The Development of Anxiety Symptoms in Adolescents

Christina Mathyssek

The study reported in this thesis was performed at the Department of Child and Adolescent Psychiatry/ Psychology, Erasmus University Medical Center – Sophia Children's Hospital, Rotterdam, The Netherlands.

This research is part of the TRacking Adolescents' Individual Lives Survey (TRAILS). Participating centers of TRAILS include the University Medical Center and University of Groningen, the Erasmus University Medical Center Rotterdam, the University of Utrecht, the Radboud Medical Center Nijmegen, and the Parnassia Bavo group, all in the Netherlands. Publication of this thesis was supported by various grants from the Netherlands Organization for Scientific Research (NOW), the Sophia Foundation for Medical Research, the Dutch Ministry of Justice (WODC), the European Science Foundation, and the participating universities.

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The Development of Anxiety Symptoms in Adolescents

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Chapter 1

General introduction

Anxiety disorders are the most frequent mental health problem in children and adolescents, with prevalence rates estimated to be around 10-15% [1] and extensive debilitating consequences [2, 3]. Adolescence is an important time window in the development of anxiety disorders, as 75% of all cases of anxiety disorders have their onset between ages 11 and 21 years [4]. Furthermore, many anxiety disorders in adolescents are characterized by low rates of remission if untreated [4, 5]. Consequently, it is relevant to study anxiety onset, development and consequences in adolescence.

Anxiety can be studied in a categorical way (diagnosis: yes or no), or in a dimensional way (symptom or severity scores). While in the past the categorical approach dominated, in recent years, increasing attention has been given to anxiety symptoms which do not meet diagnostic criteria. Due to the large variety in definitions and assessment methods of anxiety symptoms, it is difficult to estimate their prevalence. Anxiety symptoms predict the onset of anxiety disorder and depression [4, 6], and have been associated with lower levels of well-being even before they reach disorder status [7]. Hence, it is important to assess anxiety symptoms across adolescence in order to recognize potential anxiety problems and prevent the development of anxiety disorders. By merely focusing on anxiety disorders, we would disregard warning signs and an opportunity for prevention and early intervention. In this thesis, I focus on factors that are associated with anxiety symptoms in adolescence in order to better help understand potential risk factors and outcomes of anxiety symptoms. In this chapter, I will introduce the research themes of the thesis.

Proper measurement of anxiety symptoms in longitudinal studies

Longitudinal studies are an invaluable tool for tracking the development of anxiety symptoms. To study the development of anxiety, anxiety needs to be measured repeatedly over time in the same individuals. In doing so, it is tempting to assume that any change we measure with our instrument reflects true and potentially meaningful changes in the anxiety symptom levels. However, for this assumption to be true, it first needs to be established that the instrument measures anxiety symptoms similarly at different ages across adolescence - a feature called *longitudinal measurement invariance*. An instrument can be tested for its measurement invariance properties with a hierarchical set of psychometric tests [8, 9]. If longitudinal measurement invariance has been established, we can assume that a change in measured anxiety severity reflects a true change in the anxiety level across time; whereas if longitudinal measurement invariance criteria are not being met, a change in assessed anxiety symptom levels over time may reflect differences in measurement sensitivity across time rather than a true change in anxiety levels. Most importantly, if measurement invariance has not been established in an instrument, we simply cannot tell how much our findings can be trusted. Hence, it is important to first establish the measurement invariance properties of an instrument, so that the level of longitudinal measurement invariance can be taken into account when interpreting change or stability of anxiety symptom levels across time.

Puberty and anxiety

A developmental process that coincides with adolescence is puberty. Puberty is a period during which extensive physical development occurs, including physical growth and the development of primary

and secondary sexual characteristics. Along with these physical changes, social and emotional changes occur. Most research on puberty has focused on the level of physical development, which can be assessed by determining the *pubertal status* through questions or examination of the occurrence of physical changes that typically happen during puberty. Findings from studies assessing the association between anxiety symptoms and pubertal status are mixed: some found either a lack of association, or state anxiety to be higher at early stages of pubertal development (e.g., [10, 11]), while studies assessing anxiety subtypes found symptoms to positively correlate with pubertal status (e.g., [12, 13]. In summary, previous studies carefully suggest that advanced pubertal status is associated with a higher likelihood of anxiety symptoms, which cannot merely be explained by increasing chronological age [14].

More recently, studies have focused on *pubertal timing* as a potentially significant factor when assessing anxiety symptoms. Pubertal timing refers to the timing of when pubertal development occurs in relation to peers, i.e. it relates whether an adolescent is ahead of peers in pubertal development (early pubertal timing), in line with peers (on-time) or behind peers in pubertal development (late pubertal timing). Notably, while pubertal status is of influence when determining pubertal timing, it is mostly the peer reference group that determines pubertal timing, e.g. early pubertal timing can refer to almost any pubertal developmental stage. Therefore, pubertal timing is closely related to the social component of pubertal development.

Adolescents who are ahead of peers in pubertal development may experience the biological, psychological and social challenges associated with puberty before they may be psychologically prepared to cope with them effectively [15], which can be a risk factor for anxiety symptoms and disorders [15, 16]. Studies investigating the association between pubertal timing and anxiety symptoms have found mixed support for the theory that early developers have more anxiety symptoms, with several studies supporting this theory [16-18], while others finding conditional support [19], or no support [15]. These inconsistencies in findings spur new approaches to better understand this association.

In most of the studies, pubertal timing was determined once. The implicit assumption is that pubertal timing does not change across puberty. However, studies have shown that adolescents go through puberty at a different tempo, so that an adolescent who is “late” in pubertal timing at one point may “catch up” and be “on-time” at a later point. Yet, so far merely one study has explicitly adopted this dynamic approach: Reynolds and Juvonen allowed for intraperson variability when they assessed pubertal timing six times across a three year period. Indeed, they found pubertal timing to be a dynamic concept, with on average 18% of their sample changing in pubertal timing between assessment waves [20].

A related issue concerns the assumption that the association between pubertal timing and anxiety symptoms is constant across all of adolescence. The study by Reynolds and Juvonen [20] was the first to explicitly consider and confirm that the association between pubertal timing and social anxiety symptoms probably depends on age across adolescence. Both the dynamic approach to pubertal timing and an age-varying approach to the association between pubertal timing and anxiety

symptoms are new and important domains to explore as they may contribute to a better understanding of individuals at risk for anxiety symptoms.

Anxiety symptoms and sleep problems

An important health behavior that has been associated with anxiety symptoms is sleep and sleep problems. The interest in sleep research has spiked in recent years as more research revealed poor health outcomes associated with inadequate sleep, including mental health [21], physical health [22], and cognitive functioning [23, 24]. Most of the initial work on consequences of poor sleep was done in adults. However, it has been argued that these findings cannot blindly be extrapolated to children and adolescents due to their different sleep needs and characteristics [25-27]. Adolescence specifically has been recognized as a period where important changes in sleep need, sleep physiology and circadian rhythm occur. These considerations prompted sleep research in child and adolescent populations. The importance of this research is stressed by the fact that during childhood, and also adolescence, exposure to extreme stress can lead to deviant neural connections, impacting future cognitive, emotional and behavioral functioning [28]. Inadequate sleep has been hypothesized to qualify as such a stressor [29].

In most studies, it was implicitly or explicitly assumed that anxiety symptoms cause sleep problems. Longitudinal studies on the effect of anxiety problems on sleep problems in adolescents are rare and findings are mixed, as not all adolescents with anxiety symptoms experience sleep problems to the same extent: some may experience many sleep problems, while others experience fewer or none [30, 31]. Identifying factors that predict a higher risk for experiencing sleep problems in light of anxiety symptoms is important for a better understanding of who is at increased risk for developing sleep problems, and why. The mechanism underlying the association between anxiety symptoms and sleep problems is not well understood, but it has been suggested it goes through the arousal system. Specifically, one mechanism that might explain individual differences in risk for sleep problems is activity and reactivity of the parasympathetic nervous system (PNS), since PNS activity and reactivity is associated with both sleep [32, 33] and anxiety symptoms [34, 35].

Furthermore, in recent years researchers started to question the unilateral association between anxiety symptoms and sleep problems. The notion developed that the direction of this association is not unidirectional as assumed, but rather reciprocal. Indeed, one experimental study and several longitudinal studies in children and adolescents found that sleep problems preceded anxiety symptoms [30, 36-38], while another longitudinal study found that anxiety disorders preceded sleep problems [31]. However, some studies have failed to find any longitudinal association in one or the other direction [30]. Identifying temporal precedence is an important first step in understanding the etiology of anxiety symptoms and sleep problems, and longitudinal research may be the most valuable tool in adolescents, where experimental studies can be difficult to implement [39]. While the literature so far suggests a bidirectional association, much remains to be learned about the nature of this association, including the strength of this association across adolescence. Such studies are an important first step toward a better understanding of causality between these domains and can have important implications for prevention and intervention efforts.

Aim and research questions of this thesis

The main aim of this study is to further our knowledge of what factors are associated with anxiety symptoms in late childhood and adolescence. This includes predictors and outcomes of anxiety symptoms, as well as factors that may influence these associations. In this thesis, the following research questions are addressed:

1. Do internalizing and externalizing problems in childhood predict the onset of panic attacks in adolescence (chapter 2)?
2. Does the Revised Child Anxiety and Depression Scale (RCADS) measure anxiety symptoms similarly across age groups over adolescence (chapter 3)?
3. Does the association between pubertal timing and anxiety symptoms vary by age across adolescence (chapter 4)?
4. Is the longitudinal association between sleep problems and anxiety symptoms bidirectional across adolescence (chapter 5)?
5. Does (re)activity of the parasympathetic nervous system moderate the effect of anxiety on sleep problems (chapter 6)?

We investigated these research questions with data from the TRacking Adolescents' Individual Lives Survey (TRAILS). TRAILS is a longitudinal cohort study of children and adolescents from the general population in the Netherlands. Starting at age 10-12 years, 2,230 children have been followed across adolescence and into early adulthood, with assessments at 2-3 year intervals. TRAILS assessment waves were completed in 2002 (T1), 2004 (T2), 2007 (T3), and 2010 (T4). Details of TRAILS can be found in publications by de Winter et al. [40], Huisman et al. [41] and Ormel et al. [42].

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Chapter 2

Childhood internalizing and externalizing problems predict the onset of clinical panic attacks over adolescence

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ABSTRACT

Background: Panic attacks are a source of individual suffering and are an independent risk factor for later psychopathology. However, much less is known about risk factors for the development of panic attacks, particularly during adolescence when the incidence of panic attacks increases dramatically. We examined whether internalizing and externalizing problems in childhood predict the onset of panic attacks in adolescence.

Method: This study is part of the TRacking Adolescents' Individual Lives Survey (TRAILS), a Dutch longitudinal population cohort study (N=1,584). Internalizing and Externalizing Problems were collected using the Youth Self-Report (YSR) and the parent-report Child Behavior Checklist (CBCL) at baseline (age 10-12). At age 18-20, DSM-IV defined panic attacks since baseline were assessed with the Composite International Diagnostic Interview (CIDI). We investigated whether early adolescent Internalizing and Externalizing Problems predicted panic attacks between ages 10-20 years, using survival analysis in univariate and multivariate models.

Results: There were N=314 (19.8%) cases who experienced at least one DSM-IV defined panic attack during adolescence and N=18 (1.2%) who developed panic disorder during adolescence. In univariate analyses, CBCL Total Problems, Internalizing Problems and three of the eight syndrome scales predicted panic attack onset, while on the YSR all broad-band problem scales and each narrow-band syndrome scale predicted panic attack onset. In multivariate analyses, CBCL Social Problems (HR 1.19, $p<.05$), and YSR Thought Problems (HR 1.15, $p<.05$) and Social Problems (HR 1.26, $p<.01$) predicted panic attack onset.

Conclusion: Risk indicators of panic attack include the wide range of internalizing and externalizing problems. Yet, when adjusted for co-occurring problem behaviors, Social Problems were the most consistent risk factor for panic attack onsets in adolescence.

INTRODUCTION

The DSM-IV [1] classification includes clinical criteria for both panic attacks and panic disorder. The criteria for a diagnosis of panic attack are a discrete period of intense fear or discomfort, in which four or more out of thirteen (specified) panic symptoms (e.g., palpitations, sweating, trembling or shaking, feeling of choking) developed abruptly and reached a peak within ten minutes. Panic disorder requires (1) recurrent unexpected panic attacks and (2) at least one of the attacks has been followed by at least one month of persistent concern or worry about having panic attacks or its consequences and/or a significant change in behavior related to the attacks. Panic attacks may occur in the context of multiple anxiety disorders. They are considered to be amongst the most debilitating psychiatric conditions [2] and are associated with high level of mental health treatment seeking [3]. While it is known that early identification and subsequent intervention can reduce deleterious outcomes of psychiatric disorders [4], including panic disorder and panic attacks, research on risk factors for the onset of panic attacks is scarce. Some recent studies have identified panic attacks as a risk factor for other anxiety [4-6] and mood disorders [4, 5], independent of comorbid internalizing psychopathology. Although there is less consistency, there is some support for panic attacks to precede certain externalizing disorders, including alcohol use disorders [5, 7] and substance use [8, 9]. Hence, identifying predictors for the onset of panic attacks is an important research direction [7, 10].

The reported life-time prevalence of panic attacks when assessed by a clinical interview according to DSM criteria in youth samples ranges from 3.3% [4] to 11.6% [11]. This shows that the reported prevalence rate varies markedly across studies. Importantly, the lower prevalence rate was reported in a sample of 9-17 year olds, and the higher prevalence rate in a sample of 14-16 year olds, indicating that the prevalence rates increase with age in adolescent samples. Even higher lifetime prevalence rates are reported in studies using questionnaires instead of interviews to assess the DSM-criteria (21.4% [5] – 63.3% [12]. Females typically have a higher prevalence than males [12], while no differences were found in socio-demographic characteristics between adolescents with and without panic attacks [4]. In addition, a meta-analysis [13] of the heritability of panic disorder revealed that genetic factors accounted for a large proportion of variance (43%). However, to our knowledge, no study has reported heritability for panic attacks.

As the typical age of onset of panic attacks is in late adolescence or early adulthood [14], with a peak between 15 and 19 years [15], it is crucial to examine prospective associations beginning in early adolescence. Identification of predictors of panic attacks early in development is also critical as earlier onsets are associated with increased rates of later psychopathology [16].

The few longitudinal studies on predictors of panic attacks have mostly focused on internalizing problems (emotional problems, e.g. anxiety, depression, other mood disorders). In a sample of high school students assessed over a 4-year period, negative affect [17, 18], anxiety sensitivity [5, 18], as well as separation anxiety disorder [17] were associated with an increased risk for panic attack onset in adolescents. Despite the fact that our knowledge of predictors for adolescent panic attacks is limited, no study to date has prospectively incorporated a broader range of problems, including externalizing problems (behavioral problems, e.g. conduct disorder, oppositional defiant disorder) as possible predictors. Besides internalizing problems, it is important to study other mental health

problems as predictors of DSM-IV defined panic attacks since Roza et al. [19] found that both internalizing and externalizing problems in children and adolescents were predictive of anxiety disorders in young adulthood.

The aim of the current study is to extend the limited literature on predictors of panic attack onset, including both internalizing and externalizing problems in early adolescence. We hypothesized that a range of adolescent mental health problems including internalizing problems predict panic attack onset in adolescence. Furthermore, we explore if externalizing problems are part of these predictors. This study is part of the TRacking Adolescents' Individual Lives Survey (TRAILS), a Dutch general population cohort study following 2,230 children from early adolescence (age 10-12 years) into young adulthood.

METHODS

Ethics statement

Written informed consent was obtained at each assessment wave from each participant and their parents. The study was approved by the Dutch Central Medical Ethics Committee (CCMO) and all participants were compensated for their involvement in this study.

Study design and population

Participants were recruited from the general population in five municipalities in the northern part of The Netherlands, including both urban and rural areas. All children living in these municipalities and born between October 1989 and September 1990 (two sites) and October 1990 and September 1991 (three sites) were selected (N=3,483). Their date of birth and contact information was obtained through the municipality administrations. The first exclusion criterion was non-participation of the school (9.6% of schools, N=338 children). If the school of a selected child was willing to participate, parents were approached with information brochures (one for themselves and one for their children) and a follow-up phone call in which they were invited to participate. Inability to participate in the study due to severe mental retardation, a severe physical illness, or language-limitations (N=210) was the second exclusion criterion. Of the 3,483 selected children, 2,935 were eligible for the study, of whom 2,230 (76.0%, of which 50.8% girls) participated in the first wave (T1; 2001-2002; age range 10-12 years). Non-response was due to explicit refusal or inability to establish contact [20]. This response rate was considered adequate given the fact that both parent and child had to agree to participate [21]. Extensive efforts were taken to minimize non-response, including reminder letters and personal house visits [22]. Details of TRAILS have been described elsewhere [21] and are available upon request. Non-response bias was analyzed based on information about mental health determinants and outcomes as reported by teachers of responders and non-responders [20]. Responders and non-responders did not differ in prevalence of psychopathology at T1, and did not differ regarding associations between socio-demographic variables and mental health variables [20]. At T4 (2008-2010; age range 17-20 years), 1,881 respondents (84.3%) continued to participate. Of those, 1,584 subjects provided outcome data, which is 84.2% of T4 participants and 71.0% of T1 participants. When comparing the T1 sample with participants who provided T4 outcome data, we found that T1

predictors of not providing outcome data were male gender (T1 49.2% vs. T4 46.0%), low socio-economic status (T1 25.2% vs. T4 19.6%), ethnic minority background (T1 10.6% vs. T4 7.6%), one-parent family (T1 15.5% vs. T4 13.5%), and a Total Problem score of the Child Behavior Checklist (CBCL/6-18) [23] in the clinical range at baseline (T1 16.1% vs. T4 13.9%).

Of these 1,584 subjects, 405 subjects reported a life-time history of DSM-IV defined panic attacks. Subjects with panic attack onset before the T1 assessment (N=90) as well as subjects who did not report an age of onset (N=1) were excluded from the analyses to avoid potential reverse-causal inferences. This rendered N=1,493 for analyses.

Instruments

Life-time prevalence of DSM-IV [1] panic attacks and panic disorder was assessed with the Composite International Diagnostic Interview (CIDI) [24, 25]. This is a comprehensive, fully-structured clinical interview for the diagnosis of mental disorders according to the definitions and criteria from DSM-IV. The first part of the CIDI interview consists of a set of probing screening question for all conditions and disorders of interest. If the panic attack/ panic disorder screening question is endorsed, the trained interviewer uses the disorder-specific portion of the CIDI to assess exactly which DSM-IV criteria were met as well as the age of onset and frequency of the attacks. A computer algorithm uses these answers to determine whether DSM criteria for disorders were fulfilled. For this study, we used the life-time diagnosis of panic attack and the self-reported age of onset. Good reliability and validity have been reported for the CIDI [26].

For the assessment of internalizing and externalizing problems, we used the Dutch translations of the parent reported Child Behavior Checklist (CBCL/6-18) [23, 27] and the Youth Self-Report (YSR) [28, 29]. Both questionnaires assess internalizing and externalizing problems during the past six months on a 3-point scale (0=not true; 1=somewhat/sometimes true; 2=very/often true). The CBCL and YSR are scored on eight narrow-band syndrome scales: Anxious/Depressed, Somatic Complaints, Withdrawn, Aggressive Behavior, Rule Breaking Behavior, Attention Problems, Social Problems and Thought Problems. In addition, broad-band Internalizing, Externalizing and Total Problem scores can be calculated [23, 28]. The Internalizing Problems score is the sum of the three scales Anxious/Depressed, Somatic Complaints and Withdrawn. Externalizing Problems is the sum of the two scales Aggressive Behavior and Rule Breaking Behavior. The Total Problem score is the sum of the eight subscales as well as additional items not included in the subscales (CBCL: 16 additional items; YSR: 10 additional items). The items and subscales on the youth self-report and the parent-report questionnaire correspond. The Dutch translation has adequate psychometric properties [27, 29].

Socio-economic status (SES) was based on ratings of occupation and education of both mother and father, as well as income. Z-scores of all five components were calculated and categorized into low (lowest 25%), medium (mid 50%) and high (upper 25%) SES. Ethnicity was self-reported and dichotomized as Dutch or non-Dutch.

Analysis

First, to examine if the panic attack sufferers between T1 and T4 differed from the subjects without panic attacks with respect to sex, age, SES, ethnicity and Internalizing and Externalizing_Problems as assessed by their subscale scores of the CBCL and YSR at T1, we used Chi-square tests and analysis of variance (ANOVAs). All descriptive statistics and group comparisons were carried out using SPSS 18 for Windows.

To examine if internalizing and externalizing problems at T1 predict onset of panic attacks over adolescence, we performed continuous time survival analysis, using the maximum likelihood estimator with robust standard error (MLR), which adjusts for non-normality. The baseline hazard was non-parametrical and all survival analyses were carried out in MPlus 5.1 [30]. Sex and SES was included as covariate due to its relation to panic attacks and to multiple dimensions of problem behaviors. Survival time was the interval in years between participants' age at T1 and age of onset of panic attacks (uncensored), or, in case of no CIDI diagnosis, age at T4 (censored). The resulting hazard ratio of this analysis describes the association between early adolescence internalizing and externalizing problems and onset of panic attacks. They are the log odds of the incremental probability of panic attacks for a unit change in the standardized score (mean=0; standard deviation=1) of the predictor. We performed the survival analyses in univariate as well as multivariate models. For all analyses, the significance level was set to $p < .05$.

RESULTS

Prevalence of panic attacks between T1 (age 10-12) and T4 (age 17-20) was 19.8%, and the prevalence of panic disorder 1.2%. Girls were significantly more likely than boys to have had at least one panic attack between T1 and T4 and individuals from a high SES were significantly less likely to have had at least one panic attack between T1 and T4 than individuals from a low or medium SES background (Table 1). The mean age of onset of panic attacks was 15.8 years (median 16 years) and the age of onset did not differ between girls and boys, $F(1)=.837$, $p=.36$

Table 1 shows the sum scores of the CBCL and YSR scales at T1. Adolescents with at least one panic attack between T1 and T4 had higher scores for parent-rated Anxious/Depressed, Social Problems and Internalizing Problems and Somatic Complaints at age 10-12 years than adolescents without a panic attack. Adolescents with at least one panic attack between T1 and T4 had higher scores on all of the self-report YSR scales at T1 than adolescents without a panic attack.

