2.6 (2.2, 3.0)	<0.001
6 th month	396	13.6 ± 2.4	368	11.0 ± 2.7	2.5 (2.1, 3.0)	<0.001
WHO psychological						
3 rd month	399	13.6 ± 2.3	370	10.9 ± 2.2	2.7 (2.3, 3.2)	<0.001
6 th month	396	13.8 ± 2.5	368	11.4 ± 2.8	2.5 (2.0, 2.9)	<0.001
WHO social relationship						
3 rd month	399	14.7 ± 2.4	370	12.1 ± 3.5	2.5 (2.0, 3.1)	<0.001
6 th month	396	14.7 ± 2.6	368	12.0 ± 3.9	2.5 (2.0, 2.9)	<0.001
WHO environment						
3 rd month	399	12.6 ± 2.6	370	10.2 ± 2.4	2.4 (2.0, 2.9)	<0.001
6 th month	396	13.0 ± 2.9	368	10.6 ± 3.0	2.4 (1.9, 2.9)	<0.001
WHO total						
3 rd month	399	54.5 ± 8.1	370	44.0 ± 8.6	10.3 (8.6, 12.0)	<0.001
6 th month	396	55.2 ± 9.0	368	45.0 ± 11.2	10.0 (8.3, 11.7)	<0.001

(*) Difference adjusted for outcome at baseline, age of infant at baseline, education and housing type

Table 3: Parenting outcomes at 3 and 6-month follow up

Measures	N	LTP+ Mean + SD	N	TAU Mean + SD	Treatment effect (*) (95% CI)	P-value
Laxness						
3rd month	394	17.9 ± 4.3	368	17.0 ± 3.9	0.9 (0.2, 1.6)	0.01
6th month	396	17.7 ± 4.5	366	16.1 ± 4.5	1.5 (0.9, 2.2)	<0.001
Over-activity						
3rd month	394	16.6 ± 6.5	368	21.1 ± 6.7	-4.5 (-5.5, -3.5)	<0.001
6th month	396	17.4 ± 6.5	366	21.2 ± 6.5	-3.8 (-4.8, -2.7)	<0.001
Hostility						
3rd month	394	8.6 ± 4.4	368	10.9 ± 5.0	-1.4 (-2.1, -0.7)	<0.001
6th month	396	8.4 ± 4.4	366	11.2 ± 5.0	-2.8 (-3.5, -2.0)	<0.001
No Factor						
3rd month	394	68.9 ± 8.3	368	69.6 ± 8.9	-0.7 (-1.9, 0.5)	0.25
6th month	396	69.9 ± 7.6	366	69.9 ± 7.6	0.0 (-1.2, 1.2)	0.99
Parenting total						
3rd month	394	112.0 ± 12.1	368	117.7 ±	-5.8 (-7.8, -3.8)	<0.001
6th month	396	112.0 ± 12.1	366	14.4 ±	-5.0 (-7.1, -3.0)	<0.001
				118.5 ±		
				12.2		
HOME						
Responsibility	395	9.6 ± 1.7	367	7.9 ± 2.9	1.6 (1.1, 2.1)	<0.001
3rd month	391	9.6 ± 1.8	367	7.3 ± 3.5	2.2 (1.7, 2.7)	<0.001
6th month						
HOME Acceptance						
3rd month	395	5.4 ± 1.9	367	3.8 ± 2.3	1.5 (1.2, 1.9)	<0.001
6th month	391	5.7 ± 1.7	367	4.1 ± 2.2	1.6 (1.2, 1.9)	<0.001
HOME Organization						
3rd month	395	4.6 ± 1.3	367	3.9 ± 1.6	0.7 (0.5, 1.0)	<0.001
6th month	391	4.7 ± 1.2	367	3.5 ± 1.7	1.1 (0.9, 1.4)	<0.001
HOME Learning materials						
3rd month	395	3.4 ± 2.6	367	2.3 ± 2.5	1.2 (0.7, 1.6)	<0.001
6th month	391	3.5 ± 2.7	367	2.2 ± 2.4	1.3 (0.9, 1.7)	<0.001
HOME Involvement						
3rd month	394	4.5 ± 1.8	367	3.5 ± 2.1	1.0 (0.7, 1.3)	<0.001

6th month	391	4.4 ± 1.7	367	2.7 ± 1.9	1.6 (1.3, 1.9)	<0.001
HOME Variety						
3rd month	395	3.6 ± 1.0	367	3.0 ± 1.1	0.5 (0.4, 0.7)	<0.001
6th month	391	3.6 ± 1.1	367	2.9 ± 1.2	0.7 (0.5, 0.9)	<0.001
HOME						
Infant/toddler total						
3rd month	395	31.1 ± 6.7	367	24.4 ± 8.9	6.5 (5.0, 7.9)	<0.001
6th month	391	31.4 ± 6.7	367	22.7 ± 9.6	8.5 (7.0, 10.0)	<0.001
Parenting confidence						
3rd month	398	61.5 ± 6.5	369	54.6 ± 6.2	6.6 (5.4, 7.9)	<0.001
6th month	398	61.1 ± 7.4	366	54.4 ± 8.3	6.5 (5.3, 7.7)	<0.001
MAI						
3rd month	398	90 ± 13	369	82 ± 15	8 (6, 11)	<0.001
6th month	393	90 ± 12	367	80 ± 16	10 (6, 12)	<0.001
KAP						
3rd month	398	87 ± 10	369	74 ± 15	12 (10, 15)	<0.001
6th month	394	91 ± 13	365	80 ± 20	11 (8, 13)	<0.001

(*) Difference adjusted for outcome at baseline, age of infant at baseline, education and housing type

Table 4: Child development and growth at 6-month follow-up

Measures	TAU (N = 367) Mean (SD)	LTP+ (392) Mean (SD)	Difference (*) Mean (95% CI)	P- value
ASQ communication	28.8 (10.7)	49.8 (10.1)	20.7 (18.7, 22.8)	<0.001
ASQ gross motor	28.8 (10.3)	49.6 (10.3)	20.4 (18.4, 22.3)	<0.001
ASQ fine motor	28.9 (10.0)	51.5 (10.7)	21.8 (19.5, 24.2)	<0.001
ASQ problem solving	28.4 (9.8)	52.7 (10.1)	23.8 (21.5, 26.0)	<0.001
ASQ personal-social	28.4 (9.9)	53.1 (10.3)	24.0 (21.8, 26.3)	<0.001
Ages/stages (month)	20.6 (7.7)	21.1 (8.2)	-0.1 (-0.2, 0.1)	0.50
Anthropometric assessments	TAU (N = 367) Mean (SD)	LTP+ (N = 393) Mean (SD)	Difference (*) Mean (95% CI)	P- value
Height (cm)	79.0 ± 7.5	78.7 ± 7.3	0.1 (-0.3, 0.4)	0.67
Weight (kg)	10.5 ± 1.7	10.6 ± 1.8	0.0 (-0.1, 0.1)	0.62
(*) Difference adjusted for outcome at baseline, age of infant at baseline, education and housing type				

Table 5: Child health outcomes at 3 and 6-month follow up

Measures	N	LTP+ Median [IQR]	N	TAU Median [IQR]	Treatment effect (*) Ratio (95% CI)	P-value
Diarrhea days						
3 rd month	328	1 [0, 4]	338	3 [1, 5]	0.57 (0.45, 0.72)	<0.001
6 th month	397	0 [0, 3]	367	3 [0, 5]	0.60 (0.45, 0.79)	<0.001
Chest infection days						
3 rd month	323	0 [0, 3]	326	3 [0, 6]	0.57 (0.40, 0.81)	0.002
6 th month	393	0 [0, 4]	367	3 [0, 7]	0.42 (0.30, 0.58)	<0.001
	N	LTP+ Number (%)	N	TAU Number (%)		
Other illness						
3 rd month	353	105 (30%)	306	140 (46%)	0.50 (0.35, 0.70)	<0.001
6 th month	350	114 (33%)	327	134 (41%)	0.69 (0.49, 0.98)	0.04

(*) Difference adjusted for outcome at baseline, age of infant at baseline, education and housing type

Supplementary Table 1: Treatment effects after adjusting for potential mediating variables

Outcome	Analysis	Adjustments	Treatment effect (+) (95% CI)	P-value
ASQ communication	A1	Primary analysis (*)	21 (19, 23)	<0.001
	A2	A1 + I/T total (**)	20 (18, 23)	<0.001
	A3	A1 + I/T subscales (***)	21 (19, 23)	<0.001
ASQ gross motor	A1	Primary analysis (*)	20 (18, 22)	<0.001
	A2	A1 + I/T total (**)	20 (18, 22)	<0.001
	A3	A1 + I/T subscales (***)	20 (18, 22)	<0.001
ASQ fine motor	A1	Primary analysis (*)	22 (20, 24)	<0.001
	A2	A1 + I/T total (**)	22 (19, 24)	<0.001
	A3	A1 + I/T subscales (***)	22 (19, 24)	<0.001
ASQ problem solving	A1	Primary analysis (*)	24 (22, 26)	<0.001
	A2	A1 + I/T total (**)	24 (22, 26)	<0.001
	A3	A1 + I/T subscales (***)	24 (22, 26)	<0.001
ASQ personal-social	A1	Primary analysis (*)	24 (22, 26)	<0.001
	A2	A1 + I/T total (**)	24 (22, 26)	<0.001
	A3	A1 + I/T subscales (***)	24 (22, 26)	<0.001
PHQ-9	A1	Primary analysis (*)	-4.6 (-5.9, -3.3)	<0.001
	A2	A1 + I/T total (**)	-3.9 (-5.1, -2.7)	<0.001
	A3	A1 + I/T subscales (***)	-3.9 (-5.1, -2.7)	<0.001
(*) Difference adjusted for outcome at baseline, age of infant at baseline, education and housing type (**) Difference adjusted as Analysis 1 plus Infant/Toddler total score (***) Difference adjusted as Analysis 1 plus Infant/Toddler Responsivity, Acceptance, Organisation, Learning materials, Involvement & variety (+) Difference reported as results for Intervention group minus results for Control group				

Supplementary Table 2: Treatment effects after adjusting for potential mediating variables

Outcome	Analysis	Adjustments	Treatment effect ⁽⁺⁾ (95% CI)	P-value
PHQ-9	A1	Primary analysis ^(*)	-4.6 (-5.9, -3.4)	<0.001
	A2	A1 + MSPSS total ^(**)	-4.2 (-5.4, -2.9)	<0.001
	A3	A1 + MSPSS subscales ^(***)	-4.2 (-5.4, -2.9)	<0.001
EPDS	A1	Primary analysis ^(*)	-4.5 (-5.7, -3.3)	<0.001
	A2	A1 + MSPSS total ^(**)	-4.0 (-5.1, -2.8)	<0.001
	A3	A1 + MSPSS subscales ^(***)	-4.0 (-5.1, -2.8)	<0.001
^(*) Difference adjusted for outcome at baseline, age of infant at baseline, education and housing type ^(**) Difference adjusted as Analysis 1 plus MSPSS total score ^(***) Difference adjusted as Analysis 1 plus MSPSS significant other, family and friends subscales ⁽⁺⁾ Difference reported as results for Intervention group minus results for Control group				

