Unhealthy behaviors during pregnancy

Who continues to smoke and consume alcohol, and is treatment of anxiety and depressive symptoms effective?

Chantal GHM Beijers

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Table of contents

Chapter 1	General introduction and outline of the thesis	9
Chapter 2	Stressful events and continued smoking and continued alcohol consumption during mid-pregnancy	27
Chapter 3	Continued smoking and continued alcohol consumption during mid-pregnancy distinctively associated with personality	49
Chapter 4	Adverse pregnancy and delivery outcomes associated with postpartum smoking: a prospective cohort study	67
Chapter 5	Screening and treatment of anxiety and depressive symptoms during pregnancy	83
Chapter 6	Cognitive behavioral therapy for treatment of anxiety and depressive symptoms during pregnancy: a randomized controlled trial	103
Chapter 7	General discussion	125
Summary		149
Samenvatting		153
Dankwoord		159
About the author		161
SHARE theses		163

CHAPTER 1

General introduction

"I started smoking less [during pregnancy] but after several attempts I did not manage to quit. I feel very guilty about this and [I] am afraid that my smoking behavior causes things to go wrong".

"I worry about my smoking behavior. I want to smoke but I am also afraid to harm my unborn child. This is constantly crossing my mind".

These are quotes from participants of the Pregnancy Anxiety and Depression (PAD) study. Quitting smoking and alcohol consumption during pregnancy seems self-evident considering the adverse health effects these health behaviors may have on the unborn child. However, not all pregnant women succeed at quitting smoking and alcohol consumption once they know they are pregnant. How do women who do succeed at quitting smoking and alcohol consumption differ from those who do not? What about the period after childbirth; which factors may determine whether women relapse to smoking? And what is the role of anxiety and depressive symptoms with respect to these health behaviors? More importantly, can these symptoms during pregnancy be treated using psychological treatment such as cognitive behavioral therapy?

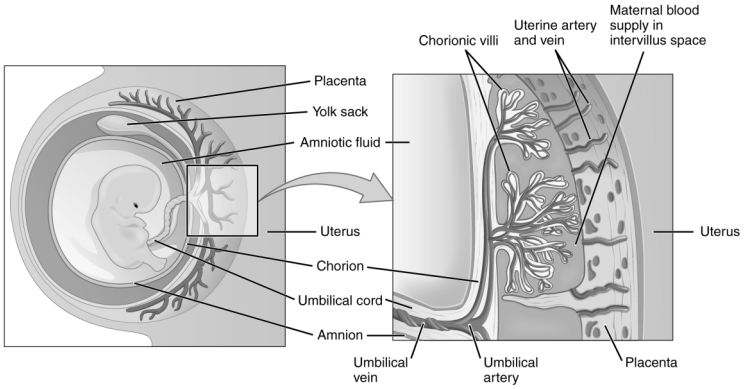
This thesis investigated smoking and alcohol consumption, and the treatment of anxiety and depressive symptoms in the period of pregnancy.

Smoking during pregnancy

Nicotine can pass the placental barrier causing several increased risks for both mother and child (figure 1). Indeed, smoking during pregnancy has been associated with numerous adverse pregnancy outcomes including miscarriage, stillbirth, low birth weight, preterm delivery, placental abruption, changes in brain development and a 150% increase in overall perinatal mortality [1-4]. Smoking during pregnancy has also been associated with problems in the long term such as obesity during adolescence, and behavioral problems and school performance in 5-11 year olds [5,6].

In The Netherlands between 26% and 33% of women of childbearing age smoke, and over the past few years smoking prevalence decreased with almost 10% [7]. Smoking prevalence during pregnancy is estimated to be 13% [8], meaning that between 39% and 50% continues to smoke when expecting. These figures are in accordance with smoking prevalence rates in other industrialized countries [8,9].

Figure 1: Chorionic villi contain the fetus's blood vessels and extend into the wall of the uturus. Maternal and fetal blood cells are not exchanged but separated by the placental barrier/membrane. The placental membrane is however permeable to substances such as nicotine and alcohol. As a result, these substances can enter the blood vessels in the villi, and the umbilical cord, working its way up to the fetus [10].



Alcohol consumption during pregnancy

Just like nicotine, alcohol freely passes the placental barrier and thereby increases the risk of adverse health outcomes for the unborn child. Alcohol consumption during pregnancy has been associated with reduced birth weight, preterm delivery, spontaneous abortion and the fetal alcohol syndrome [11-14]. The fetal alcohol syndrome is characterized by a pattern of abnormalities including growth retardation, and cognitive and behavioral dysfunction, and has been reported when consuming especially large amounts of alcohol frequently [15]. Studies investigating the effects of small to moderate amounts of alcohol show a lack in consensus regarding the negative effects of prenatal alcohol consumption [16]. Nevertheless, pregnant women in The Netherlands and other Western countries are typically advised to abstain completely from alcohol consumption throughout their pregnancy [17-19].

About 80% of women of childbearing age in The Netherlands consume alcohol [7]. Prenatal alcohol consumption prevalence rates for The Netherlands are estimated to vary between 35% and 50% [17], thus between 44% and 63% continues alcohol consumption during pregnancy. Other Western countries showed prenatal alcohol consumption estimates varying between 6% and 54% [20-25]. Large differences in the prevalence rates of prenatal alcohol consumption may reflect differences in drinking culture or attitudes towards prenatal alcohol consumption, but may also be due to the study method [26].

Determinants of continued smoking and alcohol consumption

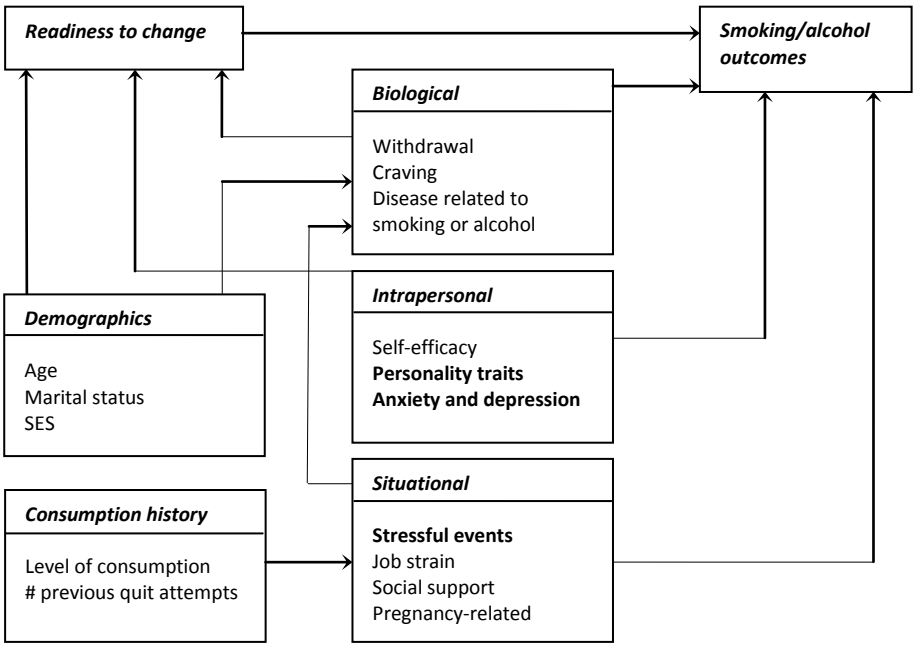
Considering the adverse effects and high prevalence rates of smoking and alcohol consumption during pregnancy, identification of determinants of continued use is important. Increased insight in determinants associated with continued use may support or add to existing healthy lifestyle strategies.

In the general population, several factors have been proposed to be associated with risky health behavior such as smoking and hazardous alcohol consumption. Level of education, level of dependence, social support, cohabiting with a substance using partner and age have all been associated with smoking and alcohol consumption status [27-30]. In addition, personality is considered an important factor with regard to risky health behaviors and may even predict health outcomes later in life [31,32]. For example, higher levels of the personality traits neuroticism and extraversion, and lower levels of conscientiousness have been reported among smokers and alcohol consumers [33-36]. Further, both smoking and alcohol consumption have been identified as a way of coping with psychological stress and negative affect like feelings of anxiety and depression [37-39]. It has been acknowledged that certain events in life can generate psychological stress [40]. Consequently, stressful events may be associated with smoking and alcohol consumption. McKee et al. concluded for example that stressful events were an important risk factor for tobacco use among women, especially events related to health and finance [41]. As for alcohol consumption, Tamers et al. found that women's alcohol consumption increased in the years following marriage or divorce [42].

In pregnancy, women are in general intrinsically motivated to change their health behaviors for the health of their unborn child [43]. In addition, women are extrinsically driven to quit risky health behaviors. For example, women have the desire to behave in a socially acceptable way and are influenced by other's opinions, especially those of friends and family [44]. Despite the motivation to quit smoking and alcohol consumption, there are numerous factors that increase the risk of continued smoking and alcohol consumption during pregnancy. Previous studies found that the level of education, being single, being multiparae, a higher age, exposure to violence or abuse, emotional symptoms (anxiety and/or depressive symptoms), personality traits, pre-pregnancy consumption levels, and high perceived psychological stress are associated with continued smoking and alcohol consumption [26,45,46]. It seems that these factors may be similar to factors reported in the general population at least to some extent.

The bio-behavioral model of smoking cessation and relapse [47], and its adapted version [48], links determinants of smoking outcome in the general population with readiness to change. We proposed to extend this model to alcohol outcomes and the period of pregnancy (figure 2). As a result, this model was used to derive hypotheses on determinants of continued smoking and alcohol consumption during pregnancy.

Figure 2: Factors proposed to be associated with continued smoking and alcohol consumption during and after pregnancy, based on the biobehavioral model of smoking cessation and relapse [47] and the adapted model by van Loon et al. [48].



In this thesis, we focused on intrapersonal and situational factors. Stressful events and personality traits in relation to continued smoking and alcohol consumption during pregnancy were further investigated. Moreover, symptoms of anxiety and depression during pregnancy were taken into account when studying the associations. In the investigation of continued

smoking and alcohol consumption, women who quit smoking or alcohol consumption after learning about their pregnancy were used as a reference group.

Stressful events

Stressful events constitute of a range of, often, adverse experiences. They can, for example, be work related (e.g. losing your job), family related (e.g. having a conflict with your parents), abuse related (e.g. domestic violence) or crime related (e.g. having your house burgled). As noted before, stressful events may be significant sources of psychological stress [40] and consequently, smoking and alcohol consumption may be used as coping mechanisms, also during pregnancy. In the present thesis we investigated stressful events that occurred during pregnancy, including pregnancy-specific stressful events. Pregnancy-specific events are experiences that are related to pregnancy itself, for example finding out about congenital anomalies or experiencing obstetric problems such as vaginal bleeding. So far, only one study investigated the association between general stressful events and continued smoking compared to quit smoking during pregnancy, and did not find an association [49]. This latter study did not take severity of stressful events into account, neither were different categories of events distinguished. To our knowledge, no study on the association between stressful events and continued alcohol consumption has been published to date.

Severity of stressful events can be assessed using three different approaches: a subjective, normative, and contextual approach including an interview to assess the context of the event that has occurred [50]. In this thesis we will focus on the first two approaches only. The subjective approach assesses the severity of the event solely experienced by the respondent. This approach may induce large variations in the appraisal of event severity as respondents may appraise the same event in a different way [51]. The normative approach deals with this response-tendency by assigning a priori a severity score to the events, for example by using the mean score provided by a large sample of individuals [50,52]. As a result, using the normative approach may increase comparability of severity scores between respondents.

Personality

Personality can be described as stable, individual differences in thinking, feeling, and behaving. Personality develops early in life and appears relatively stable throughout life [53]. Changes in personality have been associated with age and major life events (e.g. unemployment, death of a family member) [54]. Pregnancy may be considered as a major life event, although we are unaware of published studies that report on personality changes during pregnancy or as a result of being pregnant. However, previous research does show that personality may change

as a result of birth of a child (decrease in conscientiousness, increase in emotionality) [54,55]. So, it may be that personality remains stable during pregnancy until childbirth.

The well-known Five Factor Model describes personality as consisting of five domains or traits that describe individual differences between people [56]. Each trait can be further divided into six facets (table 1). As described before, in the general population personality traits are associated with smoking and alcohol consumption. Also during pregnancy personality may influence continued smoking and alcohol consumption. Surprisingly, only one study investigated personality traits and continued versus quit smoking, and found that low levels of agreeableness were associated with continued smoking [57]. No study investigating personality and continued versus quit alcohol consumption during pregnancy has been undertaken to date.

Table 1: Five personality traits and their facets

Neuroticism	Extraversion	Openness to experience	Conscientiousness	Agreeableness
Anxiety	Warmth	Fantasy	Competence	Trust
Anger	Gregariousness	Esthetics	Order	Straight-forwardness
Depression	Assertiveness	Feelings	Dutifulness	Altruism
Self-consciousness	Activity	Action	Achievement striving	Compliance
Impulsiveness	Excitement-seeking	Ideas	Self-discipline	Modesty
vulnerability	Positive emotions	Values	Deliberation	Tender-mindedness

Determinants of smoking relapse after childbirth

Although a substantial number of women quit smoking during pregnancy, abstinence does not seem to persist after pregnancy. In The Netherlands it is estimated that up to 62% of women who quit smoking during or before pregnancy start smoking again after childbirth [58]. In other industrialized countries it has also been shown that between 24% and 60% of women who quit smoking during pregnancy relapse after childbirth [59-61]. Preventing postpartum smoking relapse may be beneficial for both the health of the mother and that of other household members, including the newborn. Besides, preventing smoking relapse may be favorable for subsequent pregnancies [62]. Understanding of factors associated with postpartum smoking relapse is required to increase the percentage of abstainers and to add to existing anti-smoking strategies focused on continued abstinence.

To date, evidence suggests that smoking relapse after childbirth is associated with a younger age, a lower educational level, exposure to other smokers, pregnancy-related factors (e.g. unhappy with pregnancy, not breastfeeding, being multiparous), stressful events, depressive symptoms and psychological stress [59,60,63-66]. The depicted model in figure 2 may also be applicable for the period after pregnancy to some extent.

In this thesis we focused on situational factors, i.e. stressful events, and investigated the associations of adverse pregnancy and neonatal outcomes (APDO), as well as transfer from home-delivery to hospital-delivery with postpartum smoking relapse. We assumed that the experience of APDO and transfer to a hospital-delivery may cause psychological stress and consequently trigger smoking relapse. For example, it has been shown that an emergency cesarean section or instrumental delivery is experienced as more stressful compared to a normal vaginal delivery [67,68]. Moreover, these adverse pregnancy outcomes have even been associated with posttraumatic stress [69]. Other APDO such as preterm delivery, low birth weight, or preeclampsia also are stressful for the mother [70,71]. Postpartum depressive symptoms have shown to follow APDO, and may cause postpartum smoking relapse [64,72]. Therefore, we took these symptoms into account as a possible 'mechanistic explanation'. We included a range of APDO of the following categories: adverse antenatal conditions, adverse delivery outcomes, adverse afterbirth outcomes, and adverse neonatal outcomes. To date, the associations of APDO and transfer to a hospital-delivery with postpartum smoking relapse have not been studied before.

Anxiety and depressive symptoms

About 10-20% of all pregnant women experience anxiety and/or depressive symptoms and these symptoms may continue after pregnancy [73,74]. Symptoms of anxiety and depression during pregnancy may include feelings of hopelessness, guilt, a sense of worthlessness, and excessive worries whether or not related to pregnancy itself. Anxiety and depressive symptoms during pregnancy have been associated with a range of adverse maternal and child outcomes. For example, use of tobacco and alcohol, increased risk of suicide, adverse obstetric outcomes (e.g. low birth weight, prematurity), difficulties in mother-child attachment, and emotional and behavioral problems in the offspring have been reported [75,76].

Treatment of anxiety and depressive symptoms during pregnancy may include psychological or psychopharmacological treatment (e.g. antidepressants). Overall, women tend to prefer psychological treatment over antidepressants [77]. Moreover, safety of antidepressant use

during pregnancy remains unclear [78,79]. In the general population, cognitive behavioral therapy (CBT) seems effective in treating anxiety and depression with reported effect sizes of 0.4 or higher [80,81]. It is important to investigate whether this also holds for treatment of anxiety and depressive symptoms during pregnancy. So far, two randomized controlled trials have investigated the effect of CBT on depressive symptoms during pregnancy [82,83], and another randomized controlled trial included both anxiety and depressive symptoms during pregnancy [84]. The latter study did not found CBT to be effective while the other two studies did. However, one of these studies focused on a specific population (Latinas) [83] and the other study was a pilot study including a small number of participants (n=36), and was unable to show a statistical significant effect [82]. Clearly, more evidence is needed on the effectiveness of CBT during pregnancy. In this thesis the effectiveness of a CBT intervention was investigated among pregnant women with subclinical anxiety and depression symptoms and disorders. The intervention has been created specifically for pregnant anxious and depressed women. The treatment encompassed several optional modules with specific evidence-based CBT interventions focused on the treatment of anxiety disorders, depressive disorders, trauma and post traumatic stress disorder. In addition, the treatment was targeted at identifying and changing dysfunctional cognitions, coping styles and schemata (cognitive frameworks that help to organize and interpret information).

PAD study and PROMISES study

We used data from the Pregnancy Anxiety and Depression (PAD) and PRegnancy Outcomes after a Maternity Intervention for Stressful EmotionS (PROMISES) study [85]. Originally, the PAD study was designed to screen women for eligibility of the PROMISES study.

The PAD study is an ongoing population-based observational prospective cohort study that investigates psychological, medical and social factors during pregnancy and the postnatal period. Women in their first trimester of pregnancy are invited to participate when visiting participating primary midwifery practices and obstetric and gynecology departments of hospitals throughout The Netherlands, or through advertisements in nation-wide media. Women not mastering the Dutch language are excluded. Before entering the study, women provide written informed consent which includes the option to give researchers permission to request for medical birth records. Participants are asked to complete online questionnaires at 14, 19, 24 and 36 weeks of gestation and at 6 and 24 weeks after pregnancy. At present, over 7,500 pregnant women have been included in the PAD study.

Participants of the PAD study showing at least moderate symptoms of anxiety and/or depression are invited to participate in the PROMISES study. This study is a randomized controlled single-blind trial that examines the effects of cognitive behavioral therapy in 300 pregnant women, as compared with care as usual. Outcome measures include behavioral and emotional problems in the offspring, and changes in the level of anxiety and depressive symptoms of the mother. Enrolment of participants follows the same procedures as with the PAD study but additional exclusion criteria apply. These include: currently receiving psychotherapy, having a high suicidal risk, having a substantial physical disease, presenting with illegal substance abuse, and having a psychiatric history on bipolar disorder, psychoses or manic disorder. In addition to the assessments of the PAD study, participants complete questionnaires when the child is 12 and 18 months of age, and child outcomes at 18 months of age are assessed. Furthermore, a diagnostic interview is taken, the SCID-II interview [86].

Detailed information about the design of these studies and measures is described further on in this thesis.