Table 1: *Sample characteristics and symptom sum scores for the full sample, and separately for subjects with and without panic attack onset between T1 and T4.*

Variable	Full sample	Lifetime CIDI Panic attack		
		Yes	No	
	N=1,493	N=314 (19.8%)	N=1,179	
	% / Mean (SD)	% / Mean (SD)	% / Mean (SD)	Significant statistics
Sex				χ^2 (1)=18.89 ***
female	53.8%	25.3%	74.7%	
male	46.2%	16.1%	83.9%	
SES				χ^2 (2)=7.11 *
low	19.5%	21.9%	78.1%	
mid	49.8%	22.9%	77.1%	
high	30.7%	16.6%	83.4%	
Ethnicity				
Dutch	92.6%	20.6%	79.4%	
non-Dutch	7.4%	26.4%	73.6%	
Age at T1	11.1 (.6)	11.1 (.6)	11.1 (.6)	
Panic disorder	1.2%			
CBCL				
Aggressive behavior[1] (18 items)	5.8 (4.8)	6.0 (4.7)	5.7 (4.8)	
Delinquent behavior[1] (17 items)	2.0 (2.0)	2.0 (1.8)	2.0 (2.1)	
Anxious/depressed[2] (13 items)	3.6 (3.1)	4.0 (3.4)	3.4 (3.0)	F (1,1412)=6.17 *
Somatic complaints[2] (11 items)	2.0 (2.2)	2.4 (2.3)	1.9 (2.2)	F (1,1408)=9.64 **
Withdrawn/depressed[2] (8 items)	1.9 (2.1)	1.9 (2.1)	1.9 (2.1)	
Attention problems (10 items)	4.1 (3.2)	4.0 (3.0)	4.1 (3.3)	
Social problems (11 items)	2.9 (2.8)	3.3 (3.1)	2.8 (2.8)	F (1,1412)=6.15 *
Thought problems (15 items)	2.2 (2.3)	2.3 (2.3)	2.2 (2.3)	
Externalizing (35 items)	7.7 (6.4)	8.0 (6.1)	7.7 (6.4)	
Internalizing (32 items)	7.5 (5.8)	8.3 (6.2)	7.3 (5.7)	F (1,1412)=6.33 *
Total (119 items)	27.4 (18.0)	29.2 (18.7)	27.0 (17.8)	
YSR				
Aggressive behavior[1] (17 items)	5.2 (4.0)	5.9 (4.3)	5.0 (4.0)	F (1,1470)=11.54 **
Delinquent behavior[1] (15 items)	3.3 (2.5)	3.8 (2.8)	3.2 (2.4)	F (1,1469)=12.09 **
Anxious/depressed[2] (13 items)	4.3 (3.5)	5.1 (3.9)	4.1 (3.4)	F (1,1472)=18.97 ***
Somatic complaints[2] (10 items)	4.4 (3.1)	4.9 (3.1)	4.2 (3.0)	F (1,1467)=10.60 **
Withdrawn/depressed[2] (8 items)	2.8 (2.3)	3.3 (2.4)	2.6 (2.3)	F (1,1470)=20.82 ***
Attention problems (9 items)	4.4 (2.7)	4.8 (2.8)	4.3 (2.6)	F (1,1475)=12.12 ***
Social problems (11 items)	4.1 (3.0)	4.9 (3.4)	3.9 (2.9)	F (1,1473)=29.07 ***
Thought problems (12 items)	3.4 (3.1)	4.2 (3.5)	3.2 (3.0)	F (1,1470)=26.86 ***
Externalizing (32 items)	8.5 (6.0)	9.7 (6.6)	8.2 (5.8)	F (1,1470)=14.01 ***
Internalizing (31 items)	11.4 (7.4)	13.2 (7.9)	10.9 (7.2)	F (1,1471)=23.53 ***
Total (105 items)	35.9 (19.6)	41.2 (21.2)	34.4 (19.0)	F (1,1460)=29.55 ***

Note: *p<.05 ** p <.01 *** p <.001; SD=standard deviation; CIDI= Composite International Diagnostic Interview; CBCL=Child Behavior Checklist; YSR=Youth Self-Report; [1] part of the Externalizing scale; [2] part of the Internalizing scale

Continuous-time survival analyses were performed to examine whether problems scores at age 10-12 years predicted first onsets of panic attacks during adolescence. The hazard ratios (HR) with 95% confidence interval (CI) adjusted for gender and SES are shown in Table 2 (parent-report) and Table 3 (self-report).

Table 2: *Results of univariate and multivariate models of survival analysis, predicting the onset of panic attacks with standardized CBCL scores and adjusted for gender and SES.*

	Hazard ratio (95% CI)	
CBCL subscales	Univariate	Multivariate[a]
Aggressive behavior[1]	1.09 (0.98-1.22)	1.03 (0.86-1.22)
Delinquent behavior[1]	1.06 (0.95-1.18)	0.98 (0.84-1.15)
Anxious/depressed[2]	1.15 (1.04-1.28)**	1.08 (0.92-1.27)
Somatic complaints[2]	1.15 (1.05-1.26)**	1.11 (1.00-1.23)
Withdrawn/depressed[2]	1.04 (0.93-1.16)	0.90 (0.78-1.04)
Attention problems	1.03 (0.92-1.15)	0.90 (0.78-1.05)
Social problems	1.17 (1.05-1.30)**	1.19 (1.01-1.41)*
Thought problems	1.09 (0.98-1.21)	1.00 (0.86-1.15)
Externalizing	1.09 (0.98-1.21)	1.01 (0.90-1.14)
Internalizing	1.15 (1.04-1.27)**	1.15 (1.02-1.28)*
Total score	1.15 (1.03-1.28)**	

Note: *p<.05 **p<.01 ***p<.0001; CBCL=Child Behavior Checklist; SES= Socio-economic status; CI=confidence interval; [1] part of the Externalizing scale; [2] part of the Internalizing scale; [a] the eight subscales were entered into one multivariate model, and the subscales *Externalizing* and *Internalizing* were entered into a separate multivariate model.

Table 3: *Results of univariate and multivariate models of survival analysis, predicting the onset of panic attacks with standardized YSR scores and adjusted for gender and SES.*

	Hazard ratio (95% CI)	
YSR Subscales	Univariate	Multivariate[a]
Aggressive behavior[1]	1.25 (1.13-1.38)***	1.02 (0.87-1.20)
Delinquent behavior[1]	1.26 (1.14-1.40)***	1.11 (0.96-1.29)
Anxious/depressed[2]	1.23 (1.11-1.36)***	0.93 (0.79-1.10)
Somatic complaints[2]	1.16 (1.05-1.29)**	0.97 (0.86-1.10)
Withdrawn/depressed[2]	1.25 (1.13-1.38)***	1.03 (0.89-1.19)
Attention problems	1.21 (1.09-1.36)**	0.95 (0.81-1.11)
Social problems	1.34 (1.21-1.49)***	1.26 (1.06-1.49)**
Thought problems	1.27 (1.16-1.39)***	1.15 (1.01-1.30)*
Externalizing	1.28 (1.16-1.42)***	1.19 (1.04-1.36)**
Internalizing	1.26 (1.14-1.40)***	1.14 (1.01-1.30)*
Total score	1.33 (1.20-1.47)***	

Note: *p<.05 **p<.01 ***p<.0001; YSR=Youth Self-Report; SES= Socio-economic status; CI=confidence interval; [1] part of the Externalizing scale; [2] part of the Internalizing scale; [a] the eight subscales were entered into one multivariate model, and the subscales *Externalizing* and *Internalizing* were entered into a separate multivariate model.

The CBCL Anxious/Depressed, Social Problems, Somatic Complaints, Internalizing, and Total Problems scores significantly predicted panic attack onset between T1 and T4 (all *p*s<.01, HR range from 1.15-1.17). As the individual problem scales share variance, we performed multivariate analyses to identify the unique contribution of each CBCL syndrome scale. With all eight syndrome scales in one model, only parent-reported Social Problems (HR= 1.19, 95%CI= 1.01-1.41) at age 10-12 years independently predicted panic attack onset (p<.05). In a final model, we examined the broad-band

Internalizing and Externalizing problem scores simultaneously. In this model, only Internalizing Problems predicted panic attack onset (HR= 1.15, 95%CI=1.02-1.28, $p<.05$).

Each of the eight YSR syndrome scales, as well as the Internalizing, Externalizing and Total Problems scales significantly predicted panic attack onset between T1 and T4. When the eight subscales were entered into a multivariate model, only the Social Problems (HR=1.26, 95%CI=1.06-1.49, $p<.01$) and Thought Problems (HR=1.15, 95%CI=1.01-1.30, $p<.05$) at age 10-12 years scales independently predicted panic attack onset. When examining Internalizing and Externalizing Problems simultaneously, both Internalizing Problems (HR=1.14, 95%CI=1.01-1.30, $p<.05$) and Externalizing Problems remained significant (HR=1.19, 95%CI=1.04-1.36, $p<.01$).

DISCUSSION

While having panic attacks increases risk for psychopathology, little is known about predictors of panic attacks. In this study, we measured panic attacks and tested the power of a broad range of both parent- and self-reported problems in 10 to 12 year-old children assessed with the CBCL and YSR to predict the onset of panic attacks across adolescence.

We found a life-time prevalence rate of panic attacks of 19.8%, which is higher than the few previous studies that have assessed panic attacks with a structured interview according to DSM criteria. We suspect that the age range of our study influenced this finding. The other population samples were younger, and lifetime prevalence increases relative to the age of the sample (prevalence 3.3% at age range 9-17 years [4]; prevalence 11.6% at age range 14-16 years [11]; prevalence 19.8% at age range 17-20 years). As the peak onset of panic attacks is between 15 and 19 years, it follows that the prevalence rate of our study sample is higher than in the previous studies.

The parent-reported CBCL scales Anxious/Depressed, Social Problems, Somatic Complaints, Internalizing, and Total Problems scores predicted first onset of panic attack in adolescence. Only the Social Problems and Somatic Complaints syndrome scale predicted panic attack onset when we controlled for shared variance of the scales. All eight self-reported YSR syndrome scales, as well as the Internalizing, Externalizing and Total Problems scales predicted the onset of panic attacks. After controlling for shared variance among the eight syndrome scales and among the Internalizing and Externalizing scales in the multivariate analyses, we found that the Social Problems, Thought Problems and Externalizing scales predicted adolescent panic attack onset.

At first sight, a broad range of problem perceptions are predictive of panic attack onset. This is consistent with Hayward et al.'s suggestion that there are different pathways that lead to adolescent panic attacks [17]; however, their focus was on pathways within the internalizing spectrum of problems. Our findings extend this beyond internalizing problems to include externalizing problems and also a more wide-ranging, general perception of problematic emotions and behavior. All types of problems reported by adolescents on the YSR were risk indicators of later panic attacks. Yet, when we look closer, only a few subscales were independent risk factors. Social Problems was the most consistent risk factor for panic attacks.

This cross-informant consistent result offers broader generalizability and greater theoretical significance than if derived from just one source. The Social Problems scale comprises items such as

"acts too young for age," "too dependent," "does not get along with other kids," "gets teased a lot," "not liked by other kids," "poorly coordinated or clumsy," and "prefers being with younger kids". The long-term consequences of problems with peer relations are supported by findings in other longitudinal research, among which TRAILS: Adolescents who reported to be bullied at age 10-12 years reported persistently higher scores of anxiety symptoms, including symptoms of panic over adolescence, regardless of the continuation of victimization at later ages [31]. In another sample, Roza et al. [19] reported a unique prospective relation between the CBCL Social Problems scale (4-16 years) and lifetime incidence of anxiety disorders (among which panic disorder) assessed 14 years later.

The association found between Social Problems and onset of panic attacks may be the result of a downward spiral starting with poor social skills and difficulties in peer relations, which in turn can lead to even lower self-confidence, and feelings of lack of control and helplessness. Yet, it may also be an expression of genetic transmission of vulnerability from parents to their children, or gene-environment interaction. An adolescent who reports panic attacks is likely to have parents who experience panic attacks or panic disorder [13, 32, 33]. Cross-sectional studies show that adults with panic attacks have problems with relations with others [34-36], which may lead to transmission of less developed social skills to their offspring, eventually resulting in social problems in children.

The current study has several strengths and weaknesses. The main strength is that we used a large adolescent sample representative of the general population of adolescents, covering the age range from 10 to 20 years. Also, our predictor variables were assessed prospectively, which avoids selective recall bias. Furthermore, we used information from multiple informants and we assessed panic attacks with strictly defined criteria. The main weakness of this study is that our data were censored at age 17-20 (T4) and consequentially, they did not extend through the entire peak risk period. Generalization of our findings to panic attack onset beyond adolescence will need to be confirmed in future studies. Second, we relied on a snap-shot assessment of clinical symptoms rather than relying on information about longitudinal course of symptoms. It is possible that incorporating symptom course may result in stronger effects. Lastly, our analyses focused on clinical scales to forecast risk for future panic attacks. Additional domains of risk, including social functioning, stress reactivity, anxiety sensitivity [37], and family history could be plausibly related to the onset of panic attacks or panic disorder. Future work in these areas could be interesting. Due to the novelty of our findings, there are limited direct implications for clinical interventions. In the context of prevention, however, there are some potential areas of clinical relevance. First, as associations are found using predictors in early adolescence, early assessment of these indicators can be important for effective preventative intervention. Second, predictors of panic attacks are not limited to the internalizing spectrum only. Assessment of risk for panic attacks is warranted among youth with externalizing problems as well. Thus, by recognizing early risk for panic attacks, problems associated with panic may be averted. Importantly, additional research on predictors of panic attacks is needed before specific clinical intervention recommendations can be formulated.

An important direction for future research is to focus on identifying pathways and mechanisms that explain how early Internalizing, Externalizing and Social Problems increase the risk of panic attack

onset in adolescence. In this, an important first step is to identify specific aspects of Social Problems that predict panic attacks. Furthermore, information about panic attacks and panic disorder from first degree relatives should be included to advance understanding of how panic attacks may be transmitted across generations, including genetic and environmental means. Lastly, it is relevant to examine factors that predict and explain the progression from panic attacks to panic disorder. To conclude, we identified childhood Social Problems as consistent independent risk factor of adolescent panic attacks. In addition, we find that the risk markers of developing adolescent panic attacks are diverse and extend beyond problems in the internalizing spectrum to include externalizing problems and a broad-spectrum problems perception.

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Chapter 3

Does the Revised Child Anxiety and Depression Scale (RCADS) measure anxiety symptoms consistently across adolescence?

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ABSTRACT

We assessed if the Revised Child Anxiety and Depression Scale (RCADS) measures anxiety symptoms similarly across age groups within adolescence. This is crucial for valid comparison of anxiety levels between different age groups. Anxiety symptoms were assessed biennially in a representative population sample (N=2,226) at three time points (age range 10-17 years) using the RCADS anxiety subscales (generalized anxiety disorder [GAD], obsessive-compulsive disorder [OCD], panic disorder [PD], separation anxiety [SA], social phobia [SP]). We examined longitudinal measurement invariance of the RCADS, using longitudinal confirmatory factor analysis, by examining the factor structure (configural invariance), factor loadings (metric invariance) and thresholds (strong invariance). We found that all anxiety subtypes were configural invariant. Metric invariance held for items on the GAD, OCD, PD and SA subscales; yet, for the SP subscale three items showed modest longitudinal variation at age 10-12. Model fit decreased modestly when enforcing additional constraints across time; however, model fit for these models was still adequate to excellent. We conclude that the RCADS measures anxiety symptoms similarly across time in a general population sample of adolescents; hence, measured changes in anxiety symptoms very likely reflect true changes in anxiety levels. We consider the instrument suitable to assess anxiety levels across adolescence.

INTRODUCTION

The longitudinal course of anxiety is important to monitor since there is evidence that individuals with an earlier onset and more severe anxiety symptoms are at higher risk for anxiety disorders in childhood, adolescence and adulthood, as well as other mental disorders and impairments in adolescence and adulthood [1, 2]. For valid comparisons of anxiety symptom levels over time, in longitudinal studies, it is imperative to have questionnaires that measure anxiety subtypes similarly across time. Previous studies have acknowledged this relevance and have examined the longitudinal measurement stability (measurement invariance) of instruments assessing concepts such as borderline personality features [3], late-life functioning [4] and body image [5]. In the current study, we examined longitudinal measurement invariance of an instrument assessing anxiety symptoms from pre-/early- through middle-adolescence.

A variety of assessment methods for anxiety symptoms and disorders are available. In large, general population studies, self-report questionnaires are an attractive alternative to clinical interviews. Furthermore, in a population sample, they are valid and relatively easy and time-efficient to employ [6, 7]. Several standardized questionnaires with adequate psychometric properties are available that assess child- and adolescent anxiety symptoms. The Revised Child Anxiety and Depression Scale (RCADS) [8] is a revision of the Spence Children's Anxiety Scale (SCAS) [9, 10], adapted to more closely correspond with the DMS-IV anxiety disorder classification [8, 11]. It is a self-report questionnaire for children and adolescents between seven and eighteen years, that consists of 47 items that cover five anxiety subscales, corresponding with the DSM-IV categories of generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, separation anxiety disorder and social phobia, as well as major depression. Good reliability and validity has been established in community and clinical samples [8, 12, 13].

Whereas the previous studies on the RCADS have focused on cross-sectional structure and validity, the question remains whether the instrument measures symptoms of anxiety consistently over youth development. This question is addressed by examining longitudinal measurement invariance of the RCADS. With this procedure we examine if, given a certain level of anxiety, all individuals have the same probability of endorsing a certain answer on a certain item, irrespective of their age [3]. Examination of longitudinal measurement invariance is necessary for understanding whether observed changes in anxiety symptom scores across ages reflect true changes in symptoms or are due to changes in measurement properties of the instrument. Consistency in measurement properties is referred to as measurement invariance and supports that the individual items reflect the same psychometric information across longitudinal assessments, as investigated here, or across sub-groups (e.g., gender, racial groups). A questionnaire that is not measurement invariant across age can provide invalid conclusions regarding continuity in measurement. A lack of longitudinal measurement invariance may indicate that the interpretation or relevance of the questionnaire items changes across time. As a consequence, differences in RCADS subscale scores between age groups would not automatically reflect a true change in anxiety symptom severity between these groups. However, if longitudinal measurement invariance is established, this suggests that a change in measured anxiety symptoms reflects a true change in the anxiety level across time.

In this paper, we examined the longitudinal measure stability of the RCADS subscales from pre-adolescence to late adolescence in a large, representative, longitudinal population study.

METHODS

Study design and population

Participants were part of the TRacking Adolescents' Individual Lives Survey (TRAILS), a large Dutch population cohort study designed to examine the development and etiological mechanisms of psychopathology from pre-adolescents into adulthood. Participants were representative of the general population. They were assessed biennially from age 10-12 years onwards. Data were used from the first three waves of TRAILS: T1 (2001-2002; age range 10-12), T2 (2003-2004; age range 12-15) and T3 (2005-2007; age range 14-18).

More details of TRAILS have been described elsewhere [14, 15] and are available upon request. In short, participants were recruited from the general population in five municipalities in the northern part of The Netherlands, including both urban and rural areas. Exclusion criteria were non-participation of the school and inability to participate in the study due to severe mental retardation, a severe physical illness, or language-limitations. Extensive efforts were taken to minimize non-response, including reminder letters and personal house visits. Of the initial 3,483 pre-selected children, 2,935 proved eligible for the study, of which 2,230 (76%, of which 51% girls) responded for the first wave. At T2, N=2,149 (96.4%, of which 51% girls) continued to participate. At T3, participation in the study was impossible for 42 subjects due to severe mental or physical health problems, death, detention, emigration or because they were untraceable. Of the remaining subjects, N=1,816 (83%, of which 53% girls) continued to participate.

The vast majority of the respondents provided complete RCADS information (missing not more than one item on one subscale at T1= 99.6%, T2= 99.9%, T3= 98.8%). There was little unavailable RCADS data at T1, (N=20), at T2, (N=65), and at T3 (N=156). Of our whole sample (N=2,230), N=4 respondents did not provide any RCADS information at any time point; these respondents were excluded from the analyses. The remaining missing values were excluded pairwise and treated as MCAR, which is the default implementation for the WLSMV estimator in analyses without covariates. We have not used an algorithm to estimate missing values.

Non-response bias of the TRAILS sample was analyzed based on information about mental health determinants and outcomes as reported by teachers of responders and non-responders [14]. No difference in the prevalence of psychopathology was found at T1 or T2. Also, responders and non-responders did not differ regarding their associations between sociodemographic variables and mental health outcomes. Informed consent was obtained at each assessment wave from each participant and their parents. The study was approved by the Dutch Central Medical Ethics Committee (CCMO) and all participants were compensated for their involvement in this study.

Measures

Anxiety symptoms were assessed by the Dutch translation of the RCADS [8]. The RCADS is a self-report questionnaire, consisting of 47-items measuring five anxiety subtypes and depression

symptoms [8]. Chorpita et al. showed good reliability and internal consistency (GAD= .79, α = .77; OCD=.65, α = .73; PD=.76, α = .79; SA= .75, α = .76; SP=.80, α = .82; MDD=.77, α = .76) as well as convergent and discriminant validity in a sample of N=246 children and adolescents aged 8-18 years [8]. It is scored on a four-point Likert scale (0 = never, 1 = sometimes, 2 = often, 3 = always). Due to the infrequent endorsement of the answer category "always", we merged answer categories "often" and "always", rendering a three-point Likert scale ranging from 0 to 2. Our analysis focused on the 37 items that assess five anxiety subscales (see Table 3): generalized anxiety disorder (GAD: 6 items, ordinal coefficient α = .85/ .89/ .88 at the three waves), obsessive-compulsive disorder (OCD: 6 items, ordinal coefficient α = .76/ .81/ .84), panic disorder (PD: 9 items, ordinal coefficient α = .85/ .90/ .90), separation anxiety disorder (SA: 7 items, ordinal coefficient α = .78/ .83/ .83) and social phobia (SP: 9 items, ordinal coefficient α = .84/ .90/ .91) . The factor structure as proposed by the RCADS was replicated in the TRAILS sample for data from the first assessment wave [13].

The majority of the RCADS anxiety items were previously translated to Dutch as part of the Spence Children's Anxiety Scale [9, 10, 16] items not included in the SCAS were translated to Dutch and back-translated to English in a combined effort of a study PI and a bilingual employee of the University of Groningen language center.

Statistical analysis

To determine the level of longitudinal invariance, we examined whether the factor structure of the RCADS anxiety subscales remains invariant across age groups, adopting a Confirmatory Factor Analysis (CFA) framework. Complete examination of measurement invariance involves a four-step process where in each step, one additional restriction across age groups is imposed on the measurement model [17, 18]. Model fit of each of these nested models was compared with that of the less restricted model. Full invariance on each level is reached if the model fit itself is adequate, and if the model fit of the more restrictive model is not considerably less than that of the less restrictive model [17, 18].

