Unhealthy behaviors during pregnancy: who continues to smoke and consume alcohol, and is treatment of anxiety and depressive symptoms effective?
Beijers, Chantal

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Cognitive behavioral therapy for treatment of anxiety and depressive symptoms during pregnancy: a randomized controlled trial

Chantal Beijers
Johan Ormel
Tjitte Verbeek
Maria G. van Pampus
Judith L. Meijer
Huibert Burger
Claudi L.H. Bockting

In progress; analyses will be repeated in approximately five months after completion of follow-up measurements
Abstract

Aim: anxiety and depressive symptoms during pregnancy are associated with adverse maternal and child outcomes. Available evidence on the effectiveness of cognitive behavioral therapy (CBT) during pregnancy for treatment of these symptoms is limited and inconclusive. The aim of the present study was to investigate the effect of individual CBT on anxiety and depressive symptoms during pregnancy, as compared to care as usual (CAU), using an RCT design and including pregnant women with subclinical anxiety and/or depressive symptoms or disorders.

Method: pregnant women were screened in midwife practices or hospitals throughout The Netherlands and those with at least moderate anxiety and/or depressive symptoms in their first trimester were invited. Participants in the intervention group received 10-14 CBT sessions, of which 6-10 during pregnancy. The present preliminary analysis shows results from a secondary outcome measure: anxiety and depressive symptoms at 36 weeks of gestation as measured by the STAI and EPDS, respectively.

Findings: out of the 896 women who were invited, 269 gave informed consent. The analysis included 123 participants >35 weeks of gestation, in each arm. Fifty-three percent of our sample had anxiety and/or depressive DSM-IV disorders. Results show that levels of anxiety and depressive symptoms decrease during pregnancy (p<0.001 and p<0.05, respectively). However, no differences in scores were observed between the CBT and CAU group: difference in mean STAI score: 0.5 (95%CI -2.7;3.7), difference in mean EPDS score: 0.5 (95%CI -0.6;1.7). Stratified analyses according to socioeconomic position, parity, severity of symptoms, and DSM-IV disorder do not show statistical significant effect sizes.

Conclusions: the present study found no evidence of a beneficial effect of CBT treatment for anxiety and depressive symptoms during pregnancy, when compared to CAU. More evidence needs to be gained for which specific groups screening and treatment may be beneficial during pregnancy, including especially pregnant women with anxiety and/or depressive disorders.
Introduction

It is estimated that 10-20% of all pregnant women suffer from symptoms of anxiety and depression during pregnancy [1-4]. These symptoms may adversely affect both maternal and child health outcomes. For the mother there seems to be an increased risk for developing postpartum depression [5,6]. As for the child, it has been suggested that, in line with Barker’s “fetal origins of adult disease”-hypothesis, an adverse mental state of the mother during pregnancy may be an important and modifiable risk factor for psychosocial problems in her children [7,8]. Previous research suggests that anxiety and depression during pregnancy may affect the maternal stress system, possibly leading to an overexposure to glucocorticoid levels in the fetus, which subsequently may influence its development [9,10]. Early identification and treatment of anxiety and depression during pregnancy may therefore help to prevent adverse maternal and child outcomes.

Moderate to severe depression among adults is commonly treated with antidepressants [11]. However, during pregnancy, women prefer psychological treatment [12], mainly because the safety of medication to treat anxiety and depression during pregnancy cannot be guaranteed [13,14]. Cognitive behavioral therapy (CBT) has been shown to be effective in treating anxiety and depression in the general population [15,16]. Present NICE guidelines suggest CBT for the treatment of anxiety and depression also during pregnancy [17]. However, evidence for the effectiveness of CBT during pregnancy is sparse. We are aware of only three randomized controlled trials (RCTs) that investigated the effect of CBT on depressive symptoms during pregnancy. Out of these, only one study also investigated the effect of CBT on anxiety symptoms during pregnancy. Women who were included in the latter study (n=277) reported a prior history of depression, or scored >10 on the Edinburgh Postnatal Depression Score and/or >23 on the Antenatal Risk Questionnaire [18]. Results showed no beneficial effect of six weekly CBT sessions on levels of anxiety nor on levels of depression, when compared to the control condition that included an information booklet [18]. In a pilot RCT, conducted by Burns and colleagues, participants meeting the ICD-10 criteria on the Clinical Interview Schedule for depression, received up to 12 CBT sessions (n=36) [19]. Although not statistically significant, the intervention group showed a greater reduction in depression rates compared to the control group that received care as usual [19]. Lastly, the study by Le and colleagues (n=217) included Latina women who scored ≥16 on the Center for Epidemiological Studies Depression Scale and/or reported a prior or family history of depression, but who did not meet a current diagnosis of depression [20]. A statistical significant greater reduction of depressive symptoms during pregnancy was found in the intervention group, that received eight weekly CBT
sessions, when compared to the control condition that included care as usual [20]. Given these contradictory findings, more evidence is needed on the effectiveness of CBT when treating anxiety and depression during pregnancy, and for whom CBT may be most beneficial.

