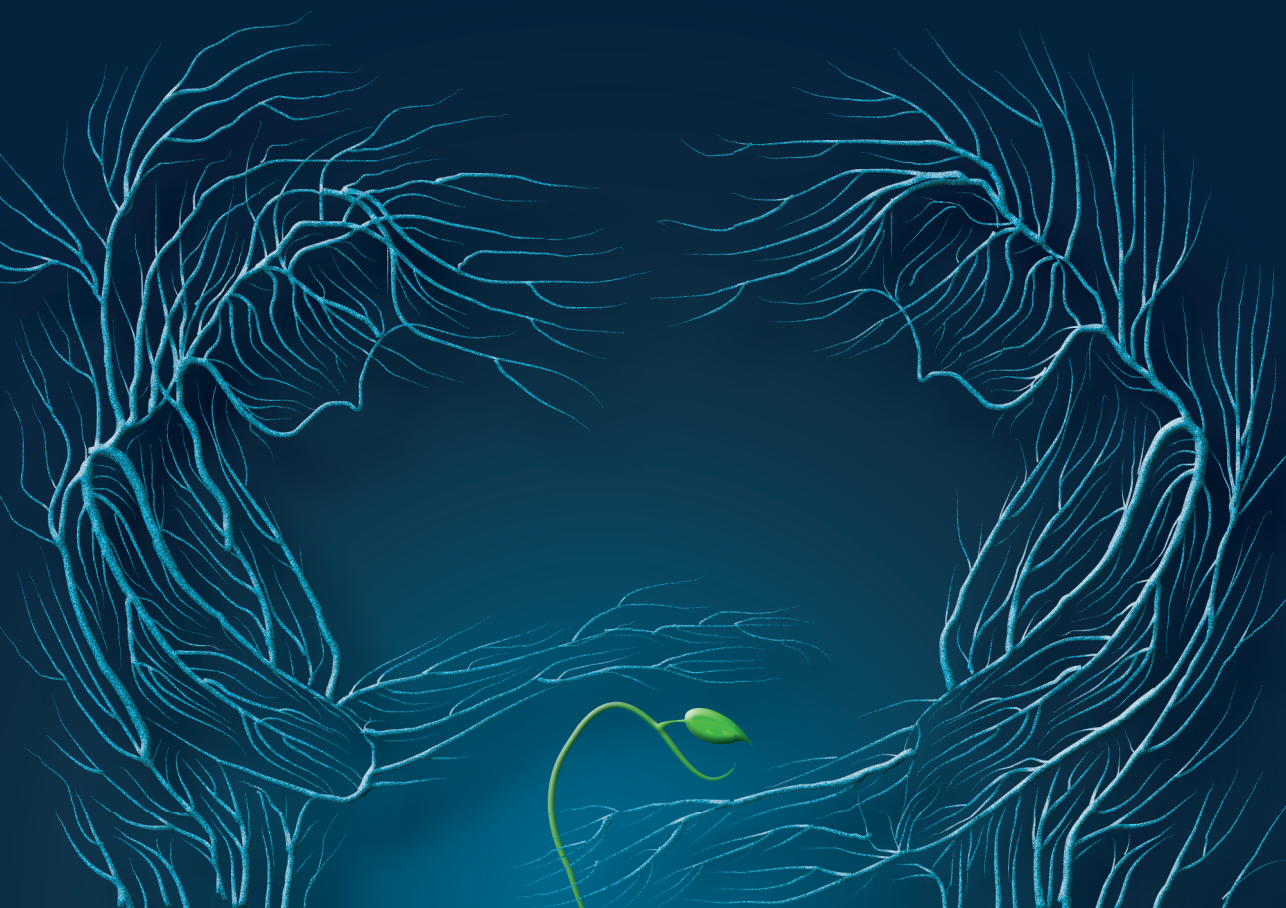
Exploring transgenerational approaches to prevent common mental disorders

MARIA ELISABETH BROUWER



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Het verkennen van transgenerationele benaderingen voor het voorkomen van veelvoorkomende psychische stoornissen (met een samenvatting in het Nederlands)

Proefschrift

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Maria Elisabeth Brouwer

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Promotor: Prof. dr. C. L. H. Bockting

Copromotoren: Dr. H. Burger
Dr. M. P. Lambregtse-van den Berg
Dr. A. D. Williams

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CONTENTS

Chapter 1

General introduction

Common mental disorders are a global phenomenon, affecting approximately one out of five people each year (Steel et al., 2014). Common mental disorders include anxiety disorders, substance-related disorders, and depressive disorders such as major depressive disorder (MDD). During pregnancy, these mental disorders in particular pose a risk for children to develop common mental disorders themselves. The perinatal period is of great importance, since interventions during this period may provide a window of opportunity to help women and mitigate or prevent the negative effects on offspring. Effective primary and relapse prevention interventions are hence highly warranted (Holmes et al., 2018; Saxena, Jané-Llopis, & Hosman, 2006). In light of preventing common mental disorders, it may even be that the earliest prevention imaginable is to prevent the disorder(s) before a person is born, i.e. by intervening in the prenatal period. On the other hand, pharmacological treatments for the prenatal common mental disorder may negatively affect the pregnant women and offspring as well (Grigoriadis et al., 2014; Ross et al., 2013). Thus, the prevention of transgenerational transmission of common mental disorders requires careful balancing the benefits and harms of prenatal treatment.

To explore transgenerational approaches to prevent common mental disorders, biological and psychological theories of the aetiology of common mental disorders, in particular transgenerational models, need to be investigated. Theories aid clinicians and researchers in explaining the transgenerational transmission of disorders, identifying individuals who are at risk of common mental disorders, and help develop and improve (relapse prevention) treatments for these disorders. Throughout the current dissertation, we will investigate the evidence for some concepts of a transgenerational model that is displayed in Figure A (as adapted from Stein et al., 2014). Results leading from this dissertation may guide clinicians and researchers to answer the question what transgenerational approaches may be available to prevent common mental disorders.

Specifically, based on the adapted model, in a series of studies we will investigate the numbered relationships displayed in Figure A. Towards exploring the idea of transgenerational approaches to prevent common mental disorders, this introductory chapter outlines the prevalence, relapse/recurrence, and burden of common mental disorders with a focus on depression and pregnancy, followed by the current knowledge concerning a selection of (transgenerational) aetiological and relapse theories of common mental disorders. This chapter then describes the vulnerability factors of depressive relapse, and the acute and relapse prevention interventions for depression. Throughout this chapter, the implications will be outlined and discussed for pregnant women and their offspring, and existing research gaps are discussed which we aim to address in the following chapters of this dissertation.

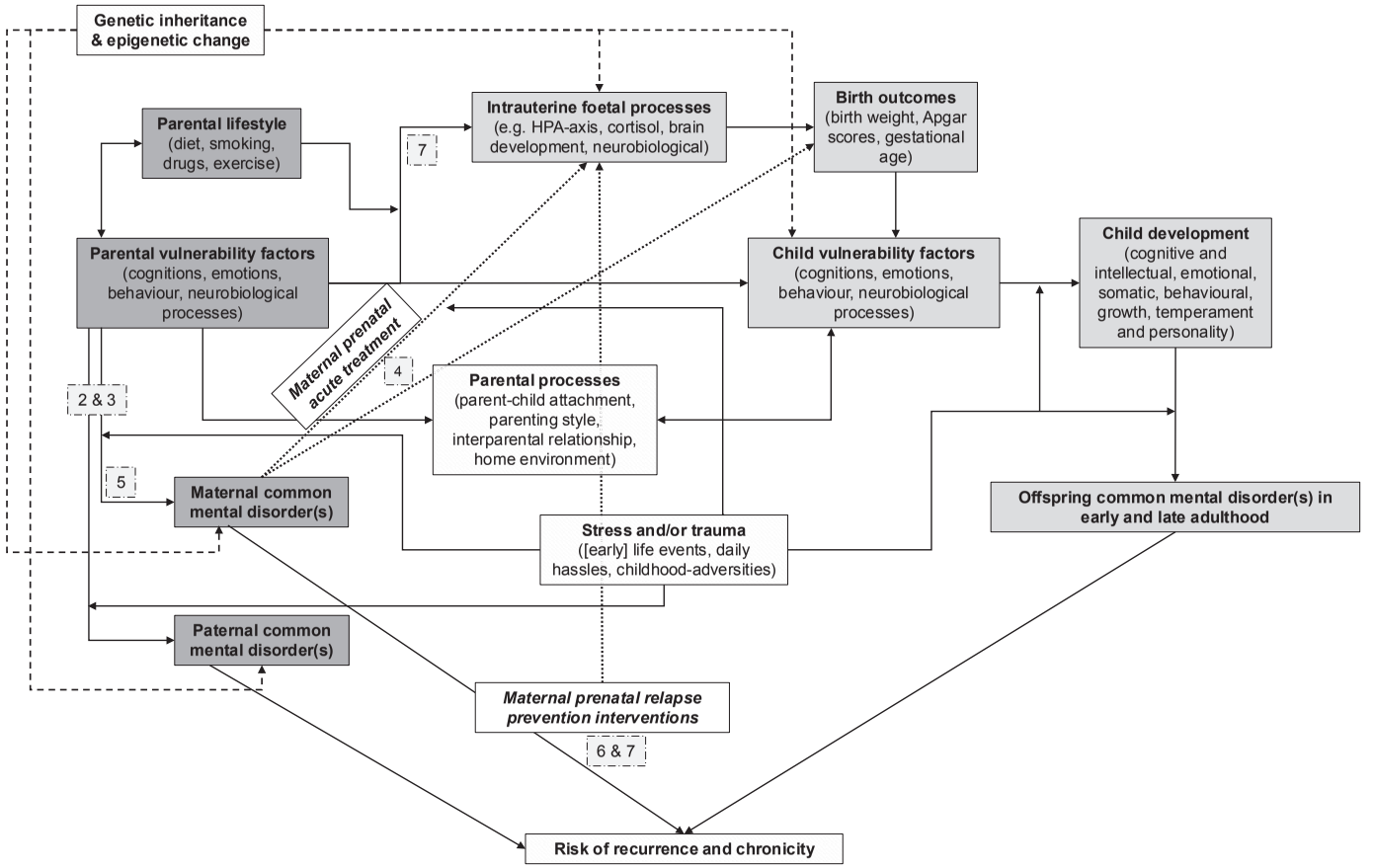

Figure A. A transgenerational model for common mental disorders.

Note: Adapted from Stein et al., 2014. Numbers refer to the dissertation chapters where the specific relationships will be investigated.

Prevalence and burden of common mental disorders

Out of all common mental disorders, depressive and anxiety disorders are most common, with lifetime prevalence rates of 11% and 14% respectively, affecting adult women twice as often as adult men (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018; Steel et al., 2014). For anxiety disorders, reported 12-month period prevalence rates are 7%, affecting 9% of the women and 4% of the men (Steel et al., 2014). Anxiety disorders are a top cause of non-fatal burden in a lifetime for women, and MDD is one of the most prevalent and one of the leading causes of disability worldwide (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). Estimated 12-month prevalence rates for MDD are five percent, with rates of 6% for women, and 3.5% for men (Ferrari et al., 2013; Steel et al., 2014). MDD is a heterogeneous disorder, as two patients both diagnosed with MDD may experience and demonstrate completely different symptoms (Zimmerman, Ellison, Young, Chelminski, & Dalrymple, 2015). MDD often runs a chronic course, and is associated with a high burden mainly due to the high relapse and recurrence rates (Burcusa & Iacono, 2007).

Relapse and recurrence rates in major depressive disorder

Once remitted or recovered from a first-time episode of MDD (MDE), people have a 40% to 60% increased lifetime risk to develop a new MDE in the future (Eaton et al., 2008; Moffitt et al., 2010). MDD refers to the disorder itself, whereas MDE is the specific episode within the MDD[1]. Remission is generally defined as the period in which the patients' symptoms are normalised for approximately two months or more (getting better, but not yet recovered), and recovery is often described as the end of an MDE after a period of remission, approximately four to six months and longer. Depressive relapse is the re-emergence of an MDE before a patient attains the status of remission, and recurrence is the development of a new MDE after a person has attained the status of recovery (e.g. Bockting et al., 2015; Buckman et al., 2018; Frank et al., 1991). Despite the consensus on the differences between relapse and recurrence, these terms are often used interchangeably to describe the re-occurrence of depressive symptoms regardless of the timing of the MDE. Throughout this dissertation, the words (depressive) relapse and recurrence are therefore both used to define the reoccurrence of MDD.

The exact relapse and recurrence rates vary in the literature. This mainly depends on the setting of research (outpatient versus inpatient versus community samples), follow-up time, number of previous MDD episodes, and methods of assessing relapse (diagnostic interview versus self-report; Ferrari et al., 2013), and risk factors (e.g.

1 In this dissertation, the word 'depression' refers to MDD or MDE

residual symptoms, partial remission, co-morbid disorders; Burcusa & Iacono, 2007). In community samples, combined recurrence rates are estimated 35% to 42% over a study period of 20 years (Eaton et al., 2008; Hardeveld, Spijker, De Graaf, Nolen, & Beekman, 2010, 2013). Among remitted Dutch individuals, recurrence rates across two years were 27% in primary care, and 33% in specialized health care (Hardeveld, Spijker, De Graaf, Hendriks, et al., 2013). In a study of individuals with a lifetime first MDD, including people with persistent depressive disorder (formerly dysthymia, i.e. depressed mood for at least two consecutive years, not meeting the full criteria of MDD), reported lifetime recurrence rates were 40% (Mattisson, Bogren, Horstmann, Munk-Jörgensen, & Nettelbladt, 2007). In the Netherlands, reported cumulative recurrence rates in a prospective study among individuals with a lifetime-first MDE were 13% within two, 23% in ten, and 42% in 20 years (NEMESIS-1; Hardeveld, Spijker, De Graaf, Nolen, et al., 2013). The updated study (NEMESIS-2) applied stricter criteria for a diagnosis of MDD, and reported recurrence rates of 4% within five, 13% in ten, and 27% within 20 years (ten Have et al., 2018). In contrast, research in clinical patient samples described lifetime prevalence rates of recurrence up to 95% (Holma, Holma, Melartin, Rytsala, & Isometsa, 2008; Kanai et al., 2003; Kennedy, Abbott, & Paykel, 2003; Lee & Murray, 1988; Maj, Veltro, Pirozzi, Lobrace, & Magliano, 1992; Solomon et al., 2004; Surtees & Barkley, 1994). These differences in recurrence rates consequently may be caused by different patient populations, as the patients in clinical setting may have had more, and more severe, depressive episodes.

The number of previous episodes is a consistent predictor of recurrence (Odds Ratio [*OR*] = 1.34, 95% CI 1.01, 1.77; Holma et al., 2008). With each MDE the risk of depression recurrence increases by 16% (Solomon et al., 2000), and after three or more MDD episodes, reported cumulative life time risk of recurrence rise up to 90% (for reviews see Bockting et al., 2015; Hardeveld et al., 2010). In the control groups of randomized controlled trials consisting of remitted individuals with at least two MDEs, where participants either receive no care or care as usual, and were in remission, reported cumulative recurrence rates were 33% and 50% within one year, 64% in two years, and 94% within ten years (Biesheuvel-Leliefeld et al., 2017; Bockting et al., 2005, 2015; Bockting, Spinhoven, Wouters, Koeter, & Schene, 2009; de Jonge et al., 2019; Ma & Teasdale, 2004; Teasdale et al., 2000). In control groups of randomized controlled trials (RCTs) of remitted individuals with at least three or more MDEs, cumulative recurrence rates ranged from 34% up to 68% in one year (Bondolfi et al., 2010; Godfrin & van Heeringen, 2010; Huijbers et al., 2015; Kuyken et al., 2008, 2015; Williams et al., 2014). To summarize, the differences in recurrence rates can be caused by different clinical settings, strictness in criteria to determine the recurrence, varying number of previous episodes, and severity of the MDD.

Prevalence of perinatal common mental disorders and depressive relapse rates

For pregnant women, prevalence rates of depressive disorders are estimated around 12%, whereas approximately 15% of the women experience an anxiety disorder during pregnancy (Bennett, Einarson, Taddio, Koren, & Einarson, 2004; Dennis, Falah-Hassani, & Shiri, 2017; Woody, Ferrari, Siskind, Whiteford, & Harris, 2017). With regard to depression in the postpartum period (i.e. after giving birth), the estimated point prevalence rate is 5.7% (Gavin et al., 2005), and a recent review showed pooled prevalence rates of 9.5% in high income countries, versus 18.7% in low- and middle-income countries (Woody et al., 2017). Another review assessed that 7.1% of the women develop an MDD between giving birth and three months postpartum (Yonkers, Vigod, & Ross, 2011). The estimated prevalence rates for any anxiety disorder after giving birth and up to one-year postpartum ranges from 9.3% to 9.9% (Dennis et al., 2017).

Like in the general population, pregnant and postpartum women with a history of MDD are at risk of depressive relapse as well (Biaggi, Conroy, Pawlby, & Pariante, 2016; Stuart-Parrigon & Stuart, 2014). The relapse rates are inconsistent for pregnant women, where reported incidence rates range from 2% to 68% (Banti et al., 2011; Cohen et al., 2006; Ornoy & Koren, 2014; Patton et al., 2015; Yonkers et al., 2011). This large difference in relapse rates is most likely due to varying number of previous episodes, different relapse prevention strategies, and setting of research. In a community sample, almost 4% of the women with a history of MDD had a depressive relapse during pregnancy, compared to 8% of the women postpartum. The study sample comprised a relatively healthy population, with moderate to highly educated married women, mostly primipara, who had a paid job, and for whom the number of previous MDEs was not reported (Banti et al., 2011). Another prospective cohort study identified high self-reported depressive symptoms during pregnancy in 22% of the pregnant women with a history of mental health problems in young adulthood and adolescence, compared to 13% eight weeks postpartum in the same group (not solely MDD; Patton et al., 2015).

Within a clinical setting, Cohen et al. (2006) reported a relapse rate of 68% during pregnancy in pregnant women discontinuing antidepressant medication (ADM), compared to relapse rate of 26% in women who continued ADM during pregnancy. Irrespective of treatment, 43% of the pregnant women relapsed (n = 86/115), of whom with four or more previous MDEs were at increased risk of relapse (Hazard Ratio [*HR*] = 3.6, 95% CI 1.9, 7.0). In contrast, another study found no difference in relapse rates in pregnant women who continued or stopped taking ADM, and found that 16% of all women had a recurrence of depression (Yonkers et al., 2011). Consistent with Cohen et al. (2006), the authors found that pregnant women with a history of four or more MDEs were at increased risk of recurrence (26% recurrence; Yonkers et al., 2011). These studies therefore suggest that the setting of research and number of MDD episodes

increase the risk of recurrence, not the (discontinued) use of ADM (Kimmel et al., 2015; Swanson et al., 2015).

In conclusion, the reported prevalence and recurrence rates in pregnant and the general population highlight the need for effective treatments for all individuals with a history of depression in particular. Effective relapse prevention treatments are particularly important for pregnant women due to the potential risks of prenatal common mental disorders on the unborn child.

A transgenerational model of common mental disorders

There are several etiological theories that explain how common mental disorders are transmitted over generations (transgenerational effects), of which this introductory chapter briefly describes a selection (Buckman et al., 2018; Newman et al., 2016; Stein et al., 2014). During the prenatal period, common mental disorders and symptoms of these disorders are believed to form a risk for the offspring, from the (expecting) mother as well as the (expecting) father (Gutierrez-Galve et al., 2018; Möller, Nikolić, Majdandžić, & Bögels, 2016; van den Berg et al., 2009). Maternal depression and anxiety during pregnancy has been associated with offspring lower birth weight, preterm birth, and a two to three times increased risk for the development of psychopathology at later ages (Madigan et al., 2018; O'Donnell, Glover, Barker, & O'Connor, 2014). This increased risk of psychopathology includes the development of anxiety disorders before the age of nine, depressive symptoms in adolescence, and developmental disorders such as autism and attention deficit hyperactivity disorder (Lahti et al., 2017; National Institute for Health and Clinical Excellence, 2014; Newman et al., 2016; O'Donnell et al., 2014; Stein et al., 2014)

Several explanations have been postulated for the transmission of common mental disorders to offspring (for example, see Goodman & Gotlib, 1999; Newman et al., 2016). According to Stein and colleagues (2014), biological processes (genetics, epigenetics and hormonal), psychological processes related to maternal and paternal psychopathology, and parenting may be related to this transmission. Factors such as socio-economic status, gender of the child, and single parenthood may moderate the relationship between parental mental disorders and child outcomes (Stein et al., 2014). Based upon previous reviews (Buckman et al., 2018; Goodman et al., 2011; Newman et al., 2016), we adapted the transgenerational model of Stein et al. (2014) to some extent. Four new concepts were included: Stress and/or trauma, birth outcomes, offspring common mental disorders (internalising problems) in the early and late adulthood, and the risk of recurrence or chronicity. Moreover, two interventions developed to prevent the transgenerational transmission of mental disorders are described in the model in Figure A. This adapted transgenerational model will be used as a framework for this dissertation. In specific, we will investigate the relationship between vulnerability factors

and depressive relapse (Chapter 2, 3, and 5), whether prenatal treatments of common mental disorders prevent negative offspring outcomes (Chapter 4), whether tapering antidepressants in combination with a relapse prevention intervention during pregnancy is as effective as continuation of antidepressants with regard to depressive relapse, how these relapse prevention interventions influence the offspring (Chapter 6 and 7), and whether fluctuations of affect are differentially related to offspring outcomes in women tapering antidepressants while they receive a psychological intervention versus continuing antidepressants during pregnancy (Chapter 7). The hereafter mentioned subheadings in this chapter correspond to the specific concepts of the model that will be investigated in the series of studies. Several parts of transgenerational models have been investigated before in previous studies, and we will summarize some of the evidence so far.

Relationship between parental vulnerability factors and the developing foetus

The model in Figure A shows a relationship between prenatal maternal common mental disorders and intrauterine foetal processes, which leads to certain birth outcomes. One of the theories behind this relationship is that the activation of stress from the maternal common mental disorder (or vice versa) activate a stress-response in the developing foetus, altering the physiology of the unborn child (e.g. the Barker theory or foetal programming hypothesis; Barker, 1990). This altered physiology is reflected in disturbed hypothalamic-pituitary-adrenal axis (HPA-axis) and increased cortisol levels (Glover, O'Connor, & O'Donnell, 2010). The HPA-axis and increased or reactive cortisol levels in turn have been linked to the development of depression, although a recent meta-analysis found inconclusive evidence that cortisol levels indeed precede the first onset of depression (Kennis et al., *under review*). In addition, previous research hypothesized that (epi)genetics, increased levels of intrauterine cytokines, or glucocorticoids increase the risk of negative effects for the offspring. These stress alterations and genes are believed to increase the risk of lower birth weight, shorter gestational age, developmental disorders, and common mental disorders in the offspring throughout life (Gluckman, Hanson, Cooper, & Thornburg, 2008; Stein et al., 2014; Talge, Neal, & Glover, 2007; van den Bergh et al., 2017).

From a socio-psychological view, the maternal common mood disorders may cause poor self-care in the pregnant women, including disturbed and/or changed appetite, smoking, poor hygiene, avoiding health care, or other unhealthy behaviours (Figure A: Moderating influence of parental lifestyle on the relationship between parental vulnerability factors and foetal processes; Beijers et al., 2014; Gluckman et al., 2008). When the child is born and the mother (or father) continues to experience symptoms of a common mental disorder, the child may be at risk of poor or disturbed attachment,

abuse, poor parenting, or maltreatment (Newman et al., 2016). This increases the risk of developing behavioural, cognitive, and emotional problems in the offspring, including common mental disorders (Goodman et al., 2011; Stein et al., 2014). It is therefore key to examine various vulnerability factors that may impact the child. For example, one study on personality traits found that higher levels of openness to experience and lower levels of conscientiousness were related to continued use of alcohol during pregnancy, which is detrimental for the unborn child (Beijers, Burger, Verbeek, Bockting, & Ormel, 2014). They moreover found that lower socio-economic status and negative life events were related to prenatal anxiety and depressive symptoms, and that low socio-economic status negatively influenced the relationship between negative life events and anxiety and depression (Verbeek et al., 2019). This underscores the importance of the transgenerational model to explain common mental disorders, however, results so far on potential vulnerability factors and moderators are inconclusive. This will therefore be to some extend investigated in this dissertation.

Relationship between parental vulnerability factors, prognostic factors, and recurrence of depression: Theories and evidence

The model in Figure A postulates that there are several parental vulnerability factors that may be related to common mental disorders, which in turn may affect offspring outcomes. These theories and factors may vary across disorders, and here we focus only on MDD and depressive relapse to explain the hypothesized vulnerability factors. The leading theories that aim to account for depressive relapse are the cognitive, behavioural, diathesis-stress, psychodynamic, and personality-based theories (Burcusa & Iacono, 2007; Fernald, 2008). Psychological theories inform researchers and health care providers on potential vulnerability factors that put an individual at risk of depressive relapse (i.e. therapeutic target points), and underpin current treatment options for common mental disorders. Some of the theories and related treatment options are the psychodynamic theory and the psychodynamic therapy, cognitive theory and cognitive therapy, behavioural theory and behavioural activation, personality-based theories related to schema-therapy, and the diathesis-stress theory, related to cognitive behavioural therapy (CBT; Beck & Bredemeier, 2016; Berlanga, Heinze, Torres, Apiquian, & Caballero, 1999; Compton, 1986; Dimidjian, Barrera, Martell, Muñoz, & Lewinsohn, 2011; Luyten & Blatt, 2012; Monroe & Simons, 1991).

The psychological vulnerability factors derived from these five theories will be described and reviewed in Chapter 2. In brief, one of the leading theories in the field of depression research is Beck's cognitive theory of depression (Beck & Bredemeier, 2016; Beck, Rush, Shaw, & Emery, 1979). In the initial cognitive model of Beck it was proposed that certain schemas or cognitive distortions are latent but can be activated

by life events that matched these schemas, resulting in automatic negative thoughts and depressive symptomatology (Beck et al., 1979). Later, the cognitive model of Beck specified that these schemas could be activated by any event (e.g. Beck & Bredemeier, 2016). Beck and Bredemeier (2016) later proposed that the aetiology of depression involves an interaction of psychological stress, genetic and biological vulnerability factors (i.e. epigenetics, HPA-axis, cortisol), traumatic experiences, biases in the information processing, and depressogenic beliefs. As for depressive relapse, it is hypothesized that an individual's schemas, which are formed in early childhood, or depressogenic beliefs, can be activated by (stressful) events or sad mood (Beck & Bredemeier, 2016; Segal et al., 2006). Other cognitive theories include the response style theory (e.g. rumination; Nolen-Hoeksema, 1991), and learned helplessness as explanations for the development of MDD (Abramson, Seligman, & Teasdale, 1978).

Cognitive theories highly overlap with the diathesis-stress theories, which combine psychological and biological dispositions ('diatheses'), such as (epi)genetics or neuroticism, with external and internal stressors to account for the development and recurrence of depression (Hankin & Abela, 2005; Monroe & Simons, 1991). From a psychodynamic perspective, factors such as parent-child attachment and interpersonal relationships are believed to explain (parts of) the development and relapse of depression (Luyten & Blatt, 2012). Behavioural theories underscore the importance of (social) learning, and place a central role on positive and negative reinforcement of an individual's behaviour (e.g. avoidance), environment (e.g. life events and social support), and depression (Dimidjian et al., 2011; Lewinsohn, 1974). Previous research moreover suggests that personality traits such as neuroticism and conscientiousness may contribute to the aetiology and recurrence of depression (Berlanga et al., 1999; Buckman et al., 2018; Klein et al., 2011).

Previous reviews and meta-analyses aimed to identify prognostic factors of depressive relapse regardless of the overarching theory (Buckman et al., 2018; Burcusa & Iacono, 2007; Hardeveld et al., 2010; Klein, Kotov, & Bufferd, 2011; Monroe & Harkness, 2011). Prognostic factors are the vulnerability factors that place an individual at risk of depressive relapse irrespective of treatment (Buckman et al., 2018; Fournier et al., 2009). In this dissertation, prognostic factors of depressive relapse will be studied in Chapter 2 and 3 and in Chapter 5 and 7. These factors are in general derived from theories that account for the development of MDD onset, relapse, and recurrences. Given the high overlap of the terms, and since we only focus on prognostic factors in this dissertation, the term 'vulnerability factors' will be used to indicate prognostic factors as well.

Some of the vulnerability factors that have been identified in previous studies were the number of previous MDEs, age, family history of mental disorders, residual depressive symptoms, (number of) comorbid psychopathology, the personality trait

neuroticism, childhood maltreatment, and negative cognitions (Buckman et al., 2018; Burcusa & Iacono, 2007; Hardeveld et al., 2010). Nonetheless, the evidence for some of these vulnerability factors is inconclusive, as these previous reviews are largely based upon evidence with varying quality, including individuals with and without an established diagnosis of MDD, and cross-sectional designs. As stated earlier, these factors (e.g. different patient groups) influence the recurrence rates, for pregnant women as well. Identifying predictors of relapse, especially in pregnant women who are at risk to develop common mental disorders, is of great importance. For that reason, the vulnerability factors of relapse among pregnant women will be investigated in Chapter 5.

Prenatal acute treatments for common mental disorders and offspring outcomes

The model in Figure A shows two approaches that may prevent the transgenerational transmission of common mental disorders: Prenatal acute treatment (Chapter 4) and prenatal relapse prevention interventions (Chapter 6). The most studied treatment options for acute symptoms of common mental disorders during pregnancy, such as anxiety or depression, include the use of ADM and/or CBT (Beck et al., 1979; van Ravesteyn, Lambregtse - van den Berg, Hoogendijk, & Kamperman, 2017). At the same time, interventions during pregnancy may affect the (unborn) baby as well. The use of ADM is one of the most used strategies to treat and prevent relapse in common mental disorders during pregnancy, and its use has been linked to offspring preterm birth, lower birth weight, and cardiovascular malformations (Grigoriadis et al., 2013; Lupattelli et al., 2018; Ross et al., 2013). International (NICE, 2014; Yonkers et al., 2009) guidelines advice health care providers to discuss (non-)treatment options with the pregnant woman, since studies so far could not identify whether the risk of ADM use is due to the medication or to underlying maternal psychopathology. Moreover, psychological treatments of prenatal common mental disorders may be an alternative to the use of ADM, and may mitigate the risk of untreated prenatal symptoms. Even though the psychotherapies seem beneficial and effective for pregnant women, the impact on offspring is unclear (Cuijpers et al., 2014; van Ravesteyn et al., 2017). For instance, psychotherapy may cause stress for the pregnant women, which in turn may as well negatively influence the child. The impact of prenatal treatments for common mental disorders on offspring will hence be reviewed and meta-analysed in Chapter 4.

Relapse prevention interventions during pregnancy

Once remitted from depression, an individual, pregnant or not, may be at increased risk to develop a new MDE. There are several existing treatment options that have been found to protect against relapse. This includes ADM, such as selective serotonin reuptake inhibitors (SSRIs), and/or psychological relapse prevention treatments such

as mindfulness-based cognitive therapy (MBCT), preventive cognitive therapy (PCT), or well-being therapy (WBT) (Beshai, Dobson, Bockting, & Quigley, 2011; Biesheuvel-Leliefeld et al., 2015; Bockting, Hollon, Jarrett, Kuyken, & Dobson, 2015; Clarke, Mayo-Wilson, Kenny, & Pilling, 2015; Guidi, Fava, Fava, & Papakostas, 2011; Guidi, Tomba, & Fava, 2016; Kuyken et al., 2016; Piet & Hougaard, 2011; Vittengl, Clark, Dunn, & Jarrett, 2007; Vittengl & Jarrett, 2015). These relapse prevention treatments can be offered sequentially (providing another intervention than used to treat MDD, such as acute ADM and/or other acute psychotherapeutic interventions and/or spontaneous remission), continuation treatment (extension of the acute treatment to prevent relapse), or by providing PCT after acute CBT (de Jonge et al., *in press*).

The use of ADM is a common strategy to treat MDD and prevent relapses, and several reviews indicate that it is an effective strategy to prevent relapses of MDD after initial response to treatment (e.g. Geddes et al., 2003; Kaymaz, van Os, Loonen, & Nolen, 2008). It is nonetheless unclear how long the ADM should be continued in order to protect an individual against relapse or recurrence. In the Netherlands, guidelines recommend to continue the use of ADM for six to twelve months, dependent on the risk of recurrence (GGZ Standaarden, 2018), whereas NICE guidelines recommend to continue ADM for six months, up to two years in case of an increased risk of recurrence (National Institute for Health and Clinical Excellence [NICE], 2009). When discontinuing the ADM without additional treatment, depressive symptoms and relapse rates increase (Bockting et al., 2015; Geddes et al., 2003; Kaymaz et al., 2008; Vittengl et al., 2007).

The preventive psychotherapies MBCT, PCT, and WBT, are likewise effective in lowering relapse risk (Beshai et al., 2011; Biesheuvel-Leliefeld et al., 2015; Bockting et al., 2005, 2009; Bockting et al., 2015; Clarke et al., 2015; Cuijpers et al., 2013; de Jonge et al., *under review*; Guidi et al., 2011; Guidi et al., 2016; Kuyken et al., 2016; Piet & Hougaard, 2011; Vittengl et al., 2007; Vittengl & Jarrett, 2015). PCT consists of eight weekly group or individual sessions and uses techniques focused on dysfunctional beliefs and schema using cognitive challenging techniques including phantasy (activation of positive network), enhance the recall of specific memories of positive experiences, positive feelings and thoughts, and formulating relapse prevention strategies (Bockting, 2009). MBCT is a skills training that combines mindfulness practices with CBT-skills (Kuyken et al., 2015; Segal, Williams, & Teasdale, 2002; Teasdale et al., 2000; Teasdale et al., 2002), whereas WBT is focused on promoting resilience and well-being, and increase mastery. WBT can be offered for six up to 20 sessions (e.g. Fava, Cosci, Guidi, & Tomba, 2017). MBCT and PCT have been studied in several adequately powered trials with independent rating of relapse. MBCT and PCT psychological relapse prevention interventions are both designed to minimize and prevent the risk of relapse (Biesheuvel-Leliefeld et al., 2017; Bockting et al., 2005, 2009, 2015, 2018; Bondolfi et al., 2010; de Jonge et al., 2019; Godfrin & van Heeringen, 2010; Huijbers et al., 2015, 2016, Kuyken

et al., 2008, 2015; Ma & Teasdale, 2004; Meadows et al., 2014; Segal et al., 2010; Shallcross et al., 2018; Teasdale et al., 2000; Williams et al., 2014).

Recent studies investigated the efficacy of relapse prevention psychotherapies versus the use of ADM, either sequential or as continuation treatment (e.g. Bockting et al., 2018; Brakemeier et al., 2014; Hollon et al., 2005; Huijbers et al., 2015; Jarrett, Minhajuddin, Gershenfeld, Friedman, & Thase, 2013; Kuyken et al., 2008, 2015; Perlis et al., 2002; Segal et al., 2010). A meta-analytic comparison of psychotherapy versus ADM use showed that psychotherapies were more effective in reducing the risk of relapse (Biesheuvel-Leliefeld et al., 2015). When compared to active treatment as usual, including ADM, CBT with or without ADM was likewise found to be superior in reducing this risk of relapse (Guidi et al., 2011; Guidi et al., 2016). These reviews did not provide information whether psychotherapies should be combined with ADM or not, or in addition to tapering ADM, as compared to ADM alone. Three randomised controlled trials therefore investigated whether psychotherapy while tapering ADM is an alternative to the continuation of ADM (Bockting et al., 2018; Kuyken et al., 2008, 2015; Segal et al., 2010). Overall, there were indications that MBCT while tapering ADM was more effective in reducing the risk of relapse than the use of ADM alone (Kuyken et al., 2008, 2015; Segal et al., 2010). However, Huijbers et al. (2016) found that MBCT while tapering ADM increased relapse risk. In a separate RCT comparing the addition of MBCT to ADM versus ADM alone, no additional preventive effect was found for MBCT on relapse risk over 15 months (Huijbers et al., 2015). In a third study, it was found that adding PCT to the continuation of ADM reduced the risk of relapse with 41%, as compared to PCT while tapering ADM and continuation of ADM. Continuing ADM as preventive strategy was not superior to PCT while tapering ADM. The combination of PCT with ADM was superior over ADM alone and PCT while tapering ADM, and the preferred relapse prevention strategy. However, for individuals who have the wish to discontinue the use of ADM, adding PCT while tapering is recommended (Bockting et al., 2018).

This is of particular interest to many pregnant women using ADM. Previous studies showed that pregnant women prefer psychotherapy over pharmacological treatment (Battle, Salisbury, Schofield, & Ortiz-Hernandez, 2013; Dimidjian & Goodman, 2014). One of the reason for the wish to discontinue can be the associated risks of ADM on the (unborn) child, as reported earlier. The efficacy and effects of relapse prevention interventions on pregnant women and their children, psychotherapy and pharmacological, have been investigated less in pregnant samples. The acute and preventive treatments for pregnant women are believed to be similarly effective as in non-pregnant populations (Cuijpers, Weitz, Karyotaki, Garber, & Andersson, 2014; Goodman, Cullum, Dimidjian, River, & Kim, 2018; van Ravesteyn, Lambregtse - van den Berg, Hoogendijk, & Kamperman, 2017). Research indicated that psychological interventions may lower the risk of depressive relapse during pregnancy (Dimidjian et

al., 2016), and there are trivial signals that preventive and acute prenatal interventions improve child functioning (Goodman et al., 2018). Up until now, it has not been investigated which relapse prevention strategy works best for pregnant women. For pregnant women who already take ADM and wish to stop their medication, minding the potential negative effects of ADM on the foetus, PCT while tapering may be a good alternative. A design to test this hypothesis is presented in Chapter 6.

One of the difficulties for clinicians and pregnant women who wish to stop ADM use is that up to now, the effects of tapering ADM while receiving PCT on the (unborn) child are unknown. Some studies found that affect fluctuations can negatively impact the unborn child as well (Hanley & Oberlander, 2014; Pesonen et al., 2016). In Chapter 7, we will investigate the emotional processes and its relation to birth outcomes in pregnant women in a randomized micro-trial (as designed in Chapter 6) who either taper ADM while receiving PCT, or continue ADM.

Dissertation outline

This dissertation will review components of a transgenerational model for common mental disorders (Figure A), to answer the main questions of this dissertation: What factors lead to the transgenerational transmission of common mental disorders, and can this transmission be prevented? In the first part, in Chapter 2, vulnerability factors derived from psychological theories that aim to account for the depressive relapse are reviewed. Thereafter, we will investigate whether a presumed vulnerability factor, i.e. dysfunctional attitudes styles predict time to depressive relapse (Chapter 3).

In the second part of the dissertation, we will explore the impact of prenatal interventions for common mental disorders on offspring. First, the impact on offspring of pharmacological and psychological treatments for common mental disorders during pregnancy will be systematically reviewed (Chapter 4). In Chapter 5, potential vulnerability factors for depressive relapse during and after pregnancy are explored. Subsequently, an RCT design is proposed that allows to investigate the impact of two relapse prevention interventions on pregnant women and their offspring (Chapter 6). Chapter 7 reports the results of a randomized controlled micro-trial that was conducted alongside the trial as reported in Chapter 6.

In Chapter 8, key finding from each chapter will be reviewed and integrated in the literature, which culminates to a guiding framework on the transgenerational transmission of common mental disorders, followed by research-, and clinical implications.

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Part 1

Chapter 2

Psychological theories of depressive relapse and recurrence: A systematic review and meta-analysis of prospective studies.

Based on: **Brouwer, M.E.**, Williams, A.D., Kennis, M., Fu, Z., Cuijpers, P. & Bockting, C.L.H. Psychological theories of depressive relapse and recurrence: A systematic review and meta-analysis of prospective studies. *Under review*.

ABSTRACT

Psychological vulnerability factors hypothesized to account for relapse of major depressive disorder (MDD) roughly originate from five main approaches: Cognitive, diathesis-stress, behavioural, psychodynamic, and personality. In a meta-analysis we investigated prospective evidence for these approaches in relation to depressive relapse. Included studies needed to establish history of MDD and prospective depressive relapse through a clinical interview, have a longitudinal and prospective design, and measure at least one theory-driven vulnerability factor before relapse. We identified 48 eligible articles out of 43,586 records published up to November 2018. Pooled odds ratios (*OR*) indicated a significant relationship between the cognitive, behavioural, and personality-based approaches and depressive relapse (cognitive: k = 17, *OR* = 1.24, 95% *CI* = 1.10, 1.40; behavioural, k = 8, *OR*= 1.15, 95% *CI* = 1.05, 1.25; personality: k = 12, *OR* = 1.26, 95% *CI* = 1.02, 1.54), but not for the psychodynamic approach (k= 4, *OR* = 1.29, *95% CI* = = 0.83, 1.99). Pooled hazard ratios of the approaches were not significant. There were no articles identified for the diathesis-stress approach. To conclude, there is a restricted number of prospective studies, and some evidence that vulnerability factors derived from the cognitive, behavioural, and personality-based approaches are related to depressive relapse.

INTRODUCTION

Major depressive disorder (MDD) has a highly recurrent nature, as approximately 40 to 60% of people with a first-time MDD episode (MDE) develop a subsequent episode (Eaton et al., 2008; Moffitt et al., 2010) and the risk increases with each new MDE (Moffitt et al., 2010). Due to the highly disabling and recurrent nature of MDD, there is a clear need for treatments that address the acute needs of individuals and mitigate the risks for relapse[2]. Nonetheless, high relapse rates of 39 to 54 percent after acute, maintenance, and preventive treatment suggest that current treatments are suboptimal and not effective for all individuals (Bockting et al., 2018; Cuijpers, 2017; Klein et al., 2018; Kuyken et al., 2016; Steinert, Hofmann, Kruse, & Leichsenring, 2014; Vittengl, Clark, Dunn, & Jarrett, 2007). Identifying vulnerability factors that increase the risk of depressive relapse is therefore necessary in order to improve existing treatment options to prevent the re-occurrence of MDD, and to inform on therapeutic targets. Proposed psychological vulnerability factors of depressive relapse generally originate from psychological theories that account for depression aetiology, and can roughly be allocated to the cognitive, diathesis-stress, behavioural, psychodynamic, and personality-based approaches (e.g. Burcusa & Iacono, 2007; Fernald, 2008). However, the evidence for these theories in relation to depressive relapse has, to our knowledge, not been reviewed thus far. The aim of the present systematic review is therefore to examine current evidence for the psychological theories and their vulnerability factors that are proposed to predict depressive relapse.

Research has identified several vulnerability factors of depressive relapse, including age of MDD onset, family history, and comorbidity of affective disorders (e.g. Burcusa & Iacono, 2007; Hardeveld, Spijker, De Graaf, Nolen, & Beekman, 2010). Recently, Buckman and colleagues (2018) proposed a framework of factors and mechanisms of change involved in depressive relapse, such as residual depressive symptoms, rumination, negative cognitions, neuroticism, and childhood maltreatment (Buckman et al., 2018). Other reviews and meta-analyses have generally focused on treatment effects instead of theoretical predictors of relapse, or on the first onset of MDD (e.g. Fu et al., in preparation; Mathews & MacLeod, 2005) which is believed to differ from relapse or recurrence of MDD (e.g. Lewinsohn, Allen, Seeley, & Gotlib, 1999).

Despite existing overviews of the clinical accounts for depressive relapse, there are some limits to the conclusions that can be drawn given the nature of the reviewed studies. Previous reviews comprised cross-sectional and low-quality studies, focused on a limited scope of potential vulnerability factors, and the factors were not derived from common psychological theories or specific treatment approaches. Lastly, the reviews

2 Of note, we use the term relapse to indicate both relapse and recurrence.

included information on vulnerability factors from individuals without necessarily meeting established criteria for the presence or absence of an MDD diagnosis. In order to support a causal relationship between vulnerability factors and depressive relapse, and to identify 'true' predictors, longitudinal prospective studies investigating vulnerability factors before depressive relapse are needed among patient populations. Previous reviews (Buckman et al., 2018; Burcusa & Iacono, 2007; Hardeveld et al., 2010) do not provide a summary of evidence specific to the leading theories that underpin current treatment options. In the current review we aim to address these issues, and provide an overview of current prospective evidence for the leading theories to predict depressive relapse.