Outline and scope of the thesis

Part of this thesis focused on identifying differences between women who continue smoking and alcohol consumption during pregnancy and those who quit. Furthermore, we studied smoking relapse in the postpartum period. Last, we investigated whether an intervention during the period of pregnancy, cognitive behavioral therapy, would be able to decrease the level of anxiety and depressive symptoms, when compared to care as usual.

Chapter 2 presents the associations of severity of stressful events with continued smoking and continued alcohol consumption during mid-pregnancy. We categorized stressful events according to their characteristics including pregnancy-specific stressful events. In addition, we explored whether anxiety or depressive symptoms could explain part of the associations. We hypothesized that increased severity of stressful events would increase the risk of continued smoking and alcohol consumption. In addition, we assumed that with increasing severity of stressful events the amount of smoking and alcohol consumption among continued users would be higher.

Chapter 3 describes the associations of personality traits with continued smoking and continued alcohol consumption during mid-pregnancy. The Five Factor Model is used to

describe personality traits. Furthermore we explored whether anxiety or depressive symptoms could explain part of the associations. In addition, we explored whether personality traits would be associated with the amount of smoking and alcohol consumption among continued users. Based on previous research and the characteristics of the personality traits, we hypothesized that continued smoking and alcohol consumption would be associated with higher levels of neuroticism and extraversion, and lower levels of conscientiousness, openness to experience and agreeableness.

Chapter 4 presents the associations of adverse pregnancy and neonatal outcomes and transfer from home-delivery to hospital delivery with smoking relapse at six months postpartum. We explored whether postpartum depressive symptoms could explain the associations. We hypothesized that participants who experienced adverse pregnancy and neonatal outcomes and transfer would have an increased risk of smoking relapse.

Chapter 5 describes the design of the PROMISES study, based on the published protocol [87]. In addition, the screening of participants in the PAD study for eligibility for participation in the PROMISES study is discussed.

Chapter 6 reports the effects of cognitive behavioral therapy on the level of anxiety and depressive symptoms at 36 weeks of gestation, as compared to care as usual. We assumed a (greater) reduction in anxiety and depressive symptoms in participants who received cognitive behavioral therapy, compared to participants who received care as usual.

Chapter 7 provides the general discussion of the thesis and gives recommendations for clinical practice and future research.

The thesis ends with a summary in English and Dutch, respectively.

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CHAPTER 2

Stressful events and continued smoking and continued alcohol consumption during mid-pregnancy

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Abstract

Aim: to examine whether the severity of different categories of stressful events is associated with continued smoking and alcohol consumption during mid-pregnancy. Also, we explored the explanation of these associations by anxiety and depressive symptoms during pregnancy. Finally, we studied whether the severity of stressful events was associated with the amount of cigarettes and alcohol used by continued users.

Method: we conducted a cross-sectional analysis using data from a population-based prospective cohort study. Pregnant women were recruited via midwifery practices throughout The Netherlands. We analyzed women who continued smoking (*n=113*) or quit (*n=290*), and women who continued alcohol consumption (*n=124)* or quit (*n=1403)* during pregnancy. Smoking, alcohol consumption, and perceived severity of stressful events were measured at 19 weeks of gestation. The State Trait Anxiety Inventory and the Edinburgh Postnatal Depression Scale were filled out at 14 weeks of gestation. Odds ratios were calculated as association measures and indicated the relative increase for the odds of continuation of smoking and alcohol consumption for the maximum severity score compared to the minimum score.

Findings: severity of the following stressful event categories was associated with continued alcohol consumption: 'conflict with loved ones' (OR=10.4, p<0.01), 'crime related' (OR=35.7, p<0.05), 'pregnancy-specific' (OR=13.4, p<0.05), and the total including all events (OR=17.2, p<0.05). Adjustment for potential confounders (age, parity and educational level) did not notably change the estimates. There was no association of anxiety and depressive symptoms with continued smoking or alcohol consumption. No associations emerged for continued smoking and severity of stressful events. The amount of cigarettes and alcohol consumption among continued users was not associated with severity of stressful events.

Conclusions: our findings may be relevant for health care providers, in particular midwives and general practitioners. The impact of stressful events may be considered when advising pregnant women on smoking and alcohol consumption.

Introduction

The hazardous effects of smoking and alcohol consumption during pregnancy are well-acknowledged. For smoking these include preterm birth, low birth weight, lower Apgar scores [1], sudden infant death syndrome [2,3], changes in brain development [4,5], increased risk for obesity in adolescence [6] and even behavioral problems in the long term [7]. Alcohol consumption during pregnancy has been associated with preterm delivery [8], spontaneous abortion [9], reduced birth weight [10], the fetal alcohol syndrome [11] and the child's IQ score at age 8 [12]. Nevertheless, smoking prevalence rates during pregnancy range from 5% to 21% [13,14] and alcohol consumption prevalence rates vary between 6% and 50% in western countries [15-20].

Among the suggested risk factors for continuation of smoking and alcohol consumption during pregnancy are a low educational level, being single, being multiparae, and high perceived psychological stress in early pregnancy [21-24]. As certain events in life can generate psychological stress [25], they may be associated with continued smoking and alcohol consumption during pregnancy. Surprisingly, not much is known about continued versus quit smoking and alcohol consumption associated with stressful events during pregnancy. Only a single previous study has examined stressful events in pregnancy and continued versus quit smoking. No association with the number of stressful events was found [21]. Yet, perceived severity of events was not taken into account. Also, no distinction was made between different categories of stressful events. In particular, pregnancy-specific stressful events such as finding out about congenital anomalies or experiencing alarming obstetric symptoms (e.g. vaginal bleeding) may be especially relevant during pregnancy. As for continued versus quit alcohol consumption, and the association with stressful events during pregnancy, no study has been undertaken, to the best of our knowledge. Some insight into the explanation of the association between stressful events and continued smoking and alcohol consumption during pregnancy may be obtained by taking antenatal symptoms of anxiety and depression into account. Several studies showed that smoking and alcohol consumption during pregnancy are related to anxiety and depression symptoms [26-28], and stressful events predict these symptoms [29,30]. Therefore, these symptoms may explain part of the association between stressful events and continued smoking and alcohol consumption during pregnancy. To our knowledge, this explanation has not been researched to date.

In the present study we examined the associations of perceived severity of different categories of stressful events, including pregnancy-specific events, with continued smoking and continued

alcohol consumption during mid-pregnancy. We hypothesized that increased perceived severity of events would be associated with continued smoking and alcohol consumption. Perceived severity of events was assessed using a subjective and normative approach. We further explored whether some proportion of the associations between severity of stressful events and continued smoking and alcohol consumption could be explained by anxiety or depressive symptoms. In addition, we assumed that with increasing severity of events the amount of smoking and alcohol consumption among continued users would be higher.

Methods

Setting and participants

The present cross-sectional analysis was performed within the Pregnancy, Anxiety and Depression (PAD) study [31]. This ongoing population-based prospective cohort study investigates psychological, medical and social factors during pregnancy and in the postnatal period. Participants are enrolled at primary midwifery practices (n= 102) and obstetric and gynecology departments of hospitals (n=9) throughout The Netherlands. Women who provide written informed consent enter the study in the first trimester of pregnancy. After two baseline measurements at approximately 14 and 19 weeks estimated gestational age (EGA), follow-up assessments using online questionnaires take place up to 6 months after pregnancy. For the present analysis, data was used from all participants that completed baseline measurements between December 2011 and July 2013. Out of 3383 women that agreed on participating in that period, 2287 (68%) women completed the baseline assessments. The PAD study was approved by the medical ethical review board of the University Medical Center Groningen.

Smoking status

Current smoking status and smoking status before pregnancy were ascertained by self-report during mid-pregnancy, i.e. at the 19-week EGA baseline measurement, using the following two questions: (1) '*Did you smoke cigarettes before finding out about your current pregnancy*?' (yes/no) and (2) '*Are you currently smoking cigarettes*?' (yes/no). "Continued smoking" was defined as a positive response to both questions 1 and 2. "Quit smoking" was defined as a positive response to question 1 and a negative response to question 2. "Not smoking" was defined as a negative response to both questions. We asked continued smokers to categorize their typical average amount of cigarettes smoked per day using five classes: 1-5, 6-10, 11-15, 16-20, and 21 or more.

Alcohol consumption status

Current alcohol consumption status and alcohol consumption status before pregnancy were ascertained by self-report during mid-pregnancy, i.e. at the 19-week EGA baseline measurement, using the following two questions: 1) *'Did you drink alcohol before finding out about your current pregnancy?'* (yes/no) and 2) *'How often do you drink during the week?*'. "Continued alcohol consumption" was defined as a positive response to question 1 and a response larger than zero to question 2. "Quit alcohol consumption" was defined as a positive response to question 1 and a zero-response to question 2. "Not drinking alcohol" was defined as a negative response to question 1 and a zero-response to question 2. Typical frequency of alcohol consumption among continued users was assessed in the following seven categories: less than once a month, once a month, 2 to 3 times a month, and 1, 2, 3, 4 or more day(s) per week. The typical amount of alcohol consumption was assessed using five categories: 1-2, 3-5, 6-10, 11-15, and over 15 glasses each time. Frequency of alcohol consumption was multiplied by the amount to provide a single estimate of the mean total amount of weekly alcohol consumption.

Stressful events

Stressful events during early and mid-pregnancy were assessed at the 19-week EGA baseline measurement using 47 translated events from the event questionnaire developed and utilized in the Avon Longitudinal Study of Parents And Children (ALSPAC study) [32]. Event items consist of different categories of events (e.g. events related to work, financial issues, family, crime), including pregnancy-specific events. Participants were asked to confirm whether these events had occurred during pregnancy and were asked about their perceived severity. Severity was rated as scores: "affected me a lot (4), affected me moderately (3), affected me mildly (2) and did not affect me at all (1)". All stressful events were divided into nine core event categories: work or study related events of self or partner, financial related events, events related to conflict with loved ones, events related to housing, events related to death of loved ones, events related to illness of self or loved ones, events related to domestic violence or abuse, crime related events, and pregnancy-specific events (table 1). To account for the severity of events, a subjective and a normative approach was followed. We followed both approaches to account for response-tendency due to large variations that may exist in the appraisal of event severity, making comparisons between participants difficult [33]. Correspondingly, two types of severity weights were calculated for each event. The individual severity weight of an event is the individual-specific rating and thus varies across participants. In contrast, and analogous to the approach followed by Holmes and Rahe in creating the social readjustment scale [34], the group severity weight of a certain event was defined as the

severity experienced on the group level. This weight was calculated as the mean of all individual severity scores given for that event in our study population. This severity weight is therefore constant across participants (table 1). For each participant we calculated, for each event category separately, an individual severity sum (ISS) score by adding up all individual severity scores of the events experienced. Likewise, a group severity sum score (GSS) was calculated. Finally, ISS and GSS scores were added up over the nine general categories to arrive at a total severity score. Some stressful events were considered ambiguous with regard to their unpleasantness, e.g. moving house. To distinct unpleasant events from ambiguous events, two raters (JM and TV) independently judged whether events were either predominantly unpleasant, or predominantly pleasant (yes/no).

Anxiety and depression

At the 14-week EGA baseline measurement, anxiety symptoms were measured using the Dutch version of the validated 6-item State Trait Anxiety Inventory [35], and depressive symptoms were measured using the Dutch version of the validated 10-item Edinburgh Postnatal Depression Scale [36].

Other variables

Age, educational level, and parity were considered potential confounders based on their association with continued smoking and alcohol consumption, and with stressful events [23,37]. Educational level was recorded as elementary education, lower tracts of secondary education, higher tracts of secondary education, higher vocational education, or university education. Parity was assessed as primiparae or multiparae. Furthermore, we registered country of birth for descriptive purposes.

Multiple imputation of missing data

To avoid the risk of bias and loss of statistical power in complete case analysis, missing data were imputed using multiple imputation by chained equations under the assumption that the missing data mechanism was missing at random (MAR) or missing completely at random. Multiple imputation is considered an appropriate method for dealing with missing data [38]. Following recommendations by Graham [39], 20 datasets were imputed and combined according to Rubin's rules [40]. The percentage of missing data was approximately 25% for the variables of interest. The imputation model included all variables of interest including the outcome variables. For each of the variables we studied the missing data mechanism. This was done by predicting missingness (yes/no) of each of these variables from the other variables in the imputation model using a multivariable logistic regression analysis. These analyses showed

explained variances ranging from 2.6% to 46.6% (Nagelkerke's R^2). This implies that data were MAR at least to some extent, and consequently multiple imputation may have minimized bias. However, data being missing not at random can never be excluded. As a sensitivity analysis, we performed complete case analyses (CCA).

Table 1: Overview of all stressful events showing the prevalence per smoking and alcohol consumption status. The unadjusted odds ratio (OR) is given for continued versus quit use. Group severity weights per event item are based on the total study sample (n=2287).

Stressful event item in questionnaire	Prevalence: n (%)				Prevalence: n (%)				
	Continued smoking (n=113)	Quit smoking (n=290)	Not smoking (n=1883)	OR (95% CIs) (continued vs quit)	Continued alcohol cons. (n=124)	Quit alcohol cons. (n=1403)	Not drinking (n=760)	OR (95% CIs) (continued vs quit)	Group severity weight (1-4)
Work or study related of self or partner									
- You had problems at work	26 (23.0)	55 (19.0)	296 (15.7)	1.3 (0.7;2.3)	27 (21.8)	236 (16.8)	114 (15.0)	1.3 (0.8;2.3)	2.7
- You lost your job	16 (14.2)	32 (11.0)	107 (5.7)	1.4 (0.6;2.9)	12 (9.7)	99 (7.1)	45 (5.9)	1.4 (0.6;3.2)	2.7
- You started a new job	9 (8.0)	28 (9.7)	170 (9.0)	0.8 (0.3;2.3)	18 (14.5)	136 (9.7)	54 (7.1)	1.5 (0.9;2.8)	1.9
- You took an important examination	6 (5.3)	21 (7.2)	142 (7.5)	0.7 (0.2;2.0)	16 (12.9)	107 (7.6)	46 (6.1)	1.7 (0.9;3.4)	2.2
- Your partner had problems at work	20 (17.7)	47 (16.2)	243 (12.9)	1.1 (0.6;2.2)	18 (14.5)	192 (13.7)	100 (13.2)	1.0 (0.6;1.9)	2.5
- Your partner lost his job	12 (10.6)	25 (8.6)	87 (4.6)	1.2 (0.5;3.0)	6 (4.8)	76 (5.4)	43 (5.7)	0.8 (0.3;2.4)	2.8
Financial related events									
- You had a major financial problem	16 (14.2)	32 (11.0)	105 (5.6)	1.3 (0.6;2.8)	6 (4.8)	94 (6.7)	52 (6.8)	0.7 (0.2;2.1)	3.0
- Your income was reduced	36 (31.9)	70 (24.1)	325 (17.3)	1.4 (0.9;2.4)	32 (25.8)	263 (18.7)	136 (17.9)	1.5 (0.9;2.5)	2.1
Events related to conflict with loved ones									
- You argued with your partner	27 (23.9)	57 (19.7)	171 (9.1)	1.3 (0.7;2.3)	23 (18.5)	151 (10.8)	81 (10.7)	1.8 (1.0;3.2)*	2.7
- You had arguments with your family and friends	19 (16.8)	51 (17.6)	213 (11.3)	0.9 (0.5;1.8)	27 (21.8)	173 (12.3)	82 (10.8)	2.0 (1.1;3.5)*	2.7
- Your partner went away	4 (3.5)	10 (3.4)	13 (0.7)	¥	3 (2.4)	15 (1.2)	9 (1.2)	¥	3.0
- You and your partner separated	5 (4.4)	6 (2.1)	7 (0.4)	2.1 (0.4;10.1)	2 (1.6)	8 (0.6)	8 (1.2)	¥	3.3
Events related to housing									
- You moved house	17 (15.0)	35 (12.1)	179 (9.5)	1.2 (0.6;2.7)	17 (13.7)	153 (10.9)	60 (7.9)	1.3 (0.7;2.6)	2.0
- You became homeless	0	0	0	na	0	0	0	na	na
Events related to death of loved ones									
- Your partner died	0	0	1 (0.1)	na	0	1 (0.1)	0	na	1.0
- One of your children died	3 (2.7)	6 (2.1)	16 (0.8)	¥	2 (1.6)	13 (0.9)	10 (1.3)	¥	4.0
- One of your parents died	5 (4.4)	8 (2.8)	26 (1.4)	1.7 (0.5;6.2)	3 (2.4)	20 (1.4)	16 (2.1)	¥	3.9
- One of your brothers or sisters died	4 (3.5)	3 (1.0)	3 (0.2)	¥	2 (1.6)	6 (0.4)	2 (0.3)	¥	3.4
- A friend or other relative died	17 (15.0)	35 (12.1)	242 (12.9)	1.3 (0.6;2.8)	14 (11.3)	171 (12.2)	110 (14.5)	0.9 (0.4;1.7)	2.8

Table 1 (Continued)

Stressful event item in questionnaire	Prevalence: n (%)				Prevalence: n (%)				
	Continued smoking (n=113)	Quit smoking (n=290)	Not smoking (n=1883)	OR (95% CIs) (continued vs quit)	Continued alcohol cons. (n=124)	Quit alcohol cons. (n=1403)	Not drinking (n=760)	OR (95% CIs) (continued vs quit)	Group severity weight (1-4)
Events related to illness of self or loved ones									
- Your partner was ill	5 (4.4)	13 (4.5)	47 (2.5)	0.9 (0.2;3.5)	3 (2.4)	41 (2.9)	21 (2.8)	¥	2.9
- One of your children was ill	6 (5.3)	9 (3.1)	45 (2.4)	2.0 (0.6;6.4)	3 (2.4)	35 (2.5)	22 (2.9)	¥	3.2
- One of your parents was ill	19 (16.8)	27 (9.3)	191 (10.1)	1.9 (0.9;4.1)	12 (9.7)	160 (11.4)	65 (8.6)	0.8 (0.4;1.8)	3.2
- One of your brothers or sisters was ill	3 (2.7)	7 (2.4)	25 (1.3)	¥	3 (2.4)	21 (1.5)	11 (1.4)	¥	3.0
- A friend or other relative was ill	12 (10.6)	35 (12.1)	222 (11.8)	0.8 (0.4;1.9)	11 (8.9)	166 (11.8)	93 (12.2)	0.7 (0.3;1.5)	2.9
- You were very ill	3 (2.7)	11 (3.8)	42 (2.2)	¥	4 (3.2)	31 (2.2)	20 (2.6)	¥	3.2
- You were admitted to hospital	4 (3.5)	14 (4.8)	77 (4.1)	¥	5 (4.0)	51 (3.6)	40 (5.3)	1.1 (0.4;3.3)	2.9
- You attempted suicide	0	1 (0.3)	0	na	0	1 (0.1)	0	na	2.0
Events related to domestic violence or abuse									
- Your partner hurt you physically	0	3 (1.0)	3 (0.2)	na	0	4 (0.3)	2 (0.3)	na	2.5
- Your partner hurt your children physically	0	0	4 (0.2)	na	0	2 (0.1)	2 (0.3)	na	1.3
- Your partner was emotionally cruel to you	6 (5.3)	13 (4.5)	31 (1.6)	1.1 (0.4;3.6)	4 (3.2)	27 (1.9)	19 (2.5)	¥	3.0
- Your partner was emotionally cruel to your children	0	0	3 (0.2)	na	0	2 (0.1)	2 (0.3)	na	3.0
- There was alcohol or drug abuse within your family or relationship	1 (0.9)	3 (1.0)	7 (0.4)	¥	0	7 (0.5)	3 (0.4)	na	2.9
Crime related events									
- Your house or car was burgled	4 (3.5)	10 (3.4)	31 (1.6)	¥	3 (2.4)	35 (2.5)	8 (1.2)	¥	2.1
- You were involved in an accident	1 (0.9)	11 (3.8)	42 (2.2)	¥	6 (4.8)	31 (2.2)	17 (2.2)	2.2 (0.8;6.3)	2.3
- You were in trouble with the law	1 (0.9)	0	3 (0.2)	na	0	3 (0.2)	2 (0.3)	na	2.1
- Your partner was in trouble with the law	2 (1.8)	5 (1.7)	10 (0.5)	¥	3 (2.4)	8 (0.6)	5 (0.6)	¥	2.6
- You were convicted for an offence	0	0	0	na	0	0	0	na	Na
- You were a victim of an offence	2 (1.8)	3 (1.0)	9 (0.5)	¥	4 (3.2)	7 (0.5)	3 (0.4)	¥	3.1
- You were a victim of sexual abuse	0	7 (2.4)	8 (0.4)	na	0	9 (0.6)	6 (0.8)	na	3.4