We examined longitudinal invariance on the first three levels by fitting a one-factor model to the data including the three assessments over adolescence, for each RCADS anxiety subscale. The first level of longitudinal invariance is configural invariance, which imposes the same pattern of fixed and free factor loadings between age groups, while not making any equality constraints. We examined configural invariance by fitting the hypothesized RCADS factor structure (i.e. which items load on which anxiety subscale) to the data for all three age groups (see Figure 1a for illustration of this model). The second level is metric (or weak) invariance, which examines if factor loadings to each item are equal across age groups. Thus, metric invariance is examined by constraining the factor loadings across age groups (see Figure 1b). The third level is strong (or scalar) invariance, which examines if the means structure is longitudinally invariant. When observed indicators are continuous variables, examination of strong invariance involves testing whether the intercepts of the indicators differ across time. However, as the RCADS consists of ordinal categorical items, we examined strong invariance by restricting each threshold per item to be equal to its corresponding threshold across the measured time points. This procedure is based on the assumption that answer category endorsement

for each item is driven by the underlying true anxiety level of the subject. The threshold parameter indicates the true (latent) anxiety level where half of the sample endorses the lower answer category (e.g. 0 “never”) and half endorses the next higher one (e.g. 1 “sometimes“). Hence, the number of thresholds per variable is equal to the number of answer categories minus one. When examining strong invariance by setting the threshold parameters of the items to be equal to each other, as described above, what is actually being estimated under the measurement invariance framework is the differences amongst the thresholds, not the absolute value of the threshold. This means that the pattern of all the thresholds together is fixed across the different time points, e.g. if one threshold of item *a* is lower that the corresponding threshold of item *b*, this has to be proportionally the same for all time points. Importantly, as a consequence of estimating the differences amongst thresholds and not their absolute value, the mean of the latent variable is not restricted and hence can vary over time. If strong invariance holds, the change in anxiety subscale scores reflects a change in true anxiety subtype levels. The fourth step is to examine strict invariance, which measures whether the indicator residual variances are equal across age groups. The relevance of strict invariance examination has been generally disputed, as residual variance equality may have limited clinical and practical utility [19].

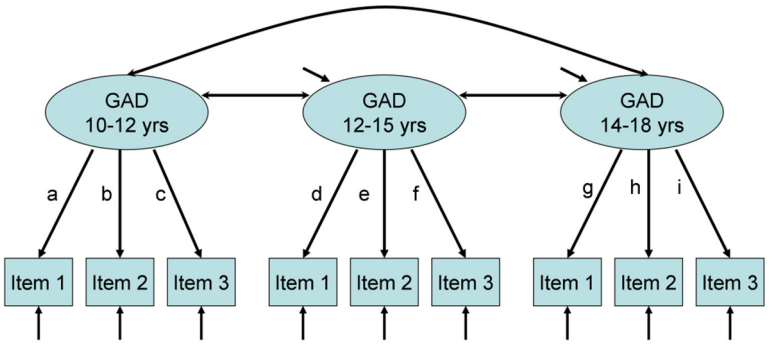

Figure 1a: *A configural invariance model with factor loadings unrestrained*

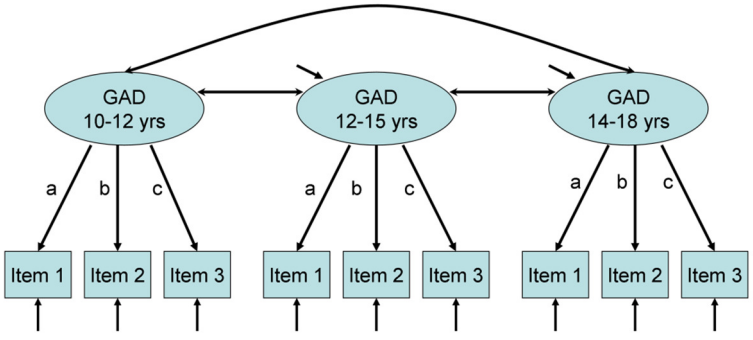

Figure 1b: *A metric invariance model with factor loadings restrained across age groups*

Depending on the construct to be measured, different levels of invariance are realistic to be expected. Few self-report questionnaires pass strong or strict invariance examination, and a recommendation is to only consider configural and metric invariance, as developmental effects are expected that would render strong invariance unrealistic [20].

We examined the model fit of all the invariance models and inspected the modification indices of each parameter in each specified model. The modification index *is a post-hoc* indicator that indicates model fit improvement when a fixed parameter is freely estimated [21]. Previous research with psychological constructs has shown that it is often necessary to allow for correlated errors between items with non-random measurement error due to similar item formulation or narrowly associated item content [22]. Therefore, we allowed for residual error correlations of two or three items in each nested anxiety subscale, provided that the modification included items with similar content or phrasing (i.e. items had very similar formulation or measured one specific aspect within an anxiety subscale). The models with correlated residuals were used for evaluation of model fit to examine longitudinal invariance (items with correlated residual error terms are indicated in Table 3). Model fit indices of the original, uncorrelated anxiety subscales are available upon request from the first author.

Model fit indices used were the comparative fit index (CFI), [23, 24] the Tucker-Lewis Index (TLI) [25] and the root mean square error of approximation (RMSEA) [26]. We did not rely on the Chi Square test as a primary indicator of model fit due to concerns about sensitivity to large sample sizes [27]. Good model fit is indicated by a CFI of .95 or higher [24, 27], a TLI of .97 or higher [27] and a RMSEA of .05 or lower [27]. Acceptable model fit is indicated by a CFI greater than .90, a TLI greater than .95 and a RMSEA smaller than .08 [27].

Model fit of each individual model was evaluated with the CFI, TLI and RMSEA. Next, model fit of each nested, more restricted model was compared with that of the less restricted model using the CFI as indicator. For nested model comparison, we used the ΔCFI test. This test is more robust against large sample sizes than the Chi-square difference test. A CFI decrease of more than .005 from the less restricted model to the more restricted model was used as indicator for worse model fit [28]. All examinations of measurement invariance were conducted using longitudinal confirmatory factor analysis with ordinal categorical data using the weighted least square mean and variance (WLSMV) adjusted estimator [29] in Mplus Version 5 [30].

RESULTS

Table 1 shows the mean anxiety subtype levels at each of the assessment waves of TRAILS. Table 2 shows the model fit of the models with configural invariance, metric invariance and strong invariance, by anxiety subscale. Table 3 gives the factor loadings of the models with configural invariance. In the configural models, items are forced to load on a specific factor, but the factor loadings of the items are estimated freely. All anxiety subscales show a good model fit on the configural level (all CFI >.95; TLI >.97; RMSEA <.05), indicating that the factor structure of the RCADS anxiety subscales fits each of the age groups across adolescence.

Table 1: *Demographic characteristics and anxiety subtype levels of the TRAILS sample at T1, T2 and T3*

Assessment wave	T1 (2001-2002)	T2 (2003-2004)	T3 (2005-2007)
Age, mean (SD); range	11.1 (.56); 10.1-12.6yrs	13.6 (.53); 12.2-15.2yrs	16.3 (.71); 14.7-18.7yrs
Anxiety mean (SD), range			
GAD	.65 (.42), 0-2.0	.48 (.40), 0-2.0	.51 (.40), 0-2.0
OCD	.57 (.40), 0-2.0	.33 (.33), 0-2.0	.28 (.33), 0-2.0
PD	.41 (.33), 0-2.0	.29 (.30), 0-2.0	.28 (.28), 0-2.0
SA	.36 (.32), 0-1.7	.23 (.27), 0-1.6	.22 (.25), 0-1.4
SP	.75 (.39), 0-2.0	.66 (.43), 0-2.0	.70 (.45), 0-2.0

Note: GAD=generalized anxiety disorder; OCD=obsessive-compulsive disorder; PD=panic disorder; SA=separation anxiety disorder; SP=social phobia.

Table 2: *Model fitting results for measurement invariance examined across three age groups*

	χ^2	*df*	# par	CFI	TLI	RMSEA
GAD						
Configural	226.647	63	78	.987	.992	.034
Metric	222.639	66	68	.988*	.993	.033
Strong	433.841	80	46	.972	.987	.045
OCD						
Configural	221.430	80	78	.974	.979	.028
Metric	210.414	80	68	.976*	.981	.027
Strong	395.729	96	46	.944	.963	.037
PD						
Configural	424.750	149	120	.958	.981	.029
Metric	366.538	139	104	.965*	.983	.027
Strong	506.312	156	70	.947	.976	.032
SA						
Configural	292.202	107	90	.963	.974	.028
Metric	260.875	98	76	.967*	.975	.027
Strong	511.463	112	50	.920	.947	.040
SP						
Configural	627.470	155	114	.964	.986	.037
Metric	929.248	128	96	.939	.971	.053
Strong	1273.453	143	62	.914	.963	.060

Note: GAD=generalized anxiety disorder; OCD=obsessive-compulsive disorder; PD=panic disorder; SA=separation anxiety disorder; SP=social phobia; df=degrees of freedom; #par=number of parameters; CFI= comparative fit index; TLI= Tucker-Lewis Index; RMSEA= root mean square error of approximation; * CFI decrease smaller than .005

The model fit of the metric model was good for GAD, OCD, PD and SA, and acceptable for SP. The last column of Table 3 shows the metric invariance factor loading of the models where items were forced to load on a specific factor and to have the same factor loadings at the three age groups. The difference in CFI compared with the configural model exceeded .005 for SP only. Hence, on the metric invariance level, the subscales for GAD, OCD, PD and SA were fully longitudinal invariant, but the subscale for SP was not. For SP, we inspected the modification indices of the metric model to find out which items had factor loadings that differed across assessment wave. For three items, modification indices were above 100 (item 4 “Worries when does poorly at things”, 7 “Scared to take a test“, and 30 “Worries about mistakes“), all at age 10-12. These items loaded lower on the SP factor at age 10-12 (T1) than at ages 12-18 (T2 and T3; see Table 3). After allowing age-specific factor loadings for these three items, the CFI difference with the configural model did not exceed .005 and the model fit of the SP subscale improved from acceptable to good (CFI=.959, TLI=.981, RMSEA=.043).

Table 3: *Standardized factor loading estimates of the configural (unrestricted) model across three age groups as well as the metric (restricted) model*

Factor	Item #	Item description	Factor loading			
			Configural			Metric
			T1	T2	T3	
GAD	1.	Worries about things	.55	.64	.67	.60
GAD	13.	Worries something awful will happen to family	.70	.75	.70	.69
GAD	22.[a]	Worries bad things will happen to self	.82	.88	.83	.81
GAD	27.[a]	Worries something bad will happen to self	.80	.85	.84	.80
GAD	35.	Worries about what will happen	.73	.78	.80	.74
GAD	37.	Thinks about death	.59	.60	.55	.56
OCD	10.[a]	Has to do things just right to stop bad events	.53	.61	.57	.52
OCD	16.	Bothered by bad or silly thoughts or images	.51	.55	.60	.51
OCD	23.[a]	Has to do things over and over again	.57	.61	.59	.54
OCD	31.	Keeps checking if things done right	.65	.75	.75	.65
OCD	42.	Can't get bad or silly thoughts out of head	.55	.61	.75	.58
OCD	44.	Has to think special thoughts to stop bad events	.66	.70	.82	.66
PD	3.[a]	When has a problem, stomach feels funny	.43	.51	.54	.46
PD	14.	Suddenly has trouble breathing for no reason	.63	.76	.67	.64
PD	24.[a]	When has a problem, heart beats really fast	.53	.59	.60	.53
PD	26.	Suddenly trembles or shakes for no reason	.65	.71	.75	.65
PD	28.[a]	When has a problem, feels shaky	.54	.65	.69	.57
PD	34.	Suddenly feels really scared for no reason	.68	.77	.82	.69
PD	36.	Suddenly becomes dizzy of faint for no reason	.64	.70	.67	.62
PD	39.	Heart suddenly beats too quickly for no reason	.76	.79	.79	.72
PD	41.	Worries will suddenly get scared for no reason	.65	.78	.76	.67
SA	5.[a]	Fears being alone at home	.62	.68	.67	.65
SA	9.	Fears being away from parents	.56	.61	.61	.59
SA	17.[a]	Scared to sleep alone	.71	.73	.69	.71
SA	18.	Trouble going to school	.53	.64	.65	.60
SA	33.	Afraid of being in crowded places	.50	.60	.59	.56
SA	45.	Worries in bed at night	.52	.53	.51	.52
SA	46.	Scared to sleep away from home	.62	.69	.75	.67
SP	4.	Worries when does poorly at things	.57	.71	.73	.68
SP	7.[a]	Scared to take a test	.39	.56	.56	.51
SP	8.	Feels worried when someone angry	.61	.69	.69	.66
SP	12.[a]	Worries will do badly at school work	.53	.67	.66	.63
SP	20.	Worries might look foolish	.74	.80	.82	.79
SP	30.	Worries about mistakes	.60	.73	.76	.71
SP	32.	Worries what others think	.73	.82	.83	.80
SP	38.	Afraid to talk in front of class	.49	.57	.56	.54
SP	43.	Afraid of looking foolish in front of people	.76	.80	.85	.81

Note: GAD=generalized anxiety disorder; OCD=obsessive-compulsive disorder; PD=panic disorder; SA=separation anxiety disorder; SP=social phobia. [a] indicates correlated items within one anxiety subscale.

For the strong invariance examination, we constrained the thresholds of each item to be equal across age groups. With this procedure we examine whether the likelihood of response endorsement is driven by the underlying true anxiety level of the subject. The model fit was good for the GAD subscale, acceptable to good for OCD, PD and SA, and acceptable for SP. When comparing this

strong invariance model with the metric model, however, the difference in CFI exceeded the .005 criteria for all anxiety subscales, indicating deterioration in model fit.

DISCUSSION

Measurement stability is critically important for longitudinal studies, yet few investigations have examined this issue in anxiety assessment instruments. The present study examined the longitudinal measurement stability in youth across three waves including pre- through late-adolescence in the general population using a confirmatory factor analysis framework.

In the RCADS, each of the anxiety subscales had the same factor patterns across age groups and the GAD, OCD, PD and SA subscales demonstrated similar factor loadings across age as well. This work suggests that each of the items comprising these specific subscales contribute equally to these domains across development. The SP subscale, however, included three items (out of nine) that had different factor loadings across time, in particular items of anxiety about self-evaluated poor performance. These items had stronger loadings from the SP latent factor for the latter two assessments (ages 12-18) than at the first assessment (ages 10-12). The SP scale includes symptoms related to social interaction as well as symptoms of performance anxiety. These symptoms often co-occur, yet evidently describe different aspects of social phobia [31, 32]. Our data show that their relative importance is not stable over time, but that performance anxiety becomes more important in the context of social phobia symptoms across adolescent development. We can only speculate on the reasons why performance anxiety becomes more important. It is possible that the increased importance of performance anxiety is caused by increased levels of depression symptoms over adolescence, such as feelings of worthlessness or incompetence, or by increased academic pressure.

The model fit of the strong invariance models decreased significantly; however, on an absolute level, they were still acceptable to good for all anxiety subscales. This indicates only small deviations from strong longitudinal invariance. We did not expect to find full strong longitudinal invariance. Indeed, as a consequence of children's development, the expression of anxiety subtypes changes across developmental stages, which can be expected to be reflected in different item endorsement [33].

To our knowledge, the only other youth anxiety assessing instrument that has been examined for longitudinal measurement invariance is the SCAS [9]. Spence examined measurement invariance of the SCAS across two age groups (younger than 11 years versus 11 years and older) and found the instrument to be configural invariant. However, metric invariance already proved to be suboptimal and the strong invariance examination did not hold. Hence, the RCADS has more favourable longitudinal measurement invariance properties than the SCAS.

The current study has several strengths and limitations. The main strength is that we used a large adolescent sample representative of the general population of adolescents in the Netherlands, assessed with a high response at three time points, describing the age range from 10 to 18 years. Each assessment point covers a narrow age range of two to four years, which minimizes the risk of making unjustified assumptions about invariance within one time point. However, this study was

limited to this age range and does not guarantee longitudinal invariance for younger ages. Due to low endorsement of the answer category “always”, we had to combine answer categories “often” and “always” to obtain reliable results from our analyses. It could be important for future work to examine similar issues with an enriched sample of anxious youth to examine the full set of response options. Lastly, we did not include any infrequency scales in the TRAILS study to detect (pseudo)random answering patterns; however, the RCADS is a questionnaire with low risk for typical (pseudo)random answering. Future longitudinal studies of anxiety symptoms in the general population will give more insight in the factors that contribute to continuity and discontinuity of anxiety, and identify youth requiring early interventions and possible prevention of anxiety disorders.

CONCLUSION

The RCADS measures anxiety subtypes similarly across time in a general population sample of adolescents; that is, the measured changes in anxiety subscales very likely reflect true changes in anxiety levels as opposed to measurement artefacts. Some caution should be exercised due to the minor adjustments made to improve the model fits, especially for the SP subscale, where additional adjustments were needed for adequate metric invariance model fit. Nonetheless, this research suggests that the RCADS is very likely suitable to compare anxiety levels in longitudinal, population based studies of adolescents.

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Chapter 4

Pubertal timing and anxiety symptoms: a dynamic association across adolescence

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Submitted for publication

ABSTRACT

Purpose: To investigate if the association between pubertal timing and anxiety symptoms varies across adolescence depending on age.

Methods: We used data from 2,230 boys and girls participating in a longitudinal cohort study in the Netherlands. Adolescents completed three assessments of pubertal development and symptoms of generalized anxiety, social anxiety, panic disorder and total anxiety. Overall, data was available from age 10 to 17 years. Pubertal timing was defined by pubertal development relative to same-sexed, same-aged peers.

Results: In boys, we found associations between pubertal timing and anxiety symptoms, and these associations were age-dependent: at age 10-11, being ahead of peers in pubertal development was associated with more anxiety symptoms while from age 14 onwards, being ahead was associated with fewer anxiety symptoms. This pattern of association held for all three anxiety symptoms and for total anxiety, but was strongest for social anxiety. In girls, we found no association between pubertal timing and anxiety symptoms, nor any age-dependency.

Conclusions: Our findings suggest that the association between pubertal timing and anxiety symptoms is not stable across adolescence. Future studies should consider age to be an important factor when investigating the association between pubertal timing and anxiety symptoms. Furthermore, they should further explore the sex differences we found.

INTRODUCTION

Anxiety symptoms in adolescents are very prevalent and have been associated with school absenteeism, poor school performance, problems maintaining friendships and increased family conflict [1, 2]. This burden, together with the fact that anxiety symptoms frequently precede the development of depression and clinical levels of anxiety, emphasizes the importance of identifying risk factors for the onset of anxiety symptoms. Adolescence has been recognized as a key developmental period marked by the onset of anxiety symptoms and anxiety disorders [3, 4].

Pubertal development is a key feature of adolescence. Puberty is associated with not just rapid biological and hormonal changes, but also with important social and psychological changes [5]. The relationship between pubertal status and social, behavioral and emotional adjustment, and specifically to anxiety symptoms (e.g. [6], see [7] for review), has received much attention in the past. More recently, however, studies have considered the relevance of relative pubertal timing, i.e., whether the pubertal development process occurs earlier, at the same time, or later compared to same aged peers. The physical maturation that is part of puberty leads adolescents to face new social expectations, which in turn leads to adjustments in their social identity and to new social relationships [8]. While these social adjustments alone can evoke anxiety [5], deviation from peers in the timing of the maturation process has been hypothesized to increase the risk for emotional and behavioral problems during adolescence [8]. Specifically, the “early-timing hypothesis” [9] suggests that early developing youth experience the biological, psychological and social challenges associated with puberty before they may be psychologically prepared to cope with them effectively [8], which can be a risk factor for anxiety symptoms and disorders [8, 10].

Studies investigating the association between pubertal timing and anxiety symptoms and disorders have found mixed support for this theory: many studies supported this theory [10-12], but others found conditional support [13], or no support [8]. What is striking in the previous studies of anxiety and pubertal timing is that they often include: 1) just girls [10-12, 14], 2) fairly basic measures of pubertal timing (e.g., age at menarche) and/or anxiety symptoms (e.g., the use of a general anxiety scale), and 3) only a single type of anxiety (e.g., just social anxiety) [12-14]. Moreover, except for one study by Reynolds and Juvonen [14], the studies assessed pubertal timing only once in adolescence. Yet, pubertal timing, relative to peers, is dynamic across adolescence, since the pace of pubertal development varies between adolescents and by age [14]. Reynolds and Juvonen examined pubertal timing as a dynamic concept, measured six times over three school years (6^{th} to 8^{th} grade), in a racially diverse sample of 1,167 girls. They found that in early adolescence (6^{th} grade), early pubertal timing was not significantly associated with symptoms of social anxiety, while later in adolescence (8^{th} grade), late pubertal timing co-occurred with significantly more symptoms of social anxiety. This study highlights the need to assess pubertal timing dynamically, and suggests that the association between pubertal timing and anxiety symptoms may vary depending on age.

In the present study, we addressed the limitations of the previous studies by 1) using a large population sample of girls and boys followed from 10 to 17 years, 2) using repeated standardized measures to assess pubertal timing and anxiety symptoms, and 3) including different types of anxiety symptoms (i.e. social anxiety, generalized anxiety, panic and total anxiety symptoms) that have been

associated with pubertal timing, but have not previously been studied together. The purpose of this present study is to examine if the association between pubertal timing and anxiety symptoms varies by age across adolescence. Based on the inherently social component to pubertal timing [14], we expect to find the strongest association with social anxiety symptoms.

METHODS

Study design and population

Data were used from TRacking Adolescents' Individual Lives Survey (TRAILS). TRAILS participants were recruited from the general population in five municipalities in the northern part of The Netherlands, including both urban and rural areas. All children living in these municipalities and born between October 1989 and September 1990 (two sites) and October 1990 and September 1991 (three sites) were selected (N=3,483). Their date of birth and contact information was obtained through the municipality administrations.

Participation of the child's school was required for enrollment. Of the 135 approached primary schools, 9.6% refused to participate, excluding N=338 children. If schools agreed to participate, parents were approached with information brochures and a follow-up phone call in which they were invited to participate. Participants were excluded from the study if they were incapable of participating due to severe mental retardation, a severe physical illness, or language-limitations (N=210). Of the 3,483 selected children, 2,935 were eligible for the study, of whom 2,230 (76%, of which 51% were girls) participated in the first wave (T1; age range 10-12 years). More details of the data collection of TRAILS have previously been reported [15]. Non-response was due to explicit refusal or inability to establish contact [16]. Extensive efforts were made to minimize non-response, including reminder letters and personal house visits [17]. Non-response bias was analyzed based on information about mental health determinants and psychopathology as reported by teachers of responders and non-responders [16]. Responders and non-responders did not differ in prevalence of psychopathology at T1, and did not differ regarding associations between socio-demographic variables and psychopathology [16]. At the second wave (T2; age range 12-15 years) 2,149 adolescents continued to participate (96%, of whom 51% were girls). At T3, participation in the study was impossible for 42 subjects due to severe mental or physical health problems, death, detention, emigration or because they were untraceable. Of the remaining subjects, N=1,816 (83%, of whom 53% were girls) continued to participate. Written informed consent was obtained at each assessment wave from each participant and their parents. The study was approved by the Dutch Central Medical Ethics Committee (CCMO).