The aim of the present study was to investigate the effect of individual CBT on maternal mental health during pregnancy, as compared to care as usual (CAU), using a RCT design and including pregnant women with subclinical anxiety and/or depressive symptoms or disorders. In the CBT arm, we expected a (greater) reduction of anxiety and depressive symptoms during pregnancy, when compared to CAU.

Methods

Setting and participants

The present study used data from the ongoing ‘Pregnancy Outcomes after a Maternity Intervention for Stressful EmotionS’ (PROMISES) trial. This single-blind-RCT investigates the effects of CBT compared to CAU in pregnant women with symptoms of anxiety and depression on maternal symptom levels during and after pregnancy, obstetric outcomes and the child’s development including behavioral and emotional problems. A detailed description of the PROMISES trial can be found elsewhere [21].

Due to a lower than expected response rate after commencement of the trial we decided to also include participants in hospitals to increase the eligible study population, as opposed to only including participants in primary care. This implied that we decided to no longer exclude multiple pregnancies and women with a history of in vitro fertilization. Obstetric healthcare in The Netherlands is organized as follows. Approximately 85%, of all pregnant women with low-risk pregnancies typically enter primary care and are monitored by independent midwives [22]. The remaining 15% is referred to a gynecologist/obstetrician in a hospital [22]. All women visiting the participating midwifery practices (n=91) and obstetric and gynecology departments of hospitals (n=7) throughout The Netherlands were invited to participate in the Pregnancy Anxiety and Depression (PAD) study. This prospective cohort study investigates psychological, social and medical factors during and after pregnancy [23]. Women are screened for anxiety and depressive symptoms in their first trimester of pregnancy (T0). Women with at least moderate levels of anxiety and/or depressive symptoms and who indicate to be interested in a follow-up study, are invited to participate in the PROMISES trial. Women fulfilling one or more of the following criteria were excluded from participation in the PROMISES trial:
1. High suicidal risk according to the suicidality subscale score on the MINI International Neuropsychiatric Interview [Sheehan, 1998]
2. Presently receiving psychotherapy
3. Substantial physical disease or illegal substance abuse
4. No mastery of the Dutch language
5. Having a psychiatric history on bipolar disorder, psychoses and manic disorder

Women who provide written informed consent are asked to fill out online questionnaires both during and after pregnancy. The present study used data collected on the following occasions: screening (T0), baseline information at 19 weeks estimated gestational age (EGA) (T1), follow-up questionnaires at 36 weeks EGA (T2) and approximately one year postpartum (T3).

Measures used for the present analysis, and their corresponding time points, can be found in table 1.

<table>
<thead>
<tr>
<th>Table 1: Assessments per time point</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T0</strong></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Anxiety symptoms (STAI)</td>
</tr>
<tr>
<td>Depression symptoms (EPDS)</td>
</tr>
<tr>
<td>Socio-demographic &amp; -economic factors</td>
</tr>
<tr>
<td>Suicidality (MINI)</td>
</tr>
<tr>
<td>Healthcare consumption</td>
</tr>
<tr>
<td>Clinical Diagnostic Interview (SCID-II)</td>
</tr>
</tbody>
</table>

STAI = State Trait Anxiety Inventory
MINI = MINI International neuropsychiatric Interview
SCID-II = Structured Clinical Interview for DSM-IV disorders

Assessments
The level of anxiety was monitored using the Dutch version of the validated 6-item State Trait Anxiety Inventory (STAI), which has also been used to measure anxiety symptoms during pregnancy [24]. Depressive symptoms were measured using the Dutch version of the validated 10-item Edinburgh Postnatal Depression Scale (EPDS) [25]. The following cut-off values were used: STAI>42 and EPDS≥12. Socio-demographic factors that were measured include questions about socioeconomic position, age, and parity. Socioeconomic status (SES) was assessed using three indicators: family income and educational level of both the father and mother. These indicators were weighted and categorized as low SES, middle SES, and high SES. Questions
about socioeconomic position were based on a questionnaire used in the Utrecht Health Project (Dutch acronym LRGP: Leidsche Rijn Gezondheids Project, http://www.zorggegevens.nl.zorg/eerstelijnszorg/leidsche-rijn-gezondheidsproject/). The Trimbos and iMTA questionnaire on Costs associated with Psychiatric illness (TIC-P) was used to assess the number of visits paid to the midwife/gynecologist, general practitioner, medical officer, and psychology workers (i.e. psychologist, psychiatrist, social worker, addiction care) between 20 weeks EGA and delivery [26]. In addition, use of antidepressants and anxiolytics was registered. Finally, the anxiety and mood disorder section of the Structured Clinical Interview for DSM-VI Disorders (SCID-II) was used to assess the presence of an anxiety or depressive disorder [27].

