Cognitive reactivity as a predictor of first depression onset

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Master Thesis

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Abstract

Background: Previous research has shown that cognitive reactivity predicts first onsets of depression over a two-year period. Its predictive power over longer periods is unknown.

Aim: To investigate the predictive power of cognitive reactivity on first depression onset over a span of six years. Secondly, to explore the possible moderating role of anxiety disorder diagnosis at baseline.

Design and methods: In a longitudinal prospective design, 719 never-depressed individuals were observed over a span of two, four, and six years. Cognitive reactivity was measured using the Leiden Index of Depression Sensitivity-Revised (LEIDS-R) (Van der Does & Williams, 2003) self-report scale. Using multivariate binary logistic regression, the prognostic value of the LEIDS-R scores for first depression onset were tested against several background variables and established risk factors of depression. Analyses were repeated in high- and low-risk groups.

Results*:* The analyses of the whole sample and the lower risk sample showed that cognitive reactivity was associated with the incidence of first depression onset over a span of two- and six years. In the higher risk sample, cognitive reactivity was not a significant predictor for depression incidence over a span of two years, but it was over a span of six years.

Conclusion**:** The outcomes of the present research suggest that cognitive reactivity is a strong predictor for first depression onset over a six-year period, both in high- and low-risk groups. These findings emphasize the need for further research on this relationship.

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I Introduction

1.1 Major Depressive Disorder

Major depressive disorder (MDD) is a highly prevalent mental health disorder (Hasin et al., 2018), and one of the leading causes of the global disease burden (Ferrari et al., 2013). Diagnostic criteria include the presence of a persistent, depressed mood, decreased interest or pleasure in activities, changes in sleep or weight, and feelings of worthlessness, amongst others (American Psychiatric Association, 2013). In over half of the cases, MDD co-occurs with at least one other psychiatric disorder, and its comorbidity with anxiety disorders is the most common one (Ter Meulen et al., 2021).

The course of MDD varies widely, with research suggesting that in about half of the cases, the disorder occurs in the form of a single depressive episode. However, 15% of individuals who experience a first-onset depressive episode do not achieve remission, 35% suffer from at least one recurrent episode after remission (Eaton et al., 2008), and another 20-30% of persons will develop a chronic depressive disorder (Schramm et al., 2020). Consequently, risk factors for depression recurrence and relapse have been studied increasingly over the past few decades. Most commonly, a history of childhood maltreatment, residual depressive symptoms at the end of treatment, and the presence of a previous recurrence have been identified as the strongest prognostic risk factors for recurrence and relapse (Buckman et al., 2018).

Even though risk factors for first depression onset have not been investigated to the same extent (Fu et al., 2021; Toenders et al., 2019), quite a few have been established, e.g., childhood abuse or negative life events (Schaakxs et al., 2017). The aetiology of depression can be explained through different psychological theories. Numerous studies focusing on cognitive theories present evidence suggesting that distinct cognitive vulnerabilities, e.g., cognitive reactivity, may predict first depression onset (Fu et al., 2021; Huang et al., 2021; Kruijt et al., 2013; Struijs et al., 2021).

1.2 Cognitive Reactivity

To properly understand cognitive reactivity (CR), one must first grasp the fundamental concept on which the majority of cognitive theories of depression are built upon. This concept

originates from Beck's (1967) cognitive model of depression (Scher et al., 2005). It states that, based on experiences during an individual's early childhood, cognitive structures, named schemas, are formed. Schemas are belief systems that guide attention, information processing, and memory recollection. According to Beck's theory, schemas can be latent, until they are activated by a life event that resembles the childhood experience which led to the formation of the schema in the first place (Beck & Alford, 1967). This process increases a person's cognitive vulnerability to depression, if the activated schema contains dysfunctional, depressive cognitions, which are characterized by a negative bias, self-devaluation, and hopelessness (Kovacs & Beck, 1978).

Complementary to Beck's assumption that dormant, depressive schemas can be activated by stressful life events, Teasdale's (1988) differential activation hypothesis proposes that depressive schemas can also be activated by dysphoric mood states – even relatively mild states of dysphoria. The extent to which such dysfunctional cognitions become activated by mild states of dysphoria is referred to as CR (Ingram et al., 1998). An individual's CR levels can be measured by using two different methods. Initially, researchers solely relied on mood challenge paradigms, in which participants' dysfunctional cognitions are assessed before and after an induction of sad mood. Alternatively, CR can be measured by asking participants to take a few moments to imagine that they are in a sad mood, and then indicate on a self-report scale how their thinking changes during dysphoric as compared to normal mood states (Raes et al., 2009).