An integrated parenting intervention for maternal depression and child development in a low-resource setting: cluster randomized controlled trial

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Abstract

Background: Rates of depression among Pakistani mothers are high, leading to poor developmental outcomes in their children. This study tested the effectiveness of a manualized integrated parenting program; Learning through Play Plus (LTP+) for maternal depression in Karachi, Pakistan. **Methods:** A cluster randomized control trial conducted from January 2014 to December 2015 across 120 villages in Karachi. A total of 774 depressed mothers aged 18 to 44 years with children aged 0-30 months old, were included. Villages were randomized to receive LTP+ added to treatment as usual (TAU) or TAU alone. Primary outcomes were severity of maternal depression at 3 and 6-months measured by the Edinburgh Postnatal Depression Scale (EPDS) and child socio-emotional development at 6-months measured by the Ages and Stages Questionnaire (ASQ). Secondary outcomes included maternal anxiety, quality of life, social support, parenting competence, and knowledge about child development. **Results:** Mothers in the LTP+ group reported significantly lower depression scores compared to those in the TAU group (6.6 vs. 13.8, effect size -7.2, 95 % CI -8.2, -6.1) at 3-months and 6-months (7.2 vs. 12.00, ES -4.6, 95% CI -5.9, -3.4). Child socio-emotional development at 6-months was significantly better in the LTP+ group on all domains of the ASQ. There were also statistically significant improvements on all secondary outcomes at 3-month and 6-month follow up. **Conclusion:** In low-resource settings like Pakistan, low-cost integrated parenting interventions delivered by lay health workers can provide effective treatment for depressed mothers, leading to improvements in child development.

Trial registration: Cinicaltrials.gov (NCT02047357).

Key Words: Maternal depression, child development, psychosocial development, low and middle-income countries, Pakistan

Introduction

~~According to the World Health Organization (WHO, 2017), 5.4 million children under the age of five years died in 2017 (1 in 26). These rates were 14 times higher in Low and Middle Income Countries (LMICs) as compared to High Income Countries (HICs). Pakistan is reported to be one of the riskiest places in the world to be born because of high rates of neonatal deaths (46 per 1,000 live births), under-five mortality rates (78.8 per 1000 live births) and high maternal mortality rates (178 per 100,000) (Unicef, 2016). According to the 2017-18 Pakistan Demographic and Health Survey, 23% of children below five years of age are underweight, 37% stunted and 7% are wasted. Such failure to thrive is associated with poor child socio-emotional development (NIPS, 2019).~~

Poor maternal mental health (~~Rahman, Surkan, Cayetano, Rwagatare, & Dickson, 2013~~) and inadequate child stimulation (Yousafzai, Rasheed, Rizvi, Armstrong, & Bhutta, 2014) have been identified as the most common causes of compromised mental health and development in children (Goodman et al., 2011; Stein et al., 2014).

According to the 2017-18 Pakistan Demographic and Health Survey, 23% of children below five years of age are underweight, 37% stunted and 7% are wasted. Such failure to thrive is associated with poor child socio-emotional development (NIPS, 2019). Meta-analyses suggest that perinatal depression and anxiety in mothers are adversely associated with child development and hence represent important targets for prevention and early intervention to support mothers and the health and well-being of their children (Rogers et al., 2020). Maternal depression is a huge global public health concern with enormous economic costs. Postnatal depression costs the UK approximately £8.1 billion per year (Bauer, Parsonage, Knapp, Iemmi, & Adelaja,

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3 2014). The condition is not only detrimental to mothers (including increased risk of
4 suicide), it also negatively impacts on mother-child attachment and child care during
5 the first three years of life, a critical period for child development (Bauer et al., 2014;
6 Shah & Lonergan, 2017). The prevalence of maternal depression in Pakistan is
7 amongst the highest in the world (28-36%) (Rahman et al., 2013). There is evidence
8 for high risk of stunting, being underweight and more diarrheal episodes in children
9 of depressed mothers as compared to non-depressed mothers in Pakistan (Saeed &
10 Saeed, 2017).
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24 Child stimulation, healthy parent-child interactions and positive parenting are
25 essential elements of child development (Tsivos, Calam, Sanders, & Wittkowski,
26 2015). Recent studies on parenting interventions in LMICs across diverse settings
27 such as Uganda found significant improvement in children's cognitive and language
28 development (Singla, Kumbakumba, & Aboud, 2015). However most interventions
29 had no impact on maternal mental health or did so under specific conditions such as
30 when sessions are delivered during home visits or in group settings (Baker-
31 Henningham, Powell, Walker, & Grantham-McGregor, 2005; Singla et al., 2015).
32 There has been a need to integrate parenting interventions with interventions targeting
33 parents' psychological wellbeing, particularly depression. Such integrated
34 interventions when delivered by community health workers (CHWs), may minimize
35 the need for involvement of already overstretched mental health professionals (Singla
36 et al., 2015; Stein et al., 2018). CHWs or lay healthcare workers are typically
37 community members who are trusted and respected, and able to provide a link
38 between people's homes and formal government primary health care clinics
39 (Olaniran, Smith, Unkels, Bar-Zeev, & van den Broek, 2017). Clinical trials and
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3 longitudinal observational studies of visits by CHWs have shown to improve maternal
4 well-being (including symptoms of maternal depression) and child development in
5 low-resource settings (Katzen et al., 2020; le Roux et al., 2020).
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12 The National Institute for Health and Clinical Excellence guidelines for England
13 (NICE CG901, 2017) as well as the Scottish Intercollegiate Guidelines Network
14 (2012) and the South Australian Perinatal Practice (2014) guidelines recommend
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19 Cognitive Behavior Therapy (CBT) as a first line treatment for postnatal depression.
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24 To our knowledge, there have been three previous studies that have used a CBT based
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To our knowledge, there have been three previous studies that have used a CBT based
intervention called the Thinking Healthy Program (THP) (Sikander et al., 2019) for
maternal depression in Pakistan, two of which have integrated a parenting
intervention called Learning Through Play with THP (Husain et al., 2020; Husain et
al., 2017; Rahman, Malik, Sikander, Roberts, & Creed, 2008). The combined
intervention, referred to as LTP Plus (LTP+), is a scalable innovation delivered by
trained CHWs. LTP+ has led to a significant reduction in maternal depression, along
with improvement in mothers' Knowledge, Attitude and Practices (KAP) scores as
well as an improved nutritional status in malnourished children (Husain et al., 2020;
Husain et al., 2017). As far as we are aware, no study has yet assessed the impact of
LTP+ on measures of child socio-emotional development. The aim of the present
study was to test the efficacy of LTP+ on improvement of maternal depression and
child socio-emotional development in low resource settings in Karachi, Pakistan.

Methods

Study Design

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3 A two-arm, community-based, cluster randomized controlled trial (RCT). 120 clusters
4 (villages) were divided equally in to the LTP+ (intervention) arm and treatment as
5 usual (TAU) (control) arm.
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10 11 12 *Study Setting*

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14 The study was conducted in Gadap town, one of the 18 towns of Karachi, Pakistan.
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16 Gadap town has 8 Union Councils (UCs) and 400 villages, with around 15,000 births
17 per year.
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22 23 24 *Participants*

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26 Inclusion criteria were: Mothers 18 to 44 years of age; having a 0-30 months old
27 child; Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)
28 diagnosis of major depressive episode and anwith Edinburgh Postnatal Depression
29 Scale (EPDS) score >12 (Husain et al., 2013); residing in the trial catchment area;
30 willing and able to provide informed consent and complete a baseline assessment.
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40 Exclusion criteria were: Serious physical health condition (e.g. cardiac, hepatic, renal
41 or respiratory disorders); residing temporarily in the catchment area and unavailable
42 for follow-up assessments; active suicidal ideation; presence of any other severe
43 mental disorder (e.g. schizophrenia or bipolar disorder).
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51 The criteria for study withdrawal were: (1) at the participant's request; (2) at the
52 discretion of the trial investigator (e.g., an adverse event, poor compliance).
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3 The study was conducted in accordance with the principles of the Declaration of
4 Helsinki. Ethical approval for the study was obtained from the ethics committee of
5 Karachi Medical and Dental College (KMDC) (Ref #0019/13). ~~All participants were
6 provided with a Participant Information Leaflet and trained CHWs provided them
7 with information about the study. Handwritten signature or thumbprints were used
8 when obtaining informed consent. Participants were assured that they were free to
9 withdraw at any time without any impact on their routine care, that assessments and
10 interventions were all by interview or questionnaires and thus there were no invasive
11 procedures involved in the study. All information was kept confidential and all
12 participant identifiable data were secured in locked cabinets.~~

23 24 25 26 27 28 *Randomisation and masking*

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30 A total of 120 villages (clusters) were selected for the study in consultation with local
31 community leaders, taking into consideration factors including safety and status of
32 crime in the villages. Some villages were out of the trial catchment area, and
33 community leaders of a few others were not prepared to participate in the trial, and as
34 such were excluded. Each village constituted the unit of randomization. The
35 randomisation resulted in 60 villages allocated to the intervention (LTP+) and 60 to
36 the TAU arm. Participants within the clusters were mother-child dyads with the child
37 being 0-30 months of age at the time of enrolment. The off-site trial statistician and
38 the researchers carrying out follow up assessments were blinded to group allocation.
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54 *Study Procedures*