Leading psychological theories are roughly based upon five major (overarching) approaches, which guided our systematic search: Cognitive, diathesis-stress, behavioural, psychodynamic, and personality-based (e.g. Burcusa & Iacono, 2007; Fernald, 2008). Within these approaches, there are various specific theories to account for the development of MDEs. For instance, cognitive therapy is in accordance with Beck's cognitive model of depression (Beck, Rush, Shaw, & Emery, 1979) and is based on the assumption that dysfunctional beliefs and thoughts are related to the onset of a new MDE in people with a history of MDD (e.g. Brouwer, Williams, Forand, DeRubeis, & Bockting, 2019; Forand & DeRubeis, 2014; Lorenzo-Luaces, German, & DeRubeis, 2015). Therefore, dysfunctional beliefs represent a theory-driven psychological vulnerability and therapeutic target in cognitive therapy (Beck & Bredemeier, 2016). In the initial cognitive model of Beck it was proposed that certain schemas or cognitive distortions are latent but can be activated by life events that matched these schemas, resulting in automatic negative thoughts and depressive symptomatology (Beck et al., 1979). Later, the cognitive model of Beck specified that these schemas could be activated by any event (e.g. Beck & Bredemeier, 2016), or even can be re-activated by sad mood (e.g. Segal et al., 2006; van Rijsbergen et al., 2013). Other cognitive theoretical accounts include the response style theory, including rumination (Nolen-Hoeksema, 1991), and learned helplessness as explanations for the development of MDD (Abramson, Seligman, & Teasdale, 1978).

Cognitive theories therefore often overlap with the diathesis-stress approach, explicitly including other vulnerability factors ('diatheses') such as stress and biological vulnerability factors (Hankin & Abela, 2005; Monroe & Simons, 1991). Generally stated, the diathesis-stress approach posits that a person may exhibit a vulnerability (such as high levels of dysfunctional beliefs or certain personality traits) that is activated by- or that in combination with- stress leads to the development of a first onset, chronic, or recurrent MDD (Conway, Slavich, & Hammen, 2015; Ingram, Miranda, & Segal, 1998; Monroe & Simons, 1991).

In terms of the historical evolution of psychological theories, the psychodynamic or psychoanalytic approach was amongst the earliest (Compton, 1986; Freud, 1917). Although the psychodynamic approach primarily explains the (first) onset of MDD, there are relapse prevention interventions based on this approach, including interpersonal therapy (IPT) and short-term psychodynamic psychotherapy (STPP) (Driessen et al., 2015; Luyten & Blatt, 2012). Relevant psychological vulnerability factors originating from the psychodynamic approach, which are often targeted in psychodynamic-oriented treatments, include parent-child attachment and interpersonal relationships (Luyten & Blatt, 2012).

Based upon animal models, and partly originating from the psychodynamic approach, behavioural theories, which includes (social) learning theory (e.g. Bandura, 2004) emerged. Within the behavioural approach there is a central role for (the levels of) positive and negative reinforcement of a person's behaviour, the person´s environment, and the development of depressive symptoms, such as the lack of pleasurable events and social support, life events, daily hassles, or behaviours that lack potential reward-value such as withdrawal and inactivity (e.g. Lewinsohn, 1974). Behavioural activation is a therapy based upon this approach, where a person is stimulated to engage in activities that have potential reward-value (e.g., going for a walk with a friend) while reducing behaviours that offer limited scope for positive experiences (e.g., staying in bed all day and avoiding completing household tasks) (Dimidjian, Barrera, Martell, Muñoz, & Lewinsohn, 2011). Similar to the cognitive approach, the behavioural approach may be perceived as a diathesis-stress approach, as life events and stress play a major role in the explanation of MDD.

Lastly, researchers have identified personality-based characteristics as vulnerability factors for depressive relapse, such as 'Big Five' traits, temperament, behavioural inhibition and activation, and personality disorders (Berlanga, Heinze, Torres, Apiquian, & Caballero, 1999; Buckman et al., 2018; Burcusa & Iacono, 2007; Klein, Kotov, & Bufferd, 2011). The Big Five model includes personality traits that may contribute to MDD onset and/or relapse (i.e. negative personality traits including neuroticism and conscientiousness), and personality traits that may protect a person from developing new episodes (positive or protective personality traits), such as extraversion (Berlanga et al., 1999; Buckman et al., 2018; Klein et al., 2011).

Although previous research identified several vulnerability factors, an overview of vulnerability factors derived from leading approaches that precede depressive relapse, and inform clinicians on targets points to prevent depressive relapse, is needed. The current systematic review and meta-analysis is, to our knowledge, the first study to investigate the (prospective) evidence for the main approaches in relation to the re-occurrence of MDD. We aim to provide an overview of evidence for the theory-driven vulnerability factors of relapse in MDD, specifically factors derived from the five major

approaches: Cognitive, diathesis-stress, behavioural, psychodynamic, and personality-based. Results of this review may in turn provide a basis for (new) therapeutic targets.

METHOD

Selection of studies

This meta-analysis followed the guidelines Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)(Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009), and was registered in Prospero (CRD42017073977). Separate searches in Pubmed, PsycInfo, Embase, and Cochrane were performed for each of the main approaches. Articles needed to be published from their origin through March 2017 (see Figure 1). The search was updated for articles published online up to November 16th, 2018. The databases were searched for relevant articles using search strings, composed using standardized vocabulary (e.g. MeSH terms), key words, terms for searching title and abstract, and Boolean operators. The four search strings included search terms relating to (1) MDD; (2) a longitudinal design or randomised controlled trials; (3) relapse/recurrence; and (4) vulnerability factors derived from the five leading psychological approaches. The search terms were adapted for each database in combination with database-specific filters for human, English language, original article (not review). A full overview of the search strategies is provided in Appendix I. To maximize finding eligible articles, the citations and references of included articles and related reviews were investigated (snowballing). Furthermore, several experts in the field of MDD were contacted to ask for relevant published trials, and to provide feedback on the search strategy (see acknowledgements).

There were several search strategies for each approach, since the current study was part of a larger project investigating psychological and biological risk factors of MDD onset and relapse (see Fu et al., *under review*; Kennis et al., *under review*). The vulnerability factors derived from the psychodynamic and personality-based approaches were searched simultaneously for both depressive onset and relapse (Fu et al., *under review*). A separate search strategy was performed for vulnerability factors from the cognitive and behavioural approach of relapse. A second search was performed for the cognitive approach, as some of the vulnerability factors were omitted from the first search. In this second search, vulnerability factors for both depressive onset and relapse were combined. For the diathesis-stress approach, an initial search was performed for psychological and biological vulnerabilities in combination with stress, daily hassles, and life events. Articles related to relapse were later identified and separately assessed for eligibility. As a result of the search strategy, vulnerability factors for different theories

could be identified in different searches. The flow chart of the selection process, as shown in Figure 1, is therefore a combined overview of all searches.

Selection criteria and selection process

Criteria for studies to be included in the review were: (1) Presence of a diagnostic status of MDD (MDD absence and/or presence) for all participants, as determined through a clinical interview (e.g., SCID, K-SADS from DSM, CIDI from ICD) or by a clinician at the start of the study; (2) At some point during the study, participants needed to be in (partial) remission or recovery as determined by a clinical interview or clinician assessment; and (3) relapse or recurrence was diagnosed through a clinical interview or by a clinician. (4) The study design was longitudinal and prospective; (5) The theory-driven predictor (i.e., the proposed vulnerability factors) was assessed before the relapse or recurrence of MDD; (6) The predictor was derived from one of the leading psychological theories; (7) Sufficient information was reported to calculate effect sizes (or was made available upon request). Exclusion criteria were the presence of bipolar disorder, dysthymia, seasonal affective disorder, postpartum depression, late-life MDD, or MDD due to medical disorders. Studies that solely included patients with a first onset MDD when they were older than 65 years, were excluded due to potential etiological differences between late-life onset MDD and MDD at younger ages (Devanand et al., 2004; Herrmann, Goodwin, & Ebmeier, 2007; Korten, Comijs, Lamers, & Penninx, 2012). Language was restricted to English. When multiple publications from the same study cohort were available, with exactly the same vulnerability factors, we included the publication with the longest follow-up time, or the largest number of participants in case of equal follow-up time.

In each step of the meta-analysis, two project members screened and selected the articles, and assessed the risk of bias using nine criteria of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for both randomized controlled trials (RCT) and observational studies. A positive score (+), indicating low risk of bias, was counted as 0, unclear (?) was scored as 1, and high risk of bias (negative score, -) was scored as 2. Hence, total scores could range from 0 to 18, with a high score indicating high risk of bias. Disagreement was solved by consultation of the research group and reaching consensus. The GRADE framework was moreover applied to assess quality of evidence for each approach, using the criteria to potentially downgrade the evidence as recommended by GRADE. Data was extracted independently by two researchers, and fully checked by another. Extracted information included participant demographics and baseline characteristics, diagnostic instrument utilized, outcomes and time of measurement, vulnerability factor assessment, and information for assessment of the risk of bias.

Vulnerability factors and outcome measures

Vulnerability factors were derived from the main psychological theories: Cognitive, diathesis-stress, behavioural, psychodynamic, and personality-based. Vulnerability factors derived from these theories were included in the meta-analysis, for example the dysfunctional attitudes scale alone (cognitive approach) or with the interaction of stressful events (diathesis-stress), behavioural activity (behavioural approach), attachment questionnaires (psychodynamic approach), and neuroticism (personality-based approach). In order to be included in the quantitative analyses, each measure, or highly similar measure, needed to be reported in at least three studies. There were no restrictions on the form of reporting the vulnerability factor, as long as an effect size could be calculated.

The main outcome measure was relapse or recurrence of MDD determined through a clinical interview or expert opinion (e.g., trained psychiatrist or psychologist), because self-reported depressive symptomatology may not reflect 'true' relapse of MDD, nor do such indices provide sufficient information to accurately indicate remission or recovery of MDD (Stuart et al., 2014). This outcome measure could be reported as time to relapse, or as an occurrence (relapse yes/no). Alternatively, studies could report a comparison between relapse/recurrence group and a non-relapse/recurrence group. However, the studies were only included if a direct comparison was provided (relapse versus non-relapse) within the original participant group from the start of the study.

Statistical approach

The software program Comprehensive Meta-Analysis (Borenstein, Hedges, Higgins, & Rothstein, 2005) was used to calculate the pooled effect sizes, forest plots, heterogeneity, and funnel plots. Due to the nature of this review, considerable heterogeneity between studies was expected and therefore we employed a random effects model to estimate pooled effect sizes. The effect sizes Risk Ratio's (*RR*), Hazard Ratio's (*HR*), and Odds ratios (*OR*) for all outcomes measures with 95% confidence intervals (*CI*s) were calculated using reported statistics from each study (including means, standard deviations, number of participants, and/or reported effect sizes). Each effect size indicates a comparison between the group of interest and comparison group. As an indicator of homogeneity among the effect sizes, we used the I^2 statistics (0% = no heterogeneity to 75% = high heterogeneity) and calculated the 95% *CI*s (Ioannidis, Patsopoulos, & Evangelou, 2007) of each I^2 using the non-central χ^2-based approach within the heterogi module for Stata (Orsini, Bottai, Higgins, & Buchan, 2006). If any study reported multiple groups (comparison group or group of interest), the effects were combined according to the Cochrane handbook (Higgins & Green, 2011). Publication bias was investigated by inspecting funnel plots, and using Egger´s test of the intercept, and Duval and Tweedie's trim and fill procedure (Duval & Tweedie, 2000).

Since some approaches include vulnerability factors that may be protective against relapse, these factors were separately analysed in the subgroup analyses described below, if applicable. Therefore, all pooled ORs, HRs, and RRs for each approach do not include the protective vulnerability factors, but the results from subgroup analyses may (as indicated). Such vulnerability factors for example include self-esteem, self-efficacy, and social support.

Meta regression and subgroup analyses

As previously stated, a random effects model (Borenstein, Hedges, Higgins, & Rothstein, 2009) was used to calculate pooled effect sizes for each approach. To perform subgroup analyses on categorical comparisons, we used a mixed effects model (Borenstein et al., 2009). In these subgroup analyses, the pooled effect sizes within subgroups were calculated with the random effects model, and the fixed effects model was used to test the difference between subgroups. The a-priori defined subgroup comparisons included the different vulnerability factors within the theories, theory-derived protective vulnerability factors, and status of the depression at the moment the theory-derived vulnerability factor was assessed. Where and if applicable, we aimed to run several meta-regression analyses for continuous comparisons, including baseline depressive symptoms, age, follow-up duration, gender, and risk of bias. Sensitivity analyses were conducted for each approach, where the pooled effect size of each approach was re-calculated with solely the studies with low risk of bias.

RESULTS

Characteristics of included studies

From the original 38,780 records that were identified in the database search and through reviews, the systematic search resulted in 58 eligible articles (0.15%; see Figure 1 for full details). The updated search up to November 2018 yielded 4,806 original records, and resulted in 8 additional eligible articles (0.17%). Most studies were excluded during the full-text screening on the basis that they did not establish an MDD diagnosis (25%), did not report a vulnerability factor (25%), or did not investigate relapse or recurrence (26%). Table 1 reports the study characteristics of the articles that were included for the qualitative and quantitative analyses. The articles reported 43 *unique* studies, of which 15 were RCTs, and 28 had a prospective, non-randomized design. There were no articles identified reporting the diathesis-stress approach for depressive relapse. Five articles did not report (unadjusted) relapse rates. Altogether, 6,874 unique participants were included, and mean reported relapse rate was 42% during follow-up assessments. Follow-up time ranged from 6 months up to 12 years

(*Median* = 24 months). The risk of bias of the included studies was in general low to moderate, as reported in Table 1. Tables 2 and 3 display the outcomes of the meta-analyses that were completed.

In total, 328 different types of vulnerability factors and analyses were reported across and within studies. These statistical analyses were generally convertible to *HR* or *OR*. One study presented a *RR* (Spinhoven et al., 2011), and two studies reported mediation results only (Vittengl, Clark, Thase, & Jarrett, 2015a, 2015b). There were an insufficient number of vulnerability factors from different articles to calculate pooled RRs, and insufficient information to recalculate the *RR* into *OR*. Since *HR* and *OR* are non-comparable, the two analyses are presented separately. Visual inspection of the funnel plot, the Egger's test ($p < 0.01$) and Duval and Tweedie's trim and fill (studies trimmed within HR meta-analysis = 4; within *OR* = 6), indicated potential publication bias, with missing articles on the left side of the funnel plot (lack of published non-significant results).

Since not all included articles reported sufficient information to calculate *HRs* or *ORs*, data from 48 articles originating from 35 unique studies was analysed. First, pooled effect sizes per approach were calculated. Figures 1 and 2 show the forest plots for *HR* (18 studies) and *OR* (25 studies) for each approach. Second, several meta-analyses were performed based on the vulnerability factors within the approaches, for *HR* and *OR* separately. There were not enough studies and participants to conduct meta-regression analyses for continuous comparisons within each approach. The outcomes of the analyses are presented below and in Table 2 for each leading approach.

Theory-driven vulnerability factors

Cognitive approach. Figures 2 and 3 show the results of the theory-driven vulnerability factors for all approaches. Overall, the cognitive approach was significantly related to the *odds* of relapse (*OR* = 1.24, 95% *CI* = 1.10, 1.40), but not to *time* to relapse (*HR* = 1.00, *95% CI* = 0.98, 1.03). Sensitivity analyses showed similar results for studies with low risk of bias only (*OR* = 1.22, 95% *CI* = 1.09, 1.38, *k* = 16; *HR* = 1.02, 95% *CI* = 0.97, 1.07, *k* = 10). The ORs differed significantly ($p < 0.001$) between the vulnerability factors within the approach. More negative attributions increased the *odds* of relapse 1.3 times (*OR* = 1.26, 95% *CI* = 1.07, 1.48). With regard to the HR subgroup analyses, it was found that higher levels of dysfunctional attitudes were related to decreased *time to* depressive relapse (*HR* = 1.01, 95% *CI* = 1.00, 1.01). The pooled *OR* and *HR* did not differ between diagnostic status (i.e. if the participants were depressed or not during the time of assessment of the vulnerability factor; *HR p* = 0.98; *OR p* = 0.19). The strength of evidence was assessed as low, according to the GRADE framework.

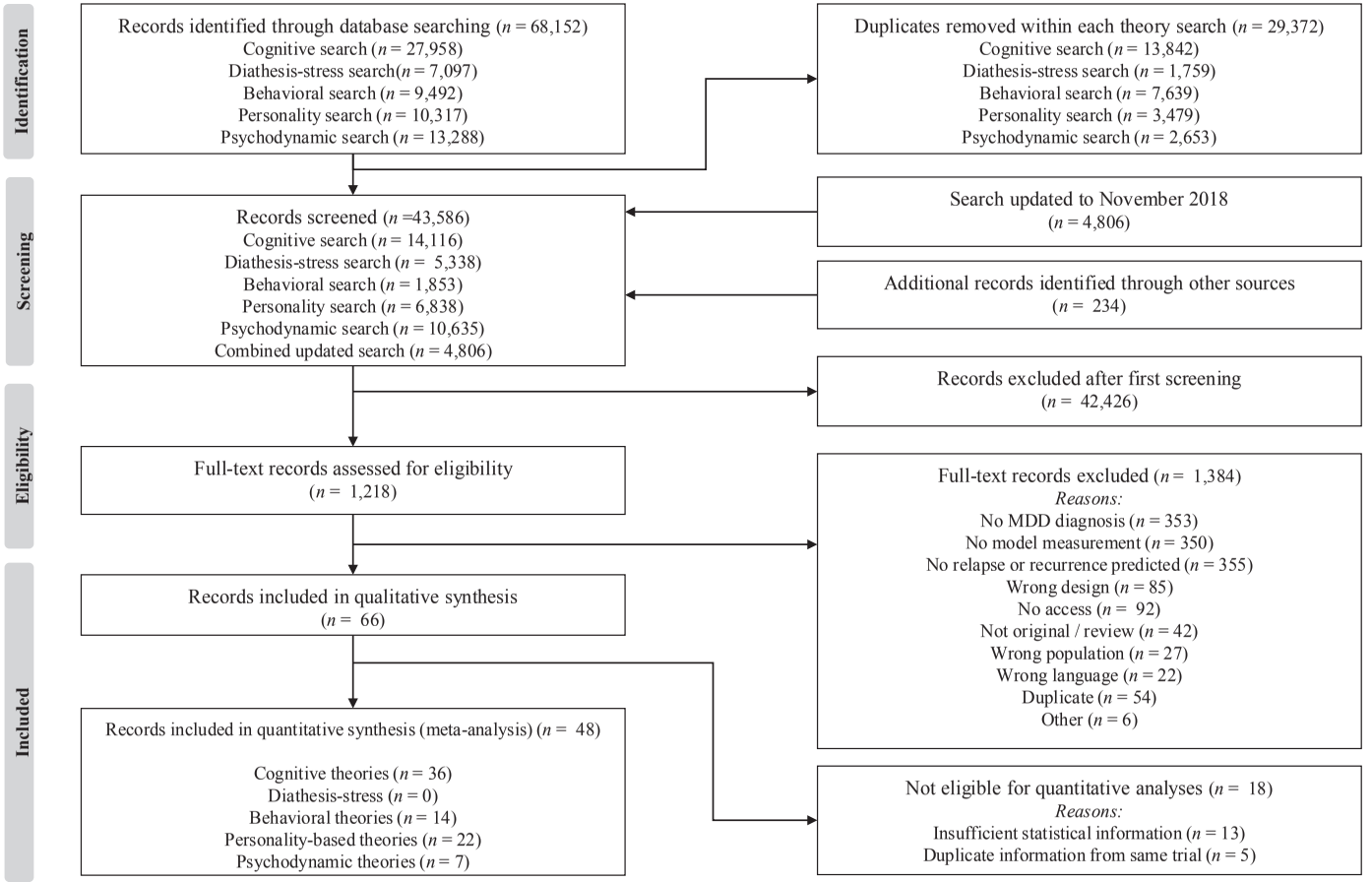

Figure 1. Flow chart of screening process.

Table 1
Characteristics of included studies

First author, year	Design, Main study & Interventions	Country	Theory & Predictors	No. of participants (*n* female)
Asano 2015	Cohort	Japan	Personality: TCI	69 (44)
Backs-Dermott 2010	Cohort	Canada	Cognitive: SAS-R, CISS Behavioural: MSPSS, social support	49 (49)
Berlanga 1999	RCT: Nefazodone vs. Fluoxetine	Mexico	Personality: EPQ	42 (32)
Birmaher 2004	Cohort	USA	Behavioural: CBCL Psychodynamic: Marshall & Tanner development	68 (29)
Bockting 2006; *Bockting 2006b;* Figueroa 2015; ten Doesschate 2010; van Rijsbergen 2013	RCT: "Delta study"; Group PCT vs. TAU	NL	Cognitive: CERQ, DAS, LEIDS Behavioural: UCL	187 (126)
Bouhuys 2006	Cohort	NL	Cognitive: Perception of facial expressions	77 (51)
Brouwer 2019	RCT: M-CT + TAU vs. TAU	NL	Cognitive: DAS, extreme responding	264 (197)
Chopra 2008 *Fresco 2007* Segal 2006	RCT: CT vs. AD	Canada	Cognitive: DAS	127 (48)
Conradi 2008 Conradi 2018	RCT: "INSTEL study"; TAU vs. PEP vs. Psychiatrist-enhanced PEP vs. CBT-enhanced PEP	NL	Behavioural: RSES, MOS-SF-36, Groningse list Psychodynamic: ECR	123 (84) 103 (75)
Craighead 2011 Hart 2001 Sheets 2014 **	Cohort	USA	Cognitive: DAS Personality: IPDE Psychodynamic: IIP-32	130 (104) 93 (50) 119 (94)
Farb 2018 Segal 2018	RCT: MBCT vs. CT	Canada	Cognitive: DAS, EQ	166 (112)
Forand 2014 Strunk 2007	RCT: CT subgroup only	USA	Cognitive: DAS, extreme responding, WOR	104 (60) 35 (18)
Gollan 2006	RCT: CBT vs. BA vs. BA + AT	USA	Cognitive: DAS, ATQ, EASQ Behavioural: PES Personality: MCMI	93 (74)
Gonzales 1985 Lewinsohn 1984	Pre-post design; several CBT based interventions	USA	Behavioural: Physical functioning	167 (80) 113 (n/a)
Gopinath 2007	RCT: Depression relapse prevention intervention vs. usual primary care	USA	Cognitive: Self-efficacy Personality: NEO-FFI Behavioural: MOS-SF-36	386 (285)
Grilo 2010	Cohort: "Collaborative Longitudinal Personality Disorders Study"	USA	Personality: DIPD-IV	303 (196)

No. of relapse / No. non-relapse	Follow-up time in months	Diagnostic tool	Diagnostic status at assessment	Depression score at assessment, tool: *M* (*Sd.*)	Risk of bias score
39 / 30	48	DSM-IV criteria	2	HDRS: 3.9 (3.1)	1
29 / 20	12	SCID-I DSM-IV-TR	2	BDI-II: 11.7 (8.8)	2
18 / 24	12	DSM-IV criteria & HDRS	1	HDRS: 26.9 (5.3)	1
27 / 68	58	K-SADS-E & K-SADS-P0	1	HDRS: 14.3 (5.5)	8
135 / 37	66	SCID-I DSM-IV-TR	2	HDRS: 3.8 (2.8)	0 0 0 0 0
21 / 56	24	CIDI interview	2	BDI: 3.6 (2.4)	1
98 / 113	24	SCID-I interview	2	HDRS: 3.55 (3)	1
40 / 38	18	LIFE interview & HDRS	1	HDRS: 5.6 (2.7)	5 7 1
n/a 56 / 47	36 84	CIDI interview	1	BDI: n/a	6 6
n/a	18	SCID-I DSM & LIFE interview	2	BDI-II: 12.3 (7.1)	2 2 2
36 / 130	24	SCID-I DSM-IV	2	HDRS: n/a	2 2
59 / 25 13 / 18	24	SCID-I DSM-IV & HDRS	3	HDRS: n/a	6 6
40 / 53	24	SCID-I DSM-III-R	3	HDRS: 4.3 (3.6)	5
24 / 21	12	SADS & Life interview	1	BDI: 22 (8.8)	2 3
120 / 266	12	SCID-I DSM-III-R & LIFE interview	2	n/a	3
183 / 77	72	SCID-I DSM-IV & LIFE interview	2	n/a	3

Table 1
Characteristics of included studies (continued)

First author, year	Design, Main study & Interventions	Country	Theory & Predictors	No. of participants (*n* female)
Hardeveld 2013 Ormel 2004	Cohort: "NEMESIS"	NL	Personality: ABI Neuroticism, Locus of control Behavioural: SSQS	687 (467) 680 (n/a)
Holma 2008 Melartin 2004	Cohort: "The Vantaa Depression Study"	Finland	Cognitive: Hopelessness Behavioural: SOFAS, social network, PSSS-R; Personality: EPQ	269 (143)
Ilardi, 1997	Cohort	USA	Cognitive: DAS, ASQ Personality: IPDE	50 (37)
Jarrett 2012 *Vittengl 2015* *Vittengl 2015b* Vittengl 2017	RCT: C-CT vs. fluoxetine 40 mg/day vs. pill placebo	USA	Cognitive: DAS Personality: SNAP	213 (137) 172 (120)
Kuehner 2013	Cohort	Germany	Cognitive: ACS-24 Behavioural: MISS	68 (37)
Lam 1996	Cohort	England	Cognitive: DAS	37 (21)
Lara 2000	Cohort	USA	Cognitive: RSQ Behavioural: ISEL, social support Psychodynamic: EHEI	88 (72)
LeMoult 2017	Cohort	USA	Cognitive: SRET	100 (100)
Lethbridge 2008	Cohort	Australia	Cognitive: DAS	52 (30)
Lin 1998	RCTs combined	USA	Personality: Neuroticism Behavioural: MOS-SF-36	251 (190)
Michalak 2011	Pre-post design: MBCT	Germany	Cognitive: RRS	24 (18)
Mongrain 2005 Mongrain 2006	Cohort: Toronto University packages	Canada	Cognitive: RSQ, PSI, EASQ, DAS Psychodynamic: DEQ Personality: BFI Neuroticism	97 (77) 158 (119)
Mulder 2009	RCT: "Christchurch Outcome of Depression study"; Fluoxetine vs. Nortriptyline	New Zealand	Personality: TCI, personality disorder traits	195 (111)
Mundt 1998	Cohort: Heidelberg Depression Study	Germany	Cognitive: ASQ Personality: MMPI	50 (33)
Noteboom 2016 *Spinhoven 2011* Spinhoven 2016 *Spinhoven 2018*	Cohort: "NESDA study"	NL	Personality: NEO-FFI Cognitive: AAQ-I, PSWQ, LEIDS-R, PTQ	437 (308) 722 (466) 977 (790) 790 (536)
O'Leary 2001	Cohort	Ireland	Personality: MPI neuroticism, MPI extraversion	84 (45)
Otto 2007	Cohort: "The Harvard Study of Moods and Cycles"	USA	Cognitive: DAS	80 (80)

No. of relapse / No. non-relapse	Follow-up time in months	Diagnostic tool	Diagnostic status at assessment	Depression score at assessment, tool: *M* (*Sd.*)	Risk of bias score
135 / 552	36	CIDI DSM-III-R	2	n/a	0 3
99 / 41	60	SCAN for DSM disorders	1	HDRS: 19.1 (6.1)	5 4
34 / 16	84	DIS for DSM-III-R & LIFE interview	1	MADRS: 14.2 (7.7)	8
113 / 128	32	SCID-I DSM-IV & LIFE interview	3	BDI, IDS-SR, and HRSD: 17.6 (7.4)	5 2 3
74 / 98					3
33 / 27	66	SCID-I DSM-IV	1	MADRS: 7.2 (7.8)	5
12 / 17	12	Psychiatrist diagnosis DSM-III	2	n/a	2
12 / 45	6	SCID-I DSM-IV & LIFE interview	1	HDRS: 21.4 (8.7)	6
29 / 30	36	SCID-I DSM-IV-R	2	BDI: 13.4 (9.5)	6
24 / 21	12	SCID-I DSM-IV-R	2	BDI: 8.1 (6.1)	4
93 / 158	12	Psychiatrist diagnosis DSM-III	2	IDS: 14.2 (10.0)	2
9 / 15	12	SCID-I DSM-IV	2	HDRS: 1.9 (2.6)	6
37 / 65	20	SCID-I DSM-IV	2	CES-D: 34.6 (11.2)	4 5
57 / 66	18	SCID-I DSM-III-R	1	MADRS: 19.9 (4.4)	6
18 / 24	12	SCID-I DSM-III-R	3	HDRS: 8.1 (7.1)	1
n/a	24	CIDI for DSM-IV	2	n/a /	1
274 / 448	24		1	IDS-SR: 34.7	1
360 / 617	72		2	(11.2) / 14.7	5
166 / 790	36		2	(9.5) / 13.8 (9.1)	4
15 / 68	18	SCAN and ICD-10 criteria	1	HDRS: 23.8 (0.7)	2
25 / 55	36	SCID-I DSM-IV	2	HDRS: 5.7 (4.6)	5

Table 1
Characteristics of included studies (continued)

First author, year	Design, Main study & Interventions	Country	Theory & Predictors	No. of participants (*n* female)
Petersen 2007	RCT: Fluoxetine + CBT vs. Fluoxetine	USA	Cognitive: DAS, ASQ	132 (72)
Pettit 2013	Cohort: "OADP study"	USA	Behavioural: Social support, health problems Cognitive: Coping skills, DAS Psychodynamic: interpersonal dependency	59 (40)
Segal 1992	Cohort: "recovery from depression"	Canada	Cognitive: DAS	59 (43)
Segal 1999 Thase 1992	Pre-post design: CBT or AD	Canada	Cognitive: DAS	44 (18) 50 (35)
Solomon 2004	Cohort: "Collaborative Depression Study"	USA	Behavioural: LIFE-RIFT	290 (175)
Teasdale 2001 *Teasdale 2002*	RCT: CT + Clinical management & drug continuation vs. Clinical management & drug continuation	England	Cognitive: ASQ, DAS, BLAME, MAQ, MACAM, UNCONTROL	158 (78)
Timm 2017	Cohort	Germany	Cognitive: PTQ, Rumination	57 (40)
Van Loo 2015	Cohort: "VATSPSUD study"	USA	Personality: EPQ	194 (194)
Vittengl 2010	RCT: Assessment + C-CT vs. Assessment only	USA	Personality: SNAP	84 (62)
Woody 2016	Cohort	USA	Cognitive: Modified dot-probe task	53 (53)

Note: ** although not explicitly reported, the study identification numbers, names, and participant groups indicate that the participants are highly overlapping or exactly the same. 1 = depressed, 2 = non-depressed / remitted, 3 = treatment responder. n/a = not applicable or not available. RCT = Randomized controlled trial; CBT = Cognitive behavioural therapy; TAU = Treatment as usual; CT = Cognitive therapy; PEP = Psycho-Educational Prevention Program; BA = Behavioural activation; AT = Automatic thought modification; C-CT = Continuation CT; M-CT = mobile preventive cognitive therapy; MBCT = Mindfulness-based cognitive therapy; PCT = Preventive cognitive therapy; AD = Antidepressant medication; CIDI = Composite International Diagnostic Interview; DIS = Diagnostic Interview Schedule; LIFE = Longitudinal Interval Follow-up Evaluation; K-SADS = Schedule for Affective Disorders and Schizophrenia-Lifetime - Age children (E = Epidemiologic version; P = present version); SADS-L = Schedule for Affective Disorders and Schizophrenia-Lifetime; SCAN = Schedules for Clinical Assessment in Neuropsychiatry; ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th edition; SCID-I = Structured Clinical Interview for DSM axis-I diagnoses; BDI = Beck Depression Inventory; CES-D = Centre for Epidemiologic Studies Depression scale; HDRS = Hamilton Depression Rating Scale; IDS = Inventory of Depressive symptomatology; MADRS = Montgomery Asberg Depression Rating Scale; DSM = Diagnostic and Statistical Manual of Mental Disorders; AAQ-I = Acceptance and Action Questionnaire-I; ABI = Amsterdam Biographic Inventory; ACS-24 = Action Control Scale; ASQ = Attributional style questionnaire; ATQ = Automatic Thoughts Questionnaire; BFI = Big Five Inventory; BLAME = Characterological Self-Blame for Depression; CBCL = Child Behaviour Checklist; CERQ = Cognitive Emotion Regulation Questionnaire; CISS = Coping inventory for stressful situations; DAS = Dysfunctional Attitudes Scale; DEQ = Depressive Experiences Questionnaire; DIPD-IV = Diagnostic interview for DSM-IV personality disorders; EASQ = Extended attributional style questionnaire; EHEI = Early home environment interview; ECR = Experiences in Close Relationships; EPQ = Eysenck Personality Questionnaire; EQ = Experiences Questionnaire; IIP-32 = Inventory of Interpersonal Problems; IPDE = International Personality Disorder Examination; ISEL = Interpersonal Support Evaluation List; LEIDS = Leiden Index of Depression Sensitivity (R = revised); LIFE-RIFT =

No. of relapse / No. non-relapse	Follow-up time in months	Diagnostic tool	Diagnostic status at assessment	Depression score at assessment, tool: *M* (*Sd.*)	Risk of bias score
n/a	9	SCID-I DSM-III-R	1	HDRS: 18.7 (2.8)	3
43 / 16	144	K-SADS & LIFE interview	1	n/a	2
30 / 29	12	SADS-L	2	BDI: 4.4 (3.3)	2
14 / 16	30 12	SADS-L	2 1	HDRS: 4.1 (3.7)	6 4
143 / 147	135	SADS-L & LIFE interview	1	HDRS: 20 (7)	3
60 / 98	17	DSM-III-R diagnosis by psychiatrist	1	HDRS: 12.1 (2.8)	4 7
28 / 29	36	SCID DSM-IV-R	2	BDI-II: 10.6 (8.8)	2
101 / 83	66	SCID DSM-III-R	2	n/a	1
n/a	24	SCID-I DSM-IV & LIFE interview	3	HDRS: 11.7 (6.9)	2
15 / 38	24	SCID-I DSM-IV		BDI-II: 10.3 (8.8)	3

Longitudinal Interval Follow-up Evaluation–Range of Impaired functioning Tool; MACAM = Measure of Awareness and Coping in Autobiographical Memory; MAQ = Metacognitive Awareness Questionnaire; MCMI = Millon Clinical Multiaxial Inventory; MISS = Mannheim Interview on Social Support; MMPI = Minnesota Multiphasic Personality Inventory; MOS-SF-36 = Physical functioning; MPI = Maudsley Personality Inventory; MSPSS = Multidimensional Scale of perceived social support; NEO-FFI = NEO Five-Factor Inventory; PES = Pleasant Events Scale; PSI = Personal Style Inventory; PSSS-R = Perceived Social Support Scale – Revised; PSWQ = Penn State Worry Questionnaire; PTQ = Perseverative Thinking Questionnaire; RRS = Ruminative Response Scale; RSES = Rosenberg Self-esteem scale; RSQ = Response Style Questionnaire; SAS-R = Revised Sociotropy-Autonomy Scale; SNAP = Schedule for Nonadaptive and Adaptive Personality; SOFAS = Social and Occupational Functioning Assessment Scale; SRET = Self-Referential Encoding Task; SSQS = Social Support Questionnaire for Satisfaction with the supportive transactions; TCI = Temperament and Character Inventory; UCL = Utrecht Coping List; UNCONTROL = Perceived Uncontrollability of Depression; WOR = Ways of Responding

Table 2
Results of meta-analyses and subgroup analyses - Hazard Ratio

Main approach	No. of studies	No. of participants	*HR* (95% CI)	I^2 (95% *CI*)	*p*-value*
Behavioural	3	420	1.06 (0.94 – 1.19)	72% (7-92)	
Vulnerability factors					0.20
Social support	4	944	0.99 (0.97 – 1.01)	34% (0-77)	
Cognitive	12	1,490	1.00 (0.98 – 1.03)	51% (5-75)	
Diagnostic status					0.98
Non-depressed	7	895	1.01 (0.97 – 1.06)	13% (0-75)	
Depressed	5	595	1.01 (0.94 – 1.09)	74% (35-89)	
Vulnerability factors					0.02
Dysfunctional attitudes	6	**870**	**1.01 (1.00 – 1.01)**	35% (0-74)	
Personality					
Diagnostic status	7	1,509	1.02 (0.97 – 1.08)	68% (30-86)	0.03
Non-depressed	5	1,197	1.05 (0.98 – 1.12)	70% (23-88)	
Vulnerability factors					0.60
Negative personality trait	5	1,146	1.02 (0.95 – 1.09)	83% (61-93)	

Note: * = *p*-value for the difference between subgroups; HR = Hazard ratio.

Behavioural approach. The behavioural approach was significantly related to the *odds* of relapse (*OR* = 1.15, 95% *CI* = 1.05, 1.25), but not to *time to* relapse (*HR* = 1.06, 95% *CI* = 0.94, 1.19). Sensitivity analyses showed the exact same results for *OR*, and there were insufficient studies within HR to conduct a sensitivity analysis. Subgroup analyses with the vulnerability factors were not significant. Diagnostic status did not influence the relationship between the behavioural approach and the *odds* of depressive relapse (*p* = 0.39). The overall strength of evidence for this approach was low, as assessed by means of the GRADE framework.

Psychodynamic approach. The psychodynamic approach was not significantly related to the *odds* of relapse (*OR* = 1.29, 95% *CI* = 0.83, 1.99). There were not enough studies to assess *time* to relapse. Within the sensitivity analysis, the same results were found for studies as all studies had a low risk of bias. The separate vulnerability factors within the approach could not be investigated due to high heterogeneity and an insufficient number of eligible studies. Strength of evidence for the psychodynamic approach was very low, as assessed with the GRADE framework.

Personality-based approach. The pooled *OR* indicated a significant relationship between the personality-based approach and *odds* of depressive relapse (*OR* = 1.26, 95% *CI* = 1.02, 1.54), but not between the personality-based approach and *time to* relapse (*HR* = 1.02, 95% *CI* = 0.97, 1.08). The sensitivity analyses showed similar results (*OR* = 1.26, 95% *CI* = 1.01, 1.57, *k* = 11; *HR* = 1.05, 95% *CI* = 0.96, 1.15, *k* = 6). Diagnostic status did not influence the relationships for OR (*p* = 0.96), yet did

Table 3
Results of meta-analyses and subgroup analyses - Odds Ratio

Main approach	No. of studies	No. of participants	*OR* (95% *CI*)	I^2 (95% *CI*)	*p*-value
Behavioural	8	1,344	**1.15 (1.05 – 1.25)**	73% (46, 87)	
Diagnostic status					0.39
Non-depressed	3	607	**1.19 (1.08 – 1.32)**	0% (0, 90)	
Depressed	5	737	**1.12 (1.01 – 1.24)**	78% (48, 91)	
Vulnerability factors					0.003
Functioning	5	1,010	1.10 (0.99 – 1.22)	74% (36, 90)	
Social support	3	306	0.98 (0.91 – 1.05)	0% (0, 90)	
Cognitive	17	2,929	**1.24 (1.10– 1.40)**	78% (65, 86)	
Diagnostic status					0.19
Non-depressed	12	2,503	**1.33 (1.06– 1.66)**	86% (78, 91)	
Depressed	5	426	1.11 (0.96 – 1.28)	73% (34, 89)	
Vulnerability factors					<0.001
Attributional style	4	274	**1.26 (1.07 – 1.48)**	0% (0, 85)	
Coping	3	788	1.10 (0.77 – 1.57)	69% (0, 91)	
Dysfunctional attitudes	9	681	1.03 (0.95 – 1.12)	33% (0, 69)	0.23
Non-depressed	6	495	**1.01 (1.01 – 1.01)**		
Depressed	3	186	1.60 (0.75 – 3.42)		
Personality	12	2,755	**1.26 (1.02 – 1.54)**	61% (27, 79)	
Diagnostic status					0.99
Non-depressed	7	2,273	1.25 (0.94 – 1.67)	70% (34, 86)	
Depressed	5	482	1.26 (0.90 – 1.74)	36% (0, 76)	
Vulnerability factors					0.40
Personality disorder traits	3	363	1.20 (0.85 – 1.67)	27% (0, 92)	
Negative personality trait	11	2,713	**1.28 (1.04 – 1.58)**	74% (52, 86)	
Neuroticism	7	2,636	**1.66 (1.13 – 2.45)**	92% (87, 96)	
Diagnostic status					0.43
Non-depressed	5	2,396	1.46 (0.94 – 2.25)	86% (70, 94)	
Psychodynamic	4	341	1.29 (0.83 – 1.99)	49% (0, 83)	

Note: * = *p*-value for the difference between subgroups; *OR* = Odds ratio.

influence the relationships for HR (p = 0.03), although HRs remained non-significant in the non-depressed subgroup (HR = 1.05, 95% *CI* = 0.98, 1.12, k = 5). Subgroup analyses indicated that negative personality traits were related to 1.3 times increased *odds* of relapse (*OR* = 1.28, 95% *CI* = 1.04, 1.58) and not to *time to* depressive relapse (*HR* = 1.02, 95% *CI* = 0.95, 1.09). Specifically, neuroticism was related to 1.7 times increased odds of relapse (*OR* = 1.66, 95% *CI* = 1.13, 2.45). Again, according to the GRADE framework, the strength of evidence was low.

Main approach	Study name	Main concept	Outcome	Hazard ratio	95% CI Lower	95% CI Upper	*p*-Value
	Conradi 2008	Combined	Combined	0.92	0.71	1.18	0.52
	Delta study	Coping	UCL Avoidant coping	1.18	1.06	1.31	0.00
	Vantaa Depression Study	Functioning	Functioning	1.02	1.00	1.04	0.05
Behavioural				*1.06*	*0.94*	*1.19*	*0.35*
	Bouhuys 2006	Cognitive bias	Combined	1.04	0.66	1.63	0.86
	Brouwer 2019	Dysfunctional attitudes	Combined	1.16	0.81	1.66	0.43
	Chopra, Fresco & Segal	Cognitive reactivity	Cognitive reactivity	1.52	1.10	2.09	0.01
	Craighead, Hart & Sheets	Combined	Combined	1.01	0.91	1.12	0.84
	Delta study	Combined	Combined	1.05	0.94	1.18	0.38
	Forand & Strunk	Combined	Combined	1.71	0.96	3.06	0.07
	Gollan 2006	Combined	Combined	1.00	0.98	1.02	0.83
	Jarrett 2012	Dysfunctional attitudes	DAS	1.01	1.00	1.02	0.05
	Kuehner 2013	Action control	Combined	0.68	0.16	2.81	0.60
	Segal 2018	EQ	Decentering slope	0.23	0.05	1.02	0.05
	Timm 2017	Combined	Combined	1.16	0.92	1.45	0.20
	Vantaa Depression Study	Hopelessness	Hopelessness	0.96	0.92	1.00	0.05
Cognitive				*1.00*	*0.98*	*1.03*	*0.72*
	Asano 2015	Personality trait	Combined	1.35	0.63	2.88	0.44
	Craighead, Hart & Sheets	Personality disorders	Combined	1.04	0.92	1.17	0.54
	Gollan 2006	Personality trait	Combined	1.00	0.97	1.02	0.84
	Grilo 2010	Personality disorders	Personality disorder	1.50	1.09	2.07	0.01
	NEMESIS	Combined	Combined	1.06	1.02	1.11	0.00
	Vantaa Depression Study	Personality trait	Neuroticism	0.95	0.90	1.00	0.06
	Vittengl 2017	Personality trait	Negative temperament	1.16	0.69	1.96	0.57
Personality				*1.02*	*0.97*	*1.08*	*0.43*

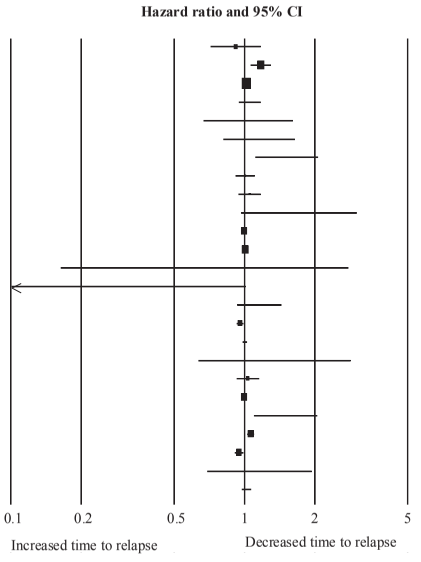

Figure 2. Forest plot for Hazard Ratio meta-analysis.
Note: Combined = combination of variables, CI = confidence interval, EQ = Experiences Questionnaire, UCL = Utrechtse Coping List.