Measures

Anxiety symptoms

The Revised Child Anxiety and Depression Scale (RCADS; [18, 19]) was used to measure anxiety symptoms at each assessment wave. The RCADS is a self-report questionnaire, including 37-items that measure symptoms of five anxiety subtypes, amongst which are generalized anxiety disorder (GAD: 6 items), panic disorder (PD: 9 items) and social anxiety (SA: 9 items). All items are scored on a four-point Likert scale (0 = never, 1 = sometimes, 2 = often, 3 = always). A "Total Anxiety" score was

calculated based on the mean item score of all 37 anxiety items. Internal consistencies of the Total Anxiety score (.91/ .93/ .92 for assessment wave one, two and three, respectively) and of the subscales (GAD= .78/ .81/ .79; PD = .75/ .79/ .77; SA= .78/ .85/ .86) were strong, and measurement invariance across adolescence for the subscales has been established [20].

Pubertal timing

Pubertal timing was calculated based on the assessment of pubertal status at each assessment wave. At T1, pubertal status was measured using the categorical system of Tanner stages [21, 22]. Tanner's pubertal development classification uses five schematic drawings of figures with secondary sex characteristics. Parents identified which drawing looked most like their child and based on this rating, adolescents were classified into 5 Tanner stages. Stage 1 corresponds to the prepubertal stage and stage 5 to the postpubertal stage. For children and early adolescents, these ratings have shown good reliability and validity [23].

At T2 and T3, pubertal status was assessed by adolescent self-report using the Physical Development Scale (PDS; [24, 25]). The PDS includes questions about growth spurt, body hair and skin changes, as well as breast development and menstrual cycle (in girls) or changes in voice and facial hair (in boys). The PDS has shown good reliability and validity [25].

For analyses, the PDS scores from T2 and T3 were recoded into the five Tanner stages with the Shirtcliff method [26]. Before coding pubertal timing the pubertal status variables (T1, T2, T3 Tanner stages), were standardized into z-scores (mean=0, standard deviation=1) by sex and age (in years). Per age group pubertal timing was coded separately for boys and girls. Adolescents with a standardized pubertal status score of more than one standard deviation *below* the mean were coded as being late in pubertal timing compared to their same aged same sex peers. Similarly, adolescents with a standardized pubertal status score of more than one standard deviation *above* the mean were coded as being early in pubertal timing. All adolescents in between were coded as being on-time in pubertal timing. Pubertal timing was calculated for each assessment wave.

Statistical analyses

We performed linear mixed model analyses in SPSS 20.0. Pubertal timing, age, age squared and the interaction between pubertal timing and age were included as fixed effects and as random effects. Age and age squared were included based on previous findings [27]. Each model estimated one scale of anxiety symptoms (Total Anxiety; GAD; PD; SA). Models were built with a first order autoregressive covariance structure and were estimated using Maximum likelihood (ML).

The pubertal timing score represents the pubertal development status of each subject relative to their same-sexed, same-aged peers at each assessment wave. Pubertal timing was allowed to vary for each adolescent across assessment waves. Treating pubertal timing as a time-varying variable allowed us to model the relation between pubertal timing and anxiety symptoms as accurately as possible, taking account of variations in pubertal timing over adolescence. We included the interaction between pubertal timing and age in the model to test whether the association between pubertal timing and anxiety symptoms changes with age across adolescence (from 10-17 years). Furthermore, we

included sex in the model, and interactions of pubertal timing with sex, and pubertal timing with age and sex, to test for sex-specific associations between pubertal timing and anxiety.

RESULTS

The pubertal timing of adolescents in relation to their same-sexed peers did change across adolescence. Between T1 and T2, 53% remained in the same pubertal timing category; 17% went from on-time at T1 to being early and 11% to being late at T2; and 12% went from being late at T1 to on-time at T2. Between T2 and T3, 55% remained in the same pubertal timing category; 15% went from being late at T2 to on-time at T3 and 24% from being early at T2 to on-time at T3. This pattern supports treating pubertal timing as a time-varying variable.

The interaction term of pubertal timing, age and sex was significant in the model for Total Anxiety ($F(2, 4178.265) = 3.26$, $p = .039$) and for Social Anxiety ($F(2, 4539.600) = 3.40$, $p = .034$). Therefore, analyses were run separately for boys and girls.

Table 1: *Pubertal timing and anxiety scores: regression coefficients with standard errors*[2]

	Total Anxiety		Gen. Anx. Disorder		Social Anxiety		Panic Disorder	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
Intercept	.73 (.06)***	.28 (.03) ***	.78 (.08)***	.78 (.05) ***	.98 (.08)***	.92 (.04)***	.52 (.06)***	.50 (.04)***
PT[1]								
On-time	-.15 (.06)*	-.05 (.04)	-.09 (.09)	-.04 (.05)	-.23 (.08)**	-.07 (.05)	-.06 (.06)	-.02 (.04)
Late	-.19 (.06)**	-.08 (.05)	-.18 (.09)*	-.10 (.07)	-.27 (.08)**	-.13 (.07)	-.12 (.06)	-.04 (.05)
Age	-.17 (.02)***	-.08 (.01)***	-.17 (.03)***	-.07 (.02)***	-.18 (.03)***	-.04 (.02)*	-.13 (.02)***	-.06 (.02)**
Age square	.01 (.00)***	.01 (.00)***	.01 (.00)**	.01 (.00)**	.01(.00)***	.01(.00)*	.01(.00)***	.01 (.00)**
PT[1] x age								
On-time	.07 (.02)**	.01 (.01)	.05 (.03)	.01 (.02)	.10 (.03)**	.01 (.02)	.03 (.02)	.00 (.02)
Late	.08 (.02)***	.02 (.02)	.07 (.03)*	.02 (.03)	.11 (.03)***	.02 (.03)	.05 (.02)*	.01 (.02)

Note: PT=pubertal timing; Gen. Anx. Disorder= Generalized Anxiety Disorder; [1] early pubertal timing is reference group; [2] fixed variables in the table, random variables in the model were age, age square, pubertal timing and pubertal timing x age; * $p<.05$; ** $p<.01$; *** $p<.001$

Table 1 shows the regression coefficients of the fixed factors in the models separately for boys and girls. As previously published on TRAILS data, there was a significant negative coefficient for age and a positive coefficient for age-squared for both sexes and each of the anxiety outcomes [27]. These coefficients describe the growth curve of anxiety symptoms, which starts with a decrease in pre/early adolescence and then levels off, and start to increase by middle/late adolescence. The first column in Table 1 shows the results for Total Anxiety. Associations between pubertal timing and Total Anxiety were non-significant in girls. In boys, pubertal timing was associated with Total Anxiety, and this relation was age dependent, as indicated by the significant interactions of pubertal timing with age. The top row of Figure 1 displays the interaction between pubertal timing and age on Total Anxiety. In girls (horizontal grey line), girls with early, on-time, and late pubertal timing did not significantly differ

on Total Anxiety over adolescence. In 10-year old boys, early pubertal timing was associated with a *higher* score for Total Anxiety than on-time and late pubertal timing. This association levels off by age 12 years, and from age 13 years onwards the boys who are early in pubertal timing have a *lower* score for Total Anxiety than those on-time or late in pubertal timing (Figure 1).

For the scores for GAD, SA, and PD, regression models showed a pattern that is very similar to Total Anxiety (Table 1, Figure 1). For GAD and PD the associations were not consistently significant, early pubertal timing did not significantly differ from on-time pubertal timing, but only from late pubertal timing (in the interactions with age).

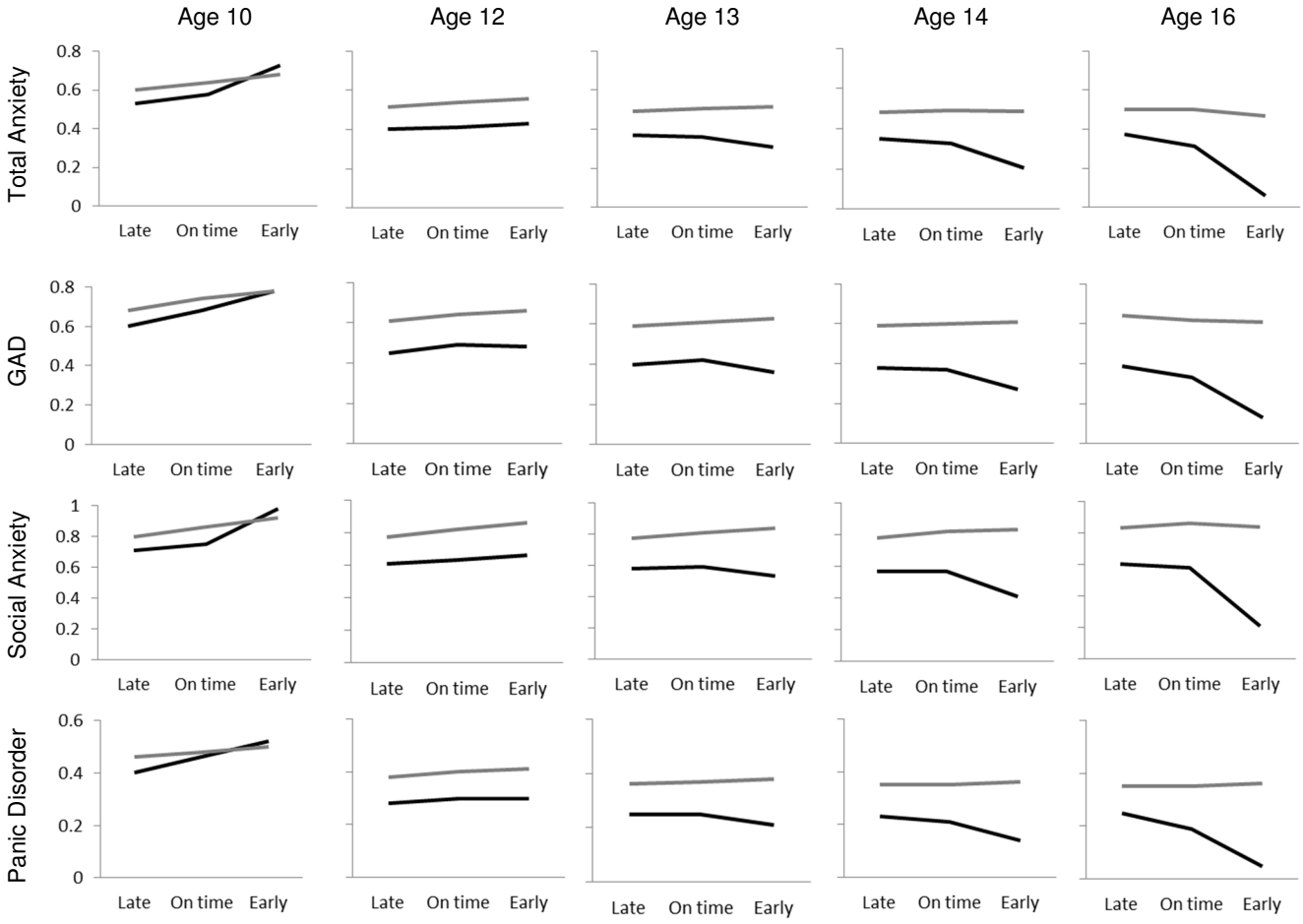

Figure 1: *The association between anxiety symptoms and pubertal timing as it changes with age across adolescence. Black line=boys; grey line=girls. GAD=generalized anxiety disorder. Shown are merely the slopes for age 10, 12, 13, 14 and 16. The associations at age 11 are similar to age 10, and associations at age 15 and 17 are similar to those at age 16.*

Post-hoc analyses

To further investigate the lack of association between pubertal timing and anxiety symptoms in girls, we performed the same analyses as described above with depressive symptoms as outcome. Depressive symptoms were measured with the Youth Self-Report [28, 29] Affective Problems subscale (13 items, rated on a 4-point Likert scale). In girls, we found a significant main effect for pubertal timing ($F(2, 4146.681) = 3.18$, $p = .042$), showing that being ahead in pubertal development at any measurement wave was associated with more depressive symptoms compared to being late in

pubertal development (γ=-.093 , SE=.04, *p*=.022). The pubertal timing by age interaction was not significant. In boys, we found a significant main effect for pubertal timing (*F*(2, 2171.813)= 3.70, *p* =.025), showing that being ahead of peers on pubertal development was associated with more depressive symptoms compared to on-time (γ=-.118 , SE=.05, *p*=.017) or late (γ=-.133 , SE=.05, *p*=.007) peers. The pubertal timing by age interaction was also significant (*F*(2, 2161.447)= 4.01, *p* =.018), showing the same pattern as for anxiety symptoms.

DISCUSSION

In this paper, we examined whether pubertal timing, relative to peers, is associated with anxiety symptoms across adolescence, and if this association varies by age across adolescence. Treating pubertal timing dynamically by measuring it repeatedly across adolescence is relatively new to the literature, and has not been done in a sample including boys and girls. In boys, we found an age-dependent association between pubertal timing and anxiety symptoms. Ten year old boys who at that time were *ahead* of their peers in pubertal development (early in pubertal timing) had significantly *more* anxiety symptoms than their peers who were on-time or behind in pubertal development (on-time or late pubertal timing). The direction of this association starts to change at the age of 13-14 years, and tips in the opposite direction after that age, such that 16-17-year old boys who were *ahead* of their peers in pubertal development have significantly *less* anxiety symptoms. This pattern was found for Total Anxiety, GAD, SA and PD symptom scores. In girls, pubertal timing was not associated with anxiety scores.

The main effect finding that in boys, being ahead of peers in pubertal development was associated with increased symptoms of anxiety is consistent with the 'early timing hypothesis'. The significant interaction between pubertal development and age, however, reveals that the association is more complex than accounted for in most previous studies. The 'early timing hypothesis' does not help us understand the observed change in association. Instead, a different theory may provide insight. In previous studies, some authors [8] have argued that it is the aspect of being most out of sync from peers when it comes to pubertal development that may lead to increased anxiety [30]. Whereas these studies assumed a fixed relationship between pubertal timing and anxiety symptoms across adolescence, this theory may still prove useful in understanding our age-dependent findings: At age 10 and 11, merely a small group of boys is ahead of peers in pubertal development; hence, these boys are indeed the most pronounced outliers within the male population, which would be associated with increased anxiety symptoms. Around age 12 to 13, the variation in pubertal development increases. This increase in variation may make even developmental outliers stand out less from peers, which would eliminate the association with anxiety symptoms. Later in adolescence, being ahead of peers in pubertal development may be associated with the display of physical features consistent with the social stereotype of desirable characteristics for boys, including more mature appearance and improved muscle strength. This may be associated with a strengthened social status, which may explain the lower anxiety symptoms from age 14 onwards. The only other study that used an age-dependent approach to investigating the association between pubertal timing and anxiety symptoms, found the same age-dependent pattern of association, albeit in an all-girls sample [14].

Secondly, our study compared different subtypes of anxiety symptoms. The associations with pubertal timing showed the same pattern for all four anxiety subtypes, but the pattern was most pronounced for social anxiety symptoms. Given the fact that pubertal timing is not defined in an absolute manner but rather as relative to peers and hence includes a strong social aspect, it is consistent with our hypothesis to find the strongest association with social anxiety symptoms. Reynolds and Juvonen [14] only included social anxiety symptoms as anxiety outcome, but they found the same age-dependent pattern of association as we did.

Thirdly, we found a clear sex difference in our findings. The association between pubertal timing and anxiety symptoms was not observed in girls. This is in contrast with previous studies [11, 31], especially the one age-dependent study, which used an all-girls sample [14]. We offer two hypothetical explanations for this inconsistency. Firstly, the main difference in sample between the study by Reynolds and Juvonen and ours is the ethnic composition of the samples: their sample consisted of 9% Whites, while the TRAILS sample consisted of 89% Whites. Reynolds and Juvonen did find ethnic differences in initial status (higher for whites) and in rate of change (slower decrease for whites) for social anxiety, suggesting that race is of influence on the association of social anxiety with pubertal timing. However, we do not know how race would affect the age-dependent association. Secondly, previous studies described a shift from anxiety symptoms towards depressive symptoms in girls across adolescence. Hence, it is possible that in girls, pubertal timing would be primarily associated with depressive symptoms, and that consequently depressive symptoms overshadow an association between pubertal timing and anxiety symptoms. To explore this hypothesis, we performed post-hoc analyses to check if depressive symptoms are associated with pubertal timing in girls. We found that being early in pubertal timing was significantly associated with more depressive symptoms; yet, this association was not age-dependent. Therefore, these findings do not suggest that depressive symptoms overshadow an association between anxiety symptoms and pubertal timing. However, they are consistent with Reynolds and Juvonen's, who also included depressive symptoms as outcome. Interestingly, for depressive symptoms, they also failed to find an effect for ethnicity. This strengthens the previous suggestion that ethnicity may be of influence on this association, and the differences in ethnic composition of our samples may help explain the inconsistencies in our findings.

This study benefitted from a large sample of boys and girls, representative of the general population of adolescents, and covering the age range from 10 to 17 years. We used repeated, standardized measures to assess pubertal timing and anxiety symptoms, and all measures were assessed prospectively over the three assessment points. We included a summary measure of Total Anxiety symptoms, as well as three anxiety subtypes. The main limitation of this study is the interval length between the assessment points of two to three years. Shorter intervals would allow us to gain more insight into the change process occurring within every adolescent. Furthermore, we assessed the association between pubertal timing and anxiety symptoms cross-sectionally; hence, the underlying direction of the association is unclear. While in most studies it is assumed that pubertal timing is a causal agent, some literature suggests that anxiety symptoms may influence pubertal timing [32].

Based on our findings, future studies should consider assessing pubertal timing as the dynamic concept it seems to be, as pubertal timing is not a stable characteristic within one person across adolescence. Furthermore, they should be mindful of the age-dependency of associations with pubertal timing. Given the fact that this is only the second study to use this dynamic, age-dependent approach to pubertal timing, and that our findings are not entirely consistent with the previous study, more studies are needed to further explore this new framework of conceptualizing pubertal timing.

CONCLUSION

Pubertal timing is a dynamic concept that shows within-person changes across adolescence. The association between pubertal timing and anxiety symptoms changes across adolescence depending on age. We found this association only on boys, but future studies should further explore the sex differences.

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Chapter 5

The bidirectional association between sleep problems and anxiety symptoms over adolescence

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ABSTRACT

Objective: Sleep problems and anxiety symptoms frequently co-occur. However, few studies have examined whether one problem type precedes the other. Thus, the direction of this association remains unclear. We hypothesized that sleep problems will prospectively predict anxiety symptoms and anxiety symptoms will prospectively predict sleep problems. We studied this in a large prospective study of adolescents.

Methods: We used data from 2,230 pre-adolescents (10-12 years) enrolled in a longitudinal cohort study, who were assessed three times across adolescence (age range at T2: 12-15 years; T3: 15-18 years). Anxiety symptoms were assessed using the anxiety scales of the Revised Child Anxiety and Depression Scale (RCADS) and sleep problems were assessed with items from the Youth Self-Report (YSR). We used Structural Equation Modeling to examine the associations between sleep problems and anxiety symptoms over time.

Results: The data fit the hypothesized bidirectional model well (CFI= .982; RMSEA= .030). Homotypic continuity was found for both anxiety symptoms (βs= .45-.59, p<.001) and sleep problems (βs = .51-.52, p<.001). Furthermore, anxiety symptoms predicted sleep problems from T1 to T2 (β= .09, p<.001) and from T2 to T3 (β= .10, p<.001); sleep problems predicted anxiety symptoms only from T1 to T2 (β= .10, p<.001).

Conclusions: Sleep problems and anxiety symptoms have a small but significant bidirectional relationship in early adolescence, over and above cross-sectional associations and homotypic continuity of anxiety symptoms and sleep problems. Later in adolescence, the relation from anxiety symptoms to sleep problems continued, but sleep problems no longer significantly predict anxiety symptoms.

INTRODUCTION

Anxiety and sleep problems are highly prevalent in childhood and adolescence. Approximately 40% of adolescents suffer from sleep problems [1] and 23% of school children are affected by significant anxiety problems [2]. Cross-sectional research has shown that sleep problems and anxiety tend to co-occur in youth (for a recent review, see [3]), with over 80% of children and adolescents with an anxiety disorder reported one or more intermittent sleep complaint(s) [4, 5].

The negative short-term and long-term consequences associated with both poor sleep and anxiety during adolescence are vast. Poor and insufficient sleep in this developmental period has been linked to problems in multiple domains, including risk for car accidents in new drivers [6], higher Body Mass Index [7], poor cognitive performance [8, 9], and problems with attention [9, 10], impulse control [11], mood [1] and suicidal behavior [12]. Similarly, youth anxiety is associated with elevated absence from and poor performance in school, problems maintaining friendships, increased family conflict and the development of depression and other psychopathology [13, 14]. Hence, anxiety and sleep problems can have severe consequences, especially during adolescence when multiple systems are undergoing neuromaturational changes, including affective and sleep systems.

While there is substantial evidence on the cross-sectional associations between anxiety and sleep problems, there is a paucity of data on the temporal relationships between anxiety and sleep problems. That is, do sleep problems precede anxiety; does anxiety precede the onset of sleep problems; or is the relationship bidirectional? Work examining the direction of these longitudinal associations may provide important suggestive evidence about the potential causal links between these domains and can have important implications for developing novel prevention and intervention efforts.

To better understand the directionality in the sleep-anxiety association, longitudinal and experimental studies are necessary. A small number of such studies have been conducted that investigate sleep problems as predictor for the development of anxiety in childhood and adolescence. For example, in longitudinal studies, Gregory et al. showed that parent-rated sleep problems in childhood and adolescence predicted anxiety levels in late-adolescence and early adulthood [15] as well as anxiety disorder in early adulthood [16]. Furthermore, Gregory and O'Connor [17] showed that parent-rated sleep problems in early childhood (four years) predicted anxiety levels in early to mid-adolescence (13y-15y). This association has also been observed in clinical samples. For example, 46% of children who reported persistent sleep problems from age 5 to 9 years developed an adult anxiety disorder [16]. However, Johnson et al. [18] failed to show a significant association between parent-reported trouble sleeping at age six years with the prevalence of subsequent anxiety at age eleven years. Also, in an adolescent sample of 13-16 year old, Johnson et al. used structural interviews to assess DSM-IV anxiety diagnoses and retrospectively assessed age of onset, and found that prior insomnia was not significantly associated with later onset of anxiety disorders [19]. In one experimental study, Talbot et al. [20] found that after two nights of partial sleep deprivation (sleep duration reduced to approximately 6.5 and 2 hours, respectively), adolescents reported a larger increase in anxiety after a catastrophising task, as compared to a condition of proper rest.

Furthermore, young adolescents rated their primary worry as more threatening following the sleep deprivation condition.