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56 CHWs approached mothers of young children either in their homes or Basic Health
57 Units (BHUs). Mothers were assessed for eligibility using a screening checklist (with
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3 the pre-defined inclusion and exclusion criteria) and the EPDS (Cox, Holden, &
4
5 Sagovsky, 1987). The EPDS is a 10-item symptoms scale for postnatal depression
6
7 that has been validated in the Pakistani population (Husain et al., 2013).
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12 CHWs were trained in using the screening checklist and EPDS by two researchers
13
14 (TK, SN). Fortnightly supervision with the same researchers involving discussion on
15
16 experiences of using the EPDS and any challenges faced were provided. In addition,
17
18 CHWs received training refreshers including role-play sessions. Potentially eEligible
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20 mothers ~~who consented for the study~~ were assessed by trained researchers at a
21
22 screening visit during which- ~~a~~ structured diagnostic interview (Clinical Interview
23
24 Schedule revised, CIS-R) (Lewis & Pelosi, 1990) was used to confirm a diagnosis of
25
26 DSM-IV current major depressive episode. The Urdu version of the CIS-R has
27
28 already been used in a previous trial with depressed mothers (Husain et al., 2017).
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31 All participants were provided with a Participant Information Leaflet and trained
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33 CHWs provided them with information about the study. Handwritten signature or
34
35 thumbprints were used when obtaining informed consent at the screening visit.
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37 Participants were assured that they were free to withdraw at any time without any
38
39 impact on their routine care, that assessments and interventions were all by interview
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41 or questionnaires and thus there were no invasive procedures involved in the study.
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43 All information was kept confidential and all participant identifiable data were
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45 secured in locked cabinets.
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54 Researchers who were blind to treatment assignment and not involved in the baseline
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56 assessment or the intervention sessions, completed 3-month follow up assessments.
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3 After the 3-month follow-up, mothers were contacted once a month for a further 3
4
5 months to ensure retention for a 6-month follow-up assessment.
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10 *LTP+ Intervention*

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12 LTP+ is a manualized, 10-session group intervention that integrates parental
13
14 information about child development and CBT (Husain et al., 2017). The elements of
15
16 the intervention are derived from two evidence-based interventions: i) the LTP
17
18 programme, which helps stimulate early child development. It includes a pictorial
19
20 calendar designed for parents, which is a key feature of this intervention. The pictorial
21
22 calendar is made up of 8 successive stages of child development from birth to 3 years,
23
24 with pictures of parent-child play and other activities that promote parental
25
26 involvement, learning, and attachment. ii) The CBT component is derived from the
27
28 Thinking Healthy Programme (THP)(Rahman et al., 2008) which has been adapted
29
30 for a group setting (Husain et al., 2017). The THP adopts a ‘here and now’ problem-
31
32 solving approach, uses CBT techniques of active listening, changing negative
33
34 thinking, engagement with the family and regular homework. This integrated
35
36 intervention, called LTP Plus (LTP+), provides information and strategies to promote
37
38 child development in the 5 areas (sense of self, physical development, relationships,
39
40 understanding of world and communication) represented in the LTP calendar and
41
42 helps participants to identify and change their unhelpful thoughts related to their own
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44 health and wellbeing, their child’s growth and development and their relationships.
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54 The intervention has been culturally adapted to the Pakistani context and designed to
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56 be delivered in Urdu. A full description of the approach to cultural adaptation has
57
58 been published previously (Husain et al., 2017). CHWs delivering the intervention
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3 attended a three-day training course (totalling 18 hours) on LTP+ involving
4 presentations, discussions and role-play. Thereafter, CHWs attended monthly training
5 refreshers on LTP+ for the duration of the study. The trained local CHWs delivered
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10 10 sessions of LTP+ intervention over a three-month period with co-facilitation from
11
12 Masters level LTP+ trained psychologists. The sessions lasted 60 to 90 minutes,
13
14 delivered weekly over 8 weeks and then fortnightly during the final 4 weeks. Sessions
15
16 took place at the home of one of the participants and was mutually agreed by all the
17
18 group members. CHWs delivering LTP+ did not deliver treatment as usual (TAU) in
19 the villages randomized to the TAU arm.

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26 For evaluation of fidelity of the intervention, the participant observation method was
27 used, in which the rater/observer not just observes, but also takes an active role in that
28 setting (Pope & Mays 1995). Therefore, two senior researchers (raters) attended the
29 LTP+ sessions as delegates. Specific observation checklists were developed by the
30 raters, which included different domains from each age range of LTP and from each
31 area of development from five areas identified in the LTP manual, as well as core
32 components of THP. During the sessions, the two raters independently rated each
33 session. All scores on the observation checklist were then reviewed for assessment of
34 fidelity. The same two raters completed the fidelity assessments to ensure
35 consistency.

51 *Treatment as Usual (TAU)*

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54 CHWs in Pakistan are called Lady Health Workers (LHWs). All participants in TAU
55
56 received routine follow-ups by LHWs as well as baseline, 3 and 6-month follow-up
57
58 assessments with research staff. In Pakistan, each LHW is responsible for 150
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3 households (around 1000 people) and they visit each household once a month
4 (visiting 5-7 homes daily). They cover all domains of maternal and child health care
5 along with family planning support and immunization. They are also trained in
6 interpersonal communication and community engagement.
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14 *Outcomes*

15 *Maternal health measures*

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17 The primary outcome measure was severity of maternal depressive symptoms at 3-
18 month follow up assessment (i.e., completion of intervention), assessed using the
19 EPDS (Cox et al., 1987). The Patient Health Questionnaire (PHQ-9) (Kroenke,
20 Spitzer, & Williams, 2001) is a 10-item questionnaire that was also used to assess the
21 severity of depressive symptoms in mothers. Secondary mental health measures
22 included severity of maternal anxiety assessed using the Generalised Anxiety
23 Disorder scale (GAD-7) (Spitzer, Kroenke, Williams, & Löwe, 2006), maternal health
24 related quality of life using the EuroQol Quality of Life Scale – 5 Dimensions (EQ-
25 5D) (Brooks & Group, 1996) and maternal social support using the Multidimensional
26 Scale of Perceived Social Support (MSPSS) (Akhtar et al., 2010). All scales were
27 translated in Urdu and have been used in previous studies in Pakistan (Husain et al.,
28 2020; Husain et al., 2017).
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49 *Parenting measures*

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51 Other secondary measures included the the Home Observation for Measurement of
52 the Environment (HOME)(Bradley & Caldwell, 1977), which is a descriptive profile
53 was used to objectively assess the caring environment in which the child is reared.
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60 There are 45 items and 6 subscales of HOME: responsivity, acceptance, organization,

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3 learning materials, involvement and variety. The Learning through Play (LTP)
4 Knowledge, Attitude and Practices (KAP) Questionnaire (Caldwell, 1967) was used to
5 assess change in maternal knowledge, attitude and practices. There are total of 114
6 items on the KAP regarding a child's physical development, sense of self,
7 understanding about the world, relationships and communication for children aged
8 between 0-3 years. Parenting Sense of Competence scale is 17-item scale (Gibaud-
9 Wallston & Wandersman, 1978), each item is rated on 6 point Likert scale. Higher
10 score on this scale indicates a higher parenting sense of competency.
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26 *Child health measures*

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28 The primary outcome for child development was the Ages and Stages Questionnaire
29 (ASQ) (Squires, Bricker, & Twombly, 2009). The ASQ consists of 21 intervals, each
30 with 30 items in five areas: (i) personal-social, (ii) gross motor, (iii) fine motor, (iv)
31 problem solving, and (v) communication for children ages 2-66 months. It has
32 excellent psychometric properties, a test-retest reliability of 92%, sensitivity of 87.4%
33 and specificity of 95.7% (Singh, Yeh, & Blanchard, 2017). The Ages and Stages
34 Social - Emotional Questionnaire (Squires, Bricker, & Twombly, 2002) was used to
35 obtain the maternal report on their child's social and emotional development. These
36 questionnaires have previously been used in Pakistan (Turner et al., 2016).
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51 All measures were assessed at baseline, 3 and 6 months by trained researchers
52 (Masters level psychologists) who were blinded to group allocation. -
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58 *Sample Size*

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3 Results from a previous cluster RCT from Pakistan (Rahman et al., 2008) were used
4
5 to calculate the sample size in the present study. In the earlier study the attrition rate
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7 at 6-month follow-up was 10%, the effect size was approximately 0.2, and the intra-
8
9 cluster correlation coefficient (ICC) was 0.09. We randomized 120 villages with 60
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11 villages allocated to the LTP+ arm and 60 to the TAU arm. We proposed
12
13 to recruit 294 new mothers in each group. Assuming the same rate of attrition, we
14
15 expected to have 6-month data on 265 mothers per group. Using a 25% one-sided
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17 significance level, the trial has a power of 90% to detect an effect of 0.2 under the
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19 same assumptions.
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Statistical analysis

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31 The trial design was a cluster RCT with randomisation performed at the village level.
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33 Multiple participants were recruited from each village. It is likely that outcomes from
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35 participants within the same village will be more similar than outcomes from
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37 participants from differing villages. As a result, the analysis was performed using
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39 multilevel regression methods. Analyses were performed for the outcomes at 3 and 6-
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41 months in a single combined model. Therefore three-level models were used with
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43 measurements at individual timepoints nested within study participants, contained
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45 within villages. Baseline summary statistics were calculated for the two randomized
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47 arms.
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54 The majority of outcomes were continuous in nature, so the treatment effect was
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56 estimated using multilevel linear modes. The outcome value at baseline was used as a
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58 covariate in the analysis. In addition, three other pre-specified covariates were also
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3 included in the analysis: age of the infant at baseline, education level and housing
4 type. The numbers of diarrhoea and chest infection days were found to have highly
5 positively skewed distributions. These were considered as counts and were analysed
6 using multilevel negative binomial regression, as the level of over dispersion meant
7 that Poisson regression was inappropriate. The occurrence of other illness was a
8 binary measure and was analysed using multilevel logistic regression.
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17 The trial design was a cluster RCT with randomisation performed at the village level.
18 Multiple participants were recruited from each village. It is likely that outcomes from
19 participants within the same village will be more similar than outcomes from
20 participants from differing villages. As a result, the analysis was performed using
21 multilevel regression methods. Two-level models were used with individual
22 participants contained within villages. Baseline summary statistics were calculated for
23 the two randomized arms.
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36 Separate analyses were performed for the outcomes at 3 and 6 months. The majority
37 of outcomes were continuous in nature, so the treatment effect was estimated using a
38 linear multilevel model with a random effect for village. The outcome value at
39 baseline was used as a covariate in the analysis. In addition, three other pre-specified
40 covariates were also included in the analysis: age of the infant at baseline, education
41 level and housing type. The numbers of diarrhoea and chest infection days were found
42 to have highly positively skewed distributions. These were considered as counts and
43 were analysed using multilevel negative binomial regression, as the level of over
44 dispersion meant that Poisson regression was inappropriate. The occurrence of other
45 illness was a binary measure and was analysed using multilevel logistic regression.
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3 To investigate the mediating effects of the infant/toddler scores and MSPSS scores,
4 these variables were added in the primary analyses as covariates. The treatment
5 groups would be expected to be balanced for the scores at baseline. To examine the
6 mediating effects, the changes in infant/toddler scores and MSPSS from baseline to 6-
7 months were added to the analyses.
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14 The following models were run:

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16 • Model 1: Adjustments as per the primary study analysis. Adjusting for
17 outcome at baseline, age of infant at baseline, education and housing type
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- 20 • Model 2: Adjustments as per Model 1, plus further adjustment for change in
21 infant/toddler total score/MSPSS score
22
23
- 24 • Model 3: Adjustments as per Model 1, plus further adjustment for change in
25 all infant/toddler subscores/MSPSS score
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33 The total infant/toddler score and infant/toddler components were considered
34 separately, as the total score would be strongly associated/dependent on all the
35 individual subscores. Hence it is not appropriate to include all in the same analysis.
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37 Similarly, the total MSPSS score and MSPSS components were considered in
38 separate analyses, as the total score would be strongly associated/dependent on all the
39 individual subscores. Therefore it would not be appropriate to include all in the same
40 analysis.
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51 **Results**

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53 In January 2014, 120 villages from Gadap town were randomly assigned to either
54 LTP+ arm (n = 60) or TAU arm (n = 60). Within the villages assigned to the
55 intervention arm, 564 mother-child dyads were recruited from January 2014 to June
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3 2015. Of those, 408 met eligibility criteria and 402 (98.5%) completed baseline
4 assessment, 399 (97.8%) completed 3 month follow-up (FU) and 396 (97%)
5 completed 6 month FU (Figure 1). Within the villages assigned to the TAU arm, we
6
7 completed 6 month FU (Figure 1). Within the villages assigned to the TAU arm, we
8
9 screened 510 mother-child dyads, 403 of who met eligibility criteria. Out of those,
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11 372 (92.3%) completed baseline assessment, 370 (91.8%) completed 3 month FU and
12
13 368 (91.3%) completed 6 month FU.
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19 On average, mothers in the intervention arm attended 7.89 (SD 2.035) group sessions,
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21 with 89.48% of mothers attending six sessions or more and 66.92% mothers attending
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23 8 or more sessions. ~~There were no significant differences in any of the Summaries of~~
24
25 ~~the~~ child, mother and family related variables in the two groups at baseline ~~(are~~
26
27 ~~presented in~~ Table 1). The results indicate significant improvements in maternal
28
29 health outcomes at 3 and 6 months (Table 2) in the intervention arm as compared to
30
31 TAU arm ($p < 0.001$). The analysis suggests that mothers in the intervention arm
32
33 showed significantly more improvements in their depression and anxiety symptoms,
34
35 health related quality of life, and perceived social support at the end of the
36
37 intervention than those in the TAU arm. The differences between groups were
38
39 maintained at 6 months (Table 2). The effect of the intervention on maternal
40
41 depression symptoms was partly mediated by mother's perceived positive support and
42
43 active ways of coping (Supplementary Table 1). The results suggest that LTP+
44
45 improves parenting at 3 and 6 months (Table 3), with mothers in the intervention arm
46
47 reporting feeling better in their roles as mothers, as compared to those in the TAU
48
49 arm (Table 3). The results suggest improvements in parenting competence and KAP
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51 scores in the intervention arm, both at 3 and 6 months (Table 3).
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Regarding the primary outcome for child development, the ASQ scores were significantly better in the LTP+ arm for all of domains ($p < 0.001$) including development of social, motor, problem solving and communication skills (Table 4). However, there were no significant differences found in infants' weight or height between the two groups (Table 4). Measures of child health outcomes in the intervention arm also showed significant improvements as compared to the TAU arm (Table 54). The number of days children suffered from diarrhoea or chest infection were found to be significantly less in the intervention arm as compared to the TAU arm (40% lower in intervention arm) (Table 54). In addition, children in the intervention arm were significantly less likely to experience illness with the odds of other illness being only half as great in the intervention arm compared to the TAU arm. The improved child health outcomes with regards to the number of diarrhoea days and number of chest infection days, was maintained at 6-month follow up (Table 54). ~~Regarding child development, the ASQ scores were significantly better in the LTP+ arm for all of domains ($p < 0.001$) including development of social, motor, problem solving and communication skills (Table 5). However, there were no significant differences found in infants' weight or height between the two groups (Table 5).~~

Analyses were also performed to compare the outcomes of the two groups at 6 months, adjusted for potential mediators such as infant/toddler HOME scores and MSPSS scores. The results of these analyses are summarised in Supplementary Tables 1 and 2. The results for all the ASQ scores suggest that the differences between treatments were almost unchanged after adjusting for the infant/toddler HOME scores (Supplementary Table 1). There was a slight reduction in treatment

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3 difference for PHQ-9 after the adjustments. However, this was relatively marginal,
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5 and a highly significant treatment difference remained. Supplementary Table 2 shows
6
7 that the differences between groups showed only minimal reduction after adjusting for
8
9 MSPSS scores.
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11 12 13 14 15 **Discussion**

16
17 This cluster RCT investigated the effect of a novel manual assisted psychosocial
18
19 intervention (LTP+) in reducing maternal depression and improving the social and
20
21 emotional development and physical health of children aged 0-3 years. Mothers in the
22
23 intervention arm showed significant improvement in depression, anxiety, health-
24
25 related quality of life (QoL) and perceived social support following participation.
26
27 More specifically, LTP+ effectively improved parenting knowledge and practices
28
29 indicated by improvement in their scores on KAP scale and all domains of the HOME
30
31 inventory. Mothers in the intervention arm had significant improvement in parenting
32
33 sense of competence as compared to the TAU arm. Along with the improvement in
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35 mothers' psychological wellbeing, their children had improved scores on
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37 communication, gross and fine motor movements, problem solving skills and social
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39 development.
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47 Consistent with findings from our previous LTP+ trial, the current study showed a
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49 beneficial effect of the intervention on maternal depression and anxiety. There is
50
51 strong evidence on the effectiveness of group CBT (Sockol, 2015) in reducing
52
53 maternal depression but not of improving the child outcomes (Rahman et al., 2008).
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55 There is mixed evidence in the literature on the role of integrated interventions in
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57 improving both mother and child health outcomes. One previous study showed
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3 improved maternal and child outcomes (Singla et al., 2015), however, another study
4 did not show improvement in child outcomes with an integrated intervention (Stein et
5 al., 2018). More recently, our group led an RCT of LTP+ for mothers of malnourished
6 children in Pakistan and showed that mothers engaged with LTP+ significantly
7 showed improvements in depression ($p < 0.001$), social support ($p = 0.02$) and quality
8 of life ($p < 0.001$) at the end of the intervention (3 months) as compared to those in the
9 TAU group. In addition, at both 3 and 6 months after baseline, the times which a child
10 suffered from diarrhoea and chest infections was significantly lower in the
11 intervention group ($p < 0.001$ for both outcomes at both time points). The number of
12 diarrhoea days was approximately 50% lower in the intervention group at both time
13 points, whilst the number of chest infection days was reduced by almost three-fold at
14 6 months in the intervention group compared to control group (Husain et al., 2020).

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33 Improvement in both depression and anxiety scores in the intervention arm of the
34 present study sustained at 6-month follow up indicates that LTP+ may help in
35 preventing worsening of these symptoms in mothers. However future studies should
36 include longer-term follow-up as evidence suggests that depressive symptoms may
37 worsen as the child grows (Evans et al., 2012). A recent cluster RCT of a peer-
38 delivered psychosocial intervention (The Thinking Healthy Program, Peer-delivered
39 Plus, THPP+) in rural Pakistan showed no significant differences between the
40 intervention group and enhanced usual care with regards to maternal depression
41 symptoms and child socio-emotional skills (strengths and difficulties questionnaire
42 [SDQ-TD]) at 36-months postnatal follow up (Maselko et al., 2020). However, LTP+
43 distinguishes itself from THPP+ by integrating a parental training program with CBT
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3 principles, and hence may have different long-term benefits when compared to
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5 THPP+ alone.
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10 Maternal depression is known to be associated with marked psychosocial difficulties
11 (Husain et al., 2011). Social support has been shown as a significant protective factor
12 for maternal depression, and the variety of support providers in a mothers' social
13 network is important (Ongeri et al., 2018). There is evidence that Pakistani mothers
14 with perceived positive support from spouses report fewer depressive symptoms
15 (Qadir, Khalid, Haqqani, & Medhin, 2013). In the present study LTP+ improved
16 perceived social support in all three areas of the MSPSS; significant other, family and
17 friends. A parenting intervention trial from Uganda highlighted that perceived
18 positive support mediates the effect of the intervention on maternal wellbeing (Singla
19 et al., 2015), however ~~our mediation analysis the current trial~~ suggests that this
20 measure had little ~~mediating~~ effect upon the treatment differences observed.
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38 Maternal depression can negatively impact quality of life (QoL) in all domains (Kang,
39 Pearlstein, & Sharkey, 2020). A recent study assessed the QoL of mothers in the
40 postnatal period using the World Health Organization Quality of Life scale
41 (WHOQOL-BREF) and concluded that the QoL decreased as the level of depression
42 and anxiety increased (Daglar, Bilgic, & Aydın Özkan, 2018). Poor health-related
43 QoL can impact mothers from fulfilling their parenting roles and other responsibilities
44 in their daily life activities, thus causing disability (Durukan, Ilhan, Bumin, & Aycan,
45 2011). Our previous LTP+ trials showed that women were supported to engage in
46 interactive activities using the LTP calendar, which offered opportunities for
47 behavioural activation resulting in reduction in depression and reduced disability
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3 (Husain et al., 2020; Husain et al., 2017). Similarly, in the current study, LTP+
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5 resulted in improvement in health related QoL. In Pakistan, most women are
6
7 housewives responsible for all domestic chores or work in fields. Our results indicate
8
9 that mothers' ability to perform work improved significantly after engaging with
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11 LTP+.
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17 Maternal self-efficacy can have a significant impact on a mothers' child rearing
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19 practices (Leerkes & Crockenberg, 2002). Maternal mood has strong association with
20
21 parenting confidence and sense of competence (Kwon, Kim, Kim, & Jang, 2006). The
22
23 present study showed that mothers engaged with LTP+ had significant improvements
24
25 in their parenting sense of competence. The synergistic effect produced as a result of
26
27 combining CBT with play activities likely led to the improvement in maternal mood
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29 and hence increased motivation for optimal interaction with children.
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35 The LTP+ intervention effectively improved all parenting practices assessed by the
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37 HOME inventory and benefited child development as assessed by the ASQ at 6-
38
39 month follow up. These findings are consistent with the results of another integrated
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41 parenting intervention tested in a community setting in Uganda (Singla et al., 2015).
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43 Similar to the existing evidence on improvement in knowledge, attitude and practices
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45 (KAP) (Husain et al., 2017; Karbhari et al., 2016; Rahman et al., 2008) with parenting
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47 interventions, KAP scores of mothers in the LTP+ arm improved significantly in this
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49 study.
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56 LTP+ is a complex intervention comprising of several components, which make it
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58 challenging to discern the mechanism of its therapeutic action. We propose that the
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3 intervention's effect on perceived social support and coping skills led to
4 improvements in depressive symptoms in mothers, while the concurrent effect of
5 increased parenting competencies had positive downstream effects on child socio-
6 emotional development and physical health (Figure 2). The study was conducted in an
7 economically deprived urban setting in Pakistan, a LMIC with limited access to
8 publicly funded healthcare. Given this context, it may be that access to structured
9 psychosocial treatment in addition to attentive and systematic assessment of mental
10 health symptoms enhanced treatment differences between groups. It remains unclear
11 if the intervention would have similar benefits in high-income settings, particularly
12 those with greater access to healthcare.
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29 The large sample size and excellent retention rate are clear strengths of the current
30 study. Furthermore, it was conducted in a community setting with the help of CHWs
31 (also known as lay health workers), who are already engaged with mothers as part of
32 routine care for mother and child health in Pakistan. Integrating LTP+ in to routine
33 care could help ensure scale-up and sustainability of this low-cost intervention. One
34 of the challenges during the study was the conservative environment of the
35 community, where female participants are often not permitted to leave the home. In
36 order to overcome this barrier, male CHWs of each village, who are highly respected
37 in the community, assisted in negotiating with male members of the household to
38 allow women to attend sessions. As mentioned, certain villages were excluded from
39 randomization due to concerns about law and order and community reticence to join
40 the study. The excluded villages may be comprised of families with differing
41 sociodemographic variables from those included in the present study and as such our
42 findings may not be generalizable to other settings. The current study is also limited
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3 by a short follow up period that does not allow an assessment on the long-term
4 benefits of LTP+ for mothers and children. A further limitation is that with the
5 exception of the HOME inventory, we relied largely on self-report measures for most
6 outcomes, which can be prone to bias. Finally, our findings cannot be applied to
7 fathers, who despite playing vital roles in child development, were not included in the
8 present study. To address this gap in the literature, our group is leading a number of
9 RCTs of LTP+ for depressed fathers in similar low-resource settings
10 (Clinicaltrials.gov identifier NCT03564847).
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24 The results of this robust cluster RCT, taken together with existing evidence, indicate
25 that low-cost integrated parenting interventions such as LTP+ can help improve
26 symptoms of acute maternal depression and benefit child socio-emotional
27 development in low-resource settings like Pakistan. Further trials with longer
28 durations of follow-up are needed to confirm whether such interventions will have
29 sustainable benefits for both mothers and children. Future studies of LTP+ involving
30 fathers may add further benefits to maternal well-being and child development. More
31 studies from LMICs are urgently needed to address the high rates of maternal
32 depression and compromised child development in these settings.
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47 **Abbreviations:**