Power calculation
The present analysis included data of all participants who were >35 weeks EGA, 246 in number. Given this sample size, an equal allocation rate, and based on an independent samples t-test (5% significance level, two-sided), we were able to detect at least an effect size of 0.36 or over with 80% power. We considered this to be a relevant effect size, given that previous studies among the general (patient) population indicated an effect size of around 0.4 or higher for anxiety and depression treatment [15,16].

Randomization
Eligible women were randomized right after baseline assessments, including the SCID-II interview, 1:1 to either CBT or CAU by an independent research assistant. To this end, a computer-generated randomization list was used, stratified for parity and socioeconomic position, with randomly permuted blocks of random size.

CBT Intervention
CBT trained psychologists throughout The Netherlands (n=31), and who are BIG registered, delivered the intervention. All psychologists received additional specific two-day training by a board certified clinical psychologist (CLHB). During this training all components of the intervention were explained and there was room for practice. The treatment protocol was developed by CLHB and consists of 10-14 weekly individual sessions, of which 6-10 are scheduled to be delivered during pregnancy. The treatment encompasses several optional modules with specific evidence-based CBT interventions focusing on the treatment of anxiety disorders, depressive disorders, or trauma and post-traumatic stress disorder. In addition, the overall focus of the treatment is targeted at identifying and changing dysfunctional cognitions and beliefs. Each session addresses pregnancy-related cognitions and attitudes. Moreover, all
sessions are structured with homework assignments, and discussion of these assignments, and the rationale of each session was explained. A treatment manual is available on request. During the period of the trial, regular supervision has been given by CLHB and treatment integrity has been checked by organizing supervision sessions.

Control group
The control group receives CAU, which is an advice to contact their general practitioner and/or midwife because of an increased risk of developing an anxiety or depressive disorder. In view of the pragmatic nature of the trial, no restrictions were imposed on treatments in the CAU group.

Outcome
The primary outcomes of the present study were the level of anxiety and depressive symptoms at 36 weeks EGA. Secondary outcomes included a measure of distress, ‘distress score’, as indexed by the equally weighted standardized mean of the STAI and EPDS scores. Besides, the amount of healthcare consumption between 20 weeks EGA and delivery was included as a secondary outcome.

Statistical analyses
Characteristics of the study participants were described according to randomized group using appropriate descriptive analyses. STAI, EPDS, and distress scores at 36 weeks EGA were analyzed as continuous dependent variables using linear regression with STAI, EPDS, and distress scores at T0 as independent variables, next to the randomized group variable. This analysis of covariance approach is favored, because it accounts for baseline imbalance across groups and generally has superior statistical power to detect intervention effects when compared to other approaches, such as change scores [28]. In each analysis, the stratification variables parity and SES were added as covariates. Primarily, the analyses were carried out according to the intention-to-treat principle. Secondary analyses were ‘per protocol’, i.e. restricted to those participants who had a minimum of 6 sessions. Predefined subgroup analyses within the primary outcome analyses were undertaken according to socioeconomic position (low vs. middle vs. high), parity (primiparae vs. multiparae), severity of anxiety and depressive symptoms (below vs above cut-off values of 42 for STAI and 12 for EPDS), and the presence of an anxiety and/or depressive disorder according to DSM-IV. Balance between the CBT and CAU group was checked for age and present DSM-IV diagnosis, and analyses were additionally adjusted for these variables when appropriate. Differences in effect of CBT between subgroups were evaluated by statistically testing the significance of
treatment*subgroup interaction terms. Effect parameters were supplied with a 95% confidence interval (95%CI).

As a sensitivity analysis we studied the influence of missing data on all results. The percentage missing data ranged from 0 to 26 (depressive symptoms at 36 weeks EGA) for the variables of main interest. We used multiple imputation by chained equations under the assumption that the missingness mechanism is missing at random or missing completely at random. We imputed 20 datasets and data were pooled using Rubin’s rules [29]. The imputation model included all variables of interest that may predict missingness in the primary outcome. We studied the missing data mechanism of the primary outcome variables by predicting missingness (yes/no) of each of these variables using a multivariable logistic regression analysis. All variables that were considered potential predictors of missingness were entered as independent variables. These analyses showed an explained variance of 43% for anxiety symptoms and 29% for depression symptoms (Nagelkerke’s $R^2$). This suggested that data were missing at random at least to some extent, but data being missing not at random can never be excluded. The level of statistical significance was set at 0.05, two-sided. All analyses were performed using IBM SPSS Statistics version 20.0.

