Unhealthy behaviors during pregnancy: who continues to smoke and consume alcohol, and is treatment of anxiety and depressive symptoms effective?
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CHAPTER 7

General discussion
The aim of this thesis was twofold. First, we investigated selected determinants of continued smoking and continued alcohol consumption during pregnancy, and postpartum smoking relapse using a bio-behavioral model of smoking cessation and relapse [1,2]. Second, we studied the effectiveness of treating anxiety and depressive symptoms during pregnancy using cognitive behavioral therapy. The following hypotheses were tested:

1. Increased perceived severity of stressful events during pregnancy is associated with continued smoking and continued alcohol consumption (chapter 2).
2. Higher levels of neuroticism and extraversion, and lower levels of conscientiousness, agreeableness and openness to experience are associated with continued smoking and continued alcohol consumption during pregnancy (chapter 3).
3. The experience of adverse pregnancy and delivery outcomes is associated with postpartum smoking relapse (chapter 4).
4. Treatment of anxiety and depressive symptoms using cognitive behavioral therapy during pregnancy leads to a (stronger) reduction of these symptoms, as compared to care as usual (chapter 6).

After listing our main findings we will discuss some methodological issues that need to be considered before interpreting our findings and discussing the clinical implications of our results. Finally, we will provide recommendations for future research.

Main findings

Chapter 2 and 3 investigate correlates of continued smoking and continued alcohol consumption. Our first hypothesis investigated in chapter 2 was confirmed for continued alcohol consumption only. We found continued alcohol consumption to be associated with the severity of the following categories of stressful events: ‘conflict with loved ones’, ‘crime related’, ‘pregnancy-specific’, and the total including all events. These associations could not be explained by anxiety or depressive symptoms during pregnancy. No associations were found between the severity of stressful events and continued smoking. In addition, we did not find associations between the severity of stressful events and the amount of cigarettes or alcohol consumed among continued users. Also regarding hypothesis 2 we found evidence for continued alcohol consumption only (chapter 3). More specifically, we found two personality traits to be associated with continued alcohol consumption: higher levels of openness to experience and lower levels of conscientiousness. The association between conscientiousness and continued alcohol consumption was partly explained by both anxiety and depressive symptoms during pregnancy. No associations were found between personality traits and...
continued smoking on the one hand, and the amount of cigarettes and alcohol consumed among continued users on the other hand.

In line with the third hypothesis studied in chapter 4, our results showed that the experience of at least one adverse pregnancy and delivery outcome (APDO) doubled the odds of postpartum smoking relapse. Also transfer from a planned home-delivery to hospital delivery was associated with postpartum smoking relapse but not independent from APDO. Depression symptoms after pregnancy could not explain these associations. Moreover, we found an independent association between adverse neonatal outcomes and postpartum smoking relapse. What is more, with every APDO that applied, the odds of smoking relapse increased.

Hypothesis 4 could not be confirmed (chapter 6). Our results showed that anxiety and depressive symptoms decrease during pregnancy. However, we observed no beneficial effect of cognitive behavioral therapy when compared to received care as usual. Stratified analyses according to parity, socioeconomic status, severity of anxiety and depressive symptoms, and DSM-IV anxiety or depression diagnosis demonstrated no statistical significant results.

**Methodological considerations**

*Dealing with missing data*

The occurrence of missing data is an issue in almost all empirical studies and therefore also in both the PAD and PROMISES study. Traditionally, investigators perform their analyses on those cases that have complete data, i.e. complete case analyses. When using for example regression techniques, software packages like SPSS typically remove all cases that have at least one missing value on the variables under study. However, the use of complete case analyses presents the problem of possibly introducing a selection bias as well as a decrease in statistical power. A selection bias can be described as ‘an error due to systematic differences in characteristics between those that are selected to study and those who are not’ [3]. It may be that people who fill out the questionnaires differ from those who do not with respect to the variables under study. To demonstrate this, we compared missingness of the personality traits for the two samples described in chapter 3: the sample of continued/quit smoking and the sample of continued/quit alcohol consumption. We found that women who continued/quit smoking had a higher percentage missing data on the questionnaire measuring personality compared to women who continued/quit alcohol consumption (p=0.03). These findings may suggest that women who continue or quit smoking are less patient to complete the questionnaire. In other words; personality itself may be associated with missingness. This
implies that when having solely relied on complete case analyses we might have introduced a selection bias regarding data on personality. A kind of selection bias common in randomized controlled trials is attrition bias which is caused by the drop-out or non-response of respondents during the course of the trial. It may be that women who dropped out or did not complete the measurements had a different outcome, i.e. the intervention was not working for them. If so, the effect of the intervention may have been overestimated. As we did not find an effect, we do not expect that a potential attrition bias influenced our findings.