1.3 Depression & Cognitive Reactivity

Research investigating the role of CR in the course of MDD has yielded several important findings. For instance, remitted-depressed individuals have been found to have higher CR levels than never-depressed individuals (Jeanne et al., 1998; Merens et al., 2008; Miranda & Persons, 1988; Segal et al., 1999; Van der Does, 2002, 2005). Similarly, the CR scores of people who are in remission from multiple depressive episodes are higher than they are of those who are in remission from only a single depressive episode (Elgersma et al., 2013). Persons who are in remission from a suicidal depressive episode show patterns in their CR scores that reflect higher levels of hopelessness than the scores of persons in remission from a non-suicidal episode do (Antypa et al., 2010). Furthermore, findings suggest that higher levels of CR during depression remission correlate with faster depression recurrence (Figueroa et al., 2015; Segal

et al., 1999; Segal et al., 2006) and they are also associated with depression chronicity (Struijs et al., 2018; Wiersma et al., 2011).

According to Teasdale's (1988) differential activation hypothesis, the relationship between CR and depression recurrence and relapse may be due to the association between the depressed mood and depressive cognitions that someone forms while experiencing a depressive episode. Even though both mood and cognitions later improve during depression remission, this association remains intact. Therefore, dysfunctional, depressive cognitions are more easily (re-)activated in previously-depressed individuals, even by non-pathological low mood (Antypa et al., 2010).

In contrast, the connection between CR and first depression onset is not understood adequately, so it is unclear whether high CR scores are also a risk factor for depression incidence in never-depressed individuals (Kruijt et al., 2013; Struijs et al., 2021). Previous research aiming to gain an improved understanding of CR in the aetiology of depression has yielded mixed results (Huang et al., 2021), and there are only few prospective, longitudinal studies which use reliable measures and present distinctive evidence that supports cognitive theories for first depression onset (Fu et al., 2021). This lack of robust findings is due to several challenges that impede the research of the aetiology of first depression onset. First, properly investigating such a concept requires a longitudinal prospective research design, and secondly, random samples of never-depressed participants usually do not provide the sufficient depression incidence that is needed to draw valid conclusions about the risk factors leading to these onsets. Therefore, first depression onset is best to be studied using a risk-enriched sample.

The ongoing Netherlands Study of Depression and Anxiety (NESDA) longitudinal cohort study (Penninx et al., 2008) has collected data from over 3000 participants for 15 years (Penninx et al., 2021). This cohort in part consists of participants that are at a greater risk of developing a depressive disorder, e.g., because they present with an anxiety disorder at baseline (Ter Meulen et al., 2021), and therefore provides an ideal sample for research on the aetiology of depression. Using this risk-enriched sample, a study by Kruijt et al. (2013) investigated the role of cognitive reactivity (CR) in the first onset of depressive disorders. By examining the CR scores of 834 NESDA participants who were never-depressed at baseline over a period of two years, Kruijt et al.(2013) found CR to be significantly associated with incidence of first depression onset, suggesting CR may be a precursor of depression.

1.4 The Current Study

Building on this finding, the current research used a longitudinal prospective research design to expand Kruijt et al.'s (2013) study and to test the robustness of their results. It examined, whether the CR scores of the same sample, as provided by the NESDA longitudinal cohort study, also predict first depression onset over a longer observation period, and whether this predictive power remains strong when other risk factors are accounted for. One of the reasons why Kruijt et al.'s (2013) sample is ideal for this investigation, is that their study is one of the few longitudinal and prospective studies that uses the LEIDS-R scale (Van der Does & Williams, 2003) to measure CR, which opposed to the widely used Dysfunctional Attitudes Scale (DAS;(Weissman, 1979)), does not require mood induction to measure CR scores, resulting in more consistent and clinically relevant research findings (Solis et al., 2017).

Based on Kruijt et al.'s (2013) finding that CR scores at baseline predict depression incidence at the 2-year follow-up assessment, it was hypothesized that high CR scores of never-depressed participants at baseline predict the incidence of first depression onset at the 6-year follow-up assessment (H1).