Ethics
The PROMISES trial has been approved by the medical ethical committee of the University Medical Centre Groningen.

Results

Descriptives
Following the screening of 7740 pregnant women, a total of 1213 women (16%) experienced at least moderate symptoms of anxiety and/or depression, of which 317 women were excluded. The remaining 896 women were invited to participate in the PROMISES trial of which 269 women (30%) decided to participate. After randomization, 23 participants were excluded from the present analysis because they were of less than 36 weeks EGA, and consequently no outcome measurement was available. Thus 246 formed the current study population, 123 in each arm (figure 1). In the CBT group, twelve participants refused to start the intervention for various reasons, including no time or expecting that the treatment would be too burdensome. Participants who finished the intervention had a mean of 9 sessions (range 1-14) and 61 participants completed 6-10 sessions. Twenty-four participants did not complete 6-10 sessions.
Treatment of anxiety and depressive symptoms during pregnancy

Figure 1: CONSORT diagram

**Enrollment**

- **Screening:** n=7740
  - **STAI>12 and/or EPDS>11:** n= 1213
    - Do not want to participate: n= 627
      - no acknowledgement of symptoms/no need for therapy: n= 29
      - no interest in PROMISES study: n= 45
      - practical issues (no time, care for other children, work): n= 25
      - reasons unknown: n= 528
    - Excluded: n= 317
      - Not meeting inclusion criteria: n=140
      - No interest in follow-up study: n=95
      - Other reasons
        - miscarriage: n= 17
        - contact information missing: n= 4
        - not reported: n= 61

**Allocation**

- Randomized n=269
  - Gestational age >35wk n= 246
- Allocated to CBT: n= 123
  - Refused: n= 12
  - Received ≥6 sessions: n= 61
  - Still receiving therapy: n= 27
  - Dropped out of treatment early: n= 24
    - no symptoms: n= 4
    - practical or personal issues: n= 8
    - pregnancy-related conditions (e.g. pain): n= 5
    - intervention too burdensome: n= 6
    - reasons unknown: n= 1
- Allocated to CAU n= 123
  - Dropped out (reasons unknown): n= 3

**Follow-Up**

- Assessed 36 weeks of gestation: n= 91
- Assessed 36 weeks of gestation: n= 97
for various reasons (e.g. not presenting with symptoms anymore, no time, pregnancy complications). Twenty-six participants were still receiving the intervention at time of the analysis.

Characteristics of the participants are shown in Table 2, according to randomization status. Both groups were comparable on all variables, although participants in the CBT group more often presented with an anxiety or depression diagnosis and participants in the CAU group more often with a comorbid diagnosis.

Table 2: Characteristics of the randomized study participants

<table>
<thead>
<tr>
<th></th>
<th><strong>Intervention (N=123)</strong></th>
<th><strong>Care as usual (N=123)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (SD)</strong></td>
<td><strong>Mean (SD)</strong></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>33.7 (4.6)</td>
<td>32.7 (4.3)</td>
</tr>
<tr>
<td>STAI-score screening (T0)</td>
<td>49.8 (8.0)</td>
<td>49.2 (7.5)</td>
</tr>
<tr>
<td>EPDS-score screening (T0)</td>
<td>10.2 (4.1)</td>
<td>10.1 (4.1)</td>
</tr>
<tr>
<td>Zscore Distress-score screening (T0)</td>
<td>0 (0.9)</td>
<td>0 (0.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N (%)</th>
<th>N (%)</th>
</tr>
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<tbody>
<tr>
<td>Multipara</td>
<td>63 (51.2)</td>
</tr>
</tbody>
</table>

**Socioeconomic status**

| Low                            | 42 (34.1)                | 45 (36.6)                |
| Moderate                       | 32 (26.0)                | 30 (24.4)                |
| High                           | 49 (39.8)                | 48 (39.0)                |

**Present diagnosis (DSM-IV)**

| Anxiety                       | 50 (40.7)                | 35 (28.5)                |
| Depression                    | 13 (10.6)                | 8 (6.5)                  |
| Anxiety and depression        | 10 (8.1)                 | 15 (12.2)                |

**Previous diagnosis (DSM-IV)**

| Anxiety                       | 13 (10.6)                | 6 (4.9)                  |
| Depression                    | 51 (41.5)                | 54 (43.9)                |
| Anxiety and depression        | 8 (6.5)                  | 13 (10.6)                |

STAI= State Trait Anxiety Inventory
EPDS= Edinburgh Postnatal Depression Score
DSM-IV= Diagnostic and Statistical Manual of Mental Disorders 4th edition
Table 3 presents healthcare consumption among both groups. Participants in the CBT group paid more visits to a medical officer compared to participants in the CAU group (p=0.04). One participant in each group reported the use of antidepressants during pregnancy. Considering the high rate of missing data (52%), these findings should be interpreted as exploratory in nature.