Studies that focused on anxiety as a predictor for sleep in a youth population are even rarer. In a longitudinal study, Johnson et al. [18] found in a large sample of 13-16 year olds that any prior anxiety disorder was associated with an increased risk of insomnia (hazard ratio=3.5) and that among those with both disorders, anxiety disorders preceded insomnia 73% of the time. Yet, another longitudinal study by Gregory and Conner [17] showed no evidence for childhood anxiety symptoms to precede sleep problems in mid-adolescence.

In summary, longitudinal studies have provided some support for sleep problems being a risk factor for anxiety as well as anxiety being a risk factor for sleep problems; yet, some studies have failed to find an association in one direction or the other. These inconsistencies may be due to a number of methodological differences, including the age ranges of participants (e.g., young children vs. late adolescents) and differences in definitions and assessments of anxiety and sleep problems. The previous studies have some limitations. First, no study has included more than two assessment points in their analyses. Since the previous studies have covered different age spans and used different methodology, it is difficult to compare and evaluate the longitudinal sleep-anxiety association across the entire range from early to late adolescence. Second, no study has identified the pathways of the longitudinal association, i.e. is there a direct, independent association, or can the association better be explained by indirect paths, for example through the consistency of one type of problem over time in combination with cross-sectional correlation at a later time-point?

The aim of this study is to examine the longitudinal association between sleep problems and anxiety symptoms across adolescence, using data from a large, representative, and longitudinal population study in the Netherlands. We employed structural equation modeling (SEM) to assess the influence of sleep on anxiety and anxiety on sleep longitudinally. By studying these associations across a longer period of time, the results can demonstrate the relative importance of each of the directions across adolescence. We tentatively hypothesized that sleep problems precede anxiety symptoms and that anxiety symptoms precede sleep problems across adolescence. No *a priori* hypotheses regarding the relative strengths of these relationships have been formulated.

METHODS

Study design and population

Participants were part of the TRacking Adolescents' Individual Lives Survey (TRAILS), a large population cohort study designed to examine the etiological mechanisms and development of psychopathology from pre-adolescence into adulthood. Data were used from the first three waves of TRAILS: T1 (2001-2002; age range 10-12), T2 (2003-2004; age range 12-15) and T3 (2005-2007; age range 14-18).

Participants were recruited from the general population in five municipalities in the northern part of The Netherlands, including both urban and rural areas. All children living in these municipalities and born between October 1989 and September 1990 (two sites) and October 1990 and September 1991 (three sites) were selected (N=3,483). Their date of birth and contact information was obtained

through the municipality administrations. Exclusion criteria were non-participation of the school (9.6% of schools, N=338 children) and severe mental retardation, a severe physical illness, or language-limitations (N=210). Extensive efforts were taken to minimize non-response, including reminder letters and personal house visits [21]. In all, 2,935 children were eligible for the study, of whom 2,230 (76%; 51% girls) agreed to participate in the first wave (T1; 2001-2002; age range 10-12 years). At T2, N=2,149 (96.4%; 51% girls) continued to participate. At T3, 42 adolescents were not included due to severe mental or physical health problems, death, detention, emigration or because they were untraceable. Of the remaining adolescents, N=1,816 (83%; 53% girls) continued to participate.

Non-response bias was analyzed based on information provided by the teachers about mental health determinants and outcomes of responders and non-responders [22]. Responders and non-responders did not differ in mean levels of psychopathology at baseline or at the second assessment wave, and did not differ regarding associations between socio-demographic variables and mental health variables [22]. Responders of the third assessment wave scored approximately 10% higher on anxiety and depression at the first assessment than non-responders. Informed consent was obtained at each assessment wave from each participant and their parents. The study was approved by the Dutch Central Medical Ethics Committee (CCMO) and all participants were compensated for their involvement in this study.

Measures

Anxiety symptoms were assessed with the Dutch translation of the Revised Child Anxiety and Depression Scale (RCADS) [23, 24], a revision of the Spence Children's Anxiety Scale [25]. The RCADS is a self-report questionnaire that consists of 37-items measuring DSM-IV symptoms on five anxiety types: generalized anxiety disorder (GAD: 6 items), obsessive-compulsive disorder (OCD: 6 items), panic disorder (PD: 9 items), separation anxiety disorder (SA: 7 items) and social phobia (SP: 9 items). Items are scored on a four-point Likert scale (0 = never, 1 = sometimes, 2 = often, 3 = always). As we had no hypothesis of specificity of the associations for any of the anxiety subtypes, and the scores on the different scales correlated, we used a measurement model where the five subscales (mean item scores) loaded on a latent factor: Total Anxiety. For descriptive purposes, we calculated a total anxiety score based on the mean item score of the 37 items.

Sleep problems at each time point were assessed using sleep-problem items from the Youth Self-Report (YSR) [26, 27], a child self-report questionnaire that assesses behavioral and emotional problems during the past six months on a 3-point Likert scale (0=not true; 1=somewhat/sometimes true; 2=very/often true). Items used were "nightmares", "overtiredness", "sleeping less than others" and "problems sleeping". Furthermore, we used the item "in the past year, did you have problems with not sleeping well" with a 4-point Likert scale (1=not; 2=a little; 3=a lot; 4=very much), which was part of a general health questionnaire.

Statistical analyses

Descriptive statistics were performed in SPSS 18 for Windows. All other analyses were carried out in MPlus 6.12 [28].

Measurement model

For both sleep problems and anxiety symptoms, we built a measurement model to form a latent variable at each time point. We tested the measurement models for meeting basic requirements regarding longitudinal measurement invariance. Examination of longitudinal measurement is necessary to help interpret observed changes in latent sleep or anxiety scores over time. If longitudinal measurement stability is absent, a measured change in sleep or anxiety over time may be due to a different interpretation of the items across adolescence, instead of a true change in the level of Sleep Problems or Total Anxiety. The two basic requirements for longitudinal measurement invariance are configural invariance and metric invariance [29]. Configural invariance implies that the same pattern of factor loadings holds across time. We tested for configural invariance by fitting the hypothesized factor structure to the data at all three time points and evaluating model fit. If the model fit is adequate (see model fit criteria below), we concluded that model is configural invariant. Metric invariance tests if the latent factor scores predict response to each item similarly across age groups. We tested for metric invariance by constraining factor loadings across age groups and evaluating model fit again.

The five sleep items of each time point were used to form the latent Sleep Problems variable, and the five RCADS subscales were used to form the latent Total Anxiety variable. Latent variables capture only the variance shared by all its items or scales, and hence are a good representation of the underlying concept. Model fit was estimated with the maximum likelihood estimator and evaluated using the comparative fit index (CFI) [30, 31] and the root mean square error of approximation (RMSEA)[32]. Good model fit is indicated by a CFI of .95 or higher [32] and a RMSEA of .05 or lower [32]. Acceptable model fit is indicated by a CFI greater than .90 and a RMSEA smaller than .08. Based on the modification indices, we considered model re-specification to improve the model fit; however, importantly, theoretical support is needed for the decision to release new paths. All sleep item scores and anxiety scales were standardized (mean=0; standard deviation=1) to allow for better comparison and interpretation of the results. This was also necessary due to the different scoring categories of sleep items and the anxiety symptom scales.

The model fit of the model as described above proved to be inadequate (CFI=.874; RMSEA=.061 (90% confidence interval (CI)=.059-.063). Inspection of the modification indices showed that each of the sleep items and anxiety items shared unique variance across time, which is not captured in the latent variable. From a theoretical perspective it makes sense that individual items assess a component of anxiety or sleep that is not shared with other items; hence, we allowed for residual covariation between the same sleep items and the same anxiety items across time (e.g., item *x* at T1, T2 and T3).

Primary analyses

Structural Equation Modeling (SEM) panel modeling was used to determine if our observed data fit the hypothesized model (Figure 1). Based on our hypothesis, we used a SEM panel design over three time points to examine prospective associations from Sleep Problems to Total Anxiety and vice versa, after accounting for homotypic continuity (e.g., sleep at T1 predicts sleep at T2) and cross-sectional

covariation between Sleep Problems and Total Anxiety (see Figure 1). Each path in the model was freely estimated.

In the final SEM panel model, we also assessed the indirect association between Sleep Problems and Total Anxiety, and vice versa. We calculated the indirect association by multiplying the homotypic continuity with the cross-sectional association with the other problem. This indirect heterotypic association was compared to the corresponding direct heterotypic association by restricting the indirect and the direct path to be equal in strength and evaluating the change in model fit. Model fit change ($\Delta\chi^2$) was evaluated by subtracting the χ^2 and degrees of freedom of the unrestricted model from the χ^2 and degrees of freedom of the restricted model. A significant change in model fit between the restricted and the unrestricted model indicates a significant difference in the strength of the compared paths.

RESULTS

Descriptives

Table 1 shows the mean sleep problems and mean anxiety symptom levels at all three time points.

Table 1: *Demographics and descriptive statistics of anxiety symptoms and the sleep problem items.*

Variable	T1	T2	T3
N	2,230	2,149 (96.4%)	1,816 (83%)
Age, mean (SD)	11.1 (.6)	13.6 (.5)	16.3 (.7)
Sex (female)	51%	51%	53%
Anxiety Total, mean (SD)	.57 (.32)	.42 (.31)	.42 (.30)
GAD	.65 (.42)	.48 (.40)	.51 (.40)
OCD	.57 (.40)	.33 (.33)	.28 (.33)
PD	.41 (.33)	.29 (.30)	.28 (.28)
SA	.36 (.32)	.23 (.27)	.22 (.25)
SP	.75 (.39)	.66 (.43)	.70 (.45)
Sleep items (%)	never smtime often very often	never smtime often very often	never smtime often very often
nightmares	50.0 45.7 4.3	69.2 28.8 1.9	77.5 20.9 1.6
overly tired	78.8 19.6 1.6	63.8 29.6 6.7	57.3 32.4 10.3
sleeping less	61.3 28.9 9.8	61.5 29.8 8.7	56.9 32.8 10.3
problems sleeping	65.8 24.4 9.7	74.4 18.6 7.0	70.1 22.1 7.9
not sleeping well	49.9 34.7 10.0 5.4	49.2 33.5 11.1 6.2	45.0 35.3 13.8 5.9

Note: SD=standard deviation; GAD=generalized anxiety disorder; OCD=obsessive-compulsive disorder; PD=panic disorder; SA=separation anxiety disorder; SP=social phobia; smtime=sometime

Measurement model

The measurement model for the latent variable “Sleep Problems” had a good model fit (CFI=.982; RMSEA=.030 (90%CI=.025-.034)), indicating that the factor structure of this model is similar for all three time points and thus that the model is configural invariant. When testing for metric invariance, the model fit was still good (CFI=.971; RMSEA=.036 (90%CI=.032-.040)), indicating that each sleep

item contributes a similar amount of variance to the Sleep Problems variable across all three time points. Similarly, the measurement model for the latent variable "Total Anxiety" was configural invariant (CFI=.989; RMSEA=.033 (90%CI=.029-.038)) and the more restricted metric invariance model still had good model fit (CFI=.978; RMSEA=.044 (90%CI=.040-.048)).

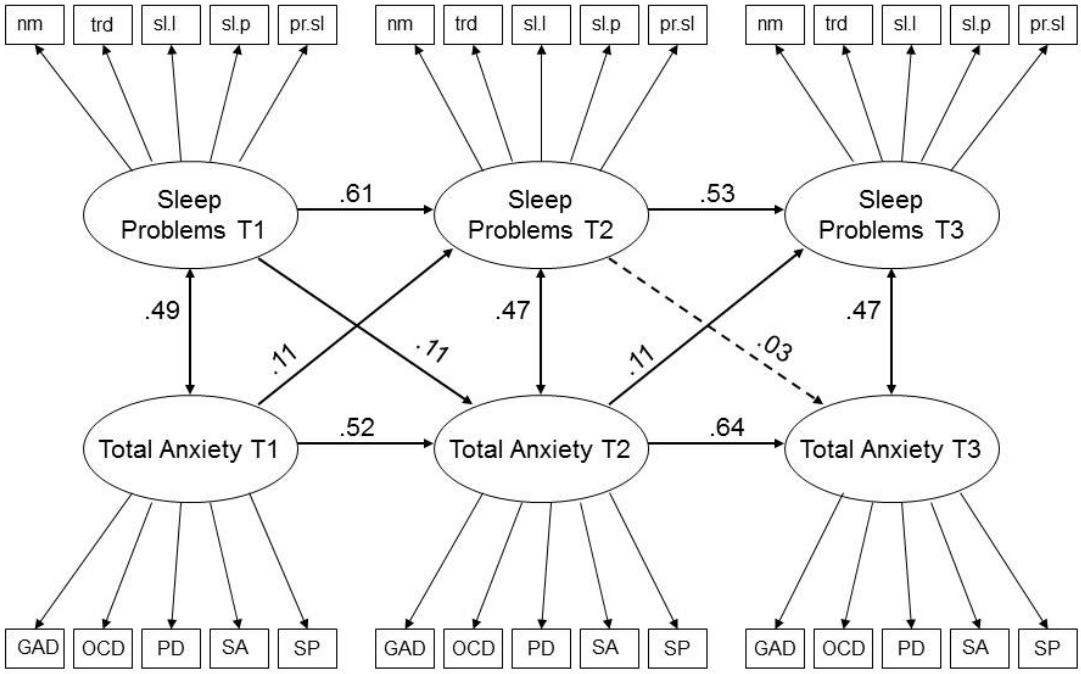

Figure 1: *Panel model between "Sleep Problems" and "Total Anxiety".*

Note: T1= assessment wave 1; T2= assessment wave 2; T3= assessment wave 3; nm=night mares; trd= overly tired; sl.l=sleeps less than others; sl.p=sleep problems; pr.sl= problems sleeping; GAD=generalized anxiety disorder; OCD=obsessive-compulsive disorder; PD=panic disorder; SA=separation anxiety disorder; SP=social phobia; dotted arrow indicates non-significant path. Covariation for the same sleep items and the same anxiety items across time was included in the model, but is not shown in the figure.

Panel model

The hypothesized panel model (Figure 1) fit the data well (CFI=.951; RMSEA=.040 (90% CI= .038-.042)). The longitudinal continuities of Total Anxiety as well as of Sleep Problems across adolescence were the strongest paths of the model (.52-.64) and were all significant. The covariance between Sleep Problems and Total Anxiety within each time point was almost as strong as the longitudinal continuity and remained similar and significant at all three time points across adolescence (.47-.49).

Of the *direct* heterotypic paths, i.e., after adjusting for the influence of cross-sectional associations and longitudinal continuity between Sleep Problems and Total Anxiety, we saw that Total Anxiety predicted subsequent Sleep Problems both from T1 to T2 (mean ages T1 11.1y and T2 13.6y) and from T2 to T3 (mean ages T2 13.6y and T3 16.3y), and Sleep Problems predicted subsequent Total Anxiety, but only from T1 to T2. The strengths of these significant independent heterotypic paths were identical across adolescence (βs= .11). Sleep problems at T2 did not significantly predict Total Anxiety at T3. Eliminating this path did not change the model fit.

Aside from the direct heterotypic association, Sleep Problems and Total Anxiety are also indirectly associated across time through longitudinal stability and cross-sectional associations. The *indirect* heterotypic paths between Sleep Problems (Slp) and Total Anxiety (Anx) showed that the indirect path of Slp T1 – Slp T2 – Anx T2 was β= .29 (95% CI= .24-.33); the indirect path from Anx T1 – Anx T2 – Slp T2 was β= .24 (95% CI= .21-.28); the indirect path from Slp T2 – Slp T3 – Anx T3 was β= .25 (95% CI= .20-.29); and the indirect path from Anx T2 – Anx T3 – Slp T3 was β= .30 (95% CI= .25-.35). All indirect paths were significant ($p< .001$). Furthermore, the heterotypic *indirect* associations were all significantly stronger than the heterotypic *direct* associations from the SEM panel model (for all $\Delta\chi^2$ between the unrestricted and restricted model, $p< .001$)

DISCUSSION

In this study, we examined the longitudinal associations between sleep problems and anxiety symptoms across adolescence. We hypothesized that sleep problems would precede anxiety symptoms and anxiety symptoms would precede sleep problems across adolescence. This study supports a bidirectional relationship between sleep problems and anxiety symptoms in adolescence: poor sleep increased the likelihood of subsequent anxiety symptoms, but anxiety symptoms also increased the likelihood of experiencing sleep problems. Our study is, to the best of our knowledge, the first to assess both directions of this association simultaneously as a means to separately investigate the direct and the indirect paths. Furthermore, this study is the first to cover the developmental span between pre- and late adolescence, including three assessment points.

Sleep problems and anxiety symptoms were most strongly related with each other within the same time-point. This cross-sectional association is consistent with previous studies showing that in adolescence, sleep problems frequently co-occur with anxiety symptoms and vice versa [1, 33]. However, our study extends this literature by showing this association at three different time points across adolescence and showing that the strength of the cross-sectional association remains stable across this developmental span.

Anxiety symptoms preceding sleep problems

Anxiety symptoms, as assessed on a standardized questionnaire, had a small, direct predictive association with subsequent sleep problems across adolescence. This association was independent of the stability of anxiety symptoms across time and independent of co-occurring sleep problems at any time point, hence indicating that anxiety at any point in adolescence is an independent risk factor for sleep problems two years later. However, the *indirect*, prospective association between anxiety and sleep problems was much stronger. This *indirect* path describes the continuity in anxiety symptoms combined with comorbid sleep problems.

Our findings are consistent with previous research findings. For instance, Johnson et al. found that anxiety disorders precede sleep problems in 13-16 year old adolescents [19]. Similarly, another study showed that treating anxiety with medication resulted in significantly greater reduction in sleep problems as compared to placebo treatment of anxiety [34]. The one study that failed to find this association differed from our study in that it assessed the predictive association of anxiety on sleep

problems across a longer time interval (eleven years), and relied on parent-reports of sleep problems in mid-adolescence [17]. It is possible that the influence of anxiety on sleep operates over a shorter time interval. Furthermore, it is debatable whether parents have enough insight into the sleep behavior of adolescents, especially as they get older, to be valid reporters of sleep problems.

The mechanisms underlying the prospective association between anxiety symptoms and sleep problems are not well understood. One plausible mechanism concerns the psychophysiological arousal processes. Dahl [35] hypothesized that a high state of arousal, which is characteristic of the vigilance and worry that occur in the context of anxiety is incompatible with the low levels of arousal mandatory for adequate sleep. Sleep requires a perception of safety since one is highly vulnerable to threat during this disengaged state; therefore, adequate sleep and anxiety may lie on opposing ends of an underlying arousal process. Not only vigilance and worry increase physiological arousal; one characteristic of anxiety is biased information processing, favoring threatening information, which may also enhance arousal [36]. This too is a plausible mechanism that may link anxiety and sleep problems, and is worth further study.

Sleep problems preceding anxiety symptoms

Sleep problems had a small, direct predictive association with subsequent anxiety symptoms in early adolescence (between T1 to T2; mean ages 11.1 to 13.6 years). This association was independent of the stability of sleep problems across time and independent of co-occurring anxiety symptoms at any time point; therefore, this indicates that sleep problems in early adolescence are an independent risk factor for anxiety symptoms in mid-adolescence. However, we did not find this independent prediction between mid and late adolescence (between T2 to T3; mean ages 13.6 to16.3 years). This lack of predictive association between sleep problems and anxiety in mid-adolescence to late adolescence was surprising: we had no a priori reason to expect that this association would fade throughout adolescence. However, it is interesting to note that key maturational changes in both sleep and affective systems appear triggered by the onset of puberty, highlighting the possibility that the influence of changing sleep systems on affective arousal may cascade more powerfully in early adolescence, relative to mid and late adolescence. It will be important to examine this hypothesis in future studies.

The *indirect*, prospective association between sleep problems and anxiety symptoms, on the other hand, was consistently present across adolescence, and stronger than the direct, independent association in early adolescence. This indicates that the observed association between earlier sleep problems and subsequent anxiety symptoms is mostly due to the stability of sleep problems across time, and the co-occurrence of sleep problems with anxiety symptoms.

The finding that sleep problems predict anxiety symptoms in adolescents is in line with previous research [15-17, 20]. Our study adds to the field in that none of the previous studies have specifically focused on the developmental period of adolescence, and none has used methodology that allows for the disentangling of the direct and indirect paths.

The underlying mechanisms between the sleep-anxiety associations remain largely elusive, but there is some evidence that the psychophysiological arousal system may again be involved. Previous

studies show that sleep problems can increase arousal, which is in turn associated with anxiety. For example, Talbot et al. found that sleep deprivation can lead to increased threat appraisal of a person's "main worry" as well as attention bias towards threat [20]. This is consistent with the assumption that adequate sleep and arousal are at opposite ends of one arousal continuum, as described above.

Strengths, limitations and future directions

This study benefitted from a large adolescent sample representative of the general population of adolescents, covering ages 10 to 18 years. Additionally, sleep problems and anxiety symptoms were both assessed prospectively, which reduces recall bias. Finally, we used advanced methodology that enabled us to assess different sleep-anxiety associations in one model, unraveling the relative contribution of each of these associations.

The main limitations of this study concern the items used to examine sleep problems. First, we did not use a validated sleep questionnaire. However, there is no questionnaire-based assessment of sleep problems in youth that has been widely studied and the YSR-based measure we used, or one akin to it, has been used in several other studies to assess sleep problems in youth (e.g. [4, 17, 33]). Furthermore, the measurement model for our variable "Sleep Problems" showed good qualities, indicating that our sleep variable captures meaningful features shared by the different sleep items, and sensitivity analyses showed no specificity in association between any sleep item and anxiety symptoms. Secondly, in our study we relied solely on self-reported sleep problems and lacked more objective measures, which would capture physiological parameters of sleep. While merely using self-report is suboptimal due to the bias that can be introduced, studies have suggested that subjective and objective measures of sleep from children and adolescents are correlated [37, 38]. Nonetheless, we argue that objective measures of sleep are indispensable for accurate estimates of sleep. Since the gold standard of objective sleep assessment, i.e. polysomnography, is not feasible to employ in large, longitudinal studies [17, 39], future studies should strive to include actigraphy data to obtain more objective sleep data.

This more objective and detailed sleep data may help guide us into relevant directions when striving to identify mechanisms underlying the anxiety-sleep association. To this day, the mechanisms underlying the sleep-anxiety association remain poorly understood. In order to move towards a more fundamental understanding of this association, studies should incorporate moderators to investigate this relationship. Insight into these factors will move the field forward by helping to identify subjects who are at increased risk for adverse outcomes, as well as furthering the development of effective interventions.

Conclusion and clinical implications

The results of this study suggest that sleep problems and anxiety symptoms have a bidirectional relationship across adolescence. This relationship seems most strongly driven by the stability of anxiety symptoms and sleep problems across time, and the independent association between anxiety symptoms and sleep problems was at best modest in size. These findings suggest that interventions may be most feasible when aiming to reduce the respective chronicity of anxiety symptoms or sleep

problems. Until the mechanisms are better understood, the effect of addressing anxiety to reduce sleep problems across time, and vice versa, promises to be small.