Previous NESDA research focusing on the comorbidity between MDD and anxiety disorders has found that in 57% of comorbid cases, anxiety disorders precede depressive disorders (Lamers et al., 2011). Kruijt et al.'s (2013) analysis did not exclude participants presenting with an anxiety disorder at the baseline assessment, which due to the risk-enriched nature of the NESDA cohort, negatively impacts the generalizability of their results. To challenge this limitation, the current study explored, whether the predictive power of CR on first depression onset remains significant when comparing the depression incidence at the 2- and 6-year follow-up assessments of participants at a lower risk (no lifetime anxiety diagnosis at baseline) to those at a higher risk (presence of a lifetime anxiety diagnosis at baseline) of developing a depressive disorder (H2).

The aim of this study was to explore the relationship and the mechanisms that underly CR and first depression onset. This is especially important, since CR scores may be modifiable (Raes et al., 2009), as opposed to some other established risk factors for depression incidence, e.g., childhood maltreatment, or negative life events (Schaakxs et al., 2017). Despite the high prevalence of MDD (Hasin et al., 2018), there currently are neither sufficient treatment options for depression (Buckman et al., 2018; Fu et al., 2021), nor are there sufficient preventative interventions for the first onset of depression in adults (Breedvelt et al., 2018). For these

reasons, identifying the exact role CR plays in first depression onset is crucial for improving early detection, early diagnosis and early treatment of the disorder (Huang et al., 2021). Earlier interventions could not only decrease the high relapse and recurrence rates of MDD, but also reduce the number of people entering a depressive episode in the first place. Thus, the outcome of this research could provide theoretical, clinal and social benefits.

II Method

2.1 Participants

The ongoing NESDA longitudinal cohort study aims to investigate the aetiology, course, and consequences of depressive and anxiety disorders. At its baseline assessment in 2004, the cohort consisted of of 2981 participants with or without depressive and/or anxiety disorders. Participants must be between 18-65 years old and have been recruited through mental health organizations, primary care practices, and in the general population. NESDA's exclusion criteria are clinically overt primary diagnoses other than anxiety or depression, such as post-traumatic stress disorder, bipolar disorder, psychotic disorders, or obsessive-compulsive disorder and not being fluent in Dutch language (Penninx et al., 2008). For the present research, all participants who had never experienced major depression or dysthymia at the baseline assessment were selected.

2.2 Materials

2.2.1 Assessment of psychopathology

The incidence of a major depressive episode, a diagnosis of dysthymia, and the presence of a lifetime anxiety diagnosis were determined using the Composite Interview Diagnostic Instrument (CIDI)–lifetime version 2.1 (CIDI; World Health Organization (WHO) Version 2.1), a standardized interview that is used to diagnose psychiatric disorders in line with the algorithm of the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition.

2.2.2 Cognitive Reactivity to sad mood

CR to sad mood was measured using the Leiden Index of Depression Sensitivity-Revised (LEIDS-R) (Van der Does & Williams, 2003), a self- report scale which intends to measure the extent to which dysfunctional cognitions become activated when an individual experiences mild sadness. It consists of 34 items and six subscales: Aggression; Hopelessness/Suicidality; Acceptance/Coping; Control/Perfectionism; Risk Aversion, and Rumination on Sadness. All items are scored on a 5-point Likert scale ranging from 'not at all' (0) to 'very strongly' (4). It is uncertain whether the LEIDS-R measures CR or another aspect of cognition that makes individuals vulnerable to depression (Solis et al., 2017). Nevertheless, it has satisfactory psychometric properties, is clinically relevant, and has research utility, as

many studies have shown (Antypa & Van der Does, 2010; Booij & Van der Does, 2007; Kruijt et al., 2013; Raes et al., 2009; Solis et al., 2017).

2.2.3 Covariates

The prognostic value of the LEIDS-R scores for depression onset were tested against several background variables and established risk factors of depression. First, the occurrence of negative life events between the baseline assessment and each follow-up assessment was detected using the Brugha questionnaire (Brugha et al., 1985), which assesses the presence of twelve negative life events. The severity of depressive symptoms was measured with the 30-item Inventory of Depression Symptomatology – Self Report (IDS-SR) (Rush et al., 1996). Each item of this inventory consists of four statements on which the severity of a given symptom can be scored from 0 to 3. Last, neuroticism was assessed using the NEO-FFI (Costa et al., 1992), a questionnaire which contains twelve items that are scored on a 5-point Likert scale ranging from 'strongly disagree' (0) to 'strongly agree' (4) in order to measure one's tendency to experience negative emotional states.