Main approach	Study name	Main concept	Outcome	Odds ratio	95% CI Lower	95% CI Upper	*p*-Value
	Backs-Dermott 2010	Coping	CISS-Avoidance	1.80	0.64	5.09	0.27
	Delta study	Coping	UCL Avoidant coping	1.18	1.06	1.31	0.00
	Gonzales & Lewinsohn	Poor physical health	Poor physical health	1.28	1.06	1.55	0.01
	Gopinath 2007	Functioning	Combined	1.36	0.92	2.02	0.12
	Pettit 2013	Functioning	Health problems	1.21	0.75	1.95	0.43
	Solomon 2004	Functioning	Psychosocial functioning	1.12	1.06	1.19	0.00
	Vantaa Depression Study	Functioning	Combined	1.01	0.99	1.04	0.28
	Vittengl 2010	Functioning	Social adjustment	2.36	1.05	5.31	0.04
Behavioural				*1.15*	*1.05*	*1.26*	*0.00*
	Backs-Dermott 2010	Combined	Combined	0.63	0.22	1.79	0.39
	Bouhuys 2006	Cognitive bias	Combined	0.94	0.38	2.34	0.90
	Delta study	Combined	Combined	1.05	0.99	1.11	0.12
	Farb 2017		Decentering	1.85	0.94	3.62	0.07
	Gollan 2006	Combined	Combined	0.99	0.47	2.09	0.98
	Lam 1996	Dysfunctional attitudes	DAS Dependency	1.16	0.97	1.38	0.10
	LeMoult 2017	SRET	Combined	3.08	1.19	7.98	0.02
	Mundt 1998	Attributional style	ASQ Internality	1.19	0.98	1.45	0.08
	NEMESIS	Coping	Depressive coping style	1.48	1.06	2.06	0.02
	NESDA	Combined	Combined	1.86	1.58	2.18	0.00
	Otto 2007	Dysfunctional attitudes	DAS	1.25	0.53	2.94	0.62
	Pettit 2013	Combined	Combined	0.96	0.89	1.05	0.39
	Segal 1992	Dysfunctional attitudes	Combined	1.14	0.44	2.96	0.78
	Thase 1992	Dysfunctional attitudes	Combined	3.71	1.22	11.24	0.02
	Toronto University Packages	Combined	Combined	1.59	0.53	4.81	0.41
	Vantaa Depression Study	Hopelessness	Hopelessness	1.10	1.03	1.18	0.01
	Vittengl 2010	Combined	Combined	2.06	0.92	4.61	0.08
Cognitive				*1.24*	*1.10*	*1.41*	*0.00*
	Asano 2015	Personality trait	Combined	1.78	0.74	4.25	0.20
	Berlanga 1999	Personality trait	Combined	4.10	1.24	13.50	0.02
	Gollan 2006	Personality trait	Combined	0.72	0.34	1.52	0.39
	Gopinath 2007	Personality trait	Neuroticism	0.64	0.43	0.94	0.02
	Lin 1998	Personality trait	Neuroticism	1.46	0.91	2.32	0.11
	Mulder 2009	Combined	Combined	1.34	0.69	2.62	0.39
	Mundt 1998	Personality	Combined	1.01	0.77	1.33	0.95
	NEMESIS	Combined	Combined	1.72	1.23	2.40	0.00
	NESDA	Personality trait	Combined	1.41	1.24	1.61	0.00
	Toronto University Packages	Personality trait	Neuroticism	1.67	0.81	3.44	0.16
	Vantaa Depression Study	Combined	Combined	1.43	0.85	2.43	0.18
	Vittengl 2010	Personality trait	Combined	0.97	0.42	2.25	0.95
Personality				*1.26*	*1.02*	*1.55*	*0.03*
	Conradi 2018	Attachment	Combined	1.75	0.64	4.80	0.27
	Pettit 2013	Interpersonal dependency	Interpersonal dependency	0.95	0.87	1.04	0.26
	Toronto University Packages	Combined	Combined	1.94	0.94	4.02	0.07
	Vittengl 2010	Interpersonal	Combined	1.50	0.58	3.89	0.40
Psychodynamic				*1.29*	*0.83*	*1.99*	*0.26*

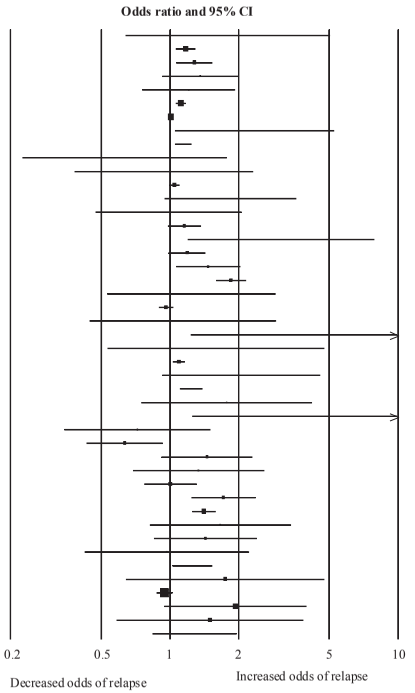

Figure 3. Forest plot for Odds Ratio meta-analysis.
Note: Combined = combination of variables, CI = confidence interval, CISS = Coping inventory for stressful situations, UCL = Utrechtse Coping List, DAS = Dysfunctional attitudes scale, ASQ = Attributional style questionnaire, SRET = Self-Referential Encoding Task.

DISCUSSION

Previous reviews have contributed greatly to clinical knowledge of depression (Buckman et al., 2018; Burcusa & Iacono, 2007; Hardeveld et al., 2010), yet a full overview of vulnerability factors derived from psychological theories that *precede* depressive relapse was needed in order to investigate the level of support for leading psychological theories. The current systematic review and meta-analysis therefore assessed the evidence for five leading psychological approaches of depressive relapse: Cognitive, diathesis-stress, behavioural, psychodynamic, and personality. Overall, there was some evidence that the cognitive, behaviour, and personality-based approaches partially account for the odds of prospectively assessed relapse in MDD. There were no articles for the diathesis-stress approach, and there was no significant support for a relationship between the psychodynamic approach and depressive relapse. Vulnerability factors derived from the cognitive and personality approaches, specifically higher levels of negative attributional style and neuroticism were found to be related to increased odds of relapse. The cognitive variable 'dysfunctional attitudes' was the only identified vulnerability factor associated to an accelerated time to prospectively assessed depressive relapse. Nonetheless, this effect was very small (*HR* = 1.01). Overall, the limited number of eligible articles prevented us from drawing strong inferences on the relationship between the approaches and depressive relapse, and to further investigate potential moderators of significant results, despite the large number of identified records within the field of MDD.

The overall finding regarding the vulnerability factors is consistent with previous reviews, showing that people scoring highly on questionnaires measuring neuroticism and dysfunctional beliefs were at increased risk of depressive relapse (e.g. Buckman et al., 2018; Klein et al., 2011). These results provide support for the notion that both negative personality traits and cognitive styles are related to the risk of depressive relapse, *or* that they both represent an underlying style that puts a person at increased risk (e.g. Brouwer et al., 2019; Forand & DeRubeis, 2014). The theory-derived vulnerability factors from different approaches may at the same time overlap largely. As previously stated, the cognitive and behavioural approaches can be perceived as a diatheses-stress approach. Personality traits, attributional style, and dysfunctional attitudes all represent a style or another factor that a person exhibits, which may represent the vulnerability factor for depressive relapse, either alone or in interaction with or activated by stress (e.g. Conway et al., 2015; Ingram et al., 1998; Monroe & Simons, 1991; Sutton et al., 2011). However, there were no studies identified that investigated the vulnerability factors in combination with stress in prospective, longitudinal trials with patient populations.

The discrepancy between the results of the hazard ratio (time to relapse) and odds ratio (odds of relapse) should be noted. This discrepancy may be due to the low number of studies that prospectively investigated (time to) depressive relapse. One would expect that if a person is at higher risk of relapse, that person may also deteriorate more quickly in the face of adversity and relapse sooner than a person who does not possess these vulnerabilities. Clinically, the findings could imply that an individual who is highly neurotic, or who adopts a negative attributional style, is likely to relapse, but within an unknown period of time. On the other hand, an individual who holds entrenched dysfunctional attitudes might be at a small increased risk to relapse sooner, relative to individuals who endorse more functional attitudes. Collectively, the discrepant finding indicates that current psychological approaches do not adequately account for the timing of depressive relapse. Given that none of the studies examined the diathesis component of the psychological approaches in a prospective longitudinal study, no firm conclusion can be drawn on the evidence for these psychological approaches.

The need for more research is likewise underscored by the relatively low number of eligible studies that were identified. At the same time, the included 43 studies from 66 articles reported more than 300 different measurements, likely biasing the reported effects due to multiple testing. To improve research in this domain, researchers are advised to 1) select an adequate patient population and prospectively assess the diagnosis; 2) use a prospective, longitudinal design (when resources permit); and 3) assess potential predictors or vulnerability factors of depressive relapse before the event itself, in order to provide a better framework of potential predictors of depressive relapse. The diathesis-stress approach in particular needs to be studied in relation to depressive relapse, given that most psychological theories are in fact diathesis-stress approaches. Conducting studies with prospective, longitudinal designs, established MDD status, and multiple vulnerability factors from one or more psychological approaches are resource intensive, as they require a significant amount of time and financial investment. A first, less expensive, step to investigate leading psychological approaches would be to collect data of similar measures across studies. Sharing data and creating (or strengthening) research networks across the globe is needed to circumvent the challenges associated with this type of research. Large, collaborative efforts seem necessary to establish the robustness of current psychological theories that account for depressive relapse. When predictors of relapse are identified through clinical evidence, preventive interventions may be improved by this knowledge.

Despite the strengths of the meta-analysis, which are the inclusion of prospective, longitudinal studies that assessed the theory-driven vulnerability factors before depressive relapse, and where MDD was established through clinical interviews, the results must be interpreted in light of a number of limitations. Firstly, the operationalisation of the psychological approaches differed highly between different studies, thereby diminishing

the amount of vulnerability factors that could be investigated, and simultaneously increasing the heterogeneity within each approach. The search terms used to identify the vulnerability factors might not have covered all concepts of the approaches. Several experts were involved to discuss the search terms; however, there was a lack of consensus. This lack of consensus is not restricted to the experts: The large amount of vulnerability factors across studies implied that there are too many operationalisations of the approaches. Specifically, some of the theory-driven predictors could be assigned to multiple approaches, dependent on the expert and focus of the included articles. Secondly, the reported effect sizes were small with wide confidence intervals and were therefore less reliable. Third, the potential for publication bias indicates caution is warranted when drawing conclusions as non-significant results were most likely unpublished. Additionally, the included studies reported outcomes that varied on a number of dimensions. For example, data of the original studies were collected at different time points, studies included varying lengths of follow-up, and samples were comprised of individuals with a varying number of prior depressive episodes and residual depressive symptoms. Due to the limited inclusions, subgroup analyses and meta-regression analyses to account for the differences were not possible. Lastly, by focusing on prospective studies that assessed vulnerability factors before depressive relapse, a causal relationship between the theories and relapse is suggested. However, prospective studies are the minimal requirement to investigate causal relationships. To explore this further, experimental studies with active manipulation of the theory-derived vulnerability factor are needed to test if there is a subsequent change in outcome (i.e. depressive relapse yes/no).

Overall, despite the limitations, the current meta-analysis found some evidence that the vulnerability factors derived from the cognitive, behavioural, and personality-based approaches are related to depressive relapse, but evidence is lacking for both the psychodynamic and diathesis-stress approaches. A limited number of prospective studies were identified that established robust evidence for the relationship between each psychological approach and depressive relapse. The overall strength of evidence was low, according to the grade assessment, and also according to the small and inconsistent pooled effect sizes for the approaches. For clinicians, the results show the value of neuroticism, attributional style, and dysfunctional attitudes as potentially therapeutically-modifiable indicators of increased odds or decreased time to the return of MDD. It is however striking that there was no convincing evidence for the approaches that are believed to support or guide the widely applied treatments.

Conclusion

The systematic search identified a limited number of studies that prospectively assessed the vulnerability factors of depressive relapse. Very small, and potentially

clinically less relevant, effects were established in this meta-analysis for the cognitive, behavioural, and personality-based approaches. It therefore remains unclear if current treatments in MDD target the potential causal vulnerability factors of relapse as proposed by the approaches. The lack of robust evidence for the relationship between each psychological approach and depressive relapse highlights the gap between putative vulnerability factors and treatment targets to prevent depressive relapse. There is a high need for more prospective, high-quality studies that investigate multiple psychological theory-driven vulnerability factors as potential predictors of depressive relapse to improve current leading psychological theories.

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Chapter 3

Dysfunctional attitudes or Extreme Response Style as Predictors of Depressive Relapse and recurrence after Mobile Cognitive Therapy for Recurrent Depression.

Based on: **Brouwer M.E.**, Williams A.D., Forand N.R., DeRubeis R.J. & Bockting C.L.H. (2019). Dysfunctional attitudes or extreme response style as predictors of depressive relapse and recurrence after mobile cognitive therapy for recurrent depression. *Journal of Affective Disorders, 243*, 48-54. doi: 10.1016/j.jad.2018.09.002

ABSTRACT

Background

According to previous research, dysfunctional attitudes and/or scoring extreme on the end-point anchors of questionnaires of dysfunctional thinking predict depressive relapse/recurrence. Evidence that these two methods represent a risk for depressive relapse/recurrence is however mixed, due to differential or poorly defined concepts. The current study aimed to test the two methods.

Methods

Remitted recurrently depressed patients with low residual depressive symptoms (*N* = 264) were recruited as part of a randomized controlled trial of the effectiveness of mobile Cognitive Therapy for recurrent depression versus treatment as usual. In the current secondary analysis, Cox regression models were conducted to test dysfunctional attitudes and extreme responding variables (assessed on the Dysfunctional Attitudes Scale [DAS]) as predictors of depressive relapse/recurrence within two years after randomization.

Results

Data from 255 participants were analysed. Results showed that DAS total scores at baseline significantly predicted depressive relapse/recurrence (*Hazard Ratio [HR]* = 1.01, $p = 0.04$). An index that reflects endorsement of habitual relative to functional responses was a significant predictor of depressive relapse/recurrence (*HR* = 2.11, $p = 0.03$).

Limitations

The current study employed a single measure to identify extreme responses and dysfunctional attitudes**.** Secondly, various statistical analyses were performed without correcting for multiple testing, which in turn increased the likelihood to finding significant results**.**

Conclusions

Current study confirmed both methods: People who scored higher on the DAS or had relatively more habitual than functional responses on the extreme positive ends of the DAS had a decreased time to depressive relapse/recurrence.

INTRODUCTION

Major depressive disorder (MDD) is predicted to be one of the lead causes of burden by 2030 (Mathers & Loncar, 2006). The high burden attributable to depression is not only due to acute episodes of the disorder, but also due to its chronic nature. Individuals with a history of MDD have a high risk of relapse or recurrence and this risk increases with each subsequent episode (Bockting, Hollon, Jarrett, Kuyken, & Dobson, 2015). Therefore, identifying variables that place individuals at risk for both acute and recurrent episodes is essential.

Based on the seminal cognitive model (Beck, Rush, Shaw, & Emery, 1979), it has been theorized that dysfunctional beliefs (e.g. as measured by the Dysfunctional Attitudes Scale [DAS]; Weissman, 1979) are important in the onset, relapse, and recurrence of MDD (Beck & Bredemeier, 2016; Beck et al., 1979), and are predictive of relapse/recurrence of MDD after cognitive behavioural therapy (CBT) treatment (Adler, Strunk, & Fazio, 2015; Beck & Bredemeier, 2016; Garratt, Ingram, Rand, & Sawalani, 2007; Lorenzo-Luaces, German, & DeRubeis, 2015; Teasdale et al., 2001). More recently, research has shifted from the overall level of dysfunctional beliefs (i.e. the total questionnaire score) as a predictor of MDD relapse or recurrence, to the "style" of responding, specifically a tendency to make responses at the ends of Likert-type scales, known as 'extreme responding' (Beevers, Keitner, Ryan, & Miller, 2003; Teasdale et al., 2001). Extreme responding is defined as the endorsement of the end of scale responses (e.g., 1's or 7's on a 1-7 Likert scale) (e.g. Beevers et al., 2003; Forand & DeRubeis, 2014; Teasdale et al., 2001).

In an initial study reporting this effect, Teasdale and colleagues (2001) found that the more extreme responses a patient gave, the higher the chance of depressive relapse within 8 weeks after the start of treatment. According to Teasdale et al. (2001), extreme responding reflected an "(..) *underlying activity of mood-dependent, developmentally early, depressogenic schematic processing*" (Teasdale et al., 2001, p. 354). The extreme responses would therefore be similar to information processing biases (Teasdale et al., 2001), consistent with the cognitive model (Beck & Bredemeier, 2016; Beck et al., 1979). Previous studies in other research areas for example indicated that the extreme responding reflects underlying (personality) traits, such as intolerance of uncertainty, rather than a response to the content of the items of a questionnaire, which may represent maladaptive behaviours and a higher reactivity to life events (Naemi, Beal, & Payne, 2009; Stange, Alloy, & Fresco, 2017; Wetzel, Carstensen, & Böhnke, 2013). This in turn may increase the risk of mental disorders such as MDD (e.g. Stange et al., 2017).

Since the initial results of Teasdale and colleagues (2001), several researchers (partly) confirmed the idea of extreme responding as a predictor of depressive relapse/recurrence (e.g. Beevers et al., 2003), whilst others failed to replicate the seminal findings (Ching & Dobson, 2010; Jacobs et al., 2010; Petersen et al., 2007; van Rijsbergen et al., 2013).

Furthermore, a distinction can be made between *negative* and *positive* extreme responses, where a negative extreme response represents full agreement with dysfunctional items and full disagreement with functional questionnaire items. Positive extreme responses represent full agreement with functional items and full disagreement with dysfunctional questionnaire items (e.g. Forand & DeRubeis, 2014; Forand, Strunk, & DeRubeis, 2016). Examples of positive extreme responses are: Full agreement with the statement "*It is possible to gain another person's respect without being especially talented at anything*"; or complete disagreement with the statement "*If I fail at my work, then I am a failure as a person*". Previous outcome studies have demonstrated that the way (i.e., positive or negative extremity) in which individuals respond to items of the DAS may provide clinical insight into who is likely to respond to therapy or be at elevated risk for later episode recurrence (e.g. Beevers et al., 2003; de Graaf et al., 2010; Forand & DeRubeis, 2014).

Evidence for the assumption that extreme or elevated, positive or negative, dysfunctional attitudes represent a risk factor for later depressive relapse/recurrence is however mixed. To make sense of the discrepant findings, Forand and DeRubeis (2014) proposed an alternative approach to conceptualize extreme responses: *Style* versus *content* positive extreme responses. These authors highlighted an important problem with the extreme responding literature that used the DAS: It is impossible to distinguish whether negative extreme responses that predict relapse/recurrence are due to the respondent possessing an "extreme response *style*" or to that person endorsing extreme levels of dysfunctional attitudes (based on the *content*). Both will predict greater rates of relapse/recurrence. These authors argued that positive extreme responding was more informative, because positive extreme responding due to an extreme response *style* is hypothesized to predict a greater rate of relapse, whereas positive extreme responding due to the presence of functional beliefs would (theoretically) predict a lower rate.

To distinguish between the two types of *positive* extreme responses, Forand and DeRubeis (2014) focused on DAS items where positive extreme responses appeared to be maladaptive. They hypothesized that individuals who responded thoughtfully to the DAS and held functional attitudes would be unlikely to provide positive extreme responses to these items, dubbed "*style*" items. On the other hand, individuals with an "extreme response style" would tend to make positive extreme responses indiscriminately to items, regardless of whether such responses are rational or adaptive. Thus, an extreme response style is determined by the relative frequency of positive extreme responding to "style" items versus "content" items, or items where such responses appear rational. A greater relative rate of positive extreme responding to "style" versus "content" items would suggest the individual has an extreme response style (Forand & DeRubeis, 2014; Forand et al., 2016) .

DAS- items were rated as *content* responses if it was considered functional to endorse the item at the extreme positive end. An example of a content item was:

'If I ask a question, it makes me look inferior' (in this case, to disagree fully with the statement). An example of a style item is *'I can find happiness without being loved by another person'.* In this case, the independent raters believed that the best answer was somewhere in the middle of the scale (Forand & DeRubeis, 2014; Forand et al., 2016).

Forand and colleagues (2014, 2016) found that MDD patients who had relatively more dysfunctional (*style*) than functional (*content*) positive extreme responses had an increased risk of depressive relapse or recurrence in responders to antidepressants (AD) and CBT in an RCT (DeRubeis et al., 2005; Hollon et al., 2005). According to Forand and colleagues (2014; 2016), a differentiation should therefore be made between extreme responses on *content* items and *style* items.

However, these findings still need to be replicated. Since all but two studies on extreme responding are from native English-speaking countries (Beevers et al., 2003; Ching & Dobson, 2010; de Graaf et al., 2010; Forand & DeRubeis, 2014; Forand et al., 2016; Jacobs et al., 2010; Petersen et al., 2007; Teasdale et al., 2001; van Rijsbergen et al., 2013), possible language and cultural differences may influence extreme responding. This may be reflected in Dutch people responding less on the extreme ends of questionnaires than American people (e.g. Douma, 1991; Harzing, 2006). The procedure used by Forand and colleagues (2014, 2016) has -to our knowledge- not yet been applied to another culture and language.

Therefore, to follow-up the previous results, the current study aimed to identify whether 1) dysfunctional attitudes or 2) having relatively more *style* than *content* positive extreme responses are predictors of depressive relapse/recurrence. We investigated this by using secondary data from an RCT in a sample of remitted Dutch recurrently depressed patients randomized to receive either mobile preventive cognitive therapy (mCT) or TAU (Bockting et al., 2011; Klein et al., 2018; Kok et al., 2015). Based on previous research in the field of depression (e.g. Forand & DeRubeis, 2014; Stange et al., 2017; Teasdale et al., 2001), and in other fields of research (e.g. Naemi et al., 2009), we hypothesized that relatively more positive extreme responses on *style* items as compared to *content* items on the DAS would predict depressive relapse/recurrence.

METHODS

Participants

Study participants were derived from an RCT of the effectiveness of mobile PCT for recurrent depression (mCT). Participant characteristics, study design, measures, and primary and secondary outcomes have been reported in previous articles (Kok et al., 2015; Klein et al., 2018). The trial protocol was approved by the Medical Ethical

Committee of the University Medical Centre Groningen. All participants provided written informed consent prior to participation.

At start of the trial, 264 participants between 18 and 65 years old (mean age = 46; 74.6% female) were in remission or recovery from recurrent MDD, as defined by the structured clinical interview for DSM axis-I disorders (SCID-I, DSM-IV-TR; First, Spitzer, Gibbon, & Williams, 2002). To be included in the trial, participants needed to have experienced at least two depressive episodes, as defined by the SCID-I, and the duration of the remission or recovery stage was not allowed to be shorter than two months, or longer than two years. Furthermore, participants had a score of 10 or lower on the Hamilton Rating Scale for Depression (HRSD-17 items; Hamilton, 1960) prior to randomization. Exclusion criteria were predominant anxiety disorder; current or past (hypo) mania, current alcohol or drug abuse, and past or present psychosis. Other exclusion criteria were no mastery of Dutch language, organic brain damage, and recent electroconvulsive therapy. Participant characteristics are reported in Table 1.

Table 1
Baseline randomized participant characteristics

	mCT (*n* = 132)	**TAU** (*n* = 132)
Mean age in years (*SD*)	45.6 (10.9)	47.1 (10.7)
Gender female (%)	105 (79.5)	92 (69.7)
Born in the Netherlands (%)	116 (88.5)	121 (92.4)
Marital status		
Single (%)	39 (29.8)	32 (24.2)
Married or cohabiting (%)	81 (62.3)	87 (65.9)
Divorced or Widowed (%)	10 (7.7)	13 (9.9)
Education		
Primary school or Secondary education (%)	7 (5.3)	13 (9.9)
Vocational or Pre-university education (%)	41 (31.1)	43 (32.6)
Higher education (%)	57 (43.2)	52 (39.4)
University (%)	26 (20.5)	25 (18.2)
Treatment as Usual (TAU), %		
No treatment	46 (34.8)	39 (30)
General practitioner	34 (25.8)	43 (33.1)
Specialized mental health (after)care	52 (39.4)	48 (36.9)
Antidepressants usage (%)	50 (41.4)	62 (53)
Mean HRSD-17 score (*SD*)	3.7 (3.1)	3.4 (2.9)
Severity last depressive episode		
Minor (%)	37 (28)	25 (18.9)
Moderate (%)	73 (55.3)	71 (53.8)
Severe (%)	22 (16.7)	36 (27.3)
Average previous MDD episodes (*SD*)	4.3 (2.5)	4.5 (2.7)

Note: Numbers are rounded. mCT = mobile preventive cognitive therapy; TAU = treatment as usual, HRSD-17 = Hamilton Rating Scale for Depression – 17 items; MDD = major depressive disorder.

Treatment

Eligible participants were randomly allocated to either mCT or TAU. The mCT was based on preventive cognitive therapy (Bockting et al., 2011), and was primarily delivered via the Internet. In addition, participants were offered minimal therapist support. Mobile CT consisted of 8 online modules, of which the participants were advised to complete one module per week. Full description of the program and the individual modules can be found in Bockting et al. (2011) and Kok et al. (2015).

TAU consisted of usual care for remitted patients in the Netherlands. This included medication treatment such as antidepressants, psychotherapy, or no treatment at all. Assessments were equal in both the mCT and TAU group.

Measures

Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). The HRSD is a 17-item semi-structured interview to measure severity of depressive symptoms. In the original trial, the HRSD was used as a telephonic interview, administered by trained researchers and psychologists. Total HRSD scores can range from 0 (no symptoms) to 52 (all depressive symptoms; Hamilton, 1960). Internal consistency of HRSD in the current study was good (α = 0.82). Threshold for depressive symptoms on the HRSD was set on a score of 10 or below (Bockting et al., 2011).

Dysfunctional Attitudes Scale (DAS; Douma, 1991; Weissman, 1979). The 40-item DAS was used to identify dysfunctional attitudes on a 7-point Likert scale ranging from 'completely disagree' to 'completely agree'. A higher DAS score indicates more dysfunctional attitudes. The DAS has good psychometric properties (α = 0.86; Dozois, Covin, & Brinker, 2003). Cronbach's alpha in the current study was 0.93, indicating good internal consistency.

Extreme responding. Total extreme responding (ER-Total) on the DAS was calculated as the total number of extreme (i.e., '1' and '7') responses. Positive extreme responding (PER) was calculated by summing all '1' scores on normal keyed items, and '7' scores on reversed keyed items. The same process was used to calculate negative extreme responding (NER), but then by summing all '1' scores on reversed keyed items, and '7' scores on normal keyed items.

Defining content vs. style items. The exact procedure of Forand and DeRubeis (2014) was followed to acquire and calculate the extreme responding variables. This included a short pilot study among clinicians to identify healthy responses on the DAS. Using the DAS, content and style items were identified and used to calculate positive extreme *style* responding (style-PER) and positive extreme *content* responding (content-PER).

The clinical perspective on Dutch 'healthy responses' was acquired in a separate pilot study to account for the different questions in the Dutch DAS (Douma, 1991)

and possible cultural differences in responding on the DAS. The aim was to identify 'optimal' healthy responses on all questionnaire items, to discriminate content from style responses. In this pilot study, 14 Dutch independent clinicians were asked to rate 'optimal' responses on the DAS. The clinicians had an average work experience of 6.4 (*SD*= 7.2) years (range 1 - 20 years) in clinical field and/or with CBT. Instructions of Forand and DeRubeis (2014) were first translated into Dutch, as well as back-translated into English by an independent researcher to assure proper translation of the original instructions[1].

In the pilot survey, clinicians rated the optimal responses for each questionnaire by using the original instruments' item scales. The intraclass correlation for the DAS was 0.94; hence the raters were in agreement on optimal responses for the questionnaire.

The averages for each item on the Dutch DAS were not consistent with US sample of Forand and DeRubeis (2014)[3]. In Forand and DeRubeis' study, *content* items were the items on which the clinicians' mean score was below 1.5 or above 6.5. Other items were defined as *style* items. Using this criterion in the present effort, only two items would be identified as content items, whereas Forand and DeRubeis found 17 content items. Since it was important to make a clear distinction between style and content items, the threshold for items being content or style, was changed[4] into a threshold below 2 or above 6 to identify content items. This is in line with the idea that Dutch people in general respond less on the extreme ends of questionnaires (Harzing, 2006).

Style and content positive extreme responses were calculated by counting the number of extreme responses on DAS items that were identified as style items (for *style*-PER) and content items (for *content*-PER) in the pilot study. Total positive extremity (PER-T) was calculated with the average scores of the standardized content items and style items (average of standardized style responses plus standardized content responses). Total positive extremity hence represents the shared variance between style and content items. The unshared term, style versus content positive extreme responding (S/C-PER), was calculated by taking the half difference score (average of the standardized style responses minus standardized content responses). Higher levels of S/C-PER indicate having more style extreme responses than content ones.

Relapse/recurrence of MDD. For the current analyses, the outcome was relapse/recurrence of MDD within 24 months after randomization. Relapse/recurrence was assessed via clinician-administered diagnostic telephonic interviews of the SCID–I (First et al., 2001). Relapse/recurrence was assessed at three, 12, and 24 months

3 An overview document is available upon request.

4 Style items were Dutch item numbers: 2, 3, 4, 14, 18, 19, 20, 21, 22, 23, 25, 27, 28, 30, 31, 32, 34, 35, 36, 38, 39, 40. Content items were Dutch item numbers: 1, 5, 6, 7, 8, 9, 10, 12, 13, 15, 16, 17, 24, 26, 29, 33, 37. USA Style items were numbers 2, 3, 7, 11, 12, 17, 18, 19, 23, 24, 27, 28, 29, 30, 31, 32, 33, 34, 35, 37, 38, 39, and 40. USA Content items were numbers 1, 4, 5, 6, 8, 9, 10, 13, 14, 15, 16, 20, 21, 22, 25, 26, and 36.

post-randomization, and could be detected at any time. Time to relapse/recurrence was measured in days (see Table 2).

Data analysis

The data analysis plan as described by Forand and DeRubeis (2014) was closely followed since the aim was to investigate the extreme response variables that were identified as predictors previously (Forand & DeRubeis, 2014; Forand et al., 2016). Outcomes and difference scores at baseline, and at the three-month and 24-month follow-up were calculated for DAS and extreme responses variables. To compare the two proposed methods, the model evaluated the predictive value of DAS scores and extreme response style scores collected at baseline. Withdrawals, failure to adhere to treatment, or loss-to-follow-up were treated as censored cases at the time of the event. Separate Cox proportional hazard models were conducted for the baseline model, DAS, and extreme responding variables. The baseline model for the Cox regressions included treatment allocation (mCT vs. TAU), type of TAU (no care, active care, or mental health care), number of previous depressive episodes, and HRSD-17 at baseline. All extreme responding variables were then analysed in separate Cox regression models with the baseline model. Hence each extreme responding variable was controlled for treatment allocation, number of previous depressive episodes, and depressive symptoms at baseline. The hypothesis was that greater relative style versus content responses (higher S/C- PER scores), predicted an increased rate of relapse/recurrence. See supplement I for model descriptions. All analyses were performed with SPSS 24.

RESULTS

At the start of the trial, 255 participants completed the DAS. At 24-months follow-up, relapse rates and DAS measurements for 235 participants were available for the current analyses (drop-out rate 11%). Table 2 includes the descriptive statistics of the DAS at baseline, 3 and 24-months follow-up. During a three-month period during which a part of the participants received mCT or TAU, 89 out of 132 participants (67.9%) completed at least five modules out of the total 8 modules of mCT. Extreme responding variables were, as expected, right-skewed. However, log-transformation did not improve the distribution. Therefore, and in line with the procedure of Forand and DeRubeis (2014), the extreme responding variables were entered untransformed into the analyses.

Based on *t*-tests, there was no significant difference between the TAU and mCT group on the DAS total score at baseline (T0; *Mdifference* = – 3.39, $t = -0.87$, $p = 0.39$), or three-month follow-up (T2; *Mdifference* = –4.81, $t = -0.93$, $p = 0.35$). There was a non-significant higher DAS total score in the TAU group as compared to the mCT

group at 24-month follow-up (T9; *Mdifference* = −12.22, t = −1.79, p = 0.08). Mann-Whitney-U showed no significant differences on extreme responding variables between groups at T0, T2, and T9. Although there was no significant difference between mCT and TAU, there was an overall difference across groups between different measurement times on the positive extreme responding variables and total extreme responding, but not on negative extreme responding variables. Table 2 displays the outcomes on the Wilcoxon Signed Rank Tests. The Wilcoxon Signed Rank Tests indicates that there was a significant decrease from T0 to T2, and T2 to T9 in total extreme responding, positive extreme responding, and content-PER. From T2 to T9, style-PER likewise significantly decreased. There were no significant differences between the two groups at T0, T2, and T9 on the HRSD-17. Paired samples t-test showed a significant change on HRSD-17 scores from T0 to T2 (M = −1.20, SD = 5.69, t = 3.19, p = .002), and from T2 to T9 (M = −0.90, SD = 6.5, t = −1.97, p = 0.05).

Prediction of depressive relapse

Outcomes of the analyses are reported in Table 3. The baseline model was tested in each Cox regression analysis, but it appears only once in the table. Mobile CT, baseline depressive symptoms, and the number of previous episodes were collectively predictive of depressive relapse/recurrence during the trial (χ^2 = 32.74, -2 log likelihood = 946.07, p < 0.001). Within the overall model, mobile CT extended the time to relapse/recurrence, whilst the number of depressive symptoms and number of previous episodes shortened the time to depressive relapse/recurrence.

Having a higher score on the DAS prior to treatment (χ^2 = 33.91, p < 0.001, *HR* = 1.007, p = 0.04) *or* having relatively more *style* than *content* extreme responses (χ^2 = 34.74, p < 0.001, *Hazard Ratio [HR]* = 2.11, p = 0.03), significantly decreased the length of time to depressive relapse/recurrence. Contrary to our hypothesis, the frequency of style extreme responding did not enhance the ability of the DAS to predict relapse/recurrence. However, the amount of content positive extreme responses did reduce the ability of the DAS to predict rate of relapse/recurrence (χ^2 = 34.26, p < 0.001), making this variable nonsignificant (*Wald* = 1.12, *HR* = 1.005, p = 0.29). These results suggest that *content* but not *style* extreme positive responses were related to the endorsement of functional attitudes on the DAS.

Post-hoc testing a pragmatic DAS scoring algorithm

The method described in this paper and developed by Forand and DeRubeis (2014) and Forand, Strunk, and DeRubeis (2016) predicts relapse/recurrence in study samples. However, the method is impractical for determining relapse risk for individuals in practice because it requires a sample of DAS scores to calculate. Therefore, we present a post-hoc exploratory analysis of a brief pragmatic method for rescoring a DAS to account

Table 2
Descriptive statistics and change scores for extreme responding

	mCT (*n* = 132)			**TAU** (*n* = 132)			**Change T0 to T2** (*n* = 255)				**Change T2 to T9** (*n* = 162)		
	T0	T2	T9	T0	T2	T9	Overall at T0	Overall at T2	*Z*	*p***	Overall at T9	*Z*	*p*
Mean DAS (*SD*)	133.1 (30.5)	135.8 (31.4)	129.1 (37.0)	129.7 (31.9)	131.0 (34.5)	116.9 (34.8)	131.4 (31.2)	133.3 (33)			122.5 (36.2)		
Median Total ER	4	3	3	4	2	4	4	2.5	−3.91	**<0.001**	4	−2.44	**0.01**
Median ER-N	0	0	0	0	0	0	0	0	−1.77	0.08	0	−1.40	0.16
Median PER	2	1	2	3	1	2	3	1	−3.77	**<0.001**	2	−2.93	**0.003**
Median Content-PER*	2	1	1	2	1	1	2	1	−4.36	**<0.001**	1	−2.44	**0.01**
Median Style-PER*	0	0	1	1	0	0	1	0	−1.80	0.07	1	−2.63	**0.01**
Median PER-T*	−0.43	−0.43	−0.42	−0.34	−0.43	−0.42	3	1	−0.72	0.47	2	−1.30	0.19
S/C PER (Median)*	0.05	0.10	0.10	0.10	0.10	0.02	0.08	0.10	−0.57	0.57	0.11	−0.93	0.35

Note: Numbers are rounded. mCT = mobile cognitive therapy; TAU = treatment as usual; T0 = baseline measurement; T2 = 3 months' follow-up measurement; T9 = 24 months' follow-up measurements; DAS = Dysfunctional attitudes scale; Total ER = total score of extreme responding; ER-N = negative extreme responding; PER = positive extreme responding; content-PER = positive extreme content responding; style-PER = positive extreme style responding; PER-T = total positive extremity; S/C PER = style versus content extremity. * These variables are standardized values. ** Wilcoxon Signed Ranks Test.

for any style and content extreme responses. The exact method is described in the supplement I.

The pragmatic DAS score (DAS-S/C) was analysed in a separate cox regression in the same statistical way as the previous models. DAS-S/C was a significant predictor of relapse rate, with higher scores indicating a greater rate of relapse. Of note, in comparison with the standard DAS score tested in Model 2, DAS-S/C resulted in a higher *Wald* (6.78 vs. 4.15) and corresponding *p*-value ($p = 0.009$ vs. $p = 0.04$), while retaining a similar hazard ratio (*HR* = 1.007, *95% CI* 1.002, 1.011 vs. *HR* = 1.007, *95% CI* 1.000, 1.014). The model also yielded a lower -2 log likelihood compared to Model 2 (907.771 vs. 910.679), indicating a better fit to the data.[5]

Table 3
Results of the Cox regression analyses

Model	Parameter	*Wald*	*p*	*Hazard Ratio*	95% *CI*	
					Lower	*Upper*
1	mCT vs. TAU[a]	7.87	**0.005**	1.81	1.19	2.73
	TAU no care	0.43	0.80	N/A	N/A	N/A
	TAU active care	0.04	0.83	1.05	0.66	1.67
	TAU specialized [b]	0.21	0.64	0.88	0.52	1.49
	HRSD	15.90	**<0.001**	1.14	1.07	1.21
	Previous episodes	7.05	**0.01**	1.09	1.02	1.17
2	DAS	4.15	**0.04**	1.007	1.00	1.01
3	DAS	4.27	**0.03**	1.008	1.00	1.02
	Style-PER	0.35	0.55	1.03	0.93	1.15
4	DAS	1.12	0.29	1.006	0.999	1.01
	Content-PER	0.23	0.63	0.79	0.48	3.33
5	PER-T	2.54	0.11	0.82	0.64	1.05
	S/C PER	4.75	**0.03**	2.11	1.08	4.12

Note: Numbers are rounded. mCT = mobile cognitive therapy; TAU = treatment as usual; T0 = baseline measurement; DAS = Dysfunctional attitudes scale; Total ER = total score of extreme responding; PER = positive extreme responding; content-PER = positive extreme content responding; style-PER = positive extreme style responding; PER-T = total positive extremity; S/C extreme = style versus content extremity; CI = 95% confidence interval for hazard ratio. All models include the terms from the baseline model. *a:* The variable ´treatment´ was dummy coded with TAU = 1, mCT = 0, mCT being the reference group. *b*: Treatment as usual specialized mental health (after)care

5 These models have identical degrees of freedom, so testing whether the model fit is improved by using DAS-S/C is not possible using a standard likelihood ratio test. However, the improvements in *Wald* scores and -2 log likelihood indicate a better fitting model with the modified DAS score.

DISCUSSION

Due to inconsistent findings and varying methods to identify whether and how dysfunctional attitudes predict MDD, the current study aimed to investigate two different methods from previous research on this topic. Results of the current study confirmed both approaches. Both a standard index of dysfunctional attitudes *and* an index reflecting relatively more *style* than *content* positive extreme responses during remission predicted depressive relapse within 24 months in a group of remitted recurrently depressed patients. In line with the findings of Forand and colleagues (2014; 2016), this may indicate that people who had a more habitual than thoughtful response style on the extreme positive ends of the Dysfunctional Attitudes Scale, had an increased risk of depressive relapse. In contrast, extreme positive responding based on *content* items of the DAS may afford a protective or prophylactic benefit against depressive relapse.

Several aspects of these findings are notable. First, the original scoring of the DAS, on which a higher score has, in previous research, indicated higher risk of depressive relapse (e.g. Cristea et al., 2015), was found to predict time to depressive relapse in the present sample. Second, our findings suggest that items on the DAS can be reliably distinguished as content or style items across the English and Dutch versions of the DAS. Third, the distinction between style and content items on the DAS appears to be a meaningful one, in that it, too, predicts relapse, even though the items it is based on all contribute to lower, ostensibly healthier scores.

As previous research points out, dysfunctional attitudes are not only traits, but are also state-dependent and influenced by depressive symptoms (Adler et al., 2015; Beck & Bredemeier, 2016; Lorenzo-Luaces et al., 2015; Teasdale et al., 2001; van Rijsbergen et al., 2013). The current study included a relatively homogeneous group of remitted recurrently depressed patients with low levels of residual depressive symptoms (roughly half taking antidepressant medication), but with overall higher levels of dysfunctional attitudes. Mobile CT (relative to TAU), levels of residual depressive symptoms, and number of previous depressive disorders all significantly predicted depressive relapse or recurrence within two years after study entry. In this sample, irrespective of whether treatment was with mCT or TAU, we observed a lower proportion of extreme responses, relative to rates obtained in past research (Forand & DeRubeis, 2014; Forand et al., 2016). The number of extreme responses of all types decreased from baseline to post-treatment, and then increased up to 24-months post-randomization. This may be related to the fact that the current study focused on remitted recurrently depressed patients, who by definition were not acutely depressed. The inconsistent results reported in previous studies may be the result of the amount of (residual) depressive symptomatology a person experienced at that moment of measuring the DAS and the related extreme responses, or due to how extreme responding was calculated.

Despite the timing in terms of level of symptomatology, yet consistent with previous literature (e.g. Cristea et al., 2015), more dysfunctional beliefs as measured on the DAS at baseline resulted in a higher risk of depressive relapse after recovery or remission. The predictive value of the pre-treatment DAS was, however, diminished when controlling for content extreme positive responses. Having more style positive extreme responses on the other hand did not influence the relationship between DAS and risk of MDD relapse or recurrence. This finding supports the validity of the method used to distinguish content and style responses. Content responses are presumed to indicate a healthy denial of dysfunctional attitudes. Therefore, covarying the number of "healthy" extreme positive responses was predicted to reduce the ability of the DAS to predict relapse, because the DAS scores in this model would provide less information about those with a lower risk. The implication of our findings is that total scores on the DAS contain discernible information that goes beyond respondents' levels of dysfunctional thinking.

We introduced and presented an exploratory test of a pragmatic method for rescoring an individual's DAS score to account for the influence of style and content responses. This index, which takes account of the endorsement of healthy attitudes as well as habitual positive responding, may be more useful as a means of determining a patient's resilience following cognitive therapy. Close attention could be paid when a remitted patient responds more often on the extreme positive ends of items identified as *style* items. Replying with total disagreement to statements such as '*I should be upset if I make a mistake'* or total agreement with '*It is possible for a person to be scolded and not get upset*' represent an additional risk factor for relapse/recurrence of depression. On the other hand, the exact mechanism of why extreme responding and depressive relapse/recurrence are related remains unclear (Forand et al., 2016). A hypothesized explanation -originated from other fields of research- is that the extreme responding style rather than content-wise response indicates that the person also shows this kind of behaviour in daily life, and therefore imposes a risk for dysfunctional behaviours and depressive relapse/recurrence (e.g. Naemi et al., 2009; Stange et al., 2017).

