# A Prospective Study: Anhedonia as Transdiagnostic Precursor of Psychopathology?

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**Abstract**

Prior studies revealed the predictive value of anhedonia during adolescence for the onset of MDD. However, anhedonia is associated with the presence of a variety of psychiatric disorders. The main aim of the present study was to examine whether anhedonia is a transdiagnostic precursor of the onset of psychopathology. This is examined with longitudinal bipolar offspring data (N=108, mean age=16.14, 51% males). Participants were clinically evaluated on anhedonia and psychopathology at 4 times in a period of 12 years. Results from cox proportional hazard models revealed that anhedonia during adolescence can be regarded as a risk factor for the development of mood disorders and comorbidity. As this study has its limitations, we provide directions for future research. These findings may help promoting the development of new, more effective, therapeutic interventions.

*Keywords:* transdiagnostic, prodromal, anhedonia, psychopathology, mood disorder, comorbidity

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**A Prospective Study: Anhedonia as Transdiagnostic Precursor of Psychopathology?**

About 20% of adolescents reports at least one episode in life characterized by a loss of interest in things they usually enjoyed, also referred to as anhedonia (Bennik, Nederhof, Ormel, & Oldehinkel, 2014). Anhedonia is one of the core symptoms of major depressive disorder (MDD; DSM-V; American Psychiatric Association, 2013) and is also associated with a variety of other psychiatric disorders. A particular vulnerable period for the development of psychopathology is adolescence (Dahl, 2004; Davey, Yücel, & Allen, 2008). More specifically, studies have shown that anhedonia experienced in adolescence is one of the strongest predictors of the onset of mood disorders in early adulthood (Bennik, Nederhof, Ormel, & Oldehinkel, 2014; Wilcox & Anthony, 2004), and this might also be the case for other psychopathology. Further, a recent meta-analysis on anhedonia, suicidal ideation, and depression, showed that anhedonia is associated with suicidality, independently of depression and other psychiatric disorders (Ducasse et al., 2017). In an attempt to detect risk factors that are present across psychopathology (i.e., transdiagnostic factors), the current study will examine whether anhedonia in adolescence is a precursor of the onset of different psychiatric disorders.

## Anhedonia

Over the recent years, research aimed to obtain a greater understanding of anhedonia (i.e., an- hēdonē = without pleasure). Anhedonia is problematic because its comes with several correlates: a lack of activation, a lack of motivation, and a loss of interest in both social activities and learning experiences (Bennik et al., 2014; Berridge, Robinson, & Aldridge, 2009; Chapman, Chapman, & Raulin, 1976; Snaith et al., 1995). Anhedonia and these psychological problems are related to difficulties in healthy maturation and the possible development of psychopathology (Treadway & Zald, 2011).

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Indeed, anhedonia is associated with the presence of multiple psychiatric disorders. First, anhedonia is one of the main symptoms of MDD (American Psychiatric Association, 2013). Furthermore, patients suffering from bipolar disorder report anhedonia during depressed episodes (Whitton, Treadway, & Pizzagalli, 2015), and anhedonia is commonly present in patients with anxiety disorder (Brown, Silvia, Myin-Germeys, & Kwapil, 2007). Secondly, anhedonia is one of the negative symptoms of schizophrenia (Koob & Le Moal, 1997; Snaith, 1993) and is, accordingly, an underlying characteristic of schizophrenia onset (Joiner, Brown, & Metalsky, 2003). Furthermore, anhedonia is typically present in alcohol dependent patients during abstinence as well in individuals suffering from other substance abuse disorders (Heinz, Schmidt, & Reischies, 1994). Finally, anhedonia is present across different personality disorders such as borderline personality disorder and schizotypal personality disorder (Widiger & Costa Jr, 1994).

Across different studies on anhedonia and psychopathology, one recurrent theme is the association of anhedonia and the brain. Neuropsychological research suggests that anhedonia may result from a defect in the brain reward system (Treadway & Zald, 2011). The reward system refers to a collection of brain structures and neural pathways that are primarily located in the cortico-basal ganglia-thalamo-cortical loop (Greenberg, Aminoff, & Simon, 2002). Treadway and Zald (2011) state that due to dysfunctions in the reward system, individuals with increased levels of anhedonia have to work harder to process rewarding experiences. During adolescence, this reward system is in full development (Dahl, 2004). That is, both synaptic pruning and neuronal development takes place (Paus, Keshavan, & Giedd, 2008). Typically, adolescents are highly responsive to rewards and increasingly show reward seeking behavior (Dahl, 2004; Davey, Yücel, & Allen, 2008; Galvan, 2010). It is possible that the experience of anhedonia is

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part of a normative brain development during adolescence (Andersen & Teicher, 2008; Giedd, 2008). However, in this critical phase adolescents are also highly susceptible for atypical development which in turn might also cause anhedonia (Paus et al., 2008). Hence, anhedonia occurs regularly in adolescents however neuroscience is inconclusive about the reasoning behind this prevalence.

A study from Wilcox and Anthony (2004) also stresses the importance of anhedonia during adolescence by studying antecedents of MDD. The study confirmed the predictive value of anhedonia during adolescence for MDD in adulthood. Importantly, this effect was stronger for females than for males (Wilcox & Anthony, 2004). More recently, Bennik et al. (2014) examined the course, stability and reciprocal relations of anhedonia and depressed mood in adolescence. They found a decrease in self-reported anhedonia from early adolescence to late adolescence in a general population. Interestingly, the proportion of females reporting anhedonia increased during this period, indicating sex differences in anhedonia development. Moreover, the association between depressed mood and anhedonia becomes stronger over time, suggesting that anhedonia at young age might be a potential target for prevention strategies (Bennik et al., 2014).

So far, we know that anhedonia is present across the clinical picture of different disorders, and anhedonia is predictive for the development of MDD. Additionally, anhedonia is related to poor treatment outcome and chronicity (Heinz et al., 1994; McMakin et al., 2012). Elevated levels of anhedonia predict poor treatment outcome in patients with depression (Spijker 2002). In line with this, recent research suggests that individuals suffering from mood disorders are difficult to treat when reporting high levels of anhedonia (McMakin et al., 2012). This treatment resistance can be seen as an indicator of complex, severe psychopathology, and is

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associated with the presence of two or more disorders at the same time (i.e., comorbidity; Caspi et al., 2014).

## A Transdiagnostic Approach of Psychopathology

One of the strongest predictors for developing a psychiatric disorder is having a parent that has a psychiatric diagnosis (Connell & Goodman, 2002; Gottesman, Laursen, Bertelsen, & Mortensen, 2010; Mesman, Nolen, Reichart, Wals, & Hillegers, 2013; Rasic, Hajek, Alda, & Uher, 2013). As a result, offspring studies have emerged as a promising field of research. Prior studies have shown that the peak age of onset of psychopathology occurs on average prior the age of 25 (Kessler et al., 2005). Hence, examining familial transmission in offspring from adolescence into adulthood could be valuable tool to explore the early course and determinants of psychopathology. Mesman et al. (2013) followed bipolar offspring prospectively and found that having a parent with a mood disorder comes with an high risk of developing a mood disorder specifically (54%), but also with a high chance of developing any psychiatric disorder as 72% of the offspring developed a DSM-IV disorder throughout life. Since being a child of a bipolar parent is an unchangeable risk factor for the development of psychopathology, we should continue our search towards other potentially *changeable* factors. By doing this, we might be able to accurately recognize and prevent the development of psychopathology.

One way of detecting important changeable factors is by focusing on the underlying common dimensionality of psychopathology, such as personality states and traits (Krueger & Eaton, 2015). This brings us to the so-called transdiagnostic prodromal approach of psychopathology, where the term ‘transdiagnostic’ refers to present in multiple disorders (Krueger & Eaton, 2015) and ‘prodromal’ refers to an early sign or symptom which often indicates the onset of pathology before diagnostically specific signs and symptoms are developed

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(Yung et al., 2003). A transdiagnostic prodromal factor (i.e., precursor; Korrelboom, Maarsingh, & Huijbrechts, 2012) can be present in a non-clinical phase of multiple disorders and might be a potential target for preventive purposes. Based on the aforementioned literature, anhedonia might be eligible as being a precursor of the development of psychopathology.

## The Current Study

This study will examine whether anhedonia in adolescence predicts the onset of different psychiatric disorders and comorbidity during later life in a high risk population. We make use of longitudinal bipolar offspring data (N=140, age range = 12-31), from adolescents that were clinically assessed on anhedonia (T1,T2) and psychopathology (T1-T4) during a period of 12 years. So far, literature only revealed the predictive value of anhedonia in MDD however the interplay with other psychopathology remains unclear. Therefore, we explore whether (1) anhedonia is predictive for the development of different psychiatric disorders. Furthermore, based on the idea that anhedonia is associated with treatment resistance, an indicator of both severity and comorbidity, there is expected that (2) anhedonia is a stronger predictive factor for comorbid disorders than for single disorders.