2.3 Procedure

The protocol for the NESDA study was approved by the Ethical Review Board of the Vrije Universiteit Medical Centre in Amsterdam (VUMC) and the review boards of the participating medical centres, Leiden University Medical Centre (LUMC) and the University Medical Centre Groningen (UMCG). All participants received verbal and printed information about the study and submitted written informed consent at the beginning of the baseline assessment in 2004. This face-to-face assessment took place at several clinic sites around the Netherlands and lasted three to four hours on average. Since it was designed to gather extensive information on demographic, psychosocial, clinical, biological, and genetic determinants of mental health outcomes, the baseline assessment consisted of interviews, medical examinations, and written questionnaires, amongst others. Demographic information was gathered during interviews, which were administered by trained research assistants using computer-assisted personalized interviewing procedures. The CIDI-lifetime version was conducted by specially trained clinical research staff. After completing the baseline assessment, participants were compensated with a 15-euro gift certificate, and they were also reimbursed for their travel costs (Penninx et al., 2008). The 2-year, 4-year, and 6-year follow-up assessments took place in 2006,

2008 and 2010, respectively and all consisted of face-to-face assessments. During each follow-up assessment, the incidence of a major depressive episode or a diagnosis of dysthymia were once again determined using the CIDI version 2.1. and the Brugha questionnaire was also administered at each follow-up to detect negative life events that had occurred in the time between the assessments (Penninx et al., 2021).

2.4 Statistical Analyses

Simple binomial logistic regression analyses were computed to assess the total effect of all predictor variables, measured at baseline, on depression incidence at the 2-year, 4-year, and 6-year follow-up assessments. To ensure that participants who experienced more than one depressive episode over the span of the six years would not be counted more than once as having a first onset of depression, a new variable for depression incidence was computed for the 4-year and the 6-year follow-up measures of depression incidence.

Following this, multiple binomial logistic regression was used to assess the predictive value of CR for the incidence of first depression onset while controlling for covariates, over a period of two years, four years, and six years. To control for age, gender, years of education, occurrence of negative life events, severity of depressive symptoms at baseline, neuroticism and a lifetime diagnosis of anxiety, these variables were entered in block 1. Levels of CR were entered in block 2. The results were interpreted in terms of odd ratios with 95% confidence intervals. If the odds ratio for CR would be greater than 1, with confidence intervals not crossing over 1, it would suggest that the chance of depression onset increases with higher levels of CR.

Finally, to explore if the predictive power of CR differs between participants at a lower risk (no lifetime anxiety diagnosis at baseline) to those at a higher risk (presence of a lifetime anxiety diagnosis at baseline) of developing a depressive disorder, the dataset was then split into these two categories. Next, multiple binomial logistic regression was applied again to both the lower risk and the higher risk sample, over a period of two years, four years, and six years. The results of these were then be compared to those of the whole population.

III Results

3.1 Participants

Applying our in- and exclusion criteria resulted in a sample of 1008 participants. After excluding dropouts and subjects with missing data, the final sample consisted of 719 participants, aged between 18 and 65 years (M_{age} = 41.27, SD_{age} = 14.42), of which 461 (64.1%) were female and 258 (35.9%) were male. Out of all participants, 509 (70.8%) were recruited from primary care, 54 (7.5%) from specialized mental health care, and 156 (21.7%) from the general population. At the baseline assessment, 497 (69.1%) participants presented without the presence of a lifetime anxiety diagnosis, and 222 (30.9%) participants presented with the presence of a lifetime anxiety diagnosis.

The number of first depression incidences at the 2-, 4-, and 6-year follow-up assessments are presented in Table 1, for each the whole sample, the lower risk (no lifetime anxiety diagnosis at baseline) sample, and the higher risk (presence of a lifetime anxiety diagnosis at baseline) sample.

Table 1.
Number of first depression incidences at each follow-up assessment

	2-year follow-up		**4-year follow-up**		**6-year follow-up**	
	***n* DD**	**%**	***n* DD**	**%**	***n* DD**	**%**
Whole sample (*n* = 719)	67	9.3%	110	15.3%	128	17.8%
Never-anxious (*n* = 497)	30	6.0%	59	11.9%	68	13.7%
Previously-anxious (*n* = 222)	37	16.7%	51	23%	60	27%

n DD = number of participants reporting a first onset of a depressive disorder at the follow-up assessment.