Loss of statistical power may be another consequence of the use of complete case analyses. Statistical power is defined as the probability that a statistical test will reject the null-hypothesis when the alternative hypothesis is true, i.e. finding a result that is actually present in the population. Statistical power is determined by: the effect size, the level of statistical significance (α-level), and the sample size. So, if cases with missing data are removed during the analysis and complete cases are analyzed only, the sample size will decrease. As a result, statistical power will decrease as well.

Missing data therefore need to be dealt with and it is recommended to think about reasons for the presence of missing data [4]. Participants in the PAD study did not receive any financial remuneration but did have to invest a substantial amount of time in filling out the questionnaires which continued until six months postpartum. So, it is probably not surprising to find missing data in this study. The PROMISES study did offer a small remuneration for participants, but this may have not been satisfactory considering the required time investment. Besides, women with anxiety and depression symptoms may experience their symptoms as barriers to fully participate in the study.

There are several methods for dealing with missing data, including mean imputation, regression imputation, hot-deck imputation, maximum likelihood estimation, and multiple imputation. We choose multiple imputation as a proper method that has shown to be superior when compared to single imputation methods [4]. Multiple imputation includes the uncertainty of the estimated values and has shown to produce satisfactory results even when high percentages (i.e. 50%) of missing data on the variables under study are present [4-6]. Multiple imputation using the multivariate imputation by chained equations algorithm is a statistical technique that consists of a three step procedure [4]:
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- Simulation of several complete datasets where imputed values are drawn from an underlying distribution that is specifically modeled for each variable with missing values
- Separate analysis of each dataset
- Pooling of all analyses using Rubin’s rules [7]

The number of datasets that is generated depends on the fraction of missing data. Based on simulation studies it has been suggested that for a fraction of 0.1-0.2 three to five complete datasets are sufficient where for a fraction of 0.3 10-20 complete datasets are needed [6,7]. For the analyses of this thesis we choose to impute 20 datasets at all times.

The use of multiple imputation relies on the assumption that the data are missing at random (MAR) or are missing completely at random (MCAR) [7]. Data being MAR means that the probability of missing data is related to the values of other variables in the dataset. In the case of MCAR data are missing for reasons that are unrelated to the data present. Another pattern of missingness is data being missing not at random (MNAR), which means that missing data depend on the values of unobserved variables. This is problematic, as we do not know these values. If the data are indeed MAR, multiple imputation provides unbiased results [8], whereas single imputation techniques would not. In this thesis we explored the pattern of missingness by running a multivariable logistic regression in which missingness (yes/no) of the variables of main interest were treated as dependent variables [9,10]. Variables that may explain missingness were included as independent variables. If missingness is well predicted, data cannot be MCAR and are thus more likely to be MAR. However, this analysis cannot prove that the data are MAR, as it cannot exclude the possibility that data are MNAR. Therefore, as a sensitivity analysis we performed additional complete case analyses in chapters 2, 3 and 4 to estimate the robustness of our results.

Further threats to internal validity

Besides the occurrence of missing data we need to consider other potential sources of bias and the possibility of confounders.

Selection bias has shortly been mentioned with respect to dealing with missing data. It became apparent that by ignoring missing data and only analyzing complete cases, selection bias may be introduced. However, selection bias may have been present in the PAD and PROMISES study already. We recruited pregnant women mainly via midwifery practices and obstetric and gynecology departments of hospitals. Unfortunately, we do not know how many women were actually invited by midwives and gynecologists. Yet, based on a survey that was conducted among participating midwives it became evident that there was no reason to believe that
selective inviting had occurred. Further, women that actually choose to participate may differ from those who did not. It is well-known that individuals with a higher level of education are more likely to participate in research. This was confirmed by our data as the samples that were investigated consisted of relatively highly educated women. Around 60% of women participating in our study is highly educated, whereas in The Netherlands this percentage is around 30 [11].