Table 1 (Continued)

Stressful event item in questionnaire	Prevalence: n (%)				Prevalence: n (%)				
	Continued smoking (n=113)	Quit smoking (n=290)	Not smoking (n=1883)	OR (95% CIs) (continued vs quit)	Continued alcohol cons. (n=124)	Quit alcohol cons. (n=1403)	Not drinking (n=760)	OR (95% CIs) (continued vs quit)	Group severity weight (1-4)
Pregnancy-specific events									
- Your pregnancy was unwanted	12 (10.6)	22 (7.6)	33 (1.2)	1.4 (0.6;3.3)	9 (7.3)	37 (2.6)	20 (2.6)	2.7 (1.1;6.7)*	2.6
- You tried to have an abortion	3 (2.7)	8 (2.8)	11 (0.6)	¥	3 (2.4)	10 (0.7)	8 (1.2)	¥	3.5
- You found out that your partner does not want your child	4 (3.5)	9 (3.1)	2 (0.1)	¥	1 (0.8)	9 (0.6)	5 (0.6)	¥	3.0
- You were bleeding and thought you might miscarry	20 (17.7)	52 (17.9)	301 (16.0)	1.0 (0.5;1.9)	26 (21.0)	226 (16.1)	121 (15.9)	1.4 (0.8;2.3)	3.3
- You had a test to see if your baby might not be normal	37 (32.7)	107 (36.9)	742 (39.4)	0.8 (0.5;1.5)	65 (52.4)	568 (40.5)	253 (33.3)	1.6 (1.0;2.5)*	2.2
- You had a result on a test that suggested your baby might not be normal	4 (3.5)	10 (3.4)	59 (3.1)	¥	5 (4.0)	38 (2.7)	30 (3.9)	1.4 (0.5;4.5)	3.3
- You were told that you were going to have twins	3 (2.7)	5 (1.7)	59 (3.1)	¥	4 (3.2)	35 (2.5)	27 (3.6)	¥	2.9
- You heard something that had happened that might be harmful to the baby	6 (5.3)	9 (3.1)	83 (4.4)	1.8 (0.5;6.2)	8 (6.5)	57 (4.1)	33 (4.3)	1.7 (0.7;4.3)	3.0

Note: for some variables numbers do not add up to the total due to rounding of imputed values

¥: Due to low numbers in cells no value is presented

* $p<0.05$

Data analysis

We calculated descriptive statistics for the total study population according to smoking and alcohol consumption status. Subsequent analyses included continued users and quitters only. To that end, two groups were identified: those who either continued or quit smoking and those who either continued or quit alcohol consumption. The number of participants who continued both smoking and alcohol consumption was too small to study (n=4). Groups were compared using t-tests, Mann-Whitney tests, Pearson Chi-Square tests where appropriate. Logistic regression analysis was used to investigate the associations of continued smoking (dependent variable) with severity of stressful events (independent variables). Likewise, continued alcohol consumption was included as dependent variable. Odds ratios (OR) from these analyses were calculated as quantitative association measures and were accompanied by 95% confidence intervals.

All ISS and GSS scores were entered as continuous variables and, to ensure comparability, were first standardized to a value ranging from 0 to 1 by division through their maximum value. Therefore, OR indicated the relative increase of the odds of continuation of smoking and alcohol consumption for the maximum compared to the minimum score. In separate analyses, ambiguous or predominantly pleasant events were excluded to specifically assess the outcome of unpleasant stressful events. In additional regression analyses, we adjusted for the potential confounders. Stability of the regression models that showed statistically significant results was checked by creating three severity score categories, based on the distribution of the ISS and GSS scores, and investigating the scores as an independent variable. As a supplementary, exploratory analysis, the associations between the occurrence of individual stressful events listed in table 1 and continued smoking and alcohol consumption was investigated, irrespective of their severity. Before exploring the explanation of the associations by anxiety or depressive symptoms, we first investigated whether these symptoms were associated with the dependent and independent variables. If so, these symptoms were added separately as independent continuous variables to the adjusted regression models. Resulting changes in beta-coefficients for the event categories were considered measures of explanation. We beforehand decided that changes more than 10% indicated the presence of explanation [41]. We limited these analyses to those event categories that showed to be statistically significantly associated with continued smoking or alcohol consumption. Spearman's rank correlation was used as a measure for the relationships between severity of stressful events, and the amount of cigarettes and alcohol used by continued users. The level of statistical significance was set at 0.05, two-sided. Multiple imputation and all analyses were performed using IBM SPSS Statistics version 20.0.

Table 2: Descriptive data (pooled) of study participants according to smoking and alcohol consumption status (n=2287). P-values are given for continued versus quit use.

	Continued smoking (n=113)	**Quit smoking (n=290)**	**P-value**	**Not smoking (n=1883)**	**Continued alcohol cons. (n=124)**	**Quit alcohol cons. (n=1403)**	**P-value**	**Not drinking alcohol (n=760)**
Age (mean, SD)	30.5 (5.6)	30.6 (4.9)	0.87	31.8 (4.4)	32.8 (4.4)	31.7 (4.5)	**0.03**	31.2 (4.7)
Education (n, %)			**0.02**				0.21	
Elementary education	3 (2.7)	4 (1.4)		4 (0.2)	0	5 (0.4)		5 (0.7)
Lower tracts of secondary education	23 (20.4)	51 (17.6)		126 (6.7)	9 (7.3)	115 (8.2)		78 (10.3)
Higher tracts of secondary education	61 (54.0)	108 (37.2)		462 (24.5)	21 (16.9)	341 (24.3)		269 (35.4)
Higher vocational education	22 (19.5)	93 (32.1)		778 (41.3)	50 (40.3)	557 (39.7)		286 (37.6)
University education	5 (4.4)	34 (11.7)		512 (27.2)	44 (35.5)	385 (27.4)		122 (16.1)
Multiparous (n, %)	63 (55.8)	154 (53.1)	0.64	1105 (58.7)	75 (60.5)	756 (53.9)	0.21	492 (64.7)
≥1 event (n, %)	104 (92.0)	246 (84.8)	0.08	1527 (81.1)	109 (87.9)	1170 (83.4)	0.23	598 (78.7)
Anxiety score (median, IQR)	36.5 (16.7)	34.1 (11.1)	0.08	33.3 (10.0)	33.3 (11.2)	33.3 (10.0)	0.15	33.3 (11.5)
Depression score (median, IQR)	5.4 (6.4)	5.0 (5.5)	0.18	4.0 (4.6)	4.5 (5.7)	4.0 (5.0)	0.20	4.0 (5.0)
Country of birth			0.35				0.17	
Netherlands	111 (97.3)	271 (93.4)		1787 (94.9)	114 (91.9)	1333 (95.0)		722 (95.0)
Maroc/Turkey/Suriname/Aruba	1 (0.9)	4 (1.4)		10 (0.5)	1 (0.8)	7 (0.5)		6 (0.8)
Other	1 (0.9)	15 (5.2)		87 (4.6)	8 (6.5)	63 (4.5)		32 (4.2)

Note: for some variables numbers do not add up to the total due to rounding of imputed values.

Results

Descriptives

Table 2 presents the characteristics of the total study population after imputation. One hundred and thirteen (28.0%) participants continued smoking and 124 (8.1%) participants continued alcohol consumption. Continued smokers had a lower educational level (p=0.02) and experienced one or more stressful event(s) during pregnancy more often compared to quitters, although this latter difference was not statistically significant (p=0.08). Continued alcohol consumers were older compared to quitters (p=0.03). Regarding the average amount of cigarettes smoked per day, 59 (52.2%) participants smoked 1-5, 35 (31.0%) smoked 6-10 and 19 (16.8%) smoked more than 10. Continued alcohol consumers drank on average one glass of alcohol per week. Table 1 shows for each stressful event its prevalence by smoking and alcohol consumption status. Prevalence rates of events related to domestic violence or abuse were low, therefore no associations were calculated for this category.

Stressful events and continued smoking

ISS and GSS scores of event categories showed a correlation >0.9, therefore ISS scores are reported only. ISS scores of event categories showed no statistical significant association with continued smoking (table 3). Adjustment for potential confounders only slightly weakened the associations. 'Starting a new job', 'moving house', and 'being told to have twins' were rated as not predominantly unpleasant by both raters. Exclusion of these events from the analyses did not markedly change the estimates. Individual stressful events were not associated with continued smoking (table 1). Results from the CCA were not notably different from the imputed results.

Table 3: Mean individual severity sum and total scores, and unadjusted odds ratios (OR) with 95% confidence intervals (95% CI) for the associations of individual severity sum scores and total scores with continuation of smoking and alcohol consumption.

Event category	Continued smoking		Continued alcohol consumption	
	Mean (min-max)	OR (95%CI)	Mean (min-max)	OR (95%CI)
Work or study related	1.9 (0-20)	1.5 (0.3;9.0)	1.5 (0-22)	3.5 (0.5;22.8)
Financially related	1.0 (0-8)	1.5 (0.6;4.0)	0.6 (0-8)	1.7 (0.6;4.9)
Conflict loved ones	1.3 (0-16)	1.8 (0.4;9.7)	0.7 (0-16)	10.4 (2.0;54.7)**
Housing related	0.3 (0-4)	1.9 (0.5;7.1)	0.2 (0-4)	1.5 (0.4;5.0)
Death of loved ones	0.7 (0-16)	3.9 (0.3;50.9)	0.5 (0-15)	2.0 (0.2;24.7)
Illness self or loved ones	1.3 (0-24)	2.3 (0.2;25.8)	1.1 (0-24)	0.6 (0.0;15.3)
Crime related	0.3 (0-17)	0.2 (0.0;16.0)	0.2 (0-17)	35.7 (1.8;711.0)*
Pregnancy-specific	2.1 (0-28)	1.2 (0.1;13.6)	1.9 (0-28)	13.4 (1.8;98.1)*
Total score	9.1 (0-104)	2.9 (0.2;40.3)	6.7 (0-104)	17.2 (1.3;235.6)*

Scores were standardized to a value ranging from 0 to 1 before entrance into logistic regression models as independent variables.
Estimates were not calculated for the category 'domestic violence and abuse' due to low prevalence rates
* $p<0.05$
** $p<0.01$

Stressful events and continued alcohol consumption

ISS and GSS scores of event categories showed a correlation >0.9, therefore ISS scores are reported only. ISS scores were statistically significantly associated with continued alcohol consumption in the following categories: 'conflict with loved ones', 'crime related', 'pregnancy-specific', and the total severity score (table 3). Adjustment did not notably affect the estimates. ISS scores of the category 'pregnancy-specific' and the total severity score showed an increase in OR with increasing category. Exclusion of events rated as not predominantly unpleasant did not noteworthy change the estimates. Individual stressful events that were associated with continued alcohol consumption consisted of: 'arguing with partner', 'arguing with family', 'having an unwanted pregnancy', and 'taking a test to see if the baby might not be normal' ($p<0.05$)(table 1). Results from the CCA were not notably different from the imputed results.

Explanation by anxiety and depression symptoms

Anxiety and depressive symptoms were not associated with continued smoking and alcohol consumption (table 2), therefore we refrained from the analyses that would investigate to what extent the associations could be explained by these symptoms.

The amount of cigarettes and alcohol consumption during pregnancy
Spearman's correlation coefficient ranged between -0.05 and 0.27 for the associations of severity of stressful events with the amount of cigarettes and alcohol consumed by continued users. None of the correlations were statistically significant.

Discussion

To our knowledge, this is the first study that investigated the associations between perceived severity of different categories of stressful events, including pregnancy-specific events, and continued versus quit smoking or alcohol consumption during mid-pregnancy. Our results showed that the total perceived severity of stressful events during early and mid-pregnancy was associated with continued alcohol consumption. Next to the total perceived severity, perceived severity of events in the following categories showed associations with continued alcohol consumption: 'conflict with loved ones', 'crime related', and 'pregnancy-specific'. No associations emerged between severity of stressful events and continued smoking. Furthermore, the associations could not be explained by anxiety and depressive symptoms during pregnancy. The amount of cigarettes and alcohol consumed by continued users was not associated with severity of stressful events.

Comparison with previous studies and explanation of findings
Our finding that the event category 'conflict with loved ones' was statistically significantly associated with continued alcohol consumption corroborates previous research. Support by and relationship with the partner assists in dealing with stress, especially during pregnancy. Rosand and colleagues suggested that relationship satisfaction during pregnancy alone can act as a protective factor for handling certain stressors [42]. Social support is in general considered an important protective factor for coping with stressful events [43,44], and especially the mother of pregnant women is an important source of social support during pregnancy [45]. In addition, our exploratory analyses of individual stressful events revealed that the occurrence of arguing with the partner or family alone may increase the odds of continued alcohol consumption. The association we observed between perceived severity of pregnancy-specific events and continued alcohol consumption confirms that it may be relevant to distinguish this category of events in particular [46-48]. For example, Lobel and colleagues showed that pregnancy-specific stress was a stronger predictor of adverse birth outcomes than general stress [46].

Overall, our findings provide insights on the impact of different categories of stressful events, including pregnancy-specific events, and continued smoking and alcohol consumption during mid-pregnancy. Our results may be especially relevant for health care providers, such as midwifes or general practitioners, who advise women on smoking and alcohol consumption during pregnancy. The impact of stressful events should be discussed during pregnancy in the context of healthy lifestyle strategies. Pregnancy-specific events may even take place in the context of prenatal care (e.g. taking a test to see if your baby might not be normal), and their impact can therefore easily be addressed by health care professionals. The given that we were not able to demonstrate statistical significant findings on event categories and continued smoking suggests that the role of perceived severity of stressful events is limited compared to continued alcohol consumption. There may be other, more prominent factors that determine continued smoking during pregnancy. For example, a low socioeconomic status, having a partner that smokes and great nicotine dependence have consistently been reported as barriers to smoking cessation [49-51].

We did not find evidence for our suggestion that the associations between perceived severity of events and continued alcohol consumption could be explained by anxiety and depressive symptoms during pregnancy. This may be because alcohol consumption is part of a coping mechanism involved in dealing with stressful events via a direct pathway or via other, unknown, factors. Arch found for example that pregnancy-specific anxiety was associated with alcohol consumption during pregnancy rather than general anxiety [52]. Therefore, our analyses could have yielded different results if we had measured pregnancy-specific anxiety.

The quitting rate found in our study was 72.0% for smoking and 91.9% for alcohol consumption, which are high rates when compared to previous studies [51,53-55]. As earlier research shows that a low educational level is associated with continued smoking and alcohol consumption during pregnancy [23,56], the relatively high quitting rates may be explained by the composition of our study population that included relatively few lower educated women.

Strengths and limitations

Despite the large total sample, the relatively small sample size of women who continued smoking and alcohol consumption forms a limitation. The statistical power to demonstrate associations with continued smoking may have been limited. Further, the prevalence rates of certain events were quite low implying that our results need to be interpreted carefully, i.e. especially the positive association between crime related events and continued alcohol

consumption. In addition, the results from the analyses of individual stressful events must be interpreted with some caution in view of the large number of associations tested, and thus should be interpreted in the context of the findings from the event categories. Replication by future prospective studies is essential, preferably including larger samples. Another Potential limitation of our study was the use of self-report data only. Especially questions about smoking and alcohol consumption during pregnancy may be susceptible to social desirable reporting, i.e. underreporting. However, it seems unlikely that any underreporting would depend on the events experienced. Therefore, the associations were likely unaffected. Furthermore, by using a self-report questionnaire to measure stressful events, we were unable to assess the context of stressful events [57] and it may be possible that reported events overlap in occurrence (e.g. 'having problems at work' and 'losing job'). Finally, we did not have data on smoking or alcohol consumption status later in pregnancy and status may have changed. Therefore, it is unclear whether our findings can be generalized to exposure to smoking and alcohol consumption beyond the period of mid-pregnancy. On the other hand, it has been shown that after the first trimester of pregnancy smoking and alcohol consumption status hardly change [58,59]. The present study also has several strengths. First, our findings contribute to the limited literature available on psychological differences between women who continue versus quit smoking and alcohol consumption during pregnancy [60]. Second, we included stressful events that had occurred during pregnancy only. Other studies assessed stressful events 'in the past 12 months', thus including events before pregnancy as well [27,61]. This may cloud the associations as events in early pregnancy are rated as more stressful [62]. Moreover, including the time period before pregnancy might increase recall bias as events may be susceptible to forgetfulness with an increased time interval between occurrence of the event and measurement. Our study aimed to reduce recall bias by assessing stressful events close to the period of interest.

Conclusion

This study showed that the total perceived severity of stressful events during early and mid-pregnancy increases the odds of continued alcohol consumption during mid-pregnancy. This increase concerned especially events in the categories 'conflict with loved ones', 'crime related', and 'pregnancy-specific'. No statistically significant associations emerged between event categories and continued smoking. The impact of stressful events during early and mid-pregnancy, including pregnancy-specific events, should be identified and targeted at in healthy lifestyle strategies conducted by health care providers. Support by especially the partner and the family may act as a protective factor for maternal distress. Pregnant women and their partners and family should be assisted in acknowledging the importance of this source of support.

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CHAPTER 3

Continued smoking and continued alcohol consumption during mid-pregnancy distinctively associated with personality

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Abstract

Aim: pregnancy is a unique period to quit smoking and alcohol consumption and although motivated, not all women succeed at this. We investigated the associations of personality with continued smoking and continued alcohol consumption during mid-pregnancy. In addition, we studied whether antenatal anxiety and depressive symptoms during pregnancy can explain these associations.

Method: two antenatal measurements from the population-based Pregnancy Anxiety and Depression cohort study were used. Pregnant women in their first trimester were recruited via midwifery practices and hospitals. We analyzed a sample of women who continued (n=101) or quit smoking (n=254), and a sample of women who continued (n=110) or quit alcohol consumption (n=1230). Measures included questions about smoking, alcohol consumption, the NEO-Five Factor Inventory (personality), the State Trait Anxiety Inventory, and the Edinburgh Postnatal Depression Scale.