Apart from the variables of interest, three crucial covariates will be taken into account. Firstly, psychiatric disorders are overrepresented in the lower social strata, and a low socio economic status (SES) can be regarded as both a cause and consequence of psychiatric disorders (Miech, Caspi, Moffitt, Wright, & Silva, 1999). Therefore, individuals' SES is included in the analyses. Secondly, research suggests there are sex differences in psychiatric problems. For instance internalizing problems are more common in girls and externalizing problems are more common in boys (Matos et al., 2017). Therefore, gender is included in the analyses. On top of that, gender differences are also apparent in anhedonia (e.g., Bennink et al., 2014; Wilcox &

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Anthony, 2004). Finally, offspring studies typically include family members (i.e., both sister and brother of the same family). This study controls for these dependent observations as children share multiple genetic and environmental factors.

Taken together, we will examine whether anhedonia in adolescence can be considered a precursor of the onset of psychopathology in later life.

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## Method

### Participants

Data for this study originates from the Dutch bipolar offspring cohort, a longitudinal research project established in 1997 (Kinderen Bipolaire Ouders; KBO; Wals et al., 2001) . The sample was composed of 140 offspring from 86 families with one bipolar parent. To avoid a selection bias, families were only included if all offspring in the age range 12-21 agreed to participate. Exclusion criteria were severe physical illness and an IQ below 70. The project consisted of four waves which all had different time intervals (i.e., 1, 5, 12 years; T1-T4 respectively). Over the 12 years of follow-up, 32 offspring dropped out. Participants did not differ significantly on demographic or clinical characteristics at T1 from offspring who continued study participation (Mesman, Nolen, Keijsers, & Hillegers, 2017). At T4 the analytic sample consisted of 108 participants (mean age at T1 =16.14, SD = 2.72, 51% males; retention rate 77.14%). For detailed sample information see Table 1. Data collection was approved by the Medical Ethics Committee of the University Medical Center Utrecht.

### Procedure

Participants were recruited between 1997 and 1999 through the Dutch Association for Manic Depressives and relatives (VMDB; 62 families, 102 children) and via out-patient clinics in nine psychiatric hospitals (24 families, 38 children). At the time of recruitment, all parents with bipolar disorder were outpatients. After a complete description of the study was given, written informed consent forms were filled out by all bipolar parents, their spouses, and their offspring. Offspring were invited to the research department of different Academic Hospitals and were tested for a day. In return for their partaking, participants received money (varying from 10 to 25 euro per wave).

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## Measures

**Lifetime Anhedonia**. Anhedonia was assessed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997) interview at T1 and T2 by the following questions about current anhedonia (past 2 months) and past anhedonia: 'Do you often get bored?; Are you bored because you do not enjoy things or because you do not even feel like starting something?; Do you feel bored when you think of the things you did before you started to feel sad?; Do you become bored when you do things that you used to like?; What things did you used to do for pleasure?" Child, parent, and clinician reports of current and past anhedonia were rated on a three-point Likert scale: *(i) symptom not present; (ii) symptom below subthreshold level; and (iii) symptom above threshold level.* In case of disagreement between child and parent about the presence of anhedonia, greater weight was given to children's reports. For the current study, compound scores of anhedonia assessed at T1 and T2 were used. Finally, anhedonia was determined as either present or absent (dichotomous; see also Supplementary Material).

**Psychopathology.** At all four assessments, bipolar offspring were psychiatrically evaluated. At T1 and T2, DSM-IV disorders were obtained by a face-to-face interview using the K-SADS-PL (Kaufman et al., 1997). This measurement includes screening questions and supplements for multiple DSM-IV disorders, which are answered by the child, parent and clinician. In case of disagreement between child and parent about the presence of a symptom, greater weight was given to parents' reports of observed behavior and children's reports of subjective experiences. After offspring reached age 18 (at T3 and T4), the K-SADS-PL was replaced by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; Gibbon, Spitzer, Williams, Benjamin, and First, 1997). In both psychopathology measures the age of

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onset of psychopathology was reported which makes the data suitable for survival analysis (Kleinbaum & Klein, 2010). A detailed description of psychopathology after 12 years of follow-up is published elsewhere (Mesman et al., 2013).

## Analytic Strategy

**Data Preparation and Power Analysis.** As proposed by Kleinbaum and Klein (2010) data was transformed to make it applicable for survival analysis (see Supplementary Material; Syntax). In short, one dichotomous lifetime anhedonia variable was created by combining current and past anhedonia scores on T1 and T2. About 80% of participants were younger than 18 at that time, with a mean age of 16.14 (SD=2.72). From now on T1 and T2 will be referred to as adolescence. Furthermore, the psychopathology variable was computed by combining the age of onset of a disorder reported at T3 and T4. About 75% of participants were older than 21 at that time, with a mean age of 24.07 (SD=4.53). From now on T3 and T4 will be referred to as adulthood. Subsequently, the data was split based on anhedonia.

For complex survival models, a rule of thumb of 8 to 10 events (i.e., onset of a psychiatric disorder) per parameter is necessary to reach 80% power (Vittinghoff & McCulloch, 2007). In Table 2, both the number of events and the number of parameters are displayed for each model separately. In order to deal with power issues, special attention is drawn to the cautious interpretation of the insufficient power models in the discussion section.

**Statistical Analysis.** To test our hypotheses, Cox Proportional Hazard models were applied. Before we did so, we evaluated the Proportional Hazard (PH) assumption, which suggests that Hazard Rates (HRs) are constant in time. As suggested by Kleinbaum and Klein (2010) this was done by inspecting the log minus log plots stratified on the level for each covariate. In these plots crossed lines in adulthood were not allowed, because crossed lines

indicate completely different and instable HRs for the anhedonia and nonanhedonia-group. Multiple Predictor Cox Proportional Hazard models [$h(t) = h0\ (t) \exp\ (\beta^1 Xi^1 + \beta^2 Xi^2 + \ldots + \beta^p Xi^p)$] were computed using IBM Statistical Package for the Social Sciences (SPSS) for Windows (version 24.0; IBM Corp, Armonk, NY, USA) examining the association of anhedonia during adolescence and the onset of psychopathology. Since some participants in this sample were already diagnosed with psychopathology at T1 or T2, we controlled for these childhood disorders. Furthermore, the following variables were included as potential confounders: SES, gender, and dependent observations (i.e., siblings sharing same environment; dependent observations). Results are presented as HRs indicating the risk of getting a disorder while belonging to either the anhedonia-group or the nonanhedonia-group, accompanied with a 95% confidence interval (CIs). HRs can be treated similar as odds ratios (Kleinbaum & Klein, 2010). That is, if the coefficient is positive and the HR is bigger than one, it can be concluded that the likelihood of getting a psychiatric diagnosis is higher compared to the reference group. If the coefficient is negative and the HR is between zero and one it can be concluded that the likelihood of getting a psychiatric diagnosis is lower compared to the reference group. Furthermore, Little's MCAR test showed that data were missing completely at random ($X^2(3) = 4.407$, $p = 0.221$), which gave us possibility to include respondents with missing data in the model estimations using Full Information Maximum Likelihood; Pituch & Stevens, 2015). Finally, to correct for multiple comparisons, a Bonferroni correction was applied for the number of main hypotheses (2; $\alpha = 0.05/2=0.025$; Weisstein, 2004).

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# Results

## Sample Characteristics

Table 1 summarizes baseline demographic and clinical characteristics of the total sample (N=140), the anhedonia-group and the nonanhedonia-group. Although no statistical differences were observed between the two groups, we decided to continue controlling for theoretical confounders (i.e., SES, gender, dependent observations). The anhedonia-group was composed of 44 participants (31% of the complete sample), of which 21 reported current (past 2 months) anhedonia (mean age of reporting anhedonia 16.46 SD = 2.82) and 35 reported anhedonia in the past. Of those 56 anhedonia reports, 12 overlapped. That is, they reported both past anhedonia and current anhedonia (for specifics see Supplementary Material Table A).

## Proportional Hazard Assumption

Before statistical models were applied, the Proportional Hazard (PH) assumption was inspected for all variables of interest (i.e., anhedonia, SES, gender, dependent observations and disorder at T1 or T2). This assumption suggests that HRs are constant in time (Kleinbaum & Klein, 2010). As shown in Supplementary Material (see Figure A) the PH assumption was not seriously affected in adulthood.