49 LTP+	Learning through Play Plus
51 TAU	Treatment As Usual
53 EPDS	Edinburg Postnatal Depression Scale
55 ASQ	Ages and Stages Questionnaire
57 LMICs	Low and Middle Income Countries

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3	HICs	High Income Countries
4		
5	CHWs	Community Health Workers
6		
7		
8	NICE	National Institute for Health and Clinical Excellence guidelines for
9		
10	England	
11		
12	CBT	Cognitive Behavior Therapy
13		
14	THP	Thinking Healthy Program
15		
16		
17	KAP	Knowledge, Attitude and Practices
18		
19	RCT	Randomized Controlled Trial
20		
21	UCs	Union Councils
22		
23		
24	KMDC	Karachi Medical and Dental College
25		
26	BHUs	Basic Health Units
27		
28	CIS-R	Clinical Interview Schedule revised
29		
30		
31	LHWs	Lady Health Workers
32		
33	GAD	Generalised Anxiety Disorder
34		
35	EQ-5D	EuroQol Quality of Life Scale – 5 Dimensions
36		
37		
38	MSPSS	Multidimensional Scale of Perceived Social Support
39		
40	HOME	Home Observation for Measurement of the Environment
41		
42	ICC	Intra-cluster Correlation Coefficient
43		
44		
45	FU	Follow up
46		
47	QoL	Quality of Life
48		
49	THPP+	Thinking Healthy Program, Peer-delivered Plus
50		
51	SDQ	Strengths and difficulties questionnaire
52		
53		
54	WHOQOL	World Health Organization Quality of Life
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Declarations

Ethics approval and consent to participate

Ethical approval for the study was obtained from the ethics committee of Karachi Medical and Dental College (KMDC) (Ref #0019/13). All participants were provided with a Participant Information Leaflet and trained CHWs provided them with information about the study. Handwritten signature or thumbprints were used when obtaining informed consent.

Consent for publication

Not applicable

Conflict of Interest:

MIH is a PI for a trial sponsored by COMPASS Pathways Limited. IBC and NH have given lectures and advice to Eli Lilly, Bristol Myers Squibb, Lundbeck, Astra Zeneca and Janssen pharmaceuticals for which they or their employing institution have been reimbursed. MIH, IBC and NH were previously trustees of the Pakistan Institute of Learning and Living (PILL). NC is currently Chief Executive Officer for PILL.

None of the companies listed above have a financial interest in this research.

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Authorship

NH and NC had the overall responsibility of the trial. NH, NC, BF and CR were involved in the design of the study. All authors were involved in preparing the manuscript. BF, FN, MIH, MH, ZZ and AR were involved in training and supervision of the research team. TK was involved in screening, recruitment and delivery of the

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3 intervention. IBC was leading on data management. PB led the statistical analysis. FJ,
4
5 SS and SN were responsible for participant and public involvement and engagement.
6
7

8 ***Data sharing and data accessibility:***
9

10 Requests for sharing the anonymised trial database should be addressed to the lead
11
12 author.
13

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15

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17
18 Department of Psychiatry, University of Toronto.
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Table 1. Baseline characteristics of participants

	TAU (N=372)	LTP+ (N=402)
Family (Mean \pm SD)		
Total number of household family member	9.7 (6.0)	9.3 (5.4)
Total Monthly household Income	11729.(9943)	11648.5(13232)
Family Status <i>f</i> (%age)		
Nuclear	190 (51.1%)	184 (45.8%)
Joint	182 (48.9%)	218 (54.2%)
Status of house (Rental or ownership) <i>f</i> (%age)		
Ownership	329 (88.4%)	366 (91.0%)
Rental	43 (11.6%)	36 (9.0%)
Mother Health Related Variables (Mean \pm SD)		
GAD-7	12.9 \pm 3.3	12.7 \pm 3.2
EPDS	18.2 \pm 3.1	18.4 \pm 3.1
PHQ-9	15.2 \pm 3.7	15.4 \pm 3.6
Rosenberg self-esteem	12.9 \pm 4.1	12.4 \pm 4.1
MSPSS-Significant other	16.7 \pm 6.6	16.5 \pm 6.7
MSPSS Family	16.3 \pm 6.0	15.3 \pm 6.2
MSPSS Friends	13.8 \pm 6.1	12.8 \pm 5.9
MSPSS Total score	46.9 \pm 15.8	44.5 \pm 15.1
EQ-5D Health Index	0.34 \pm 0.33	0.32 \pm 0.34
EQ-VAS	39 \pm 13	39 \pm 13
WHO physical health	9.7 \pm 1.8	9.8 \pm 1.9
WHO psychological health	9.6 \pm 1.9	9.4 \pm 1.9
WHO social relationship	10.8 \pm 3.4	10.9 \pm 3.4

WHO environment	8.8 ± 2.0	8.6 ± 1.8
WHO total	38.9 ± 7.1	38.8 ± 6.9
Parenting variables (Mean ± SD)		
Laxness	20.3 ± 5.1	20.5 ± 5.6
Over-activity	21.6 ± 6.4	21.54 ± 6.2
Hostility	10.42 ± 4.8	10.87 ± 4.97
No Factor	71.3 ± 9.0	72.07 ± 9.6
Parenting total	123.7 ± 14.3	125 ± 15.54
HOME Responsibility	7.2 ± 3.1	7.8 ± 2.8
HOME Acceptance	3.6 ± 2.1	3.5 ± 2.1
HOME Organisation	3.6 ± 1.7	3.6 ± 1.5
HOME Learning materials	1.8 ± 2.2	1.9 ± 2.3
HOME Involvement	2.7 ± 1.8	2.9 ± 1.7
HOME Variety	2.7 ± 1.1	2.8 ± 1.1
HOME Infant/toddler total	21.7 ± 8.2	22.5 ± 7.4
Parenting confidence	53.4 ± 6.0	54.6 ± 6.7
MAI	80 ± 15	80 ± 16
KAP	80 ± 15	80 ± 17
Child health variables		
Child's age, months Mean (SD)	13.7 (7.9)	14.1 (8.5)
Child's (Female) – <i>f</i> (%age)	186 (50.0%)	196 (48.8%)
Total Number of children	3.38 (1.82)	3.31 (2.06)
ASQ Communication – Mean (SD)	37.6 (11.5)	39.4 (10.9)
ASQ Gross motor - Mean (SD)	37.2 (13.0)	36.7 (12.8)
ASQ Fine motor - Mean (SD)	35.1 (13.3)	36.1 (12.9)
ASQ Problem solving - Mean (SD)	35.1 (13.8)	36.1 (13.5)
ASQ Personal-social - Mean (SD)	36.5 (12.3)	36.5 (11.8)
Ages/stages (month) - Mean (SD)	13.9 (7.8)	14.5 (8.4)
Height (cm) - Mean (SD)	70.0 ± 9.1	70.2 ± 9.4
Weight (kg)	8.1 ± 2.0	8.1 ± 2.1
Diarrhea days - Median [IQR]	3 [0, 5]	2 [0, 5]
Chest infection days - Median [IQR]	4 [0, 7]	4 [0, 7]
Other illnesses – <i>f</i> (%age)	113 (35%)	129 (37%)