3.2 Main Analyses

The results of the bivariate binary logistic regression analyses showed that, as single predictors, most variables, including CR, were significantly associated with first onset of depressive disorders, not only at the 2-year follow-up, but also the 4-year follow-up and the 6-year follow-up, see Table 2.

Table 2.
Bivariate binary logistic regression for depression incidence

	2-year follow-up		4-year follow-up		6-year follow-up	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
gender	1.25	[0.73-2.15]	1.6*	[1.02-2.5]	1.54*	[1.01-2.34]
age	0.99	[0.98-1.01]	0.99	[0.98-1.00]	0.99	[0.98-1.00]
education (yrs)	0.90*	[0.83-0.98]	0.90**	[0.85-0.97]	0.91**	[0.86-0.96]
lifetime anxiety	3.11***	[1.87-5.19]	2.21***	[1.46-3.35]	2.34***	[1.58-3.46]
n NLE	1.54***	[1.30-1.84]	1.38***	[1.16-1.63]	1.39***	[1.18-1.62]
IDS-SR	1.10***	[1.07-1.13]	1.10***	[1.08-1.13]	1.10***	[1.08-1.13]
neuroticism	1.10***	[1.07-1.13]	1.10***	[1.07-1.13]	1.10***	[1.08-1.13]
CR	1.06***	[1.04-1.08]	1.06***	[1.04-1.07]	1.06***	[1.04-1.07]

OR=Odds Ratio, 95% CI = 95% Confidence Interval.
* = p<.05;
** = p<.01;
*** = p<.001.
NLE = Negative Life Events; IDS-SR = Inventory of Depressive Symptomatology-Self Report; Neuroticism = neuroticism subscale of the NEO-FFI; CR = Cognitive Reactivity (LEIDS-R).

Since these simple analyses showed that most predictors were significant, complex analyses were employed to explore, whether the predictive power of CR on depression incidence would remain strong when the other predictors were accounted for. As seen in Table 3, the results of the multivariate binary logistic regression for depression incidence of the whole sample showed that, even when other predictors were controlled for, CR was associated with increased odds of experiencing a first onset of depression, over the span of 2 years (OR = 1.04 [1.02-1.07], $p < 0.001$), 4 years (OR = 1.04 [1.02-1.06], $p < 0.001$), and 6 years (OR = 1.04 [1.02-1.06], $p < 0.001$). Depressive symptoms at baseline were also a highly significant predictor of depression incidence at each follow-up assessment. Age and years of education were only associated with increased odds of depression incidence at the 4- and the 6-year follow-up. Number of negative life events was also a highly significant predictor of first depression onset at the 2-year follow-up, and a significant predictor at the 6-year follow-up. However, it was not a significant predictor at the 4-year follow-up assessment.

Table 3.
Multivariate binary logistic regression for depression incidence (whole sample) – final block

	2-year follow-up		4-year follow-up		6-year follow-up	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
gender	0.92	[0.50-1.70]	1.28	[0.77-2.12]	1.26	[0.79-2.02]
age	0.98	[0.96-1.00]	0.98*	[0.97-1.00]	0.98*	[0.97-1.00]
education (yrs)	0.92	[0.84-1.01]	0.91*	[0.85-0.98]	0.92*	[0.86-0.99]
lifetime anxiety	1.36	[0.74-2.52]	0.85	[0.50-1.42]	0.90	[0.55-1.47]
n NLE	1.46***	[1.20-1.79]	1.19	[0.99-1.44]	1.29**	[1.08-1.54]
IDS-SR	1.07***	[1.03-1.12]	1.08***	[1.04-1.12]	1.08***	[1.04-1.11]
neuroticism	0.98	[0.93-1.03]	0.99	[0.95-1.03]	1.00	[0.96-1.04]
CR	1.04***	[1.02-1.07]	1.04***	[1.02-1.06]	1.04***	[1.02-1.06]

OR=Odds Ratio, 95% CI = 95% Confidence Interval.
* = p<.05;
** = p<.01;
*** = p<.001.
NLE = Negative Life Events; IDS-SR = Inventory of Depressive Symptomatology-Self Report; Neuroticism = neuroticism subscale of the NEO-FFI; CR = Cognitive Reactivity (LEIDS-R).