Findings: we found associations between continued alcohol consumption and higher levels of openness to experience, and lower levels of conscientiousness ($p<0.05$). The association between conscientiousness and continued alcohol consumption was partly explained by both anxiety and depressive symptoms. No associations between personality and continued smoking emerged.

Conclusions: this study contributes to the limited literature on personality differences between women who continue and quit smoking and alcohol consumption during mid-pregnancy. General population studies have not confirmed the association between openness to experience and alcohol consumption which implies that pregnancy is indeed a unique period. Increased insight in how personality influences continued smoking and alcohol consumption during pregnancy can help health professionals to improve lifestyle interventions targeted at pregnant women.

Introduction

Smoking and alcohol consumption during pregnancy hold several risks for both mother and child. Smoking during pregnancy increases the risk of adverse pregnancy outcomes such as reduced birth weight, lower Apgar scores, preterm delivery [1], placental abruption [2], changes in brain development [3] and a 150% increase in overall perinatal mortality [4]. Prenatal alcohol consumption has been associated with reduced birth weight [5], preterm delivery [6], spontaneous abortion [7] and the fetal alcohol syndrome [8]. However, studies investigating the effects of small to moderate amounts of alcohol show a lack in consensus regarding the negative effects [9]. Nevertheless, pregnant women are typically advised to abstain completely from alcohol consumption throughout their pregnancy [10].

Pregnancy is considered a unique window of opportunity to quit smoking and alcohol consumption. Indeed, women appear to be both intrinsically and extrinsically motivated to change their health behavior [11-13]. Notwithstanding these motivations, many women do not try or do not succeed in quitting smoking or alcohol consumption when pregnant. In western countries it is estimated that between 5% and 21% of all women smoke during pregnancy [14,15]. The prevalence rate of alcohol consumption shows a wider range and is estimated to vary between 6% and 50% in western countries [10,16-20]. Quitting rates during pregnancy are between 23% and 47% for smoking [21] and vary between 27% and 80% for alcohol consumption [22-24].

Risk factors associated with smoking and alcohol consumption during pregnancy include the level of education, being multiparae, being single, and experiencing anxiety or depressive symptoms [21,25,26]. General population studies have shown that personality traits predict both health behavior and risky health behavior (e.g. excessive drug and alcohol consumption) [27,28]. In pregnancy, continued smoking and alcohol consumption can be considered as a form of risky health behavior and therefore personality traits are likely predictors of these behaviors. The well-known Five Factor Model explains personality as consisting of five domains or traits, each accompanied by six facets, that describe individual differences between people (table 1) [29]. Neuroticism is characterized by a tendency to experience negative affects. Extraversion is characterized by being social, energetic, and adventurous. Openness to experience relates to curiosity, intellect and creativity. Conscientiousness is related to responsibility, carefulness, and conforming to societal norms. Agreeableness refers to avoiding conflict, being sensitive to social cues, and being considerate [29].

Table 1: Five personality traits and their facets

Neuroticism	Extraversion	Openness to experience	Conscientiousness	Agreeableness
Anxiety	Warmth	Fantasy	Competence	Trust
Anger	Gregariousness	Esthetics	Order	Straight-forwardness
Depression	Assertiveness	Feelings	Dutifulness	Altruism
Self-consciousness	Activity	Action	Achievement striving	Compliance
Impulsiveness	Excitement-seeking	Ideas	Self-discipline	Modesty
vulnerability	Positive emotions	Values	Deliberation	Tender-mindedness

As far as we know, personality has been related to continued smoking and alcohol consumption during pregnancy in only two studies. Maxson and colleagues found an association between lower levels of agreeableness and continued smoking, compared to smoking cessation, using the NEO-Five Factor Inventory [29,30]. Another study, using the Big Five Inventory [31], did not find an association between personality and continued smoking, but found that higher levels of extraversion and lower levels of conscientiousness increased the risk for continued alcohol consumption [32]. However, the latter study included non-smokers and non-drinkers as reference groups which provide little information if one is particularly interested in how continued users differ from quitters during pregnancy. To our knowledge, no study has investigated personality associated with continued alcohol consumption compared to discontinued consumption during pregnancy. Furthermore, the association of personality with the amount of smoking and alcohol consumption among continued users during pregnancy has not been investigated to date.

Smoking and alcohol consumption are, particularly in women, considered to be a strategy to regulate or cope with feelings of negative affect [33-35]. Therefore, we propose that anxiety and depressive symptoms may explain part of the association of personality with continued smoking and alcohol consumption during pregnancy.

The present study investigated the relationships of personality traits with continued smoking and continued alcohol consumption during mid-pregnancy. Based on the characteristics of the traits and previous research, we expected to find an association of continued smoking and alcohol consumption with higher levels of neuroticism and extraversion and with lower levels of conscientiousness, agreeableness, and openness to experience. Furthermore, we assumed that some proportion of the associations would be explained by anxiety or depressive

symptoms. Finally, we explored the associations between personality and the amount of smoking and alcohol consumption among continued users.

Methods

Setting and Participants

Data from the ongoing 'Pregnancy, Anxiety and Depression' (PAD) study were used. This population-based prospective cohort study investigates psychological, medical and social factors during pregnancy and the postnatal period. Participants in the PAD study are enrolled at primary midwifery practices (n= 102) and obstetric and gynecology departments of hospitals (n=9) throughout The Netherlands. Women who provide written informed consent enter the study before 16 weeks of gestation and complete online questionnaires during and after pregnancy. For the present study we used data from the first two assessments at 14 and 19 weeks of gestation, collected between December 2011 and April 2013. Out of the 3,102 women who agreed to participate, 2,033 (66%) completed the online questionnaires. The PAD study was approved by the medical ethical review board of the University Medical Center Groningen.

Smoking status

Smoking status was recorded at the second assessment in three categories; "not smoking before pregnancy", "quit smoking during pregnancy", and "continued smoking during pregnancy". "Continued smoking" was defined as a positive response to the question '*Are you currently smoking cigarettes*?' (yes/no) and '*Did you smoke before finding out about your current pregnancy*?'. "Quit smoking" was defined as a positive response to '*Did you smoke before finding out about your current pregnancy*?' (yes/no) and a negative response to '*Are you currently smoking cigarettes*?'. "Not smoking before pregnancy" was defined as a negative response to '*Did you smoke before finding out about your current pregnancy*?' (yes/no). The mean amount of cigarettes smoked per day by continued smokers was assessed in five different categories: 1-5, 6-10, 11-15, 16-20, and 21 or more.

Alcohol consumption status

Alcohol consumption status was recorded at the second assessment in three categories; "not drinking alcohol before pregnancy", "quit alcohol consumption during pregnancy", and "continued alcohol consumption during pregnancy". "Continued alcohol consumption" was defined as a response larger than zero to; *'How often do you drink during the week?'* and a positive response to *'Did you drink alcohol before finding out about your current*

pregnancy?' (yes/no). "Quit alcohol consumption" was defined as a positive response to *'Did you drink alcohol before finding out about your current pregnancy?'* (yes/no) and zero-response to *'How often do you drink during the week?'.* "Not drinking before pregnancy" was defined as a negative response to *'Did you drink alcohol before finding out about your current pregnancy?'* (yes/no). Frequency of alcohol consumption among continued users was assessed in the following seven categories: less than once a month, once a month, 2 to 3 times a month, and 1, 2, 3, 4 or more day(s) per week. The typical amount of alcohol consumption was assessed using five categories: 1-2, 3-5, 6-10, 11-15, and over 15 glasses each time. Frequency of alcohol consumption was multiplied by the amount to provide a single estimate of the mean total amount of weekly alcohol consumption.

Personality traits

Personality traits were measured at the first assessment using the Dutch validated version of the NEO-Five Factor Inventory [29,36]. Questions in this 60-item self-report questionnaire are based on a 5-point Likert scale with a range from 1 (strongly disagree) to 5 (strongly agree). In the present study Cronbach's alpha reliabilities were good: 0.89 for neuroticism, 0.81 for extraversion, 0.73 for openness to experience, 0.80 for conscientiousness, and 0.71 for agreeableness.

Anxiety and depressive symptoms

Anxiety and depressive symptoms were recorded at the first assessment. Anxiety symptoms were measured using the Dutch version of the validated 6-item State Trait Anxiety Inventory (STAI) [37]. The Dutch version of the 10-item Edinburgh Postnatal Depression Scale (EPDS) was used to measure depressive symptoms [38], and has also been validated for measuring depressive symptoms during pregnancy [39].

Other variables

Socio-demographic variables were measured at both assessments. They included level of education (assessed as elementary education, lower tracts of secondary education, higher tracts of secondary education, higher vocational education, and university education), age, parity (primiparae or multiparae), and relationship status (in a relationship or not in a relationship). These variables were analyzed for descriptive purposes only. They were not considered confounders based on existing knowledge. However, we examined whether the associations were stronger in a lower education group as it has been shown that educational level and personality traits may interact with regard to health outcomes, including smoking

status [40,41]. Lower education was defined as elementary education, lower tracts of secondary education, and higher tracts of secondary education.

Multiple imputation of missing data

To avoid the risk of bias and loss of statistical power in complete case analyses, missing data in the total sample were imputed. This was performed using multiple imputation by chained equations under the assumption that the missing data mechanism is missing at random or missing completely at random. As suggested by Graham [42], 20 datasets were imputed and combined according to Rubin's rules [43]. The percentage missing data was approximately 25% for the variables of interest. The imputation model included the following variables: smoking status, alcohol consumption status, amount of smoking and alcohol consumption, anxiety and depressive symptoms, level of education, age, parity, and relationship status. The missing data mechanism of each variable was studied by predicting missingness (yes/no) of each of these variables from the other variables in the imputation model using a multivariable logistic regression analysis. These analyses showed explained variances ranging from 4.0% to 35.3% (Nagelkerke's R^2), implying that data were missing at random at least to some extent. Consequently, multiple imputation may have minimized bias in the present study. Nevertheless, data being missing not at random can never be excluded, and therefore we included complete case analyses as a sensitivity analysis.

Data analysis

The analyses focused on the comparison of continued and quit use. Therefore, two samples were identified: those participants who either continued or quit smoking, and those who either continued or quit alcohol consumption. The sample of participants who continued both smoking and alcohol consumption was too small to study (n=4). However, this latter group may be a distinct group; therefore we conducted an additional, exploratory analysis excluding this group. Subsequent changes in the odds ratios of 10% or more were considered noteworthy changes.

Groups were compared using t-tests, Mann-Whitney tests, and Pearson Chi-Square tests where appropriate. Logistic univariable regression analyses were used to investigate the independent associations of continued smoking and alcohol consumption (dependent variables) with the personality traits (independent variables). Odds ratios from these analyses were calculated as quantitative association measures and were accompanied by 95% confidence intervals. Before exploring the explanation of the associations by anxiety or depressive symptoms, we first investigated whether these symptoms were associated with the dependent and independent

variables. If so, anxiety- and depressive symptoms were added separately (model 1 and 2) to those models that showed statistical significance. Any resulting changes in the beta-coefficient of the personality traits were considered as measures of explanation of the associations of personality traits and continued smoking and alcohol consumption. In a supplementary analysis we stratified the analyses according to the level of education (low versus high), and differences between subgroups were statistically tested by including education*personality trait interaction terms. Values of the personality traits, anxiety and depressive symptoms were converted into z-scores prior to the analyses to ensure comparability of the magnitude of the associations. Associations between personality traits and the amount of smoking and alcohol consumed by continued users were tested using Spearman's rank correlation. The level of statistical significance was set at 0.05, two-sided. Imputation and all analyses were performed using IBM SPSS Statistics version 20.0.

Results

Descriptives

Characteristics of the study participants after imputation of missing data are presented in table 2. Women who continued smoking reported a lower educational level compared to women who quit smoking ($p<0.001$). Women who continued alcohol consumption differed from those who quit regarding the personality traits openness to experience and conscientiousness ($p=0.012$ and $p=0.038$, respectively). Furthermore, women who continued alcohol consumption had somewhat higher levels of anxiety and depressive symptoms ($p=0.048$ and $p=0.056$, respectively), compared to those who quit.

Table 2: Characteristics of the study participants (pooled) according to smoking status (continued versus quit) and alcohol consumption status (continued versus quit).

	Continued smoking (n = 101)	**Quit smoking (n =254)**	**P-value**	**Continued alcohol cons. (n =110)**	**Quit alcohol cons. (n=1230)**	**P-value**
Age, mean yrs (SD)	29.7 (4.8)	29.8 (4.9)	0.836	31.85 (4.5)	30.97 (4.4)	0.096
Education, n (%)			**P<0.001**			0.123
Elementary education	3 (3.0)	3 (1.2)		0 (0)	5 (0.4)	
Lower tracts of secondary education	20 (19.8)	43 (16.9)		8 (7.3)	96 (7.8)	
Higher tracts of secondary education	58 (57.4)	93 (36.6)		19 (17.3)	319 (25.9)	
Higher vocational education	17 (16.8)	85 (33.5)		44 (40.0)	499 (40.6)	
University education	3 (3.0)	30 (11.8)		39 (35.5)	311 (25.3)	
Personality traits, mean (SD)						
Neuroticism	30.9 (8.8)	29.5 (7.5)	0.316	29.4 (8.1)	28.5 (7.0)	0.318
Extraversion	41.0 (6.2)	41.7 (5.6)	0.495	42.1 (6.2)	42.3 (5.5)	0.863
Openness to experience	36.5 (5.5)	36.9 (5.7)	0.671	38.9 (5.9)	37.1 (5.5)	**0.012**
Conscientiousness	45.4 (5.6)	45.5 (4.9)	0.876	44.7 (6.1)	46.1 (4.8)	**0.038**
Agreeableness	44.2 (4.7)	45.3 (4.6)	0.133	46.3 (4.7)	46.3 (4.3)	0.973
Multiparous, n (%)	56 (55.4)	139 (54.7)	0.337	66 (60.0)	676 (55.0)	0.182
In a relationship, n (%)	96 (95.0)	246 (96.8)	0.274	108 (98.2)	1217 (99.0)	0.471
Anxiety score, median (IQR)	36.3 (14.7)	33.3 (10.3)	0.080	33.5 (13.5)	33.3 (10.0)	**0.048**
Depression score, median (IQR)	5.1 (5.8)	4.6 (4.8)	0.164	4.6 (5.5)	4.0 (4.0)	0.056

Note: for some variables the numbers do not add up to the total due to rounding of imputed values.

Personality traits and continued smoking

None of the associations between the personality traits and continued smoking were statistically significant (table 3). Subgroup analyses did not show substantial differences in the associations between a low and high educational level. Results of the complete case analyses were not notably different from the results of imputed data. When excluding women who continued both smoking and alcohol consumption, the odds ratios changes less that 10%.

Table 3: Odds ratios (OR) with 95% confidence intervals (95% CI) for continued smoking.

	Unadjusted OR (95% CI)
Neuroticism	1.19 (0.85;1.66)
Extraversion	0.89 (0.63;1.25)
Openness to experience	0.93 (0.68;1.29)
Conscientiousness	0.98 (0.69;1.39)
Agreeableness	0.80 (0.60;1.07)

Note: each personality trait was entered in a univariable regression model. Values for personality traits were included as z-scores.

Personality traits and continued alcohol consumption

Unadjusted odds ratios for the personality traits associated with continued alcohol consumption are presented in table 4. Each unit increase in openness to experience z-score increased the odds of continued alcohol consumption by 38%. Higher scores of conscientiousness decreased the odds of continued alcohol consumption by 23% per unit z-score. The association with continued alcohol consumption was stronger in the lower education group compared to the higher education group for the traits neuroticism and conscientiousness (lower education group: OR 1.56, CI 1.02;2.38 and OR 0.60, CI 0.40;0.90, and higher education group: OR 1.02, CI 0.79;1.33 and OR 0.80, CI 0.61;1.04, respectively). However, the interaction terms for these traits were not statistically significant (p= 0.110 and p=0.259, respectively). Results of the complete case analyses were not notably different from the results of imputed data. When excluding women who continued both smoking and alcohol consumption, the odds ratios changes less than 10%, although the association with conscientiousness showed a confidence interval including 1.00.

Table 4: Odds ratios (OR) with 95% confidence intervals (95% CI) for continued alcohol consumption.

	Unadjusted OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95%CI)
Neuroticism	1.13 (0.91;1.39)		
Extraversion	0.98 (0.77;1.25)		
Openness to experience	1.38 (1.07;1.77)*		
Conscientiousness	0.77 (0.62;0.95)*	0.84 (0.66;1.06)	0.83 (0.65;1.06)
Agreeableness	1.00 (0.76;1.30)		

Note: each personality trait was entered in a univariable regression model. Values for personality traits, anxiety and depressive symptoms were included as z-scores.
Model 1: anxiety symptoms added to unadjusted model
Model 2: depressive symptoms added to unadjusted model
* P<0.05

Explanation by anxiety and depressive symptoms

Although depressive symptoms were associated with continued alcohol consumption only borderline statistically significantly (table 2), we did explore explanation by these symptoms. After adding anxiety and depressive symptoms to the statistical significant association between conscientiousness and continued alcohol consumption, the beta decreased by 32.3% and 27.0%, respectively (table 4). Openness to experience appeared unrelated to both anxiety and depressive symptoms (r_s=0.02 and r_s=0.05, respectively), therefore we refrained from exploring explanation by these symptoms.

The amount of cigarettes and alcohol consumption during pregnancy

Spearman's correlation coefficients ranged between -0.01 and 0.11 for the correlations of the personality traits with the amount of smoking and alcohol consumption. None of the correlations were statistically significant.

Discussion

This study investigated the associations of personality traits with continued smoking and alcohol consumption during mid-pregnancy. Our results showed that continued alcohol consumption is associated with higher levels of openness to experience and lower levels of conscientiousness, compared to women who quit. Moreover, the association between conscientiousness and continued alcohol consumption was partly explained by both anxiety and depressive symptoms. Conversely, continued smoking was not associated with the personality traits. No associations emerged between the personality traits and the amount of

smoking, and alcohol consumption among continued users. Surprisingly, we did not find an association between higher levels of neuroticism and extraversion, and continued smoking and alcohol consumption. General population studies did find higher levels of neuroticism and extraversion to be associated with smoking and alcohol consumption [44-47]. This discrepancy suggests that pregnancy may be a unique period accompanied by different motivations to quit smoking and alcohol consumption, and associated personality traits [12]. On the other hand, more information could have been gained if personality traits had been assessed using a fine-grained approach (i.e. measuring personality at the facet level using for example the 240-item NEO-Personality Inventory)[29].

Continued alcohol consumption

The association between lower levels of conscientiousness and alcohol consumption has been found in the general population as well [45]. Conscientiousness has been identified as a relevant health-related trait [48], and high scores of conscientiousness are consistently associated with health promoting behavior [28]. Individuals scoring high on conscientiousness also tend to follow societal norms and rules [29,31]. This may be an important motivating factor for them especially during pregnancy, as in this time period smoking and alcohol consumption is often actively discouraged by health professionals and the social environment.