Smoking and alcohol consumption status were measured using self-report questionnaires. Therefore, responses may inevitably be subject to social desirable reporting, possibly leading to misclassification (underreporting). Regarding our findings in chapter 2 and 4, we assume that underreporting did not depend on the events that were experienced and misclassification is most likely non-differential. As a result, misclassification is unlikely to have influenced the associations under study [12]. Underreporting of smoking and alcohol consumption status in chapter 3 may be associated with personality traits and misclassification is therefore most likely differential. This is clearly a limitation and may have biased the results. On the other hand, it has been shown that, for example, self-report of smoking during pregnancy is rather accurate [13].

Regarding the subject of confounding, we chose to adjust analyses in chapter 2, 3 and 4 based on previous evidence. Factors associated with both the predictor and outcome variable, and not being on the causal pathway between predictor and outcome, were included as confounders. Residual confounding may remain after adjustment due to measurement error (imprecision) in confounders. Furthermore, unmeasured confounding is likely to be present as well. There may be other, unknown factors that provide an alternative explanation for the observed associations. In contrast to the observational PAD study, the influence of confounding is less likely to be an issue in the PROMISES randomized controlled trial. Due to randomization it can be assumed that both the intervention and control group do not differ more than expected by chance. In other words, the groups are most likely interchangeable at baseline.

Generalizability
The PAD study is a population-based study; pregnant women attending primary and secondary care throughout The Netherlands were included. As a result the sample under study may be representative for the pregnant population in The Netherlands, keeping the aforementioned potential selection bias in mind. As highly educated women were overrepresented in our study sample, it is unclear whether our findings can be generalized to low-educated women.
However, in chapter 3 we studied the moderating effect of level of education for the association of personality with continued smoking and alcohol consumption, and found no moderating effect. The PAD study sample was used to screen pregnant women on anxiety and depressive symptoms as well. Thus, participants in the PROMISES study may be considered representative for pregnant women with anxiety and depressive symptoms in The Netherlands, although these participants had higher levels of anxiety and depression than women who refused participation. So, the results presented in this thesis can most likely be generalized to the Dutch pregnant population at least to some extent.

Comparing our findings with previous studies
When comparing our findings with those obtained in previous studies some issues arise regarding heterogeneity of reference groups, definitions of the study sample and measures used.

For chapter 2 and 3 we were interested in how women who continue smoking and alcohol consumption differ from those who manage to quit. Thus, in the analyses we compared continued users with quitters. Many studies available on smoking and alcohol consumption during pregnancy compare continued users with non-users. This may lead to differences in the associations found. Maxson et al. demonstrated differences in findings as a result of making several different comparisons [14]. The authors investigated the association between personality traits and continued smoking. When comparing continued smokers with non-smokers they found four traits (neuroticism, extraversion, agreeableness, and conscientiousness) to be significantly associated with continued smoking, whereas only one trait (agreeableness) was significantly associated with continued smoking when quitters were used as the reference group [14].

Furthermore, smoking and alcohol consumption during pregnancy, as well as postpartum smoking relapse, have been defined differently in studies. For example, smoking relapse may be defined as smoking again at 6 weeks, 3, 6 or 12 months after pregnancy [15]. Although common in research, the use of heterogeneous definitions of smoking and alcohol consumption status cause studies to not be completely comparable, thus this heterogeneity needs to be taken into account when comparing our findings with previous studies.

As for assessing anxiety and depressive symptoms, often standardized, validated questionnaires are used. This facilitates comparison with previous research as measures such as the State Trait Anxiety Inventory (STAI) and the Edinburgh Postnatal Depression Scale (EPDS)
are widely used. However, for the screening of patients different cut-off values may be used, and different eligibility criteria may be used before pregnant women enter the study. For example, studies may include pregnant women at risk for depression [16], whereas others include only women meeting criteria for a diagnosis [17].

**Determinants of continuation of smoking and alcohol consumption during pregnancy and postpartum smoking relapse**

Overall, our findings on continued smoking and alcohol consumption contribute to the limited literature available on continued versus quit use during pregnancy [14]. To our knowledge, we were the first to study the associations of personality and stressful events with continued versus quit alcohol consumption. The association between stressful events and continued versus quit smoking has not been investigated extensively including the perceived severity of events and different categories. Furthermore, our findings of postpartum smoking relapse contribute to previously identified determinants. To date, no prior study considered the association of APDO with postpartum smoking relapse before.