**Table 3:** Healthcare consumption during pregnancy: week 20 estimated gestational age until delivery (complete case analyses).

<table>
<thead>
<tr>
<th></th>
<th>Intervention (N=123)</th>
<th>Care as usual (N=123)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (SD) number of visits</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Practitioner</td>
<td>0.7 (1.1)</td>
<td>0.5 (1.0)</td>
</tr>
<tr>
<td>Midwife/gynecologist</td>
<td>8.6 (7.0)</td>
<td>9.0 (5.5)</td>
</tr>
<tr>
<td>Medical officer</td>
<td>0.3 (0.7)</td>
<td>0.1 (0.6)</td>
</tr>
<tr>
<td>Psychological support</td>
<td>3.9 (5.3)</td>
<td>0.5 (1.3)</td>
</tr>
<tr>
<td><strong>Use of antidepressants/anxiolytics N (%)</strong></td>
<td>1 (0.8)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td><strong>Data missing, N (%)</strong></td>
<td>59 (48.0)</td>
<td>69 (56.1)</td>
</tr>
</tbody>
</table>

**Therapy integrity**
All psychologists successfully finished the specific training for the treatment under study. Four supervision sessions have been organized for which all psychologists were invited for participation. All psychologists except four attended at least one session while treating a participant. Content of the discussions in the supervision sessions did not give rise to believe that treatment was given otherwise than intended. Allocation of participants receiving CBT was based on location and availability of the psychologists.

**Intention to treat analyses**
Table 4 and 5 show the mean STAI and EPDS scores at 36 weeks EGA and the mean differences between the CBT and CAU group. Compared to STAI and EPDS scores at screening (T0), both the CBT and CAU group showed a decrease in anxiety and depressive symptoms (p<0.001 and p<0.05, respectively). Participants in the CBT group showed slightly higher STAI and EPDS scores compared to the CAU group but differences were not statistically significant. After adjustment for imbalance between groups, i.e. present DSM-IV diagnosis, STAI score was slightly higher in the CAU group (β=0.6, 95% CI -3.7;2.6) and the mean difference in EPDS score attenuated (β=0.1, 95% CI -1.1;1.2). Furthermore, no differences in the distress score...
were observed between groups (table 6). After multiple imputation, slightly lower STAI scores were observed in the CBT group and estimates attenuated somewhat for EPDS scores at 36 weeks EGA, when compared to estimates from complete case analyses (table 4 to 6).

**Table 4:** Anxiety symptom scores at 36 weeks EGA. Values are differences in means (95% CI) unless stated otherwise.

<table>
<thead>
<tr>
<th></th>
<th>Intervention (N=123)</th>
<th>Care as usual (N=123)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STAI score, mean (SD)</strong></td>
<td>42.7 (10.2)</td>
<td>42.0 (12.5)</td>
</tr>
<tr>
<td><strong>Intention to treat (N=188)</strong></td>
<td>0.5 (-2.7, 3.7)</td>
<td>-0.4 (3.5, 2.7)</td>
</tr>
<tr>
<td><strong>MICE</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Subgroups</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety and/or depressive disorder (N=103)</td>
<td>-0.8 (-5.4, 3.8)</td>
<td></td>
</tr>
<tr>
<td>Anxiety diagnosis (N=69)</td>
<td>0.8 (-4.2, 5.9)</td>
<td></td>
</tr>
<tr>
<td>Comorbid diagnosis (N=17)</td>
<td>-6.3 (-17.6, 5.1)</td>
<td></td>
</tr>
<tr>
<td>Above cut-off STAI (N=177)</td>
<td>0.6 (-2.8, 3.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Per protocol† (N=53)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MICE</td>
<td>-1.5 (-5.3, 2.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Data missing, N (%)</strong></td>
<td>32 (26.0)</td>
<td>26 (21.1)</td>
</tr>
</tbody>
</table>

Differences between groups are studied using linear regression and are adjusted for STAI scores at T0, parity and SES.
† adjusted for present DSM-IV diagnosis according to SCID-II
MICE= multiple imputation by chained equations
STAI= State Trait Anxiety Inventory, used cut-off value >42