In contrast to our finding in a pregnant sample, alcohol consumption seems unrelated to openness to experience in the general population [45,49-51], which further emphasizes that pregnancy may indeed be a unique period. As openness to experience is associated with intellectual curiosity [29], this may imply that women scoring high on this trait are familiar with information about the risks of alcohol consumption during pregnancy. Current literature is inconclusive about the negative effects of small to moderate amounts of alcohol consumption [9], and studies also reported the absence of negative effects on the development of young children [52,53] or on birth outcomes [54]. The lack of consistent evidence regarding negative effects may explain why women scoring high on openness to experience choose to continue alcohol consumption during pregnancy.

Continued smoking

It is difficult to establish whether our findings of non-significant associations with continued smoking is due to the nature of our study population, i.e. consisting of relatively well educated women, or due to a lack of statistical power. Maxson and colleagues studied 482 predominantly low income, non-Hispanic black pregnant women in the United States and found an association between lower levels of agreeableness and continued smoking [30].

However, as low income is related to smoking during pregnancy [21], including a sample of predominantly low income women may hamper generalizibility to the total pregnant population. Moreover, our findings on continued smoking suggest that the role of personality is limited compared to continued alcohol consumption. Possibly other factors such as a low socioeconomic status, having a partner who smokes, and great nicotine dependence are more important determinants of continued smoking during pregnancy [21,55,56]. Future studies should address the topic of personality and continued smoking during pregnancy in a large representative sample as we cannot exclude the possibility of a small effect.

Anxiety and depressive symptoms

The association between lower levels of conscientiousness and continued alcohol consumption was partly explained by anxiety and depressive symptoms. These findings suggest that continued alcohol consumption may indeed be a strategy to cope with feelings of negative affect during pregnancy.

Strengths and limitations

To our knowledge, this is the first study that investigated the associations between personality traits and continued versus quit alcohol consumption during mid-pregnancy. Also the relationships of the personality traits with the amount of smoking and alcohol consumption during pregnancy have not been explored before. As the present study investigated both smoking and alcohol consumption behavior, we were able to perform an additional, exploratory analysis in which we excluded women who continued both risky behaviors. Results from this analysis suggested that this latter group may be a distinct group to a small extent only as we observed changes in the odds ratios of less than 10%, compared to our primary analyses. Due to a small number, our study was not able to properly investigate the association between personality traits and continuation of both risky behaviors. Future studies including a larger sample may further investigate this association. Consequently, the results from the present study can be generalized to Dutch women who smoked and/or consumed alcohol before pregnancy. Some limitations should be considered. First, questions about smoking and alcohol consumption may have been subject to social desirable reporting which in turn may be related to personality. Second, we did not assess the exact time point in which women quit smoking or alcohol consumption. However, as personality is seen as a relatively stable factor [57], it is not likely that this influenced the associations under study, perhaps with the exception of the associations of anxiety and depressive symptoms. These symptoms could have been the result rather than the cause of quitting smoking and alcohol consumption. Third, regarding the amount of smoking and alcohol consumption among continued users,

studies performed among the general population did show associations with personality [58]. In our study the amount of smoking and alcohol consumption was measured categorically which has inevitably caused some loss of detail in outcome assessment and consequent dilution of associations. Fourth, we were not able to assess the level of dependence, which is considered an important factor with respect to smoking and alcohol consumption during pregnancy [21,25]. Finally, we did not measure personality traits at the facet level and it may well be that there are associations at the facet level.

Conclusion

This study demonstrated that two personality traits, openness to experience and conscientiousness, are related to continued alcohol consumption during mid-pregnancy, but none of the traits to continued smoking. Increased insight in how personality influences continued smoking and alcohol consumption during pregnancy can help health professionals, such as midwifes, gynecologists, and general practitioners, to improve lifestyle interventions targeted at pregnant women.

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CHAPTER 4

Adverse pregnancy and delivery outcomes associated with postpartum smoking: a prospective cohort study

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Abstract

Aim: many women who quit smoking during pregnancy relapse postpartum. Postpartum smoking has been identified as a way of coping with stressful situations. We investigated the associations of adverse pregnancy and delivery outcomes (APDO), e.g. emergency cesarean section and preterm delivery, and transfer from planned home-delivery to hospital-delivery (transfer) with postpartum smoking.

Method: data from a prospective population-based cohort study among pregnant women (n=2,477) from midwifery practices and hospitals were used. We selected participants who reported smoking prior to but not during the current pregnancy (n=923). Postpartum smoking was defined as a self-report of smoking at six months postpartum. We used multiple imputation because of a high proportion of missing data (up to 44%).

Findings: there were 130 (14%) postpartum smokers. The experience of at least one APDO was associated with over a two-fold increased odds of postpartum smoking (odds ratio 2.1, 95% confidence interval 1.3 to 3.5). With each APDO category that applied, the odds of postpartum smoking increased by approximately 60% (1.2 to 2.2). Similarly, transfer increased the odds of postpartum smoking (2.0, 1.2 to 3.3), but not independent from APDO. These associations were not affected by smoking intensity and duration prior to the current pregnancy.

Conclusions: the experience of APDO was associated with a doubled odds of postpartum smoking and the odds increased with increasing exposure to APDO. The high proportion of missing data necessitates cautious interpretation. The experience of APDO should be considered in targeting anti-smoking strategies that focus on continued abstinence after pregnancy.

Introduction

Pregnancy is considered an important motivator to quit smoking [1]. Unfortunately, between 24% and 60% of women who quit smoking during pregnancy relapse within six months after childbirth [2-5]. Smoking after pregnancy not only exposes the newborn to the health risks of environmental tobacco smoke [6,7], it also increases the risk of adverse health outcomes in the mother and other household members [8]. In addition, there is evidence that women who remain abstinent are more likely to breastfeed for a longer duration [9].

Smoking has been identified as a way of coping with feelings of negative affect and stressful situations, also in the postpartum period [10,11]. We hypothesized that because adverse pregnancy and delivery outcomes (APDO) and transfer from planned home-delivery to hospital-delivery may induce psychological stress, they may trigger postpartum smoking. For example, emergency cesarean section and instrumental vaginal delivery are experienced as more stressful compared to a normal vaginal delivery [12,13] and may even initiate posttraumatic stress reactions [14]. In addition, pregnancies complicated by preeclampsia, preterm delivery or low birth weight have been shown to be stressful for the mother [15,16]. Also, negative birth experiences have been linked to transfer from planned home-delivery to hospital-delivery [17,18]. A possible explanation of the association of these events with postpartum smoking may lie in postpartum depressive symptoms, which are known to be related to both APDO and postpartum smoking [19,20].

The present study investigated the associations of APDO and transfer from planned home-delivery to hospital-delivery with smoking within six months postpartum. In addition, we explored if these associations could be explained by postpartum depressive symptoms or smoking intensity and duration prior to the current pregnancy. To our knowledge, these associations have not been studied to date.

Methods

Setting and participants

The present analysis was carried out using data from the ongoing Pregnancy Anxiety and Depression (PAD) study [21]. This population-based, prospective cohort study examines psychological, medical and social factors during and after pregnancy. Women in their first trimester of pregnancy are invited to participate when visiting one of the collaborating primary midwifery practices (n=109) or obstetric and gynecology departments of hospitals (n=7)

throughout The Netherlands. Women who provide written informed consent and master the Dutch language enter the study. Written informed consent includes permission to retrieve medical birth records. Participants are asked to complete online questionnaires at several occasions both during and after pregnancy. Data collected between May 2010 and June 2013 were used for the present analysis. Of the 3,426 women who agreed to participate in the PAD study 2,477 (72%) completed the follow-up questionnaires at six months postpartum and formed the eligible study population. Out of these, women who reported smoking prior to but not during the current pregnancy, were selected for the present analysis. The PAD study was approved by the medical ethical review board of the University Medical Center Groningen.

Smoking status

Smoking status prior to and during pregnancy was ascertained by self-report at 19 and 36 weeks estimated gestational age (EGA) using the following two questions: 1) '*Are you a former smoker*?' (yes/no) and 2) '*Are you currently smoking cigarettes?*' (yes/no). Question 2 was repeated at six months after childbirth. Our study population consisted of women who reported at both the 19 and 36 weeks EGA assessment 'yes' to question 1 and 'no' to question 2. Postpartum smoking and smoking abstinence was defined as reporting 'yes' and 'no' to question 2 six months postpartum, respectively. Furthermore, we measured smoking intensity and duration prior to the current pregnancy as these variables likely predict postpartum smoking and may be associated with APDO. Therefore they may act as confounders. Measuring smoking intensity and duration prior to pregnancy was done by assessing the average amount of cigarettes per day (1-5; 6-10; 11-15; 16-20; 21 or more), and the number of years (1-5; 6-10; more than 10) a participant had been smoking. Smoking intensity and duration were multiplied to arrive at a crude measure of total smoking exposure (intensity X duration). The average amount of cigarettes smoked per day by postpartum smokers was assessed in the same categories as smoking intensity prior to pregnancy.

Adverse pregnancy and delivery outcomes

APDO, as registered in medical birth records, were provided by midwifes and gynecologists, and included four categories: 1) adverse antenatal conditions (hypertension: diastolic >90 mm/ Hg and preeclampsia or HELLP syndrome), 2) adverse delivery outcomes (emergency cesarean section and instrumental birth: forceps delivery and vacuum extraction), 3) adverse afterbirth outcomes (postpartum blood loss >1 liter and manual placenta removal), 4) adverse neonatal outcomes (meconium-stained fluid, preterm delivery (<37 weeks), low birth weight (<2500g) adjusted for gestation, low Apgar score (first minute <7), perinatal death, and the presence of a congenital defect). For the analyses, we created a variable 'any APDO' indicating the

presence of at least one APDO. Furthermore, we created a variable indicating the number of APDO categories that applied. In addition to APDO, we registered 'transfer' if a participant had to transfer from home-delivery to hospital-delivery.

Depressive symptoms

Depressive symptoms were assessed six weeks postpartum using the Dutch version of the validated 10-item Edinburgh Postnatal Depression Scale [22].

Other variables

Socio-demographic variables included age, educational level, and parity. Educational level was assessed in the following categories: elementary education, lower tracts of secondary education, higher tracts of secondary education, higher vocational education, and university education. Parity was assessed as primiparae or multiparae.

Multiple imputation of missing data

The percentage missing values for the questionnaire variables ranged from 0% (smoking status at six months postpartum) to 29% (parity). As for medical birth records, data from 1096 (44%) participants were not available because they were either not provided by midwifes/ gynecologists, or participants did not give permission to retrieve their medical birth record. To avoid the risk of bias and loss of statistical power, we imputed missing data using multiple imputation under the assumption that data were missing completely at random or missing at random (MAR) [23]. Multiple imputation is considered an appropriate method to deal with missing data, even when rates of missing data are relatively high [24,25]. We used the Multivariate Imputation by Chained Equations (MICE) algorithm and imputed 20 datasets following recommendations by Graham given the high percentages of missing data [24]. We compared observed and imputed data following the recommendations made by Sterne et al. for occasions in which large proportions of data are missing [23]. Differences between observed and imputed values ranged from 0% to 5.9%. The imputation model included all variables that were either considered predictive of the missing values or predictive of missingness of a variable [23]. Consequently, the imputation model included age, parity, level of education, APDO, transfer, depressive symptoms at six weeks postpartum, smoking intensity and duration, smoking status before, during and six months after pregnancy. Datasets were pooled using Rubin's rules [26]. Using multivariable logistic regression models, we studied the missing data mechanism by predicting the probability of a value being missing for each variable of main interest. In these models the independent variables were those variables that were also included in the imputation models. These analyses showed explained variances ranging

from 22.0% to 30.0% (Nagelkerke's R^2). This implied that data were likely missing at random to some extent but data being missing not at random cannot be excluded. Consequently, as a sensitivity analysis, we performed complete case analyses (CCA) and compared the results with those obtained using MICE. Missing data analysis and multiple imputation was performed in the total eligible study population.

Data analysis

After imputation, 1,068 out of 2,477 women (43%) reported smoking prior to the current pregnancy. One hundred and forty-nine women reported smoking during pregnancy, and were excluded for the analyses. Postpartum smokers and abstainers were compared on socio-demographic variables using independent samples t-tests, Mann-Whitney tests or Pearson Chi-Square tests where appropriate. Logistic regression was used to investigate the associations of postpartum smoking with 'any APDO', the individual APDO categories, or 'transfer' entered as independent dichotomous variables. To investigate a possible trend, we additionally entered 'number of APDO categories that applied' as a continuous independent variable. Because only 3.8% and 0.2% of women had three or four APDO, respectively, we first categorized 'number of APDO categories that applied' in 0, 1, and 2 or more APDO. In addition, we studied the mutual independence of APDO categories, as well as the independent contributions of 'transfer' and 'any APDO' to the risk of postpartum smoking, by entering the respective variables simultaneously in two multivariable regression models. Before exploring the explanation of the associations by depressive symptoms, we first investigated whether these symptoms were associated with APDO, transfer, and postpartum smoking. If so, depressive symptoms were added as an independent variable to the models in which the association of APDO or transfer with postpartum smoking were statistically significant. Subsequent relative changes in the beta coefficient for APDO or transfer were considered measures of explanation with an arbitrary percentage larger than 10 being regarded as substantial. Age and parity were considered as potential confounders [27]. In the total sample including never smokers (n=2,477), APDO was not associated with smoking intensity (OR=1.0, p=0.72) nor with duration (OR=1.0, p=0.93), nor with intensity X duration (OR=1.0, p=0.88) prior to pregnancy. Similar findings were obtained for the associations with transfer. Based on these findings we did not include smoking intensity, duration, and intensity X duration prior to pregnancy as confounders. Instead, we explored these variables as effect modifiers. We stratified the analyses according to these variables, in which category 3, 4, and 5 of smoking intensity were combined into one, and values of intensity X duration were arbitrarily categorized into three categories based on their distribution. Differences between subgroups were statistically tested by adding interaction terms to the regression models. The level of statistical significance was set at 0.05, two-sided. All analyses were performed using IBM SPSS Statistics version 20.0.

Results

Descriptives

Table 1 presents the characteristics of the study population, and shows that 130 (14%) women reported postpartum smoking and 793 (86%) women abstained. These numbers do not add up to the total number of 1068 former smokers minus 149 pregnancy smokers due to the pooling of datasets in the imputation process. Postpartum smokers were slightly younger ($p=0.03$), reported at least one APDO more often ($p<0.01$), and had adverse neonatal outcomes as well as a transfer to a hospital-delivery more often ($p<0.01$), compared to abstainers. Further, postpartum smokers reported higher smoking intensity ($p=0.03$) and duration ($p<0.01$) prior to the current pregnancy. As for the average amount of cigarettes smoked per day among postpartum smokers, 71 (54.6%) participants smoked 1-5, 40 (30.8%) smoked 6-10, 12 (9.2%) smoked 11-15, and 8 (6.2%) smoked 16-20.

Table 1: Characteristics of study participants (n=923) according to smoking status (pooled)

	Postpartum smokers (n=130)	**Abstainers (n=793)**	**P-value**
Age in years, mean (SD)	31.6 (4.4)	32.6 (4.1)	**0.03**
Education, n (%)			0.23
Elementary education	1 (0.8)	1 (0.1)	
Lower tracts of secondary education	14 (10.8)	78 (9.8)	
Higher tracts of secondary education	53 (40.8)	277 (34.9)	
Higher vocational education	48 (36.9)	318 (40.1)	
University education	14 (10.8)	122 (15.4)	
Multiparous, n (%)	74 (56.9)	493 (62.2)	0.28
Any APDO, n (%)	89 (68.5)	398 (50.2)	**<0.01**
Adverse antenatal outcomes	14 (10.8)	64 (8.1)	0.43
Adverse delivery outcomes	37 (28.5)	167 (21.1)	0.17
Adverse afterbirth outcomes	36 (27.7)	158 (20.0)	0.12
Adverse neonatal outcomes	51 (39.2)	206 (26.0)	**0.03**
Number of APDO categories that applied, n (%)			**<0.01**
0 APDO	38 (29.2)	376 (47.4)	
1 APDO	52 (40.0)	270 (34.0)	
≥ 2 APDO	40 (30.8)	147 (18.5)	
Transfer, n (%)	55 (42.3)	212 (26.7)	**<0.01**
EPDS-score at 6 weeks postpartum, median (IQR)	4.2 (5.1)	4.0 (4.0)	0.49
Smoking intensity prior to pregnancy, number of daily cigarettes, n (%)			**0.03**
1-5	36 (27.7)	331 (41.7)	
6-10	37 (28.5)	193 (24.3)	
11-15	33 (25.4)	135 (17.0)	
16-20	18 (13.8)	104 (13.1)	
21 or more	7 (5.4)	30 (3.8)	
Smoking duration prior to pregnancy, number of years, n (%)			**<0.01**
1-5	22 (16.9)	342 (43.1)	
6-10	51 (39.2)	273 (34.4)	
More than 10	57 (43.8)	178 (22.4)	

Imputed data set. Unimputed data included 119 postpartum smokers and 722 abstainers
Due to rounding numbers may not add up to the total
APDO= Adverse Pregnancy and Delivery Outcomes
EPDS= Edinburgh Postnatal Depression Scale

Postpartum smoking

In an unadjusted analysis, 'any APDO' and 'transfer' were both associated with an approximately two-fold increased odds of postpartum smoking (table 2). Adjusted for each other, 'any APDO' was still independently associated with postpartum smoking (OR=1.9, 95%CI 1.1;3.2) but 'transfer' no longer showed a statistically significant association (OR=1.9, 95%CI 1.0;3.2). With each APDO category that applied, the odds of postpartum smoking increased by approximately 60%. Each individual APDO category showed an odds ratio above 1.0, but the association was statistically significant for 'adverse neonatal outcomes' only, and remained unaltered when adjusted for the other APDO categories (OR=1.8, 95%CI 1.0;3.2). Adjustment for age and parity did not notably change the associations (table 2). The CCA showed that the unadjusted estimates in general attenuated when compared to the results using MICE, and that the association of 'adverse neonatal outcomes' with postpartum smoking was no longer statistically significant. The CCA further showed that after adjustment for age and parity, most associations lost their statistical significance. Stratified analyses according to prior smoking intensity and duration showed that the magnitude of the associations were not substantially different and none of the interaction terms were statistically significant.

Explanation by depressive symptoms

Depressive symptoms were not associated with postpartum smoking (table 1), therefore we refrained from our analyses on their explanatory potential.