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Chapter 6

Does heart rate variability moderate the effect of anxiety on sleep problems?

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ABSTRACT

Anxiety symptoms predict sleep problems in some, but not all adolescents. Parasympathetic nervous system activity and reactivity are potential moderators in this relationship. With data from the TRacking Adolescents' Individual Lives Survey (N=1,570, 51% girls), we examined whether the relation between anxiety symptoms and sleep problems is moderated by (re)activity of the parasympathetic nervous system. At baseline, subjects were 10-12 years and at follow-up 12-15 years. Anxiety symptoms were measured with the Revised Child Anxiety and Depression Scale, and parasympathetic nervous system activity was assessed by high-frequency heart-rate variability in rest and *re*activity during orthostatic challenge. Sleep problems included trouble sleeping, nightmares, overtiredness, and sleeping less than others. Cross-sectionally, neither parasympathetic nervous system measure moderated the association between anxiety symptoms and sleep problems. However, prospectively, the association between Total Anxiety at T1 and Sleep Problems at T2 was moderated by parasympathetic reactivity (B=-.06, *p*=.031). Among adolescents with higher levels of anxiety, those with high reactivity have less sleep problems, whereas among adolescents with lower levels of anxiety, those with low reactivity have less sleep problems. In adolescents with high levels of anxiety symptoms, low parasympathetic nervous system reactivity can indicate a sensitivity to develop sleep problems in mid adolescence. When evaluating risk for developing sleep problems later in adolescence, including parasympathetic nervous system reactivity could help identify which adolescents are at an increased risk. Identifying profiles that are associated with increased risk for developing sleep problems can ultimately help to efficiently target high-risk individuals with prevention techniques.

INTRODUCTION

An estimated 40% of adolescents suffer from sleep problems [1], that are associated with vast negative short-term and long-term consequences, including difficulties with attention, impulse control and behavior and mood problems. Cross-sectional studies show that sleep problems co-occur with anxiety symptoms, both in the general population clinical samples (see [2] for review). In children and adolescents with an anxiety disorder, 66% to 82% reported two or more intermittent sleep complaint(s) [3, 4]. Further, two studies report prospective associations between childhood anxiety and future sleep problems [5, 6]. In a community-based sample of 1,014 adolescents between 13-16 years, Johnson et al. retrospectively assessed ages of onset of lifetime DSM-IV diagnosis of insomnia and any anxiety disorder and found that any prior anxiety disorder was associated with an increased risk of insomnia [6]. However, a prospective study of 490 children in adoptive and non-adoptive families that were followed from age 4 to age 15 did not find support for childhood anxiety symptoms prospectively predicting sleep problems in mid-adolescence [5].

These inconsistent results suggest that not all patients with anxiety symptoms experience sleep problems to the same extent; some may experience many sleep problems, while others experience fewer or none. To date, it is not known which factors forecast high-risk for sleep problems in the presence of anxiety symptoms. Identifying these factors is important to help recognize who is at increased risk for developing sleep problems and why they are at-risk. One mechanism that might explain individual differences in risk for sleep problems is (re)activity of the parasympathetic nervous system (PNS).

State and trait anxiety are closely associated to the emotion of fear, which evokes a stress-response [7]. This response is characterized by sympathetic activation and parasympathetic withdrawal. Several studies found an association between anxiety symptoms and low PNS activity [8, 9] and reactivity [9] in adults. In youth, similar associations have been found both in clinical (e.g. [10, 11] and population samples (e.g. [12, 13], but the associations were weaker than in adults. For example, Greaves-Lord et al. found that low parasympathetic activity was associated with anxiety symptoms in healthy 10-13 year olds [12] and Mezzacappa et al. found that anxiety symptoms were associated with reduced parasympathetic reactivity to challenge in a sample of 15 year old males [13].

While anxiety symptoms are associated with low PNS activity and reactivity, it is known that for adequate sleep, high PNS (re)activity is necessary. Falling asleep is preceded by an increase in parasympathetic tone and reduction of sympathetic drive [14]. It is the parasympathetic dominance and its associated restorative functions that may be key to the subjective experience of restorative sleep [15]. To our knowledge, there is one study on daytime PNS activity and reactivity, and sleep in children. In this study, lower PNS reactivity during a reaction-time task, but not PNS activity predicted a higher level of sleep problems [16].

In summary, we see that in adults, and possibly also in children, the (re)activity of the PNS is associated with both anxiety symptoms and with sleep problems. The lower PNS (re)activity levels associated with anxiety symptoms may increase risk for developing sleep problems. This assigns PNS (re)activity a plausible moderating role in the sleep-anxiety association. We hypothesize that the

relation between anxiety symptoms and sleep problems is stronger in adolescents with lower levels of PNS (re)activity than in adolescents with higher levels of PNS (re)activity. Given previous studies on moderation by PNS activity [16, 17], this may be more likely for PNS *re*activity than for PNS activity.

METHODS

Study design and population

Participants were recruited from the general population in five municipalities in the northern part of The Netherlands, including both urban and rural areas. All children living in these municipalities and born between October 1989 and September 1991 were eligible (N=3,483). Their date of birth and contact information was obtained through the municipality administrations.

Participation of the child's school was required for enrollment. Of the 135 primary schools approached, 9.6% refused to participate, excluding N=338 children. If schools agreed to participate, parents were approached with information brochures and a follow-up phone call in which they were invited to participate. Participants were excluded from the study if they were incapable of participating due to severe mental retardation, a severe physical illness, or language-limitations (N=210). Of the 3,483 selected children, 2,935 were eligible for the study, of whom 2,230 (76.0%, of which 50.8% girls) participated in the first wave (T1; age range 10-12 years). Details of the TRacking Adolescents' Individual Lives Survey (TRAILS) have been described elsewhere [18]. Non-response was due to explicit refusal or inability to establish contact [19]. Extensive efforts were taken to minimize non-response, including reminder letters and personal house visits. Non-response bias was analyzed based on information about mental health determinants and outcomes as reported by teachers of responders and non-responders [19]. Responders and non-responders did not differ in mean levels of psychopathology at T1, and did not differ regarding associations between socio-demographic variables and mental health variables [19]. At the second wave (T2; age range 12-15 years) 2,149 adolescents continued to participate (96.4%, of which 51.2% girls). Of the T1 sample 1,868 (83.8%) children participated in the autonomic nervous system (ANS) measurements. Valid measures were obtained for 1,762 participants in supine position and 1,636 children had assessments in both supine and standing position that permitted computing ANS reactivity.

The present study included all children with at least one valid autonomic nervous system (ANS) measure and with valid data available on sleep problems at both waves as well as anxiety symptoms and covariates at the first wave (N=1,570). The included children did not differ from the excluded of the full T1 sample in terms of sex, body mass index (BMI), physical activity, sleep problems or anxiety symptoms; however, the children with complete data available were less advanced in their pubertal development, ($F\ (1, 1569)$=15.71, p≤.0001; mean 1.83 vs. 1.98) and low socio-economical position (SES) was underrepresented (23.3% vs. 30.3%) while mid SES was overrepresented (51.8% vs. 43.9%)(χ^2=14.27 (2), p=.001). Written informed consent was obtained at each assessment wave from each participant and their parents. The study was approved by the Dutch Central Medical Ethics Committee (CCMO) and all participants were compensated for their involvement in this study.

Measures

Anxiety symptoms

Anxiety symptoms were assessed by the Revised Child Anxiety and Depression Scale (RCADS; [20], a revision of the Spence Children's Anxiety Scale. The RCADS is a self-report questionnaire, including 37-items that measure five anxiety subtypes: generalized anxiety disorder (GAD: 6 items), obsessive-compulsive disorder (OCD: 6 items), panic disorder (PD: 9 items), separation anxiety disorder (SA: 7 items) and social phobia (SP: 9 items). All items are scored on a four-point Likert scale (0 = never, 1 = sometimes, 2 = often, 3 = always). A "Total Anxiety" score was calculated based on the mean item score of all anxiety items. Internal consistency of the Total Anxiety scale is good (α = .91). To enhance interpretation, we centered (mean=0) the Total Anxiety variable.

Sleep problems

Sleep problems at both T1 and T2 were assessed using sleep-problem items from the Youth Self-Report (YSR) [21, 22], a child self-report questionnaire that assesses behavioral and emotional problems during the past six months on a 3-point scale (0=not true; 1=somewhat/ sometimes true; 2=very/ often true). Items used were 47 "nightmares", 54 "overtiredness", 76 "sleeping less than others" and 100 "problem sleeping". Furthermore, we used the item "did you have problems with not sleeping well in the past year", which was part of a general health questionnaire, using a 4-point answer scale (1=not; 2=a little; 3=a lot; 4=very much). As the items had different numbers of response options, we created an aggregated "Sleep Problems" variable using confirmatory factor analyses (CFA) in Mplus 6.12 [23]. To this end, we fit a one factor model with the five sleep variables as the observed indicators for each time point. The model fit was excellent for both waves of data collection (Sleep Problems T1: CFI=.981; TLI=.961; RMSEA=.063; Sleep Problems T2: CFI=.983; TLI=.966; RMSEA=.060). Using this model, the latent factor scores were used as the total Sleep Problem variables. As the distribution of Sleep Problems variables (T1, T2) was skewed, we used the natural logarithm transformation of the Sleep Problems variables in our analyses.

Parasympathetic (re)activity

Autonomic nervous system measurements were taken individually in a quiet room in the child's school, typically before noon, but occasionally in the early afternoon. Heart rate (HR) registration was done by a three-lead electrocardiogram and spontaneous fluctuations in continuous beat-to-beat systolic finger blood pressure (BP) were assessed non-invasively by the Portapress device (FMS Finapres Medical Systems BV, Amsterdam, the Netherlands).

Recordings did not start until after a few minutes of supine rest and only after the signals reached a stabilized steady-state after circulatory readjustments of body fluid changes. Then, HR and BP were recorded for four minutes in supine position, during which participants were instructed to breathe spontaneously and not to speak or move. Subsequently, HR and BP were recorded in standing position for two minutes, again after the signals had stabilized.

Calculation of high-frequency heart-rate variability (HF-HRV) was performed by power spectral analysis in the CARSPAN software using estimation techniques based on Fourier transformations of

interbeat-intervals series. HF-HRV is defined as the power in the high-frequency band (ms^2) in the 0.15-0.40 Hz respiratory band. The analyzed time series were corrected for artifacts and checked for stationarity. To approximate a normal distribution, both HF-HRV measures were transformed to their natural logarithm. The reactivity measure of the PNS (ΔHF-HRV) was calculated by subtracting the HF-HRV values in supine position from the HF-HRV values in standing position.

Other characteristics

Known correlates of HRV, including sex, BMI, pubertal development, SES and physical activity, all measured at T1, were included as covariates. BMI was calculated by dividing the measured weight (kg) by the square of the measured height (m^2). Pubertal stage was categorized using Tanner stages. Tanner's pubertal development classification uses five schematic drawings of figures with secondary sex characteristics. Parents were asked to identify which drawing looks most like their child. For children and early adolescents, these ratings have shown good reliability and validity [24]. SES was based on ratings of occupation and education of the mother and father, as well as family income. Z-scores of all five components were calculated and categorized into low (lowest 25%), medium (mid 50%) and high (upper 25%). Physical activity was assessed by asking how often they perform sports such as swimming, soccer or horseback riding on a 5-point Likert scale from (almost) never (0) to 6-7 times a week (4). Other possible confounders, such as oral contraceptive use and smoking, were not included due to no or very low endorsement.

Statistical analyses

Descriptive analyses were performed in SPSS 20.0. Moderation analyses were performed in SPSS 20.0 using the PROCESS macro [25]. We investigated if PNS activity and reactivity moderated the association between anxiety symptoms and sleep problems, both cross-sectionally and across time. Moderation analyses were performed with T1 Total Anxiety as independent variable, T2 Sleep Problems as dependent variable and per model one of the PNS measures (HF-HRV supine, ΔHF-HRV) as moderator. Furthermore, T1 Sleep Problems was included as additional covariate (see *Figure 1*). This model also included main effects of HF-HRV measures on Sleep Problems at T1 and T2. All analyses were adjusted for sex, BMI, Tanner stage, SES and physical activity.

RESULTS

Table 1 shows total sample descriptive statistics, as well as mean scores and standard deviations of the variables used in this study.

Table 1: *Descriptive statistics of sample included in HF-HRV analyses (N=1,570)*

Variables	Mean (sd) or %
Age (years) T1	11.0 (0.5)
Age (years) T2	13.5 (0.5)
Sex female	51.4%
BMI (kg/m^2) T1	18.0 (3.1)
Tanner stage T1	1.8 (0.8)
SES T1 low	23.3%
mid	51.8%
high	24.9%
Physical activity (0-4) T1	1.9 (1.2)
Total Anxiety T1 (0-3)T1	0.6 (0.3)$^{\#}$
Sleep factor T1	0.5 (0.4)*
Sleep factor T2	0.5 (0.4)*
HF-HRV supine (ln ms^2) T1	7.4 (1.4)
ΔHF-HRV(ln ms^2) T1	1.4 (1.3)

Note: BMI=body mass index; SES= socio-economical position; HF-HRV=high frequency heart rate variability; ΔHF-HRV=difference between standing any supine high frequency heart rate variability; $^{\#}$uncentered mean and standard deviation; *not natural log transformed.

PNS activity: HF-HRV supine

Figure 1 and Table 2 show that Total Anxiety in 10-12 year olds (T1) was strongly and positively associated with Sleep Problems in 10-12 year olds (T1). At T1, HF-HRV in supine position was not related to Sleep Problems, nor did HF-HRV supine moderate the association between Total Anxiety and Sleep Problems (upper panel Table 2). Across time, HF-HRV supine also did not moderate the association between Total Anxiety (T1) and Sleep Problems (T2) (see upper panel right column in Table 2).

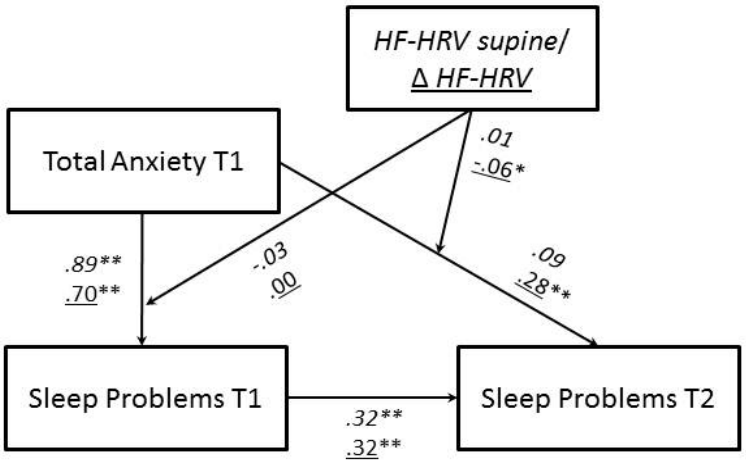

Figure 1: *Conceptual representation of our model, with path estimates.*

Note: *The statistical model also includes direct paths from HF-HRV to Sleep Problems at T1 and T2. Italic* represents the coefficients of the HF-HRV supine model; underlined represents the coefficients of the ΔHF-HRV model; *p<.05; **p<.001

Table 2: *Regression models with Total Anxiety and its interaction with HF-HRV as predictor for Sleep Problems.*

	Outcome variables					
	Sleep Problems T1			Sleep Problems T2		
	B	**SE**	***p***	**B**	**SE**	***p***
HF-HRV supine						
Total Anxiety[a]	**.89**	**.22**	**<.0001**	.09	.19	.634
HF-HRV supine[a]	.00	.01	.897	**.02**	**.01**	**.002**
Sleep Problems T1[b]				**.32**	**.02**	**<.0001**
HF-HRV supine x Total Anxiety	-.03	.03	.374	.01	.03	.570
ΔHF-HRV						
Total Anxiety[a]	**.70**	**.06**	**<.0001**	**.28**	**.05**	**<.0001**
ΔHF-HRV[a]	**.02**	**.01**	**.032**	**.02**	**.01**	**.022**
Sleep Problems T1[b]				**.32**	**.02**	**<.0001**
ΔHF-HRV x Total Anxiety	.00	.03	.960	**-.06**	**.03**	**.031**

Note: HF-HRV=High-frequency heart rate variability; ΔHF-HRV=difference in HF-HRV between supine and standing position. Significant coefficients are in bold; [a]main effect on Sleep Problems T1 and T2, respectively; [b] main effect on Sleep Problems T2; HF-HRV supine based on N=1,570; ΔHF-HRV based on N=1,458; All models were adjusted for sex, BMI, pubertal development, SES and physical activity.

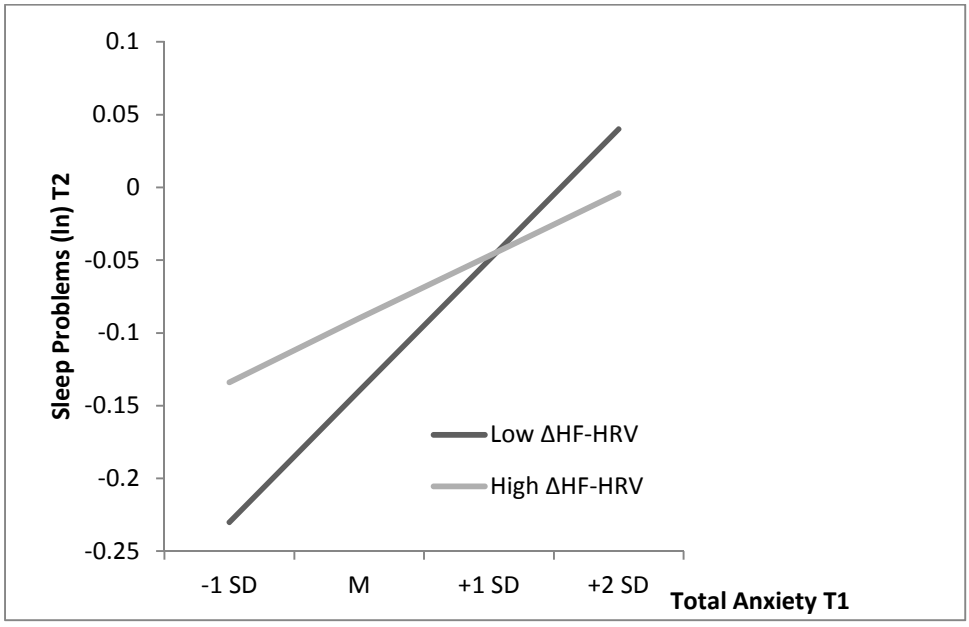

Figure 2: *Interaction between PNS reactivity (T1) and Total Anxiety (T1) and Sleep Problems (T2).*

PNS reactivity: ΔHF-HRV

At T1 (10-12 years), Total Anxiety and ΔHF-HRV were positively associated with Sleep Problems, but the association between Total Anxiety and Sleep Problems did not vary based on ΔHF-HRV (see Table 2 lower panel left column). Prospectively, the association between Total Anxiety at T1 and Sleep Problems at T2 varies based on the level of ΔHF-HRV. Figure 2 shows that in adolescents with higher levels of anxiety, those with higher ΔHF-HRV have less sleep problems compared to adolescents with lower ΔHF-HRV. On the other hand, adolescents with lower levels of anxiety, those with higher ΔHF-HRV have more sleep problems compared to adolescents with lower ΔHF-HRV.

DISCUSSION

In the present study, we examined whether PNS activity and reactivity would moderate the relation between anxiety symptoms and sleep problems in adolescents. We hypothesized that the relation between anxiety symptoms and sleep problems would be stronger at low levels of PNS (re)activity than at high levels. Our findings indeed suggest that not all adolescents with anxiety symptoms are at equal risk for developing sleep problems and that this risk is dependent on PNS *re*activity.

Among adolescents with a high level of anxiety symptoms (>1SD above the mean), those with lower PNS reactivity have more sleep problems than those with higher PNS reactivity. However, at lower levels of anxiety symptoms, adolescents with higher PNS reactivity have more sleep problems than those with lower PNS reactivity. These findings indicate that the effect of higher PNS reactivity depends on the context, i.e., higher PNS reactivity may be a protective factor under conditions of high anxiety symptoms, while being a risk factor under conditions of low anxiety symptoms. This bivalent effect of high reactivity is in line with the Biological Sensitivity to Context theory (BSC; [26], which states that the effect of high reactivity can be both risk-augmenting and risk-protective, depending on the context. Hence, when identifying individuals at increased risk for sleep problems, it is important to take into account anxiety levels as well as stress reactivity.

The effect size of PNS reactivity as moderator was modest. This may partially be related to the rather mild problem levels for both anxiety symptoms and sleep problems in our community sample. Whether the moderating effect is stronger in adolescents with anxiety disorders or sleep disorders deserves further attention. However, subclinical levels of anxiety have been associated with an increased risk for adverse outcomes [27], underlining the importance of including subclinical levels of anxiety in research that works towards early recognition and identification of adolescents at risk for sleep problems.

It was surprising to find the moderating effect only in the prospective association between anxiety symptoms at age 10-12 years and sleep problem at age 12-15 years. Speculatively, a plausible explanation concerns the presence of more potent moderators that overshadow the cross-sectional moderation of PNS reactivity, such as depressive symptoms or specific problems within anxiety, such as worry or rumination.

PNS activity, as measured by HF-HRV in supine position, did not moderate the association between anxiety symptoms and sleep problems, neither cross-sectionally, nor prospectively. Thus, lower PNS activity does not increase the risk for sleep problems among adolescents with anxiety symptoms. This finding is consistent with other studies that investigated the moderating effects of PNS activity and PNS reactivity, for example on sleep problems or on externalizing problems, and found moderation only by PNS reactivity, not PNS activity (e.g. [16, 17]).

This study benefitted from a large adolescent sample, especially as compared to many other studies involving physiological measurements, and was representative of the general population of adolescents. Also, we used a longitudinal design which allowed us to investigate moderation of the prospective path between anxiety symptoms and sleep problems. Further, we investigated both PNS activity and reactivity, allowing a better understanding of whether these concepts relate differently to the associations between anxiety symptoms and sleep problems.

A limitation of this study concerns the measurement of sleep problems. The YSR, or parent-reported version (CBCL), has been used in several other studies to measure sleep problems (e.g. [3, 5]), and provides subjective information on sleep problems. While objective and subjective sleep assessments correspond reasonably well [28], more objectively assessed information about sleep (e.g., with actigraphy) may add to our understanding of the moderation effect, either by solidifying our findings or by offering a complementary perspective. Our HF-HRV assessment was typically done in the morning measurements; however, HF-HRV shows circadian variations [29]. Thus, the moderating effect of PNS (re)activity may be different for HF-HRV activity at bedtime or during the night.

CONCLUSION AND CLINICAL RELEVANCE

In young adolescents with high levels of anxiety symptoms, low PNS reactivity can indicate a sensitivity to develop sleep problems in mid-adolescence. When evaluating risk for developing sleep problems later in adolescence, including PNS reactivity could help identify which adolescents are at an increased risk. Identifying profiles that are associated with increased risk for developing sleep problems can ultimately help to efficiently target high-risk individuals with prevention techniques.