	N	LTP+ Mean \pm SD	N	TAU Mean \pm SD	Treatment effect (*)-(95% CI)	P-value
PHQ-9						
-3 rd month	399	6.6 \pm 4.5	370	13.8 \pm 5.3	-7.2 (-8.2, -6.1)	<0.001
-6 th month	396	7.2 \pm 5.0	368	12.0 \pm 6.3	-4.6 (-5.9, -3.4)	<0.001
GAD-7						
-3 rd month	399	6.1 \pm 3.9	370	11.2 \pm 4.1	-5.1 (-5.9, -4.3)	<0.001
-6 th month	396	6.3 \pm 4.0	368	10.0 \pm 4.7	-3.6 (-4.5, -2.6)	<0.001
EPDS						
-3 rd month	399	8.2 \pm 5.1	370	15.6 \pm 5.2	-7.4 (-8.3, -6.4)	<0.001
-6 th month	395	9.1 \pm 5.1	368	13.6 \pm 6.3	-4.5 (-5.7, -3.3)	<0.001
Rosenberg self-esteem						
-3 rd month	399	19.4 \pm 3.9	370	13.5 \pm 4.8	5.8 (5.0, 6.7)	<0.001
-6 th month	396	19.2 \pm 4.1	368	15.0 \pm 5.7	4.1 (3.0, 5.2)	<0.001
MSPSS-Significant other						
-3 rd month	398	21.1 \pm 4.7	370	18.1 \pm 6.0	3.1 (2.1, 4.0)	<0.001
-6 th month	396	21.3 \pm 4.7	368	17.7 \pm 6.5	3.5 (2.4, 4.6)	<0.001
MSPSS Family						
-3 rd month	398	20.1 \pm 5.2	370	16.2 \pm 6.2	4.0 (3.1, 4.9)	<0.001
-6 th month	396	19.8 \pm 5.7	368	16.7 \pm 6.6	3.0 (1.9, 4.1)	<0.001
MSPSS Friends						
-3 rd month	398	19.1 \pm 5.7	370	15.0 \pm 6.1	4.2 (3.4, 5.0)	<0.001
-6 th month	396	18.9 \pm 6.1	368	15.8 \pm 6.9	3.0 (1.8, 4.3)	<0.001
MSPSS Total score						
-3 rd month	398	60.3 \pm 12.5	370	49.3 \pm 15.4	11.3 (9.0, 13.6)	<0.001
-6 th month	396	60.0 \pm 13.5	368	50.2 \pm 17.6	9.6 (6.4, 12.8)	<0.001
EQ5D health index						
-3 rd month	399	0.69 \pm 0.26	370	0.39 \pm 0.36	0.30 (0.24, 0.36)	<0.001
-6 th month	396	0.69 \pm 0.23	368	0.45 \pm 0.36	0.24 (0.18, 0.30)	<0.001
EQVAS						
-3 rd month	399	58 \pm 14	370	43 \pm 13	15 (13, 17)	<0.001
-6 th month	396	60 \pm 13	368	47 \pm 16	12 (10, 15)	<0.001

Table 2: Maternal health outcomes at 3 and 6-month follow up

WHO physical health						
—3 rd month	399	13.6 ± 2.2	370	10.9 ± 2.2	2.6 (2.2, 3.0)	<0.001
—6 th month	396	13.6 ± 2.4	368	11.0 ± 2.7	2.5 (2.0, 3.1)	<0.001
WHO psychological						
—3 rd month	399	13.6 ± 2.3	370	10.9 ± 2.2	2.8 (2.3, 3.2)	<0.001
—6 th month	396	13.8 ± 2.5	368	11.4 ± 2.8	2.4 (1.9, 3.0)	<0.001
WHO social relationship						
—3 rd month	399	14.7 ± 2.4	370	12.1 ± 3.5	2.6 (2.0, 3.1)	<0.001
—6 th month	396	14.7 ± 2.6	368	12.0 ± 3.9	2.6 (1.9, 3.3)	<0.001
WHO environment						
—3 rd month	399	12.6 ± 2.6	370	10.2 ± 2.4	2.5 (2.0, 2.9)	<0.001
—6 th month	396	13.0 ± 2.9	368	10.6 ± 3.0	2.4 (1.8, 3.0)	<0.001
WHO total						
—3 rd month	399	54.5 ± 8.1	370	44.0 ± 8.6	10.4 (8.8, 12.0)	<0.001
—6 th month	396	55.2 ± 9.0	368	45.0 ± 11.2	10.0 (7.7, 12.2)	<0.001
(*) Difference adjusted for outcome at baseline, age of infant at baseline, education and housing type						
Measures	N	LTP+ Mean ± SD	N	TAU Mean ± SD	Treatment effect (*) (95% CI)	P-value
PHQ-9						
—3 rd month	399	6.6 ± 4.5	370	13.8 ± 5.3	-7.1 (-8.1, -6.1)	<0.001
—6 th month	396	7.2 ± 5.0	368	12.0 ± 6.3	-4.7 (-5.7, -3.6)	<0.001
GAD-7						
—3 rd month	399	6.1 ± 3.9	370	11.2 ± 4.1	-5.1 (-5.8, -4.3)	<0.001
—6 th month	396	6.3 ± 4.0	368	10.0 ± 4.7	-3.6 (-4.4, -2.8)	<0.001
EPDS						
—3 rd month	399	8.2 ± 5.1	370	15.6 ± 5.2	-7.4 (-8.4, -6.3)	<0.001
—6 th month	395	9.1 ± 5.1	368	13.6 ± 6.3	-4.5 (-5.5, -3.5)	<0.001
Rosenberg self-esteem						
—3 rd month	399	19.4 ± 3.9	370	13.5 ± 4.8	5.8 (4.9, 6.7)	<0.001
—6 th month	396	19.2 ± 4.1	368	15.0 ± 5.7	4.1 (3.2, 5.0)	<0.001
MSPSS-Significant other						
—3 rd month	398	21.1 ± 4.7	370	18.1 ± 6.0	3.0 (2.0, 3.9)	<0.001
—6 th month	396	21.3 ± 4.7	368	17.7 ± 6.5	3.6 (2.7, 4.6)	<0.001
MSPSS Family						
—3 rd month	398	20.1 ± 5.2	370	16.2 ± 6.2	3.9 (3.0, 4.8)	<0.001
—6 th month	396	19.8 ± 5.7	368	16.7 ± 6.6	3.1 (2.2, 4.0)	<0.001
MSPSS Friends						
—3 rd month	398	19.1 ± 5.7	370	15.0 ± 6.1	4.1 (3.2, 5.1)	<0.001
—6 th month	396	18.9 ± 6.1	368	15.8 ± 6.9	3.1 (2.1, 4.0)	<0.001
MSPSS Total score						
—3 rd month	398	60.3 ± 12.5	370	49.3 ± 15.4	11.0 (8.5, 13.5)	<0.001
—6 th month	396	60.0 ± 13.5	368	50.2 ± 17.6	9.8 (7.3, 12.3)	<0.001
EQ5D health index						
—3 rd month	399	0.69 ± 0.26	370	0.39 ± 0.36	0.30 (0.25, 0.36)	<0.001
—6 th month	396	0.69 ± 0.23	368	0.45 ± 0.36	0.24 (0.19, 0.29)	<0.001
EQVAS						
—3 rd month	399	58 ± 14	370	43 ± 13	15 (12, 17)	<0.001
—6 th month	396	60 ± 13	368	47 ± 16	12 (10, 15)	<0.001
WHO physical health						
—3 rd month	399	13.6 ± 2.2	370	10.9 ± 2.2	2.6 (2.2, 3.0)	<0.001
—6 th month	396	13.6 ± 2.4	368	11.0 ± 2.7	2.5 (2.1, 3.0)	<0.001
WHO psychological						
—3 rd month	399	13.6 ± 2.3	370	10.9 ± 2.2	2.7 (2.3, 3.2)	<0.001

<u>6th month</u>	<u>396</u>	<u>13.8 ± 2.5</u>	<u>368</u>	<u>11.4 ± 2.8</u>	<u>2.5 (2.0, 2.9)</u>	<u><0.001</u>
<u>WHO social relationship</u>						
<u>3rd month</u>	<u>399</u>	<u>14.7 ± 2.4</u>	<u>370</u>	<u>12.1 ± 3.5</u>	<u>2.5 (2.0, 3.1)</u>	<u><0.001</u>
<u>6th month</u>	<u>396</u>	<u>14.7 ± 2.6</u>	<u>368</u>	<u>12.0 ± 3.9</u>	<u>2.5 (2.0, 2.9)</u>	<u><0.001</u>
<u>WHO environment</u>						
<u>3rd month</u>	<u>399</u>	<u>12.6 ± 2.6</u>	<u>370</u>	<u>10.2 ± 2.4</u>	<u>2.4 (2.0, 2.9)</u>	<u><0.001</u>
<u>6th month</u>	<u>396</u>	<u>13.0 ± 2.9</u>	<u>368</u>	<u>10.6 ± 3.0</u>	<u>2.4 (1.9, 2.9)</u>	<u><0.001</u>
<u>WHO total</u>						
<u>3rd month</u>	<u>399</u>	<u>54.5 ± 8.1</u>	<u>370</u>	<u>44.0 ± 8.6</u>	<u>10.3 (8.6, 12.0)</u>	<u><0.001</u>
<u>6th month</u>	<u>396</u>	<u>55.2 ± 9.0</u>	<u>368</u>	<u>45.0 ± 11.2</u>	<u>10.0 (8.3, 11.7)</u>	<u><0.001</u>
(*) Difference adjusted for outcome at baseline, age of infant at baseline, education and housing type						

Table 3: Parenting outcomes at 3 and 6-month follow up

<u>Measures</u>	<u>N</u>	<u>LTP+</u> <u>Mean + SD</u>	<u>N</u>	<u>TAU</u> <u>Mean +</u> <u>SD</u>	<u>Treatment</u> <u>effect (*)</u> <u>(95% CI)</u>	<u>P-value</u>
<u>Laxness</u>						
<u>3rd month</u>	<u>394</u>	<u>17.9 ± 4.3</u>	<u>368</u>	<u>17.0 ± 3.9</u>	<u>0.9 (0.2, 1.6)</u>	<u>0.01</u>
<u>6th month</u>	<u>396</u>	<u>17.7 ± 4.5</u>	<u>366</u>	<u>16.1 ± 4.5</u>	<u>1.5 (0.9, 2.2)</u>	<u><0.001</u>
<u>Over-activity</u>						
<u>3rd month</u>	<u>394</u>	<u>16.6 ± 6.5</u>	<u>368</u>	<u>21.1 ± 6.7</u>	<u>-4.5 (-5.5, -3.5)</u>	<u><0.001</u>
<u>6th month</u>	<u>396</u>	<u>17.4 ± 6.5</u>	<u>366</u>	<u>21.2 ± 6.5</u>	<u>-3.8 (-4.8, -2.7)</u>	<u><0.001</u>
<u>Hostility</u>						
<u>3rd month</u>	<u>394</u>	<u>8.6 ± 4.4</u>	<u>368</u>	<u>10.9 ± 5.0</u>	<u>-1.4 (-2.1, -0.7)</u>	<u><0.001</u>
<u>6th month</u>	<u>396</u>	<u>8.4 ± 4.4</u>	<u>366</u>	<u>11.2 ± 5.0</u>	<u>-2.8 (-3.5, -2.0)</u>	<u><0.001</u>
<u>No Factor</u>						
<u>3rd month</u>	<u>394</u>	<u>68.9 ± 8.3</u>	<u>368</u>	<u>69.6 ± 8.9</u>	<u>-0.7 (-1.9, 0.5)</u>	<u>0.25</u>
<u>6th month</u>	<u>396</u>	<u>69.9 ± 7.6</u>	<u>366</u>	<u>69.9 ± 7.6</u>	<u>0.0 (-1.2, 1.2)</u>	<u>0.99</u>
<u>Parenting total</u>						
<u>3rd month</u>	<u>394</u>	<u>112.0 ± 12.1</u>	<u>368</u>	<u>117.7 ±</u>	<u>-5.8 (-7.8, -3.8)</u>	<u><0.001</u>
<u>6th month</u>	<u>396</u>	<u>112.0 ± 12.1</u>	<u>366</u>	<u>14.4</u> <u>118.5 ±</u> <u>12.2</u>	<u>-5.0 (-7.1, -3.0)</u>	<u><0.001</u>
<u>HOME</u>						
<u>Responsibility</u>						
<u>3rd month</u>	<u>395</u>	<u>9.6 ± 1.7</u>	<u>367</u>	<u>7.9 ± 2.9</u>	<u>1.6 (1.1, 2.1)</u>	<u><0.001</u>
<u>6th month</u>	<u>391</u>	<u>9.6 ± 1.8</u>	<u>367</u>	<u>7.3 ± 3.5</u>	<u>2.2 (1.7, 2.7)</u>	<u><0.001</u>
<u>HOME Acceptance</u>						