According to the proposed extended bio-behavioral model (figure 1) both stressful events (situational) and personality traits (intrapersonal) are directly associated with smoking and alcohol consumption outcomes. However, our findings suggest that these situational and intrapersonal factors are only directly associated with alcohol consumption outcomes during pregnancy and postpartum smoking outcomes. No direct associations were found for smoking outcomes during pregnancy. There may be other determinants that are more important with respect to continued smoking, these will be discussed further on. As for continued alcohol consumption and postpartum smoking relapse, we were able to further specify the model in figure 1. We identified categories of stressful events that are important for continued alcohol consumption during pregnancy and smoking relapse, as well as which personality traits may be relevant for continued alcohol consumption during pregnancy.
Next, we will further interpret our findings on continued smoking, continued alcohol consumption and postpartum smoking relapse separately, and make comparisons with previous research.

**Continuation of alcohol consumption during pregnancy**

The associations we found between severity of stressful events and continued alcohol consumption corroborate previous research. We explained our finding on events related to ‘conflict with loved ones’ by describing the importance of social support (chapter 2). Both during and outside pregnancy social support seems to be an important protective factor for handling psychological stress [18-21]. Furthermore, we found an association with severity of pregnancy-specific events. This finding confirms previous suggestions that pregnancy-specific stress should be distinguished from non-pregnancy-related sources of psychological stress [22-24].
Interestingly, the associations we found with personality traits seem different from those observed in the general population, except for conscientiousness. For example, higher levels of neuroticism and extraversion have previously been linked to alcohol consumption in general population studies [25-27]. Our findings suggest that these associations are not present during pregnancy with regard to continued use. We suggest that the discrepancies found support the idea that pregnancy may be a unique period to quit unhealthy behaviors because of different motivations [28,29]. Pregnant women are for example strongly motivated to change their behaviors for the health of the unborn child [28]. Moreover, during pregnancy unhealthy behaviors are actively discouraged by both health professionals and the social environment. Further, we found a positive association with openness to experience that has not been reported in the general population. In fact, general population studies commonly report no association between openness to experience and alcohol consumption [25,30]. In chapter 3 we explained that openness to experience has been associated with intellectual curiosity [31], and may therefore suggest that women are familiar with the risks of alcohol consumption during pregnancy. As alcohol related risks are not consistently reported for small to moderate amounts of alcohol [32], women may choose to continue alcohol consumption because they do not consider themselves at risk.

Besides stressful events and personality traits, other determinants (as depicted in figure 1) have been linked to continued alcohol consumption during pregnancy. Determinants that have consistently been reported are a higher age, higher pre-pregnancy consumption, higher income/social class, positive screen for alcohol problems, exposure to abuse/violence, and psychiatric symptoms including anxiety and depression [33]. In addition, ethnicity, unintended pregnancy, smoking during pregnancy, living in a large city, lower social support have been reported as determinants of alcohol consumption during pregnancy [34,35]. Except for age and anxiety/depressive symptoms, these previously identified determinants were not taken into account in this thesis. These other factors may determine continued alcohol consumption as well but were not included in the causal pathway of the associations we studied. Otherwise, these factors may influence the associations we found by acting as potential moderators. So for example, the associations we found may be different for women who used to be exposed to abuse or violence. In chapter 3 we studied the level of education as a potential moderator but found no moderating effect.

We explored whether the associations of stressful events and personality with continued alcohol consumption were (partially) mediated by anxiety or depressive symptoms (figure 2).
We found that both anxiety and depressive symptoms during pregnancy could explain the association between lower levels of conscientiousness and continued alcohol consumption only. We concluded that alcohol consumption may be a strategy to cope with feelings of negative affect, as has been suggested before [36,37]. We should note that a proper mediation analysis is needed to confirm our findings. Interestingly, it has been suggested that pregnancy-specific anxiety may be a more important predictor of alcohol consumption during pregnancy than depression or other forms of anxiety [38]. Measures assessing pregnancy-specific anxiety may be more relevant when investigating associations in the period of pregnancy as compared to measures assessing general anxiety such as the STAI [23]. Thus, it may be that the associations we found of stressful events and other personality traits with continued alcohol consumption can be explained by pregnancy-specific anxiety rather than general anxiety.