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Chapter 7

General discussion

The primary aim of this thesis was to further our knowledge as to which factors are associated with anxiety symptoms in late childhood and adolescence, including predictors and outcomes of anxiety symptoms, as well as factors that may influence these associations. Anxiety symptoms predict the onset of anxiety disorder and depression, and have been associated with lower levels of well-being even before they reach disorder status. Consequently, it is important to understand the development of anxiety symptoms in more detail, so that we eventually can aim to prevent negative consequences of anxiety symptoms, among which the development of anxiety disorders. Much still remains to be learned about predictors and outcomes of anxiety symptoms; therefore, in this thesis I have chosen to focus on the precursors of panic attacks and the role of sleep problems and pubertal timing in the development of anxiety symptoms. In this chapter, I discuss the findings, as well as strengths and limitations of this study, and provide suggestions for future research.

MAIN FINDINGS AND INTERPRETATIONS

The prediction of panic attacks

I examined whether Internalizing and Externalizing problems in childhood (age 10-12 years) predict the onset of panic attacks in adolescence. The most important finding of this paper was that the wide range of Internalizing and Externalizing problems were predictors of adolescent's first panic attack. However, when I adjusted for co-occurrence of different problem behaviors, I found a unique contribution only for Social Problems. This was a striking finding as it was consistent over self-report and parent-report. The long-term consequences of problems with peer relations for anxiety have also been found in other TRAILS papers and in other large epidemiological studies. For example, Roza et al. have reported a unique relation between parent-reported Social Problems in childhood and adolescence (4-16 year-olds) and self-reported lifetime incidence of anxiety disorders (among which panic disorder) assessed 14 years later in young adulthood (age 18-30 year-olds) [1]. Others have demonstrated that an adolescent who reports panic attacks is likely to have parents who experience panic attacks or panic disorder [2-4]. Furthermore, studies have shown that adults with panic attacks have problems in relations with others [5-7]. It is possible that poor social skills are transmitted from parents to their offspring, resulting in social problems in children. This could explain the association between parents and adolescents in risk for panic attacks and the observed link in both with Social Problems. The transmission of poor social skills may be partially genetically driven, but likely also reflects a behavioral component in that parents fail to model adequate social skills to their offspring. By identifying an independent predictor for panic attack onset, this study has contributed to a better understanding of the development of panic attacks.

Measurement invariance of the RCADS

In the introduction, I have explained the importance of assessing longitudinal measurement invariance for any instrument that is being used to assess symptoms across time. If longitudinal measurement invariance has been *established*, we can assume that a change in measured anxiety severity reflects a true change in the anxiety level across time; whereas if longitudinal measurement invariance criteria are not met, a change in assessed anxiety symptom levels over time does not necessarily reflect a

true change in anxiety levels. I examined if the instrument used in TRAILS to assess anxiety symptoms, the Revised Child Anxiety and Depression Scale (RCADS)[8, 9], measures anxiety symptoms similarly across age groups over adolescence (10-17 years). For each of the subscales I examined the factor structure (configural invariance), factor loadings (metric invariance) and thresholds (strong invariance) [10, 11].

All five RCADS subscales had a time- invariant factor structure across adolescence and thus met criteria for configural invariance. The GAD, OCD, PD and SA subscales had time-invariant factor loadings and thus fully met criteria for metric invariance. Of the Social Phobia (SP) subscale, three items out of nine contributed less to the SP factor early is adolescence (age 10-12 years) than later in adolescence (age 12-18); yet the model fit of the metric invariance model for SP was still acceptable. These items shared a concern about self-evaluated poor performance. Although model fit for each of the scales decreased modestly when enforcing strong invariance constraints across time (i.e., keeping thresholds fixed), the model fit for strong invariance models was still acceptable to excellent for all subscales.

In summary, most criteria for longitudinal measurement invariance were fully met, and the ones that were not fully met were only mildly violated. Some have argued that meeting configural and metric invariance criteria is sufficient to establish longitudinal invariance [12]. Also, one might challenge the expectation of strong longitudinal invariance across adolescence, after all, adolescence is characterized by emotional and cognitive development and we expect, to varying degrees, that e.g. the likelihood of endorsement of some items may change, depending on developmental stage of the adolescent. Importantly, Little et al. state that in order to conclude that a change in measured anxiety severity reflects a true change in the anxiety level across time, an instrument should at a minimum have partial weak invariance and partial strong invariance [13]. Both of these criteria have been met for the RCADS. Therefore, I conclude that measured changes in anxiety symptoms using the RCADS subscales very likely reflect true changes in anxiety levels, and I consider the instrument suitable to meaningfully interpret changes in anxiety levels across adolescence measured with the RCADS.

Anxiety symptoms and pubertal timing

Previous study results have been inconsistent in the observed associations between pubertal timing and anxiety symptoms and disorders; some found early pubertal timing to be associated with more anxiety symptoms while others found only partial or no support for this association [14-18]. Importantly, all of these studies assessed pubertal timing only once in adolescence, implicitly assuming that pubertal timing does not change across puberty. Using an age-dependent approach to investigate the association between pubertal timing and anxiety symptoms could lead to a better understanding of this association and eventually help explain some of the inconsistencies in findings from previous studies that assessed pubertal timing only once.

Therefore, in chapter 4, I examined if the association between pubertal timing and anxiety symptoms varies by age. As part of this research question, I first examined if pubertal timing changes across adolescence, e.g. if an adolescent can move from being early in pubertal timing at age 11 to being on-time at age 13. Assessing pubertal timing as a dynamic concept is new to the literature. Only

in two studies pubertal timing was measured multiple times [19, 20]. These studies indeed reported intraperson variability in pubertal timing across adolescence. My findings are consistent with these findings and support treating pubertal timing as a time-varying variable in future studies.

Subsequently, I assessed changes in symptoms of generalized anxiety, social anxiety, panic disorder and total anxiety using linear mixed model analyses. In boys, at age 10-11, being ahead of peers in pubertal development (early pubertal timing) was associated with more anxiety symptoms, while from age 14 onwards, early pubertal timing was associated with fewer anxiety symptoms. This pattern of association held for the three subscales of anxiety symptoms and for the total anxiety scale. The associations were most pronounced for social anxiety symptoms. In girls, I found no association between pubertal timing and anxiety symptoms for any age (10-17 years).

I initially considered the “early timing hypothesis” which stipulates that early development is associated with more problems to help explain my findings; yet, this hypothesis has been formed based on the assumption of a static association between pubertal timing and anxiety symptoms. To explain the change in relation between pubertal timing and anxiety symptoms over adolescence in boys, it may be valuable to also consider the aspect of being most out of sync from peers when it comes to pubertal development. Some researchers have suggested that when it comes to pubertal development, it is the deviation from peers that may increase the risk for emotional and behavioral problems during adolescence [18] and lead to increased anxiety [21]; yet, the possibility of an age-dependent association has not been taken into account when this hypothesis was formulated. Peers are considered to be a very important reference group in adolescence [22] and suddenly differing from peers, for instance through changes in developmental status, can be threatening to the peer group membership and social status. However, depending on the characteristics of the deviation (evaluated as favorable or unfavorable), the change in social status can be positive or negative.

In early adolescence, when puberty has not yet begun for the majority of boys, there is a small group of boys for whom puberty has started. These boys are ahead of peers in pubertal development (early pubertal timing) and are outliers compared to the other boys. Furthermore, the early changes associated with pubertal development may be evaluated as awkward. This would then be associated with increased levels of anxiety symptoms – as I indeed found in TRAILS. A few years later, at age 12-13 years, the variation in pubertal development has increased, causing even developmental outliers to stand out less from peers, which would eliminate the association of early and late pubertal timing with anxiety symptoms. A few more years later (14-17 year olds), the deviation from peers by being developmentally ahead may be viewed as more favorable due to the display of physical features consistent with the social stereotype of desirable characteristics for boys, which may be associated with a strengthened social status and hence lower anxiety symptoms. Our findings suggest that the nature of the association between pubertal timing and anxiety symptoms depends on the age of the sample. Using this dynamic, age-dependent approach will probably help explain some of the inconsistencies in findings from studies that only used one assessment of pubertal timing.

Anxiety symptoms and sleep problems

The fourth and fifth papers in my thesis focus on the relations between sleep problems and anxiety symptoms. I found that early in adolescence, sleep problems and anxiety symptoms have a small but significant *direct* bidirectional relationship over and above cross-sectional associations and longitudinal continuity of anxiety symptoms and sleep problems. Later in adolescence, the relation from anxiety symptoms to sleep problems continued, but sleep problems no longer significantly predicted anxiety symptoms. This finding could be attributed to the fact that important maturational changes in both sleep and affective systems are related to the onset and progression of puberty [23], which occurs in mid adolescence. It is possible that the influence of changing sleep systems on affective arousal may be more pronounced before the onset of puberty. I also assessed the *indirect* association between anxiety symptoms and sleep problems, the resultant of the longitudinal continuity of anxiety symptoms (or sleep problems) combined with cross-sectional associations between them (i.e., anxietyT1 →anxietyT2 →sleepT2, and sleepT1 →sleepT2 →anxietyT2; same from T2 to T3). The *indirect* associations were all significant, and the strengths of the associations were all stronger than those of the *direct* associations. These findings are consistent with the few other studies in children that have shown that anxiety symptoms predict sleep problems and vice versa [24-27]. However, none of the previous studies have a focus on the developmental period of adolescence, and none used statistical methodology that allows for separate estimation of the direct and indirect paths.

In the second study, I investigated one of the potential mechanisms underlying the prospective association between anxiety symptoms and sleep problems: psychophysiological arousal processes. Dahl [28] hypothesized that a high state of arousal (related to anxiety symptoms) is incompatible with the low levels of arousal mandatory for adequate sleep. In TRAILS, the association between Total Anxiety at age 10-12 and Sleep Problems at age 12-15 was moderated by parasympathetic reactivity. In adolescents with high levels of anxiety symptoms, low parasympathetic nervous system reactivity can indicate a vulnerability to develop sleep problems in mid-adolescence. Thus, not all adolescents with anxiety symptoms are at equal risk for developing sleep problems. This risk is dependent on parasympathetic reactivity. The moderation effect was significant, but the magnitude of the moderating effect was small, which may be related to the low levels of anxiety symptoms and sleep problems in TRAILS. For a healthy sample of adolescents, the clinical value of my findings is likely limited. I would expect the moderation effect to be larger in a sample with more anxiety symptoms, since higher levels of anxiety tend to be associated with higher levels of arousal. Yet, the nature of the association between anxiety symptoms and sleep problems is complex and I suspect that there are many other moderators, all of which describe a small difference in vulnerability to experience sleep problems after having anxiety symptoms.

METHODOLOGICAL STRENGTHS AND LIMITATIONS

All research questions were investigated with data from TRAILS, a large, longitudinal general population study. One of the greatest strengths of TRAILS is the extent – in length and breadth – of the data it produced. The length of the follow-up of (pre)adolescents over 10 years with up to four assessment waves (fifth in progress) rendered multiple data points with prospective data. Having

more than two data points available is important for studying the development of anxiety symptoms, as age-dependency or differences in the association of anxiety symptoms with other factors in early and late adolescents would be overlooked if merely one interval is available.

Another strength of TRAILS is the breadth of factors that have been assessed over the years, including different facets of psychological health, as well as social functioning and physical health. This provides an opportunity to study an array of different factors in association with anxiety symptoms. Yet, a consequence of the breadth of TRAILS is the fact that few concepts can get studies in great depth. Especially in this context, it is remarkable to have an instrument that specifically and elaborately assesses subtypes of anxiety symptoms consistently across the first three assessment points. This breadth of TRAILS in combination with the detailed assessment of anxiety symptoms, invites one to investigate and explore different factors in association with anxiety symptoms.

Limitations

Internal validity

Different sources of bias can be a threat to the internal validity of studies in this thesis. I will discuss two important sources of information bias for internal validity. Possible sources of bias specific to each of the study questions have been discussed in the previous chapters.

Assessment of sleep problems. The only construct I measured with a self-constructed scale was sleep problems. I used five questions: four were part of the YSR and one was part of a general health questionnaire. To assess sleep problems, I built a measurement model to form a latent variable at each assessment. The latent variable captures the variance shared by all sleep items per assessment; because the items shared a large amount of variance, the latent variable is a good representation of the underlying concept. Because I assessed sleep problems over time, I also confirmed that the measurement model for sleep problems met basic criteria for longitudinal measurement invariance, i.e. factor structure (configural) and factor loading (metric) invariance [29]. While a self-constructed scale with only 5 items is not ideal to measure sleep problems, the measurement model for our sleep problems variable showed good qualities, indicating that our sleep variable captures important features shared by the different sleep items.

The self-constructed scale relied on self-reported sleep problems and hence is a subjective way to assess sleep problems. Sleep assessment with wrist actigraphy does not rely on self-report data; it involves a watch-like devise that detects motion patterns to determine sleep and wakefulness. Previous studies showed that self-reported and actigraphy-assessed sleep problems are moderately correlated [30], but also some differences in subjective and objective sleep assessments have been reported. For example, subjective sleep duration tends to be overestimated when compared to actigraphy in healthy subjects [31]. On the other hand, in psychologically distressed subjects, sleep duration and quality tends to be underestimated [32]. These findings suggest that the strength of the association between anxiety symptoms and sleep problems could be overestimated when using subjective sleep measures.

The second issue is the *time interval between assessments*. In longitudinal studies a design has to be chosen matching with the main hypothesis of the study. One of the aspects of the design is the

time interval between the assessments. For many research questions in TRAILS a time interval of two to three years between assessments is adequate. However, for other questions a shorter time interval would be preferable. For example, when associations change in direction or strength (e.g., associations between anxiety symptoms and pubertal timing or sleep problems), timing of this change cannot be estimated very precisely. Also for the moderation of the association between anxiety symptoms and sleep problems by parasympathetic measures, a design with multiple measurements shortly after another, would have given more detailed information of the underlying process.

External validity

External validity refers to the generalization of the results. The TRAILS general population cohort is a rather healthy cohort, which was reflected in the low endorsement of anxiety symptoms across all three assessment waves, particularly for panic disorder symptoms and symptoms of separation anxiety. The large sample size of TRAILS provided the power to find statistically significant associations; yet, the strength of associations I found was often small. This raises questions about the clinical significance of our findings. TRAILS successfully went to great lengths to select a sample representative of the general population in the Netherlands, and to encourage participation and reduce attrition. Hence, I consider the findings from TRAILS generalizable to other healthy populations, but would expect stronger associations in other, more anxious populations. It is relevant to explore if the magnitude of effects would indeed increase when severity of symptoms increases.

RECOMMENDATIONS FOR FUTURE RESEARCH

Methodological recommendation

In chapter 1 and chapter 3, I explained that longitudinal measurement stability is critically important for longitudinal studies; however, few investigations have examined this issue in commonly used instruments. This is especially surprising in the field of developmental psychology and psychiatry, since emotional and cognitive development (i.e., change) is a key feature of childhood and adolescence, and meaningfully tracking the evaluation of change over adolescence is a core part of this area of research.

The developmental change in adolescence emphasizes the need for measurement invariance assessment; yet, it also is important to understand that some degree of measurement variation may occur and is acceptable across this developmental phase. Importantly, adolescence is different from adulthood when it comes to evaluating cognitive and emotional change across time. Across adolescence, we expect to varying degrees that some items will change in relevance or meaning, depending on the age or developmental stage of the adolescent. In adulthood, cognitive and emotional changes occur much slower and we do not expect systematic changes in interpretation, relevance and endorsement of items. Assessing an instrument for longitudinal measurement invariance is the only way to find out to what degree criteria for longitudinal measurement invariance are met, and to evaluate potential deviations from absolute invariance. Therefore, ideally, longitudinal measurement invariance information should be evaluated for instruments that are used to assess change or stability across time, just like cross-sectional validity and reliability is currently evaluated for

instruments. Assessing measurement invariance will aid valid interpretation and inform about limitations in interpretations of changes in symptom scores.

Further understanding of the relation between sleep problems and anxiety symptoms

The association between anxiety symptoms and sleep problems remains a fascinating area of research, with much work remaining towards a better understanding of the nature of their association. Incorporating objective measures of sleep in epidemiological studies should be encouraged, as these measurements can provide physiology-based, detailed descriptions of sleep and sleep problems. Wrist actigraphy has already successfully been used in some longitudinal studies to compliment subjective (questionnaire-based) sleep data. Importantly, the current opinion on objective and subjective sleep data is not a qualitative one in terms of better or worse, but rather one that considers both in order to make an important contribution to the understanding of sleep problems in relation to other health problems [30, 33].

In addition to adding objective sleep data, future research should include different facets of sleep (e.g., sleep duration, sleep quality) and sleep problems. Sleep problems can cover a spectrum of difficulty around sleep, such as trouble falling asleep, trouble staying asleep, or restless sleep. The association with anxiety symptoms is not the same for all types of sleep problems [34]. By investigating sleep problems separately, stronger associations with anxiety symptoms may appear for some types of sleep problems. In those associations, vulnerability factors such as PNS activity may become more important in specifying increased risk for a specific sleep problem. Hence, specifying the association between anxiety symptoms and different types of sleep problems can allow us to also be more specific in directing prevention and intervention efforts to specific sleep problems.

Continuity of anxiety symptoms across adolescence and into adulthood

Due to the low levels of anxiety symptoms in our population sample, although initially intended, I found out that I was not able to investigate the continuity of different anxiety symptom subtypes across adolescence and into adulthood. I was, however, able to investigate continuity of problems across adolescence in a broader sense: in chapter 2, I found that a very broad range of internalizing and externalizing symptoms early in adolescence predicted the onset of panic attacks during adolescence.

While we know that anxiety symptoms predict later onset of anxiety disorders, we have very limited insight into the pathways of anxiety symptoms across adolescence that lead to elevated anxiety symptoms or anxiety disorders. Due to the high co-morbidity of different anxiety subtypes, it is plausible that across adolescence, the focus of the content of anxiety symptoms can shift from one subtype to another. For example, a child showing separation anxiety symptoms at age 11 may shift in presentation of symptoms to generalized anxiety symptoms by age 15. Therefore, exploring the homotypic (e.g., social phobia symptoms predicting social phobia later) and heterotypic (e.g., social phobia symptoms predicting generalized anxiety later) developmental pathways of anxiety subtypes is an important domain to study. Studying these pathways in a population with more anxiety symptom endorsement, such as an at-risk population, can be promising as it would still allow the focus on

anxiety symptoms (rather than focusing merely on diagnosis), while providing data with more variation in anxiety symptom severity across the anxiety subtypes.

CONCLUSIVE REMARKS

Research into the development of anxiety symptoms across adolescence and associated factors is an important research domain, and many aspects require more attention. The breadth of the TRAILS data, in combination with the thorough measurement of anxiety symptoms across three assessment points, offered a unique opportunity to study different factors in association with the development of anxiety symptoms in adolescence. Hence, this thesis contributes to multiple domains associated with anxiety symptoms, rather than just one. The first general conclusion from this thesis is that even mild anxiety symptoms are associated with other health predictors and outcomes. This finding supports the notion that it is important to study anxiety in a dimensional way and to include symptoms of anxiety when assessing possible predictors and outcomes of anxiety. The second general conclusion is that we oversimplify reality if we disregard the possibility of dynamic relations of predictors and outcomes with anxiety symptoms over adolescence.

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Summary

Anxiety symptoms predict the onset of anxiety disorder and depression, and have been associated with lower levels of well-being even before they reach disorder status. Adolescence is a primary period of interest when it comes to anxiety research, since anxiety disorders most commonly have their onset at an early age, and they are the most frequent mental health problem in children and adolescents. The aim of this thesis is to further our knowledge of the development of anxiety symptoms from late childhood into young adulthood. For my research, I used data from the TRacking Adolescents' Individual Lives Survey (TRAILS), a longitudinal cohort study of children and adolescents (N=2,230) from the general population in the Netherlands.

The incidence of panic attacks increases dramatically during adolescence, yet little is known about risk factors for the development of panic attacks. Chapter 2 describes the relation between Internalizing and Externalizing Problems in childhood (10-12 years) and the onset of panic attacks in adolescence. We used self-report [Youth Self-Report (YSR)] and parental report [Child Behavior Checklist (CBCL)] of problem behavior of the child at age 10-12. Onset of panic attacks in adolescence was assessed through an interview with the adolescent at age 18-20 [Composite International Diagnostic Interview (CIDI)]. Almost 20% of the adolescents experienced at least one DSM-defined panic attack during adolescence (19.8%). Most of the problem scales, including internalizing and externalizing scales, of the YSR and CBCL were associated with an increased risk of experience of a panic attack. In multivariate analyses, only Social Problems had a unique association with onset of panic attacks.

Chapter 3 describes a thorough analysis of measurement invariance of the Revised Child Anxiety and Depression Scale (RCADS) across adolescence (10-17 years). The RCADS measures anxiety symptoms in 5 scales: generalized anxiety disorder [GAD], obsessive-compulsive disorder [OCD], panic disorder [PD], separation anxiety [SA] and social phobia [SP]. Longitudinal measurement invariance was evaluated with a hierarchical set of psychometric tests: (1) invariance of the factor structure (configural invariance); (2) invariance of the factor loadings (metric invariance); and (3) invariance of the thresholds (strong invariance). Each of the anxiety scales met criteria for configural invariance. Metric invariance was fully reached for items on the GAD, OCD, PD and SA subscales, whereas three items of the SP subscale contributed less to the SP scale at age 10-12 than later in adolescence. When testing for strong invariance by restricting the thresholds across time, the model fit decreased; however, model fit for the strong invariant models still ranged from adequate to excellent. In conclusion, changes in anxiety symptoms measured by the RCADS very likely reflect true changes in anxiety levels. Therefore, the RCADS is suitable to study the development of anxiety symptoms across adolescence.

The relation between pubertal timing and anxiety symptoms is the topic of chapter 4. Pubertal timing refers to the timing of pubertal development in relation to peers, i.e., it describes whether an adolescent is ahead of peers in pubertal development (early pubertal timing), in line with peers (on-time) or behind peers in pubertal development (late pubertal timing). In this paper we explicitly took into account that pubertal timing can change over adolescence, since the pace of pubertal

development varies between adolescents and is not stable. Indeed, in TRAILS pubertal timing changed across adolescence. In boys, the relation between pubertal timing and anxiety symptoms was age-dependent: at age 10-11, being ahead of peers in pubertal development was associated with more anxiety symptoms, while from age 14 onwards, being ahead was associated with fewer anxiety symptoms than in peers. In girls, pubertal timing was not associated with anxiety symptoms. In conclusion, pubertal timing is not stable across adolescence, and the association between pubertal timing and anxiety symptoms is dynamic and age dependent.