Results from the current and previous studies (Forand & DeRubeis, 2014; Forand et al., 2016) are not consistent with the theory that depressed individuals react in extreme styles due to a dichotomous, automatic, thinking style that is active specifically during depressive episodes (Teasdale et al., 2001). Instead, the extreme responding seems to reflect an avoidant coping style, or intolerance of ambiguity (e.g. Naemi et al., 2009). Results of the current study support the argument of Forand and colleagues (2014; 2016) that depressed individuals might provide style positive extreme responses as a means of avoiding the content of the questions, which might be painful to contemplate. The ratio of style versus content positive extreme responses would hence represent the tendency to avoid the content of the dysfunctional attitudes.

Lastly, in the current study we tested if the strategy of calculating positive extreme variables was also applicable to a Dutch sample, given that cultural and language differences may affect the assessment or meaning of extreme responses. Despite different questions in the Dutch DAS and different coding system for content and style items, the results were a partial replication to the results found in the United States (Forand et al., 2016; Forand & DeRubeis, 2014). Although the current results are only partly in accordance with previous results from Dutch trials (de Graaf et al., 2010; van Rijsbergen et al., 2013), this may be due to different methods to define and identify extreme responses.

Limitations

In interpreting the results, some limitations should be noted. As in previous research, the current study employed a single measure to identify extreme responses and dysfunctional attitudes. The Dutch dysfunctional attitudes scale is different with regard to some items, yet still confirms the importance of extreme responding. Secondly, various statistical analyses were performed without correcting for multiple testing, which in turn increased the likelihood to finding significant results (Type-I error). However, the exact same procedure was followed as in previous studies, with equivalent results.

Conclusion

To conclude, results of the current study not only indicate that the level of dysfunctional attitudes during remission or recovery are predictive of relapse, but also indicate that relative positive extreme responses on style versus content are predictive of relapse. Future research should therefore focus on processes of change in relation to dysfunctional attitudes, positive extreme responses, and depressive symptoms. In clinical practice, positive extreme responding could be measured using the proposed pragmatic calculations to help identify those most at risk of relapse or recurrence, rather than the DAS total score.

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Part 2

Chapter 4

Offspring outcomes after prenatal interventions for common mental disorders: A meta-analysis.

Based on: **Brouwer M.E.**, Williams A.D., van Grinsven S.E., Cuijpers P., Lambregtse-van den Berg M.P., Burger H. & Bockting C.L.H. Offspring outcomes after prenatal interventions for common mental disorders: a meta-analysis. *BMC Medicine, 16 (1)*, 208. doi: 10.1186/s12916-018-1192-6

ABSTRACT

Background

It is presumed that pharmacological and non-pharmacological treatment of prenatal common mental disorders can mitigate associated adverse effects in offspring, yet strong evidence for the prophylactic benefits of treatment is lacking. We therefore examined the effect of prenatal treatments for common mental disorders on offspring outcomes.

Methods

For this meta-analysis, articles published up to August 31, 2017, were obtained from PubMed, PsycInfo, Embase, and Cochrane databases. Included studies needed to be randomized controlled trials (RCTs) on the effect of treatment of prenatal common mental disorders comparing an intervention to a control condition, including offspring outcome(s). Random effects models were used to calculate Hedges' *g* in the program Comprehensive Meta-Analysis© (version 3.0).

Results

Sixteen randomized controlled trials among 2,778 pregnant women compared offspring outcomes between prenatal interventions and control groups. There were zero pharmacological, 13 psychological, and three other interventions (homeopathy, relaxation interventions, and short psycho-education). Birth weight (Mean difference 42.88 grams, $g = 0.08$, 95% *CI* = −0.06, 0.22, $p = 0.27$, $n = 11$), Apgar scores ($g = 0.13$, 95% *CI* = −0.28, 0.54, $p = 0.53$, $n = 4$) and gestational age ($g = 0.03$, 95% *CI* = −0.06, 0.54, $p = 0.49$, $n = 10$) were not significantly affected. Other offspring outcomes could not be meta-analysed due to the inconsistent reporting of offspring outcomes and an insufficient number of studies.

Conclusions

Non-pharmacological interventions had no significant effect on birth outcomes, although this outcome should be considered with caution due to the risk of biases. No randomized controlled trial examined the effects of prenatal pharmacological treatments as compared to treatment as usual for common mental disorders on offspring outcomes. Present clinical guidelines may require more research evidence on offspring outcomes, including child development, in order to warrant the current recommendation to routinely screen and subsequently treat prenatal common mental disorders.

Trial registration

PROSPERO (CRD42016047190).

INTRODUCTION

Leading clinical guidelines advise to screen and treat common mental disorders and symptoms among all pregnant women (National Institute for Health and Clinical Excellence, 2014; O'Connor, Rossom, Henninger, Groom, & Burda, 2016). Common mental disorders and symptoms generally refer to mood and anxiety disorders, including depression, phobias (including extreme fear of childbirth 'tokophobia'), generalized anxiety disorder, post-traumatic stress disorder, and obsessive-compulsive disorders (National Institute for Health and Clinical Excellence, 2014). Prevalence rates of mental disorders during pregnancy are estimated as high as 12.4% for mood disorders and 15.2% for anxiety disorders (Bennett, Einarson, Taddio, Koren, & Einarson, 2004; Dennis, Falah-Hassani, & Shiri, 2017). Next to the burden of these common mental disorders for the pregnant women, these disorders may be harmful for the offspring (Alder, Fink, Bitzer, Hösli, & Holzgreve, 2007). Adverse effects on the offspring include almost 20% increased odds of low birth weight as compared to offspring from mothers without mental problems (Grote et al., 2010). Low birth weight in turn has repeatedly been linked to negative (long term) somatic outcomes such as all-cause mortality, stunted growth, respiratory problems, and obesity (Belbasis, Savvidou, Kanu, Evangelou, & Tzoulaki, 2016). In addition, low birth weight is associated with an increased risk for the development of mental problems (Loret de Mola, Araujo de Franca, Quevedo, & Horta, 2014). Other adverse effects of prenatal mental disorders on the (unborn) child include a 13% increased risk of premature birth (Grote et al., 2010), and lower Apgar scores (Alder et al., 2007). Similar to the effects of low birth weight, children from women who had a mental disorder during pregnancy have a two to three times increased risk for the development of psychopathology (O'Donnell, Glover, Barker, & O'Connor, 2014). This includes an increased risk of symptoms of depression in (late) adolescence (Stein et al., 2014), and an increased risk of anxiety in the ages six to nine years old, and internalizing and externalizing (psychiatric) problems at the ages two to six (Lahti et al., 2017; National Institute for Health and Clinical Excellence, 2014; Newman et al., 2016). Other risks for the offspring of pregnant women with common mental disorders include behavioural, motor, developmental, and cognitive problems such as attention deficit hyperactivity disorder, and an atypical (functional and structural) brain development (National Institute for Health and Clinical Excellence, 2014; O'Donnell et al., 2014; van den Bergh, Dahnke, & Mennes, 2018; van den Bergh et al., 2017). Theoretical accounts of the associations between prenatal mental health and offspring outcomes focus on a cascade of processes, such as activation of the stress-response (hypothalamic-pituitary-adrenal [HPA] axis), (epi)genetics e.g. methylation of "stress" genes, elevated levels of intrauterine cytokines or glucocorticoids, and poor self-care during pregnancy (e.g. smoking, disturbed appetite) or poor mother-child attachment in the postpartum

period due to the disabling nature of mental health problems (Barker, 1990; Gluckman, Hanson, Cooper, & Thornburg, 2008; Pearson et al., 2013; Stein et al., 2014; Talge, Neal, & Glover, 2007; van den Bergh et al., 2017).

Effective treatments for prenatal common mental disorders are therefore of paramount importance given the recurrent and life-long course of most mental disorders and their association with (chronic) somatic conditions (Bockting, Hollon, Jarrett, Kuyken, & Dobson, 2015). Although the exact mechanisms through which prenatal mental disorders exert an effect on offspring are currently unknown, the adverse outcomes themselves are clear. Current evidence-based treatments for mental disorders during pregnancy, i.e. medication and/or psychological interventions, are (implicitly) presumed to not only address mental needs of pregnant women, but also to confer prophylactic mental and physical benefits for offspring (Lewis, Galbally, Gannon, & Symeonides, 2014; Rahman et al., 2013). As implied in the NICE guidelines: *"The impact of any mental health problem may often require more urgent intervention than would usually be the case because of its potential effect on the foetus/baby (..)"* (National Institute for Health and Clinical Excellence, 2014). The most used treatment for these disorders during pregnancy is antidepressant medication (AD; 3.7% of all pregnant women in the UK up to 6.2% in the USA [Charlton et al., 2015; Ko, Farr, Dietz, & Robbins, 2012]), followed by psychological therapies including cognitive behavioural therapy (CBT; van Ravesteyn, Lambregtse - van den Berg, Hoogendijk, & Kamperman, 2017). Supporting evidence for the benefits of these treatments is however limited, and the impact is typically restricted to the pregnant woman (Cuijpers, Weitz, Karyotaki, Garber, & Andersson, 2014; National Institute for Health and Clinical Excellence, 2014; O'Connor et al., 2016; van Ravesteyn et al., 2017). Previous meta-analyses indicate that the evidence is restricted to psychological interventions for prenatal depression, for which CBT and interpersonal psychotherapy were shown to be most effective (van Ravesteyn et al., 2017).

Given that the recommended treatments for prenatal common mental disorders might paradoxically have an adverse effect on the offspring intrauterine, it is crucial to examine the effects of prenatal maternal treatments on offspring. To our knowledge, no meta-analyses of randomized controlled trials (RCTs) have examined the effect of various treatments on common mental disorders during pregnancy on offspring (Cuijpers et al., 2014; National Institute for Health and Clinical Excellence, 2014; O'Connor et al., 2016; van Ravesteyn et al., 2017). One meta-analysis indicated a positive, but small effect of prenatal preventive and acute treatments for depression on child functioning only (Goodman, Cullum, Dimidjian, River, & Kim, 2018). Nonetheless, no conclusions regarding the effect of acute treatment for prenatal common mental disorders on offspring could be made, given that the majority of the studies that were included in this review included healthy pregnant women without (a history of) MDD

or depressive symptoms (not acute treatment). Moreover, in the review the authors did not assess the effects of acute treatment alone on child functioning. The last is the main aim of this meta-analysis, i.e. to examine the effect of prenatal treatments for common mental disorders on offspring outcomes. Some studies furthermore report adverse effects of prenatal antidepressants use on preterm birth, birth weight, and Apgar scores (Ross et al., 2013), persistent pulmonary hypertension (PPHN; Grigoriadis et al., 2014; Huybrechts et al., 2015), development (Man et al., 2017; Rai et al., 2017), and cardiovascular malformations (Grigoriadis, VonderPorten, Mamisashvili, Roerecke, et al., 2013) in offspring. However, these reports are derived from non-randomized studies that do not permit conclusions of causality. The beneficial, or possibly iatrogenic effects of psychological interventions on offspring are however less clear, despite the beneficial effects of psychotherapies for perinatal major depressive disorders as reported in previous meta-analyses (Cuijpers et al., 2014; van Ravesteyn et al., 2017). A review of the evidence from RCTs is timely and warranted. The primary aim of the current study was to conduct a meta-analysis to examine whether treatments for pregnant women with common mental disorders, as recommended in leading clinical guidelines (including antidepressants and psychotherapy; National Institute for Health and Clinical Excellence, 2014; O'Connor et al., 2016), prevent adverse effects in offspring, both in terms of somatic and mental outcomes.

METHOD

Search strategy and selection criteria

This meta-analysis was conducted in accordance with the PRISMA guidelines, and registered on PROSPERO (van Grinsven, Brouwer, & Bockting, 2016). A search in PubMed, PsycInfo, Embase, and the Cochrane database of randomized trials, was performed on articles published from their origin through April 2016 and updated up to August 31, 2017. Five search strings were composed using standardized vocabulary (e.g. MeSH terms and text words), terms for searching title and abstract, and Boolean operators. The full search string is presented in Additional file 1. The five key strings targeted pregnancy, common mental disorders, interventions, offspring outcomes, and study design.

Included studies needed to 1) be a (cluster) randomized controlled trial; 2) treat 3) one or more prenatal common mental disorders or high levels of symptoms; 4) compare an intervention to a control condition; 5) include at least one offspring outcome; 6) report sufficient information to calculate effect sizes (or provide this information available upon request). Included common mental disorders and symptoms were mood disorders and anxiety disorders according to the definition of DSM-IV axis I and

older (American Psychiatric Association, 2000). These included obsessive-compulsive disorders, and trauma- and stress-related disorders/symptoms. Severe mental illnesses like bipolar disorder, psychosis, schizophrenia or substance abuse were excluded due to the low prevalence rates (National Institute for Health and Clinical Excellence, 2014). The common mental disorder or symptoms could be assessed by self-report measures or clinical interviews, provided that the participants were primarily selected based upon the presence of mental disorders or high symptom levels. The control condition was defined as care or treatment as usual, wait-list control, or placebo medication. Language was restricted to English and Dutch due to the language proficiency of the authors. Two authors (MEB and SG) independently screened and selected the articles, and assessed the risk of bias using the seven criteria as proposed by the Cochrane Handbook for Systematic Reviews of Interventions. Disagreement was solved by consultation of a third rater (CLB) and reaching consensus. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework (Guyatt et al., 2011) was used to assess the overall level of certainty and strength of evidence for each of the main offspring outcomes. The evidence for each of the main offspring outcomes was potentially downgraded based upon risk of bias, inconsistency, indirectness, imprecision, number of participants, and pooled effect sizes.

Offspring outcome measures

The primary outcomes included all offspring variables collected in the neonatal period, during infancy and early childhood. They included Apgar scores, birth weight, gestational age, and measures of cognitive, motor, and emotional development. Examples of these variables are offspring depressive and anxiety symptoms (e.g. as assessed by the strengths and difficulties questionnaire; Goodman, 1997), general development (e.g. Bayley scales of infant development; Bayley, 2006), child behaviour (e.g. child behaviour checklist; Rescorla, 2005), neurodevelopmental problems (e.g. Brazelton neonatal behaviour assessment scale; Brazelton, 1978), and biological measures (e.g. cortisol levels, height, weight). No restrictions were made on the assessment instruments (self-report, reports, observations). Offspring outcomes needed to be reported as continuous outcomes in order to be able to calculate Hedges' *g* effect sizes. Where applicable, these outcomes were converted to the international system of units (SI), or to equal units (e.g. months to weeks, days to weeks, kilograms to grams). Data was extracted by one author (SG) using a standardized form, and fully checked by a second author (MEB). Offspring measures that were reported in less than three studies were excluded from analyses.

Data analysis

The effect sizes for all child outcomes were calculated using Hedges' *g* and 95% confidence intervals (CI) to correct for small sample bias. Each effect size thus indicates a standardized comparison between the intervention group and control group. To calculate the pooled effect sizes, we extracted the reported mean scores, standard deviations, and number of participants for each group (intervention and control groups separately) for each offspring measurement. The software program Comprehensive Meta-Analysis© (version 3.0) was used to calculate pooled effect sizes, mean differences, forest plots, heterogeneity, and funnel plots. The effect sizes were interpreted according to Cohen's rule of thumb (small= 0.20-0.49; medium= 0.50-0.79; large = 0.80 and higher). As an indicator of heterogeneity among the effect sizes, we used the I^2 statistics (0% = no heterogeneity to 75% = high heterogeneity). We calculated 95% confidence intervals (Ioannidis, Patsopoulos, & Evangelou, 2007) around I^2, using the non-central χ^2-based approach within the heterogi module for Stata (Orsini, Bottai, Higgins, & Buchan, 2006). Funnel plots were used to visually inspect for publication bias, which was statistically checked with Egger´s test of the intercept and Duval and Tweedie's trim and fill procedure (Duval & Tweedie, 2000).

A priori we expected substantial heterogeneity between studies and therefore used a random effects model (Borenstein, Hedges, Higgins, & Rothstein, 2009) in which a pooled effect size was calculated for each offspring outcome, and one random effects model for the overall pooled effect size. Secondly, several post-hoc subgroup analyses were performed, in which pooled effect sizes were calculated for the main DSM disorders or symptoms, DSM disorders or symptoms and the offspring outcomes, type of intervention (psychotherapy, supplements or medication, and other), diagnostic status (through clinical interview or self-reported symptoms), risk of bias (high, low), and whether the author's indicated a significant and positive effect of the intervention on maternal main DSM disorders or symptoms (yes, no). A mixed effects model was used in the subgroup analyses, where the pooled effect sizes within subgroups were calculated with the random effects model, and the fixed effects model was used to test the difference between subgroups.

RESULTS

The search yielded 10,160 results up to April 2016. Citations and references of included articles and 207 reviews resulted in 129 additional articles. The search was updated up to August 2017, which resulted in 968 additional articles. A total of 9,770 articles were screened after removal of duplicates. The systematic search resulted in 18 eligible articles (0.18%; see Figure 1 for full details) reporting results of 16 RCTs,

which are reported in Table 1. In total 2,778 pregnant women were randomized over 11 different treatment types. Treatment types included (variations of) CBT, massage therapy, psycho-education, relaxation treatments, and couples' therapy. Intensity of the interventions ranged from two psycho-education phone sessions up to 16 CBT-based home visits. Details of treatment type, intensity, and the effects on maternal psychopathology are reported in Table 1. Seven studies focused on depression only (Field, Diego, Hernandez-Reif, Deeds, & Figueiredo, 2009; Maselko et al., 2015; Milgrom et al., 2015; Netsi, Evans, Wulff, O'Mahen, & Ramchandani, 2015; Rahman, Malik, Sikander, Roberts, & Creed, 2008; Urizar & Muñoz, 2011; Zhao, Munro-Kramer, Shi, Wang, & Luo, 2017), two on both depression and anxiety (Karamoozian & Askarizadeh, 2015; Verbeek, 2016), three on anxiety only (Bastani, Hidarnia, Montgomery, Aguilar-Vafaei, & Kazemnejad, 2006; Cappon, 2015; Chambers, 2009), two on fear of childbirth (Fenwick et al., 2015; Rouhe et al., 2013), one on posttraumatic stress disorder (PTSD; Madigan, Vaillancourt, McKibbon, & Benoit, 2015), one on stress in general (Rothberg & Lits, 1991), and one on various common mental disorders (de Vilhena & de Castilho, 2016). The risk of bias in the included studies was in general high, as reported in Table 1.

The included studies reported 28 different offspring outcome measures. Most outcomes were reported in a single study only. Analyses were restricted to the outcomes that were reported in at least three studies, which resulted in three eligible outcomes: Birth weight, Apgar (1, 5, and 10 minutes combined), and gestational age. For five studies it was therefore not possible to aggregate any of the reported offspring outcomes in the meta-analysis, both in terms of target outcome (e.g. cognitive vs. emotional development) and measurement instrument. Effect sizes of the removed outcomes for each study are reported in Figure 3. The mean values for each included study, and the overall highest and lowest values on the three offspring outcomes are displayed in Table 2.

Since there were no RCTs of pharmacological interventions during pregnancy reporting offspring outcomes, data from 11 non-pharmacological RCTs (reported in 13 articles) were analysed. First, pooled effect sizes for each selected outcome were calculated. Outcomes of the meta-analysis are reported in Table 3 and displayed in Figure 2. Birth weight was not significantly affected by interventions as compared to control conditions, corresponding to a mean difference of 42.88 grams (95% *CI* = −33.06, 118.83, *N* = 11, *n* = 1,583, I^2 = 39% [Bastani et al., 2006; Cappon, 2015; Chambers, 2009; de Vilhena & de Castilho, 2016; Field et al., 2009; Milgrom et al., 2015; Netsi et al., 2015; Rothberg & Lits, 1991; Rouhe et al., 2013; Verbeek, 2016; Zhao et al., 2017]) between intervention and control groups. Gestational age and Apgar scores did not significantly improve or worsen by prenatal interventions (gestational age mean difference = 0.08 weeks [95% *CI* = −0.09, 0.24], *N* = 10, *n* = 1,669, I^2 = 0% [Bastani et al., 2006; Chambers, 2009; de Vilhena & de Castilho, 2016; Fenwick et al., 2015; Milgrom et al., 2015; Rothberg & Lits, 1991; Rouhe et al., 2013; Verbeek, 2016;

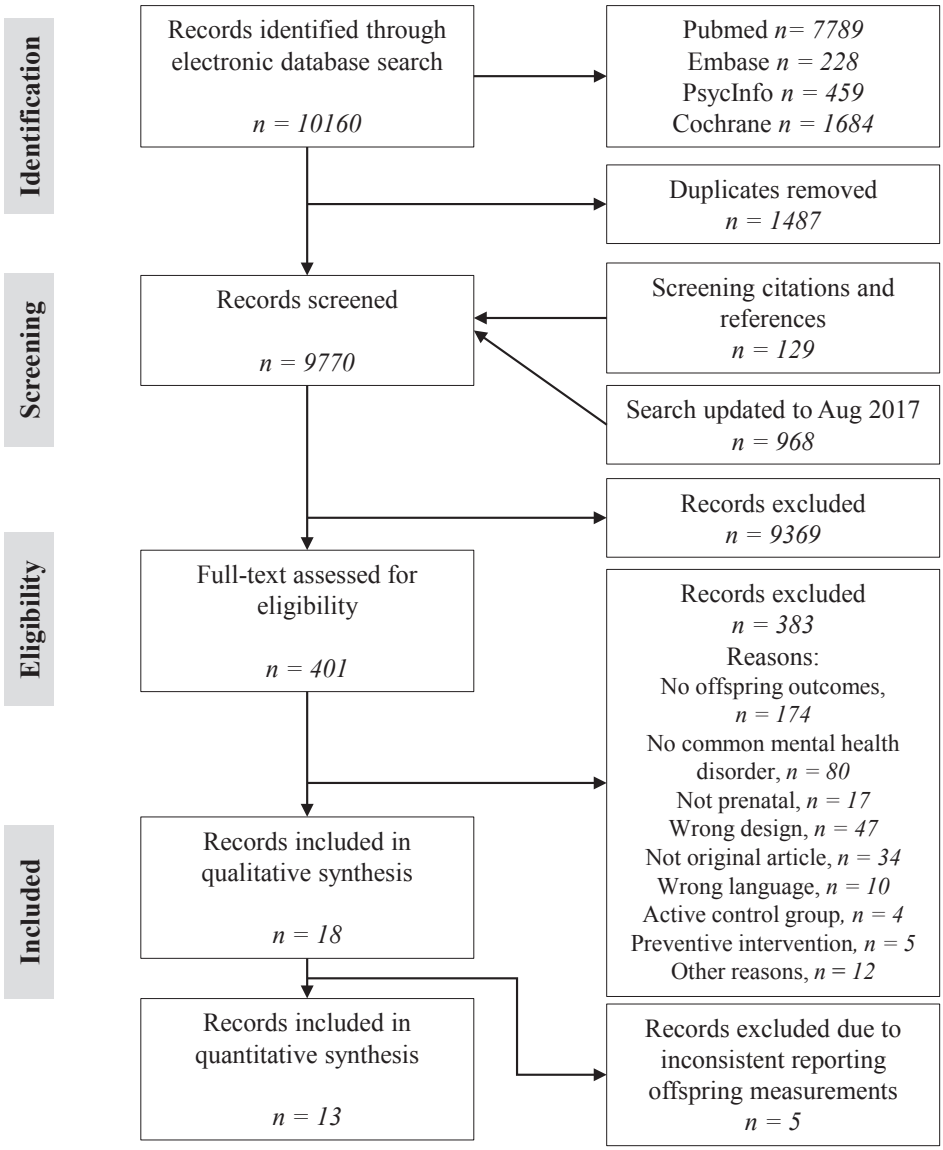

Figure 1. Flowchart of included studies

Zhao et al., 2017]; Apgar mean difference = 0.21 [95% *CI* = –0.28, 0.71], *N* = 4, *n* = 663, I^2 = 68% [Chambers, 2009; Karamoozian & Askarizadeh, 2015; Rouhe et al., 2013; Verbeek, 2016]). The pooled effect size indicated an overall non-significant effect on Apgar scores, birth weight, and gestational age together. Since these three offspring outcomes are heterogeneous in interpretation, this overall result is not further discussed. Heterogeneity across the outcomes was low, I^2 = 23% (95% *CI* = 0, 60%). There was

Table 1
Overview of included studies

Author, year	Study focus	Selection criteria	Conditions and timing of intervention	No. of participants	Authors conclude sign. effect of intervention on mother?	Offspring measures	Country	Risk of bias							
								S	C	B	A	I	R	O	T
Bastani, 2006	Anxiety	STAI >30	IG: Applied relaxation training, 7 wk group sessions CG: TAU Prenatal	IG: 52; CG: 52; Total: 104	Yes, on anxiety symptoms	*Medical records:* BW & GA	Iran	?	?	?	?	+	-	?	H
Cappon, 2015[x]	Anxiety	BAI ≥ 21	IG: Listening to music, 20 to 296 times individually CG: TAU Prenatal	IG: 36; CG: 37; Total: 73	Yes, on anxiety symptoms	*Questionnaire:* BW & GA. *IBQ-r* at age 2 to 3 months	USA	?	?	+	+	-	+	+	L
Chambers, 2009[x]	Anxiety	STAI; State or trait subscale ≥ 40	IG: 6 wk individual relaxation training CG: List of tips for reducing stress Prenatal	IG: 10; CG: 12; Total: 22	No	*Medical records:* BW & GA & Apgar scores	USA	+	?	-	+	-	+	-	H
Fenwick, 2015	Fear of childbirth	W-DEQ ≥ 66	IG: Telephone psycho-education, 2 sessions CG: TAU Prenatal	IG: 91; CG: 93; Total: 184	Yes, on flashbacks	*Medical records:* GA. Hospitalization up to 6 weeks	Australia	+	-	-	+	+	+	+	L
Field, 2009	Depression	SCID diagnosis MDD	IG: Massage therapy, 12 wk sessions CG: TAU Prenatal	IG: 88; CG: 61 Total: 149	Yes, on depressive symptoms	*Medical records:* BW & GA. *Saliva* (cortisol) & *BNBAS* at age 2 days	USA	+	?	-	+	-	-	-	H
Karamoozian, 2015	Depression & Anxiety	EPDS > 9 & PRAQ high score	IG: 12 wk group CBSM CG: TAU Prenatal	IG:14; CG: 15; Total: 29	Yes, on anxiety and depressive symptoms	*Apgar scale:* Apgar scores	Iran	?	?	?	?	+	+	-	H

Table 1
Overview of included studies (continued)

Author, year	Study focus	Selection criteria	Conditions and timing of intervention	No. of participants	Authors conclude sign. effect of intervention on mother?	Offspring measures	Country	Risk of bias							
								S	C	B	A	I	R	O	T
Madigan, 2015	PTSD in adolescents	CPTSDI PTSD diagnosis *or* AAI unresolved state of mind	IG: 12 wk trauma focused CBT plus 12 sessions parenting course CG: Parenting course (TAU) Prenatal	IG: 12; CG: 14; Total: 26	No	*ASSP* at age 12 months	Canada	?	?	?	+	+	+	-	L
Maselko, 2015[a]*	Depression	SCID diagnosis MDD	IG: Thinking healthy programme (CBT based), 7 wk visits and 9 monthly visits CG: Enhanced routine care Prenatal and postpartum	IG: 289; CG: 295; Total: 584	Yes, less MDD diagnoses in IG	*SDQ, SCAS,* weight, height, and BMI at age 7 years	Pakistan	+	+	+	+	+	-	-	L
Milgrom, 2015	Depression	SCID diagnosis MDD *and* EPDS≥ 13	IG: Beating blues before birth (CBT based), 8 sessions CG: TAU. Prenatal	IG:16; CG: 13; Total: 29	Yes, on depressive and anxiety symptoms	*Medical records:* BW & GA. *IBQ-R, ASQ-3, and ASQ-SE* at age 9 months	Australia	+	+	?	+	+	-	-	M
Netsi, 2015	Depression	CIS diagnosis MDD	IG: 12 sessions individual CBT CG: TAU Prenatal	IG: 14; CG: 11; Total: 25	Yes, on depressive symptoms	*Medical records:* BW. *ICQ and BISQ* at age 2 months	UK	+	+	-	+	-	+	-	H
Rahman, 2008*	Depression	SCID diagnosis MDD	IG: Thinking healthy programme (CBT based), 7 wk visits and 9 monthly visits CG: Enhanced routine care Prenatal and postpartum	IG: 440; CG: 463; Total: 903	Yes, on MDD diagnoses	*Records*: Weight, height, health at ages 6 and 12 months	Pakistan	+	+	+	+	+	+	+	L

Table 1
Overview of included studies (continued)

Author, year	Study focus	Selection criteria	Conditions and timing of intervention	No. of participants	Authors conclude sign. effect of intervention on mother?	Offspring measures	Country	Risk of bias							
								S	C	B	A	I	R	O	T
Rothberg, 1991	Stress	SRRS ≥39	IG: Psychosocial support during each antenatal clinic visit CG: TAU Prenatal	IG: 43; CG: 43; Total: 86	No	*Medical records & Ballard score:* BW & GA. *Height, hospitalization* at birth	South Africa	+	?	?	+	-	+	-	H
Rouhe, 2013	Fear of childbirth	W-DEQ ≥100	IG: 6 sessions psycho-educative group therapy CG: TAU Prenatal and postpartum	IG: 131; CG: 240; Total: 371	Yes, on fear symptoms	*Medical records:* BW & GA & Apgar scores. Arterial Ph. at birth	Finland	+	+	-	-	-	+	-	H
Urizar, 2011	Depression	CES-D ≥ 16 *or* past history of MDD	IG: 12 wk group CBSM CG: TAU Prenatal	IG: 24, CG: 29, Total: 53	No	*Saliva* (cortisol) at ages 6 and 18 months	USA	?	?	?	?	+	+	-	H
Verbeek, 2016[x]	Depression & Anxiety	EPDS ≥ 12 *or* STAI ≥42	IG: 10 to 12 sessions individual CBT CG: TAU Prenatal and postpartum	IG: 121; CG: 120; Total: 241	No	*Medical records:* BW & GA & Apgar scores	NL	+	+	-	+	+	+	+	L
Verbeek, 2016b[b x]	Depression & Anxiety	EPDS ≥ 12 *or* STAI ≥42	IG: 10 to 12 sessions individual CBT CG: TAU Prenatal and postpartum	IG: 97; CG: 99; Total:196	No	*CBCL and BSID* at age 18 months	NL	+	+	-	+	+	+	+	L
Vilhena, 2017	Common mental disorder in obese women	SRQ-20 ≥ 8	IG: Homeopathy, 2 times a day, 4 days a week CG: Placebo Prenatal	IG: 62; CG: 72; Total: 134	No	*Records:* GA, BW, Apgar of 10 at 5 minutes after birth	Brazil	+	+	+	?	?	+	-	L

Table 1
Overview of included studies (continued)

Author, year	Study focus	Selection criteria	Conditions and timing of intervention	No. of participants	Authors conclude sign. effect of intervention on mother?	Offspring measures	Country	Risk of bias							
								S	C	B	A	I	R	O	T
Zhao, 2017	Depression	EPDS ≥ 9 or PDSS ≥ 20	IG: 6 sessions couple-separated psycho-educational program for first time parents CG: TAU Prenatal	IG: 175; CG: 174; Total: 349	Yes, on depressive status	*Medical records:* GA, BW	China	+	?	?	?	+	+	?	L

Note: All presented studies were randomized controlled trials (RCT), except for *cluster RCT. [x] Doctoral dissertation. [a] Follow up for Rahman 2008. [b] Follow up for Verbeek 2016. IG = intervention group, CG = control group, TAU = treatment as usual, wk = weekly, MDD = major depressive disorder, CBSM = cognitive-behavioural stress management, CBT = cognitive behavioural therapy, BW = birth weight, GA = gestational age, USA = United States of America, UK = United Kingdom, NL = the Netherlands, BAI = Beck anxiety inventory, STAI = state trait anxiety inventory, W-DEQ = Wijma delivery expectancy/experience questionnaire, SCID = structured clinical interview for DSM disorders, EPDS = Edinburgh postnatal depression scale, PRAQ = pregnancy-related anxiety questionnaire, CPTSDI = children's PTSD inventory, PTSD = posttraumatic stress disorder, AAI= adult attachment interview, MDD = major depressive disorder, CIS = clinical interview schedule, SRRS = social readjustment rating scale, CES-D = Centre for Epidemiological Studies depression Scale, SRQ-20 = self-report questionnaire, IBQ-R = infant behaviour questionnaire revised, ASQ-3 = ages and stages questionnaire, ASQ-SE = ages and stages questionnaire social emotional, SDQ= strengths and difficulties questionnaire, SCAS = Spence children's anxiety scale, ASSP = Ainsworth strange situation procedure, BNBAS = Brazelton neonatal behaviour assessment scale, ICQ = infant characteristic questionnaire, BISQ = brief infant sleep questionnaire, BSID = Bayley scales of infant development, CBCL = child behaviour checklist. Risk of bias criteria are represented as S = sequence generation, C = allocation concealment, B = blinding of participants and personnel, A = blinding of outcome assessors, I = incomplete outcome data, R = selective reporting, O = other sources of bias, and are coded as + = low risk of bias (0 points), - = high risk of bias (2 points), ? = unclear risk of bias (1 point). T = total risk of bias, in which H = high risk of bias, L = low risk of bias. Total risk of bias is scored as <6 = low risk, >6 high risk.

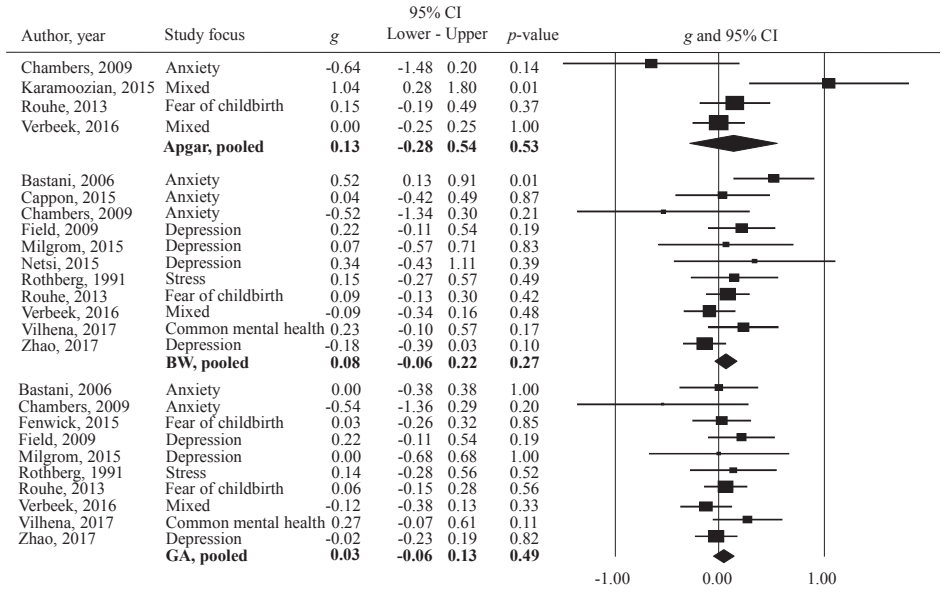

Figure 2. Forest plots for Apgar scores, birth weight, and gestational age

Note: BW = birth weight, GA = gestational age, g = Hedges' g, mixed = combination of multiple common mental disorders and/or symptoms

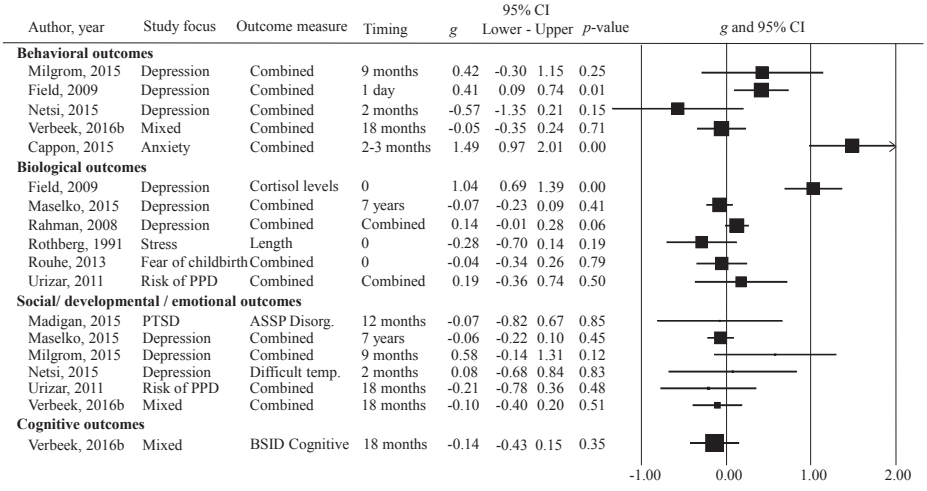

Figure 3. Forest plots of excluded offspring outcomes

Note: *g* = Hedges' *g*, mixed = combination of multiple common mental disorders and/or symptoms, combined = combination of multiple offspring outcomes and/or timing of offspring outcomes, PPD = peripartum depression, ASSP Disorg = Ainsworth stranger situation disorganized attachment measure, BSID Cognitive = Bayley scales of infant development - cognitive subscale, difficult temp = difficult temperament.

Table 2
Study offspring outcomes

Author, year	**Mean birth weight (Sd.)** in grams	**Mean Apgar score (Sd.)**	**Mean gestational age (Sd.)** in weeks
Bastani, 2006	IG: 3168 (420) CG: 2883 (640)	n/a	IG: 38 (5.9) CG: 38 (4.4)
Cappon, 2015	IG: 3366 (523) CG: 3344 (773)	n/a	n/a
Chambers, 2009	IG: 3232 (695) CG: 3562 (529)	IG, Apgar 1 minute: 7.8 (1.3) CG, Apgar 1 minute: 8 (1.1) IG, Apgar 5 minutes: 8.5 (0.7) CG, Apgar 5 minutes: 9.1 (0.3)	IG: 38.4 (2.5) CG: 39.5 (1.4)
Fenwick, 2015	n/a	n/a	IG: 39.2 (1.6) CG: 39.1 (2.0)
Field, 2009	IG: 3318 (360) CG: 3226 (492)	n/a	IG: 39 (1.2) CG: 38.7 (1.6)
Karamoozian, 2015	n/a	IG, Apgar 1 minute: 8.9 (0.3) CG, Apgar 1 minute: 8.1 (0.8) IG, Apgar 5 minutes: 9.7 (0.5) CG, Apgar 5 minutes: 9.3 (0.7)	n/a
Milgrom, 2015	IG: 3626 (786) CG: 3575 (595)	n/a	IG: 40 (1) CG: 40 (2)
Netsi, 2015	IG: 3423 (503) CG: 3180 (871)	n/a	n/a
Rothberg, 1991	IG: 3214 (649) CG: 3113 (690)	n/a	IG: 38.7 (3) CG: 38.3 (2.7)
Rouhe, 2013	IG: 3532 (550) CG: 3486 (518)	IG, Apgar 1 minute: 8.7 (1.1) CG, Apgar 1 minute: 8.5 (1.4) IG, Apgar 5 minutes: 9.3 (1.0) CG, Apgar 5 minutes: 9.1 (1.2) IG, Apgar 10 minutes: 9.7 (0.8) CG, Apgar 10 minutes: 9.5 (0.9)	IG: 39.7 (1.5) CG: 39.6 (1.6)
Verbeek, 2016; Verbeek, 2016b	IG: 3419 (651) CG: 3474 (561)	IG, Apgar 1 minute: 8.6 (n/a) CG, Apgar 1 minute: 8.6 (n/a) IG, Apgar 5 minutes: 9.5 (n/a) CG, Apgar 5 minutes: 9.5 (n/a) IG, Apgar 10 minutes: 9.8 (n/a) CG, Apgar 10 minutes: 9.8 (n/a)	IG: 38.9 (2.3) CG: 39.2 (1.8)
Vilhena, 2017	IG: 3390 (440) CG: 3270 (560)	n/a	IG: 39.4 (1.2) CG: 38.9 (1.9)
Zhao, 2017	IG: 3256 (522) CG: 3349 (529)	n/a	n/a
Combined range per offspring outcome:	*Lowest value: 2883* *Highest value: 3626*	*Lowest value: 7.8* *Highest value: 9.8*	*Lowest value: 38* *Highest value: 40*

Note: IG = intervention group, CG = control group.

Table 3
Meta-analyses and subgroup analyses results

		N	No. of participants	*g*	95% CI	*p*	I^2	95% CI	p^a
Effect of prenatal interventions on offspring outcomes (BW, GA, Apgar)	All studies	13	1,796	0.09	-0.03 – 0.21	0.14	23	0 – 60	
Effect of prenatal interventions for each offspring outcome	BW	11	1.583	0.08	-0.06 – 0.22	0.27	39	0 – 70	
	GA	10	1,669	0.03	-0.06 – 0.13	0.49	0	0 – 53	
	Apgar	4	663	0.13	-0.28 – 0.54	0.53	68	0 – 87	
Subgroup analyses									
Type of diagnosis*	Anxiety	6	852	-0.01	-0.22 – 0.20	0.89	40	0 – 75	0.41
	BW	5	668	0	-0.33 – 0.32	1	70	22 - 88	
	GA	5	779	-0.06	-0.24 – 0.12	0.54	27	0 - 71	
	Depression	5	575	0.02	-0.15 – 0.18	0.86	0	0 – 79	
	BW	5	575	0.01	-0.20 – 0.23	0.90	22	0 - 68	
	GA	4	550	0.05	-0.12 – 0.21	0.58	0	0 - 85	
	Other	4	283	0.22	-0.90 – 0.54	0.17	62	0 – 85	
	BW	3	254	0.06	-0.15 – 0.27	0.57	22	0 - 97	
	GA	3	254	0.07	-0.19 – 0.33	0.60	45	0 - 84	
Risk of bias	High	7	786	0.21	-0.00 – 0.42	**0.05**	31	0 – 70	0.09
	Low	6	1,010	-0.00	-0.13 – 0.12	0.97	0	0 – 61	
Diagnosis through clinical interview or self-report	Clinical interview	3	203	0.20	-0.07 – 0.47	0.15	0	0 - 90	0.43
	Self-report	10	1,593	0.08	-0.06 – 0.22	0.28	36	0 - 70	
Type of intervention	Psychotherapy	7	1,130	0.08	-0.10 – 0.27	0.40	39	0 - 75	0.67
	Other	6	666	0.13	-0.02 – 0.28	0.09	0	0 - 74	
Report of sign. effect of intervention on mother?	No	4	483	0.05	-0.18 – 0.28	0.68	31	0 – 75	0.64
	Yes	9	1,313	0.11	-0.04 – 0.26	0.14	29	0 - 67	

Note: [a] The *p*-value indicates whether the subgroups differ from each other. *g* = Hedges' g, 95% CI = confidence interval 95% of Hedges' g. * In this subgroup analysis, the Verbeek 2016 study subgroups depression, anxiety, and combined (other) were analysed separately. BW = Birth weight, GA = gestational age. Superscript numbers refer to included studies in each analysis.

some indication of publication bias, as indicated by Duval and Tweedie's trim and fill procedure (studies trimmed = 2, adjusted g = 0.05, 95% CI = –0.05, 0.15). Visual inspection of the funnel plot and the Egger's test (p = 0.16) did not indicate publication bias. The evidence for each of the three pooled effect sizes was downgraded using the GRADE assessment to very low certainty of evidence. For each of the outcomes, there was a serious risk of bias, consistency in measures, serious indirectness, and serious

imprecision. Birth weight and gestational age were rated as important outcomes, and Apgar scores was rated as not important.