Continuation of smoking during pregnancy
Although hypothesized, we did not find an association of stressful events and personality traits with continued smoking. We proposed that there may be other determinants that are more important with regard to continued smoking during pregnancy. Factors that have consistently been associated with continued smoking during pregnancy include a low level of education, low income, amount of cigarette consumption, being multiparae, and having a partner that smokes [39]. These determinants fit the proposed model in figure 1. Although we did not find a direct association with stressful events during pregnancy, psychological stress symptoms (e.g. anxiety, depression) have been reported by several studies as correlates of continued smoking, but not consistently [14,40-42]. Methodological heterogeneity may explain inconsistencies in findings to some extent. However, it may be that different concepts of psychological stress should be distinguished. In line with the discussion to distinguish pregnancy-specific stress from general forms of stress, there is evidence that this distinction may be relevant for continued smoking during pregnancy as well [40]. Goedhart et al. found that high and low levels of pregnancy-specific anxiety rather than general anxiety and depression are associated with continued smoking during pregnancy [14]. Unfortunately, our study did not find an association between the perceived severity of pregnancy-specific stressful events and continued smoking.

Figure 2: potential pathway explanation by anxiety or depressive symptoms.

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Continuation of both alcohol consumption and smoking could not be studied properly in this thesis due to the low number of participants reporting both risky health behaviors.

**Postpartum smoking relapse**

The association we found between APDO and postpartum smoking relapse fits previous findings suggesting that psychological stress is an important determinant with regard to postpartum smoking relapse. For example, Polanska et al. found that three factors contributed to smoking relapse with a population attributable fraction of 84%: ‘type of quitting attempt (i.e. long-term or only for pregnancy), smoking perceived as a means of coping with stressful situations, and smoking environment at home’ [43]. In chapter 4 we hypothesized that because the experience of APDO and transfer may cause psychological stress, they may cause smoking relapse. Indeed, our findings seem to confirm this hypothesis, and the experience of APDO may increase the risk of smoking relapse. Additional qualitative data verifies that APDO are in fact acknowledged as being stressful:

"It appeared that my daughter has a serious heart disease. [We spent] three weeks in the hospital including the first surgery (...) lots of stress and worries, including a lack of sleep".

"[I developed] the HELLP syndrome which caused my child to be born four weeks in advance. I experienced this as very stressful and frightening".

Moreover, we explored whether psychological stress symptoms (i.e. depressive symptoms) may act as a potential mediator for the association between APDO and postpartum smoking relapse. Although depressive symptoms seem to be associated with postpartum smoking relapse [44], these symptoms do not seem to be a mediator for the association with APDO. Perceived stress symptoms as measured using the Perceived Stress Scale appear to be associated with postpartum smoking relapse as well [44], and may act as mediators rather than depressive symptoms. Furthermore, we investigated four categories of APDO and their associations with smoking relapse. Although the categories were relatively low in numbers, our findings suggested that adverse neonatal outcomes are the most relevant with respect to smoking relapse. Previous research shows that having a newborn in the neonatal intensive care unit, commonly as a result of adverse neonatal outcomes, may be an important factor in the development of psychological stress [45,46]. Besides the worries about the child, other factors such as a lack of sleep and the physical separation between mother and child may contribute to psychological stress symptoms [46,47]. Apart from APDO and other sources of psychological stress, there are further determinants that are associated with postpartum smoking relapse. These determinants include a lower level of education, a lower age, being
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Multiparae, dependency, not breastfeeding, and smoking behavior of the partner or other household members [15,48-50]. These determinants may influence postpartum smoking relapse as well. In addition, they may even act as potential moderators in the associations we studied.

Clinical implications

Current interventions promoting smoking and alcohol cessation during pregnancy seem effective [51-53]. It has been estimated that anti-smoking interventions were in general effective in helping women to stop smoking by 6% (absolute difference) [51]. Anti-smoking interventions may include motivational interviewing, offering incentives, nicotine replacement therapy, or medications. As for the cessation of alcohol consumption, particularly brief interventions such as motivational interviewing have been mentioned [53]. Based on our findings on continued smoking and alcohol consumption we concluded that increased insight in how stressful events and personality traits influence continued smoking and alcohol consumption can help health professionals to improve targeted lifestyle strategies. We identified women who may be (more) at risk for having difficulties in quitting risky health behaviors during pregnancy. Targeting healthy lifestyle strategies at these women may be most beneficial. Moreover, we proposed that support from the partner and family may be valuable, thus pregnant women should be assisted in acknowledging this source of support.