In chapters 5 and 6, anxiety symptoms are studied in relation to sleep problems. Chapter 5 shows that sleep problems and anxiety symptoms hold a direct bidirectional longitudinal association in early adolescence (10-15 years), over and above the indirect association of anxiety symptoms and sleep problems. Later in adolescence, anxiety symptoms still predicted sleep problems, but sleep problems no longer significantly predicted anxiety symptoms. The indirect associations were all significant and the strengths of the associations were all stronger than those of the direct associations.

Anxiety symptoms predict sleep problems in some, but not all adolescents, and activity or reactivity of the parasympathetic nervous system (PNS) are potential moderators in this relationship. Findings in chapter 6 show that the association between anxiety symptoms at age 10-12 and sleep problems at age 12-15 was moderated by parasympathetic reactivity. In adolescents with high levels of anxiety symptoms, low parasympathetic nervous system reactivity can indicate a sensitivity to develop sleep problems in mid adolescence.

In chapter 7, the main findings, strengths and limitations of the research reported in this thesis are discussed. Furthermore, recommendations for future research are given. Two main conclusions of this thesis are (1) that even mild anxiety symptoms are associated with other health predictors and outcomes and (2) that we oversimplify reality if we disregard the possibility of dynamic relations of predictors and outcomes with anxiety symptoms during adolescence.

Samenvatting (Dutch summary)

Angstsymptomen kunnen voorspellend zijn voor de ontwikkeling van een angststoornis of depressie. Echter, al voordat er sprake is van een angststoornis, gaan angstsymptomen vaak samen met een verminderd welbevinden. Angststoornissen beginnen vaak op jonge leeftijd en zijn de meest voorkomende psychische klachten bij kinderen en adolescenten. Veelvoorkomende angstsymptomen bij kinderen zijn separatieangst, schoolangst en specifieke fobieën. In de adolescentie komen hier andere soorten van angst bij zoals paniek, sociale angst en gegeneraliseerde angst. Vooral deze angstsoorten zijn sterk voorspellend voor angstsymptomen en -stoornissen bij (jonge) volwassenen. De adolescentie is daarom een belangrijke periode voor onderzoek naar angst. Het doel van dit proefschrift is het vergroten van de bestaande kennis over de ontwikkeling van angstsymptomen in de late kindertijd en gedurende de adolescentie. Voor dit onderzoek heb ik data gebruikt van de TRacking Adolescents' Individual Lives Survey (TRAILS), een cohortstudie, waarbij 2230 kinderen van 10-12 jaar uit de algemene Nederlandse bevolking zijn gevolgd tot ze jonge volwassenen zijn.

Tijdens de adolescentie neemt de incidentie van paniekaanvallen fors toe; tegelijkertijd is er weinig bekend over de risicofactoren voor het ontwikkelen hiervan. In hoofdstuk 2 onderzocht ik of emotionele en gedragsproblemen op leeftijd 10-12 jaar voorspellend zijn voor het ontstaan van paniekaanvallen in de adolescentie. Emotionele en gedragsproblemen zijn gemeten met vragenlijsten voor de kinderen zelf en hun ouders [de Youth Self-Report (YSR) en Child Behavior Checklist (CBCL)]. Op leeftijd 18-20 jaar is het ontstaan van paniekaanvallen gedurende de adolescentie nagegaan met een klinisch interview met de jongeren [Composite International Diagnostic Interview (CIDI)]. Bijna 20% van de jongeren rapporteerden minimaal één paniekaanval in de adolescentie (19.8%). Scores op de meeste probleemschalen van de YSR en CBCL waren geassocieerd met een hogere kans op het meemaken van een paniekaanval. Na correctie voor comorbiditeit binnen de YSR en CBCL schalen, bleek een unieke associatie voor de schaal Sociale Problemen.

Voor longitudinale analyses van scores voor angstsymptomen is het belangrijk dat het meetinstrument leeftijd-invariant is, dat wil zeggen dat de vragenlijst hetzelfde meet bij iedere meting. Hoofdstuk 3 beschrijft de resultaten van een analyse van de meetinvariantie van de Revised Child Anxiety and Depression Scale (RCADS). De RCADS heeft 37 items, verdeeld over vijf angstschalen: gegeneraliseerde angststoornis [GAD], obsessief-compulsieve stoornis [OCD], paniekstoornis [PD], separatieangst [SA], en sociale angst [SP]. Longitudinale meetinvariantie is beoordeeld aan de hand van een drietal hiërarchische psychometrische tests: (1) invariantie van de factorstructuur (configural invariance), (2) invariantie van de factorladingen (metric invariance) en (3) invariantie van de drempelwaardes (strong invariance). Alle angstschalen waren invariant in de factorstructuur (configural invariance). Invariantie van de factorladingen (metric invariance) werd gevonden voor items op de GAD, OCD, PD en SA schalen; bij de SP schaal leverden drie items op T1 (10-12 jaar) een kleinere bijdrage aan de schaal dan op T2 en T3. Ook bij het testen voor invariantie van de drempelwaardes (strong invariance) bleef de modelfit adequaat tot excellent. Op basis van deze resultaten is de conclusie dat met de RCADS gemeten verschillen in angstsymptomen zeer waarschijnlijk een weerspiegeling zijn van werkelijke veranderingen in angstniveaus. De RCADS is

een geschikt instrument voor het onderzoeken van ontwikkelingen in angstniveaus gedurende de adolescentie.

Hoofdstuk 4 beschrijft de relatie tussen timing van puberteitsontwikkeling en angstsymptomen. Timing van puberteitsontwikkeling verwijst naar de timing waarin de puberteitsontwikkeling plaatsvindt in vergelijking met leeftijdsgenoten. Adolescenten kunnen vóórlopen op leeftijdsgenoten in hun puberteitsontwikkeling (vroege timing), gelijk opgaan met leeftijdsgenoten of minder snel zijn in puberteitsontwikkeling dan leeftijdgenoten (late timing). In dit paper is expliciet rekening gehouden met veranderingen in timing van puberteitsontwikkeling, door meerdere metingen van puberteitsontwikkeling mee te nemen. Dit is belangrijk want het tempo van puberteitsontwikkeling varieert tussen jongeren en is niet stabiel over adolescentie. Bij TRAILS jongeren bleek inderdaad dat de timing van puberteitsontwikkeling verandert gedurende de adolescentie. Bij jongens was een duidelijk verband zichtbaar tussen timing van puberteitsontwikkeling en angstsymptomen. Jongens die vóórliepen in de puberteisontwikkeling op leeftijd 10-11 jaar rapporteerden meer angstsymptomen dan de overige jongens. Vanaf 14 jaar veranderde dit verband en was vóórlopen juist geassocieerd met minder angstsymptomen. Bij meisjes was er geen verband tussen timing van puberteitsontwikkeling en rapportage van angstsymptomen.

Hoofdstuk 5 en 6 bespreken de resultaten van onderzoek naar de relatie tussen slaapproblemen en angstsymptomen. Uit hoofdstuk 5 blijkt dat de longitudinale relatie tussen slaapproblemen en angstsymptomen bidirectioneel is in de vroege adolescentie (10 to 15 jaar). In de latere adolescentie (12-18 jaar) was er een verband tussen angstsymptomen en latere slaapproblemen, maar geen verband tussen slaapproblemen en latere angstsymptomen. Angstsymptomen voorspellen slaapproblemen bij sommige adolescenten, maar niet bij alle. Reactiviteit van het parasympathische zenuwstelsel (PNS-activiteit en reactiviteit) zijn hierbij potentiële moderatoren. Uit hoofdstuk 6 blijkt dat het verband tussen angstsymptomen op de leeftijd van 10-12 jaar en slaapproblemen bij 12-15 jarigen gemodereerd werd door parasympathische reactiviteit: voor 10-12-jarigen met meer angstsymptomen kan een lage PNS-reactiviteit wijzen op een gevoeligheid voor het ontwikkelen van slaapproblemen op leeftijd 12-15 jaar.

Hoofdstuk 7 geeft een discussie van de bevindingen in dit proefschrift, inclusief de sterke punten en de beperkingen. Deze zijn aangevuld met aanbevelingen voor toekomstig onderzoek. De belangrijkste conclusies uit het onderzoek beschreven in dit proefschrift zijn (1) dat zelfs milde angstsymptomen al geassocieerd worden met predictoren en met andere gevolgen voor het welbevinden (paniekaanvallen en slaapproblemen) en (2) dat we de werkelijkheid simplificeren wanneer we de mogelijkheid van dynamische relaties tussen voorspellers en uitkomstmaten enerzijds en angstsymptomen in de adolescentie anderzijds veronachtzamen.

I held on tight and pretended it was a plan

(Adapted from Dr. Who)

Acknowledgements

A journey of a thousand miles begins with a single step. Of course, so does falling down a flight of stairs.
(Slightly adapted from Laozi, Chinese philosopher)

The past five years have been a wonderful journey that encompassed thousands of miles traveled, oceans crossed, mountains scaled, stair flights fallen. Little did I know about the journey ahead when I took my first step by moving to Groningen for TRAILS data collection. Little did I know that this journey of a thousand miles would not just be a figurative one, but would literally encompass traveling 3887 miles to find a new home with the person I love. *Journeys end in lovers meeting; Every wise man's son doth know (William Shakespeare, Twelfth Night)*. Now, I am not a Shakespeare fan, but the fella was on to something when he wrote that… Luckily, my journey didn't end when I met my love - it just took a detour.

A German proverb says: *Der Weg ist das Ziel (The journey is the goal)*. While this is great wisdom for life in general, it applies less to the life of a graduate student. Throughout a PhD program, the goal should remain very clear. I certainly did not take the most straightforward road to that goal, but I never lost sight of it. It is especially because of my little "detour" that I have a lot of people to thank for helping me achieve this goal.

Frank and Floor: You were willing to take a chance when I proposed the idea of letting me do my research and writing from America. Being far away certainly didn't make things easier and there were times where we all doubted if our arrangement would work out. I am very happy that it did and I want to thank you both very much for this opportunity! Floor, thank you for going out of your way to provide long distance supervision. Through your spot-on input and feedback I learned a great deal, not just about scientific writing and text structuring, but also about statistics and research procedures.

Tom Olino, your spontaneous willingness to get involved in my dissertation project was beyond anything I could have ever hoped for. Thank you so very much for sharing your psychological and statistical knowledge with me, for your guidance, your patience, kindness and always open door. This thesis wouldn't be what it is if it weren't for your input.

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To each and every TRAILS participant: I want to thank you for the time and effort you put in to complete endless questionnaires and sit through hour-long assessments. I am especially grateful that so many of you stuck with us for so long and shared your life with us for all these years – from the time you were children to the young adults you are today.

I would like to extend a sincere *thank you* to the members of my small committee, Prof.dr. Hans Ormel, Prof.dr. Ingmar Franken and Dr. Lisbeth Utens for taking the time to read and evaluate my dissertation, and Prof.dr. Frits Boer and Prof.dr. Fop Verheij for joining in the large committee.

The episode of my life I refer to as "Groningen" holds a special place in my heart: not just the beautiful city itself, but also my colleagues. To the TRAILS-cc data-team, Neeltje, Marjan and Aukelien: you were fantastic colleagues to work with. Thank you for welcoming me and trusting me to revamp the stress-experiment for our cohort. I'd also like to extend a special thank you to data manager Dennis Raven, the most competent, helpful and communicatively capable data manager any project could ever hope for.

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Thank you to all my Rotterdam colleagues who made me feel at home every time I'd show up for several weeks before disappearing again for months. A special thanks to my desk-mates Floor, Lisette and Ilse – we discussed many work related and non-work related problems, solved some of them, but always had a great time trying! Laureen, thank you so much for your great organizational help in the end. Sylvana, we hit it off during my first visit to Rotterdam, and not just because you also see that working with data trumps writing about data. Thank you for being my friend and paranymph!

Sonia, *you and I are more than friends. We're like a really small gang*. Your friendship means more to me than you'll ever know. Thanks for believing in me and for always being there for me – even if that literally means traveling the world, whether it is to be maid of honor in Pittsburgh or paranymph in Rotterdam.

Mama, Papa: als ich klein war hing im Gang ein einziges Poster. Drauf abgebilded war ein fliegender Vogel im Sonnenuntergang, und ein Text den ich damals nicht lesen konnte. Das Poster habe ich nach Jahren wiedergefunden, drauf stand: *There are two great things you can give your children: one is roots, the other is wings*. You couldn't have done a better job in giving me just that. With your love and encouragement, you gave me strong *roots* to rely on in tumultuous times; and about the *wings* – well, we all know how that worked out… Thank you for raising me according to that poster, for I wouldn't be who I am without it. Roman, you always kept an interest in my project and my progress. Thank you for that!

Joe, I bet that "dating a foreign college girl" was a lot more enticing than "being married to a busy graduate student". You went through this crazy journey with me every step of the way. You celebrated my achievements and helped me get up when I found myself at the bottom of a flight of stairs with an ego bruise or two. I know that it wasn't always a picnic for you either, but you stuck it out with me and that means so much to me!

It is because of the support of all you wonderful people that I can say: I wouldn't have wanted to miss it! Things haven't always come easy on this journey, but remember…

…if everything is coming your way, you are in the wrong lane.

Chris

Curriculum Vitae

Christina Maria Mathyssek was born on September 27th, 1981 in Starnberg (Germany). In 2000, she obtained her high school diploma from "the German School, The Hague". She began her Psychology studies at Leiden University in 2001 and graduated in 2005, obtaining a Master's degree equivalent (Dutch *doctoraal*) in Social and Organizational Psychology. After completing additional clinical psychology classes, she started her Master's degree in Clinical Psychology in August of 2006. In August of 2007, Christina started her one-year Master's thesis research in the Department of Sleep Medicine at the Western Psychiatric Institute and Clinic, part of the University of Pittsburgh Medical Center (UPMC). Her Master's thesis, *The Dynamic Interplay between Worry and Sleep – A time-series investigation in a multi-ethnic sample of midlife women,* was nominated for *best thesis of the year* within the Psychology department, and she graduated *cum laude*. After returning to the Netherlands, she completed her clinical internship between September, 2008 and May, 2009 in the Department of Medical Psychology of the Slotervaart Hospital in Amsterdam, where she focused on sleep medicine. From August of 2009 to July of 2012, Christina was employed as a junior researcher at Erasmus MC – Sophia Children's Hospital, Department of Child and Adolescent Psychiatry/ Psychology (Head of Department: Prof. Dr. Frank Verhulst). Here, she conducted research for her PhD dissertation, the results of which are described in this book. During the first nine months, she collected data for the TRAILS (TRacking Adolescents' Individual Lives Survey) clinical cohort, conducting a stress experiment at the University Medical Center, Groningen. In April of 2010, she moved to Pittsburgh, PA and continued working on her dissertation with regular travel from Pittsburgh to Rotterdam. Since February of 2013, Christina has worked as senior research principle for Tri-State Neurosurgery of UPMC, where she is responsible for conducting research and publishing on dietary supplements and surgical devices.

Erasmus MC
Universitair Medisch Centrum Rotterdam

PhD Portfolio

Summary of PhD training and teaching

Name PhD student:	Christina Maria Mathyssek
PhD period:	08/2009 – 07/2012
Erasmus MC Department:	Child and Adolescent Psychiatry/ Psychology
Promotor:	Prof.dr. F.C. Verhulst
Supervisor:	Dr. F.V.A. van Oort

1. PhD training

General courses	**Year**	**Workload (Hours)**
Exploring longitudinal modeling & Mplus Oregon State University, Corvallis, OR	2010	20
Structural Equation Modeling (SEM) summer camp University of Kansas, Lawrence, KS	2011	60
Biomedical English Writing and Communication Erasmus MC, Rotterdam	2011	50

2. Conferences

International conferences	**Year**	**Workload (Hours)**
Anxiety and Depression Association of America (ADAA), poster presentation New Orleans, LA	2011	40
Anxiety and Depression Association of America (ADAA), oral presentation Washington, DC	2012	50
Associated Professional Sleep Societies (APSS "Sleep"), poster presentation Boston, MA	2012	40

3. Other	**Year**	**Workload (Hours)**
Short presentation "What is heart rate variability?", Groningen	2009	10
Weekly *Families, Emotion, Neuroscience & Development* (FEND) lab meetings, including presentations. Pittsburgh, PA	2010-11	80
Clinical interviewer Sleeping TIGERS study, Pittsburgh, PA	2012	80
(Bi)weekly Sleeping TIGERS study meetings, Pittsburgh, PA	2012	30
Developmental Affective Science Collective (DASC) meetings, Pittsburgh, PA	2012-13	10

TRAILS Dissertations

Sondeijker, FEPL (2006) Neuroendocrine and autonomic risk factors for disruptive behaviors in adolescents. Promotores: Prof.dr. F.C. Verhulst, Prof.dr. J. Ormel. Copromotor: Dr. R.F. Ferdinand. Erasmus Universiteit Rotterdam.

Brunnekreef, JA (2007) Information processing and problem behavior in preadolescents. Promotores: Prof.dr. J. Ormel, Prof.dr. R.B. Minderaa. Copromotores: Dr. M. Althaus, Dr.ir. L.M.J. de Sonneville. Rijksuniversiteit Groningen.

Dietrich, A (2007) Autonomic nervous system function and behavioral characteristics in (pre)adolescents from a general population cohort. Promotores: Prof.dr. J. Neeleman, Prof.dr. J. Ormel. Copromotor: Dr. J.G.M. Rosmalen. Rijksuniversiteit Groningen.

Greaves-Lord, K (2007) Roots of Anxiety. The role of cardiovascular regulation and cortisol in the development of anxiety in early adolescence. Promotores: Prof.dr. F.C. Verhulst, Prof.dr. J. Ormel. Copromotor: Dr. A.C. Huizink. Erasmus Universiteit Rotterdam.

Dijkstra, JK (2007) Status and affection among (pre)adolescents and their relation with antisocial and prosocial behavior. Promotor: Prof.dr.S. Lindenberg. Copromotor: Dr. R. Veenstra. Rijksuniversiteit Groningen.

Amone, KP (2009) Examining the link between socio-economic position and mental health in early adolescents. Promotores: Prof.dr. J. Ormel, Prof.dr. A.J. Oldehinkel. Copromotor: Dr. H. Burger. Rijksuniversiteit Groningen.

Noordhof, A (2010) In the absence of a gold standard. Promotores: Prof.dr. J. Ormel, Prof.dr. A.J. Oldehinkel. Rijksuniversiteit Groningen.

Sentse, M (2010) Bridging contexts: the interplay between family, child, and peers in explaining problem behavior in early adolescence. Promotor: Prof.dr. S. Lindenberg. Copromotor: Dr. R. Veenstra. Rijksuniversiteit Groningen.

Creemers, HE (2010) High Times - The role of temperament and other risk factors in the onset and continuation of cannabis use during adolescence. Promotores. Prof. F.C. Verhulst, Prof. A.C. Huizink. Erasmus Universiteit Rotterdam.

Bouma, EMC (2010) The sensitive sex. Depressive symptoms in adolescence and the role of gender, genes and physiological stress responses. Promotores: Prof.dr. A.J. Oldehinkel, Prof.dr. J. Ormel. Co-promotor: Dr. H. Riese. Rijksuniversiteit Groningen.

Liem, ET (2010) Development of overweight in adolescence. Genes, growth & mood. Promotores: Prof. dr. R.P. Stolk, Prof. dr. P.J.J. Sauer. Rijksuniversiteit Groningen.

Bakker, MP (2010) Stressful life events and adolescents' mental health: the TRAILS study. Promotores: Prof.dr. A.J. Oldehinkel, Prof.dr. J. Ormel. Rijksuniversiteit Groningen.

Buschgens, CJM (2010) It runs in the family – Early biological factors and family environment in children with ADHD symptoms. Promotores: Prof. dr. J.K. Buitelaar, Prof. dr. M.A.G. van Aken. Universitair Medisch Centrum St. Radboud Nijmegen.

Sijtsema, JJ (2010) Adolescent aggressive behavior - Status and stimulation goals in relation to the peer context. Promotor: Prof.dr. S. Lindenberg. Co-promotor: Dr. R. Veenstra. Rijksuniversiteit Groningen.

Bosch, NM (2011) Adolescents in stress: The ups and downs of the psychophysiological stress response. Promotores: Prof.dr. A.J. Oldehinkel, Prof.dr. J. Ormel. Co-promotor: Dr. H. Riese. Rijksuniversiteit Groningen.

Wigman, JTW (2011) Persistence of the extended psychosis phenotype in young people: Link between vulnerability and clinical need. Promotores: Prof.dr. W.A.M. Vollebergh, Prof.dr. J. van Os. Universiteit Utrecht.

Janssens, KAM (2011) The etiology of functional somatic symptoms in adolescents. A new perspective on lumping and splitting. Promotores: Prof.dr. J.G.M. Rosmalen, Prof.dr. A.J. Oldehinkel. Rijksuniversiteit Groningen.

Ivanova, KO (2012) From parents to partners: the impact of family on romantic relationships in adolescence and emerging adulthood. Promotores: Prof.dr. M.C. Mills, Prof.dr. R. Veenstra. Rijksuniversiteit Groningen.

Jaspers, M (2012) Prediction of psychosocial problems in adolescents: do early childhood findings of the preventive child healthcare help? Promotores: Prof.dr. S.A. Reijneveld, Dr. A.F. de Winter. Rijksuniversiteit Groningen.

Verboom, CE (2012) Depression and role functioning. Their relation during adolescence and adulthood. Promotores: Prof. dr. J. Ormel, Prof. dr. W.A. Nolen, Prof. dr. B.W.J.H. Pennix. Copromotor: Dr. J.J. Sijtsema. Rijksuniversiteit Groningen.

Marsman, H (2013) HPA-axis, genes and environmental factors in relation to externalizing behaviors. Promotor: Prof. dr. J.K. Buitelaar. Universitair Medisch Centrum St. Radboud Nijmegen.

Griffith-Lendering, MFH (2013) Cannabis use, cognitive functioning and behaviour problems. Promotores: Prof. dr. H. Swaab. Co-promotor: Dr. S.C.J. Huijbregts. Universiteit van Leiden.

Vink, NM (2013) The role of stress in the etiology of asthma. Promotores: Prof.dr. H.M. Boezen, Prof.dr. J.G.M. Rosmalen, Prof.dr. D.S. Postma. Rijksuniversiteit Groningen.

Laceulle, OM (2013) Programming effects of adversity on adolescent adaptive capacity. Promotores: Prof. dr. J. Ormel, Prof. dr. M.A.G. van Aken. Co-promotor: Dr. E. Nederhof. Rijksuniversiteit Groningen.

Prince, A (2013) Blunt Vulnerabilities: Identifying Risks for Initiation and Continued Use of Cannabis in a Dutch Adolescent Population. Promotores: Prof. dr. A.C. Huizink, Prof. dr. F.C. Verhulst. Co-promotor: Dr. H.E. Creemers. Erasmus Universiteit Rotterdam.