Table 2: Unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (95%CI) for the associations of APDO and 'transfer' with postpartum smoking

	Unadjusted OR (95%CI) MICE	Adjusted† OR (95%CI) MICE	Adjusted‡ OR (95%CI) MICE	Unadjusted OR (95%CI) CCA	Adjusted† OR (95%CI) CCA	Adjusted‡ OR (95%CI) CCA
Any APDO	2.1** (1.3;3.5)	2.2** (1.3;3.6)	2.2** (1.3;3.6)	1.8* (1.0;3.0)	1.6 (0.9;2.8)	1.8 (0.9;3.4)
Adverse antenatal outcomes	1.3 (0.5;3.3)	1.3 (0.5;3.3)	1.3 (0.5;3.3)	1.2 (0.4;3.2)	0.9 (0.3;2.7)	1.0 (0.3;3.9)
Adverse delivery outcomes	1.5 (0.8;2.7)	1.5 (0.8;2.6)	1.5 (0.8;2.7)	1.2 (0.6;2.3)	1.3 (0.7;2.5)	1.3 (0.6;3.0)
Adverse afterbirth outcomes	1.6 (0.9;2.7)	1.6 (0.9;2.8)	1.6 (0.9;2.8)	1.4 (0.7;2.7)	1.5 (0.7;2.9)	1.4 (0.6;3.3)
Adverse neonatal outcomes	1.8* (1.0;3.2)	1.9* (1.1;3.4)	1.9* (1.1;3.4)	1.6 (0.9;2.9)	1.5 (0.8;2.8)	1.4 (0.7;2.8)
Number of APDO categories that applied	1.6** (1.2;2.2)	1.6** (1.2;2.2)	1.7** (1.2;2.3)	1.6* (1.1;2.3)	1.6* (1.0;2.3)	1.5 (0.9;2.5)
Transfer	2.0** (1.2;3.3)	1.9** (1.2;3.2)	1.9** (1.2;3.2)	1.8* (1.0;3.1)	1.6 (0.9;2.9)	1.4 (0.7;2.8)

Note: each variable was entered in a univariable regression model
APDO= Adverse Pregnancy and Delivery Outcomes
MICE= Multivariate Imputation by Chained Equations
CCA= Complete Case Analysis
* p<0.05
** p<0.01
† adjusted for age
‡ adjusted for age and parity

Discussion

To our knowledge, this is the first study that investigated the associations of postpartum smoking with APDO and transfer from planned home-delivery to hospital-delivery. Our findings showed that women who had at least one APDO have a more than two-fold increased odds of postpartum smoking. Transfer increased the odds of postpartum smoking as well, although not independent from APDO. Furthermore, 'adverse neonatal outcomes' showed a positive association with postpartum smoking. We also found a trend of increasing 'number of APDO categories that applied' with increasing odds of postpartum smoking. Depressive symptoms could not explain the associations, nor could smoking intensity and duration prior to pregnancy.

Strengths and limitations

Strengths of the present study include the prospective cohort design, which has limited the potential for recall bias, and a favorable follow-up rate. Data were mainly collected in primary obstetric care throughout The Netherlands, which may warrant generalizability of our results to pregnant women from the general population, although highly educated women were somewhat overrepresented. Study limitations should be mentioned. First, a major limitation is the relatively large proportion of missing data from medical birth records. Still, the use of data from medical birth records is preferred over self-report data, as it has been shown that parental recall of birth outcomes lacks precision [28]. We aimed to tackle the limitations caused by missing data by using multiple imputation, which is a preferred method [23]. However, our results should be interpreted with some caution. Second, despite the large total sample, the sample size of women who smoked postpartum was relatively small. This may partly explain the differences in statistical significance between results of the analyses using MICE and results of the CCA. Third, we did not measure smoking behavior by the partner, which could have been a confounder [29]. Finally, smoking status was measured using self-report questionnaires and thus may have been underreported. Although it cannot be excluded that women who experienced APDO feel guilty and are less likely to report their true postpartum smoking status, we assume that possible underreporting at six months postpartum is largely independent of APDO.

Comparison with previous studies and explanation of findings

The present study provides new insights into predictors of postpartum smoking, and adds to existing literature showing that having to cope with stressful situations is a major risk factor for postpartum smoking [11]. Our findings suggest that although APDO may trigger postpartum

smoking, not necessarily all categories of APDO are associated with postpartum smoking. The association between adverse neonatal outcomes and postpartum smoking connects to previous research on psychological stress. For example, parents of low birth weight infants are concerned about the health of the newborn [30]. In addition, the consequences of having a newborn in the neonatal intensive care unit, i.e. having poor sleep quality and the physical separation, may be important factors in the development of psychological stress [31,32]. No association with postpartum smoking was found for other APDO categories. However, previous research showed that adverse delivery outcomes are associated with postpartum psychological problems. Women who had an unplanned cesarean section or instrumental delivery showed a higher risk of exhibiting posttraumatic stress symptoms [13,33]. It is also suggested that specifically in individuals with posttraumatic stress symptoms, smoking is considered as a way of coping with negative affect [34]. Nevertheless, our data could not provide evidence for a direct association between adverse delivery outcomes and postpartum smoking . Our finding that 'transfer' may increase the risk of postpartum smoking connects to our main finding that APDO is related to postpartum smoking; when presenting with APDO, a hospital setting will most likely be required. Consequently, when adjusting for the experience of APDO, the association for 'transfer' attenuated.

The rate of postpartum smoking in the present study was 14%, which seems low in comparison to rates reported by others [2,3,5]. We defined prior smoking as smoking before pregnancy irrespective of a time period, whereas others defined prior smoking as smoking status three or twelve months before pregnancy [2,3]. Consequently, our study included a larger proportion of former smokers, including women who may have quit long before pregnancy, which may have led to a lower rate of postpartum smoking. Nevertheless, we regard it as plausible that a large proportion of participants reporting postpartum smoking were probably also smoking in the period close to the beginning of pregnancy.

Implications of study findings

Our findings could have serious implications, given that taking up smoking again after childbirth has multiple detrimental health effects not only on the mother, but also on the child and other household members [8]. In addition, postpartum smoking may cause women to quit breastfeeding earlier [9]. If women can abstain for a longer period after pregnancy they are more likely to meet WHO breast feeding guidelines and thus promote the health of their newborn [36]. In turn, breastfeeding has been suggested as a facilitator for maintaining postpartum smoking abstinence [37].

Furthermore, the present study may be of important clinical relevance. Women presenting with APDO will most likely spend some time in the hospital, thus providing nurses with the opportunity to address the psychological impact of the experience of APDO. Interestingly, it has been shown that an anti-smoking intervention in a hospital setting, including enhanced support for the mother-infant bonding during a newborn's hospitalization after childbirth, can be effective [38]. Women who had the intervention were more likely to be smoke free and breast feeding at eight weeks postpartum, compared to those who did not receive additional support [38]. Our findings suggest that it may be most efficient to target suchlike anti-smoking interventions specifically at women with APDO.

Conclusion

This study demonstrated that APDO increase the risk of postpartum smoking, and this risk increases in a graded way with the number of APDO. The experience of APDO should be considered in targeting anti-smoking strategies that focus on continued abstinence after pregnancy. In addition, women who experience APDO may be supported psychologically in handling the resulting stress. Future studies, preferably including larger samples and lower rates of missing data, may confirm our findings and could explore the underlying mechanism behind the associations found in our study.

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CHAPTER 5

Screening and treatment of anxiety and depressive symptoms during pregnancy:

*The **P**regnancy **A**nxiety and **D**epression cohort study and the **PR**egnancy **O**utcomes after a **M**aternity **I**ntervention for **S**tressful **E**motion**S** randomized controlled trial**

This chapter is based on:

- Meijer JL, Bockting CL, Beijers C, Verbeek T, Stant AD, Ormel J, Stolk RP, de Jonge P, van Pampus MG, Burger H. PRegnancy Outcomes after a Maternity Intervention for Stressful EmotionS (PROMISES): study protocol for a randomized controlled trial. *Trials*. 2011 Jun 20;12:157.
- Burger H, Bockting CLH, Beijers C, Verbeek T, Stant D, Ormel J, Stolk RP, de Jonge P, van Pampus, MG, Meijer JL. PRegnancy Outcomes after a maternity Intervention for Stressful EmotionS (PROMISES): a randomized controlled trial. In: Perinatal Programming of Neurodevelopment. Edited by M. Antonelli, 2013

*Both studies are still in progress

Abstract

Background: there is ample evidence from observational prospective studies that maternal anxiety or depression during pregnancy is a risk factor for adverse psychosocial outcomes in the offspring. However, to date no previous study has demonstrated that treatment of depressive or anxious symptoms in pregnancy actually could prevent psychosocial problems in children. Preventing psychosocial problems in children will eventually bring down the huge public health burden of mental disease. The main objective of this study is to assess the effects of cognitive behavioral therapy in pregnant women with symptoms of anxiety or depression on the child's development as well as behavioral and emotional problems. In addition, we aim to study its effects on the child's development, maternal mental health, and neonatal outcomes, as well as the cost-effectiveness of cognitive behavioral therapy relative to usual care.

Method: women in primary midwifery practices and gynecology departments of hospitals are screened for anxiety and depressive symptoms. We will include 300 women with at least moderate levels of anxiety or depression at the end of the first trimester of pregnancy. By including 300 women we will be able to demonstrate effect sizes of 0.35 or over on the total problems scale of the child behavioral checklist 1.5-5 with alpha 5% and power (1-beta) 80%. Women in the intervention arm are offered 10-14 individual cognitive behavioral therapy sessions, 6-10 sessions during pregnancy and 4-8 sessions after delivery (once a week). Women in the control group receive care as usual. The primary outcome is behavioral/emotional problems at 1.5 years of age as assessed by the total problems scale of the child behavior checklist 1.5 – 5 years. Secondary outcomes are mental, psychomotor and behavioral development of the child at age 18 months according to the Bayley scales, maternal anxiety and depression during pregnancy and postpartum, and neonatal outcomes such as birth weight, gestational age and Apgar score, health care consumption and general health status (economic evaluation).

Trial Registration: NTR2242

Background

The burden of mental disorders is huge and at least comparable to the burden caused by many severe physical diseases. In the WHO Global Burden of Disease project it was estimated that 50% of all daily adjusted life years (DALY's) in the 15-44 years old are due to nine psychiatry-related conditions [1]. Depressive disorders are projected to rank second on a list of 15 major diseases in terms of burden of disease in 2030 [2]. In addition, a substantial part of the costs are caused by new cases, which account for 39.2% of the costs at population level [3]. Therefore, prevention of mental disorders is essential.

Maternal anxiety and depression during pregnancy are important and potentially modifiable risk factors for cognitive, behavioral and emotional problems among the offspring [4-9]. Around 10-20% of all women are suffering from anxiety or depression during pregnancy [10-13]. The magnitude of the effects of maternal anxiety or depression on the child's psychosocial problems is considerable: it is estimated that up to 22% of the variance in behavioral problems is linked with prenatal anxiety, stress or depression [8]. The adverse effects seem to be lasting. For example, antenatal anxiety of the mother was related to behavioral or emotional problems of 4 year old children, independent of the mother's postnatal anxiety or depression [4]. Higher anxiety levels of the mothers early in pregnancy were related to an increase in ADHD and other externalizing problems in their 8-9 year old children [14].

There are several mechanisms through which anxiety or depression during pregnancy could have an adverse effect on the offspring. These mechanisms can be divided into direct and indirect. A direct mechanism that has been researched for decades is one in which anxiety or depression activate the maternal stress system leading to elevated glucocorticoid levels, which subsequently influence the development and long-term physiology of the fetus' brain by passing the placenta. This direct mechanism falls under the rubric of "early life programming" and has been a popular hypothesis for the explanation of not only brain disorders but has been suggested to play a role in cardiovascular disease as well [15]. Further, epigenetic variation has been proposed as a mediating mechanism in linking early life exposures to long-term psychological and behavioral outcomes [16].

The effect of maternal stress on the developing fetus might also be indirect. Women who suffer from antenatal depression have the tendency to take less good care of themselves (e.g. neglecting personal hygiene, the occurrence of sleeping problems, disturbed drinking and smoking habits, denying prenatal care). These consequences might all influence the

development of the fetus [17-20]. Another indirect way in which depression might influence the mental development of the offspring is when the antenatal depression remains after delivery and turns into a postnatal depression. In this way, mother-child attachment might be endangered, because the mother has a reduced ability to respond to the child. Children from depressed mothers have a higher risk of insecure attachment, which in turn is associated with cognitive, behavioral and emotional problems [1,21-23]. In addition, the association between antenatal depression and adverse outcomes in the offspring might be indirect because it could be explained by a shared genetic predisposition between mother and child.

Whatever the actual mechanisms involved are, there is presently convincing evidence that children whose mothers suffered from anxiety or depression during pregnancy constitute a high risk group for behavioral and emotional problems. On population level, substantial total mental health gains may be accomplished when depressed or anxious women are adequately treated during their pregnancy, even if the effect size of the treatment is relatively small.

Maternal anxiety and depression is under-detected and thus remains untreated. Current NICE guidelines (UK) and Beyondblue guidelines (Australia) suggest to screen for depression [24,25]. NICE guidelines propose to ask two questions at a woman's first contact with primary care [25]:

1) 'During the past month, have you often been bothered by feeling down, depressed or hopeless?'
2) 'During the past month, have you often been bothered by having little interest or pleasure in doing things?'

Beyondblue guidelines suggest to screen women at least once during pregnancy for depression using the Edinburgh Postnatal Depression Scale (EPDS) [24]. The EPDS has shown quite good test performances with sensitivity and specificity ranging from 80-90% [26]. Furthermore, overall, screening during pregnancy seems to be accepted by most pregnant women and health professionals [27]. As for the effectiveness of screening, it is suggested that screening needs to be 'part of an integrated, well-resourced process with clear pathways to diagnostic assessment and effective accessible treatment' [27].

As for treatment, the effectiveness of psychological therapy in the treatment of both anxiety and depression has been shown during the past 50 years, especially for cognitive behavioral therapy (CBT) [28-32]. Although guidelines state that medication is an alternative effective treatment, the safety of antidepressants and anxiolytics during pregnancy remains insecure [33]. Besides, pregnant women prefer psychological treatment over pharmaco-therapy [34]. To

date, current evidence on the effectiveness of CBT for treatment of anxiety and depression during pregnancy is limited and inconclusive [35-37]. Also, it is too early to implement CBT for depressed or anxious women to prevent psychosocial problems in the offspring. This is because in the development of such a preventive strategy, demonstration of the causality and size of the effect of the reduction of symptoms of anxiety and depression on child outcomes is a crucial step, a step that has not been taken to date.

We set up the 'Pregnancy Anxiety and Depression' (PAD) cohort study to screen pregnant women in participating primary midwifery practices and gynecology departments of hospitals for anxiety or depression symptoms. Women presenting with at least moderate symptoms of anxiety or depression are eligible to enter the 'PRegnancy Outcomes after a Maternity Intervention for Stressful EmotionS (PROMISES) study. This latter study is a randomized controlled trial (RCT) that studies the effect of CBT as compared to care as usual (CAU) on the offspring's behavioral and emotional problems. In the CBT arm, we expect beneficial neonatal outcomes, in particular higher birth weight and less prematurity, which are risk factors for adverse cognitive and behavioral outcomes themselves [5]. We also anticipate reduced smoking and less drinking, with many physical and mental health benefits for the child as a result [20]. Since prenatal depression has shown to be related to postnatal depression, we hypothesized that our intervention will also counter postnatal depression, which in turn will benefit the mother – child attachment [38]. Finally, but not unimportantly, the reduction of symptoms of anxiety or depression during pregnancy and the early postnatal period is valuable in itself. CBT may further provide for a safer approach to reducing symptoms in pregnancy than antidepressant medication [33]. To date, no such study has been performed as far as we are aware of.

Methods

Objective

The aim of the present study is to examine the effect of CBT in women with at least moderate symptoms of anxiety and/or depression at the end of the first trimester of pregnancy, on the extent of total behavioral and emotional problems in their children at 1.5 years of age, as compared with care as usual (CAU).

Setting

The source population consists of all pregnant women in The Netherlands in the first trimester of their pregnancy. Obstetric health care in The Netherlands is arranged a bit differently

compared to other western countries. In case of no (increased risk for) complications, pregnant women typically enter primary care and are monitored by independent midwifes. About 85% of all pregnant women enter obstetric health care this way [39]. The remaining 15% is referred to a gynecologist/obstetrician in a hospital (secondary and tertiary care). For the present study, women were recruited in primary, secondary and tertiary obstetric care.

Screening

All pregnant women in their first trimester (<16 weeks) mastering the Dutch language are invited to participate in the PAD study. This prospective population-based cohort study investigates psychological, social, and medical factors during pregnancy. In the PAD study, women are screened on both anxiety and depressive symptoms. Women are asked to fill out the Dutch version of the 6-item State Trait Anxiety Inventory (STAI) [40] and the 10-item EPDS [41]. Women with at least moderate symptoms of anxiety and/or depression are invited to participate in the PROMISES study. Cut-off values of ≥42 are used for STAI and ≥12 for EPDS.

Exclusion

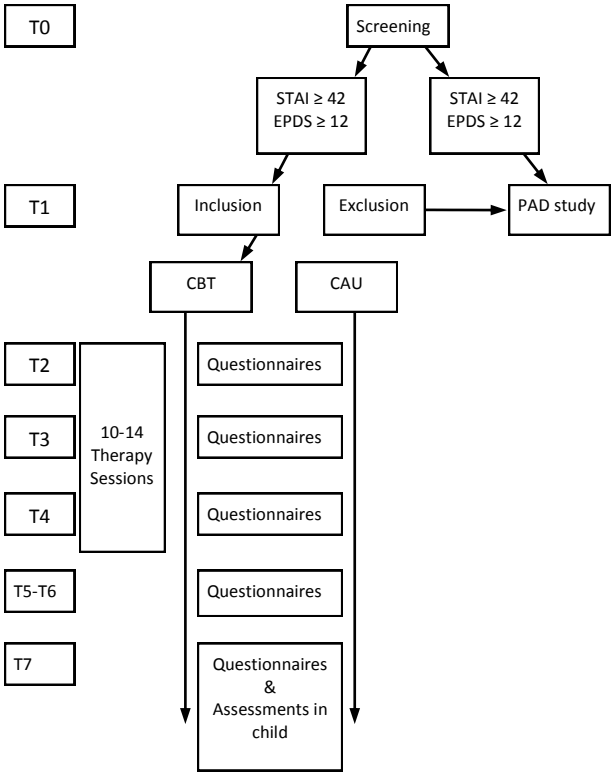
Women fulfilling one or more of the following criteria are excluded from participation in the PROMISES study:

1. High suicidal risk according to the suicidality subscale score on the MINI International Neuropsychiatric Interview (MINI, defined as a positive response on the question on concrete suicide plans)
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

Design

Women eligible for the PROMISES study are either randomized to the intervention group in which they receive 10-14 sessions of CBT, or to the control group in which they receive care as usual. Figure 1 shows the detailed design of the study.

Figure 1: Flow diagram



Study outcome measures

The primary outcome of the PROMISES study is the total emotional and behavioral problems score of the child according to the Child Behavior Check List 1.5 – 5 (CBCL 1.5-5) at 18 months of age. Secondary outcomes are the child's mental and psychomotor development at 18 months of age, the change in anxiety and depressive symptoms in the mother, obstetric variables such as birth weight, gestational age and Apgar score, socio-demographic and lifestyle factors, such as alcohol use, smoking and education, and cost-effectiveness of the therapy.