As seen in Table 4a, the results of the multivariate binary logistic regression for depression incidence of the low-risk sample (sample without the presence of a lifetime anxiety diagnosis) also showed that CR was associated with increased odds of experiencing a first onset of depression, over the span of 2 years (OR = 1.07 [1.03-1.10], p < 0.001), 4 years (OR = 1.06 [1.04-1.09], p < 0.001), and 6 years (OR = 1.05 [1.02-1.07], p < 0.001). Depressive symptoms at baseline were a significant predictor of depression incidence at the 2-year follow-up, and a highly significant predictor at the 4- and 6-years follow-up assessments. Age was a significant predictor at the 4- and the 6-year follow-up, and number of negative life events was significant at the 2 and the 6-year follow-up.

Table 4a.
Multivariate binary logistic regression for depression incidence (sample without a lifetime anxiety diagnosis) – final block

	2-year follow-up		4-year follow-up		6-year follow-up	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
gender	0.56	[0.24-1.32]	0.99	[0.50-1.94]	0.85	[0.46-1.56]
age	0.97	[0.94-1.00]	0.96**	[0.94-0.99]	0.97**	[0.95-0.99]
education (yrs)	0.94	[0.82-1.08]	0.93	[0.83-1.03]	0.95	[0.86-1.05]
n NLE	1.51*	[1.09-2.09]	1.10	[0.85-1.42]	1.38*	[1.08-1.78]
IDS-SR	1.10**	[1.03-1.17]	1.12***	[1.06-1.189	1.09***	[1.04-1.15]
neuroticism	0.95	[0.88-1.03]	0.96	[0.90-1.02]	1.00	[0.94-1.05]
CR	1.07***	[1.03-1.10]	1.06***	[1.04-1.09]	1.05***	[1.02-1.07]

OR=Odds Ratio, 95% CI = 95% Confidence Interval.
* = p<.05;
** = p<.01;
*** = p<.001.
NLE = Negative Life Events; IDS-SR = Inventory of Depressive Symptomatology-Self Report; Neuroticism = neuroticism subscale of the NEO-FFI; CR = Cognitive Reactivity (LEIDS-R).

The results of the multivariate binary logistic regression for depression incidence of the high-risk sample (sample with the presence of a lifetime anxiety diagnosis), as seen in Table 4b, showed that CR was only a significant predictor of depression incidence at the 6-year follow-up (OR = 1.03 [1.01-1.06], p = 0.016). Depressive symptoms at baseline were a significant predictor at the 2- and the 6-year follow-up assessments, and number of negative life events was a significant predictor at the 2-year follow-up. No other variables were associated with increased odds of depression incidence at any of the follow-up assessments.

Table 4b.
Multivariate binary logistic regression for depression incidence (sample with the presence of a lifetime anxiety diagnosis) – final block

	2-year follow-up		4-year follow-up		6-year follow-up	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
gender	1.42	[0.57-3.51]	1.49	[0.67-3.32]	2.13	[0.98-4.64]
age	0.99	[0.97-1.02]	1.01	[0.98-1.03]	1.00	[0.98-1.03]
education (yrs)	0.92	[0.81-1.04]	0.92	[0.82-1.02]	0.91	[0.82-1.01]
n NLE	1.37*	[1.06-1.76]	1.33	[0.99-1.78]	1.22	[0.94-1.59]
IDS-SR	1.06*	[1.01-1.12]	1.05	[1.00-1.10]	1.06*	[1.02-1.11]
neuroticism	0.99	[0.92-1.06]	1.02	[0.95-1.08]	1.00	[0.94-1.06]
CR	1.03	[1.00-1.06]	1.02	[1.00-1.05]	1.03*	[1.01-1.06]

OR=Odds Ratio, 95% CI = 95% Confidence Interval.
* = p<.05;
** = p<.01;
*** = p<.001.
NLE = Negative Life Events; IDS-SR = Inventory of Depressive Symptomatology-Self Report; Neuroticism = neuroticism subscale of the NEO-FFI; CR = Cognitive Reactivity (LEIDS-R).

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IV Discussion

The purpose of the current study was to further investigate the role of CR in first depression onset. By building on Kruijt et al.'s (2013) finding that CR was significantly associated with first depression onset in never-depressed individuals over a span of two years, this study aimed to test this predictive power of CR over a longer period. It was hypothesized that high CR scores would also predict the incidence of first depression onset over a span of four and six years. We also repeated the analyses in in participants at a lower vs. higher risk (lifetime anxiety diagnosis at baseline). The results of the current study suggest that the CR scores of the same sample that was studied by Kruijt et al. (2013), also predict first depression onset over a span of four and six years. However, when higher risk and lower risk participants were examined separately, the results showed that the CR scores of higher risk participants were not significantly associated with depression incidence at the 2-year follow-up assessment, but instead at the 6-year follow-up assessment.