<u>3rd month</u>	<u>395</u>	<u>5.4 ± 1.9</u>	<u>367</u>	<u>3.8 ± 2.3</u>	<u>1.5 (1.2, 1.9)</u>	<u><0.001</u>
<u>6th month</u>	<u>391</u>	<u>5.7 ± 1.7</u>	<u>367</u>	<u>4.1 ± 2.2</u>	<u>1.6 (1.2, 1.9)</u>	<u><0.001</u>
HOME Organization						
<u>3rd month</u>	<u>395</u>	<u>4.6 ± 1.3</u>	<u>367</u>	<u>3.9 ± 1.6</u>	<u>0.7 (0.5, 1.0)</u>	<u><0.001</u>
<u>6th month</u>	<u>391</u>	<u>4.7 ± 1.2</u>	<u>367</u>	<u>3.5 ± 1.7</u>	<u>1.1 (0.9, 1.4)</u>	<u><0.001</u>
HOME Learning materials						
<u>3rd month</u>	<u>395</u>	<u>3.4 ± 2.6</u>	<u>367</u>	<u>2.3 ± 2.5</u>	<u>1.2 (0.7, 1.6)</u>	<u><0.001</u>
<u>6th month</u>	<u>391</u>	<u>3.5 ± 2.7</u>	<u>367</u>	<u>2.2 ± 2.4</u>	<u>1.3 (0.9, 1.7)</u>	<u><0.001</u>
HOME Involvement						
<u>3rd month</u>	<u>394</u>	<u>4.5 ± 1.8</u>	<u>367</u>	<u>3.5 ± 2.1</u>	<u>1.0 (0.7, 1.3)</u>	<u><0.001</u>
<u>6th month</u>	<u>391</u>	<u>4.4 ± 1.7</u>	<u>367</u>	<u>2.7 ± 1.9</u>	<u>1.6 (1.3, 1.9)</u>	<u><0.001</u>
HOME Variety						
<u>3rd month</u>	<u>395</u>	<u>3.6 ± 1.0</u>	<u>367</u>	<u>3.0 ± 1.1</u>	<u>0.5 (0.4, 0.7)</u>	<u><0.001</u>
<u>6th month</u>	<u>391</u>	<u>3.6 ± 1.1</u>	<u>367</u>	<u>2.9 ± 1.2</u>	<u>0.7 (0.5, 0.9)</u>	<u><0.001</u>
HOME Infant/toddler total						
<u>3rd month</u>	<u>395</u>	<u>31.1 ± 6.7</u>	<u>367</u>	<u>24.4 ± 8.9</u>	<u>6.5 (5.0, 7.9)</u>	<u><0.001</u>
<u>6th month</u>	<u>391</u>	<u>31.4 ± 6.7</u>	<u>367</u>	<u>22.7 ± 9.6</u>	<u>8.5 (7.0, 10.0)</u>	<u><0.001</u>
Parenting confidence						
<u>3rd month</u>	<u>398</u>	<u>61.5 ± 6.5</u>	<u>369</u>	<u>54.6 ± 6.2</u>	<u>6.6 (5.4, 7.9)</u>	<u><0.001</u>
<u>6th month</u>	<u>398</u>	<u>61.1 ± 7.4</u>	<u>366</u>	<u>54.4 ± 8.3</u>	<u>6.5 (5.3, 7.7)</u>	<u><0.001</u>
MAI						
<u>3rd month</u>	<u>398</u>	<u>90 ± 13</u>	<u>369</u>	<u>82 ± 15</u>	<u>8 (6, 11)</u>	<u><0.001</u>
<u>6th month</u>	<u>393</u>	<u>90 ± 12</u>	<u>367</u>	<u>80 ± 16</u>	<u>10 (6, 12)</u>	<u><0.001</u>
KAP						
<u>3rd month</u>	<u>398</u>	<u>87 ± 10</u>	<u>369</u>	<u>74 ± 15</u>	<u>12 (10, 15)</u>	<u><0.001</u>
<u>6th month</u>	<u>394</u>	<u>91 ± 13</u>	<u>365</u>	<u>80 ± 20</u>	<u>11 (8, 13)</u>	<u><0.001</u>
(*) Difference adjusted for outcome at baseline, age of infant at baseline, education and housing type						
Secondary outcome	N	LTP+ Mean ± SD	N	TAU Mean ± SD	Treatment effect^(*) (95% CI)	P-value
Laxness						
—3 rd month	394	17.9 ± 4.3	368	17.0 ± 3.9	0.9 (0.2, 1.6)	0.009
—6 th month	396	17.7 ± 4.5	366	16.1 ± 4.5	1.5 (0.8, 2.3)	<0.001
Over-activity						
—3 rd month	394	16.6 ± 6.5	368	21.1 ± 6.7	-4.5 (-5.6, -3.5)	<0.001
—6 th month	396	17.4 ± 6.5	366	21.2 ± 6.5	-3.7 (-4.9, -2.5)	<0.001
Hostility						
—3 rd month	394	8.6 ± 4.4	368	10.9 ± 5.0	-1.5 (-2.2, -0.7)	<0.001
—6 th month	396	8.4 ± 4.4	366	11.2 ± 5.0	-2.7 (-3.6, -1.9)	<0.001
No Factor						
—3 rd month	394	68.9 ± 8.3	368	69.6 ± 8.9	-0.8 (-2.0, 0.5)	0.24
—6 th month	396	69.9 ± 7.6	366	69.9 ± 7.6	0.0 (-1.1, 1.2)	0.99
Parenting total						

—3 rd month	394	112.0 ± 12.1	368	117.7 — ±	-5.9 (-8.0, -3.9)	<0.001
—6 th month	396	112.0 ± 12.1	366	14.4	-5.9 (-8.0, -3.9)	<0.001
				118.5 — ±		
				12.2		
HOME						
Responsibility	395	9.6 ± 1.7	367	7.9 ± 2.9	1.6 (1.2, 2.1)	<0.001
—3 rd month	391	9.6 ± 1.8	367	7.3 ± 3.5	2.2 (1.5, 2.8)	<0.001
—6 th month						
HOME Acceptance						
—3 rd month	395	5.4 ± 1.9	367	3.8 ± 2.3	1.5 (1.2, 1.9)	<0.001
—6 th month	391	5.7 ± 1.7	367	4.1 ± 2.2	1.6 (1.2, 2.0)	<0.001
HOME Organization						
—3 rd month	395	4.6 ± 1.3	367	3.9 ± 1.6	0.7 (0.5, 1.0)	<0.001
—6 th month	391	4.7 ± 1.2	367	3.5 ± 1.7	1.1 (0.8, 1.4)	<0.001
HOME Learning materials						
—3 rd month	395	3.4 ± 2.6	367	2.3 ± 2.5	1.2 (0.7, 1.6)	<0.001
—6 th month	391	3.5 ± 2.7	367	2.2 ± 2.4	1.3 (0.8, 1.7)	<0.001
HOME Involvement						
—3 rd month	394	4.5 ± 1.8	367	3.5 ± 2.1	1.0 (0.7, 1.3)	<0.001
—6 th month	391	4.4 ± 1.7	367	2.7 ± 1.9	1.6 (1.3, 1.9)	<0.001
HOME Variety						
—3 rd month	395	3.6 ± 1.0	367	3.0 ± 1.1	0.6 (0.4, 0.7)	<0.001
—6 th month	391	3.6 ± 1.1	367	2.9 ± 1.2	0.7 (0.5, 0.9)	<0.001
HOME Infant/toddler total						
—3 rd month	395	31.1 ± 6.7	367	24.4 ± 8.9	6.6 (5.1, 8.0)	<0.001
—6 th month	391	31.4 ± 6.7	367	22.7 ± 9.6	8.4 (6.6, 10.2)	<0.001
Parenting confidence						
—3 rd month	398	61.5 ± 6.5	369	54.6 ± 6.2	6.7 (5.6, 7.9)	<0.001
—6 th month	398	61.1 ± 7.4	366	54.4 ± 8.3	6.4 (4.9, 7.9)	<0.001
MAI						
—3 rd month	398	90 ± 13	369	82 ± 15	8 (6, 11)	<0.001
—6 th month	393	90 ± 12	367	80 ± 16	10 (6, 13)	<0.001
KAP						
—3 rd month	398	87 ± 10	369	74 ± 15	13 (11, 15)	<0.001
—6 th month	394	91 ± 13	365	80 ± 20	10 (7, 14)	<0.001
(*) Difference adjusted for outcome at baseline, age of infant at baseline, education and housing type						

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Table 4: Child development and growth at 6-month follow-up