## Anhedonia as Predictor for the Development Psychopathology

During the follow-up from adolescence into adulthood, 33 (of 44; 75%) participants in the anhedonia-group developed a (new) psychiatric disorder, while 44 (of 96; 46%) of the nonanhedonia-group developed a (new) psychiatric disorder ($X^2$ (1) = 10.37, $p$ = .001; see Figure 1). Hence, the onset of new psychopathology was found to be significantly more prevalent in the anhedonia-group compared to the nonanhedonia-group.

In the unadjusted cox proportional hazard analysis, an association between reporting

anhedonia during adolescence and onset of a (new) psychiatric disorder was detected (HR = 2.97; 95% CI, 1.82-4.44; Table 3). None of the covariates were significantly associated with an increased risk of developing psychopathology. Yet, the strength of the association between anhedonia and psychopathology onset was reduced, suggesting a confounding effect. Taken together, the full model suggests that above and beyond prior childhood diagnosis, an individual in the anhedonia-group is 1.8 times more likely to develop psychopathology compared to an almost identical individual in the non-anhedonia-group (HR = 1.80, 95% CI: 1.02-3.18; Table 3). The effects are illustrated by the cumulative hazard function displayed in Figure 2. Subsequently, we explored whether anhedonia is associated with specific disorders (mood disorders, anxiety disorder, substance abuse, externalizing problems, other disorders). As shown in Figure 1, for all disorders -except for the substance abuse disorder- the weighted percentage participants that developed psychopathology was higher in the anhedonia-group than in the nonanhedonia-group. When zooming in on the different disorders we detected an association between reporting adolescent anhedonia and developing a mood disorder (HR =5.10; 95% CI, 2.95-8.83; Table 3) or anxiety disorder (HR =2.58, 95% CI, 1.19-5.60; Table 3). When controlling for covariates, only the association between anhedonia and mood disorder remained significant (adjusted model: HZ =4.18, 95% CI: 2.23-7.82; Table 3). That is, above and beyond prior childhood diagnosis, an individual in the anhedonia-group is 4.18 times more likely to develop mood disorders compared to an almost identical individual in the non-anhedonia-group. The main effect of anhedonia on mood disorders is illustrated by the cumulative hazard function displayed in Figure 3. Despite the fact that no main effect of anhedonia on the development of substance abuse disorders and externalizing problems was detected, we did found an increased risk for boys (effect of gender; HZ=4.86, 95%CI: 1.63-14.45, HZ=10.62, 95% CI: 1.26-89.24,

respectively; Table 3).

**Anhedonia as Predictor for the Development of Comorbidity**

During the follow-up from adolescence into adulthood, 24 (of 44; 54.5%) of the participants in the anhedonia-group developed comorbidity. Of the nonanhedonia-group, 22 (of 96; 22.9%) developed comorbidity ($X^2$ (1) = 13.68, $p$ = .000; see Figure 1). Hence, comorbidity was found to be significantly more prevalent in the anhedonia-group compared to the nonanhedonia-group.

In the unadjusted cox proportional hazard analysis, an association between reporting anhedonia during adolescence and developing comorbidity in adulthood was detected (HR = 3.42; 95% CI, 2.12-5.52; Table 4). None of the covariates were significantly associated with an increased risk of developing comorbidity Yet, the strength of the association between anhedonia and comorbidity was reduced (HR = 2.81, 95% CI: 1.59-4.96; Table 4), suggesting a confounding effect. Figure 1 illustrates that only 5% of the anhedonia-group suffers from psychopathology different than mood disorders, the rest therefore is comorbid. Because of the overrepresentation of mood disorders in comorbidity, we decided to add mood disorder as covariate in a post hoc analysis. The model revealed a decrease in effect size of anhedonia on comorbidity, but the effect remained present (HR=2.10; 95% CI, 1.12-3.74; Table 4). Results of this post hoc analysis indicate that above and beyond prior childhood diagnosis and mood diagnosis an individual in the anhedonia-group is 2.05 times more likely to develop comorbidity compared to an almost identical individual in the non-anhedonia-group. The effects are illustrated by the cumulative hazard function displayed in Figure 3.

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## Discussion

This study aimed to examine whether anhedonia can be regarded as a transdiagnostic prodromal factor for the development of psychopathology. This study was performed in a bipolar offspring sample (i.e., high risk population). Main findings reveal that individuals who experience anhedonia during adolescence have an increased risk for developing a mood disorder. Results also indicate that individuals who experience anhedonia during adolescence, are more at risk for developing multiple disorders.

### Anhedonia and the Development of Mood Disorders

The first hypothesis that anhedonia is predictive for the development of different psychiatric disorders, was not confirmed. Findings of this study indicate that individuals who reported anhedonia during adolescence are at greater risk for developing psychopathology. However, when zooming in on specific psychopathology, only the predictive effect of anhedonia in mood disorders remained present. One way of explaining why we did not find what was expected, is that the sample was limited by the occurrence of other disorders than mood disorders. Still, an effect of anhedonia on the onset of mood disorders was found and this is in line with prior studies. For instance, Dryman and Eaton (1991) suggested that clinical features of MDD, such as anhedonia, could serve as precursors of mood disorders. Empirically, Wilcox and Anthony (2004) found that individuals who develop MDD in their later life, mostly reported (persistent) anhedonia during adolescence. Anhedonia during adolescence might be of great importance because anhedonia becomes more stable over adolescence and anhedonia becomes more tied to depressed mood in late adolescence (Bennink, 2014). Moreover, adolescence is a common time for the presence of precursors which are part of the prodromal phase (Kelleher et al., 2011). Theoretically, factors that are part of the prodromal phase are general, not specified

and occur before the onset of psychopathology (Yung et al., 2003). Assuming stages of psychopathology, i.e., running from broad factors to specific diagnoses, (Kupka, Hillegers, & Scott, 2015) anhedonia might be part of the beginning of this staging. Taken together, findings of this study suggests that anhedonia in late adolescence might play an important role in the prodromal phase of mood disorders.

**Anhedonia and the Development of Comorbidity**

The second hypothesis that anhedonia is a stronger predictive factor for comorbid disorders than for single disorders, was confirmed. Our findings indicate that having a history of anhedonia is associated with a greater risk factor for the development of multiple psychiatric diagnoses. One of the possible explanations for this effect is that comorbidity can be seen as an indicator of complex severe psychopathology (Caspi et al., 2014), while anhedonia is also related to severity indicators (i.e., chronicity, treatment resistance; Heinz et al., 1994; McMakin et al., 2012; Spijker, 2002). However, as this study examined bipolar offspring, the participants that developed mood disorders are overrepresented in the sample. Moreover, we know that mood disorders are among the most comorbid disorders of all psychopathology (e.g., T. A. Brown, Campbell, Lehman, Grisham, & Mancill, 2001). Interestingly, this study still suggests that regardless of mood disorders, anhedonia during adolescence is a precursor of complex and severe psychopathology in an bipolar offspring sample.

**Strengths and Limitations**

This study has the potential to set one step on the road in disentangling why some individuals develop psychopathology and others remain resilient. Several strengths and limitations need to be recognized. First of all, a major strength of this study is the longitudinal dataset which is characterized by long follow up and high retention rate. Another strength of this

study is the use of the elaborated clinical interviews that are commonly used and well validated (K-SADS; e.g., Ambrosini, 2000; Kaufman et al., 1997; Nock & Banaji, 2007) in order to measure psychopathology even at the symptom level (i.e., anhedonia). Moreover, hypotheses were preregistered before seeing the data in order to prevent statistical errors such as p-hacking (e.g., Nuijten, 2016). Furthermore, this study benefits from a suitable analytic approach. That is, the cox proportional hazard model is the most well-known robust semiparametric regression model for survival data and comes with three advantages. Firstly, the model takes into account the time to an event which makes it distinct from logistic regression (e.g., Kleinbaum & Klein, 2010). Secondly, the model reports not solely whether there is an effect -as done in basic survival analysis- but also reports the size of the effect (Cox, 1972). Moreover, it allows to take into account censored data (i.e., participants leaving the sample without developing psychopathology; handling missing data; Kleinbaum & Klein, 2010). Another strengths of this study is that builds up on existing studies on anhedonia and sheds light on the importance of anhedonia.