**Per protocol analyses**
Sixty-one participants received 6 or more sessions and were thus included in the per protocol analyses. Groups were balanced for the variables age, parity, and SES, but not for present diagnosis (p=0.01), therefore analyses were adjusted for this latter variable. Participants who completed 6 or more sessions showed lower STAI, EPDS and distress scores at 36 weeks EGA compared to women in the CAU group, but there was no evidence of a difference between groups. Estimates after multiple imputation attenuated somewhat when compared to the estimates from complete case analyses (table 4 to 6).
Subgroup analyses

The number of participants in the subgroups was low, therefore results from these analyses need to be interpreted as exploratory. Compared to the overall effectiveness estimates, the analyses in subgroups of SES, parity and scoring above cut-off value of STAI or EPDS showed no substantial differences in effect size. In the subgroup of participants with a present comorbid DSM-IV diagnosis (n=17), participants in the CBT group showed notably lower STAI scores at 36 weeks EGA, compared to the CAU group ($\beta$=-6.3, 95%CI -17.6;5.1), although the interaction term was not statistically significant (p=0.16). In the imputed analyses this finding attenuated ($\beta$=-1.7, 95%CI -13.9;10.4). Other subgroup analyses on present DSM-IV diagnosis did not show substantial differences in effect size (table 4 to 6).

Table 5: Depressive symptom scores at 36 weeks EGA. Values are differences in means (95% CI) unless stated otherwise.

<table>
<thead>
<tr>
<th></th>
<th>Intervention (N=123)</th>
<th>Care as usual (N=123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPDS score, mean (SD)</td>
<td>9.3 (4.4)</td>
<td>8.6 (4.7)</td>
</tr>
<tr>
<td>Intention to treat (N=183)</td>
<td>0.5 (0.6;1.7)</td>
<td>0.1 (-1.0;1.2)</td>
</tr>
<tr>
<td>MICE</td>
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<tr>
<td>Subgroups</td>
<td></td>
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<tr>
<td>Anxiety and/or depressive diagnosis (N=99)</td>
<td>0.3 (-1.5;2.1)</td>
<td></td>
</tr>
<tr>
<td>Depression diagnosis (N=17)</td>
<td>1.9 (-5.6;9.3)</td>
<td></td>
</tr>
<tr>
<td>Comorbid diagnosis (N=17)</td>
<td>-1.0 (-6.7;4.7)</td>
<td></td>
</tr>
<tr>
<td>Above cut-off EPDS (N=63)</td>
<td>0.1 (-2.3;2.5)</td>
<td></td>
</tr>
<tr>
<td>Per protocol† (N=53)</td>
<td>-0.2 (-1.7;1.2)</td>
<td>0 (-1.2;1.3)</td>
</tr>
<tr>
<td>MICE†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data missing, N (%)</td>
<td>33 (26.8)</td>
<td>30 (24.4)</td>
</tr>
</tbody>
</table>

Differences between groups are studied using linear regression and are adjusted for EPDS scores at T0, parity and SES.
† adjusted for present diagnosis DSM-IV according to SCID-II
MICE= multiple imputation by chained equations
EPDS= Edinburgh Postnatal Depression Score, used cut-off value ≥12
Comparison with sample that declined to participate
We compared participants in the PROMISES trial with women who declined participation, but were still included in the PAD study, on the variables anxiety and depression at time of screening (T0) and at 36 weeks EGA. We found that participants in the PROMISES trial had higher levels of anxiety and depression at T0 (p<0.01), compared to women who declined participation. Furthermore, in the group of women who declined participation, both anxiety and depressive symptoms decreased by 36 weeks EGA. For depressive symptoms, this decrease was even higher when compared to the PROMISES participants (p=0.01).

Discussion
The present study investigated the effect of CBT compared to CAU, in pregnant women presenting with at least moderate levels of anxiety and/or depressive symptoms during the first trimester. Although levels of anxiety and depressive symptoms decreased during pregnancy, we found no evidence that receiving CBT reduced anxiety and depressive symptoms during pregnancy more than CAU.

Table 6: Distress scores at 36 weeks EGA. Values are differences in standardized means (95% CI), unless stated otherwise.