<u>Measures</u>	<u>TAU (N = 367)</u> <u>Mean (SD)</u>	<u>LTP+ (392)</u> <u>Mean (SD)</u>	<u>Difference (*) Mean</u> <u>(95% CI)</u>	<u>P-</u> <u>value</u>
ASQ communication	28.8 (10.7)	49.8 (10.1)	20.7 (18.7, 22.8)	<0.001
ASQ gross motor	28.8 (10.3)	49.6 (10.3)	20.4 (18.4, 22.3)	<0.001
ASQ fine motor	28.9 (10.0)	51.5 (10.7)	21.8 (19.5, 24.2)	<0.001
ASQ problem solving	28.4 (9.8)	52.7 (10.1)	23.8 (21.5, 26.0)	<0.001
ASQ personal-social	28.4 (9.9)	53.1 (10.3)	24.0 (21.8, 26.3)	<0.001
Ages/stages (month)	20.6 (7.7)	21.1 (8.2)	-0.1 (-0.2, 0.1)	0.50
Anthropometric assessments	<u>TAU (N = 367)</u> <u>Mean (SD)</u>	<u>LTP+ (N = 393)</u> <u>Mean (SD)</u>	<u>Difference (*) Mean</u> <u>(95% CI)</u>	<u>P-</u> <u>value</u>
Height (cm)	79.0 ± 7.5	78.7 ± 7.3	0.1 (-0.3, 0.4)	0.67
Weight (kg)	10.5 ± 1.7	10.6 ± 1.8	0.0 (-0.1, 0.1)	0.62
(*) Difference adjusted for outcome at baseline, age of infant at baseline, education and housing type				

Table 54: Child health outcomes at 3 and 6-month follow up

Secondary outcomes/Measures	N	LTP+ Median [IQR]	N	TAU Median [IQR]	Treatment effect (*) Ratio (95% CI)	P-value
Diarrhea days						
3 rd month	328	1 [0, 4]	338	3 [1, 5]	0.57 (0.45, 0.72)	<0.001
6 th month	397	0 [0, 3]	367	3 [0, 5]	0.60 (0.45, 0.79)	<0.001
Chest infection days						
3 rd month	323	0 [0, 3]	326	3 [0, 6]	0.57 (0.40, 0.81)	0.002
6 th month	393	0 [0, 4]	367	3 [0, 7]	0.42 (0.30, 0.58)	<0.001
Secondary outcome	<u>N</u>	<u>LTP+Intervention</u> (n = 353) Number (%)	<u>N</u>	<u>TAU Control</u> (n = 306) Number (%)	<u>Treatment effect</u> (*) Odds Ratio (95% CI)	<u>P-value</u>
Other illness						
3 rd month	353	105 (30%)	306	140 (46%)	0.50 (0.35, 0.70)	<0.001
6 th month	350	114 (33%)	327	134 (41%)	0.69 (0.49, 0.98)	0.04

(*) Difference adjusted for outcome at baseline, age of infant at baseline, education and housing type

Table 5: Child development and growth at 6-month follow-up

Secondary outcomes	TAU (N = 367) Mean (SD)	LTP+ (392) Mean (SD)	Difference^(*)—Mean (95% CI)	P-value
ASQ communication	28.8 (10.7)	49.8 (10.1)	20.7 (18.7, 22.8)	<0.001
ASQ gross motor	28.8 (10.3)	49.6 (10.3)	20.4 (18.4, 22.3)	<0.001
ASQ fine motor	28.9 (10.0)	51.5 (10.7)	21.8 (19.5, 24.2)	<0.001
ASQ problem solving	28.4 (9.8)	52.7 (10.1)	23.8 (21.5, 26.0)	<0.001
ASQ personal-social	28.4 (9.9)	53.1 (10.3)	24.0 (21.8, 26.3)	<0.001
Ages/stages (month)	20.6 (7.7)	21.1 (8.2)	-0.1 (-0.2, 0.1)	0.50
Anthropometric assessments	TAU (N = 367) Mean (SD)	LTP+ (N = 393) Mean (SD)	Difference^(*)—Mean (95% CI)	P-value
Height (cm)	79.0 ± 7.5	78.7 ± 7.3	0.1 (-0.3, 0.4)	0.67
Weight (kg)	10.5 ± 1.7	10.6 ± 1.8	0.0 (-0.1, 0.1)	0.62
(*) Difference adjusted for outcome at baseline, age of infant at baseline, education and housing type				

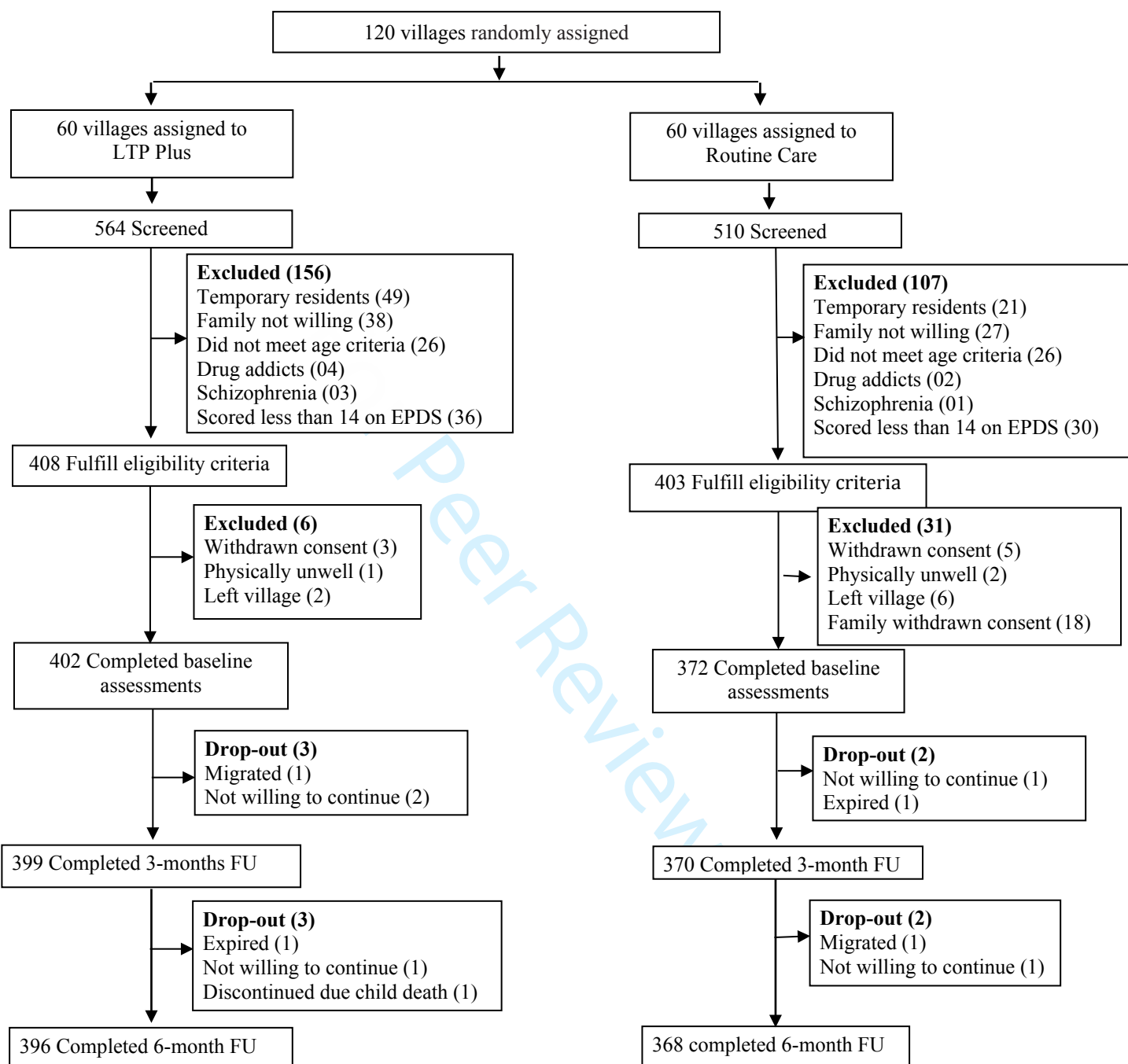
Supplementary Table 1: Treatment effects after adjusting for potential mediating variables

Outcome	Analysis	Adjustments	Treatment effect (+) (95% CI)	P-value
ASQ communication	A1	Primary analysis (*)	21 (19, 23)	<0.001
	A2	A1 + I/T total (**)	20 (18, 23)	<0.001
	A3	A1 + I/T subscales (***)	21 (19, 23)	<0.001
ASQ gross motor	A1	Primary analysis (*)	20 (18, 22)	<0.001
	A2	A1 + I/T total (**)	20 (18, 22)	<0.001
	A3	A1 + I/T subscales (***)	20 (18, 22)	<0.001
ASQ fine motor	A1	Primary analysis (*)	22 (20, 24)	<0.001
	A2	A1 + I/T total (**)	22 (19, 24)	<0.001
	A3	A1 + I/T subscales (***)	22 (19, 24)	<0.001
ASQ problem solving	A1	Primary analysis (*)	24 (22, 26)	<0.001
	A2	A1 + I/T total (**)	24 (22, 26)	<0.001
	A3	A1 + I/T subscales (***)	24 (22, 26)	<0.001
ASQ personal-social	A1	Primary analysis (*)	24 (22, 26)	<0.001
	A2	A1 + I/T total (**)	24 (22, 26)	<0.001
	A3	A1 + I/T subscales (***)	24 (22, 26)	<0.001
PHQ-9	A1	Primary analysis (*)	-4.6 (-5.9, -3.3)	<0.001
	A2	A1 + I/T total (**)	-3.9 (-5.1, -2.7)	<0.001
	A3	A1 + I/T subscales (***)	-3.9 (-5.1, -2.7)	<0.001
(*) Difference adjusted for outcome at baseline, age of infant at baseline, education and housing type				
(**) Difference adjusted as Analysis 1 plus Infant/Toddler total score				
(***) Difference adjusted as Analysis 1 plus Infant/Toddler Responsivity, Acceptance, Organisation, Learning materials, Involvement & variety				
(+) Difference reported as results for Intervention group minus results for Control group				

Supplementary Table 2: Treatment effects after adjusting for potential mediating variables

Outcome	Analysis	Adjustments	Treatment effect ⁽⁺⁾ (95% CI)	P-value
PHQ-9	A1	Primary analysis (*)	-4.6 (-5.9, -3.4)	<0.001
	A2	A1 + MSPSS total (**)	-4.2 (-5.4, -2.9)	<0.001
	A3	A1 + MSPSS subscales (***)	-4.2 (-5.4, -2.9)	<0.001
EPDS	A1	Primary analysis (*)	-4.5 (-5.7, -3.3)	<0.001
	A2	A1 + MSPSS total (**)	-4.0 (-5.1, -2.8)	<0.001
	A3	A1 + MSPSS subscales (***)	-4.0 (-5.1, -2.8)	<0.001
(*) Difference adjusted for outcome at baseline, age of infant at baseline, education and housing type (**) Difference adjusted as Analysis 1 plus MSPSS total score (***) Difference adjusted as Analysis 1 plus MSPSS significant other, family and friends subscales (+) Difference reported as results for Intervention group minus results for Control group				

Figure 1: CONSORT Flow Diagram



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Figure 2: Putative conceptual framework for maternal depression and impact on child development