Of course, the study also has its limitations. Therefore, we provide directions for future research. Operationalization of anhedonia is different across literature. That is, anhedonia can be seen as a state or a trait (Loas, Monestes, Ingelaere, Noisette, & Herbener, 2009). This study assessed a loss of interest which refers to anhedonia as a state-like phenomena. Moreover, the current study inspected anhedonia as dichotomous variable whereas anhedonia can be severe but also mild. In addition, anhedonia is multi-faced concept. In some contexts anhedonia might be more problematic than in other contexts (e.g., Shankman et al., 2014). For instance, puberty is inherent to some anhedonic feelings about cleaning your bedroom Yet, anhedonic feelings about going to a party with friends might be more problematic. In order to examine fluctuations over

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time and context, future research could make use of experience sampling research methods (daily diary measurements; Csikszentmihalyi,& Larson, 2014).

Although offspring samples can be an eminent tool for studying the onset of psychopathology, the current research design consisted of some limitations. In a bipolar offspring sample mood disorders are the most common disorders (Mesman et al., 2013). The overrepresentation of mood disorders resulted in power issues for the models on other specific diagnoses. Moreover, not all DSM-V diagnoses were present in the offspring sample and therefore future research should be done in an extensive (normative) sample, including the onset of all kinds of psychopathology (i.e., also schizophrenia and personality disorders). In addition, because comorbidity typically occurs after age 25 (Kessler et al., 2005), a measurement later in life could be useful to examine comorbidity more closely. Furthermore, the composition of the anhedonia-group has its shortcomings regarding the generalizability of anhedonia during adolescence. Since a compound score of both current and past anhedonia on T1 and T2 was used, it is possible that anhedonia was present during adolescence (12-16), but it is also possible that anhedonia was present before that time. One way to solve this in future research is by questioning participants about the onset and duration of anhedonia. Noteworthy, all results are found in a sample of bipolar offspring, therefore they are interesting for this specific risk population but might not be generalizable to the general population.

**Clinical Implications**

It is commonly known that it is difficult to detect early risk factors however, as shown, anhedonia is an important risk factor for at least mood disorders and comorbidity. By detecting risk factors for the development of psychopathology, we might be able to accurately recognize, early intervene, and hopefully influence the development of psychopathology. This study shows

the importance of anhedonia during adolescence for the development of mood disorders and comorbidity. But what do we do with these results regarding psychological treatment? Insel (2012) describes in his review the shift in treatments of psychopathology and states that anhedonia is recognized as a neglected clinical target. Indeed, besides deep brain stimulation, which is costly and invasive, almost no effective treatments for anhedonia are known (Giacobbe & Kennedy, 2006). Yet, promising steps are being made by giving individuals personalized lifestyle advice (van Roekel et al., 2016; van Roekel et al., 2017).

**Conclusion**

In sum, this study sets one step towards emphasizing the importance of anhedonia as precursor of the development of mood disorders and comorbidity in an at risk population. Results add to our understanding of the prodromal phase of mood disorders and comorbidity. Although these results should be confirmed in larger populations, they provide a potential target for early recognition and the development of prevention programs and might serve as inspiration for clinicians towards more effective treatments.

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# Appendix

Hypotheses and methods were preregistered on the Open Science Framework (OSF; June 15, 2018), and embargoed until September, 30, 2018. The registration form can be found on: https://osf.io/qpu4s/

Table 1

*Baseline Sample Descriptives of Total Study Population, Anhedonia-group, and Nonanhedonia-group accompanied by Tests Statistics*

| | **Total (N=140)** | **Anhedonia-group (N=44)** | **Nonanhedonia-group (N=96)** | **Test statistic** | **P-value** |
|---|---|---|---|---|---|
| *Age* | 16.14 (2.72) | 16.36(2.75) | 16.04(2.71) | T (138,000) = -0.646 | 0.520 |
| *Gender, males* | 72 (51%) | 28 (63.6%) | 44(45.8%) | $X^2$ (1) =3.83 | 0.051 |
| *SES* | 4.90 (2.13) | 5.00(2.06) | 4.82(2.17) | T (138,000)= -0.463 | 0.644 |
| *Bipolar mother* | 84 (60%) | 26 (59.1%) | 58(60.4%) | $X^2$ (1) =0.02 | 0.882 |
| *Divorced parents* | 28 (20%) | 10 (22.7) | 18 (18.8%) | $X^2$ (1) =0.298 | 0.585 |

Note: SES= Socio economic status

Hypotheses and methods were preregistered on the Open Science Framework (OSF; June 15, 2018), and embargoed until September, 30, 2018. The registration form can be found on: https://osf.io/qpu4s/

Table 2

*Power Estimation for Main Effects in Cox Proportional Hazard Models*

| | # Events | # Parameters | Power for unadjusted model | Power for adjusted model | Preferred # Parameters |
|---|---|---|---|---|---|
| *1. Disorder* | 77 | 5 | Sufficiënt | Sufficiënt | 5 |
| *2. Mood disorder* | 58 | 5 | Sufficiënt | Sufficiënt | 5 |
| *3. Anxiety disorder* | 26 | 5 | Sufficiënt | Insufficiënt | 2 |
| *4. Substance abuse disorder* | 24 | 5 | Sufficiënt | Insufficiënt | 2 |
| *5. Externalizing disorder* | 11 | 5 | Sufficiënt | Insufficiënt | 1 |
| *6. Other disorder* | 25 | 5 | Sufficiënt | Insufficiënt | 2 |
| *7. Comorbidity* | 46 | 5 | Sufficiënt | Sufficiënt | 5 |

Note: Other disorder includes enuresis, encopresis, pervasive developmental disorder, tic disorder, body dysmorphic disorder, and eating disorders.

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Table 3

*Unadjusted and Adjusted Hazard Ratios of Psychopathology Risk associated with Anhedonia*

| | | Unadjusted Model | | Adjusted Model | |
|---|---|---|---|---|---|
| **Model** | **Parameter** | **HR** | **C.I.95%** | **HR** | **C.I.95%** |
| **1** | **Psychopathology** | 2.97*** | 1.82-4.84 | 1.80 | 1.02-3.18 |
| | *Childhood Diagnosis* | | | 2.39** | 1.39-4.10 |
| | *SES* | | | 1.00 | 0.89-1.12 |
| | *Gender* | | | 1.07 | 0.67-1.71 |
| | *Dependent Observations* | | | 0.99 | 0.98-1.00 |
| **2** | **Mood disorder** | 5.10*** | 2.95-8.83 | 4.18*** | 2.23-7.82 |
| | *Childhood Diagnosis* | | | 1.73 | 0.94-3.18 |
| | *SES* | | | 1.07 | 0.94-1.22 |
| | *Gender* | | | 0.39 | 0.39-1.16 |
| | *Dependent Observations* | | | 0.99 | 0.98-1.00 |
| **3** | **Anxiety** | 2.58* | 1.19-5.60 | 1.69 | 0.67-4.25 |
| | *Childhood Diagnosis* | | | 2.57 | 0.95-6.97 |
| | *SES* | | | 1.05 | 0.86-1.30 |
| | *Gender* | | | 0.83 | 0.37-1.86 |
| | *Dependent Observations* | | | 1.00 | 0.98-1.02 |
| **4** | **Substance** | 0.89 | 0.37-2.17 | 0.55 | 0.16-1.66 |
| | *Childhood Diagnosis* | | | 1.45 | 0.57-3.69 |
| | *SES* | | | 1.09 | 0.88-1.35 |
| | *Gender* | | | 4.86** | 1.63-14.45 |
| | *Dependent Observations* | | | 1.00 | 0.98-1.02 |

Hypotheses and methods were preregistered on the Open Science Framework (OSF; June 15, 2018), and embargoed until September, 30, 2018. The registration form can be found on: https://osf.io/qpu4s/

Continuation of Table 3

*Unadjusted and Adjusted Hazard Ratios of Psychopathology Risk associated with Anhedonia*

| | | Unadjusted Model | | Adjusted Model | |
|---|---|---|---|---|---|
| **Model** | **Parameter** | **HR** | **C.I.95%** | **HR** | **C.I.95%** |
| **5** | **Externalizing** | 3.54 | 1.04-12.08 | 1.76 | 0.41-7.56 |
| | *Childhood Diagnosis* | | | 1.97 | 0.42-9.35 |
| | *SES* | | | 0.87 | 0.61-1.23 |
| | *Gender* | | | 10.62* | 1.26-89.24 |
| | *Dependent Observations* | | | 0.98 | 0.95-1.01 |
| **6** | **Other** | 2.36 | 1.06-5.25 | 0.99 | 0.41-2.37 |
| | *Childhood Diagnosis* | | | 7.83*** | 2.51-24.37 |
| | *SES* | | | 0.94 | 0.76-1.16 |
| | *Gender* | | | 0.80 | 0.36-1.82 |
| | *Dependent Observations* | | | 0.99 | 0.97-1.01 |

Note: HR = Hazard Ratio, *p < .025. **p < .01. *** p <.001
Other disorder includes enuresis, encopresis, pervasive developmental disorder, tic disorder, body dysmorphic disorder, and eating disorders.