Table 3 displays several subgroup analyses. Studies targeting depression, anxiety, or with a focus on other disorders, did not show a significant pooled effect size, hence did not improve offspring outcomes based on the three selected outcomes. According to the mixed effects analysis, the subgroups did not differ significantly. When investigating the separate offspring outcomes for each disorder (depression, anxiety, and other), it appeared that there was no significant effect of intervention on offspring outcomes within each disorder. The overall effect size in the risk of bias subgroup analysis was not significant. Although studies with a high risk of bias were significantly related to positive birth outcomes (g = 0.21, 95% CI = 0.00, 0.42, p = 0.05, N = 7, n = 786, I^2 = 31% [Bastani et al., 2006; Chambers, 2009; Field et al., 2009; Karamoozian & Askarizadeh, 2015; Netsi et al., 2015; Rothberg & Lits, 1991; Rouhe et al., 2013]), the mixed effects analysis indicated no significant difference between high and low risk of bias studies (p = 0.09). The method through which the (possible) diagnosis was established, i.e. through clinical interview or self-report, whether the authors reported that the intervention had a significant effect on treating maternal common mental disorder (symptoms) compared to the control group, and the type of intervention (psychotherapy versus other types), did not significantly affect offspring outcomes, nor did the mixed effects analyses show differences between the subgroups (Table 3).

DISCUSSION

Leading international clinical guidelines (National Institute for Health and Clinical Excellence, 2014; O'Connor et al., 2016) recommend screening and treatment of pregnant women for mental disorders and symptoms, with the clinical view to additionally prevent adverse effects on the offspring. The systematic search identified 16 non-pharmacological RCTs, including 14 psychological interventions that reported offspring outcomes. The results from the current meta-analysis indicate that non-pharmacological interventions do not have a significant effect on improving birth outcomes, and their effects could not be meta-analysed for (developmental) offspring outcomes. Therefore, based on the current evidence, there is no strong indication of prophylactic effects. Although no statistically significant result was obtained for birth weight, all effect sizes within the 95% confidence interval around the pooled effect estimate were small, indicating that the true effect of prenatal interventions on birth weight is most likely small. Furthermore, the quality of most studies was low and the studies were relatively heterogeneous. An explanation for the non-significant effect size may be a ceiling effect since offspring in the control and intervention groups had a

birth weight within the normal range. The birth weight in the trials ranged from 2,883 to 3,626 gram, indicating there was no low birth weight according to the worldwide standards for low birth weight, that is less than 2,500 gram (United Nations Children's Fund and World Health Organization, 2004).

Secondly, the meta-analysis did not show that the somatic outcomes indexed by Apgar scores and gestational age were significantly associated with the non-pharmacological interventions. As for birth weight, the confidence intervals around the pooled effect estimates for Apgar scores and gestational age indicate that a true effect is most likely small. It was furthermore not possible to investigate the impact of prenatal interventions on preventing preterm birth, since the included studies had different definitions of preterm birth (different gestational age), or did not report enough information to calculate effect sizes. Additionally, five out of 16 studies reported different measures of (long term) offspring outcomes. It was therefore not possible to investigate the effects of interventions on non-somatic outcomes, such as psychopathology or developmental problems. Although previous research and clinical guidelines (National Institute for Health and Clinical Excellence, 2014; O'Connor et al., 2016) report on harmful effects of prenatal mental disorders on offspring, including an increased risk of low birth weight (Grote et al., 2010), the current meta-analysis could not support the notion that treatment can mitigate this effect. Furthermore, the current results did not indicate that pregnant women in the care as usual or placebo groups had worse or better offspring outcomes. This is to some extent in contrast to a recent meta-analysis, in which it was concluded that prenatal preventive and acute interventions for MDD (symptoms) improved overall child functioning. This effect was however primarily based upon preventive interventions and offspring behaviour (Goodman et al., 2018).

The current meta-analysis found zero RCTs on the effects of antenatal treatment of common mental disorders with medication (i.e. antidepressants) on offspring. This is noteworthy given the fact that antidepressant medication is one of the most used treatments during pregnancy (Charlton et al., 2015). Furthermore, previous reviews of non-randomized trials indicate an association between prenatal antidepressant use and adverse offspring outcomes, including lower birth weight, preterm birth, lower Apgar scores (Grigoriadis, VonderPorten, Mamisashvili, Eady, et al., 2013; Ross et al., 2013), and cardiovascular malformations (Grigoriadis, VonderPorten, Mamisashvili, Roerecke, et al., 2013). Correspondingly, untreated maternal mental disorders have been associated with similar adverse effects, which in turn are linked to other subsequent offspring problems (Belbasis et al., 2016). Other studies suggest that the effects of antidepressants on offspring might be minimal (Brown et al., 2017; Huybrechts et al., 2014; Sujan et al., 2017). Due to the nature of the studies (non-randomized cohort trials), there is insufficient evidence of the possible effects of prenatal antidepressant usage. It is therefore not clear what the net effects of antidepressants are for offspring.

RCTs and comparative treatment trials are needed to disentangle whether these offspring outcomes are related to antidepressant use, or are predominantly the result of the mental disorders of the mother. To estimate the (enduring) relative effects of pharmacological and non-pharmacological interventions on offspring, an RCT comparing the two intervention types may provide more information on the prophylactic effects on offspring. Such design would be more ethical since the pregnant woman receives treatment according to clinical recommendations. Moreover, it would provide more information on the effects of antidepressants.

Collectively the findings of the meta-analysis indicate that there is insufficient data to support the beneficial effects of prenatal treatments on offspring, and that more research on the effects of prenatal treatments on offspring is needed. These results of the meta-analysis must be interpreted in the context of some limitations. In general, the included trials had a high risk of bias, reported different offspring outcomes, and the GRADE assessment indicated very low certainty of evidence, thereby limiting the results. Overall, there is some indication that non-pharmacological interventions may have a positive influence on offspring birth weight; however, the effect was not significant and could be overestimated due to the small sample sizes and high risk of bias. The small sample size of pregnant women, and the small amount of included studies, increases the risk of false positive and false negative birth outcomes. Furthermore, other birth outcomes including preterm birth, low birthweight for gestational age, or child development, could not be analysed due to the inconsistent reporting and lack of studies. There is no conclusive evidence that interventions aimed to target prenatal mental disorders are beneficial or iatrogenic for offspring, especially with regard to long-term and psychological impact.

For health care professionals, there is little evidence that prenatal non-pharmacological interventions are beneficial for the offspring with respect to birth weight, gestational age, and Apgar scores. There is not enough support that commonly used treatments for prenatal mental disorders are beneficial to offspring and hence do not provide a scientific foundation to support recommendations of specific treatment options with respect to the benefit for the child. More systematic research with long-term follow-up of the offspring is consequently needed to support (inter)national guidelines for prenatal mental disorders. As a first step, research on prenatal interventions may register birth outcomes from birth reports of (former) participants in RCTs. RCTs focusing on pharmacological interventions as compared to psychotherapy during pregnancy are needed, even though this may be challenging due to ethical considerations and preferences of pregnant women and their health care providers.

Conclusions

The results from the current meta-analysis indicate no significant effects of nonpharmacological interventions on improving birth outcomes. No firm conclusion of prophylactic effects can be drawn due to the reported limitations. Despite the recommendation of leading international clinical guidelines (National Institute for Health and Clinical Excellence, 2014; O'Connor et al., 2016) to routinely screen pregnant women for common mental disorders and symptoms, and subsequently treat the mother to reduce perinatal symptomatology and prevent adverse effects on the offspring, there is insufficient data to support the clinical recommendation regarding the safety of prenatal treatments for the offspring. Prior research implies that prenatal interventions improve maternal psychopathology (Cuijpers et al., 2014; van Ravesteyn et al., 2017), yet more research is warranted to draw stronger conclusions on the impact of prenatal interventions on offspring, especially regarding child development. Potential adverse effects on offspring cannot be ruled out, thereby underscoring the urgent need for properly controlled trials to best inform care approaches for mothers and their offspring.

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Chapter 5

Recurrence of depression in the perinatal period: Clinical features and associated vulnerability markers in an observational cohort

Based on: **Brouwer, M.E.** & Molenaar, N.M., Kamperman, A.M., Burger, H., Williams, A.D., Hoogendijk, W.J.G., Bockting, C.L.H. & Lambregtse-van den Berg, M.P. (2019). Recurrence of depression in the perinatal period: Clinical features and associated vulnerability markers in an observational cohort. *PlosOne, 14*(2), e0212964. doi: 10.1371/journal.pone.0212964

ABSTRACT

Objective

Antidepressant medication is commonly used for the prevention of depression recurrence in the perinatal period, yet it is unknown what vulnerability markers may play a role in recurrence. The objective of the current study was to provide a descriptive overview of the associated characteristics of women who experienced a perinatal recurrence of depression despite ongoing antidepressant use in detail, and further to identify clinically measurable vulnerability markers associated with recurrence.

Methods

Eighty-five pregnant women with a history of depression who used antidepressants (e.g. Selective Serotonin Reuptake Inhibitors or Serotonin and Noradrenaline Reuptake Inhibitors) at the start of the study were included. Clinical features, including information on psychiatric history and antidepressant use, were collected throughout the perinatal period (in this study defined as the period between 12 weeks of pregnancy until three months postpartum). The clinical features of women experiencing recurrence of depression were described in detail. To identify vulnerability markers associated with recurrence of depression, we performed exploratory univariable logistic regression analyses.

Results

Eight women (9.4%) experienced a recurrence of depression; two during pregnancy and six in the first 12 weeks postpartum. All women with recurrence of depression had first onset of depression during childhood or adolescence and had at least two psychiatric co-morbidities. Identification of vulnerability markers associated with recurrence of depression yielded associations with depressive symptoms around 16 weeks of pregnancy (*OR* = 1.28, 95% *CI* = 1.08, 1.52), number of psychiatric co-morbidities (*OR* = 1.89, 95% *CI* = 1.16, 3.09) and duration of antidepressant use (*OR* = 1.01, 95% *CI* = 1.00, 1.02).

Conclusion

Implementing adequate risk assessment in pregnant women who use antidepressants can help identify predictors for recurrence of depression in future studies and thus ultimately lead to improved care.

INTRODUCTION

Mental illness during the perinatal period (i.e. during pregnancy up to three months postpartum) is a common health problem (Howard et al., 2014), with approximately 25% of women experiencing any psychiatric disorder in this period (Vesga-López et al., 2008). Perinatal depressive disorder is most common, with a recent meta-analysis observing a pooled prevalence of 11.9% (Woody, Ferrari, Siskind, Whiteford, & Harris, 2017). Untreated perinatal depression is not only unfavourable for the mother; it is also associated with adverse outcomes in the offspring (Brockington et al., 2011). Exposure to antenatal depressive disorder is associated with increased risks of premature delivery, low birth weight (Grigoriadis et al., 2013; Grote et al., 2010; Jarde et al., 2016), and behavioural, emotional, cognitive and motor problems in early childhood (Field, 2011; Hay, Pawlby, Waters, Perra, & Sharp, 2010; Talge, Neal, & Glover, 2007). Ante- and postnatal depression can furthermore influence the mother-infant relationship, posing increased risks for poor infant development (Cuijpers, Weitz, Karyotaki, Garber, & Andersson, 2014; Goodman et al., 2011; Tronick & Reck, 2009).

Prevention or treatment of perinatal depression is therefore of importance. Several treatment options are available (van Ravesteyn, Lambregtse - van den Berg, Hoogendijk, & Kamperman, 2017), but international guidelines differ in their recommendations (Molenaar, Kamperman, Boyce, & Bergink, 2018) and clinicians are frequently noncompliant (Molenaar et al., 2018). Antidepressant medication is an increasingly used treatment option, either for prevention of recurrence of depression or as acute treatment in newly depressed patients (Charlton et al., 2015; Cooper, Willy, Pont, & Ray, 2007; Daw, Mintzes, Law, Hanley, & Morgan, 2012). Perinatal prescription rates of antidepressants vary per study setting and range from 2.1% to 13.4% (Bakker, Kölling, van den Berg, de Walle, & de Jong van den Berg, 2008; Charlton et al., 2015; Cooper et al., 2007; Jimenez-Solem et al., 2013).

The preventive effect of continued antidepressant use in recovered women during the perinatal period remains unclear. A systematic review assessing the effectiveness of antidepressants for prevention of postnatal depression, based on observational studies, could not draw any clear conclusions due to low statistical power (Molyneaux et al., 2018). Two studies with a prospective naturalistic design followed women who continued or tapered antidepressants, from their first trimester throughout their pregnancy (Cohen et al., 2006; Yonkers et al., 2011). One study showed an increased risk of recurrence in women who discontinued their medication compared to women who continued their medication (68% vs. 26%; Cohen et al., 2006), the other study observed similar recurrence rates in women continuing or discontinuing antidepressants (16% in total; Yonkers et al., 2011). A large retrospective administrative data study comparing women who continued antidepressants during pregnancy to those who discontinued showed

women who continued were twice as likely (*OR* = 2.0, 95% *CI* = 1.80, 2.20) to have a depression inpatient stay (Swanson et al., 2015).

From a clinical perspective, recognizing which pregnant women using antidepressants are at risk for recurrence is vital. With this knowledge, clinicians could more accurately identify and inform patients, and subsequently arrange additional guidance when necessary. Collectively these efforts could help promote the use of individualized patient-centred care, and potentially prevent negative effects in the offspring. The purpose of the current study was to describe cases with perinatal recurrence of depression out of a group of pregnant women using antidepressants in their first trimester in detail. Clinical features of the women with recurrence were inspected and reported. Additionally, vulnerability markers associated with recurrence that are easily collected during routine care, were explored.

METHODS

Setting and population

The present study is an observational study of 85 pregnant women that used antidepressants at the start of the study and had a history of depression. This study was part of a larger nation-wide research project on antidepressants, including both a randomized controlled trial (RCT), called 'Stop or Go', in which women are randomized to continue or discontinue antidepressants during pregnancy (Molenaar et al., 2016) and an observational cohort. The present manuscript does not report on women from the RCT. The Medical Ethical Committee of the Erasmus Medical Centre approved both the RCT and observational cohort (MEC-2014-505).

Women were recruited for both studies during their prenatal booking visit in midwifery practices and hospitals, through general practitioners, or through advertisement in (social) media. When a potential eligible woman was identified, study researchers gave counselling about the RCT and observational cohort. When women were unwilling or not eligible to participate in the RCT, they were counselled for the observational cohort. Written informed consent was necessary for participation.

For the present observational study, participants were considered eligible if they 1) were between 12 and 16 weeks pregnant, 2) used a Selective Serotonin Reuptake Inhibitor (SSRI), Selective Serotonin and Noradrenalin Reuptake Inhibitor (SNRI) or Tricyclic Antidepressant (TCA), 3) had a history of at least one depressive episode as assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First, Spitzer, Gibbon, & Williams, 2002), and 4) did not have a current diagnosis of depression according to the SCID-I. Women without sufficient proficiency in Dutch or English were excluded. No intervention was given in the observational cohort and participants were

free to decide their selves whether to continue or taper their antidepressants during study follow-up. Participants were recruited between April 2015 and February 2018.

Perinatal recurrence of depression

We assessed relapse and recurrence, as defined by the SCID-I, during pregnancy and up to 12 weeks postpartum. Relapse is defined as the re-emergence of depressive symptoms during the remission phase (being symptom-free from illness), but before full recovery (the absence of symptoms for at least 4 months following the onset of remission). Recurrence is defined as the onset of a new depression episode during the recovery phase or long remission phase. We use the word recurrence for further reference to both relapse and recurrence. The SCID-I was assessed before 16 weeks of pregnancy (baseline assessment) and around 12 weeks postpartum.

Clinical features of women with recurrence of depression

Clinical features including information on psychiatric history and antidepressant use were documented. SCID-I DSM-IV diagnoses, age of first and last onset of depression (SCID-I), number of depressive episodes (SCID-I), history of psychiatric hospital admission, psychiatric family history, antidepressant prescriber, current antidepressant dosage and number of previous discontinuation attempts were all determined around 16 weeks of pregnancy (baseline assessment).

The Edinburgh Postnatal Depression Scale (EPDS) was administered at baseline, 24 and 36 weeks of pregnancy and 4 and 12 weeks postpartum for the assessment of depressive symptoms (Bergink et al., 2011; Bunevicius, Kusminskas, Pop, Pedersen, & Bunevicius, 2009). The Beliefs about Medicine Questionnaire, specific version (BMQ-s) was administered at baseline (Horne, Weinman, & Hankins, 1999). The BMQ-s consists of two scales assessing 1) personal beliefs about the necessity of prescribed medication for controlling one's illness (score range 5-25) and 2) concerns about the potential adverse consequences of taking medication (score range 6-30). Higher scores indicate stronger beliefs in the concepts of the scale. During follow-up, data on healthcare use was collected using the Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (TIC-P) for number of visits to the general practitioner (GP), psychiatrist, psychologist, psychiatric nurse, psychotherapist and mental health care practice assistant (Bouwmans et al., 2013).

Vulnerability markers associated with recurrence of depression

Potential vulnerability markers of recurrence focused on sociodemographic characteristics, illness (history) and antidepressant specifications. Included participant characteristics were age, level of education, having a paid job, parity and planned

pregnancy (yes/no). Level of education was categorized in low (primary/secondary education) and higher education.

Included illness (history) determinants were EPDS score around 16 weeks of pregnancy, number of depressive episodes, number of axis I psychiatric co-morbidities (the sum of both previous and current diagnoses) as measured with the SCID-I and a history of psychiatric hospital admission.

Antidepressant specifications included duration of antidepressant use, number of previous tapering attempts, and dose equivalency in early pregnancy. Dose equivalency was calculated by dividing the prescribed dosage by standard initial dosages, which are: citalopram 20mg, escitalopram 10mg, fluoxetine 20mg, fluvoxamine 100mg, paroxetine 20mg, sertraline 50mg and venlafaxine 75mg. Standard dosages were based on American and Dutch pharmaceutical treatment guidelines (U.S. Department of Health & Human Services; Zorginstituut Nederland). During prospective follow-up, tapering and discontinuation was reported and divided into three categories: 1) no tapering, 2) intention to taper, but did not completely discontinue antidepressants during follow-up and 3) participant completely discontinued antidepressants at any point during follow-up, whether or not this discontinuation afterwards persisted throughout follow-up.

Statistical analysis

We performed a case-series study describing individual characteristics of participants. Additionally, exploratory univariable analyses were used to qualify associations between recurrence and vulnerability markers (previous section). We used logistic regression analyses with recurrence as the outcome variable and the vulnerability markers entered one at a time as independent variables. Given the explorative nature of the study the issue of multiple testing is not relevant in our view. All associations were expressed as odds ratios (*OR*) with 95% confidence intervals (95% *CI*). All statistical analyses were performed with SPSS, version 25.0.

RESULTS

A total of 478 pregnant women were referred for further counselling for both the RCT and the observational cohort. Thirty-one women (6.5%) were unreachable for counselling, 44 (9.2%) decided to participate in the RCT and 248 (51.7%) declined to participate in both trials. Of the remaining 155 women willing to participate in the observational cohort, another 70 (14.6%) were excluded for the current study: Six had an incomplete baseline record, 49 did not have a history of depressive disorder, two were currently depressed, three had a miscarriage and ten were lost to follow-up. This resulted in a total sample of 85 women (Figure 1).

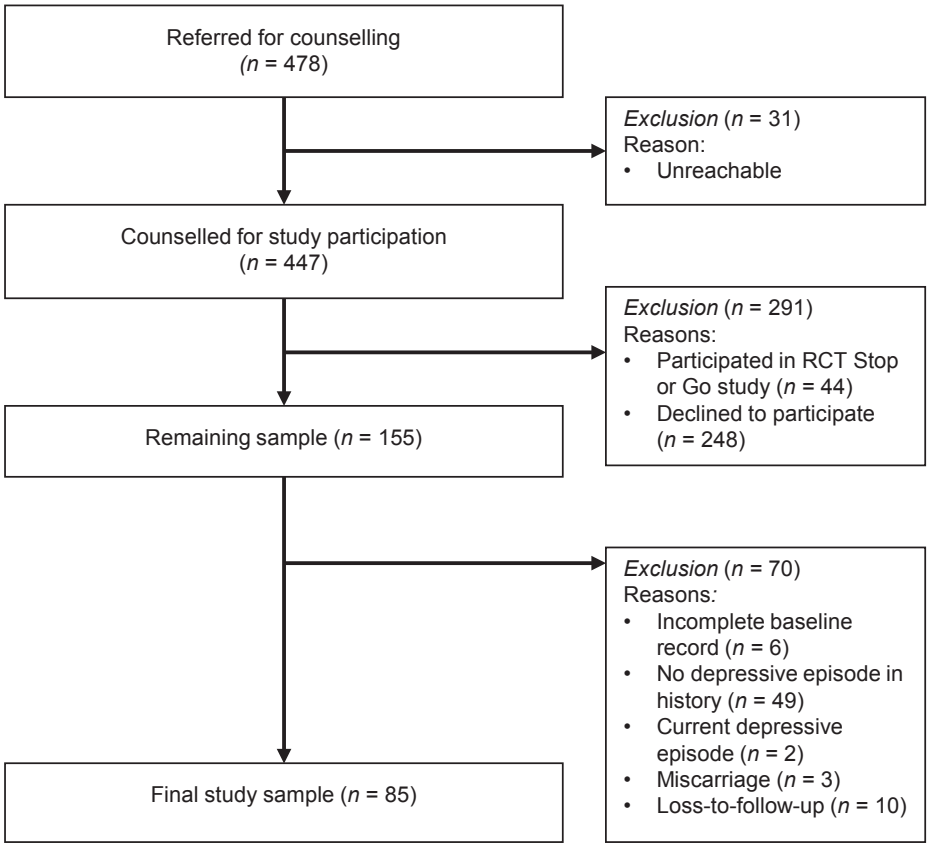

Figure 1. Flowchart of inclusion of participants.

Table 1 illustrates the characteristics of all participants, including those with and without depression recurrence. Eight women (9.4%) experienced a perinatal recurrence of depression, none experienced relapse. Overall, mean age was 31.7 years (*SD* 4.1), 98.8% was of Dutch origin and 91.5% was living with her partner. Over half of the participants had a high level of education and for 50% it was their first pregnancy. Of all 85 women, 44 (51.8%) had one previous depressive episode and 7.1% had more than 3 episodes. Psychiatric co-morbidity was present in 71.8% of women (22.4% with current co-morbidity and 67.1% with previous co-morbidity), with panic disorder and agoraphobia most common (both 24.7% of participants). Overall, the median duration of antidepressant use was 60 months, during which a limited number of tapering attempts were undertaken; 81.0% either did not try or only once attempted to discontinue their antidepressants before study participation. During follow-up, 12 women (14.1%) completely discontinued their medication and four (4.7%) intended to taper medication, but did not completely discontinue during follow-up.

Table 1
Characteristics of pregnant women with a history of depression, with and without recurrence of depression during the perinatal period.

	All (*n* = 85)	**Recurrence** (*n* = 8)	**No recurrence** (*n* = 77)	***OR*** (95% *CI*)
Sociodemographic characteristics				
Age, mean (SD)	31.7 (4.1)	30.8 (5.1)	31.8 (4.0)	0.94 (0.78, 1.12)
High level of education, yes (%)	51 (65.4)	4 (57.1)	47 (66.2)	0.68 (0.14, 3.29)
Paid job, yes (%)	65 (79.3)	6 (75.0)	59 (79.7)	0.76 (0.14, 4.17)
Parity, median (range)	1.5 (1-11)	1 (1-5)	2 (1-11)	0.76 (0.38, 1.54)
Planned pregnancy, yes (%)	64 (78.0)	7 (87.5)	57 (77.0)	0.48 (0.06, 4.17)
Illness (history)				
EPDS score around 16 weeks of pregnancy, mean (*SD*)	6.7 (4.7)	11.6 (4.1)	6.2 (4.4)	1.28 (1.08, 1.52)*
No. of depressive episodes, median (range)	1 (1-10)	2.5 (1-6)	1 (1-10)	1.40 (0.94, 2.07)
No. of psychiatric co-orbidities, median (range)	1 (0-6)	2.5 (2-4)	1 (0-6)	1.89 (1.16, 3.09)*
History of admission to psychiatric institute, yes (%)	12 (14.1)	3 (37.5)	9 (11.7)	4.53 (0.92, 22.26)
Antidepressant specifications				
Duration of antidepressant use in months, median (range)	60.0 (4-252)	120 (12-228)	48 (4-252)	1.01 (1.00, 1.02)*
No. of tapering attempts in history, median (range)	1 (0-6)	0.5 (0-2)	1 (0-6)	0.65 (0.25, 1.70)
Dose equivalent at start study, mean (*SD*)	1.3 (0.6)	1.7 (0.7)	1.3 (0.6)	2.32 (0.84, 6.42)
Tapering antidepressants during follow up, *n* (%)	16 (18.8)	3 (37.5)	13 (16.9)	2.00 (0.89, 4.53)
Intention to taper, did not discontinue, *n* (%)	4 (4.7)	0 (0.0)	4 (5.2)	
Discontinued during study, *n* (%)	12 (14.1)	3 (37.5)	9 (11.7)	

Note: Columns may not sum due to missing data. *p-value < 0.05

Women with perinatal recurrence of depression

Out of eight women with a recurrence, six experienced recurrence after childbirth. Three of the women discontinued antidepressants during follow-up. A visual representation of timing of onset of recurrence can be seen in Figure 2. Clinical features of individual women are listed in Table 2 (case numbers correspond with case numbers in Figure 2). The mean age at first onset of depression was 16 years. None of these women had a previous episode with postpartum onset (for six women this was their first pregnancy). Four women had a positive family history of psychopathology; case 2 had a father with depression and obsessive-compulsive disorder, case 3 a brother with attention-deficit hyperactivity disorder and antidepressant use, case 7 a cousin who committed suicide and case 8 a mother, aunt and grandma with depression. All women had two

or more psychiatric co-morbidities, mostly anxiety disorders. Most women received their medication through the general practitioner (GP). Overall, beliefs about necessity of their medication (BMQ-necessity) was high. However, the women with the lowest scores were also the women that discontinued their antidepressants during follow-up. The beliefs about adverse consequences were mild and homogeneous. All women had a history of (added) non-pharmacological treatment, receiving therapy for multiple years including cognitive therapy. Three women still received non-pharmacological therapy in early pregnancy.

All eight women visited the GP on average four times during study follow-up. Women had several psychiatric healthcare professionals. Five women visited a psychiatrist (mean number of visits 4.2), four a psychologist (mean number of visits 7.8), four a psychiatric nurse (mean number of visits 10.8), four a mental health care practice assistant (mean number of visits 2.0) and two a psychotherapist (mean number of visits 5). Case 7 only visited her GP (four times in total). The other women visited at least one more healthcare professional (range 1-5).

During pregnancy, the mean EPDS scores of the eight women remained stable (11.6, 12.1 and 11.1 consecutively), but increased after childbirth, around the time six women had a recurrence of depression. Mean EPDS scores around four weeks postpartum were 16.3 and 15.3 at 12 weeks postpartum. Figure 3 shows EPDS scores per case over time.

Vulnerability markers associated with perinatal recurrence of depression

Univariable associations between the independent determinants and recurrence of depression are presented in Table 1. A higher EPDS score around 16 weeks of pregnancy (*OR* = 1.28, 95% *CI* = 1.08, 1.52), a higher number of psychiatric co-morbidities (*OR* = 1.89, 95% *CI* = 1.16, 3.09) and a longer duration of antidepressant use in months (*OR* = 1.01, 95% *CI* = 1.00, 1.02) were associated with an increased risk of recurrence.

DISCUSSION

In this prospective cohort study, 85 pregnant women with a history of depression and baseline antidepressant use were assessed for depression recurrence. In total, eight women (9.4%) experienced a recurrence of depression at follow-up. All women with recurrence had experienced their first onset of depression during childhood/adolescence and had at least two psychiatric co-morbidities. Due to the low rate of recurrence, we were only able to explore univariable vulnerability markers associated with recurrence. Results yielded associations for recurrence with depressive symptoms around 16 weeks of pregnancy, number of psychiatric co-morbidities and duration of antidepressant use.

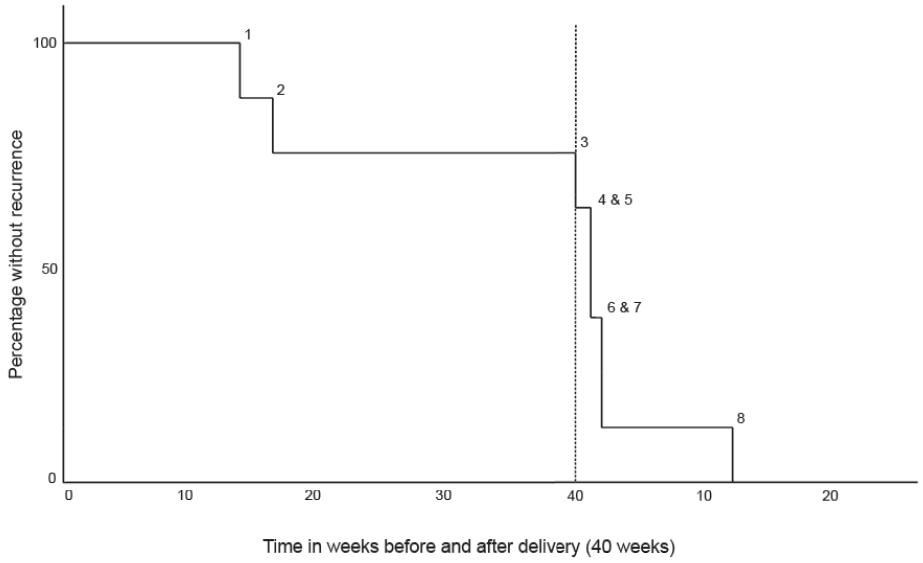

Figure 2. Survival curve of women with recurrence of depression in the perinatal period.
Note: Numbers in figure represent separate cases and match with case numbers listed in Table 2.

Table 2
Clinical features of women with recurrence of depression in the perinatal period.

			Illness characteristics						**Antidepressant specifications**				**Follow-up**		
Case no.	Age	Parity	Age at first onset	Age at last onset	No. of episodes	No. of Psych. co-morb.	Adm. history	Family history	Prescriber AD	BMQ nec/adv	Duration AD use	Baseline dose equiv.	No. tapering attempts	Disc. AD	No. psych care visits
1	31	1	14	14	1	2	-	-	GP	17/19	180	2.0	1	-	14
2	32	2	12	28	3	2	+	+	GP	23/21	120	3.0	1	-	18
3	37	5	17	28	3	3	-	+	GP	15/15	228	1.0	0	+	3
4	37	1	18	27	6	3	-	-	Psych	23/16	120	2.0	2	-	22
5	22	1	16	19	2	3	+	-	Psych	14/18	60	1.5	0	+	26
6	29	1	13	24	3	2	+	-	GP	21/17	96	1.0	0	-	15
7	32	1	20	27	2	2	-	+	GP	23/19	120	2.0	0	-	0
8	26	1	18	24	2	4	-	+	GP	13/18	12	1.0	1	+	15

Note: No.=number, AD= antidepressants, BMQ= beliefs about medicines questionnaire (necessity [nec]; score range 5-25, higher score indicates stronger belief in necessity, adverse [adv]; score range 6-30, higher score indicates stronger belief in potential adverse consequences), (-) No/negative, (+) Yes/positive, GP = general practitioner, Psych = psychiatrist, No. of Psych. co-morb. = number of current and past co-morbid mental disorders, Adm. history = history of hospital admissions., equiv. = equivalent, Disc = discontinued.

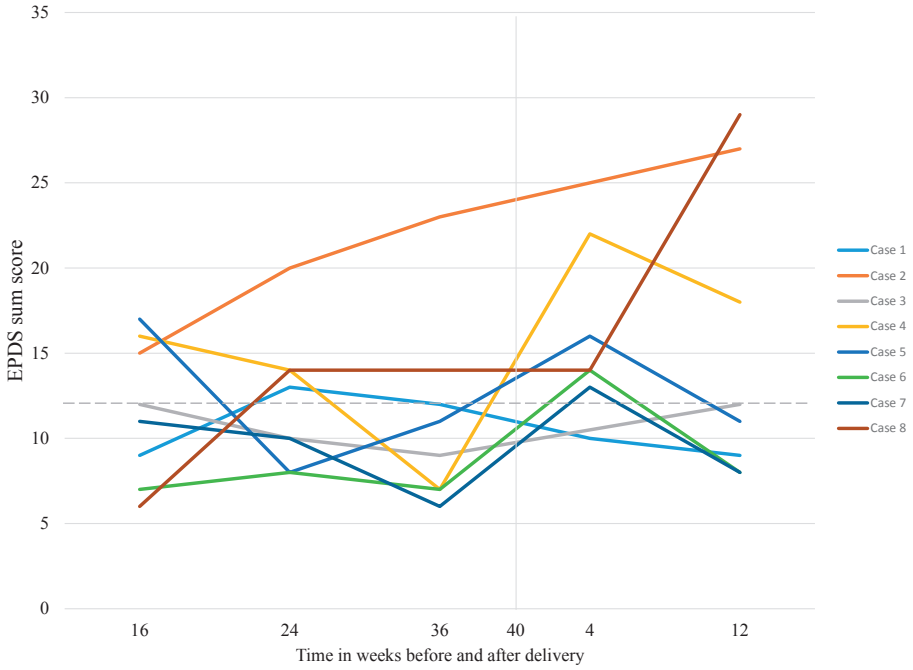

Figure 3. Edinburgh Perinatal Depression Scale (EPDS) sum score in the perinatal period.
Note: Each line represents a case with recurrence of depression. Case numbers match with case numbers listed in Table 2. The horizontal dotted line represents the EPDS cut-off score.

Two previous observational studies investigated recurrence rates of depression in women using antidepressant during pregnancy and reported rates ranging from 68 to 16% (Cohen et al., 2006; Yonkers et al., 2011). Our overall recurrence rate (9.4%) is remarkably lower, despite the longer follow-up period. Of the women discontinuing, 25% experienced recurrence compared to 7% of the women continuing. A possible explanation may be the difference in study populations. Cohen et al. (2006) included women through psychiatric institutes and reported that 76.6% had three or more previous depressive episodes. In the Yonkers study (2011), 38% of the women had four or more previous depressive episodes, compared to 7.1% in our population. Number of previous episodes in the general population is one of the strongest predictors for recurrence (Hardeveld, Spijker, De Graaf, Nolen, & Beekman, 2010). Another explanation is that both previous studies reported most women had onset of recurrence in the first trimester (Cohen et al., 2006; Yonkers et al., 2011), whereas in our study, women with onset of recurrence in the first trimester (at start study) were excluded.

During follow-up, 14% of women completely discontinued their medication. This rate is in accordance with Dutch discontinuation rates during pregnancy as recorded in insurance and pharmacy databases (Charlton et al., 2015; Ververs et al., 2006).

Similar to Yonkers et al. (2011), our exploratory analysis did not find a significant effect of antidepressant discontinuation on recurrence risk. Outside of the perinatal period, antidepressants seem to be more protective than placebos in preventing recurrences, although this effect is not uniform (36) and recent trials have demonstrated tapering of antidepressants is safe when preventive cognitive therapy is provided (Bockting et al., 2018; Kuyken et al., 2015).

There were some noticeable details regarding the women with recurrent depression. All eight women had a first onset of depression during childhood or adolescence, and all but one of the women had multiple depressive episodes. Age of first onset has been associated with risk of recurrence, although it is difficult to disentangle the effect of age of first onset from the number of depressive episodes, as these two are highly correlated (Burcusa & Iacono, 2007). This early-onset depression has previously been associated with a more severe and chronic course of depression, often affecting women, with a longer duration of illness, more episodes, higher symptom severity, more psychiatric co-morbidity and more tendency to attempt suicide (Zisook et al., 2007; Zisook et al., 2004).

Number of visits to psychiatric health care professionals during study follow-up ranged between 0 and 26 in all recurrence cases. Two women did not receive any, or only very limited, additional psychiatric healthcare, indicating that they did not receive adequate treatment for their recurrent depressive episode. This is unwanted as a review of 23 longitudinal studies found that 38% of mothers with postpartum depression (PPD) continued to have major depression during their child's first year of life and even beyond, with previous history of depression as a predictor for a chronic course of PPD (Vliegen, Casalin, & Luyten, 2014), affecting the child as well (Cuijpers et al., 2014). Ideally, all women would be offered additional care, even before recurrence takes place, as a recent study among adults showed that adding preventive cognitive therapy to antidepressant treatment resulted in a 41% relative risk reduction of relapse or recurrence of depression compared with antidepressants alone (Bockting et al., 2018).

The exploratory analyses identified three predictors for recurrence: Depressive symptoms around 16 weeks of pregnancy, number of psychiatric co-morbidities and duration of antidepressant use. In early pregnancy, five women already had an EPDS score above cut-off (Bergink et al., 2011), although they did not fulfil the SCID-I criteria yet for depressive disorder. The EPDS consists of ten questions and can thus be easily assessed in early pregnancy. International clinical guidelines encouraging routine screening for perinatal depression have been available for over a decade (National Institute for Health and Clinical Excellence, 2014). Previous validation research of the EPDS found that a cut-off value of 11 in the first trimester, and ten in the second and third trimesters gave the most adequate combination of sensitivity, specificity, and positive predictive value (Bergink et al., 2011). Clinicians may use these cut-off

scores to initiate and monitor additional treatment, to prevent recurrence and decrease current symptoms of depression. The second characteristic was number of psychiatric co-morbidities. Psychiatric co-morbidity has been associated with shorter time to recurrence in a non-pregnant population (ten Have et al., 2018). During pregnancy, clinicians should therefore assess presence of psychiatric co-morbidities, and determine whether additional treatment targeting these co-morbidities is necessary. Lastly, a longer duration of antidepressant use was associated with recurrence. The *OR* must be interpreted as an increase of around 1% in the odds or recurrence per month. Longer antidepressant duration indicates maintenance treatment, which international guidelines recommend for patients with three or more depressive episodes (American Psychiatric Association, 2010).

Strengths and limitations

A strength of the current study is that recruitment of participants took place in various settings (hospitals, midwifery practices, GP's and social media) and detailed information was gathered prospectively, thereby preventing recall bias and providing insight into this specific population across the perinatal period. Moreover, clinical interviews were used to determine (history of) diagnoses throughout study participation instead of relying on self-report.

However, several limitations should be noted. Due to the inclusion and exclusion criteria, only women with recurrence of depression after the first trimester were included, limiting our sample size and thereby potentially the number of recurrences. With these limited numbers, only exploratory analyses could be conducted, and the possibility of confounding variables could not be ruled out. Results will have to be replicated in other studies with larger sample sizes. Other vulnerable groups of women, e.g. women with a history of depressive disorder who discontinue antidepressants before pregnancy, were not observed. In the Netherlands approximately 40% of women discontinue antidepressant treatment in the year before pregnancy and even higher figures are reported in other countries (Charlton et al., 2015). In the current study, women who discontinued antidepressants before pregnancy were excluded. To fully examine safety of antidepressant discontinuation, future studies should also include women discontinuing antidepressants before pregnancy. Yet, the main aim of the current study deliberately was to investigate the effects of continuation and discontinuation of antidepressants specifically during pregnancy. Another limitation is the limited number of women discontinuing their medication. To specifically examine the effect of discontinuation on recurrence rates, it would have been preferential to include more women discontinuing antidepressants, for example by oversampling this group. Lastly, we cannot guarantee generalizability of our results. Out of the 478 women referred for counselling, 248 women declined to participate, without providing a reason

or background information, conforming to common and local ethical procedures. It remains unknown whether these women would have been eligible for participation and, if so, whether they would have differed significantly from our current study population. These women might have differed in their psychiatric history, current symptomatology and treatment management.

Conclusion and future recommendations

The current study presented descriptive data on a prospective cohort of pregnant women with antidepressant use in early pregnancy and a history of depressive disorder. Three vulnerability markers associated with recurrence of depression were identified: Depressive symptoms in early pregnancy, number of current and past psychiatric co-morbidities and duration of antidepressant treatment. Importantly, if future studies can more robustly establish the predictive value of these vulnerability markers, these markers could easily be assessed as part of routine care procedures by clinicians. Implementing adequate and accessible risk assessment in daily practice can lead to improved individualized patient-centred care. No effect of discontinuation of risk of recurrence was observed, however, the proportion of women discontinuing medication was small and results should therefore be interpreted with caution. Future studies should aim to define additional predictors for recurrence of depression in pregnancy, assess the effects of implementing screening instruments during this phase, and to evaluate the effect of treatments in the perinatal period in order to benefit women and (potentially) their offspring (Molenaar et al., 2016; Brouwer et al., 2018).

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Chapter 6

Stop or Go? Preventive cognitive therapy with guided tapering of antidepressants during pregnancy: study protocol of a pragmatic multicentre non-inferiority randomized controlled trial

Based on: **Brouwer M.E.** & Molenaar N.M., Bockting C.L.H., Bonsel G.J., van der Veere C.N., Torij H.W., Hoogendijk W.J., Duvekot J.J., Burger H. & Lambregtse-van den Berg M.P. (2016). Stop or go? Preventive cognitive therapy with guided tapering of antidepressants during pregnancy: study protocol of a pragmatic multicentre non-inferiority randomized controlled trial. *BMC Psychiatry, 16*, 72. doi: 10.1186/s12888-016-0752-6

ABSTRACT

Background

Approximately 6.2% of women in the USA and 3.7% of women in the UK, use Selective Serotonin Reuptake Inhibitors (SSRIs) during their pregnancies because of depression and/or anxiety. In the Netherlands, this prevalence is around 2%. Nonetheless, SSRI use during pregnancy is still controversial. On the one hand SSRIs may be toxic to the intrauterine developing child, while on the other hand relapse or recurrence of depression during pregnancy poses risks for both mother and child. Among patients and professionals there is an urgent need for evidence from randomized studies to make rational decisions regarding continuation or tapering of SSRIs during pregnancy. At present, no such studies exist.

Methods/Design

'Stop or Go' is a pragmatic multicentre randomized non-inferiority trial among 200 pregnant women with a gestational age of less than 16 weeks who use SSRIs without clinically relevant depressive symptoms. Women allocated to the intervention group will receive preventive cognitive therapy with gradual, guided discontinuation of SSRIs under medical management (STOP). Women in the control group will continue the use of SSRIs (GO). Primary outcome will be the (cumulative) incidence of relapse or recurrence of maternal depressive disorder (as assessed by the Structured Clinical Interview for DSM disorders) during pregnancy and up to three months postpartum. Secondary outcomes will be child outcome (neonatal outcomes and psychomotor and behavioural outcomes up to 24 months postpartum), and health-care costs. Total study duration for participants will therefore be 30 months. We specified a non-inferiority margin of 15% difference in relapse risk.

Discussion

This study is the first to investigate the effect of guided tapering of SSRIs with preventive cognitive therapy from early pregnancy onwards as compared to continuation of SSRIs during pregnancy. We will study the effects on both mother and child with a pragmatic approach. Additionally, the study examines cost effectiveness. If non-inferiority of preventive cognitive therapy with guided tapering of SSRIs compared to intended continuation of SSRIs is demonstrated for the primary outcome, this may be the preferential strategy during pregnancy.

Trial registration

Netherlands Trial Register (NTR): NTR4694; registration date: 16-jul-2014

INTRODUCTION

Depressive disorder and anxiety disorders are the primary indications for the use of Selective Serotonin Reuptake Inhibitors (SSRIs). Worldwide, the SSRI prescription rate during pregnancy ranges from 6.2% in the USA (Andrade et al., 2008), to 3.7% in the UK (Charlton et al., 2015). The actual Dutch nationwide estimated use of SSRIs during pregnancy is about two percent (Bakker, Kölling, van den Berg, de Walle, & de Jong van den Berg, 2008; Ververs et al., 2006); while in the Rotterdam area this number is even as high as five percent (Quispel, Schneider, Bonsel, & Lambregtse-van den Berg, 2012). Nonetheless, SSRI use during pregnancy is still controversial. On the one hand SSRIs may be toxic to the intrauterine developing child, while on the other hand, relapse of depression and/or anxiety during pregnancy poses risks for both mother and child (Nederlandse Vereniging voor Obstetrie en Gynaecologie, 2012).

The preventive effect of SSRIs for relapse of depression during pregnancy seems equivocal. One naturalistic study showed a significant increased risk of relapse in pregnant women who discontinued their medication compared to continuing medication (68% vs. 26%), while another naturalistic study showed no clear difference relapse rates of depression (16 % in total) between pregnant women continuing or discontinuing antidepressants (Cohen et al., 2006; Yonkers et al., 2011).