4.1 The Predictive Power of CR over an extended observation period

The results of the present study show that both as a single predictor, and in the multivariate model, CR was significantly associated with the incidence of first depression onset, not only over a span of two years, but also over a span of six years, as it was hypothesized (H1). The multivariate analyses of the whole sample further showed that other known risk-factors of first depression onset, such as negative life events that occurred between baseline and each the 2- and 6-year follow-up assessment, as well as depressive symptoms at baseline, were also significant predictors of depression incidence over a span of two years and six years. However, other common risk-factors, such as neuroticism, or the presence of a lifetime anxiety diagnosis, could not predict depression incidence at any of the follow-up assessments. All of these results are in line with Kruijt et al.'s (2013) outcomes at the 2-year follow-up assessment.

The finding that CR remained a highly significant predictor of first depression onset, even over an extended observation period, provides supporting evidence for cognitive theories of depression, which propose that distinct cognitive vulnerabilities, such as CR, may predict first depression onset (Scher et al., 2005). This is also consistent with the limited research that is available on this topic. A recent meta-analysis by Fu et al. (2021), concludes that individuals with higher levels of CR have increased odds of developing a depressive disorder, but notes that the lack of robust research on CR and first depression onset makes it difficult to draw strong

inferences. The outcome of the current study further emphasizes the need for future research on this relationship. It supports the idea that CR is not only a risk factor for depression relapse and recurrence in previously-depressed individuals, but also a risk factor for first depression onset in never-depressed individuals, as it was also predicted by Kruijt et al. (2013). Additionally, the finding that CR was significantly associated with increased odds of developing a depressive disorder over an extended observation period, further indicates that CR may play a crucial role in improving preventative interventions for first depression onset in adults, since CR scores may be modifiable (Raes et al., 2009).

4.2 The Predictive Power of CR in higher risk vs lower risk participants

When splitting the whole sample into both a lower risk (no lifetime anxiety diagnosis at baseline), and a higher risk (presence of a lifetime anxiety diagnosis at baseline) group, and comparing the results of their multivariate analyses to those of the whole population, several outcomes are worth discussing.

First, the results of the lower risk group were similar to those of the whole sample. CR remained a highly significant predictor at each follow-up assessment, and other known risk-factors of first depression onset, such as negative life events that occurred between baseline and each the 2- and 6-year follow-up assessment, as well as depressive symptoms at baseline, remained significant predictors of depression incidence over a span of two years and six years. The outcome that, in the lower risk group, CR was also significantly associated with increased odds of developing a depressive disorder over the span of both two and six years, was to be expected. For one, the majority of the whole sample consisted of lower risk participants (69.1%), so it was likely that both analyses would produce similar results. Additionally, removing the presence of a lifetime anxiety diagnosis, which is a known risk factor for depression incidence (Ter Meulen et al., 2021), from the analysis, could have resulted in an increase of the predictive power of the other variables in the multivariate analysis of the never-anxious sample. Nevertheless, this finding suggests that CR may not only predict depression incidence in never-depressed, but also in never-anxious individuals (H2).

As expected, the percentages of first depression onsets at each follow-up assessment were higher in the previously-anxious than in the never-anxious sample (H2). At the 2-year follow-up assessment, 16.7% of participants in the higher risk group experienced a first depression incidence, whereas only 6% of participants in the lower risk group did. Similarly, at

the 6-year follow-up assessment, 27% of participants in the higher risk group had a first onset of depression, and only 13.7% of participants in the lower risk group did. These outcomes are in line with previous NESDA research, which found that depressive disorders are often preceded by anxiety disorders (Lamers et al., 2011). Despite this, the results of the current study showed that in the multivariate analysis of the whole sample, the presence of a lifetime anxiety diagnosis was not a significant predictor of depression incidence at any of the follow-up assessments. This could be due to the strong predictive power of other variables present in this multivariate model, such as depressive symptoms at baseline or CR. This is further supported by the results of the bivariate analysis of the whole sample, which showed that as a single predictor, lifetime anxiety was significantly associated with first depression onset at each follow-up assessment.