Hypotheses and methods were preregistered on the Open Science Framework (OSF; June 15, 2018), and embargoed until September, 30, 2018. The registration form can be found on: https://osf.io/qpu4s/

Table 4

*Unadjusted and Adjusted Hazard Ratios of Comorbidity Risk associated with Anhedonia*

| | | **Unadjusted Model** | | **Adjusted Model (Step 1)** | | **Adjusted Model (Step 2)** | |
|---|---|---|---|---|---|---|---|
| **Model** | **Parameter** | **HR** | **C.I.95%** | **HR** | **C.I.95%** | **HR** | **C.I.95%** |
| **7** | **Comorbidity** | 3.42*** | 2.12-5.52 | 2.81*** | 1.59-4.96 | 2.05* | 1.12-3.74 |
| | *Childhood Diagnosis* | | | 1.53 | 0.90-2.60 | 1.30 | 0.77-2.22 |
| | *SES* | | | 1.01 | 0.90-1.14 | 0.97 | 0.85-1.10 |
| | *Gender* | | | 1.49 | 0.93-2.39 | 1.87* | 1.14-3.07 |
| | *Dependent Observations* | | | 0.99 | 0.98-1.00 | 1.00 | 0.99-1.01 |
| | *Mood Disorder* | | | | | 3.19*** | 1.67-6.10 |

Note: HR = Hazard Ratio, *p < .025. **p < .01. *** p <.001
Step 1: adjusted model including theoretical covariates; Step 2: post hoc analysis including covariate mood disorder.

Hypotheses and methods were preregistered on the Open Science Framework (OSF; June 15, 2018), and embargoed until September, 30, 2018. The registration form can be found on: https://osf.io/qpu4s/

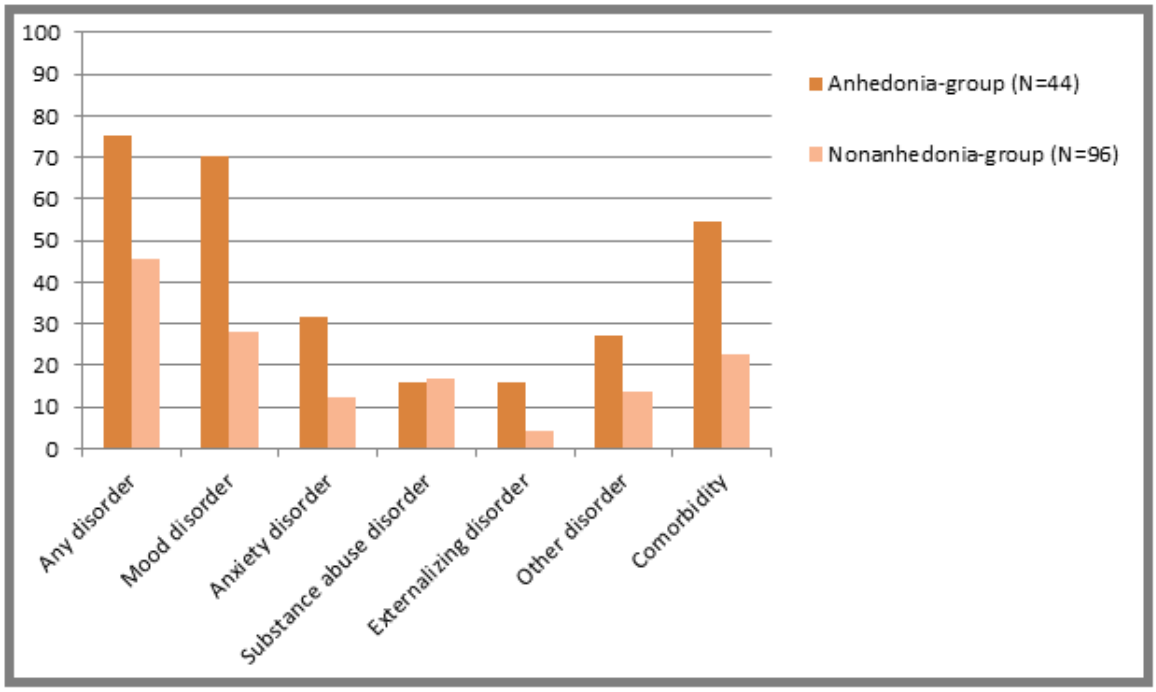


*Figure 1:* Percentage of Participants Developing Psychopathology Stratified by Anhedonia-group and Nonanhedonia-group.
Note: Other disorder includes enuresis, encopresis, pervasive developmental disorder, tic disorder, body dysmorphic disorder, and eating disorders.

Hypotheses and methods were preregistered on the Open Science Framework (OSF; June 15, 2018), and embargoed until September, 30, 2018. The registration form can be found on: https://osf.io/qpu4s/

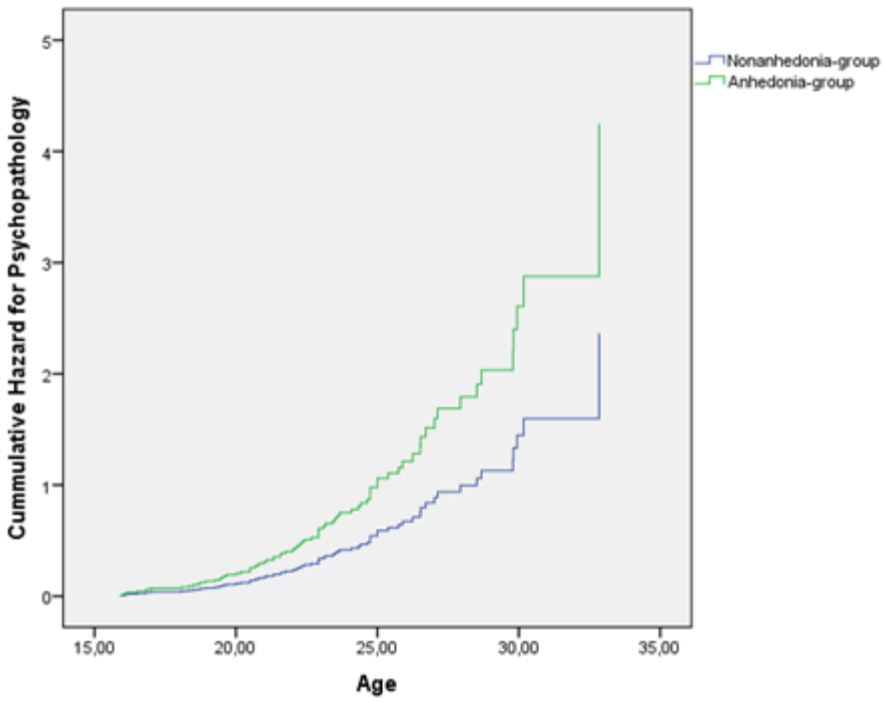


*Figure 2:* Cummulative Hazard Function for Developing Psychopathology Stratified by Nonanhedonia-group and Anhedonia-group.

Hypotheses and methods were preregistered on the Open Science Framework (OSF; June 15, 2018), and embargoed until September, 30, 2018. The registration form can be found on: https://osf.io/qpu4s/

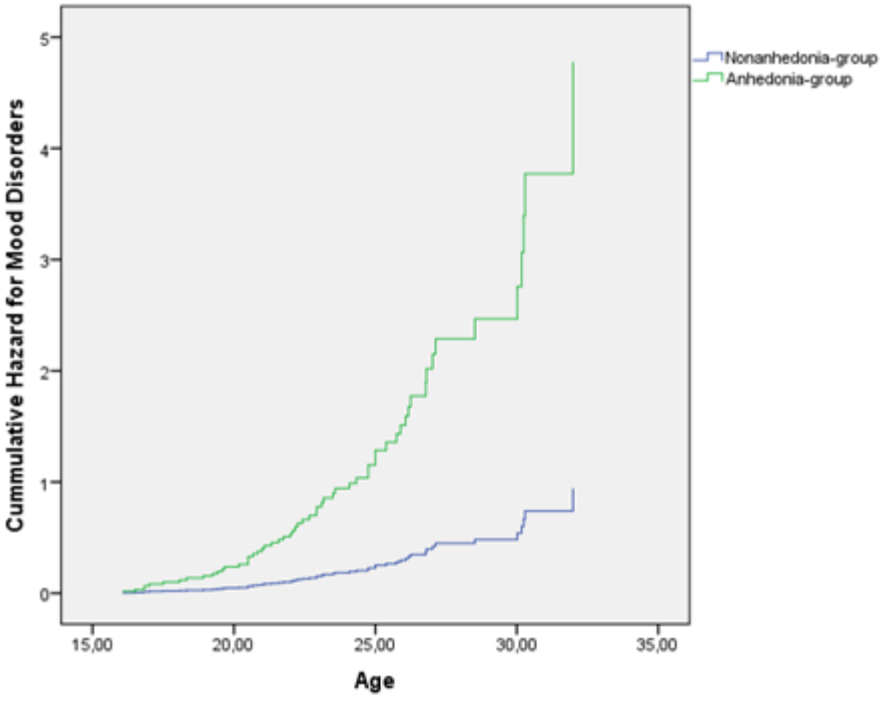


*Figure 3:* Cummulative Hazard Function for Developing Mood Disorders Stratified by Nonanhedonia-group and Anhedonia-group.