Ideally, smoking and alcohol consumption behavior is addressed before pregnancy. This may not always be feasible, for example in the case of an unplanned pregnancy. Quitting smoking and alcohol consumption in the first trimester of pregnancy may be just as beneficial though. For example, previous studies showed that women who quit smoking in the first trimester have a risk of adverse pregnancy outcomes comparable to that of non-smokers [54,55]. Health professionals like midwives, gynecologists or general practitioners may advise women to quit or cut back on their risky behaviors, or refer them to an intervention program. Unfortunately, it seems that health professionals are sometimes prevented from discussing risky health behaviors or do not provide consistent advice. Reported barriers include insufficient time, inadequate skills and knowledge, fear of damaging the relationship with patients [56,57]. Our findings may contribute to existing knowledge among health professionals.

Our findings on postpartum smoking relapse may aid in targeting anti-smoking strategies for continued abstinence, and identified a group of new mothers who are particularly at risk for smoking relapse. Women with APDO may need support to deal with psychological stress. Health professionals such as midwives, nurses or general practitioners may have a role to play...
here. These may discuss the psychological stress resulting from APDO or refer women. Anti-smoking strategies to prevent relapse may be implemented starting as soon as women and their newborn are in a hospital setting. For example, an early anti-smoking intervention in a neonatal intensive care unit has shown to be effective with respect to smoking abstinence and breastfeeding [58]. Yet, it should be noted that anti-smoking interventions that are successful during pregnancy may not be able to maintain cessation rates postpartum [59]. It has been suggested that for maintaining postpartum abstinence contextual factors (e.g. level of education, poor social support, psychopathology) should be addressed [59]. Furthermore, it has been recommended that partner smoking should be dealt with in interventions focusing on continued abstinence [15]. Although social support from the partner may act as an important protective determinant, the significance of this determinant decreases if the partner is smoking [15]. Increased risks of adverse health outcomes for the newborn and other household members as a result of secondhand smoking may be raised as a key argument to maintain smoking cessation by both parents [60]. On the other hand, it has been argued that intrinsic motivation needs to be build [28], which may be achieved using for example motivational interviewing techniques.

**Treatment of anxiety and depression during pregnancy**

Guidelines from the National Institute for Health and Clinical Excellence (NICE) provide recommendations for the prediction, detection and treatment of anxiety and depression during pregnancy [61]. Although based on limited evidence, cognitive behavioral therapy (CBT) has been suggested as a treatment option for handling anxiety and depression during pregnancy, also for women having symptoms that do not meet the threshold for an official diagnosis [61]. In The Netherlands the procedure to handle anxiety and depression symptoms during pregnancy may vary from watchful waiting to referral to treatment. Furthermore, the so-called ‘pop-pol’ may be present in hospitals. These are departments that are specialized in the care for pregnant women with mental problems or pregnant women that are at risk for developing mental problems. Health professionals from various disciplines (e.g. gynecology, psychiatry, pediatrics) cooperate to support women both during and after pregnancy. Women may be referred to a pop-pol by for example a midwife or a general practitioner. Although the number of the pop-pol’s is increasing, not every hospital has one yet. To date, around 30 pop-pol’s are active in The Netherlands [62].
Screening
All women participating in the PAD study were screened on anxiety and depressive symptoms. Screening for these symptoms is not standard practice in obstetric care in The Netherlands. According to NICE guidelines pregnant women should be asked two questions about their mental health at their first contact with primary care; 1) During the past month, have you often been bothered by feeling down, depressed or hopeless? and 2) During the past month, have you often been bothered by having little interest or pleasure in doing things? [61]. In Australia, current BeyondBlue guidelines recommend screening for every pregnant woman using the EPDS [63]. Taken together, it has been suggested that universal screening may be beneficial as well as acceptable for both pregnant women and health professionals [64]. It has been noted though that screening may be effective only if it is ‘part of an integrated, well-resourced process with clear pathways to diagnostic assessment and effective accessible treatment’ [64].