<table>
<thead>
<tr>
<th></th>
<th>Intervention (N=123)</th>
<th>Care as usual (N=123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z score distress score, mean (SD)</td>
<td>0 (0.8)</td>
<td>0 (1.1)</td>
</tr>
<tr>
<td>Intention to treat (N=180)</td>
<td>0.1 (-0.2;0.4)</td>
<td></td>
</tr>
<tr>
<td>MICE</td>
<td>0 (-0.2;0.2)</td>
<td></td>
</tr>
<tr>
<td>Subgroups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety and/or depression diagnosis (N=99)</td>
<td>0 (-0.4;0.4)</td>
<td></td>
</tr>
<tr>
<td>Per protocol† (N=53)</td>
<td>-0.1 (-0.4;0.2)</td>
<td></td>
</tr>
<tr>
<td>MICE†</td>
<td>0 (-0.3;0.2)</td>
<td></td>
</tr>
<tr>
<td>Data missing, N (%)</td>
<td>34 (27.6)</td>
<td>32 (26.0)</td>
</tr>
</tbody>
</table>

Differences between groups are studied using linear regression and are adjusted for distress scores at T0, parity and SES.
† adjusted for present DSM-IV diagnosis according to SCID-II
MICE= multiple imputation by chained equations
Comparison with other studies and explanation of findings

Our results are surprising in that there is ample evidence that CBT is effective in treating anxiety and depression outside pregnancy. Nevertheless, our findings are in line with a study by Austin and colleagues (n=277) that also included a sample of women with subclinical symptoms or anxiety and depressive disorders. The authors found no beneficial effect of CBT on both anxiety and depressive symptoms during pregnancy [18]. They suggested that the control condition, i.e. an information booklet including strategies to prevent and handle postnatal distress, can be considered as an equal form of psychosocial support [18]. In contrast, the study by Le et al (n=217) found a significant reduction in depressive symptoms as a result of CBT among pregnant women with subclinical symptoms. Yet, this study included a sample of Latina women, and the authors admit that findings are limited in generalizability. Burns and colleagues conducted a small pilot study (n=36) including a home-based CBT intervention and also found a decrease in depressive symptoms as a result of CBT, although this decrease was not statistical significant [19]. In this study among pregnant women with a depressive disorder, EPDS baseline scores were relatively high (median: 16-20) compared to the scores in our sample (mean: 10), thus providing more room for improvement. Furthermore, there is evidence indicating that interventions in a home setting may be especially valuable due to an active involvement with mothers [30]. Moreover, women participating in this study indicated at time of screening that they wanted help themselves, that may have made them more motivated to handle their depressive symptoms. It appears that patient engagement in CBT is a predictor of greater reductions in both anxiety and depressive symptoms [31].

Interestingly, we found an overall decrease in both anxiety and depressive symptoms, which is in line with previous studies [19,20,32]. There may be several explanations for this overall decrease of symptoms. First, as the study population is selected based on a high score of anxiety and/or depressive symptoms, regression to the mean may have contributed to the overall decrease of symptoms during pregnancy. Second, anxiety and depressive symptoms may be confused with or be the result of other symptoms common in pregnancy, such as hormonal changes or sleep deprivation. Hormonal changes are highest in first trimester, which may partly explain why anxiety and depressive symptoms decrease during pregnancy [33]. Third, it may be that overall participation in the study (i.e. filling out questionnaires and follow-up) is an intervention per se, having the potential to improve levels of anxiety and depression in both groups [34]. As for the lack of a beneficial effect of CBT in the present study, it should be stressed that our sample was heterogeneous in the sense that we included women with anxiety and depressive disorders (53% of our sample), and the other half consisted of women...
with subclinical symptoms. Also, overall the mean level of anxiety and depressive symptoms was relatively low. It may be that for the group of women presenting with relatively low levels of anxiety and depressive symptoms, the level of these symptoms cannot decrease much further. Consequently, a beneficial effect of CBT cannot be demonstrated when compared to care as usual. Another explanation of observing no beneficial effect of CBT may be found in underlying biological mechanisms during pregnancy. There is convincing evidence that the HPA-axis functions differently during pregnancy. Cortisol levels increase during pregnancy and the HPA-axis responsiveness to stress decreases (see Duthie & Reynolds for an overview [35]). These changes in the physiological stress system may be reflected in a diminished appraisal of stress [36], and possibly explain why decreases in reported anxiety and depressive symptoms are reported. Concurrently, women may be less susceptible to interventions that target anxiety and depression during pregnancy. Finally, it may be argued that we were not able to adequately measure the effect of CBT using self-report measures for anxiety and depression. In a previous RCT study (n=61) by Richter et al., the effect of CBT during pregnancy was studied on perceived stress and salivary cortisol levels [37]. Compared to the control group, women in the intervention group showed a decrease in diurnal cortisol but not in perceived stress. There is more evidence that objective measures, such as cortisol measures, may not correlate with self-report questionnaires [38,39]. Thus, CBT may, despite our findings, still have reduced the activity of the maternal stress system. Obstetric and child outcomes of the present study may shed light on this.