Hypotheses and methods were preregistered on the Open Science Framework (OSF; June 15, 2018), and embargoed until September, 30, 2018. The registration form can be found on: https://osf.io/qpu4s/

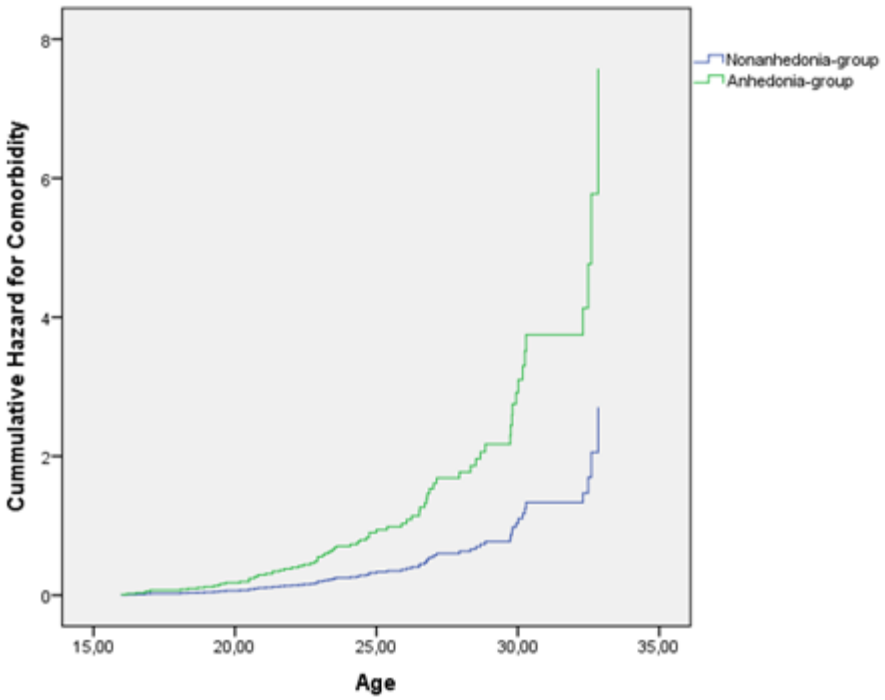


*Figure 4*: Cummulative Hazard Function for Developing Comorbidity Stratified by Nonanhedonia-group and Anhedonia-group.

Hypotheses and methods were preregistered on the Open Science Framework (OSF; June 15, 2018), and embargoed until September, 30, 2018. The registration form can be found on: https://osf.io/qpu4s/

**Supplementary Material**

Hypotheses and methods were preregistered on the Open Science Framework (OSF; June 15, 2018), and embargoed until September, 30, 2018. The registration form can be found on: https://osf.io/qpu4s/

Table A

*Composition of Anhedonia Dichotomous Outcome Variable*

| **Anhedonia reports** | **T1(140)** | **T2(108)** | |
|---|---|---|---|
| Anhedonia present | 13 | 12 | |
| Anhedonia past | 26 | 16 | |
| Lifetime (present + past) | 36 (26%) | 25(23%) | |
| **Total** | | | 44 individuals reporting anhedonia (31%) |

Hypotheses and methods were preregistered on the Open Science Framework (OSF; June 15, 2018), and embargoed until September, 30, 2018. The registration form can be found on: https://osf.io/qpu4s/

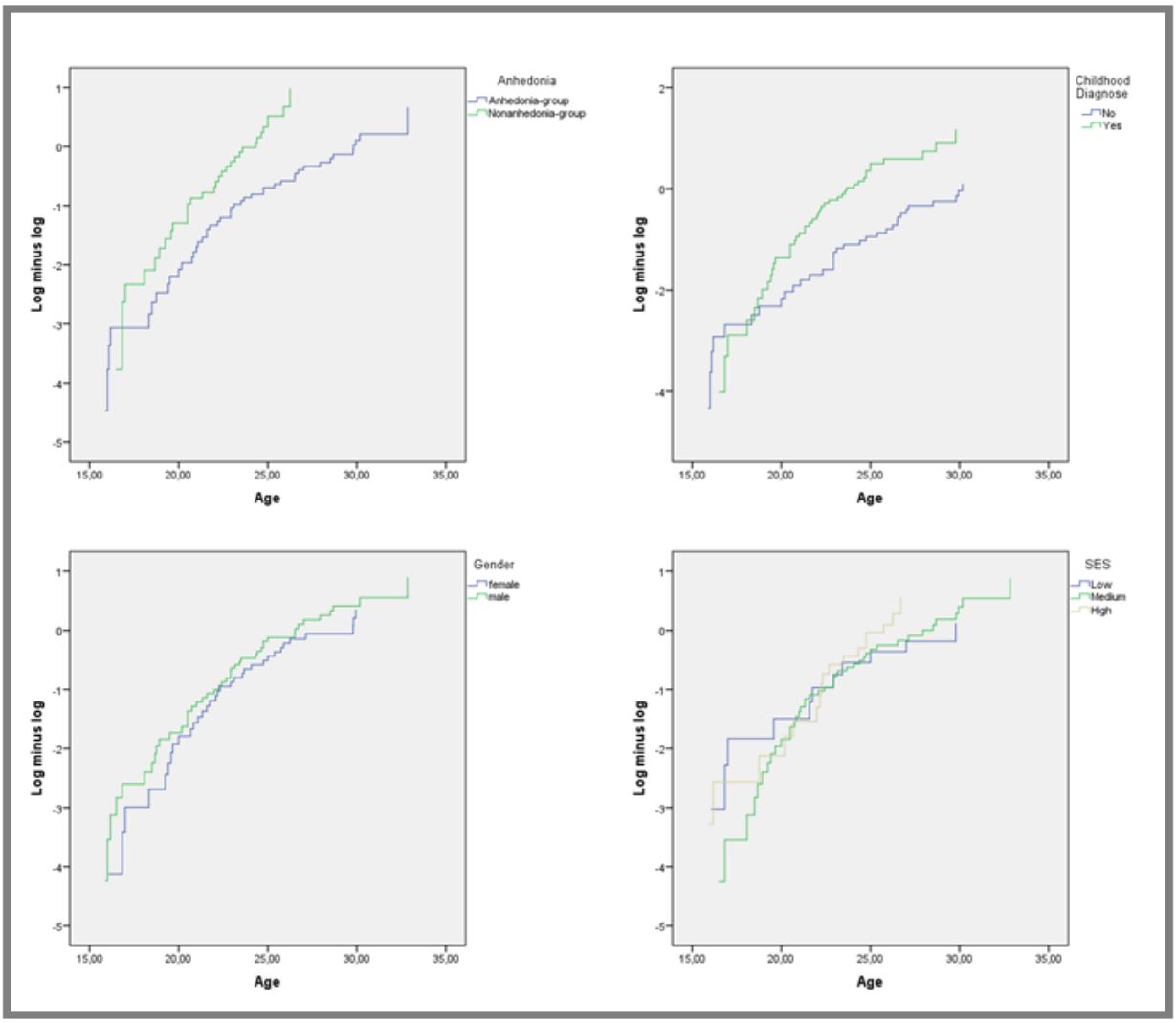


*Figure A*: Inspecting the Proportional Hazard Assumption using Log Minus Log Plots stratified on the Level for each Covariate (from left to right from top to down: Anhedonia, Childhood Diagnosis, Gender, SES = socio economic status).