Next, in the multivariate analysis of the higher risk sample, CR was no longer a significant predictor of depression incidence at the 2-, or at the 4-year follow-up assessments, but instead at the 6-year follow-up assessment. Number of negative life events were only significantly associated with first depression onset over a span of two, instead of six years, and depressive symptoms at baseline were a significant predictor at the 2- and 6-year follow-up assessments, but not at the 4-year follow-up assessment. In comparison to the outcomes of the analyses of both the whole, and the lower risk sample, the analysis of the higher risk group found overall fewer variables to be significantly associated with depression incidence, which could be due to the smaller sample size of the previously-anxious group (n = 222).

The finding that CR was only a predictor of first depression onset at the 6-year follow-up assessment could also indicate that in such high-risk samples, CR renders individuals more vulnerable to developing a depressive disorder the more time passes. However, the present study does not provide sufficient data to draw valid conclusion about this, and previous research has not yet identified the exact risk-factors that contribute to the comorbidity of depressive and anxiety disorders (Ter Meulen et al., 2021). Further research focusing on the role CR plays in the aetiology of this comorbidity could provide valuable insights that could aid in adapting the prevention and treatment of both disorders more efficiently.

4.3 Strengths, Limitations and Future Directions

The main strengths of the current study are its large sample size and longitudinal design, as its data was provided by the ongoing NESDA longitudinal cohort study, which was specifically designed to investigate risk factors for depressive and anxiety disorders on a large

scale (Penninx et al., 2008). So far, only a few other studies have examined the predictive power of CR on first depression onset prospectively (Fu et al., 2021; Huang et al., 2021; Kruijt et al., 2013; Struijs et al., 2021). Therefore, the present research offers valuable new insights into the relationship between CR and the aetiology of depressive disorders.

Since many of NESDA's participants were recruited among depressive and anxious patients, the cohort is risk-enriched (Kruijt et al., 2013; Penninx et al., 2008). This is useful for studying the aetiology of depressive disorders, but can also result in a limited generalizability of findings. In the whole sample of the current study, 9.3% of participants reported a first depression onset at the 2-year follow-up, even though the 12-month incidence of depressive disorders in the Netherlands was only around 2.7% at the time that this data was collected (Bijl et al., 2002; Kruijt et al., 2013). The issue of limited generalizability was also discussed in the study by Kruijt et al. (2013) on which the present research is built on. The current study aimed to challenge the limited generalizability of the NESDA sample by separately examining the results of participants with- and without the presence of a lifetime anxiety diagnosis at baseline, and participants in the never-anxious sample reported a depression incidence of only 6% at the 2-year follow-up assessment, which is an improvement.

Another potential limitation to the present research is that it is not a true replication of Kruijt et al.'s (2013) findings, since the same sample was used.

Furthermore, in the present study CR was measured using the LEIDS-R (Van der Does & Williams, 2003), which results in more consistent and clinically relevant research findings than the widely used Dysfunctional Attitudes Scale (Solis et al., 2017; Weissman, 1979). However, it is uncertain whether the LEIDS-R measures CR or another aspect of cognition that makes individuals vulnerable to depression, which could be another limitation of the current research.

The results of present study support the idea that CR predicts first depression onset over an observation period of both two and six years, even in a never-anxious, lower risk sample, which shows the usefulness of further researching this relationship. The finding that, in the previously-anxious sample, CR could only predict first depression incidence at the 6-year follow-up assessment, raises an interesting question about the role CR plays in the comorbidity of depressive and anxiety disorders. Future prospective studies could focus more on previously-anxious-, but never-depressed participants to examine this dynamic further.

4.4 Conclusion

The findings of the present research provide evidence suggesting that over an observation period of two years, four years, and six years, CR is a strong predictor for first depression onset in never-depressed individuals, even when other risk-factors for depression incidence are taken into account. Furthermore, the predictive power of CR on first depression onset appears to remain strong in a lower risk sample, that presents without the presence of a lifetime anxiety diagnosis at baseline. The current study therefore contributes to previous research on cognitive theories of depression and supports the need to further investigate the exact role CR plays in the aetiology of depressive disorders. In a higher risk sample, that presents with a lifetime anxiety diagnosis at baseline, CR could not predict depression incidence over two years, but instead over six years. A replication of the present results with an independent sample is needed, and further research focusing on CR as a risk factor for the comorbidity of depressive and anxiety disorders is necessary to gain a better understanding of these findings.

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