Sample size

Studies on the prevention of mental disorders tend to suffer from problems of insufficient statistical power [42]. In the current study we aimed to get around this problem by using a continuous primary outcome measure and by including a high risk group, i.e. selective prevention. We decided that effect sizes of 0.35 (midpoint of small – medium effect size) or over on the total problems scale of CBCL 1.5-5 are to be detected. With alpha 5% and power (1-beta) 80%, we have to include 260 participants in our analyses. To account for some drop out we aim at 300 women entering the trial. If 50% eventually meets all criteria and gives informed consent, 600 screen-positives must be identified. The 50% rate is based on studies with psychological interventions during pregnancy aimed at reducing the occurrence of postnatal depression [38]. Given the figures in the literature [10] we can expect amply 10% screen-positives on either the anxiety or depression screener. With an estimated 50% comorbidity between anxiety and depression this means that approximately 15% are eligible for the randomization. Therefore, 4,000 women needed to be screened. Assuming a response rate of 75% [43] this implicates that 5,333 women must be offered screening. To be on the safe side, we aimed at screening 6,000 women. During the trial it appeared that only 25% rather than 50% of all screen-positive women meets all criteria and gives informed consent. Therefore, we adjusted the number needed to screen for including 300 women to approximately 8,000.

Assessments

Participating women are asked to fill out questionnaires until their child is 1.5 years. This is done at eight time points: the screener at baseline (T0), the additional baseline information at 19 weeks of gestation (T1), and follow-up questionnaires at 24 and 36 weeks of gestation (T2 and T3), at 6 weeks postpartum (T4), 6 months postpartum (T5), 12 months postpartum (T6) and 18 months postpartum (T7). After screening at T0, women agreeing to participate are asked to provide additional baseline data at T1, as to find in figure 2. After providing baseline data both in print and online, women are telephoned for the Structured Clinical Interview for DSM-VI Disorders (SCID-II). The SCID-II will allow us to study treatment effects additionally according to diagnostic categories rather than symptom levels. At each time point, the levels of anxiety and depression are monitored by the STAI and the EPDS. As depicted in table 1, all other questionnaires are filled out once or at several time points and are available online.

Table 1: Assessment per measurement

	T0	T1	T2	T3	T4	T5	T6	T7
Anxiety (STAI)	X	X	X	X	X	X	X	X
Depression (EPDS)	X	X	X	X	X	X	X	X
Personality (NEO-FFI)		X		X		X		
Life events before pregnancy (NLEQ)		X						
Life events during pregnancy		X		X		X		
Perceived social support (SSQ)		X						
Coping styles (UCL)		X	X	X	X			
Attitudes (DAS)		X	X	X	X			
Maternal attachment (ECR)		X					X	
Quality of life (EQ-5D)		X	X	X	X	X	X	
Sociodemographic & -economic factors		X						
Lifestyle		X		X		X		
Breastfeeding						X		
General health		X						
Health care consumption		X			X	X	X	
Previous pregnancies		X						
Suicidality (MINI)		X						
Clinical Diagnostic Interview (SCID-II)		X						
Child Behavior (CBCL)								X
Child development (BSID-II)								X

The following information is obtained from participants. The exact time of administration of the corresponding instrument can be found in table 1.

- Life events before pregnancy are assessed at baseline, using the Negative Life Events Questionnaire (NLEQ) [44].
- Perceived social support is measured according to the 9-item Social Support Questionnaire (SSQ)-short form [45].
- General health, socioeconomic position, ethnicity, smoking behavior, alcohol use, psychiatric history (whether the participant has had anxiety and/or depressive symptoms before, whether she was treated for this and whether she is presently in treatment for these symptoms) is assessed. Socioeconomic position is measured using five indicators: family income, educational level (father and mother). This questionnaire is based on a questionnaire used in the Utrecht Health Project (Dutch acronym LRGP: Leidsche Rijn Gezondheids Project, www.lrgp.nl). General health status will also be taken into account according to the EuroQOL five dimensions questionnaire (EQ-5D) [46].

- Personality is assessed using the NEO Five Factor Inventory (NEO-FFI). The NEO-FFI is a shortened version of the NEO Personality Inventory (NEO-PR-I) [47] and covers the Big Five of personality (neuroticism, extraversion, openness to experience, agreeableness and conscientiousness). These aspects each contain six subscales. The NEO-FFI contains 60 questions, two on each subscale. The present study added four full subscales to the short version; two subscales of neuroticism, one of extraversion and one of conscientiousness. This is because we expected them to have the strongest association with persistence of anxiety and/or depression. The NEO-FFI is translated and validated in Dutch [48].
- Information on previous pregnancies, family size and composition, pregnancy related life events and on reactions on becoming a parent is gathered using questionnaires from the ALSPAC study (www.bristol.ac.uk/alspac).
- Suicide risk is measured using six screening questions from the MINI International Neuropsychiatric Interview [49].
- Maternal attachment style is measured according to the Experiences in Close Relationships questionnaire ECR [50], which has been translated and validated for The Netherlands by Conradi et al. [51].
- Health care consumption is assessed based on the Trimbos and iMTA questionnaire on Costs associated with Psychiatric illness (TIC-P) [52]. This instrument allows reliable recall over the past six months [53].
- Coping style is assessed using the Utrechtse Coping Lijst, the UCL [54].
- A Dutch version of the Dysfunctional Attitude Scale (DAS) is used to measure cognitions and attitudes [55].
- Obstetric variables such as gestational age, birth weight, Apgar score, complications such as (pre)eclampsia or HELLP, were obtained from midwifes. Women were asked to give consent for this.
- Finally, we use the SCID-II to screen for a possible clinical anxiety or depressive disorder [56]. The SCID-II is the only questionnaire used that has to be taken in a personal interview.

Besides questionnaires for the mother during her pregnancy and the first 1.5 years postpartum, there are assessments of the child at 1.5 years of age. One of the assessments concerns the Bayley Scale of Infant Development (BSID-II) [57]. This is a formal neuropsychological tool to assess the developmental level of a child between 1 and 42 months. It is individually administered by one of the researchers and consists of three subscales:

cognitive development (mental development index), gross and fine motor development, and the behavioral rating scale. This tool is widely used in both research and clinical settings and is considered the best and most applied method for the assessment of the child's development to date [58]. Importantly, the instrument has shown to be sensitive. In the context of our proposal, maternal anxiety in pregnancy explained as much as 11% of the variance in the Bayley scores in a study among two year old toddlers by LaPlante et al. [59].

The second assessment is the Child Behavior Check List 1.5 – 5 (CBCL 1.5-5) including the Caregiver-Teacher Report form (C-TRF) and the Language Development Survey (LDS) [60]. This well established, reliable and valid scale designed for parents and caregivers comprises seven syndrome scales: emotionally reactive, anxious depressed, somatic complaints, withdrawn, sleep problems, attention problems and aggressive problems. In addition, it contains scales for internalizing, externalizing and total problems. Symptom scores may further be related to formal DSM-diagnostic criteria. The LDS provides a screen for delays in vocabulary and word combinations. For the assessment of psychopathology in preschool children it is essential to obtain information from different sources [61]. Therefore we decided to include the C-TRF for the caregivers of the children other than their parents. Parents are asked to hand these lists to the actual caregivers of their children, e.g. grandparents, baby-sitters, kindergarten-coaches, et cetera. Relevant in this respect, a review by Skovgaard et al. [58] underlined the significance of both the developmental aspects (e.g. as measured with the BSID-II) and the infant caregiver relation in the assessment of children 0-3 years of age. The CBCL has been used successfully in several studies, amongst others on externalizing problems [62]. It has been translated and standardized for use in around 60 countries, including The Netherlands. The CBCL 1.5-5 is considered a sensitive instrument also deployed in current intervention studies [63,64]. Also, mother-child interaction are measured by taping them for 15 minutes on video and scoring them afterwards on interaction points.

Randomization

Right after the SCID-II interview, women are randomized 1:1 to either CBT or CAU.
We created randomization lists, stratified for parity and socioeconomic position, with randomly permuted blocks of random size. Women randomized to the CAU arm are informed about being at risk of anxiety or depression disorder by the researchers and are advised to contact their GP. A close record is kept of all care provided in the CAU arm.

CBT Intervention

The intervention consists of 10-14 individual sessions: 6-10 sessions during pregnancy and 4-8 sessions after delivery (once a week). The CBT is conducted by registered psychologists, specialized in conducting CBT. CBT posits that an individual's biased information processing leads to maladaptive feelings and behaviors which can culminate in psychological distress and eventually in psychiatric disorders. The main focus of the proposed intervention is targeted on identifying and changing dysfunctional cognitions and schemata (attitudes) specifically for pregnant women with anxiety and depressive symptoms. Furthermore, several optional modules are available that focus specifically on the treatment of anxiety disorders, depressive disorders, and post traumatic stress disorder. In CBT, the Socratic dialog is used aiming to change these dysfunctional cognitions and attitudes permanently. CBT may therefore result in long term protection against psychosocial problems. It is therefore not surprising that cognitive therapy during the acute phase of depression also appears to be effective in reducing subsequent recurrence rates [28].

The first session will focus on the rationale of CBT, i.e. the influence of (irrational or dysfunctional) cognitions and attitudes on feelings and behaviors. Additionally, goal setting is initiated. These therapy goals are unique for each participant. The subsequent sessions are targeted at identifying and amending irrational cognitions and attitudes related to pregnancy, delivery, concerns about the (unborn) child and the future family situation. Each session will address specific pregnancy-related cognitions. Additionally, patients are taught how dysfunctional cognitions and attitudes affect adversely feelings and behaviors. These dysfunctional cognitions and attitudes are challenged and replaced by functional cognitions and attitudes. After each session, patients are given home work. For example, participants are asked to register negative experiences, and accompanying cognitions, feelings and behaviors. Finally, in the last two to four sessions, the newly learned cognitions and attitudes are consolidated.

Data analysis

If necessary, skewed continuous variables will be transformed to normality prior to the analyses. The primary outcome, i.e. the CBCL scores at month 18, will be compared between both arms using the unpaired t-test. This test will also be used for detecting differences in the Bayley scores by month 18 and the obstetric variables measured at birth. The latter group of variables will be tested using the Chi^2 test if categorical. Differences in attachment style at month 12 will be analyzed using analysis of covariance with the baseline variable as a covariate. Continuous outcomes that were measured more than twice (e.g. EPDS and STAI) will

be analyzed as dependent variables using linear mixed models for fixed and random effects. These models are superior for the analysis of longitudinally correlated data and can optimally deal with missing values [65]. A mixed model ascribes a unique intercept and slope estimate to each individual, while making use of information across individuals for predicting these quantities. In these analyses, a treatment*time variable indicating the effect of the intervention will be included as an independent variable. If despite randomization important baseline differences exist in prognostically important variables such as the extent of social support or history of life events, they will be adjusted for. Additional analyses will be conducted to demonstrate mediation of the effect of CBT on the child's outcomes by maternal symptom level, alcohol or nicotine consumption in pregnancy, medication use or neonatal outcomes. The analyses will primarily be carried out according to the intention-to-treat (ITT) principle, i.e. the participants will be analyzed according to their randomized allocation, regardless of the actual CBT undergone, or time in study after baseline. Aside from the optimal validity of ITT analyses, they quantify the effects on the outcome measures that would be obtained in practice. The magnitude of the effect measured in an ITT analysis incorporates the effects caused by non-adherence to CBT, behavioral changes, et cetera. Secondary analyses will be of the 'per protocol' type meaning that they will be restricted to those women that had all of the CBT sessions.

Considering specific target populations, there is evidence that the socioeconomically deprived may benefit more from treatment of depression during pregnancy [17]. Therefore, subgroup analyses will be undertaken according to socioeconomic position. Subgroup analyses will also be undertaken according to parity. Differences in effect of CBT between subgroups will be statistically evaluated by testing treatment by subgroup interaction terms. Effect parameters will be supplied with a 95% confidence interval.

Economic evaluation

An economic evaluation will be conducted alongside the trial to assess the cost-effectiveness of CBT compared to CAU in the current study population. Information on costs and health outcomes will be prospectively collected during 24 months (starting at baseline until 18 months after birth) for both mother and child. Two complementary economic analyses will be conducted. The primary outcome measure of the planned cost-effectiveness analysis is the total emotional and behavioral problems score of the child according to the CBCL at 18 months of age. In the additionally planned cost-utility analysis, QALYs (Quality Adjusted Life Years) will be used as the primary outcome measure. The study will be performed from a societal perspective. Medical costs that will be assessed include costs related to CBT, contacts with

healthcare professionals, and medication use. Outside the healthcare sector, costs of informal care and productivity losses will be taken into account. Unit prices will largely be based on Dutch standard prices in order to facilitate comparisons with other economic evaluations. Cost-effectiveness acceptability curves will be used to inform decision-makers on the probability that the studied intervention is cost-effective.

This study protocol was approved by the medical ethical committee of the University Medical Centre Groningen.

LIST OF ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
ALSPAC	Avon Longitudinal Study Parents And Children
BSID-II	Bayley Scale of Infant Development
CAU	Care As Usual
CBCL	Child Behavioral CheckList
CBT	Cognitive Behavioral Therapy
C-TRF	Caregiver-Teacher Report Form
DALY	Daily Adjusted Life Years
DAS	Dysfunctional Attitudes Scale
DSM	Diagnostic and Statistical manual of Mental disorders
ECR	Experiences in Close Relationships scale
EPDS	Edinburgh Postnatal Depression Scale
EQ-5D	EuroQol
HELLP	Hemolytic anemia, Elevated Liver enzymes and Low Platelet count
ITT	Intention To Treat
LDS	Language Development Survey
MINI	Mini International Neuropsychiatric Interview
NEO-FFI	NEO Five Factor Inventory
NEO-PI-R	Revised NEO Personality Inventory
NLEQ	Negative Life Events Questionnaire
PROMISES	PRegnancy Outcomes after Maternity Intervention for Stressful EmotionS
QALY	Quality Adjusted Life Years
RCT	Randomized Controlled Trial
SCID	Structured Clinical Interview for DSM-VI Disorders
SSQ	Social Support Questionnaire
STAI	State and Trait Anxiety Inventory
TiC-P	Trimbos/iMTA questionnaire for Costs associated with Psychiatric illness
UCL	Utrechtse Coping Lijst

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CHAPTER 6

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

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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 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 midwifes [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 1: Assessments per time point

	T0	T1	T2	T3
Anxiety symptoms (STAI)	x	x	x	
Depression symptoms (EPDS)	x	x	x	
Socio-demographic & -economic factors		x		
Suicidality (MINI)		x		
Healthcare consumption				x
Clinical Diagnostic Interview (SCID-II)		x		

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

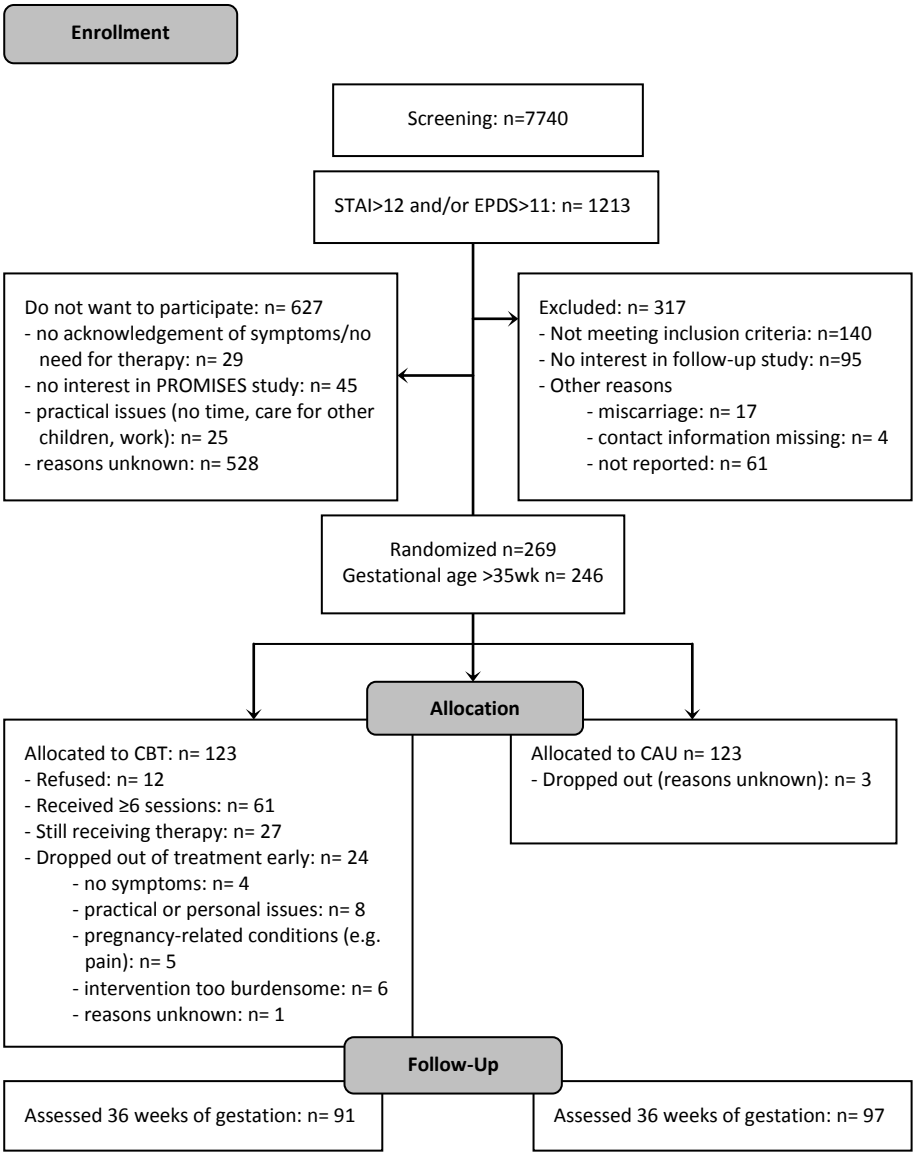
The PROMISES trial has been approved by the medical ethical committee of the University Medical Centre Groningen.

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

Figure 1: CONSORT diagram



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

	Intervention (N=123)	**Care as usual (N=123)**
	Mean (SD)	*Mean (SD)*
Age (years)	33.7 (4.6)	32.7 (4.3)
STAI-score screening (T0)	49.8 (8.0)	49.2 (7.5)
EPDS-score screening (T0)	10.2 (4.1)	10.1 (4.1)
Zscore Distress-score screening (T0)	0 (0.9)	0 (0.8)
	N (%)	*N (%)*
Multipara	63 (51.2)	66 (53.7)
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).

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

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.

	Intervention (N=123)	**Care as usual (N=123)**
STAI score, mean (SD)	42.7 (10.2)	42.0 (12.5)
Intention to treat (N=188)	0.5 (-2.7;3.7)	
MICE	-0.4 (-3.5;2.7)	
Subgroups		
Anxiety and/or depressive disorder (N=103)	-0.8 (-5.4;3.8)	
Anxiety diagnosis (N=69)	0.8 (-4.2;5.9)	
Comorbid diagnosis (N=17)	-6.3 (-17.6;5.1)	
Above cut-off STAI (N=177)	0.6 (-2.8;3.9)	
Per protocol† (N=53)	-1.5 (-5.3;2.3)	
MICE	-0.9 (-4.5;2.7)	
Data missing, N (%)	32 (26.0)	26 (21.1)

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).