Pregnancy-related complications both exist for women using SSRIs during pregnancy and women with untreated depression/anxiety during pregnancy, posing a dilemma for the treating physician who considers SSRI withdrawal. For example, studies found significantly increased risks for preeclampsia among women who use SSRIs and increased risks for pregnancy-induced hypertension in women with depression/anxiety during pregnancy compared to healthy controls (De Vera & Bérard, 2012; Kurki, Hiilesmaa, Raitasalo, Mattila, & Ylikorkala, 2000).

Whether or not SSRIs are of direct influence on the new-born, both short- and long-term, is another unresolved issue. For example, a recent meta-analysis showed an increased risk for cardiovascular malformations (*RR* = 1.36) and septal heart defects (*RR* = 1.40) with use of SSRIs (Grigoriadis, VonderPorten, Mamisashvili, Roerecke, et al., 2013). These findings were however not supported by a recent Nordic cohort study, which – after a sibling-controlled analysis – found no substantial increase in prevalence of overall cardiac birth defects for any SSRI (*OR* = 0.92) (Furu et al., 2015). Another example of evidence of a potential direct toxic effect is the association of SSRI use with persistent pulmonary hypertension (PPHN) of the neonate. A large cohort study from the Scandinavian national health registers showed a twofold-increased risk of PPHN with exposure later than gestational week 20 (*OR* = 2.1; Kieler et al., 2012). However, this risk appeared more modest (*OR* = 1.51) in a large cohort study from 46 US states (Huybrechts et al., 2015).

Several other effects of SSRIs during pregnancy have been described, such as a higher risk of poor neonatal adaptation (*OR* = 5.07), respiratory distress (*OR* = 2.20), tremors (*OR* = 7.89), preterm delivery and small for gestational age, lower birth weight and lower Apgar scores at one and five minutes after birth (Grigoriadis, VonderPorten, Mamisashvili, Eady, et al., 2013; Ross et al., 2013). Long-term effects on children are less often investigated. One systematic review found an adverse effect on children's motor development but not on emotional or behavioural development (Gentile & Galbally, 2011). Two large studies reported on the association between maternal SSRI use and childhood autism spectrum disorders, but found conflicting results (Croen, Grether, Yoshida, Odouli, & Hendrick, 2011; Hviid, Melbye, & Pasternak, 2013).

On the other hand, leaving depression or anxiety disorders untreated may be hazardous to the unborn child as well. At present, it is well known that children of women who suffered from anxiety or depression during pregnancy have an increased risk of adverse perinatal health outcomes, and behavioural, emotional, cognitive, and motor problems in early childhood (Field, 2011; Talge, Neal, & Glover, 2007). It is also shown that the infant cortisol stress response is altered if the mother suffered from depression during pregnancy (Oberlander et al., 2008). One meta-analysis showed an association of depression during pregnancy with preterm birth and low birth weight (Grote et al., 2010). Another more recent meta-analysis showed that depression during pregnancy is associated with premature delivery, but did not find associations with birth weight, neonatal intensive care unit admissions, preeclampsia, gestational age or Apgar scores (Grigoriadis, VonderPorten, Mamisashvili, Tomlinson, et al., 2013).

Overall, in clinical practice and literature, pregnant women express a strong preference for non-pharmacologic treatment of depression over antidepressant medication (Battle, Salisbury, Schofield, & Ortiz-Hernandez, 2013). Hence, cognitive behavioural therapy (CBT) could be a good alternative for SSRI use during pregnancy. According to a recent meta-analysis there is strong evidence that CBT interventions are effective for preventing depressive relapse during the perinatal period (Sockol, 2015). A recent follow-up study showed that preventive cognitive therapy (PCT) has long-term effects in preventing depressive relapse in patients with recurrent depression for over 5.5 to 10 years after the sessions ended (Bockting et al., 2005, 2015). This preventive psychological strategy therefore seems promising in preventing depressive relapse, presumably also during pregnancy. Moreover, a recent study in the UK among non-pregnant patients showed that tapering antidepressants with therapy was as effective as continuation of antidepressants (Hazard Ratio 0.89; Kuyken et al., 2015). Nevertheless, further investigation is necessary to assess effectiveness of tapering antidepressants with added PCT during the perinatal period.

In conclusion, pregnant women and their clinicians face a dilemma, which is widely experienced in current practice (Ververs, van Dijk, Yousofi, Schobben, & Visser, 2009).

At present, there are no suitable data available to guide evidence-based decisions on SSRI continuation or discontinuation during pregnancy (Hampton, 2006). Both the National Institute for Health and Clinical Excellence in the United Kingdom (NICE) guideline (National Institute for Health and Clinical Excellence, 2014), and American Psychiatric Association (APA; Yonkers et al., 2009) therefore recommend to discuss both possibilities with women. The recently developed Dutch multidisciplinary guideline advises to continue SSRI use during pregnancy, and furthermore advises a hospital delivery and neonatal observation based on the increased risk and the severity of the (rare) condition of PPHN and prevalence (25 to 30%) of children with neonatal abstinence after maternal SSRI use (Levinson-Castiel, Merlob, Linder, Sirota, & Klinger, 2006). Nonetheless, the need of randomized trials was stressed. Indeed, existing studies are observational and therefore their results do not fully allow causal inference nor definite conclusions for practice.

Trial objectives

In this randomized controlled trial (RCT), the effect of preventive cognitive therapy (PCT) with guided tapering of SSRIs in early pregnancy will be compared to continuation of SSRIs during pregnancy. We will study effects on both mother and child with a pragmatic approach. The expectation is that tapering of SSRIs with added PCT does not increase the risk of clinically relevant maternal relapse or recurrence[6] of depression or onset of anxiety disorders during pregnancy up to three months postpartum in excess of (absolute) 15% compared to continuation of SSRIs. If so, discontinuation is deemed non-inferior with regard to relapse/recurrence risk. Furthermore, we expect that tapering of SSRIs is better than continuation of SSRIs with respect to child development. Finally, but not unimportantly, we hypothesize that discontinuation will decrease total costs per woman and child on a 3 months and projected long-term base, assuming no relevant effects of discontinuation on the mother and no effects on the child are found.

METHODS

Design & setting

The Stop or Go study is a pragmatic multi-centre randomized controlled non-inferiority trial (RCT) in obstetric care. Women will be recruited during their first prenatal visit in midwifery practices (first echelon care) and hospitals (second and third

6 Relapse is defined as the re-emergence of depressive symptoms during the remission phase, but before full recovery. Recurrence is defined as the onset of a new depression episode during the recovery phase or long remission phase.

echelons care), or through advertisement in (social) media. After inclusion, women will be randomly allocated into two groups: STOP or GO. Both groups will receive regular assessments throughout their pregnancy and up to three months post-partum. Permission will be asked to contact the Centre of Childhood (CJG) at 24 months after delivery for information on the development of the child. Total duration of the study for participants will therefore be 30 months. In Fig. 1 an overview of the study design and main procedures is shown.

Participants

Women who are less than 16 weeks pregnant and use a SSRI primarily for depressive disorder, and are currently at least in remission or recovered (Bockting, Hollon, Jarrett, Kuyken, & Dobson, 2015), are invited to participate in the trial. Exclusion criteria are multiple pregnancy, as these women have a markedly increased obstetric risk, thereby threatening the homogeneity of the study population and thus potentially complicate the statistical analysis, and insufficient proficiency in Dutch or English, since our intervention is not yet available in other languages. Also, women will be excluded with severe medical conditions, such as oncology-related conditions or conditions that need urgent medical interventions, which involve treatment decisions overriding research participation. Exclusion criteria related to mental health are: current mania or hypomania or a history of bipolar illness, suicidality and serious self-harm, any psychotic disorder (current and previous), current alcohol or drug misuse, predominant anxiety disorders and personality disorders that require psychotherapeutic treatment for more than 2 sessions a month.

Assessment of eligibility

After informed consent is obtained, a pre-assessment interview will be conducted, with the Structured Clinical Interview for DSM-disorders (SCID; First, Spitzer, Gibbon, & Williams, 2002) and the Hamilton Depression Rating Scale (HDRS; Hamilton, 1980) to assess major DSM-IV Axis I psychiatric diagnoses and actual remission status and depressive symptoms respectively. Before randomization, study researchers will contact the medical professional who prescribed the SSRI medication to inform the professional about the study and discuss exclusion criteria as described above for study participation.

Randomisation

Two hundred women will be randomized in a 1:1 allocation ratio to either the intervention arm (STOP) or the care as usual arm (GO). Randomization will be done with a web based computer-generated randomization schedule (a validated TENALEA Clinical Trial Data Management System; http://www.formsvision.com/) using permuted blocks of random size with a maximum of 16 and stratified for the number of previous

depressive episodes (dichotomized). Based on a recent review (Bockting, Hollon, et al., 2015), the participants are divided into groups of participants with 3 or less previous depressive episodes, versus 4 or more. Allocation of participants is concealed for study researchers.

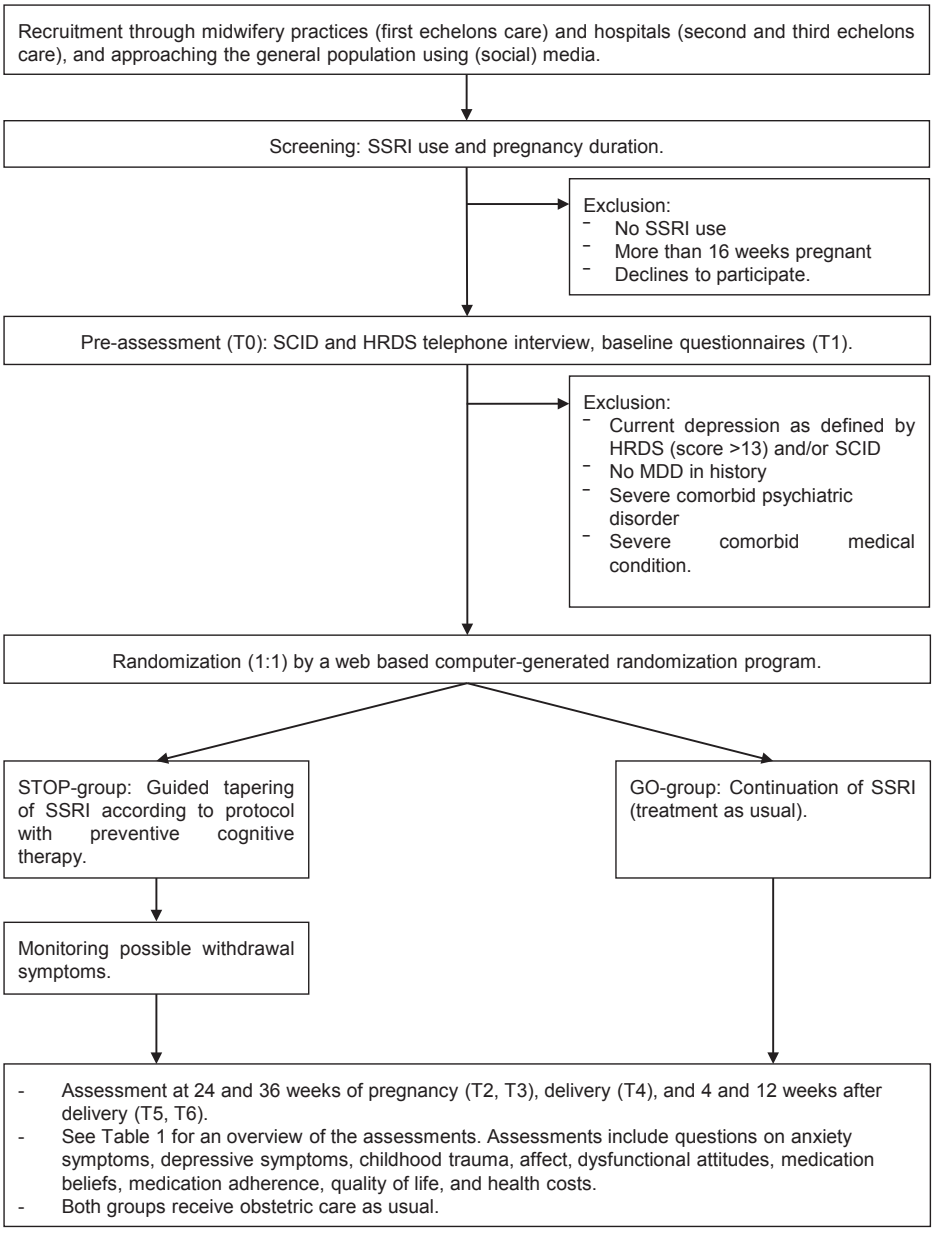

Figure 1. Study flow chart

Interventions

Tapering SSRI. Women assigned to discontinuation of SSRIs will be referred to a psychiatrist trained in guiding tapering of SSRIs during pregnancy. They will plan and carry out SSRI discontinuation using an expert-based discontinuation protocol (Bockting et al., 2011). The aim is to taper the use of SSRIs within four weeks, depending on patient preferences and on drug characteristics (e.g., half-life in the body). There are no restrictions on the use of medication like sleeping pills, paracetamol, and mild tranquillizers. All co-medication will be monitored during the study period.

Preventive cognitive therapy. Trained psychologists will provide preventive cognitive therapy in the discontinuation arm. This psychological intervention has proven to be effective in relapse prevention (Bockting et al., 2005; Bockting, Spinhoven, Wouters, Koeter, & Schene, 2009; Guidi, Fava, Fava, & Papakostas, 2011; Guidi, Tomba, & Fava, 2016; Vittengl, Clark, Dunn, & Jarrett, 2007). The current manual was evaluated in previous studies (Bockting et al., 2005, 2009; Bockting, Elgersma, et al., 2011; Bockting, Kok, et al., 2011).

The intervention will be applied through VSee (http://www.vsee.com), a HIPAA-compliant telehealth app. Several studies demonstrated that psychological intervention as applied by telephone support is effective and there is some evidence that it might be effective to decrease postpartum depressive symptomatology (Bee et al., 2008; Dennis & Kingston, 2008; Kingston et al., 2014; Tina et al., 2013). Although not tested during pregnancy, there are indications that antenatal telephone or online therapy is effective and convenient (Beyondblue, Austin, Highet, & National Health and Medical Research Council (Australia), 2011).

The preventive psychological intervention consists of a minimum of eight weekly VSee sessions. These sessions are led by professional psychologists trained in cognitive behavioural therapy and may occur at any time of the day. The focus of the sessions is on identifying and teaching the participants to challenge dysfunctional beliefs, enhance recall of positive feelings and cognitions and a personal prevention plan is developed in which it is specified how the participant can prevent a depressive episode in the future. For each session the participant will receive some assignments of approximately 10 min per day. Treatment adherence will be monitored.

Care as usual. Women assigned to continuation of SSRIs (GO) obtain usual care. They will be instructed to consult their doctor as they regularly do, in line with the pragmatic nature of the study. All the care that is provided will be monitored.

Outcome measures

Mother. Primary outcome of this trial is (cumulative) incidence of relapse or recurrence of a depressive episode (as defined by the SCID-I; First et al., 2002) during pregnancy and up to 12 weeks postpartum. The SCID-I is assessed at baseline (T0)

and 12 weeks postpartum (T6). If – based on assessment with the HDRS at fixed time-points – relapse/recurrence is suspected, the SCID-I will be performed intermittently.

For registration of severity of depressive symptoms, the HDRS will telephonically be assessed additionally, at baseline (T0), at 36 weeks of gestation (T3), and 12 weeks postpartum (T6), and also intermittently, if necessary (Hamilton, 1980). When the HDRS at any stage turn out above cut-off scores, the participant will be called one week after initial measurement. The HDRS will be repeated to confirm or reject elevated scores. An adjusted telephonic version of the everyday problem checklist (EPCL) and pregnancy related life events will be assessed during each telephonic measurement (T0, T2, T3, T5 and T6).

Women will be asked to fill in questionnaires during five occasions: baseline (T1), 24 and 36 weeks of gestation (T2 and T3), and 4 and 12 weeks postpartum (T5 and T6). The questionnaires differ in composition at the five measurement moments, as shown in Table 1. During these occasions, participants are variably asked to report on anxiety symptoms (Dutch version of the State Trait Anxiety Inventory STAI), short and long version (Rescorla, 2005; Spielberger, 1989), depressive symptoms (the Dutch version of the Edinburgh Postnatal Depressions Scale [EPDS]; Bergink et al., 2011), childhood trauma (Childhood Trauma Questionnaire [CTQ]; Bernstein et al., 2003), affect (the International Short-Form of the Positive and Negative Affect Schedule [I-PANAS-SF]; Thompson, 2007), dysfunctional attitudes (Dysfunctional Attitude Scale [DAS]; Weissman, 1979), medication beliefs (Beliefs about Medicines Questionnaire [BMQ]; Horne, Weinman, & Hankins, 1999), medication adherence (Medication Adherence Rating Scale [MARS]; Horne & Weinman, 1999), and Quality of Life (EQ-5D-5L; Herdman et al., 2011). Socioeconomic position, ethnicity, smoking behaviour, alcohol use, family history and information on previous pregnancies and family size will be assessed using the Mind2Care questionnaire (Quispel et al., 2014), a screen-and-advice instrument to detect mental health problems among pregnant women.

Health care cost data is registered using the TIC-P (Bouwmans et al., 2013). This instrument allows reliable recall over the past six months (van den Brink et al., 2005). We will adapt scoring for 'normal' absenteeism and sickness leave for pregnant and recently delivered women. Care will be taken for secondary effects on child-care for other children (if present) in case of postpartum hospitalisation.

Using the Discontinuation Emergent Signs and Symptoms checklist (DESS; Rosenbaum, Fava, Hoog, Ascroft, & Krebs, 1998), the discontinuation group will be monitored by telephone weekly during tapering, to collect information about dosages and potential symptoms of withdrawal. Both groups will receive telephonic monitoring of medication use, including psychiatric co-medication, at 24 and 36 weeks of gestation (T2 and T3) and 4 and 12 weeks postpartum (T5 and T6).

Alongside the self-report measures, several sources of biological materials will be collected during the study. At baseline, immediately after delivery and 12 weeks postpartum (T1, T4 and T6) we will collect maternal hair strands to measure cortisol levels. Hair cortisol is a validated biomarker for long-term cortisol exposure and makes it possible to create a timeline of cortisol exposure during follow-up (Staufenbiel, Penninx, Spijker, Elzinga, & van Rossum, 2013). At baseline a maternal buccal swab will be collected in order to enable epigenetic and pharmacogenetic analysis. Maternal blood sampling will be performed 12 weeks postpartum (T6) to enable additional epigenetic and pharmacogenetic testing, but also for measurement of SSRI concentration and immunological factors.

Health care professional. We will send a Case Report Form (CRF) to the participant's obstetric caregiver, either a midwife or a gynaecologist, to request information about the pregnancy and delivery. Complications during pregnancy and delivery, such as hypertensive disorders or pregnancy, foetal growth retardation, preterm labour, induced labour and caesarean section will be registered as well as information about the neonate (e.g., Apgar scores, birth weight, congenital malformations and admission to paediatric ward).

Child. At 12 weeks postpartum we will perform a General Movements (GM) assessment by taking video recordings at home (Einspieler & Prechtl, 2005). This assessment method evaluates the function of the young nervous system. GMs are spontaneous movements that are present from early foetal life onwards until the end of the first half-year of life. GMs are complex, occur frequently and last long enough to be observed properly. If the nervous system is impaired, GMs lose their complex and variable character and become monotonous and poor (Zuk, 2011).

For mapping of the SSRI exposure of the new-born, samples of meconium and breast milk (if breastfeeding) will be collected. SSRI in meconium will be measured by a validated method according to LCH guidelines on LC-MS/ MS (European Medicines Agency, 2009). If feasible, hair strands and a buccal swab of the new-born will be collected at 12 weeks after birth (T6).

Long-term follow-up includes the well-established, reliable and valid Child Behaviour Check List 1.5-5 years, including the Caregiver Teacher Report Form (C-TRF) and the Language Development Survey (LDS) at 18 months postpartum (Rescorla, 2005). Also, permission will be asked to obtain routine data from Centres for Childhood (CJG) until 24 months (in particular on length gain, weight gain, normal development, and any information on abnormal behavioural development).

Sample size

Sample size calculation is based on the main aim of this study, which is to demonstrate non-inferiority of preventive CT with guided discontinuation of SSRIs (STOP) compared

Table 1
Assessment per measurement moment.

	Method	T0	T1	T2	T3	T4	T5	T6	T7
Clinical Diagnostic Interview (SCID-I)	Int	X		…	…	…	…	X	
Depressive symptoms (HDRS)	Int	X		…	X	…	…	X	
Peripartum depression (EPDS)	SR		X	X	X		X	X	
Anxiety (STAI)	SR		X	X	X		X	X	
Affect (I-PANAS-SF)	SR		X	X	X		X	X	
Attitudes (DAS)	SR		X	X	X				
Daily hassles	Int	X		X	X		X	X	
Life events	Int	X		X	X		X	X	
Sociodemographic & -economic factors (Mind2Care)	SR		X						
Substance use (Mind2Care)	SR		X	X	X		X	X	
Medication use	Int	X		X	X		X	X	
Medication adherence	SR		X						
Medication beliefs	SR		X						
Childhood trauma (CTQ)	SR			X					
Quality of Life (EQ-5D-5L)	SR		X	X	X		X	X	
Health care consumption (TIC-P)	SR		X		X		X	X	
Pregnancy related outcomes	CG					X			
Neural development (GM)	ME							X	
Child behaviour (CBCL)	SR								X
Cortisol (hair strands)	BM		X			X		X	
Buccal swab	BM		X					X	
Blood sample	BM							X	
Meconium (SSRI concentration)	BM					X			
Breast milk (SSRI concentration)	BM					X			

Note: Int = interview, SR = self-report, CG = caregiver, BM = biological materials, T0 = pre-assessment, T1 = baseline, T2 = 24 weeks of gestation, T3 = 36 weeks of gestation, T4 = delivery, T5 = 4 weeks postpartum, T6 = 12 weeks postpartum, T7 = 18 months postpartum.

to continuation (GO), with respect to relapse or recurrence of a depressive episode up to 3 months postnatal. We will use a non-inferiority margin (tolerance threshold, 'delta') of 15%. This is based on the assumption that this excess relapse (taking into account the possibility of restoring SSRI treatment) is still in balance with the expected beneficial effects of discontinuation of SSRI for the remaining mothers. We also anticipate that this balance is acceptable for women.

With this non-inferiority margin, and the assumption that the overall absolute risk of relapse will be around 15% (Yonkers et al., 2011), we need 178 women, given alpha 0.025, power 80%, and a one-sided test. To account for some attrition, we aim to include 200 women in total. Given this sample size, we have sufficient power to demonstrate small to moderate effect sizes of 0.42 or over on continuous secondary outcomes. With

respect to dichotomous secondary outcomes, we will be able to detect odds ratios of 1.5 or over when the base probability is 0.50.

Statistical analysis

Analysis will primarily be carried out according to the intention-to-treat principle, i.e., the participants will be analysed according to their randomized allocation, regardless of the actual interventions received by the participant. Supplementary, we will perform analyses per protocol, i.e., according to actual SSRI use, irrespective of randomized arm.

The primary outcome, risk (cumulative incidence up to 3 months postnatal) of relapse of depression, will be compared between the randomized groups. Differences will be assessed statistically using a one-sided Chi-Square Test at a significance level of 0.025 and will be presented as a risk difference. The remainder of statistical tests will be performed two-sided at a significance level of 0.05.

Time to relapse will be compared between the randomized groups using survival analysis. Kaplan-Meier curves will be constructed and differences will be tested using the log-rank test. A Cox proportional hazard model will be used to calculate hazard ratios.

Continuous outcomes, e.g., the General Movements scores at 3 months, will be compared between the groups using the unpaired t-test. Categorical secondary outcomes, e.g. obstetric complications, will be tested using Chi-Square Tests. For the continuous variables and categorical variables that are assessed more than twice, we will deploy linear mixed models and generalized linear mixed models respectively. These models use all available data (do not exclude persons with missing values) under the assumption of data being missing at random, and account for within-subject correlation over time. If despite randomization prognostically important factors differ between the groups, they will be adjusted for in supplemental analyses by including these factors in the pertaining regression models.

Subgroup analyses will be undertaken according to: Dutch/non-Dutch, nulliparous/multiparous, yes/no history depressive disorder and/or anxiety disorder, yes/no comorbid anxiety symptoms or disorder. All effect parameters will be supplied with a 95% confidence interval.

Economic evaluation

In the present study we will also evaluate the outcome in the two study groups (Stop and Go) from a societal, economic perspective. It is therefore important to weigh cost savings for both groups against their clinical value. If relapse/recurrence incidence is within the predefined threshold (15%), hence non-inferiority is confirmed; a straightforward cost minimization analysis will be executed focussing on cost savings. However, successful tapering of SSRIs will reduce SSRI use for years. Hence, with a

sensitivity analysis on maternal effects and costs we will project cost estimations for 10 years. We expect that the upfront investment in PCT for women with previous psychiatric disorders will then be balanced by reduced SSRI use and less healthcare consumption. A previous RCT in a non-pregnant population demonstrated that a brief CT intervention is cost effective in remitted depressed individuals that stop antidepressants, compared to continuation of antidepressants (Kuyken et al., 2008).

If, however, relapse/recurrence incidence is higher than the predefined tolerance threshold, thus discontinuation is clinically inferior and rejected, a cost-effectiveness analysis will be executed as primary analysis, which estimates the costs avoided per additional relapse. This is the opposite of the extra costs per prevented relapse, if the starting point would have been no SSRI, and starting SSRI would be considered. Regardless the relapse outcome, we will conduct a cost utility analysis which estimates the impact of SSRI on the costs per Quality Adjusted Life Year (QALY), at least with a 3-month time horizon.

Ethics approval and consent to participate

The Medical Ethical Commission of the Erasmus Medical Centre approved this study. Participants will sign informed consent form before participation.

DISCUSSION

The use of SSRIs during pregnancy remains a clinical dilemma for both clinicians and patients. Given the increase of SSRI use among pregnant women and studies reporting conflicting results (Cohen et al., 2006; Croen et al., 2011; Furu et al., 2015; Grigoriadis, VonderPorten, Mamisashvili, Roerecke, et al., 2013; Huybrechts et al., 2015; Hviid et al., 2013; Kieler et al., 2012; Yonkers et al., 2011), there is dire need of randomized controlled trials investigating the use of SSRIs during pregnancy. This study will be the first to investigate the effect of preventive cognitive therapy with guided tapering of SSRIs from early pregnancy onwards as compared to continuation of SSRIs during pregnancy. Additionally, the study focuses on child outcomes and cost effectiveness.

Previous studies on relapse prevention showed promising results for tapering antidepressants with added relapse prevention (Kuyken et al., 2015). Preventive cognitive therapy moreover showed promising long-term effects in nonpregnant women with a history of depression (Bockting et al., 2005, 2015). Preventive cognitive therapy with guided tapering of antidepressants may therefore be a good alternative for SSRI use during pregnancy.

To our knowledge, no randomized controlled trials have been performed during pregnancy that investigated alternative treatment options versus SSRI use. This may be

the result of the complex ethical situation of studies in pregnant women who are taking SSRIs and must be willing to either taper or continue SSRI use. Logistics of a nationwide randomized controlled trial are also difficult in a multidisciplinary setting. Although a multidisciplinary guideline exists, health care givers still have different views on best practice and therefore give different advices to their patients. This study will therefore be as pragmatic as possible, while still providing the intervention in a protocoled manner.

Results of this study will be published and will contribute to further development of (international) guidelines. The results will provide a first step in giving pregnant women an answer to the question whether it is better to stop or to continue the use of SSRIs during pregnancy.

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Chapter 7

Affect fluctuations during preventive cognitive therapy versus continuation of antidepressants during pregnancy and its effect on offspring: Results from a randomized controlled micro-trial

Based on: **Brouwer, M.E**. & Molenaar, N.M., Burger, H., Williams, A.D., Albers, C.J., Lambregtse-van den Berg & Bockting, C.L.H. Affect fluctuations in pregnant women during preventive cognitive therapy versus continuation of antidepressants and its effect on offspring: Results from a randomized controlled micro-trial. *Under review*.

ABSTRACT

Background

Fluctuations of affect have been linked to an increased risk of recurrence of depression. During pregnancy, affect fluctuations and depression have been linked to various adverse effects in the offspring, including low birth weight. We sought to compare positive and negative affect fluctuations in pregnant women receiving Preventive Cognitive Therapy (PCT) while tapering antidepressant medication (ADM) to pregnant women continuing ADM, and to investigate if affect fluctuations in early pregnancy were related to birth weight.

Method

A Dutch randomized controlled trial (RCT) and prospective observational cohort of women using ADM at the start of pregnancy. In a micro-trial, experience sampling methodology was used during the first eight weeks of participation to assess fluctuations of positive and negative affect. Recurrences of depression were assessed up to 12 weeks postpartum, and birth records were used to assess birth weight.

Results

In total, 146 (44 RCT, 102 cohort) pregnant women using ADM at start of their pregnancy participated. Nineteen women participated in the micro-trial. There were no significant differences in positive and negative affect fluctuations or recurrence rates between women receiving PCT while tapering ADM versus women continuing ADM. We found no association between affect fluctuations and prenatal depressive symptoms and birth weight.

Conclusion

This explorative study showed that tapering antidepressants with the guidance of preventive cognitive therapy may protect a pregnant woman against recurrence of depression and affect fluctuations, without negative effects on birth weight. Subsequent controlled studies on tapering ADM with psychological interventions in pregnant women is highly needed.

INTRODUCTION

Major depressive disorder (MDD) is a highly disabling and recurrent disorder that affects people worldwide, including pregnant women. Prevalence rates of MDD during pregnancy are estimated around 12% (Woody, Ferrari, Siskind, Whiteford, & Harris, 2017). Women with a history of mental disorders may be at increased risk of perinatal depression (Biaggi, Conroy, Pawlby, & Pariante, 2016; Stuart-Parrigon & Stuart, 2014). Reported recurrence rates of MDD *during* pregnancy range widely from 2.5% to 68%, depending on the population, treatment, and follow-up period (Cohen et al., 2006; Ornoy & Koren, 2014; Patton et al., 2015; Yonkers, Vigod, & Ross, 2011). Preventing new episodes of MDD (MDE) is important to help mitigate the adverse effects of the disorder on functioning. This is especially true during pregnancy, since recurrences of depression in this period can place both the women and their unborn children at risk of short- and long-term psychological and somatic problems.

Current preventive treatments of MDD during pregnancy include the use of antidepressant medication (ADM). ADM use during pregnancy is estimated to be around two to eight percent, to treat or prevent various psychiatric disorders including MDD and anxiety disorders (Andrade et al., 2008; Bakker, Kölling, van den Berg, de Walle, & de Jong van den Berg, 2008; Charlton et al., 2015; Ververs et al., 2006). Alternatively, sequentially offering a specific psychological relapse prevention treatment after (partial) remission (i.e. mindfulness-based cognitive therapy [MBCT], preventive cognitive therapy [PCT], wellbeing therapy [WBT]) protects against recurrences of MDD, when compared to active (e.g. ADM or treatment as usual [TAU]) or non-active (waitlist) control groups (Beshai, Dobson, Bockting, & Quigley, 2011; Biesheuvel-Leliefeld et al., 2015; Bockting, Hollon, Jarrett, Kuyken, & Dobson, 2015; Clarke, Mayo-Wilson, Kenny, & Pilling, 2015; Guidi, Fava, Fava, & Papakostas, 2011; Guidi, Tomba, & Fava, 2016; Kuyken et al., 2016; Piet & Hougaard, 2011; Vittengl, Clark, Dunn, & Jarrett, 2007; Vittengl & Jarrett, 2015). Psychological prevention treatments have also been demonstrated to be effective in lowering depressive symptoms during pregnancy (Goodman, Cullum, Dimidjian, River, & Kim, 2018; Sockol, 2015), and may lower the risk of recurrence of MDD (Dimidjian et al., 2016). Which prevention strategy is more effective in preventing recurrences during pregnancy (i.e. ADM or psychological treatment) has, to our knowledge, not yet been studied. However, research conducted in non-pregnant samples has addressed this issue.

A recent study compared the effectiveness of PCT to the use of ADM for prevention of recurrence of depression in a general population of people with a history of MDD (Bockting et al., 2018). In that study, remitted previously depressed people using ADM were randomized to either 1) PCT with ADM, 2) PCT combined with tapering of ADM, or 3) ADM continuation. PCT plus ADM was superior to ADM continuation, and PCT with

tapering of ADM was not superior to ADM continuation in preventing recurrence after recovery of MDD (Bockting et al., 2018). This indicates that preventive psychotherapies may be a viable alternative for individuals who wish to stop taking ADM. Although, the participants that received PCT and tapered ADM had a slightly higher recurrence rate in the first few months compared to the two other groups (Bockting et al., 2018).

Previous research indicates that high variability of affect within an individual may indicate that the individual is prone to depressive relapse or recurrence (Boumparis, Karyotaki, Kleiboer, Hofmann, & Cuijpers, 2016; Wichers et al., 2010; Wichers, Groot, Psychosystems, ESM Group, & EWS Group, 2016). Specifically, low positive affect and high negative affect are thought to be related to increased depressive symptoms, and increased risk of recurrence of MDD (de Jonge et al., 2017; Dunkley et al., 2017; Höhn et al., 2013). On the other hand, a case study and a study in depressed patients (n = 93) showed that the inertia of affect, or the lack of variability, may also serve as a warning that a person may relapse (van de Leemput et al., 2014; Wichers et al., 2016), although this was not confirmed in a recurrently depressed patient sample (n = 42, Slofstra et al., 2018). Overall, the results of the last study were inconclusive whether variability or inertia of affect are a warning sign for the recurrence of MDD. The variability of affect is nevertheless still believed to be clinically relevant, and need further investigation, especially in individuals wanting to taper ADM.

Affect and affect fluctuations are also important to consider in the context of pregnant women and their offspring. Previous studies showed that increased positive affect may prevent preterm birth, although without improving birth weight (Pesonen et al., 2016), and that positive and negative affect fluctuations are associated with poorer offspring outcomes such as disturbed foetal physiology (e.g. decreased foetal heart rate and intrauterine artery flow; Hanley, Rurak, Lim, Brain, & Oberlander, 2014). At the same time, symptoms of depression and anxiety, and stress levels commonly vary throughout pregnancy (Bennett, Einarson, Taddio, Koren, & Einarson, 2004; Mughal et al., 2018; Rallis, Skouteris, McCabe, & Milgrom, 2014), which in turn are associated with negative affect (reported by the mother) in one to seven-year-old children (Glynn et al., 2018) and delayed child development (Mughal et al., 2018). These studies highlight the importance of fluctuations in positive and negative affect and its relation with offspring outcomes. There are therefore two areas of attention in pregnant women with a history of MDD: Affect fluctuations and recurrences of MDD.

The prevention of recurrence of MDD or subsyndromal mood symptoms is not only of importance to the mother as research indicates that the (unborn) child might be affected as well. Maternal depression and anxiety during pregnancy are associated with various negative outcomes for the offspring, including low birth weight and lower gestational age, which in turn are associated with psychopathology at later ages (Madigan et al., 2018; O'Donnell, Glover, Barker, & O'Connor, 2014). It is presumed that

psychological and pharmacological treatment of prenatal common mental disorders can mitigate associated adverse effects in offspring, yet strong evidence for the prophylactic benefits of (preventive) treatment is lacking (Brouwer et al., 2018; Goodman et al., 2018). Systematic reviews have linked the use of ADM during pregnancy as an acute or preventive treatment of depression to negative offspring outcomes, which includes low birth weight, shorter gestation, development of psychopathology, and cardiovascular problems (Grigoriadis et al., 2013; Lupattelli et al., 2018; Ross et al., 2013).

To our knowledge, the question of whether pregnant women receiving PCT while tapering ADM have higher affect fluctuations and/or more recurrences of MDE as compared to pregnant women continuing ADM has not been investigated. Furthermore, it is currently unknown whether affect fluctuations can predict the return of depressive symptoms or recurrence of MDD in pregnant women and predict offspring health (as measured with birth weight and gestational age). The aims of the current study therefore are to 1) explore whether there are more fluctuations in negative and positive affect in pregnant women receiving PCT while tapering ADM versus continuing ADM, 2) explore whether affect fluctuations predict more recurrences and/or prenatal depressive symptoms, and 3) explore whether affect fluctuations predict worse offspring birth outcomes.

METHODS

Participants

This article focuses on an experience sampling methodology (ESM) micro-trial. Participants for the micro-trial were drawn from a randomized controlled trial (RCT; "Stop or Go study") and a prospective, longitudinal, observational cohort, to investigate the effects of Preventive Cognitive Therapy while tapering antidepressant medication versus the continuation of antidepressant medication (Molenaar et al., 2016). The studies were approved by the Medical Ethical Committee of the Erasmus Medical Centre Rotterdam, the Netherlands (MEC-2014-505). All participants provided written informed consent prior to participation.

ESM Micro-trial. Participants from the RCT and observational cohort were invited to participate in the ESM micro-trial after providing written informed consent for the RCT or observational cohort. Participant in-and exclusion criteria and procedures for the RCT and observational cohort are described below. There were no additional criteria to participate in the micro-trial.

RCT and observational cohort. To participate, women needed to 1) be less than 16 weeks pregnant; 2) use an ADM at the start of the pregnancy, such as selective serotonin reuptake inhibitors (SSRI), or selective noradrenaline reuptake inhibitor

(SNRI); 3) and be proficient in Dutch and/or English. Additionally, to participate in the RCT, pregnant women needed to 1) have a history of at least one MDD episode according to the DSM-IV Axis-I (First, Spitzer, Gibbon, & Williams, 2002); 2) be in remission or recovery, i.e. not have a diagnosis of MDD according to the DSM-IV Axis-I criteria since at least four months before participation; and 3) be willing to be randomized to either PCT with tapering of ADM ("Stop") or continuation of ADM ("Go").

Procedure

ESM Micro-trial. All participants of the RCT and observational cohort were invited to participate in the micro-trial. Inclusion for the micro-trial was from August 2016, up to February 2018.[7] The micro-trial started immediately after baseline assessments and (when applicable) randomization of the RCT and observational cohort.

RCT and observational cohort. Participants for the RCT and observational cohort were recruited between April 2015 and February 2018 through various strategies. Pregnant women were recruited during their first prenatal visits at the midwifery practices or hospitals in the Netherlands, through general practitioners, psychiatrists, or through advertisements in (social) media. After study researchers received contact information of potential eligible pregnant women, the study researchers counselled the women about the RCT and the observational cohort. After the counselling and a waiting period to think about participation, pregnant women decided to either 1) not participate; 2) participate in the RCT; or, 3) participate in the observational cohort. After this decision and written informed consent, there was a baseline assessment by means of a structured clinical interview through telephone (SCID-I DSM-IV), and a self-report questionnaire. If participants met inclusion criteria, they were randomized into one of the two groups, or started participation in the observational cohort. Hereafter, women were assessed with questionnaires and interviewed at 24 and 36 weeks of pregnancy, and 4 and 12 weeks after the due-date. See Figure 1 for a flowchart of all studies.

Measurements

A full overview of this schedule and all assessments can be found in the protocol article, Molenaar et al., 2016.

Clinical diagnosis. Absence and history of MDD at the start of, and relapse and recurrence of MDD throughout study participation was assessed with the SCID-I for DSM-IV disorders (First et al., 2002) up to 12-weeks postpartum. Comorbidities on the Axis-I scale were assessed with the SCID-I as well.

7 The micro-study started in a later stage of the studies due to the development and coordination of the mobile application and is therefore not reported in the protocol article (Molenaar et al., 2016).

Experience sampling methodology. The ESM Micro-trial consisted of questions that were sent in the first eight weeks of study participation through the mobile telephone with the use of a pre-installed study application using TEMPEST (Batalas & Markopoulos, 2012). This application was programmed on the participants' own phone, or on a study-smartphone that was available during study participation. It was programmed to send predefined questions five days a week, five times a day, for eight consecutive weeks. The triggers were set semi-randomly between 9:00 AM and 7:00 PM, triggering once every 100 minutes, including a pause of 10 minutes minimum between triggers. The questions consisted of 25 items, including questions regarding positive and negative affect. The questions were derived from previous research (Slofstra et al., 2018) and are based upon the positive and negative affect schedule (PANAS; Watson, Clark, & Tellegen, 1988).[8] Time to complete the questions was one to two minutes. Participants were instructed to respond to the trigger as soon as possible. To monitor reasons for non-response, a student assistant contacted the participants to discuss problems or questions regarding the application.

Assessments. Participants' characteristics were assessed at baseline, including age, parity, and ADM usage. At baseline, and 24- and 36-weeks of pregnancy, the Edinburgh postnatal depression scale (EPDS; Bergink et al., 2011) for depressive symptoms, and the state-trait anxiety inventory (STAI; Marteau & Bekker, 1992) for anxiety symptoms were assessed. The positive and negative affect scale (PANAS; Watson et al., 1988) was used to assess different affective states of the participants at baseline, and 24- and 36-weeks of pregnancy. In addition, birth weight, gestational age and pregnancy-related complications were collected. In the RCT, birth outcomes were obtained from the reports from midwives and gynaecologists. Participants in the cohort provided this information themselves during the four weeks postpartum assessment.

Statistical plan

To explore the affect fluctuations in the first eight weeks of study participation, the ESM micro-trial data was used. An average positive affect and negative affect score was calculated for each reply to the trigger, minimizing the number of separate variables. That way, there was one score for each trigger for both positive and negative affect. To estimate individual affect fluctuations, an individual linear regression equation was calculated using participants' average scores on the positive and negative affect items. For this individual linear regression equation, the dependent variable was the mean affect score for each trigger, and elapsed time was the independent variable. The individual beta coefficient, the coefficient of determination (R^2), and one minus R^2 (as a measure of fluctuations) for both positive and negative affect were saved for each participant and

8 A full overview of the ESM micro-study questions is available upon request.

used in subsequent analyses. The responses and individual regression lines were plotted for each individual, to visually inspect patterns of positive and negative affect fluctuations.

For the analyses, group differences (PCT while tapering ADM versus continuation of ADM) on positive and negative affect fluctuations (ESM micro-trial data), with and without correction for depressive symptoms (assessed with the EPDS), and number of recurrences were analysed with multivariate analysis of variance (MANOVA). Second, three separate linear regression analyses were conducted; to 1) predict depressive symptoms with ESM positive and negative affect fluctuations, 2) predict recurrences with ESM positive and negative affect fluctuations, 3) predict birth weight with ESM positive and negative affect fluctuations corrected for prenatal depressive symptoms. All regression analyses were corrected for number of previous episodes, as this was used to stratify the randomization in the RCT sample and is a known predictor of depressive recurrences (Buckman et al., 2018).

RESULTS

Overall, 478 pregnant women were referred to the studies for counselling. Out of these referrals, 24 women agreed to participate in the ESM Micro-trial. Since the current study focused only on pregnant women using ADM at the start of study participation (who had a singleton pregnancy, a history of MDD, and no current MDD), data from 19 women were available for the analyses. This included 12 RCT participants of whom seven received PCT and tapered the ADM, and four continued ADM usage. Additionally, seven participants from the observational cohort participated in this micro-trial. The overarching trials included 44 participants in the RCT and 155 in the observational cohort. An overview of baseline characteristics is displayed in Table 1, and the study flow-chart is shown in Figure 1. The results of the follow-up measurements are reported in Table 2.

Micro-trial results. There was no significant group effect (RCT women tapering ADM versus RCT women continuing ADM) on positive or negative affect fluctuations (positive affect: $F(1, 9) = 1.85$, $p = 0.20$; negative affect: $F(1 ,9) = 0.44$, $p = 0.52$). When including women from the observational cohort into the micro-trial analyses, this effect between tapering and continuing ADM remained non-significant (positive affect: $F(1, 15) = 0.16$, $p = 0.69$; negative affect: $F(1, 15) = 3.86$, $p = 0.07$). Correcting the analyses for depressive symptoms at baseline did not change the main results (positive affect: $F(1, 14) = 0.21$, $p = 0.65$; negative affect: $F(1, 14) = 3.45$, $p = 0.08$). As an example of the micro-trial outcomes, Figure 2 displays the positive and negative affect scores for a pregnant woman who received PCT and tapered ADM (RCT participant), and a pregnant woman who continued ADM (cohort participant).