Strengths and limitations
Some strengths of this study should be mentioned. This study is one of the few RCT studies investigating the effect of CBT on treatment of anxiety and depression during pregnancy. We included a population-based sample that may allow us to generalize our findings to a larger Dutch pregnant population presenting with anxiety and/or depressive symptoms, as opposed to if we would have recruited a sample from clinical settings only. Furthermore, we used a manualized CBT intervention utilized by trained CBT psychologists to increase reliability. Limitations include the low number of participants in subgroups. As a result, subgroup analyses were underpowered and we were unable to investigate the effect of CBT among participants with various DSM-IV anxiety, depressive, and comorbid disorders (35%, 9%, and 10% of the study sample, respectively). Another limitation comprises the low participation rate of women who were invited to participate in the trial. Only 30% of the participants in the PAD study presenting with at least moderate anxiety and/or depressive symptoms also agreed to participate in our intervention trial. Our response rate was somewhat low when compared to that of other similar studies that included pregnant women who were not active help-seekers.
The study of Austin et al., that included pregnant women with subclinical symptoms or anxiety and depressive disorders, showed a response rate 39% [18]. The study by Le et al. that included women with subclinical symptoms or a previous depression had an even higher response rate of 70% [20]. Also the response rate of a non-CBT RCT, i.e. self-help workbook and telephone support, that was aimed at reducing anxiety and depressive symptoms among pregnant women with and without symptoms was higher than ours, that is 61% [40]. At baseline and 36 weeks of gestation we had some missing data, but the sensitivity analyses suggested that missing data probably did not majorly affect our findings. However, the TIC-P questionnaire on healthcare consumption showed a substantial amount of missing data, which clearly is a limitation. Moreover, this questionnaire was assessed approximately one year after pregnancy, and recall bias may be present. Finally, we were unable to measure cortisol levels in the present study. Such physiological stress measure could have provided us with more information about the lack of a beneficial effect of CBT during pregnancy that we observed.

**Clinical relevance**

The clinical significance of treating anxiety and depression symptoms during pregnancy using CBT remains unclear. Our study was unable to detect an effect size of 0.36 or above in pregnant women who were not actively help-seeking. We have to be cautious to conclude that CBT is not effective during pregnancy as we could not properly study the effect in women with DSM-IV disorders. We observed for instance a favorable mean STAI score in participants with a comorbid disorder as a result of the intervention, but cannot draw conclusions due to the small sample size of this exploratory subgroup analysis (n=17). Nevertheless, post-hoc analyses show that the mean level of anxiety at screening (T0) is higher for participants with a comorbid diagnosis (STAI score 54.1) when compared to participants with a depression (51.8) or anxiety diagnosis (49.5), although not statistically significant. Consequently, there may be more room for improvement among participants with a comorbid diagnosis. Moreover, CBT sessions provided in our study continued after pregnancy, and CBT may show a beneficial effect once treatment is completed. Follow-up assessments after pregnancy may provide more information on this.

Treatment acceptability is important to consider given the relatively low response rate in our study. Following treatment during pregnancy may compete with other factors such as work, care of other children, and pregnancy-related issues (e.g. fatigue). Furthermore, almost half of our study sample consisted of participants with subclinical anxiety and/or depressive symptoms. It may be suggested that for this group of women, at risk for developing a disorder, minimal interventions (e.g. psycho-education, a general practitioner or midwife
symptom-focused consult) may be sufficient to treat these symptoms.

Despite the lack of clear evidence, current NICE guidelines suggest CBT as an appropriate treatment option for both anxiety and depression following the screening for anxiety and depressive symptoms [17]. However, it has been suggested that screening in itself should be part of a process including access to effective treatment [41]. As such, our data suggests that it seems not solid to introduce universal screening for all pregnant women yet. More evidence needs to be gained for which specific groups screening and treatment may be beneficial during pregnancy, including pregnant women with anxiety and/or depressive disorders.

**Conclusion and future directions**

This study found no evidence for a beneficial effect of CBT treatment for anxiety and depressive symptoms during pregnancy, when compared to CAU. We propose that the lack of a beneficial effect of CBT during pregnancy may be due to our heterogeneous sample including pregnant women with subclinical symptoms and DSM-IV anxiety and/or depressive disorders. RCT studies are needed on the treatment of anxiety and depressive symptoms during pregnancy, especially focused on pregnant women with anxiety and/or depressive disorders, that also study treatment acceptability. Finally, future studies could explore potential underlying biological mechanisms and the effect of CBT during pregnancy on the offspring.
Reference list