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

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

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

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

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

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 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.

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.

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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]:

- 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], where 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 midwifes and gynecologists. Yet, based on a survey that was conducted among participating midwifes 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)

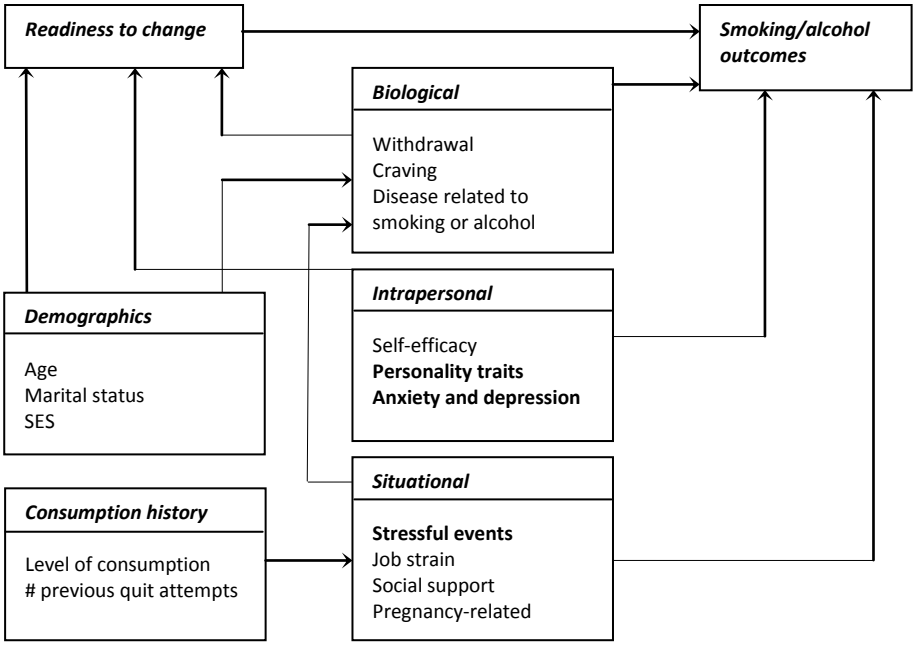
are widely used. However, for the screening of patients different cut-off values may be used, and different eligibility criteria may be used before pregnant women enter the study. For example, studies may include pregnant women at risk for depression [16], whereas others include only women meeting criteria 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.

Figure 1: the proposed extended bio-behavioral model of continued smoking and alcohol consumption during pregnancy and postpartum smoking relapse (based on Ward et al. [2] and van Loon et al. [1]).



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

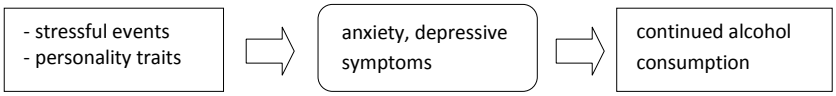
The associations we found between severity of stressful events and continued alcohol consumption corroborate previous research. We explained our finding on events related to 'conflict with loved ones' by describing the importance of social support **(chapter 2).** Both during and outside pregnancy social 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).

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



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.

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

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 midwifes, 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 midwifes, 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-poli’ 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-poli by for example a midwife or a general practitioner. Although the number of the pop-poli’s is increasing, not every hospital has one yet. To date, around 30 pop-poli’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 en 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,

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.

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Summary

Nicotine and alcohol can pass the placental barrier and thereby increases the risk of adverse health outcomes for the unborn child. Quitting smoking and alcohol consumption during pregnancy seems self-evident but not all pregnant women succeed at quitting these risky health behaviors. Smoking prevalence during pregnancy is estimated to be 13% and the prevalence of alcohol consumption is up to 50%. Even if women manage to quit smoking during pregnancy, this abstinence does not seem to persist after pregnancy. Up to 60% of women who quit smoking during pregnancy start again after childbirth. Several determinants have been proposed to be associated with continued smoking and alcohol consumption during pregnancy, as well as postpartum smoking relapse. We used the bio-behavioral model of smoking cessation and relapse and extended this model to alcohol outcomes and the period of pregnancy. In the first part of this thesis we focused on situational and intrapersonal determinants.

The last part of this thesis focused on treatment of anxiety and depressive symptoms during pregnancy. It is estimated that 10-20% of women experience anxiety and/or depression during pregnancy. Anxiety and depressive symptoms during pregnancy are associated with a range of adverse maternal and child outcomes. As for the treatment of these symptoms, studies from the general population suggest cognitive behavioral therapy (CBT) as an effective treatment. So far, there is few evidence that CBT is also effective during pregnancy. We investigated the effectiveness of CBT, created specifically for pregnant women, for the treatment of anxiety and depressive symptoms during pregnancy, compared to care as usual (CAU).

Chapter 2 and 3 investigate correlates of continued smoking and continued alcohol consumption. In **chapter 2** we report findings on the association of the severity of stressful events during pregnancy with continued smoking and alcohol consumption. We investigated different categories of stressful events, including pregnancy-specific events such as experiencing obstetric problems (e.g. vaginal bleeding). We hypothesized that increased perceived severity of stressful events during pregnancy is associated with continued smoking and alcohol consumption. In addition, we studied whether anxiety and depressive symptoms during pregnancy could explain the associations. Severity of stressful events was measured using two approaches: the subjective and normative approach. We found that both approaches were highly correlated, and findings on the subjective approach were reported only. We found that severity of the following categories was associated with continued alcohol consumption: ‘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. In **chapter 3** we studied the associations of personality traits with continued smoking and alcohol consumption. We hypothesized that higher levels of neuroticism and extraversion, and lower levels of conscientiousness, agreeableness and openness to experience are associated with continued smoking and alcohol consumption. In addition, we studied whether the associations could be explained by anxiety and depressive symptoms during pregnancy. We found that higher levels of openness to experience and lower levels of conscientiousness were associated with continued alcohol consumption. The association between conscientiousness and continued alcohol consumption was partly explained by both anxiety and depressive symptoms. No associations were found of personality traits with continued smoking and with the amount of cigarettes and alcohol consumed among continued users.

In **chapter 4** we investigated postpartum smoking relapse. We investigated the association of adverse pregnancy and delivery outcomes (APDO), and transfer from planned home-delivery to hospital-delivery (transfer) with postpartum smoking relapse. It was hypothesized that the experience of such stressful events would increase the risk of smoking relapse. Furthermore, we investigated if postpartum depressive symptoms could explain the associations. In line with our hypothesis, our results showed that the experience of at least one APDO doubled the odds of postpartum smoking relapse. Also, transfer was associated with postpartum smoking relapse but not independent from APDO. Depression symptoms after pregnancy could not explain these associations. Moreover, we studied the association of four different categories of APDO and found an independent association between adverse neonatal outcomes and smoking relapse. What is more, with every APDO that applied, the odds of postpartum smoking relapse increased.

Chapter 5 and 6 discuss the design of the Pregnancy Outcomes after a Maternity Intervention for Stressful EmotionS (PROMISES) study, and its findings on the effectiveness of CBT for treatment of anxiety and depressive symptoms during pregnancy, respectively. Participants of the Pregnancy Anxiety and Depression (PAD) study were screened on anxiety and depressive symptoms and assessed for eligibility for participation in the PROMISES study. Only 30% of the eligible women agreed to participate. Results showed that anxiety and depressive symptoms decrease during pregnancy. Our hypothesis that CBT leads to a (stronger) reduction in anxiety and depressive symptoms, when compared to CAU, could not be confirmed. Stratified analyses according parity, socioeconomic status, severity of anxiety and depressive symptoms, and DSM-IV anxiety or depression diagnosis did not show a statistical significant beneficial effect of

CBT during pregnancy, when compared to CAU.

This thesis ends with a general discussion (**chapter 7)** in which the results are discussed. Important methodological considerations are presented, as well as the clinical implications of our findings. In addition, recommendations for future research are provided. In conclusion, situational and intrapersonal determinants such as stressful events and personality seem to be associated with continued alcohol consumption during pregnancy, but not with continued smoking. In contrast, after pregnancy, stressful events (i.e. APDO) are related to smoking outcomes, that is postpartum smoking relapse. We identified women who may be (more) at risk for having difficulties in quitting risky health behaviors during pregnancy, and to persist abstinence after childbirth. Targeting healthy lifestyle strategies at these women may be most beneficial. Moreover, we concluded that CBT did not show a beneficial effect, when compared to CAU, among a group of pregnant women with subclinical anxiety and depressive symptoms and disorders that were not active help-seekers. Our findings raise new questions on the treatment of anxiety and depression symptoms during pregnancy. Our results suggest that more evidence is needed for which specific groups screening and treatment may be beneficial during pregnancy, including pregnant women with disorders.

Nederlandse samenvatting

Nicotine en alcohol kunnen de placenta passeren en zo het risico op nadelige uitkomsten voor het ongeboren kind verhogen. Stoppen met roken en alcoholgebruik tijdens de zwangerschap lijkt vanzelfsprekend, maar niet alle zwangere vrouwen lukt het om te stoppen. Geschat wordt dat 13% van alle Nederlandse zwangere vrouwen rookt tijdens de zwangerschap. Voor alcohol ligt deze prevalentie tot aan de 50%. Als het vrouwen al lukt om te stoppen met roken tijdens de zwangerschap dan blijkt deze onthouding niet stand te houden na de bevalling. Tot 60% van de vrouwen die gestopt zijn met roken tijdens de zwangerschap beginnen weer met roken na de bevalling (terugval in rookgedrag). Deze percentages van roken en alcoholgebruik tijdens de zwangerschap, alsook het percentage van terugval in rookgedrag na de bevalling, komen overeen met de percentages gerapporteerd in andere westerse landen. Verschillende determinanten van zowel doorgaan met roken en alcoholgebruik tijdens de zwangerschap als terugval in rookgedrag na de bevalling zijn voorgesteld. We hebben gebruik gemaakt van het 'bio-gedragsmodel voor stoppen met roken en terugval', dat verschillende determinanten verbindt aan rookgedrag. Dit model hebben we uitgebreid naar de periode van zwangerschap en alcoholgebruik en gebruikt om hypothesen te genereren ten aanzien van de determinanten van doorgaan met roken en alcoholgebruik tijdens de zwangerschap alsmede terugval in rookgedrag na de bevalling. Voor dit proefschrift hebben we ons gericht op situationele (stressvolle gebeurtenissen) en intrapersoonlijke (persoonlijkheid, angst en depressie) determinanten.

Het laatste deel van dit proefschrift richt zich op de behandeling van angst- en depressieklachten tijdens de zwangerschap. Geschat wordt dat 10-20% van alle vrouwen klachten van angst en/of depressie ervaart tijdens de zwangerschap. Deze klachten hangen samen met uiteenlopende nadelige uitkomsten voor zowel de moeder als haar (ongeboren) kind. Wat betreft de behandeling van deze klachten blijkt uit studies gedaan onder de niet-zwangere populatie, dat cognitieve gedragstherapie ('CBT') een effectieve behandeling is. Tot dusver is er nog weinig bewijs dat CBT ook effectief is tijdens de zwangerschap. In dit proefschrift zijn de effecten van CBT voor de behandeling van angst- en depressieklachten tijdens de zwangerschap onderzocht onder een groep zwangere vrouwen met subklinische klachten en stoornissen en zonder hulpvraag. De therapie is specifiek ontworpen voor angstige en/of depressieve zwangere vrouwen, is modulair voor de behandeling van een stoornis, en richt zich op het identificeren en veranderen van disfunctionele cognities en schemata (cognitieve raamwerken die helpen bij het organiseren en interpreteren van binnenkomende informatie).

In **hoofdstuk 2 en 3** worden determinanten van doorgaan met roken en alcoholgebruik tijdens

de zwangerschap beschreven. In **hoofdstuk 2** rapporteren we bevindingen voor de relatie tussen de ernst van stressvolle gebeurtenissen tijdens de zwangerschap en doorgaan met roken en alcoholgebruik. We hebben verschillende categorieën van stressvolle gebeurtenissen onderzocht, inclusief zwangerschapsspecifieke gebeurtenissen zoals het meemaken van obstetrische problemen (bijvoorbeeld een vaginale bloeding). Onze hypothese was dat een verhoogde waargenomen ernst van stressvolle gebeurtenissen tijdens de zwangerschap geassocieerd is met doorgaan met roken en alcoholgebruik. Daarnaast hebben we onderzocht of angstige en depressieve klachten tijdens de zwangerschap de onderzochte associaties kunnen verklaren. De ernst van stressvolle gebeurtenissen is gemeten via twee verschillende benaderingen: de subjectieve en normatieve benadering. Onze analyse liet een hoge correlatie zien tussen beide benaderingen en we hebben daarom alleen de bevindingen gerapporteerd die gemeten zijn via de subjectieve benadering. Uit onze resultaten bleek dat de ernst van de volgende categorieën geassocieerd is met alcoholgebruik tijdens de zwangerschap: 'conflict met geliefden', 'misdaad gerelateerd', 'zwangerschapsspecifiek' en de totaalscore die alle gebeurtenissen bevat. Angst- en depressieklachten tijdens de zwangerschap konden de gevonden associaties niet verklaren. We vonden geen verband tussen de ernst van stressvolle gebeurtenissen en doorgaan met roken. Verder vonden we ook geen relatie tussen de ernst van stressvolle gebeurtenissen en de hoeveelheid sigaretten of alcohol die geconsumeerd werd door vrouwen die doorgingen met roken of alcoholgebruik tijdens de zwangerschap. In **hoofdstuk 3** zijn de relaties tussen persoonlijkheidstrekken en doorgaan met roken en alcoholgebruik tijdens de zwangerschap bestudeerd. We veronderstelden dat hogere niveaus van neuroticisme en extraversie en lagere niveaus van consciëntieusheid, altruïsme en openheid geassocieerd zijn met doorgaan met roken en alcoholgebruik. Daarnaast hebben we onderzocht of angst- en depressieklachten tijdens de zwangerschap de onderzochte associaties kunnen verklaren. We vonden dat hogere niveaus van openheid en lagere niveaus van consciëntieusheid geassocieerd zijn met alcoholgebruik tijdens de zwangerschap. De associatie tussen consciëntieusheid en alcoholgebruik tijdens de zwangerschap kon deels verklaard worden door zowel angst- als depressieklachten tijdens de zwangerschap. Er werd geen relatie gevonden tussen persoonlijkheidstrekken en doorgaan met roken. Verder vonden we ook geen verband tussen persoonlijkheidstrekken en de hoeveelheid sigaretten of alcohol die geconsumeerd werd door vrouwen die doorgingen met roken of alcoholgebruik tijdens de zwangerschap.

Hoofdstuk 4 richt zich op de terugval in rookgedrag na de bevalling. We onderzochten de relaties van nadelige zwangerschaps- en geboorte-uitkomsten ('APDO'), en overdracht van een geplande thuisbevalling naar een ziekenhuisbevalling ('transfer') met terugval in rookgedrag.

We veronderstelden dat de ervaring van dergelijke stressvolle gebeurtenissen het risico op terugval in rookgedrag zou verhogen. Verder hebben we onderzocht of depressieve klachten na de bevalling de onderzochte associaties kunnen verklaren. In overeenstemming met onze hypothese lieten de resultaten zien dat de ervaring van minstens één APDO de 'odds' op terugval verdubbelde. Ook transfer was geassocieerd met terugval maar niet onafhankelijk van APDO. Depressieklachten na de bevalling konden de gevonden associaties niet verklaren. Verder hebben we vier categorieën van APDO bestudeerd en vonden een onafhankelijke relatie tussen nadelige neonatale uitkomsten en terugval. Verder lieten onze resultaten ook zien dat met iedere APDO die een vrouw meemaakte, het risico op terugval toenam.

In **hoofdstuk 5 en 6** worden respectievelijk het design van de 'PRegnancy Outcomes after a Maternal Intervention for Stressful EmotionS' (PROMISES) studie en de effectiviteit van cognitieve gedragstherapie voor de behandeling van angst- en depressieklachten tijdens de zwangerschap besproken. Deelneemsters aan de 'Pregnancy Anxiety and Depression' (PAD) studie werden gescreend op het hebben van angst- en depressieklachten en werden beoordeeld op de inclusiecriteria voor deelname aan de PROMISES studie. Slechts 30% van de vrouwen die uitgenodigd was om mee te doen met PROMISES stemden in met deelname. De resultaten lieten zien dat angst- en depressieklachten dalen tijdens de zwangerschap. We zagen echter geen verschil tussen de groep deelneemsters die de therapie volgde en de groep die de gebruikelijke zorg kreeg. Gestratificeerde analyses naar pariteit, socio-economische status, ernst van symptomen en DSM-IV angst of depressie diagnose lieten soortgelijke resultaten zien.

Het proefschrift besluit met een algemene discussie (**hoofdstuk 7**) van onze bevindingen. Belangrijke methodologische overwegingen worden besproken alsmede de klinische implicaties van de resultaten. Verder worden er aanbevelingen gedaan voor toekomstig onderzoek. Alles bij elkaar genomen blijken situationele en intrapersoonlijke determinanten als stressvolle gebeurtenissen en persoonlijkheid geassocieerd te zijn met doorgaan met alcoholgebruik, maar niet met doorgaan met roken tijdens de zwangerschap. Echter, na de zwangerschap zijn stressvolle gebeurtenissen (APDO) wel gerelateerd aan rookgedrag, namelijk terugval. We hebben vrouwen geïdentificeerd met een verhoogd risico op het ervaren van moeilijkheden bij het stoppen met risicovol gezondheidsgedrag tijdens de zwangerschap en het volhouden van onthouding na de bevalling. Het kan erg gunstig zijn om strategieën gericht op een gezonde leefstijl tijdens de zwangerschap specifiek op deze vrouwen te richten. Verder blijkt uit dit proefschrift dat cognitieve gedragstherapie niet effectief lijkt voor de behandeling van angst- en depressieklachten tijdens de zwangerschap wanneer vergeleken

met de gebruikelijke zorg. Echter kunnen we niet concluderen dat deze behandeling helemaal niet effectief is omdat we niet goed konden onderzoeken of cognitieve gedragstherapie mogelijk effectief is voor vrouwen met een stoornis. Onze bevindingen roepen nieuwe vragen op over de behandeling van angst- en depressieklachten tijdens de zwangerschap. Ook suggereren onze bevindingen dat er meer bewijs nodig is voor welke zwangere vrouwen screening en behandeling van angst- en depressieklachten effectief kan zijn, waaronder vrouwen met een stoornis.

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Chantal Beijers was born in Maastricht, The Netherlands, on the 4th of June 1987. After finishing secondary school at the Porta Mosana College in Maastricht she started her Bsc in Nutrition and Health at Wageningen University. After approximately one year she switched to the BSc Public Health and Society and obtained her MSc in Public Health and Society in 2010. Her interest in research emerged after doing a research internship in Melbourne, Australia. Back in The Netherlands she applied for a PhD position in Groningen at the Interdisciplinary Center Psychopathology and Emotion regulation at the UMCG, which resulted in this thesis. During her PhD project she completed training to obtain the Epidemiologist-B registration. Chantal currently works at CBO on guideline development.

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