Hypotheses and methods were preregistered on the Open Science Framework (OSF; June 15, 2018), and embargoed until September, 30, 2018. The registration form can be found on: https://osf.io/qpu4s/

## Syntax

***Recode anhedonia scores into dichotomous outcomes, add labels 0=no anhedonia, 1=anhedonia).**

```
RECODE anhe_nut1 anhe_verledent1 anhe_nut2 anhe_verledent2 (1=0) (2=1) (3=1)
(ELSE=99).
EXECUTE.
COMPUTE anhedonia_lifet1=0.
IF  (anhe_nut1=1 OR anhe_verledent1=1) anhedonia_lifet1=1.
IF (anhe_nut1=99 AND anhe_verledent1=99) anhedonia_lifet1=99.
EXECUTE.
COMPUTE anhedonia_lifet2=0.
IF  (anhe_nut2=1 OR anhe_verledent2=1) anhedonia_lifet2=1.
IF (anhe_nut2=99 AND anhe_verledent2=99) anhedonia_lifet2=99.
EXECUTE.
COMPUTE anhedonia_life=0.
IF  (anhedonia_lifet1=1 OR anhedonia_lifet2=1) anhedonia_life=1.
EXECUTE.

* Encoding: UTF-8.
COMPUTE censored=1.
EXECUTE.
IF  (t3afgeno=0 OR T4afgeno=0) censored=0.
EXECUTE.
```

***Creating survival data stepwise**
**MOOD DISORDERS**

```
COMPUTE moodyesno=0.
IF (BDlft4=1 OR mdd.lft4=1 OR dysthymie.lft=1 OR deprnos.lft4=1 OR adj.mood.lft4=1)
moodyesno= 1.
IF (bd.lft3=1 OR mdd.lft3=1 OR omd.lft3=1) moodyesno=1.
EXECUTE.
IF (t3afgeno=0 OR T4afgeno=0) moodyesno= 99.
EXECUTE.

COMPUTE moodt34=99.
IF (BDlft4=0 OR mdd.lft4=0 OR dysthymie.lft=0 OR deprnos.lft4=0 OR adj.mood.lft4=0)
moodt34 = age.t4.
IF (bd.lft3=0 OR mdd.lft3=0 OR omd.lft3=0) moodt34=age.t4.

IF (BDlft4=1 OR mdd.lft4=1 OR dysthymie.lft=1 OR deprnos.lft4=1 OR adj.mood.lft4=1)
moodt34 = age.t4.
IF (bd.lft3=1 OR mdd.lft3=1 OR omd.lft3=1) moodt34=age.t3.
EXECUTE.

IF (t4afgeno=0) moodt34= age.t3.
IF (t3afgeno=0) moodt34 = age.t2.
```

```
IF (t2afgeno=0) moodt34 = age.t1.
execute.
```

**ANXIETY DISORDERS**

```
COMPUTE anxietyesno=0.
IF (axd.lft3=1) anxietyesno= 1.
IF (axd.lft4=1) anxietyesno=1.
EXECUTE.

IF (t3afgeno=0 OR T4afgeno=0) anxietyesno= 99.
EXECUTE.

COMPUTE anxiet34=99.
IF (axd.lft4=0) anxiet34 = age.t4.
IF (axd.lft3=0) anxiet34=age.t4.
EXECUTE.

IF (axd.lft4=1) anxiet34 = age.t4.
IF (axd.lft3=1) anxiet34 = age.t3.
EXECUTE.

IF (t4afgeno=0) anxiet34= age.t3.
IF (t3afgeno=0) anxiet34 = age.t2.
IF (t2afgeno=0) anxiet34 = age.t1.
execute.
```

**EXTERNALIZING DISORDERS**

```
COMPUTE extyesno=0.
IF (adhd.lft3=1 OR cd.lft3=1) extyesno= 1.
IF (adhd.lft4=1 OR cd.lft4=1) extyesno=1.
EXECUTE.

IF (t3afgeno=0 OR T4afgeno=0) extyesno= 99.
EXECUTE.

COMPUTE ext34=99.
IF (adhd.lft4=0 OR cd.lft4=0) ext34 = age.t4.
IF (adhd.lft3=0 OR cd.lft3=0) ext34 = age.t4.
EXECUTE.

IF (adhd.lft4=1 OR cd.lft4=1) ext34 = age.t4.
IF (adhd.lft3=1 OR cd.lft3=1) ext34 = age.t3.
EXECUTE.

IF (t4afgeno=0) ext34= age.t3.
```

```
IF (t3afgeno=0) ext34 = age.t2.
IF (t2afgeno=0) ext34= age.t1.
execute.
```

**SUBSTANCE ABUSE**

```
COMPUTE substanyesno=0.
IF (aad.lft3=1) substanyesno= 1.
IF (aad.lft4=1) substanyesno=1.
EXECUTE.

IF (t3afgeno=0 OR T4afgeno=0) substanyesno= 99.
EXECUTE.

COMPUTE subst34=99.
IF (aad.lft4=0) subst34 = age.t4.
IF (aad.lft3=0) subst34=age.t4.
EXECUTE.

IF (aad.lft4=1) subst34 = age.t4.
IF (aad.lft3=1) subst34 = age.t3.
EXECUTE.

IF (t4afgeno=0) subst34= age.t3.
IF (t3afgeno=0) subst34 = age.t2.
IF (t2afgeno=0) subst34 = age.t1.
execute.
```

**OTHER DISORDERS**

```
COMPUTE otheryesno=0.
IF (otherlft3=1) otheryesno= 1.
IF (otherlft4=1) otheryesno=1.
EXECUTE.

IF (t3afgeno=0 OR T4afgeno=0) otheryesno= 99.
EXECUTE.

COMPUTE other34=99.
IF (otherlft4=0) other34 = age.t4.
IF (otherlft3=0) other34=age.t4.
EXECUTE.

IF (otherlft4=1) other34 = age.t4.
IF (otherlft3=1) other34 = age.t3.
EXECUTE.

IF (t4afgeno=0) other34= age.t3.
```

```
IF (t3afgeno=0) other34 = age.t2.
IF (t2afgeno=0) other34 = age.t1.
EXECUTE.
```

**PSYCHOPATHOLOGY**

```
COMPUTE disorderyesno=0.
IF (moodyesno=1 OR anxietyesno=1 OR otheryesno=1 OR substanyesno=1 OR extyesno=1)
disorderyesno= 1.
EXECUTE.

COMPUTE disorder34=99.
IF (disorderlft4=0) disorder34 = age.t4.
IF (disorderlft3=0) disorder 34=age.t4.
EXECUTE.

IF (t4afgeno=0) disorder34= age.t3.
IF (t3afgeno=0) disorder34 = age.t2.
IF (t2afgeno=0) disorder34 = age.t1.
execute.
```

**COMORBIDITY**

```
COMPUTE comortussen=0.
IF (moodyesno=1 AND anxietyesno=1) comortussen=2.
IF  (moodyesno=1 AND otheryesno =1) comortussen=2.
IF (moodyesno=1 AND substanyesno=1) comortussen=2.
IF (moodyesno=1 AND extyesno=1) comortussen=2.
IF (anxietyesno=1 AND otheryesno=1) comortussen=2.
IF (anxietyesno=1 AND substanyesno=1) comortussen=2.
IF (anxietyesno=1 AND extyesno=1) comortussen=2.
IF (otheryesno=1 AND substanyesno=1) comortussen=2.
IF (otheryesno=1 AND extyesno=1) comortussen=2.
IF (substanyesno=1 AND extyesno=1) comortussen=2.
EXECUTE.

compute comoryesno=0.
IF (disorderyesno=1) comoryesno=1.
IF (comortussen=2) comoryesno=2.
EXECUTE.
```

**COVARIATE CHILDHOOD DIAGNOSIS**

```
COMPUTE diagnoseT1T2=0.
IF (diagnv1=1 OR diagnt2=1) diagnoseT1T2=1.
EXECUTE.
```

**TESTEN VAN DE PH ASSUMPTIE**

**SES**

```
**recode ses for PH assumption*.
```

```
RECODE ses1tot9 (2=1) (3=1) (4=2) (5=2) (6=2) (7=3) (8=3) (9=3) INTO SES1to3.
EXECUTE.

COXREG disordert34
  /STATUS=disorderyesno(1)
  /STRATA=SES1to3
  /PLOT SURVIVAL HAZARDS LML
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

**DiagnoseT1T2**

```
COXREG disordert34
  /STATUS=disorderyesno(1)
  /STRATA=diagnoseT1T2
  /PLOT SURVIVAL HAZARDS LML
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

**ANHEDONIA**

```
COXREG disordert34
  /STATUS=disorderyesno(1)
  /STRATA=anhedonia_life
  /PLOT SURVIVAL HAZARDS LML
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

**GENDER**

```
COXREG disordert34
  /STATUS=disorderyesno(1)
  /STRATA=geslacht
  /PLOT SURVIVAL HAZARDS LML
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

**RQ1: Dichotomous, do anhedonics have higher change of getting a disorder?**

missing values moodyesno anxietyesno otheryesno substanyesno extyesno comoryesno disorderyesno (99).