The effectiveness of CBT for treatment of anxiety and depressive symptoms during pregnancy
Although present guidelines suggest CBT as an appropriate treatment for handling anxiety and depression symptoms during pregnancy, we could not demonstrate a beneficial effect of CBT as compared to care as usual on the observed reduction of symptoms. Our study sample consisted of pregnant women that were not active help-seekers and consisted of a heterogeneous group including women with subclinical symptoms (47% of the sample) or anxiety and depressive disorders. In chapter 6 we propose several explanations for the decrease in symptoms as well as why CBT may not be effective during pregnancy when compared to CAU. We suggested that an important explanation of the lack of a beneficial effect of CBT during pregnancy comprises the heterogeneity of our study sample. Mean levels of anxiety and depressive symptoms were overall relatively low. It may be that for the group of women presenting with subclinical anxiety and depressive symptoms the level of these symptoms cannot decrease much further. Thus, there was not much room for improvement and for CBT to demonstrate a beneficial effect, when compared to CAU. As subgroup analyses were underpowered, we were unable to investigate the effect of CBT among participants with anxiety and depressive disorders. Nonetheless, results from the exploratory analyses among participants with a present comorbid diagnosis (N=17) suggested that this group may especially benefit from CBT, although this finding was not statistically significant. It should be noted that participants with a comorbid diagnosis had a relatively high mean STAI score at time of screening, when compared to participants with an anxiety or depressive disorder, and thus may have had more room for improvement.
Furthermore, there is evidence to believe that the biological stress response mechanism may function differently compared to the period outside pregnancy. During the course of pregnancy cortisol levels increase, and as a result the HPA-axis response diminishes (see Duthie & Reynolds et al. for an extensive description of changes in the physiological stress system during pregnancy [65]). This diminished response may protect the fetus from the adverse effects of psychological stress during pregnancy. Moreover, in line with findings on changes in the physiological stress system, it seems that the diminished response may be reflected in the appraisal of stress which decreases during pregnancy [66]. So, reporting of anxiety and depressive symptoms may decrease as well. It has been suggested that for women who do not show a decrease in HPA axis response, there is an increased risk of preterm delivery [67], and possibly other adverse birth outcomes. As for the ineffectiveness of CBT we observed, it may be speculated that, due to the changes in the physiological stress system, women are less susceptible to interventions targeted at anxiety and depressive symptoms during pregnancy.

An interesting point of discussion regarding the measurement of the effect of the intervention is the use of different measures. It may be that different ‘constructs’ of psychological stress can be distinguished. For example, besides general anxiety the intervention under study focuses on pregnancy-specific cognitions and attitudes, and may therefore most likely have targeted pregnancy-specific anxiety. Previous research suggests that pregnancy-specific anxiety should be regarded as a distinctive syndrome [23]. Thus, when assessing the beneficial effect of the intervention under study, it may be appropriate to measure pregnancy-specific anxiety as well, as the STAI measures this construct only to some extent [23]. Furthermore, there is evidence that self-report questionnaires and objective measures (e.g. cortisol measurement) do not necessarily correlate [68,69]. Unfortunately the PROMISES study was not able to include cortisol measurements as this was considered not ethical. So, we cannot exclude the possibility that the intervention had some effect on the biological stress response level. For example, Richter et al. conducted a randomized control trial and investigated the effects of cognitive behavioral group therapy on perceived stress and diurnal cortisol during pregnancy [70]. They found that the intervention brought about a decrease in cortisol levels, but not in perceived psychological stress, when compared to the control group [70]. If the CBT intervention studied in this thesis may indeed have affected the biological stress response, this may be reflected in obstetric, behavioral and emotional outcomes of the offspring.

Clinical implications
The clinical relevance of treating anxiety and depressive symptoms during pregnancy using CBT remains unclear. Results of available studies are inconsistent and our results add to this that,
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based on self-reported symptoms of anxiety and depression, CBT does not seem to have a beneficial effect during pregnancy when compared to CAU. However, we should be careful to conclude that CBT is not effective at all during pregnancy. To rule out whether CBT is indeed not helpful as applied during pregnancy, future studies should examine whether CBT could have a beneficial effect for pregnant women with anxiety and depressive disorders.

Only 30% of the participants in the PAD study presenting with at least moderate anxiety and/or depressive symptoms also agreed to participate in the PROMISES study. It should be noted that, because we screened for anxiety and depressive symptoms, women participating in our study did not necessarily show a need for help themselves, and, as a result, may be less motivated to handle their symptoms. Nevertheless, women presenting with increased symptoms are at risk for or already presenting with an anxiety or depressive disorder and therefore form a relevant group. Following recommendations (as provided by NICE and Beyondblue) that screening may be implemented as standard practice, it is important to know what treatment options are considered acceptable by pregnant women. To learn more about the acceptability of CBT during pregnancy amid a group of women with anxiety and/or depressive symptoms, a qualitative study [71] was performed among a small sample (n=17) of women who declined participation in the PROMISES study. Results of this qualitative study revealed that women declined participation in our trial for several reasons including practical difficulties, e.g. too time-consuming and having to care for other children. With respect to following CBT treatment during pregnancy women felt that: it was not the right time, they had insufficient energy, it would be too confronting, symptoms could be attributed to factors outside pregnancy, there was no need for therapy, and it was difficult to discuss symptoms especially during this period.