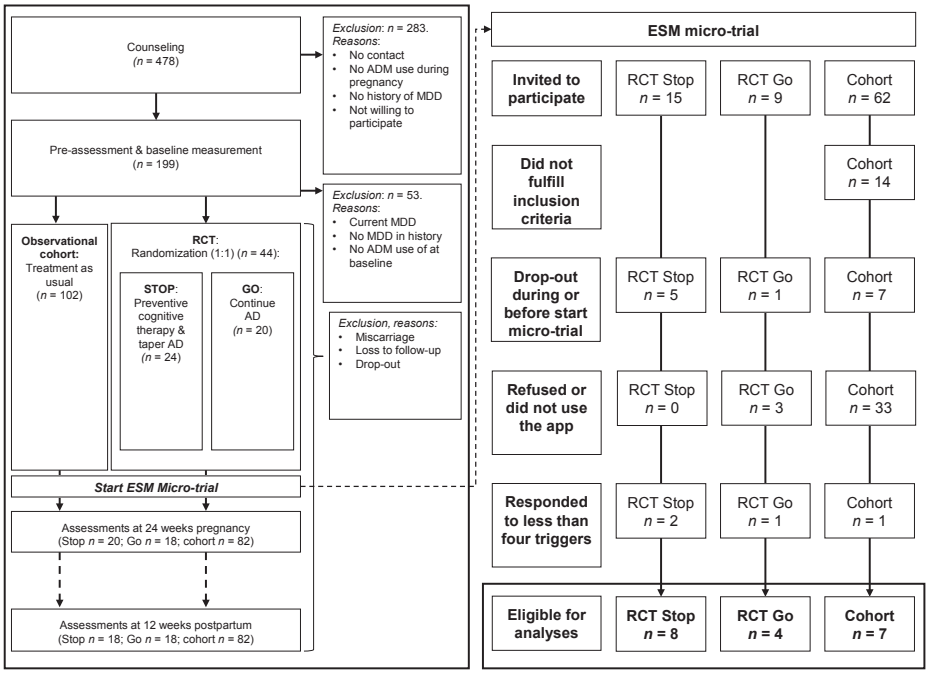

Figure 1. Flow chart of study participation and exclusion (reasons).
Note: RCT = Randomized controlled trial, RCT Stop = RCT group receiving preventive cognitive therapy while tapering ADM, RCT Go = RCT group continuing ADM, ADM = antidepressant medication, ESM = experience sampling methodology.

Recurrence, depressive symptoms, and birth weight. In total, 2 out of 19 women participating in the ESM micro-trial had a recurrence of MDD during the study period. Overall, thirteen women in the two main trials (RCT and observational cohort) had a recurrence of MDD during the study period (8.9 %). The number of recurrences did not significantly differ between the groups in the RCT (PCT with tapering ADM n = 3 versus ADM continuation n = 3), but did in the full group (taper ADM with or without PCT n = 8 versus ADM continuation n = 5; $X^2[1, n = 117] = 8.60$, $p = 0.003$). Linear regression analyses indicated that: 1) Positive or negative affect fluctuations did not significantly predict depressive symptoms at 36 weeks pregnancy (positive affect β = 0.20, 95% CI = –15.63, 34.87, p = 0.43; negative affect β = –0.24, 95% CI = –21.03, 7.86, p = 0.35); and 2) there was no significant relationship between affect fluctuations and birth weight (positive affect β = –0.19, 95% CI = –3,170.41, 2,000.80, p = 0.63; negative affect β = 0.23, 95% CI = –874.67, 2,110.18, p = 0.39) or corrected birth weight for gestational age (positive affect β = 0.10, 95% CI = –135.73, 196.70, p = 0.70; negative affect β = 0.24, 95% CI = –53.51, 138.37, p = 0.36). There was an insufficient number of recurrences in the ESM micro-trial to investigate the relationship between affect fluctuations and recurrences of MDD.

Table 1
Baseline participant characteristics

	RCT Stop (*n* = 24)	**RCT Go** (*n* = 20)	**Cohort** (*n* = 94)	**ESM micro-trial** (*n* = 19)
Mean age in years (*SD*)	31.6 (5.3)	31.4 (4.3)	31.3 (4.3)	32.3 (4.8)
Nulliparous (%)	3 (20)	1 (8)	7 (16)	2 (15)
Born in the Netherlands (%)[a]	22 (100)	14 (87)	89 (99)	18 (100)
Marital status				
Single (%)	1 (4)	1 (5)	3 (3)	1 (5.3)
Partner, living apart (%)	1 (4)	1 (5)	5 (5)	1 (5.3)
Married or cohabiting (%)	22 (92)	17 (89)	86 (91)	17 (89)
Smoking (%)	3 (12)	1 (5)	5 (5)	2 (10)
Education				
Primary school or Secondary education (%)	1 (4)	1 (5)	4 (4)	0 (0)
Vocational or Pre-university education (%)	11 (46)	8 (40)	27 (30)	8 (44)
Higher education (%)	12 (50)	11 (55)	58 (65)	10 (56)
Duration ADM usage, in months (*SD*)	56.0 (50.0)	50.6 (38.0)	72.3 (65.0)	72.9 (59.0)
Number of previous MDD episodes (*SD*)	2.2 (1.2)	1.9 (1.5)	1.9 (1.5)	1.9 (1.0)
Comorbid DSM-IV Axis-I disorders, yes (%)	9 (37)	7 (35)	28 (29)	7 (37)
Mean EPDS score (*SD*)	6.3 (3.6)	4.5 (3.1)	6.5 (4.4)	5.5 (3.3)
Mean STAI score				
STAI – state (*SD*)	34.0 (8.2)	32.6 (7.6)	35.2 (9.5)	33.3 (9.1)
STAI – trait (*SD*)	39.3 (7.1)	35.4 (6.5)	40.4 (9.6)	39.5 (7.8)
Mean PANAS score				
Positive affect (*SD*)	2.0 (0.6)	2.2 (0.7)	2.0 (0.7)	2.1 (0.6)
Negative affect (*SD*)	0.8 (0.7)	0.5 (0.5)	0.9 (0.7)	0.7 (0.7)

Note: Not all information is available for each participant, resulting in small variations of percentages. Numbers are rounded. RCT = Randomized controlled trial, RCT Stop = RCT group receiving preventive cognitive therapy while tapering ADM, RCT Go = RCT group continuing ADM, ADM = antidepressant medication, ESM = experience sampling methodology, HRSD-17 = Hamilton Rating Scale for Depression – 17 items, MDD = major depressive disorder, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders fourth edition, EPDS = Edinburgh postnatal depression scale, STAI = state-trait anxiety inventory, PANAS = positive and negative affect scale. [a] Chi-square indicates significant differences between RCT Stop, RCT Go, and Cohort group (p = 0.02).

DISCUSSION

The aim of the current study was to explore differences in affect fluctuations between pregnant women receiving preventive cognitive therapy while tapering antidepressants and pregnant women continuing antidepressants, where more affect fluctuations and recurrences of MDD were expected in the women tapering ADM. It was furthermore hypothesized that increased positive and negative affect fluctuations would be related to lower birth weight in offspring. Results did not support these hypotheses. There were no indications that pregnant women tapering ADM with PCT showed more affect fluctuations or recurrences than women continuing ADM. Nonetheless, the study

Table 2
Group results follow-up measurements and EMA micro-trial

	RCT Stop (*n* = 19)	**RCT Go** (*n* = 19)	**Cohort** (*n* = 83)
Mean birthweight, in gram (*SD*)	3,632.1 (474.3)	3,369 (422.9)	3,382.6 (463.2)
Mean gestational age, in days (*SD*)	277 (6.9)	275 (5.5)	275 (9.3)
Mean BW for GA, percentile (*SD*)	43.4 (33.7)	41.6 (31.2)	48.2 (29.8)
ESM micro-trial (*n* = 19)	**RCT Stop** (*n* = 8)	**RCT Go** (*n* = 4)	**Cohort** (*n* = 7)
No. of recurrences	1	0	1
Mean number of responses (*SD*)	40.9 (34.4)	19.2 (13.9)	48.9 (27.4)
Positive affect			
B	0.07 (0.31)	0.25 (0.44)	-0.04 (0.12)
R^2	0.09 (0.13)	0.19 (0.12)	0.03 (0.05)
Negative affect			
B	1.06 (3.15)	-0.25 (0.49)	0.10 (0.20)
R^2	0.21 (0.26)	0.11 (0.18)	0.09 (0.13)
Stress	31.79 (14.16)	23.35 (11.65)	25.52 (31.82)

Note: Numbers are rounded. RCT = Randomized controlled trial, RCT Stop = RCT group receiving preventive cognitive therapy while tapering ADM, RCT Go = RCT group continuing ADM, ADM = antidepressant medication, ESM = experience sampling methodology, BW = birthweight, GA = gestational age, Mean BW for GA = birthweight corrected for gestational age.

provides first evidence that preventive therapy while tapering ADM may be a viable alternative to ADM usage for both the remitted pregnant women and their (unborn) child.

This study was the first to show individual fluctuations of positive and negative affect and depression recurrence rates in an RCT and observational cohort of pregnant women using ADM at the start of their pregnancy. Although the study had an explorative nature with a small group of women, nevertheless with a large amount of individual responses, the results of the ESM micro-trial give indication that women receiving PCT while tapering ADM remained stable in positive and negative affect throughout pregnancy. This may be due to the effects of PCT which is designed to support/improve emotion regulation skills (Bockting et al., 2015). As a result, women receiving this preventive psychotherapy did not show increased fluctuations in their affect, thereby potentially lowering the risk of recurrence of MDD.

This is in contrast to a previous study among formerly depressed remitted participants that showed that people receiving PCT while tapering ADM showed a slightly higher risk of recurrence in the first four months of tapering, indicating there may have been an imbalance in these participants due to various reasons (e.g. imbalance such as withdrawal symptoms, or fear of recurrence; Bockting et al., 2018). In the current study, there was no difference in the number of recurrences in the group of women

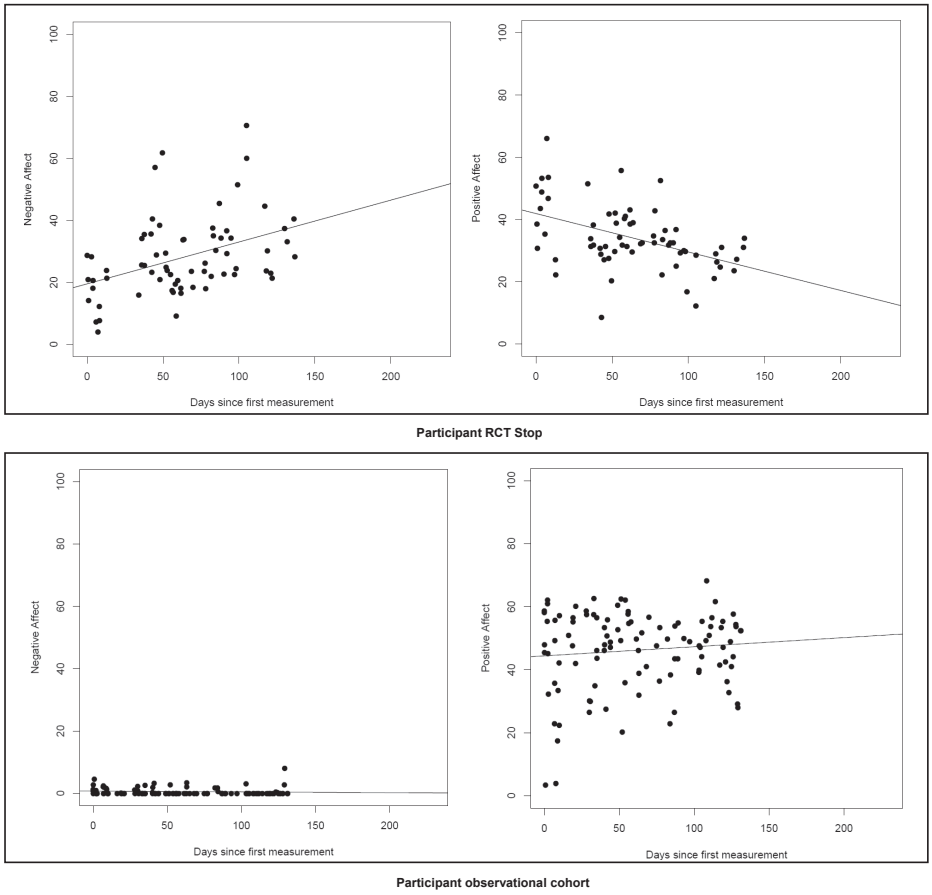

Figure 2. Two participant examples of positive and negative affect fluctuations in the ESM micro-trial

receiving PCT while tapering ADM, implying there was none or less emotional imbalance in this group, such as withdrawal or discontinuation symptoms, or fear of recurrences. The finding of the current study that there were no differences in positive and negative affect fluctuations between the two groups may reflect this lack of imbalance. The absence of significant differences in affect fluctuations may on the other hand reflect a common phenomenon that depressive symptoms and stress vary throughout pregnancy (e.g. Bennett et al., 2004; Rallis et al., 2014), regardless of the prevention strategy. Alternatively, unknown factors caused by the pregnancy itself might have protected the women from fluctuating more in affect while tapering ADM versus continuation of ADM.

Another potential explanation for the absence of significant differences in affect fluctuations between PCT while tapering ADM versus continuation of ADM, may be the low recurrence rates among the participants, with no significant differences in recurrence rates between women receiving PCT while tapering ADM and women continuing ADM.

Previous studies investigating recurrence rates in pregnant women discontinuing ADM are scarce and have produced conflicting results. Although previous research found even lower recurrence rates in a group of pregnant women with a history of MDD (2.5%; Banti et al., 2011), another study showed an increased risk of recurrence after prenatally tapering ADM compared to continuation of ADM (Cohen et al., 2006). Yet another study found comparable recurrence rates in both groups (16%; Yonkers et al., 2011). One of the main differences between these studies is the selection of specific populations using different prevention strategies. For example, the pregnant women from previous studies had a history of more severe MDD and/or more or severe comorbid psychopathology, tapered ADM without guidance or complementary psychotherapy, or were actively seeking help and therefore may have had subsyndromal depressive symptoms for which they needed help. In contrast, the current study focused on the results of the RCT and cohort with stable remitted previously depressed pregnant women. Therefore, previous studies may not be comparable in recurrence rates.

The results furthermore did not indicate that affect fluctuations, with or without correction for depressive symptoms, were related to birth weight. There were also no differences in the birth weight off offspring from women tapering or continuing ADM. Birth weight may already be affected by ADM use in early pregnancy, as previous reviews indicated (Lupattelli et al., 2018). On the other hand, psychotherapy may likewise positively or negatively influence birth weight. A recent meta-analysis found that birth weight could be negatively or positively affected when pregnant women with common mental disorders received psychotherapy, depending on the disorder and type of treatment (Brouwer et al., 2018). The absence of a direct influence of affect fluctuations on birth weight does not necessarily mean that these fluctuations do not affect the offspring. It may be the case that adverse effects are expressed later in life. For example, one study showed that levels of maternal mood symptoms during pregnancy predicted negative affect in the offspring at age one, two, and seven (Glynn et al., 2018), and another study demonstrated that elevated anxiety symptoms increased the risk of offspring having delayed development at the age of three years (Mughal et al., 2018).

Despite several strengths of the current study, being the first study to investigate two preventive strategies in pregnant women using ADM, there were several limitations that need to be addressed. First, the small sample size in the micro-trial prevented us from drawing firm conclusions about the potential role of affect fluctuations. Second, the low recurrence rates and low variation of depressive symptoms throughout pregnancy may have minimized the likelihood of detecting clinically meaningful associations. Lastly, the participant group may have comprised relatively healthy women at low risk of recurrence or return of depressive symptoms.

Overall, the current study and explorative analyses provide some indication that pregnant women do not show more fluctuations in positive/negative affect, nor recurrences, when they taper ADM and receive preventive cognitive therapy compared to when women continue ADM. Pregnant women may not be at increased risk of recurrence when they aim to taper ADM, or put their child at risk of negative outcomes such as lower birth weight. Future research should explore recurrence risk in larger samples and individual pathways of affect fluctuations and MDD recurrence in pregnant women with a history of MDD who use ADM. A first step would be to use ESM in clinical practices, and to monitor treatment effects and individual trajectories among pregnant women. Moreover, the effects and effectiveness of relapse prevention treatments for both mother and child need to be further investigated.

To conclude, the current explorative study showed that tapering antidepressants with the guidance of preventive cognitive therapy may protect a pregnant woman against recurrence of depression and affect fluctuations, without negative effects on birth weight.

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Chapter 8

General discussion

Interventions in the perinatal period may provide a window of opportunity to help women (and men) and mitigate or prevent the negative effects of psychopathology on offspring. On the other hand, pharmacological and psychological treatments for the prenatal common mental disorder may negatively affect offspring as well. Finding this balance in the prevention of transgenerational transmission of common mental disorders is a big challenge. With the use of the proposed transgenerational model of common mental disorders in Figure A as described in the introduction, the aim of the current doctoral dissertation was to investigate the evidence for leading psychological theories of depression (Chapter 2), the use of dysfunctional attitudes as a predictor of depressive relapse (Chapter 3), potential clinical and psychological predictors of depressive relapse during pregnancy (Chapter 5 and 7), and the impact of acute and preventive treatments for prenatal common mental disorders on offspring (Chapter 4 and 6). In this dissertation we aimed to answer main question: What factors lead to the transgenerational transmission of common mental disorders, and can this transmission be prevented? Figure B shows the factors and relations that we could (partly) confirm. In the current chapter, the key findings from this doctoral dissertation are discussed and integrated in the literature, and implications and directions for future research and clinical practice are discussed.

Key findings – Part I

In Chapter 2, evidence for vulnerability factors derived from five leading psychological theories that explain depressive relapse were meta-analysed: The cognitive, diathesis-stress, behavioural, psychodynamic, and personality-based theories. Out of 43,586 published records, only 48 articles were identified out that prospectively assessed depressive relapse through a clinical interview, had a longitudinal and prospective design, established history of depressive episode with a clinical interview, and measured at least one theory-driven vulnerability factor before relapse. A negative attributional style and higher levels of neuroticism were found to predict increased odds of relapse, whereas dysfunctional attitudes were associated to an accelerated time to depressive relapse. We did not identify any study that investigated whether diathesis-stress factors predicted onset of depressive relapse. Even though cognitive and behavioural theories can be perceived as diatheses-stress theories, this diathesis was not studied in combination with stress. There was no significant support that psychodynamic factors predicted onset of depressive relapse. Current evidence for the leading psychological theories of depressive relapse nonetheless remains limited.

The evidence for the cognitive theory was further tested in Chapter 3, by examining dysfunctional attitudes as a predictor of time to depressive relapse in 264 remitted recurrently depressed individuals with low residual depressive symptoms. It was found that remitted recurrently depressed individuals who had a high levels of dysfunctional

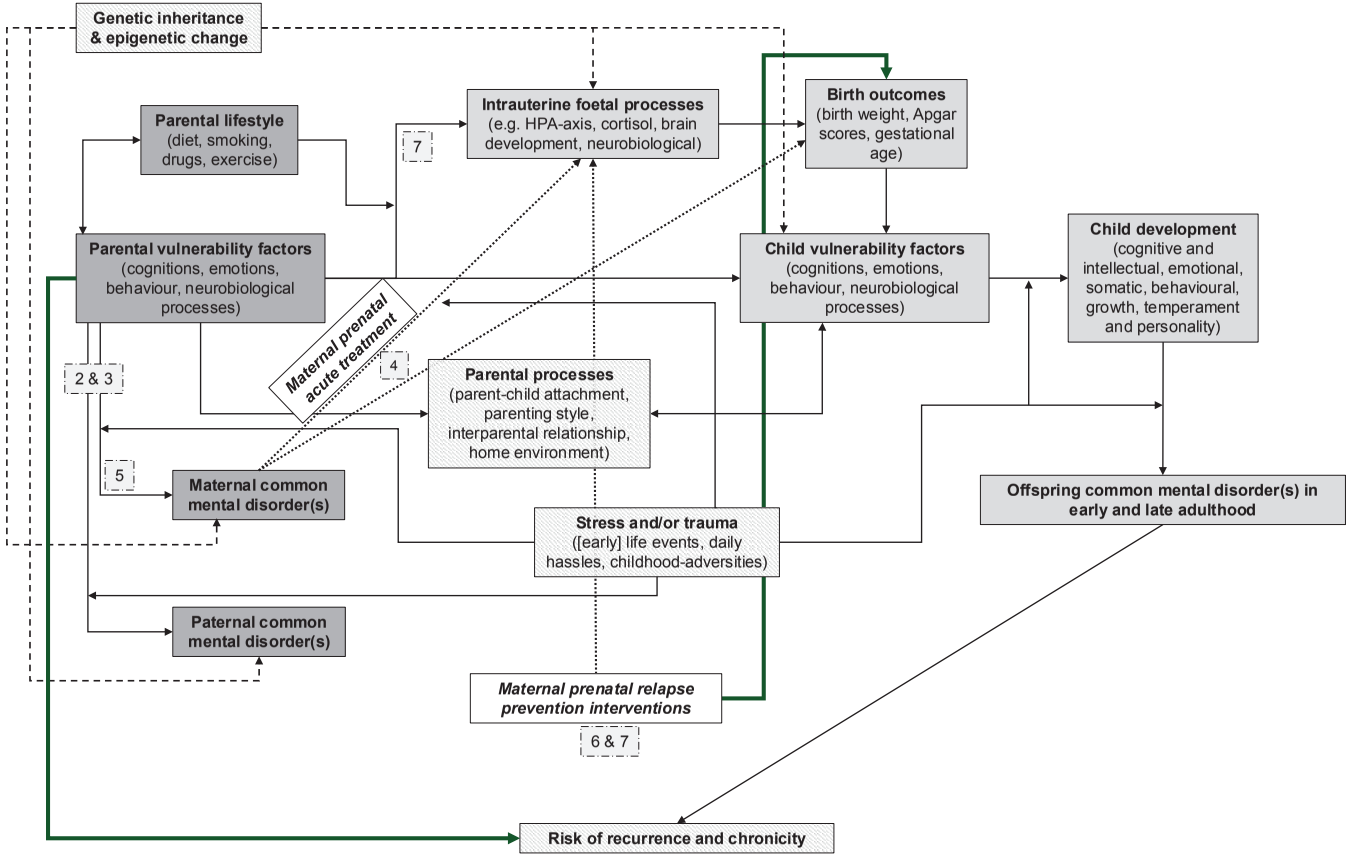

Figure B. Exploration of the transgenerational model for common mental disorders.

Note: Adapted from Stein et al., 2014. Numbers refer to the dissertation chapters where the specific relationships will be investigated. Green thick line refers to the concepts that were (partly) confirmed in this dissertation.

attitudes (DAS; Douma, 1991; Weissman, 1979) relapsed earlier than individuals with a lower levels. Individuals who rated the DAS in a relatively more habitual than functional way were also at increased risk to relapse sooner than individuals who did not. The results from Chapter 3 therefore supports the notion of Chapter 2 that dysfunctional beliefs as specific factor of the cognitive theory (partially) explains depressive relapse.

Key findings – Part II

It is presumed that the negative effects for the offspring of maternal prenatal common mental disorders can be mitigated or even prevented by intervening with either pharmacological, psychological, or other treatments. At the same time, antidepressant medication (ADM) use during pregnancy may pose a child at risk of cardiovascular malformations, preterm birth, lower birth weight, and psychiatric disorders throughout life (for reviews, see Grigoriadis et al., 2013; Huybrechts et al., 2015; Man et al., 2017; Rai et al., 2017; Ross et al., 2013). The meta-analytical review in Chapter 4 (including 2,778 pregnant women with anxiety, depression, and/or posttraumatic stress-disorders), showed that up to now, no randomized controlled trials examined the beneficial nor adverse robust effects of pharmacological treatments for acute common mental disorders on offspring. Where for non-pharmacological interventions for common mental disorders (n = 16), overall no significant beneficial nor adverse robust effects on offspring as measured with birth weight, gestational age, and Apgar scores was found. Long term follow-up assessments of the offspring were often not or inconsistently reported, and could not be analysed.

To explore the effects of prenatal pharmacological treatments as relapse prevention strategy, we first investigated the predictors and recurrence rates of MDD in pregnant women using antidepressant medication (ADM). In Chapter 5, we presented the results of a longitudinal prospective cohort of pregnant women with a history of MDD who used ADM to prevent depressive relapse. Although there was a low number of recurrences in the cohort (9.4%), several clinical prognostic factors could be identified, which may guide health care providers in identifying pregnant women at risk of MDD recurrences. These prognostic factors were residual depressive symptoms in the first months of pregnancy, number of current and past psychiatric co-morbidities, and duration of ADM use. Tapering of ADM (n = 16/85), did not significantly increase the odds of recurrence.

Despite the information from Chapter 4 and 5, and previous studies, the efficacy of ADM as relapse prevention strategy, and the influence of prenatal ADM use on offspring remained unclear. In Chapter 6, a randomized controlled trial was proposed to investigate the impact of Preventive Cognitive Therapy (PCT) and ADM (in particular selective serotonin reuptake inhibitors [SSRIs]) on mother and (unborn) child. The proposed study (*Stop or Go study*) is internationally the first to investigate if remitted formerly depressed pregnant women have comparable recurrence rates when they

receive PCT and taper ADM, as compared to when they continue the ADM. Second, the design allows to explore whether continuation of ADM versus tapering ADM with PCT positively or negatively affect offspring, and explore the cost effectiveness of both relapse prevention strategies.

Chapter 7 reported the results of the micro-trial that was run alongside the Stop or Go study. The results of this proof of principle study indicated that tapering ADM with the guidance of PCT was not associated with more affect fluctuations in the first eight weeks while tapering ADM, and recurrence during pregnancy up to three months postpartum. The fluctuations of affect were not related to negative effects on birth weight or birth weight after correction for gestational age. Collectively, this proof of principle study (micro-trial) in combination with the Stop or Go study, and the prospective observational cohort, provide some indication that remitted pregnant women may not be at increased risk of depressive relapse when they aim to taper ADM. Furthermore, these women do not appear to put their child at risk of negative outcomes such as lower birth weight.

Transgenerational model of common mental disorders

Altogether, Chapters 2 to 7 provide some guidance for transgenerational approaches to prevent common mental disorders. Throughout the dissertation, we used a transgenerational model that was proposed in Figure A in the introduction. The hypothesis that vulnerability factors (dysfunctional attitudes, extreme response style, personality traits, and behavioural activity) are related to depressive relapse, could partly be confirmed. Unfortunately, no prospective study examined the interaction between psychological vulnerability factors and stress (diathesis-stress theories). The influence of ADM during pregnancy on offspring and the exact mechanisms why and how this happens remain unclear. Nonetheless, the results from the dissertation is a first indication that tapering ADM in combination with PCT is safe for mother and child, that is, without negative effects on offspring birth weight and increased risk of depressive relapse. With regard to acute symptoms of depression or anxiety during pregnancy, it is not yet evident whether pharmacological treatments for common mental disorders impact the offspring positively or negatively. Acute prenatal psychological treatments for common mental disorders did not seem to be beneficial or teratogenic for the offspring. The evidence from the current dissertation in support of the transgenerational model depicted in Figure A will be discussed below.

Vulnerability factors and recurrence of depression

To test the transgenerational model in Figure A, we first investigated if theory-derived vulnerability factors were indeed related to depressive relapse. The first part of the dissertation confirmed that the cognitive, behavioural, and personality-based theories (partly) account for the development of new MDEs in individuals with a history

of depressive episodes. The vulnerability factors neuroticism, dysfunctional attitudes, and attributional style, were identified as specific factors that predicted depressive relapse. Chapter 3 confirmed the finding that a higher number of dysfunctional attitudes decreased the time to depressive relapse. Following the idea that dysfunctional attitudes predict depressive relapse, it was theorized that extreme responding to the questionnaires such as the DAS or attributional style questionnaire (ASQ; Peterson et al., 1982) was predictive of relapse. The idea was that this extreme responding reflected a dichotomous, automatic, thinking style that puts an individual at risk of depressive relapse (Teasdale et al., 2001). Chapter 3 and previous studies (Forand & DeRubeis, 2014; Forand et al., 2016) instead imply that the extreme responding reflects an avoidant coping style, or intolerance of ambiguity (e.g. Naemi, Beal, & Payne, 2009).

This dissertation showed that negative personality traits or styles put an individual at risk of depressive relapse. At a minimum, the factors dysfunctional attitudes, neuroticism, and negative attributional style after remission of MDE increase the risk of depressive relapse. Although these concepts originate from the cognitive (Abramson, Seligman, & Teasdale, 1978; Beck & Bredemeier, 2016; Beck, Rush, Shaw, & Emery, 1979) and personality-based theories (Berlanga, Heinze, Torres, Apiquian, & Caballero, 1999; Klein, Kotov, & Bufferd, 2011), the concepts overlap highly. The three vulnerability factors all represent a style or another factor that a person exhibits, which may reflect an overarching vulnerability factor for depressive relapse, either alone or in interaction with or activated by stress (Conway, Slavich, & Hammen, 2015; Monroe & Simons, 1991). Nevertheless, we did not identify any prospective, longitudinal study that investigated the vulnerability factors in combination with stress in patient populations.

In a recent meta-analytical review, Buckman et al. (2018) proposed that residual depressive symptoms after acute treatment, childhood maltreatment, current or past comorbid psychopathology, and rumination may be prognostic (vulnerability factors) and prescriptive risk factors (treatment moderators) of relapse or recurrence of MDD. The idea that residual depressive symptoms and current and past comorbid disorders increased the risk of recurrence, was confirmed in Chapter 5 in a sample of pregnant women. This is consistent with our and previous reviews, that in addition indicated that neuroticism and negative cognitions are related to depressive relapse, which we similarly found in Chapter 2 (Burcusa & Iacono, 2007; Hardeveld et al., 2010; Klein et al., 2011; Monroe & Harkness, 2011). However, in Chapter 5, due to a small number of participants (n = 85), a non-randomized design, and a low number of recurrences in the full sample (n = 8), we could only tentatively indicate which factors were likely to predict recurrence, but not which factors influenced the treatment of ADM during pregnancy. Knowledge of prognostic and prescriptive factors is important in order to 1) identify who is at risk of relapse or recurrence, and 2) know which (relapse prevention) treatment works for whom. In pregnant women, it is furthermore of importance to know the

impact of these two factors on their unborn child. This requires to know which treatment options for common mental disorders and relapse are available to specific individuals, including the impact on the child.

Impact of maternal prenatal interventions on offspring

Within the transgenerational model in Figure A, we furthermore hypothesized that there were two interventions that could potentially prevent the transmission of common mental disorders from parents to offspring. As described previously, prenatal common mental disorders are associated with various negative offspring outcomes. Previous reviews showed that psychological interventions, in particular cognitive behaviour therapy and interpersonal therapy, are beneficial for women with perinatal depression (Cuijpers et al., 2014; National Institute for Health and Clinical Excellence, 2014; O'Connor et al., 2016; van Ravesteyn et al., 2017). The benefits of these therapies for the unborn child, or whether it paradoxically would have an adverse effect on the offspring intrauterine, were unknown.

Consistent with previous reviews, the authors of ten out of 16 included studies in the meta-analysis of Chapter 4 reported that the intervention was effective for the pregnant women in lowering symptoms of the common mental disorders. In contrast, the review provides a first indication that the treatments for common mental disorders do not improve or worsen birth outcomes. Birth weight, Apgar scores, and gestational age, were not significant different in the treatments groups as compared to the control groups. The long-term effects, i.e. the effects on the development of the offspring, could not be meta-analysed. Based on the evidence as reported in Chapter 4, there is no strong indication of prophylactic effects of prenatal interventions on offspring. Most remarkable, but not unexpected, the meta-analysis did not find any RCT that investigated the impact of ADM on offspring.

The use of ADM, in particular SSRIs, during pregnancy has been associated with low birth weight, shorter gestation, lower Apgar scores, developmental problems, and minor cardiovascular problems (Furu et al., 2015; Grigoriadis et al., 2013; Lupattelli et al., 2018; Ross et al., 2013). These associations were largely based upon observational studies so causal inference can be made only very cautiously. The use of SSRIs was, and still is, a clinical dilemma for health care providers and pregnant women. There was a need for RCTs to be able to identify which of the negative offspring outcomes were related to actual ADM use, and which to other, underlying factors, such as maternal psychopathology. ADM is one of the most used treatments for common mental disorders during pregnancy, and clinical guidelines need information from these resources. RCTs and comparative treatment trials are needed to unravel whether the negative offspring outcomes are related to ADM use. An RCT comparing two (relapse prevention) intervention types may provide more information on the prophylactic effects of prenatal

treatment of common mental disorders on offspring. The Stop or Go study, as presented in Chapter 6, was partly designed to investigate this.

Relapse prevention interventions during pregnancy

The design of the Stop or Go study (Chapter 6), was on account of the uncertainty about the impact of ADM use and tapering ADM in combination with PCT during pregnancy on pregnant women and the offspring, and its efficacy of both strategies to protect against depressive relapse in the perinatal period. The international clinical guidelines regarding ADM use during pregnancy are based upon uncertainty, because there was no suitable data from RCTs to guide evidence-based decisions regarding starting, continuing, or tapering ADM (National Institute for Health and Clinical Excellence, 2014; O'Connor et al., 2016).

To advise pregnant women on available relapse prevention interventions (ADM and/or psychotherapy), and to personalize the advice for women based on their vulnerability factors, researchers need to investigate what relapse prevention interventions are safe and effective for the woman and her child. Outside pregnancy, research indicated that it was equally or more effective to receive PCT or mindfulness-based cognitive therapy (MBCT) while tapering ADM versus the continuation of ADM (Bockting et al., 2018; Guidi et al., 2011; Guidi et al., 2016; Kuyken et al., 2015; Segal et al., 2010). In Chapter 7, the micro-study results showed that there were no indications that pregnant women who received PCT while tapering ADM showed more affect fluctuations or recurrences than women continuing ADM.

Although this was an explorative micro-study alongside a larger RCT, the proof of principle study provides first evidence that preventive therapy while tapering ADM may be a viable alternative to ADM use with regard to the mental health of pregnant women who are vulnerable to develop new episodes of depression. Preventive Cognitive Therapy may have improved or helped support emotion regulation skills in pregnant women tapering ADM, which is shown in equal fluctuations of positive and negative affect throughout pregnancy compared to ADM continuation. This may be due to the effects of PCT which is designed to support/improve emotion regulation skills (Bockting, 2009). Alternatively, unknown factors caused by the pregnancy itself may protect the women from fluctuating more in affect while tapering ADM versus continuation of ADM. One approach to disentangle this, is by means of a randomized controlled micro-trial among pregnant women versus non-pregnant women who continue ADM, or receive PCT while they taper ADM.

These results are encouraging, because large fluctuations in affect, or the opposite; inertia of affect (lack of fluctuations), have been identified as early warning signs of depressive relapse, and have been linked to increased depressive symptoms (de Jonge et al., 2017; Dunkley et al., 2017; Höhn et al., 2013; van de Leemput et al., 2014;

Wichers, Groot, Psychosystems, ESM Group, & EWS Group, 2016). Previous research furthermore implied that early warning signs such as prenatal affect fluctuations, and increases in depressive, anxiety, and stress levels, are linked to negative offspring outcomes (Bennett, Einarson, Taddio, Koren, & Einarson, 2004; Glynn et al., 2018; Hanley, Rurak, Lim, Brain, & Oberlander, 2014; Mughal et al., 2018; Rallis, Skouteris, McCabe, & Milgrom, 2014). Increased positive affect may prevent preterm birth, whereas increased negative affect is associated with disturbed foetal physiology such as decreased foetal heart rate (Hanley et al., 2014; Pesonen et al., 2016). It is hence not only important to the pregnant women to recognise early warning signs of depression and prevent relapse, it is of high importance to the unborn child as well.

In the micro-trial in Chapter 7, we exploratively showed that affect fluctuations, with or without correction for depressive symptoms, were not related to birth weight, and that there were no significant differences in birth weight in offspring from women tapering or continuing ADM. One possibility is that birth weight was already affected by ADM use in early pregnancy, as previous reviews indicated (Lupattelli et al., 2018). On the other hand, PCT may also positively or negatively influence birth weight, consistently with what was found in Chapter 4 for acute psychological treatments. Long term follow-up of offspring is needed to investigate if the PCT while tapering ADM, or the continuation of ADM, influence the offspring's (mental) health throughout life. Hopefully, future research will continue to explore transgenerational approaches to prevent common mental disorders.

Strengths and methodological considerations

There are several strengths and limitations of this dissertation that need to be addressed. With regard to the strengths, the systematic reviews and meta-analyses of evidence provided an opportunity to systematically review the evidence for the vulnerability factors derived from psychological theories of depressive relapse and the impact of prenatal treatment for common mental disorders on offspring. These meta-analytic reviews allowed us to include prospective, longitudinal studies, increasing the likelihood that the effect sizes that were found, were most likely due to the intervention or measured vulnerability factor (Chapter 2 and 4). The designs that were used in the dissertation, randomized controlled trials and a micro-trial, enabled us to investigate the impact of treatment on the recurrence of MDD (Chapter 3, 6, 7). Furthermore, the prospective observational cohort in Chapter 5 was based upon clinical interviews to assess current and past psychological disorders, and prospectively followed the pregnant women in their decision to taper or continue using ADM. Furthermore, Chapters 5, 6, 7, specifically included pregnant women who were remitted from MDD, and currently had no diagnosis of MDD. This decreases the chance that (subclinical) depression or psychopathology influenced the findings. The randomised controlled micro-trial design

(Chapter 7) even enabled us to use information from 800 data points across 24 pregnant women, providing detailed information regarding positive and negative daily fluctuations of affect and the return of depressive symptoms or recurrences. Moreover, Chapter 4, 6, and 7 provided first indications whether PCT while tapering ADM may be an alternative to the use of ADM, especially regarding the impact of these interventions on the unborn child. The Stop or Go study is the first tapering study among pregnant women worldwide (Chapter 6). These studies furthermore provided more information regarding the impact of interventions during pregnancy on offspring (Chapters 4 to 7).

On the other hand, some limitations and potential biases need to be noted as well. One of the common issues in epidemiological research is the information bias. The results of Chapter 2, 3, 4, 5, and 7, were partly based upon self-reports, including questionnaires and retrospective interviews to assess history of psychopathology. These kinds of assessment are prone to over-or underreporting and recall bias, which may influence the results (Newport et al., 2008; Patten, 2003; Solhan, Trull, Jahng, & Wood, 2009). As a result of potential relations between vulnerability factors and depressive relapse may have been missed. In Chapter 5, there was a risk of interviewer bias, since the clinical interviews to assess psychopathology were conducted by researchers who were aware of study participation and background information of the women. All women in this prospective cohort used antidepressants at the start of pregnancy and were remitted from MDD. A potential risk is that the interviewers influenced the outcomes, although standardized interviews and protocols were used to conduct the interviews. To minimize bias, the diagnoses of women in Chapter 7 were established by independent assessors who were blinded for treatment allocation. Because Chapter 2 and 4 relied on the input from other RCTs, we cannot rule out that the recall bias or interviewer bias influenced some of the outcomes.

In the trials of Chapter 3, 5, and 7, may have been limited by a selection bias. The participants in these trials may have already been preselected based on their willingness to participate, or by the health care provider who referred the pregnant women in Chapter 5 and 7. Consequently, the trials reported in Chapter 4 may have been influenced by this selection bias as well. Chapter 5 was a prospective, observational, longitudinal cohort that did not allow to make firm causal inferences. Chapters 5 and 7 relied on a small sample of pregnant women with a history of MDD who used ADM at the start of pregnancy with limited precision as a result. In order to be able to investigate the impact of ADM, or the preventive effects of PCT while tapering ADM better, more research including other designs among larger populations of pregnant women is needed.

One of the main considerations in systematic reviews and meta-analyses, is the risk of publication bias or other selection biases. Although in Chapter 4 we tried to reduce this risk by including doctoral dissertations and inspecting the funnel plots and statistics for indications of publication bias. Although there were no such indications,

this may still have affected the results. Reviews furthermore rely on the search terms that are used in selected digital databases, which increases the chance that articles that use different terminologies may have been missed. One of the other considerations is the operationalisation of the psychological theories in Chapter 2. In the reviews of vulnerability factors for depressive relapse, we identified numerous factors that were believed to test the same theories. This operationalisation problem of the psychological approaches diminished the number of vulnerability factors that could be investigated in Chapter 2, and increased the heterogeneity within each approach. This also emphasized the importance of developing falsifiable theories.

Within the identified theory-driven vulnerability factors, a causal relationship between the factors and depressive relapse could not be confirmed with certainty. The sole fact that the vulnerability factor preceded depressive relapse, does not rule out confounding variables or other processes of change. This relates to Chapter 5, where an observational cohort was used to identify predictors of relapse, yet confounding factors could not be ruled out. Results will have to be replicated in other studies with larger sample sizes, or in experimental studies where some variables are actively manipulated. Randomized controlled trials, as the ones proposed in Chapter 6 and 7, would enable to draw such inferences .

Clinical implications

Despite the limitations, this dissertation allows to explore some of the constructs as proposed in the transgenerational model in Figure A. Current international guidelines advise to routinely screen and treat pregnant women with common mental disorders (National Institute for Health and Clinical Excellence, 2014; O'Connor et al., 2016). Despite the focus of international guidelines on the potential teratogenic effects of ADM on the foetus, we can cannot rule out that psychological and other non-pharmacological interventions may as well negatively impact the unborn child. At the same time, it may positively affect the offspring and improve the attachment between mother and child. Due to the lack of well-designed studies with long term follow up assessments, this remains uncertain. Clinicians and policy makers should be hesitant in recommending universal screening for common mental disorders such as depression and anxiety, considering the impact on the offspring is unclear. Although it still important to identify women with severe depressive disorders and/or anxiety disorders. Clinicians, policy makers, and researchers need to balance the potential gains of screening and subsequent treatment of all treatment modalities (including psychological) of prenatal common mental disorders, versus the adverse outcomes for both mother and child.

The dissertation indicates that tapering ADM in combination with PCT may be a viable alternative to the continuation of ADM in remitted pregnant women who wish to stop ADM use as a relapse prevention strategy. However, more research is needed

before clinicians can recommend this as an alternative to ADM. The use of alternative study designs should be explored and used among the difficult-to-reach populations, including the pregnant women. It is of importance to early identify the development of MDD or any common mental disorder among pregnant women. The micro-trial as described in Chapter 7 may be an example of such design. Up till then, with regard to the offspring, health care providers need to be careful in their recommendations in using or tapering ADM or providing psychotherapy in pregnant women with common mental disorders. The use of ADM and psychotherapy might be restricted to severe depression and anxiety disorders in the prenatal period.

Future research

The results presented and described in this doctoral dissertation do not provide enough support to conclude that the transgenerational transmission of common mental disorders can be prevented by intervening before or during pregnancy. Not yet. First, a general recommendation for future research is to internationally cooperate in large consortia. There are many pregnant women in the world, of whom a significant proportion has a common mental disorder and is in need of treatment. However, the traditional RCT design is difficult to conduct among pregnant women with common mental disorders, yet necessary to investigate treatment options for pregnant women with mental health problems. Including pregnant women in RCTs is ethically challenging, and these women are difficult to motivate for participation as they are already overloaded with clinical visits, health checks, and various preparations before the baby arrives. Moreover, since pregnancies last nine months or less, there is a restricted window of time during which pregnant women can be recruited for trials. By cooperating in international consortia, these issues may be resolved to a large extend. In addition, sharing data between research groups across the globe provides more information among larger and diverse populations

Future studies should further investigate the influence of ADM use during pregnancy on offspring. The design described in Chapter 6 is one of the approaches, but there are more options. One such option is to conduct an RCT among pregnant women with depression, with two or more well-supported acute treatments in an RCT, for example ADM versus Cognitive Behavioural Therapy (CBT). Doing so, the effect of ADM on the offspring can be compared to the effect of CBT on offspring. It is ethically challenging to randomize pregnant women to no treatment versus ADM treatment, although this would provide clinicians and researchers a lot of information on the effect of ADM on the offspring. A way to surpass this is by developing computer models or using non-animal lab experiments to model the potential net-effect of ADM on offspring. With regard to psychological interventions, researchers are advised to monitor the impact on offspring as well. As Chapter 4 showed, a lot of the conducted RCT among pregnant

women did not include such outcomes. This includes the long-term effects of acute and relapse prevention interventions on offspring. Therefore, the offspring from women who participated in the trials should be followed for longer durations, if resources allow.