***unadjusted model**

```
COXREG disordert34
  /STATUS=disorderyesno(1)
  /PATTERN BY anhedonia_life
  /CONTRAST (anhedonia_life)=Indicator(1)
  /METHOD=ENTER anhedonia_life
  /PLOT SURVIVAL HAZARDS
  /PRINT=CI(95) CORR
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

***step1**

```
COXREG disordert34
  /STATUS=disorderyesno(1)
  /PATTERN BY anhedonia_life
  /CONTRAST (anhedonia_life)=Indicator(1)
  /METHOD=ENTER anhedonia_life diagnoseT1T2
  /PLOT SURVIVAL HAZARDS
  /PRINT=CI(95) CORR
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

***step2: adjusted model**

```
COXREG disordert34
  /STATUS=disorderyesno(1)
  /PATTERN BY anhedonia_life
  /CONTRAST (anhedonia_life)=Indicator(1)
  /METHOD=ENTER anhedonia_life diagnoseT1T2 ses1tot9 geslacht famid
  /PLOT SURVIVAL HAZARDS
  /PRINT=CI(95) CORR
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

**RQ2: For which disorders specifically , seperately**

**MOOD**

***unadjusted model**

```
COXREG moodt34
  /STATUS=moodyesno(1)
  /PATTERN BY anhedonia_life  /CONTRAST(anhedonia_life)=Indicator(1)
  /METHOD=ENTER anhedonia_life
  /PLOT SURVIVAL HAZARDS
  /PRINT=CI(95) CORR
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

***step 1**

```
COXREG moodt34
  /STATUS=moodyesno(1)
  /PATTERN BY anhedonia_life  /CONTRAST(anhedonia_life)=Indicator(1)
  /METHOD=ENTER anhedonia_life diagnoseT1T2
  /PLOT SURVIVAL HAZARDS
  /PRINT=CI(95) CORR
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

***step 2: adjusted model**

```
COXREG moodt34
  /STATUS=moodyesno(1)
  /PATTERN BY anhedonia_life  /CONTRAST(anhedonia_life)=Indicator(1)
  /METHOD=ENTER anhedonia_life diagnoseT1T2 ses1tot9 geslacht famid
  /PLOT SURVIVAL HAZARDS
  /PRINT=CI(95) CORR
```

```
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

**ANXIETY**

***unadjusted model**

```
COXREG anxiet34
  /STATUS=anxietyesno(1)
  /PATTERN BY anhedonia_life  /CONTRAST(anhedonia_life)=Indicator(1)
  /METHOD=ENTER anhedonia_life
  /PLOT SURVIVAL HAZARDS
  /PRINT=CI(95) CORR
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

***step 1**

```
COXREG anxiet34
  /STATUS=anxietyesno(1)
  /PATTERN BY anhedonia_life  /CONTRAST(anhedonia_life)=Indicator(1)
  /METHOD=ENTER anhedonia_life  diagnoseT1T2
  /PLOT SURVIVAL HAZARDS
  /PRINT=CI(95) CORR
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

***step 2: adjusted model**

```
COXREG anxiet34
  /STATUS=anxietyesno(1)
  /PATTERN BY anhedonia_life  /CONTRAST(anhedonia_life)=Indicator(1)
  /METHOD=ENTER anhedonia_life diagnoseT1T2 ses1tot9 geslacht famid
  /PLOT SURVIVAL HAZARDS
  /PRINT=CI(95) CORR
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

**OTHER**

***unadjusted model**

```
COXREG other34
  /STATUS=otheryesno(1)
  /PATTERN BY anhedonia_life  /CONTRAST(anhedonia_life)=Indicator(1)
  /METHOD=ENTER anhedonia_life
  /PLOT SURVIVAL HAZARDS
  /PRINT=CI(95) CORR
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

***step 1**

```
COXREG other34
  /STATUS=otheryesno(1)
/PATTERN BY anhedonia_life  /CONTRAST(anhedonia_life)=Indicator(1)
  /METHOD=ENTER anhedonia_life diagnoseT1T2
  /PLOT SURVIVAL HAZARDS
```

```
  /PRINT=CI(95) CORR
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

*__step 2: adjusted model__

```
COXREG other34
  /STATUS=otheryesno(1)
/PATTERN BY anhedonia_life  /CONTRAST(anhedonia_life)=Indicator(1)
  /METHOD=ENTER anhedonia_life diagnoseT1T2 ses1tot9 geslacht famid
  /PLOT SURVIVAL HAZARDS
  /PRINT=CI(95) CORR
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

*SUBSTANCE*

***unadjusted model**

```
COXREG subst34
  /STATUS=substanyesno(1)
  /PATTERN BY anhedonia_life  /CONTRAST(anhedonia_life)=Indicator(1)
  /METHOD=ENTER anhedonia_life
  /PLOT SURVIVAL HAZARDS
  /PRINT=CI(95) CORR
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

*__step 1__

```
COXREG subst34
  /STATUS=substanyesno(1)
/PATTERN BY anhedonia_life  /CONTRAST(anhedonia_life)=Indicator(1)
  /METHOD=ENTER anhedonia_life diagnoseT1T2
  /PLOT SURVIVAL HAZARDS
  /PRINT=CI(95) CORR
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

*__step 2: adjusted model__

```
COXREG subst34
  /STATUS=substanyesno(1)
/PATTERN BY anhedonia_life  /CONTRAST(anhedonia_life)=Indicator(1)
  /METHOD=ENTER anhedonia_life  diagnoseT1T2 ses1tot9 geslacht famid
  /PLOT SURVIVAL HAZARDS
  /PRINT=CI(95) CORR
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

*EXTERNALIZING*

***unadjusted model**

```
COXREG ext34
  /STATUS=extyesno(1)
  /PATTERN BY anhedonia_life  /CONTRAST(anhedonia_life)=Indicator(1)
  /METHOD=ENTER anhedonia_life
```

```
  /PLOT SURVIVAL HAZARDS
  /PRINT=CI(95) CORR
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

*__step 1__

```
COXREG ext34
  /STATUS=extyesno(1)
/PATTERN BY anhedonia_life  /CONTRAST(anhedonia_life)=Indicator(1)
  /METHOD=ENTER anhedonia_life diagnoseT1T2
  /PLOT SURVIVAL HAZARDS
  /PRINT=CI(95) CORR
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

*__step 2: adjusted model__

```
COXREG ext34
  /STATUS=extyesno(1)
/PATTERN BY anhedonia_life  /CONTRAST(anhedonia_life)=Indicator(1)
  /METHOD=ENTER anhedonia_life diagnoseT1T2 ses1tot9 geslacht famid
  /PLOT SURVIVAL HAZARDS
  /PRINT=CI(95) CORR
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

*_*COMORBIDITY*_*

***Unadjusted model**

```
COXREG comort34
  /STATUS=comoryesno(1 2)
  /PATTERN BY anhedonia_life  /CONTRAST(anhedonia_life)=Indicator(1)
  /METHOD=ENTER anhedonia_life
  /PLOT SURVIVAL HAZARDS
  /PRINT=CI(95) CORR
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

*__step 1__

```
COXREG comort34
  /STATUS=comoryesno(1 2)
  /PATTERN BY anhedonia_life  /CONTRAST(anhedonia_life)=Indicator(1)
  /METHOD=ENTER anhedonia_life diagnoseT1T2
  /PLOT SURVIVAL HAZARDS
  /PRINT=CI(95) CORR
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

***step 2: adjusted model**

```
COXREG comort34
  /STATUS=comoryesno(1 2)
/PATTERN BY anhedonia_life  /CONTRAST(anhedonia_life)=Indicator(1)
  /METHOD=ENTER anhedonia_life diagnoseT1T2 ses1tot9 geslacht famid
```

```
  /PLOT SURVIVAL HAZARDS
  /PRINT=CI(95) CORR
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

***additionally, post hoc analysis**

```
COXREG comort34
  /STATUS=comoryesno(1 2)
/PATTERN BY anhedonia_life  /CONTRAST(anhedonia_life)=Indicator(1)
  /METHOD=ENTER anhedonia_life diagnoseT1T2 ses1tot9 geslacht famid mooddisorderyesno
  /PLOT SURVIVAL HAZARDS
  /PRINT=CI(95) CORR
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```