“This is a very busy period and I want to focus on my pregnancy. There is too much on my mind and I need to take care of things. That is why I think this is not the right time to follow therapy”.

“Honestly, I do not think following therapy right now would be a good idea. I think that it would make me more stressful instead of leading to a decrease in stress”.

“I think having to follow therapy is a bit exaggerated. I think I am tired because of all the hormones and cannot take as much that causes me to be easily irritated. This influences my mood and I am aware of that. However, I do not need therapy, I do not feel that bad”.

Furthermore, women reported motivations to decline CBT that were not necessarily related to the period of pregnancy. For example, women had therapy before and do not want to start new treatment, or they do not feel that their symptoms are that serious.
“To be in therapy with a psychologist, that is pretty heavy. I would think of people who are really depressed and cannot get up in the morning. I would not easily start therapy, then things should be really severe. (...) Everybody has got some of those days that are more difficult right? That is part of life, I do not need a psychologist for that”.

Clearly, there are various motivations for women not wanting to follow CBT during pregnancy. Based on these motivations and the lack of a beneficial effect of CBT as provided in the PROMISES study, we would not suggest this treatment as appropriate for treatment of anxiety and depressive symptoms among a group of women with subclinical symptoms without having a need for help themselves. Women presenting with subclinical symptoms may sufficiently benefit from minimal interventions, for instance including psycho-education, emotional or instrumental support and/or internet-based interventions. The effects of these minimal interventions among women with subclinical symptoms should be studied first.

Given that screening for anxiety and depressive symptoms should be part of a process including access to effective treatment, we do not recommend to implement 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.

Recommendations for future research

Regarding continued smoking and alcohol consumption during pregnancy, and postpartum smoking relapse, the results of this thesis have contributed to the knowledge about correlates of these risky health behaviors. More research is however needed to replicate these findings, preferably including large samples. Future studies could further investigate different categories of stressful events, including categories of APDO. The prevalence of events in categories was often low, thus our statistical power to detect associations may have been limited. Regarding the associations of personality traits and continued smoking and alcohol consumption, we suggest that future studies include the measurement of facets. The use of such fine-grained approach may provide more information as opposed to measuring dimensions of personality only. Furthermore, future research may focus on the underlying mechanisms of the associations we found. In this thesis we explored anxiety and depressive symptoms as mediators, but there may be other psychological stress related constructs, including
pregnancy-specific anxiety, that explain the associations we found. Moreover, more could be learned regarding potential moderators of the relationships with continued smoking and alcohol consumption, and postpartum smoking relapse. By revealing underlying mechanisms, future interventions may be able to better target at specific groups of pregnant women.

As for treatment of subclinical anxiety and depressive symptoms in pregnant women who are not active help-seekers, other forms of interventions should be explored and studied, including minimal interventions like psycho-education, support, and internet based interventions women can do from home. Moreover, it is important to further explore the acceptability of psychological treatment by pregnant women. It may be that pregnant women are more attracted to internet-based forms of treatment [72]. Also, the sample we studied was heterogeneous, including women with subclinical symptoms and disorders. Women with subclinical symptoms may find treatment by a psychologist a step too far. As subgroups in our study were underpowered we cannot rule out that CBT is effective for specific groups of pregnant women, including women with disorders. Future RCT studies may shed light on this. With respect to the measurement of the effectiveness of psychological therapy during pregnancy we suggest to include both pregnancy-specific measures as well as biological assessments such as measurement of cortisol.

The findings of this thesis add to the limited evidence on correlates of continued smoking and alcohol consumption, and the effectiveness of cognitive behavioral therapy during pregnancy. Relevant situational and intrapersonal determinants of continued smoking and alcohol consumption during pregnancy as well as postpartum smoking relapse were identified. Our results also raise new questions regarding the treatment of anxiety and depression during pregnancy in which we distinct pregnant women with subclinical symptoms from women with disorders. Overall, the findings presented in this thesis provide important implications for current practice and future research.
Reference list