Another recommendation for future research is to compare relapse prevention interventions in pregnant women and women who are trying to conceive. With these two groups of women, future research can identify 1) whether the pregnancy itself protects against relapse, or 2) whether the relapse prevention intervention does. Moreover, based upon prior research and this dissertation, the best timing to taper ADM (and provide PCT), may even be better before conception.

Lastly, with regard to relapse prevention interventions, there may be more interventions that improve or activate positive affect while tapering ADM, as we indicated in Chapter 7. The use of micro-trials, i.e. ecological momentary assessment or experience sampling methodology, allows researchers to investigate dynamics of change and early warning signs of depressive relapse in pregnant women in more depth. The ESM design could also be used in clinical practice. Using ESM in clinical practice permits researchers to investigate fewer pregnant women, while gathering as much information as needed. Lastly, RCTs or alternative studies should include the (expecting) father as well in the prevention of transgenerational transmission of common mental disorders (e.g. Gutierrez-Galve et al., 2018; van der Sluis, van Steensel, & Bögels, 2015). Fathers likewise increase the risk of common mental disorders in offspring, through biological and socio-/psychological processes, including the relationship with the biological mother (as shown in Figure A). Research therefore should include the fathers more often.

Concluding remarks

The present dissertation demonstrated that international guidelines need to be cautious in their recommendation to screening and subsequently treat pregnant women with common mental disorders. We cannot rule out or confirm potential beneficial or adverse effects of antidepressants on the offspring, nor the effects of psychological treatments on offspring. To date there have been no randomized controlled trials conducted that examined whether treating pregnant women with acute depression and/or anxiety disorders with antidepressants are indeed beneficial for their offspring. With regard to prenatal maternal psychological treatments, there have been some randomized controlled trials (n = 16) that investigated the effects of on mother and (unborn) child. However, evidence was inconclusive for the beneficial or adverse effect on the offspring. Keeping in mind that the prevalence rates of mental disorders during pregnancy are estimated as high as 15% for anxiety disorder, and 12% for depressive disorders (Bennett et al., 2004; Dennis, Falah-Hassani, & Shiri, 2017; Woody, Ferrari, Siskind, Whiteford, & Harris, 2017), there is an urgent need to study the impact of prenatal interventions on offspring, especially regarding (long-term) child development.

Potential adverse effects on offspring cannot be ruled out, underscoring the urgent need for controlled trials to better inform clinicians and (expecting) mothers.

For pregnant women who use antidepressants to prevent depressive relapse, preventive cognitive therapy may be an alternative. In our proof of principle study, we found, compared to ADM continuation, no indications that preventive cognitive therapy while tapering antidepressant medication increased the number of recurrences, or negatively affected emotion regulation. Nor did it negatively affect birth weight in the offspring. In addition, the identified vulnerability factors of depressive relapse, some of which originated from the cognitive, behavioural, and personality-based theories, can guide clinicians and researchers to identify who is at risk of depressive relapse, and help improve and personalize existing relapse prevention interventions.

Throughout this dissertation we aimed to answer the main question: What factors lead to the transgenerational transmission of common mental disorders, and can this transmission be prevented? In part 1 we identified several factors that were related to the onset of a subsequent depressive episode (relapse or recurrence), including neuroticism, dysfunctional attitudes, behavioural activity, and attributional style. Evidence remains scarce for the leading psychological theories of depressive relapse. More studies are needed that examine in what way, for whom, and within what time period, factors contribute to depressive relapse. Further, we need to study whether (and how) these factors are transmitted across generations. In part 2 of this dissertation we found that acute prenatal non-pharmacological interventions for maternal common mental disorders on did not mitigate or worsen somatic outcomes in the offspring. Moreover, preventive interventions such as tapering antidepressants with Preventive Cognitive Therapy, are potentially efficacious in lowering the risk of maternal depressive relapse, without negative effects on offspring birth weight. However, more research is warranted to investigate whether these acute and preventive interventions also prevent the transgenerational transmission of common mental disorders.

This dissertation hopefully contributed to getting insight in the impact of prenatal acute pharmacological and psychological treatment for common mental disorders on mother and child, factors that contribute to depressive relapse during pregnancy, and diverse relapse prevention interventions including the effects on offspring. Further exploration of transgenerational approaches to prevent common mental disorders are highly needed.

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English summary

Common mental disorders are a global phenomenon, affecting approximately one out of five people each year. Common mental disorders include anxiety disorders, substance-related disorders, and depressive disorders. During pregnancy, these mental disorders may negatively affect a woman and her unborn child. For example, there is an increased risk that the child develops a common mental disorder in his or her childhood or later in life. Early effective preventive and acute interventions, preferably during pregnancy, are therefore of importance. Interventions during the prenatal period may provide a window of opportunity to help the pregnant woman as well as to prevent the negative effects on her child, including common mental disorders. To prevent the transgenerational transmission of common mental disorders, theories or models are needed that explain this process, and support or improve current preventive and acute treatments. Such a model is displayed in Figure A of the Introduction (this dissertation). This dissertation described parts of the research on this model of transgenerational transmission of common mental disorders.

As shown in Figure A, it is assumed that there are certain vulnerabilities that can lead to mental disorders. In Chapter 2 and 3 we investigated these vulnerabilities from the perspective of five leading psychological theories that aim to account for depressive relapse: The cognitive, behavioural, diathesis-stress, psychodynamic, and personality-related theories. In Chapter 2, a systematic review and meta-analysis was conducted to investigate these theories and related vulnerabilities. Out of 43,586 identified records in scientific databases, we identified 48 articles that met the minimum criteria for causality: Prospective studies that measured the vulnerabilities before depressive relapse. The results of Chapter 2 endorse that the cognitive, behavioural, and personality-related theories indeed partly explain depressive relapse, primarily the factors 'dysfunctional attitudes', 'attributional style', and 'neuroticism'. There was no evidence that psychodynamic theories account for depressive relapse. Remarkably, no articles were identified that examined diathesis-stress theories, despite the fact that multiple theories and treatments of depression are based upon this approach. The evidence for the five leading psychological theories that aim to account for depressive relapse remains restricted.

One of the vulnerabilities derived from Beck's Cognitive Theory of depression was further investigated in Chapter 3. It is assumed that the mere total score on the dysfunctional attitudes' questionnaire is predictive of depressive relapse. On the other hand, it is believed that scoring on the extreme response categories of the questions is predictive of relapse. In Chapter 3 we investigated, among 264 remitted recurrently depressed participants of a randomized controlled study, whether the total score or the extreme score was predictive of the time to depressive relapse. It was found that both factors were predictive: Higher scores on the dysfunctional attitudes' questionnaire, as

well as extreme scores on the questionnaire due to a personal style (versus content-oriented), were predictive of depressive relapse.

In Figure A (Introduction), two potential interventions were described that could potentially mitigate the transgenerational transmission of common mental disorders. The first option is acute treatment during pregnancy in pregnant women with common mental disorders. In Chapter 4 we first described a meta-analysis on the impact of maternal treatments during pregnancy on the offspring. Sixteen randomized studies were found that reported offspring outcomes (birth weight, Apgar score and gestational age) after prenatal maternal interventions for common mental disorders. Despite the common assumption that interventions during pregnancy may prevent adverse effects on the offspring, we found no evidence for this assumption. We likewise found no negative effects of these interventions on offspring. In addition, this meta-analysis showed that, to date, no randomized studies have been conducted on the negative or positive effects of pharmacological treatments (such as antidepressants) for common mental disorders during pregnancy on the baby. Thus far, the available and investigated prenatal interventions for common mental disorders do not seem to prevent transgenerational transmission in the short term. Long-term studies must show whether these treatments are beneficial for the children's long-term development.

A second option to potentially prevent the transgenerational transmission of common mental disorders, is the prevention of (depressive) relapse in pregnant women. In Chapter 5, the results of a prospective observational cohort study were described. In this cohort, recovered pregnant women were followed (n = 85) who took an antidepressant at the start of pregnancy to prevent a subsequent depressive episode. We found that a higher number of depressive symptoms in early pregnancy, longer duration of antidepressant use, and the number of current and past co-morbid psychiatric disorders were related to relapse. Tapering or discontinuation of the antidepressant had no evident impact on the depressive relapse. With regard to Figure A, this indicates that these factors, if replicated, may be important in identifying pregnant women who are at increased risk of depressive relapse.

For remitted pregnant women with the desire to stop taking antidepressant, it is unclear which relapse prevention options are available. Previous research showed that taking antidepressants does not provide a better protection against relapse than tapering antidepressants in combination with Preventive Cognitive Therapy (PCT). However, the effects of tapering antidepressants on the unborn child are not known, nor is it known whether tapering of the antidepressant in combination with PCT likewise protects pregnant women against depressive relapse. For this reason, in Chapter 6, the design of a randomized study was presented: The Stop or Go study. In this study, pregnant women who are recovered from a depressive episode, are taking an antidepressant, and are less than 16 weeks pregnant, will be randomized to either taper the antidepressant

in combination with PCT ('Stop') or continue the use of the antidepressant ('Go'). The main outcome is cumulative time to depressive relapse during pregnancy, up to three months after delivery. In addition, various outcomes are measured, including the effects on the (unborn) child, and cost-effectiveness of both treatments.

In Chapter 7, we showed the exploratory outcomes of a micro-trial that was run alongside the Stop or Go study. Using daily momentary assessments by means of a telephone app, twelve pregnant women of the Stop or Go study (Stop group n = 7; Go group n = 4) tracked their mood several times a day, including positive and negative affect, and daily stress. This app was used in the first eight weeks of study participation, when some pregnant women tapered antidepressants and received PCT, and the other pregnant women continued antidepressants. There were no indications that pregnant women tapering antidepressants with PCT showed more or less positive or negative affect fluctuations than women continuing antidepressants. This is favorable, as fluctuations in affect are considered to be a precursor of depressive relapse. Moreover, in nine months' time, women in the 'Stop' group did not have more depression recurrences than pregnant women in the 'Go' group. The results also indicated that the reduction of antidepressants with the monitoring of PCT did not lead to lower birth weight. This is a first indication that tapering antidepressants in combination with PCT is a potential option for pregnant women who wish to discontinue the use of an antidepressant.

Finally, in Chapter 8, all findings were presented and discussed for some of the transgenerational approaches to prevent common mental disorders. We conclude that there is not sufficient evidence for the prevention of the transgenerational transmission of common mental disorders. Current international guidelines advise to screen and subsequently treating all pregnant women with common mental disorders such as depression and anxiety. This is advised based upon the underlying idea that what works and is good for the pregnant woman, will also prevent or mitigate the negative consequences on the offspring. An advice from the studies in this dissertation is that one should be careful with this recommendation with regard to the offspring. Potential negative consequences for the offspring of antidepressant use and psychological treatments during pregnancy cannot be excluded. This dissertation implies that tapering antidepressants while receiving PCT may as well protect against affect fluctuations and depressive relapse, compared to the continued use of antidepressants, without negatively affecting the baby. In conclusion, in this dissertation we were able to investigate parts of the relationships in a model of transgenerational transmission of common mental disorders. Transgenerational research is crucial to identify target points for interventions to prevent common mental disorders, so that future generations are less burdened by these highly disabling psychological disorders.

Nederlandse samenvatting (Dutch summary)

Psychische stoornissen zijn een wereldwijd fenomeen die 1 op de 5 mensen treft. Veelvoorkomende stoornissen zijn onder andere angst-, en depressieve stoornissen. Deze veelvoorkomende psychische stoornissen kunnen tijdens de zwangerschap zowel de vrouw als haar ongeboren kind negatief beïnvloeden. Er bestaat bijvoorbeeld het risico dat het kind zelf een veelvoorkomende psychische stoornis ontwikkelt in zijn of haar jeugd of op latere leeftijd. Vroege effectieve preventieve en acute interventies, het liefst al tijdens de zwangerschap, zijn daarom zeer belangrijk. Interventies in deze prenatale periode bieden een kans om de zwangere vrouw te helpen alsook het voorkomen van de negatieve effecten op haar kind, waaronder veelvoorkomende psychische stoornissen. Om deze transgenerationele overdracht van veelvoorkomende psychische stoornissen te voorkomen, zijn theorieën of modellen nodig die dit proces verklaren en de huidige preventieve en acute behandelingen kunnen ondersteunen of verbeteren. Dit is modelmatig weergeven in Figuur A van de introductie (dit proefschrift). Delen van het onderzoek naar dit model van transgenerationele overdracht van veelvoorkomende psychische stoornissen werd in dit proefschrift beschreven.

Zoals weergeven in Figuur A wordt verondersteld dat er bepaalde kwetsbaarheden zijn die kunnen leiden tot psychische stoornissen. In Hoofdstuk 2 en 3 onderzochten wij deze kwetsbaarheden vanuit het perspectief van vijf vooraanstaande psychologische theorieën die terugval in depressie achten te verklaren: de cognitieve, gedrags-, diathese-stress, psychodynamische en persoonlijkheid-gerelateerde theorieën. In Hoofdstuk 2 werd een systematische review en meta-analyse uitgevoerd om deze theorieën en gerelateerde kwetsbaarheden te onderzoeken. Uit 43.586 geïdentificeerde artikelen in wetenschappelijke zoekmachines werden 48 artikelen gevonden die voldeden aan de minimale voorwaarde voor causaliteit: prospectief onderzoek welke de kwetsbaarheden gemeten heeft voordat terugval van depressie plaatsvond. De resultaten van Hoofdstuk 2 onderschrijven dat de cognitieve, gedrags- en persoonlijkheid-gerelateerde theorieën de ontwikkeling van depressieve terugval inderdaad deels verklaren, voornamelijk de factoren 'disfunctionele attituden', 'attributie stijl', en 'neuroticisme'. Er werd geen ondersteuning gevonden voor de psychodynamische theorieën in relatie tot depressieve terugval. Opmerkelijk genoeg werden er geen artikelen gevonden die de diathese-stress theorieën onderzocht, ondanks dat deze theorie ten grondslag ligt aan meerdere theorieën en behandelingen voor depressie. Het bewijs dat de vijf leidende psychologische theorieën depressieve terugval verklaren blijft tot op heden beperkt.

Een van de kwetsbaarheden vanuit de cognitieve theorie van Beck werd verder onderzocht in Hoofdstuk 3. Er wordt verondersteld dat de totaalscore op de vragenlijst over disfunctionele attituden voorspellend is voor depressieve terugval. Aan de andere kant wordt er gedacht dat juist het scoren op de extreme antwoordcategorieën van de vragen voorspellend zijn voor terugval. In Hoofdstuk 3 onderzochten wij onder 264 herstelde, recidiverende, depressieve deelnemers van een gerandomiseerde

gecontroleerde studie of de totaalscore of juist het extreem scoren voorspellend was voor de tijd tot depressieve terugval. Er werd gevonden dat beide factoren voorspellend waren: zowel het hoger scoren op de disfunctionele attituden vragenlijst, als extreem scoren op de vragenlijst vanuit een persoonlijke stijl (versus inhoud-gericht), was voorspellend voor depressieve terugval.

In Figuur A (Inleiding) werden verder twee potentiële interventies beschreven die mogelijk de transgenerationele overdracht van veelvoorkomende psychische stoornissen tegen kan gaan. De eerste optie is acute behandelingen tijdens de zwangerschap bij zwangere vrouwen met veelvoorkomende psychische stoornissen. In Hoofdstuk 4 beschreven wij eerst een meta-analyse van de impact van maternale behandelingen tijdens de zwangerschap op de kinderen. Er werden 16 gerandomiseerde studies gevonden naar behandeling van zwangere vrouwen met veelvoorkomende psychische stoornissen waarbij kind uitkomsten (geboortegewicht, Apgar score en zwangerschapsduur) werden gerapporteerd. Ondanks de aanname dat interventies tijdens de zwangerschap nadelige effecten bij het kind kunnen voorkomen, vonden wij geen bewijs voor deze aanname. We vonden ook geen negatieve effecten op het kind. Daarnaast toonde deze meta-analyse aan dat, tot op heden, er geen gerandomiseerde studies zijn gedaan naar de negatieve of positieve effecten van farmacologische behandelingen (zoals antidepressiva) voor veelvoorkomende psychische klachten tijdens de zwangerschap op het kindje. Vooralsnog lijken de beschikbare en onderzochte behandelingen voor veelvoorkomende psychische stoornissen niet de transgenerationele overdracht te voorkomen op de korte termijn. Lange termijn studies moeten uitwijzen of deze behandelingen wel bevorderend zijn voor de ontwikkeling van de kinderen op lange termijn.

Een tweede optie die mogelijk de transgenerationele overdracht van veelvoorkomende psychische stoornissen tegen kan gaan is de preventie van (depressieve) terugval bij zwangere vrouwen. In Hoofdstuk 5 werden de resultaten van een prospectieve observationele cohortstudie beschreven. In dit cohort werden herstelde zwangere vrouwen gevolgd (n = 85) die aan het begin van de zwangerschap een antidepressivum slikten om een volgende depressieve episode te voorkomen. We vonden dat een hoger aantal depressieve symptomen in het begin van de zwangerschap, langere duur van het antidepressivum-gebruik en het aantal huidige en verleden co-morbide psychiatrische stoornissen gerelateerd waren aan terugval. Het afbouwen of staken van het antidepressivum had geen duidelijke invloed op de depressieve terugval. Met betrekking tot Figuur A geeft dit aan dat deze genoemde factoren, mits gerepliceerd, mogelijk belangrijk zijn in het identificeren van zwangere vrouwen die een verhoogd risico hebben voor depressieve terugval.

Voor herstelde zwangere vrouwen met de wens om antidepressivum af te bouwen is het onduidelijke welke terugvalpreventie-optie zij hebben. Voorgaand onderzoek wees uit dat het doorslikken van antidepressiva niet meer bescherming biedt tegen terugval

dan het afbouwen van antidepressiva in combinatie met Preventieve Cognitieve Therapie (PCT). De effecten van het afbouwen van een antidepressivum op het ongeboren kindje zijn echter nog niet bekend, noch is het bekend of het afbouwen van het antidepressivum in combinatie met PCT ook zwangere vrouwen beschermt tegen depressieve terugval. Om deze reden werd in Hoofdstuk 6 het ontwerp van een gerandomiseerde studie gepresenteerd: de Stop or Go studie. In deze studie worden zwangere vrouwen die hersteld zijn van een depressieve episode, antidepressiva slikken en minder dan 16 weken zwanger zijn, gerandomiseerd tot ofwel het begeleid afbouwen van antidepressiva in combinatie met PCT ('Stop'), ofwel het doorslikken van het antidepressivum ('Go'). De hoofduitkomstmaat is cumulatieve tijd tot depressieve terugval tijdens de zwangerschap tot drie maanden na de bevalling. Daarnaast worden diverse uitkomsten gemeten, zoals de effecten op het (ongeboren) kind en de kosteneffectiviteit van beide behandelingen.

In Hoofdstuk 7 laten we de exploratieve uitkomsten zien van een micro-trial die was uitgevoerd tijdens de Stop or Go studie. Met behulp van dagelijkse metingen via een app op de telefoon hielden 12 zwangere vrouwen van de Stop or Go studie (Stop-groep $n = 7$; Go-groep $n = 4$) meerdere malen op de dag bij hoe zij zich voelden. In de app werd gevraagd naar positief en negatief affect en dagelijkse stress. Dit gebeurde in de eerste acht weken van studiedeelname, de periode waarin sommige vrouwen het antidepressivum afbouwden en PCT volgden en andere vrouwen het antidepressivum doorslikten. Het positief en negatief affect van zwangere vrouwen in de 'Stop'-groep fluctueerden niet meer of minder dan het affect van de vrouwen in de 'Go'-groep. Dit is gunstig aangezien fluctuaties in affect wordt beschouwd als een voorloper van depressieve terugval. Ook hadden de vrouwen in de 'Stop'-groep niet vaker een depressieve terugval dan de zwangere vrouwen in de 'Go'-groep over negen maanden tijd. Tevens lieten de resultaten zien dat het afbouwen van antidepressiva met het volgen van PCT niet leidde tot lager geboortegewicht. Dit is een eerste indicatie dat het afbouwen van antidepressiva in combinatie met PCT een mogelijke optie is voor zwangere vrouwen die geen antidepressivum meer willen slikken.

Ten slotte werden in Hoofdstuk 8 alle bevindingen gepresenteerd en bediscussieerd voor enkele transgenerationele benaderingen voor het voorkomen van veelvoorkomende psychische stoornissen. We concluderen dat er niet genoeg bewijzen zijn voor de preventie van de transgenerationele overdracht van veelvoorkomende psychische stoornissen. Huidige internationale richtlijnen adviseren alle zwangere vrouwen te screenen en vervolgens te behandelen voor de veelvoorkomende psychische stoornissen zoals depressie en angst. Dit gebeurt met de onderliggende gedachte dat wat werkt en goed is voor de zwangere vrouw, ook de negatieve gevolgen van de psychische stoornissen voorkomt of vermindert bij de kinderen. Een advies vanuit deze combinatie van studies is dat men voorzichtig moet zijn met deze aanbeveling wat betreft de kinderen. Negatieve gevolgen voor het kind van het gebruik van antidepressiva én van psychologische

behandelingen tijdens de zwangerschap kunnen niet worden uitgesloten. Dit proefschrift impliceert dat PCT bij het afbouwen van antidepressiva mogelijk even goed beschermt tegen fluctuaties van affect en depressieve terugval als het gebruik van antidepressiva, zonder negatieve gevolgen voor de baby. Concluderend hebben we in dit proefschrift enkele relaties in een model van transgenerationele overdracht van veelvoorkomende psychische stoornissen kunnen onderzoeken. Transgenerationeel onderzoek is cruciaal om aangrijpingspunten te vinden waarmee veelvoorkomende psychische stoornissen kunnen worden voorkomen zodat toekomstige generaties minder belast worden met deze belastende psychische stoornissen.

Appendices

APPENDICES CHAPTER 2

Appendix A. List of included studies and references

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Appendix B. Search terms for each theory, Pubmed example only

Search cognitive: relapse/recurrence

((“depressive disorder”[MeSH Terms] OR “depression”[MeSH Terms] OR depression[Title/Abstract] OR depressive[Title/Abstract] OR depressed[Title/Abstract] OR affective[Title/Abstract]) AND (recurrence[Title/Abstract] OR “recurrence”[MeSH Terms] OR recurrent[Title/Abstract] OR relapse[Title/Abstract] OR “recurrence”[MeSH Terms] OR remission[Title/Abstract] OR Predictor [Title/Abstract] OR prognostic [Title/Abstract] OR prescriptive [Title/Abstract] OR mediator [Title/Abstract] OR moderator [Title/Abstract] OR intervening [Title/Abstract])) AND (“cognitive theory” [Title/Abstract] OR “cognitive model”[Title/Abstract] OR “cognitive therapy”[MeSH Terms] OR “cognitive therapy”[Title/Abstract] OR “cognitive intervention” [Title/Abstract] OR cognitive [Title/Abstract] OR hopelessness[Title/Abstract] OR helplessness[Title/Abstract] OR “dual processing”[Title/Abstract] OR “information processing”[Title/Abstract] OR “information processing bias”[Title/Abstract] OR “cognitive bias”[Title/Abstract] OR “cognitive biased”[Title/Abstract] OR “cognitive biases”[Title/Abstract] OR “scar model”[Title/Abstract] OR “scarring”[Title/Abstract] OR “diathesis-stress”[Title/Abstract] OR “attitude”[MeSH Terms] OR “attitude”[Title/Abstract] OR “attitudes”[Title/Abstract] OR “dysfunctional attitude*”[Title/Abstract] OR “dysfunctional belief”[Title/Abstract] OR “self-control”[Title/Abstract])

Search behavioural: relapse/recurrence

((“depressive disorder”[MeSH Terms] OR “depression”[MeSH Terms] OR depression[Title/Abstract] OR depressive[Title/Abstract] OR depressed [Title/Abstract] OR affective[Title/Abstract])

AND

(recurrence[Title/Abstract] OR “recurrence”[MeSH Terms] OR recurrent[Title/Abstract] OR relapse[Title/Abstract] OR “recurrence”[MeSH Terms] OR remission[Title/Abstract] OR Predictor [Title/Abstract] OR prognostic [Title/Abstract] OR prescriptive [Title/Abstract] OR mediator [Title/Abstract] OR moderator [Title/Abstract] OR intervening [Title/Abstract] OR maintenance[Title/Abstract] OR “maintenance”[MeSH Terms] OR resistance[Title/Abstract] OR chronicity[Title/Abstract] OR Persistence[Title/Abstract] OR “Chronic depression”[Title/Abstract] OR “treatment resistant depression”[Title/Abstract]))

AND

(“behavior* theory”[Title/Abstract] OR “behaviour* theory” [Title/Abstract] OR “behavioral model” [Title/Abstract] OR “behavioural model” [Title/Abstract] OR “behavioral intervention” [Title/Abstract] OR “behavioural intervention” [Title/Abstract]

OR "behaviour* therapy"[Title/Abstract] OR "behaviour* therapy"[Title/Abstract] OR "social learning"[Title/Abstract] OR "self-efficacy" [Title/Abstract] OR "observational learning" [Title/Abstract] OR "self-regulation" [Title/Abstract] OR conditioning [Title/Abstract] OR conditioned [Title/Abstract] OR "classical condition*"[Title/Abstract] OR "operant condition*"[Title/Abstract] OR reinforcement [Title/Abstract] OR "learning theory" [Title/Abstract] OR "behavior* activation" [Title/Abstract] OR "behaviour* activation" [Title/Abstract] OR "functional analysis" [Title/Abstract] OR "problem solving" [Title/Abstract] OR "social skills" [Title/Abstract])
AND (Humans[Mesh] AND English[lang]) NOT ("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "review"[All Fields])

Search Psychodynamic: onset and relapse/recurrence

(("depressive disorder"[MeSH Terms] OR "depression"[MeSH Terms] OR depression[Title/Abstract] OR depressive[Title/Abstract] OR depressed[Title/Abstract] OR affective[Title/Abstract]) AND ("attachment anxiety"[Title/Abstract] OR "secure attachment"[Title/Abstract] OR "insecure attachment"[Title/Abstract] OR "avoidant attachment"[Title/Abstract] OR "withdrawn attachment"[Title/Abstract] OR "attachment style"[Title/Abstract] OR "dismissive attachment"[Title/Abstract] OR "object relations"[Title/Abstract] OR "object relational functioning"[Title/Abstract] OR "self object"[Title/Abstract] OR "loved object"[Title/Abstract] OR "self object representations"[Title/Abstract] OR "depressive position"[Title/Abstract] OR "mirroring"[Title/Abstract] OR "twinship"[Title/Abstract] OR "poignant sadness"[Title/Abstract] OR "remorseful guilt"[Title/Abstract] OR "guilt"[Title/Abstract] OR "shame"[Title/Abstract] OR "compromise formation"[Title/Abstract] OR "narcissistic identification"[Title/Abstract] OR psychodynam*[Title/Abstract] OR psychoanal*[Title/Abstract]) AND Humans[Mesh] AND English[lang]) NOT ("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "review"[All Fields])

Search personality: onset and relapse/recurrence

(("depressive disorder"[MeSH Terms] OR "depression"[MeSH Terms] OR depression[Title/Abstract] OR depressive[Title/Abstract] OR depressed[Title/Abstract] OR affective[Title/Abstract])
AND
(recurrence[Title/Abstract] OR "recurrence"[MeSH Terms] OR recurrent[Title/Abstract] OR relapse[Title/Abstract] OR "recurrence"[MeSH Terms] OR remission[Title/Abstract] OR Predictor [Title/Abstract] OR prognostic [Title/Abstract] OR prescriptive [Title/Abstract] OR mediator [Title/Abstract] OR moderator [Title/Abstract] OR intervening [Title/Abstract] OR maintenance[Title/Abstract] OR "maintenance"[MeSH Terms] OR resistance[Title/Abstract] OR chronicity[Title/Abstract] OR Persistence[Title/Abstract]

OR "Chronic depression"[Title/Abstract] OR "treatment resistant depression"[Title/Abstract] OR onset [Title/Abstract] OR "first-ever" [Title/Abstract] OR predictor [Title/Abstract] OR preventi* [Title/Abstract] OR prospective [Title/Abstract] OR risk [Title/Abstract] OR vulnerability[Title/Abstract] OR longitud*[Title/Abstract] OR precipitating [Title/Abstract] OR protective [Title/Abstract] OR resilience[Title/Abstract] OR susceptibility[Title/Abstract] OR epidemiology[Title/Abstract])
AND
(personality[Title/Abstract] OR Eysenck[Title/Abstract] OR Neuroticism[Title/Abstract] OR Psychoticism[Title/Abstract] OR BAS[Title/Abstract] OR FFFS[Title/Abstract] OR BIS[Title/Abstract] OR Big Five[Title/Abstract] OR volatility[Title/Abstract] OR Agreeableness[Title/Abstract] OR "Openness to experience"[Title/Abstract] OR Conscientiousness[Title/Abstract] OR Cloninger[Title/Abstract] OR "Novelty seeking"[Title/Abstract] OR "Harm avoidance"[Title/Abstract] OR Persistence[Title/Abstract] OR "Reward dependence"[Title/Abstract] OR "Self-directedness"[Title/Abstract] OR "Watson & Tellegen"[Title/Abstract] OR Constraint[Title/Abstract]))
AND
(Humans[Mesh] AND English[lang]) NOT ("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "review"[All Fields])
NOT
("eating disorder*"[Title/Abstract] OR ADHD[Title/Abstract] OR pain[Title/Abstract] OR diabetes[Title/Abstract] OR stroke[Title/Abstract] OR dementia[Title/Abstract] OR cardiovascular[Title/Abstract] OR HIV[Title/Abstract] OR AIDS[Title/Abstract])

Search interactions and trauma: onset and relapse/recurrence

("depressive disorder"[MeSH Terms] OR "depression"[MeSH Terms] OR depression[Title/Abstract] OR depressive[Title/Abstract] OR depressed [Title/Abstract] OR affective[Title/Abstract])
AND
(recurrence[Title/Abstract] OR "recurrence"[MeSH Terms] OR recurrent[Title/Abstract] OR relapse[Title/Abstract] OR "recurrence"[MeSH Terms] OR remission[Title/Abstract] OR Predictor [Title/Abstract] OR prognostic [Title/Abstract] OR prescriptive [Title/Abstract] OR mediator [Title/Abstract] OR moderator [Title/Abstract] OR intervening [Title/Abstract] OR maintenance[Title/Abstract] OR "maintenance"[MeSH Terms] OR resistance[Title/Abstract] OR chronicity[Title/Abstract] OR Persistence[Title/Abstract] OR "Chronic depression"[Title/Abstract] OR "treatment resistant depression"[Title/Abstract] OR "TRD"[Title/Abstract] OR onset [Title/Abstract] OR "first-ever" [Title/Abstract] OR predictor [Title/Abstract] OR preventi* [Title/Abstract] OR prospective [Title/Abstract] OR risk [Title/Abstract] OR vulnerability[Title/Abstract] OR longitud*[Title/Abstract] OR precipitating [Title/Abstract] OR protective [Title/Abstract] OR resilience[Title/Abstract]

OR susceptibility[Title/Abstract] OR epidemiology[Title/Abstract] OR "epidemiological" [Title/Abstract])
AND
("predisposition nature" [Title/Abstract] OR "predisposition nurture" [Title/Abstract] OR "diathesis stress"[Title/Abstract] OR "diathesis-stress"[Title/Abstract] OR "diathesis stressor"[Title/Abstract] OR diathesis[Title/Abstract] OR diatheses [Title/Abstract] OR interaction [Title/Abstract] OR "nurture nature" [Title/Abstract] OR "nature/nurture model"[Title/Abstract] OR gene [Title/Abstract] OR SNP [Title/Abstract] OR "single nucleotide polymorphism" [Title/Abstract] OR genetic [Title/Abstract] OR genotype [Title/Abstract] OR 5-HT[Title/Abstract] OR serotonin [Title/Abstract] OR HPA[Title/Abstract] OR cortisol[Title/Abstract] OR "social support" [Title/Abstract] OR coping [Title/Abstract] OR "gene-environment" [Title/Abstract] OR self-esteem [Title/Abstract] OR vulnerab* [Title/Abstract])
AND
("stress/stressor" [Title/Abstract] "stress/trauma" [Title/Abstract] OR "stress/vulnerability" [Title/Abstract] OR "stress/vulnerability stress" [Title/Abstract] OR "stress/death" [Title/Abstract] OR "stress/stressful" [Title/Abstract] OR "stress/stressors" [Title/Abstract] OR "stress/adversity" [Title/Abstract] OR "stress/affect" [Title/Abstract] OR "stress/anxiety/depression" [Title/Abstract] OR "adverse event*" [Title/Abstract] OR trauma[Title/Abstract] OR "life event*" [Title/Abstract] OR "traumatic" [Title/Abstract] OR "bereavement" [Title/Abstract] OR "grief" [Title/Abstract] OR "humiliation" [Title/Abstract] OR "social rejection" [Title/Abstract] or maltreatment [Title/Abstract] OR "childhood trauma" [Title/Abstract] OR "early trauma" [Title/Abstract])
AND
(Humans[Mesh] AND English[lang])
NOT ("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "review"[All Fields])
NOT
("eating disorder*"[Title/Abstract] OR ADHD[Title/Abstract] OR pain[Title/Abstract] OR diabetes[Title/Abstract] OR stroke[Title/Abstract] OR dementia[Title/Abstract] OR cardiovascular[Title/Abstract] OR HIV[Title/Abstract])

Additional search cognitive: onset and relapse/recurrence

("depressive disorder"[MeSH Terms] OR "depression"[MeSH Terms] OR depression[Title/Abstract] OR depressive[Title/Abstract] OR depressed [Title/Abstract] OR affective[Title/Abstract])
AND (recurrence[Title/Abstract] OR "recurrence"[MeSH Terms] OR recurrent[Title/Abstract] OR relapse[Title/Abstract] OR "recurrence"[MeSH Terms] OR remission[Title/Abstract] OR prognostic [Title/Abstract] OR prescriptive [Title/Abstract] OR mediator

[Title/Abstract] OR moderator [Title/Abstract] OR onset [Title/Abstract] OR "first-ever" [Title/Abstract] OR predictor [Title/Abstract] OR preventi* [Title/Abstract] OR prospective [Title/Abstract] OR risk [Title/Abstract] OR vulnerability[Title/Abstract] OR longitud*[Title/Abstract] OR precipitating [Title/Abstract] OR protective [Title/Abstract] OR resilience[Title/Abstract] OR susceptibility[Title/Abstract] OR epidemiology[Title/Abstract] OR maintenance[Title/Abstract] OR "maintenance"[MeSH Terms] OR resistance[Title/Abstract] OR chronicity[Title/Abstract] OR Persistence[Title/Abstract] OR "Chronic depression"[Title/Abstract] OR "treatment resistant depression"[Title/Abstract])

AND (ruminat*[Title/Abstract] OR "repetitive thought"[Title/Abstract] OR "repetitive thinking"[Title/Abstract] OR worry[Title/Abstract] OR persev*[Title/Abstract] OR "intrusive thought"[Title/Abstract] OR "intrusive thinking"[Title/Abstract] OR "negative thought"[Title/Abstract] OR "negative thinking"[Title/Abstract] OR "stress thought"[Title/Abstract] OR "stress thinking"[Title/Abstract] OR "obsessive thought"[Title/Abstract] OR "obsessive thinking"[Title/Abstract] OR "unconscious stress"[Title/Abstract] OR "implicit stress"[Title/Abstract] OR "anticipatory stress"[Title/Abstract] OR "anticipation stress"[Title/Abstract] OR "cognitive intrusion*"[Title/Abstract] OR reflection[Title/Abstract] OR brooding[Title/Abstract] OR "reflect*"[Title/Abstract] OR "self referential thought"[Title/Abstract] OR "counterfactual thinking"[Title/Abstract] OR "mind wandering"[Title/Abstract] OR "post-event processing"[Title/Abstract] OR "habitual negative self-thinking"[Title/Abstract] OR "catastrophizing"[Title/Abstract] OR "automatic thoughts questionnaire"[Title/Abstract] OR "Crandell cognitions inventory"[Title/Abstract] OR "cognitions checklist"[Title/Abstract] OR "cognitive style test"[Title/Abstract] OR "sociotropy-autonomy scale"[Title/Abstract] OR attribution[Title/Abstract] OR schema[Title/Abstract] OR "automatic thoughts"[Title/Abstract] OR "depressive realism"[Title/Abstract] OR "illusion of control"[Title/Abstract] OR "cognitive distortion"[Title/Abstract] OR "judgment of contingency"[Title/Abstract] OR "attentional bias"[Title/Abstract] OR "response styles theory"[Title/Abstract] OR preoccupation[Title/Abstract] OR "self-focus"[Title/Abstract] OR "self-focused attention"[Title/Abstract] OR "emotion regulation" OR "coping strategy"[Title/Abstract] OR "coping style"[Title/Abstract] OR metacognit*[Title/Abstract])

AND (Humans[Mesh] AND English[lang]) NOT ("review"[Publication Type] OR "review literature as topic"[MeSH Terms])

APPENDIX CHAPTER 3

Appendix A. Models and hypotheses

The series of models and hypotheses are as follows. Model 1 is the main (baseline) model. Model 2 tests the standard DAS score in order to test the hypothesis that the score on the DAS predicts depressive relapse/recurrence. Model 3 tests the DAS score in conjunction with Style-PER (higher score indicating high levels of style responses). Controlling for this variable will improve the ability of the DAS to predict relapse/recurrence, given that Style-PER is intended to reflect unhealthy responding to the DAS, but given that they are positive, they contribute to lower (ostensibly more functional) DAS scores. In Model 4 the DAS score is tested in conjunction with Content-PER (higher score indicating high levels of content responses). It was hypothesized that the inclusion of this variable in the model will reduce the significance of the DAS total score in predicting relapse/recurrence since Content-PER, like the overall DAS score, is intended to reflect healthy responding to the DAS. In Model 5 we test the PER-T (the shared variance of the style and content items) and S/C PER (the unshared variance). The hypothesis was that higher S/C PER scores, indicating greater relative style versus content responses, will predict an increased rate of relapse/recurrence.

Post-hoc testing procedure

The post-hoc procedure consisted of the following steps: Subtract the total number of content-PERs and from the total number of style-PERs, such that high positive scores represent a preponderance of style-PER, relative to content-PER, and high negative scores reflect a preponderance of content-PER relative to style-PER. Multiply this number by 10, and add it to the original DAS score. Insofar as content responses are "good" and style responses are "bad," this method will tend to increase (worsen) the DAS score for those with a preponderance of style responses and decrease (improve) the DAS score for those with a preponderance of content scores. It will have little or no effect on the scores of patients who either gave no PER responses, or who gave a similar number of content and style PERs. In this way, the influences of the two types of positive extreme responding are combined with the standard DAS score. The DAS-S/C variable was added in a separate Cox regression model together with baseline Model 1.

APPENDIX CHAPTER 4

Appendix A. Search terms, Pubmed example only

((((((((((((((((((((((Pregnancy[MeSH Terms]) OR peripartum period[MeSH Terms]) OR pregnancy[Title/Abstract]) OR pregnancies[Title/Abstract]) OR pregnant[Title/Abstract]) OR perinatal[Title/Abstract]) OR peripartum[Title/Abstract]) OR prenatal[Title/Abstract]) OR prepartum[Title/Abstract]) OR antenatal[Title/Abstract]) OR antepartum[Title/Abstract]) OR postnatal[Title/Abstract]) OR postpartum[Title/Abstract]) OR post-partum[Title/Abstract]) OR trimester[Title/Abstract]))))

And

(((((((((((((((((((((((((“Depression”[Mesh]) OR “Depressive Disorder”[Mesh]) OR “Mood Disorders”[Mesh]) OR “Anxiety Disorders”[Mesh]) OR “Anxiety”[Mesh]) OR (“Trauma and Stressor Related Disorders”[Mesh])) OR depress*[Title/Abstract]) OR mood[Title/Abstract]) OR dysthym*[Title/Abstract]) OR “seasonal affective”[Title/Abstract]) OR anxiety[Title/Abstract]) OR anxious[Title/Abstract]) OR agoraphobi*[Title/Abstract]) OR obsessive-compulsive[Title/Abstract]) OR disorder*[Title/Abstract]) OR hoarding[Title/Abstract]) OR panic[Title/Abstract]) OR phobic[Title/Abstract]) OR adjustment[Title/Abstract]) OR stress[Title/Abstract]) OR posttraumatic[Title/Abstract]) OR post-traumatic[Title/Abstract]) OR “combat disorder”[Title/Abstract]) OR generalized anxiety[Title/Abstract]))))

And

((Psychotherapy[MeSH Terms]) OR Drug therapy[MeSH Terms]) OR Mental health services[MeSH Terms]) OR Psychiatric somatic therapies[MeSH Terms]) OR Psychopharmacology[MeSH Terms]) OR Complementary therapies[MeSH Terms]) OR Perinatal care[MeSH Terms]) OR Maternal health services[MeSH Terms]) OR Psychotropic drugs[MeSH Terms]) OR Neurotransmitter uptake inhibitors[MeSH Terms]) OR Monoamine oxidase inhibitors[MeSH Terms]) OR Benzodiazepines[MeSH Terms]) OR Dibenzazepines[MeSH Terms]) OR Amoxapine[MeSH Terms]) OR Amitriptyline[MeSH Terms]) OR Bupropion[MeSH Terms]) OR Buspirone[MeSH Terms]) OR Citalopram[MeSH Terms]) OR Chlormezanone[MeSH Terms]) OR Clomipramine[MeSH Terms]) OR Clorgyline[MeSH Terms]) OR Desipramine[MeSH Terms]) OR Desvenlafaxine succinate[MeSH Terms]) OR Dothiepin[MeSH Terms]) OR Doxepin[MeSH Terms]) OR fluoxetine[MeSH Terms]) OR Flunitrazepam[MeSH Terms]) OR Fluvoxamine[MeSH Terms]) OR Iprindole[MeSH Terms]) OR Iproniazid[MeSH Terms]) OR isocarboxazid[MeSH Terms]) OR maprotiline[MeSH Terms]) OR meprobamate[MeSH

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And

((((((((((infant[MeSH Terms]) OR child[MeSH Terms]) OR adolescent[MeSH Terms]) OR adult child[MeSH Terms]) OR offspring) OR baby*) OR babie*) OR newborn*) OR infant*) OR toddler*) OR child*) OR adolescent*))

And

((((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])))

Dankwoord

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About the author

Maria Elisabeth (Marlies) Brouwer was born on 27 May 1988 in Schiedam, the Netherlands. She grew up in Vlaardingen and graduated high school in 2006. In 2008 she decided to study Clinical Psychology at the Erasmus University Rotterdam. Here she discovered her interest in research and clinical work, and worked for several research projects during the Bachelor program. In 2011 she started the Research Master Clinical and Health Psychology and the Master Clinical Psychology at Leiden University. At the same time, she stayed involved in the Advanced Research Program at Erasmus University Rotterdam, where she completed her Master thesis. After obtaining her Research Master's degree in 2014, she first started working at Leiden University as a research assistant. Soon after, in September 2014, she started her PhD project ('Stop or Go study') at the University of Utrecht. During her PhD, Marlies -among other things- presented her research at international and national conferences, was a student member of the educational committee of the Experimental Psychopathology graduate school, supervised Bachelor and Master students, and organised various workshops and symposia. As of December 2017, she continued her PhD at Amsterdam UMC, location AMC, psychiatry department. Here she started working as a project coordinator of a psychiatric outpatient centre for young adults with affective disorders ('Transitiecentrum Affectieve Stoornissen'). In April 2019, Marlies started her clinical training to become a mental health care psychologist (GZ-psycholoog) at Amsterdam UMC, location AMC, where she will also continue her career in research.

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