



Childhood-onset versus adolescent-onset anxiety and depression: Epidemiological and neurodevelopmental aspects

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ABSTRACT

Anxiety and depression are common in youth and are frequently accompanied by attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). However, it is unclear how common ADHD, ASD, and other neurodevelopmental disorders (NDDs, i.e., ADHD, ASD, developmental coordination disorder, learning disorder, and tic disorders) are in children versus adolescents with anxiety and depression. We aimed to delineate whether different anxiety/depression age-of-onset groups show distinguishable NDD patterns. The study was based on 4492 twins born in Sweden between 1998 and 2003 from the nation-wide population-based Child and Adolescent Twin Study in Sweden. Prevalence and odds ratios were calculated using screening measures of anxiety and depression at ages 9 and 15, and NDDs at age 9. Individuals with childhood-onset anxiety/depression had a substantially higher NDD prevalence compared to individuals with adolescent-onset anxiety/depression. Highest prevalence was found for individuals with anxiety/depression both in childhood and adolescence. In this group, individuals also had substantially higher odds of having at least one NDD (14.7, 95% CI 6.3 – 34.0) compared to individuals without anxiety/depression. This emphasizes the need to further investigate the etiology of childhood and adolescent anxiety/depression, as they most likely represent different constructs depending on age-of-onset, lending support for possibly different treatment approaches.

1. Introduction

Anxiety and depression are conceptualized as “internalizing” mental disorders that are diagnosable in childhood and constitute among the most common mental disorders in children and adolescents. They are, by definition, associated with impairment in daily life (Essau et al., 2000; Ezepeleta et al., 2001; Strauss et al., 1987). It is estimated that between 15% and 20% of children and adolescents have been affected by anxiety disorders before adult age; rates for depressive disorders are also high, up to 13% (Kessler et al., 2012; Merikangas et al., 2010; Costello et al., 2004).

In the fifth and current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013), no distinction is made regarding age of onset for anxiety and depressive disorders. While strong associations have been found between adolescent anxiety and depression with the same disorders later

in life (Doering et al., 2019; Fergusson and Woodward, 2002; Woodward and Fergusson, 2001), viewing anxiety and depression as a developmental continuum from childhood to adolescence is problematic. In contrast to adolescent-onset depressive disorders, onset in childhood does not appear to be linked to the same disorder later in life, but rather to subsequent antisocial behavior (Rutter et al., 2006). Furthermore, results from twin studies indicate that anxiety and depression show etiological heterogeneity depending on age of assessment. Studies have reported that there is an increase in anxiety and depression symptoms from childhood to adolescence, while heritability estimates simultaneously appear to decrease from childhood to adolescence (Nivard et al., 2015; Waszczuk et al., 2014), suggesting that childhood and adolescent anxiety and depression might be partially distinct phenotypes.

Neurodevelopmental disorders (NDDs, e.g., attention-deficit/hyperactivity disorder [ADHD], autism spectrum disorder [ASD],

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developmental coordination disorder [DCD], learning disorder [LD], and tic disorders [TD]) appear to share symptoms with anxiety and depression in childhood, e.g., excessive crying, disturbances of sleep, restlessness, impaired concentration, irritability, and avoidance of, or reluctance to, engage in social situations (American Psychiatric Association, 2013). Furthermore, NDDs have been shown to share etiology with anxiety and depression (Doering et al., 2021). Towbin et al. (2005) investigated ASD symptoms in clinically referred children with mood and anxiety disorders and found that almost half of the children with a depressed/anxious symptomatology showed symptoms of ASD, and another 15% had elevated ADHD symptomatology. Pine et al. (2008) reported that in individuals with a depressed/anxious symptomatology, between 4% and 25% (anxious group) and 7% and 60% (depressed group) scored above an ASD screening cutoff, compared to none of the healthy children. In an earlier study (Doering et al., 2022), it was shown that anxious/depressive symptoms at age 15 shared little phenotypical variance with anxious/depressive- and NDD symptoms at age 9. Furthermore, Masi et al. (2004) investigated externalizing disorders (i.e., ADHD, oppositional defiant disorder, and conduct disorder) in children and adolescents with anxiety disorders and found a higher proportion of externalizing disorders in the child-group compared to the adolescent-group (26.0% vs 18.7%). Only one NDD (i.e., ADHD) was included, but the results indicate that NDDs might be more prevalent in children with anxiety disorders than in adolescent anxiety disorders. Rice et al. (2019) compared depressive symptom trajectories in adolescents (i.e., one trajectory with depressive symptoms emerging in early adolescence and a trajectory with later-adolescence onset). Contrary to the later-adolescence onset trajectory, the trajectory with early-adolescence onset was associated with elevated levels of ADHD and other NDD symptoms in childhood, suggesting that childhood/early-onset forms of depression may be more closely associated with NDD symptomatology.

Taken together, the results from the above mentioned studies suggest that NDDs are differentially associated depending on age of onset of the anxiety/depression construct. However, only clinical samples have been used to assess NDDs and the age span was wide. It is yet unclear how common NDDs are in communal settings in children and adolescents with anxiety and depression. Related, most studies only assess more common NDDs, i.e., ADHD and ASD, why there is a paucity of studies that have included a variety of different NDDs.

The current study aimed to delineate whether different anxiety/depression groups (childhood-onset, i.e., age 9 vs adolescent-onset, i.e., age 15) show distinguishable patterns with respect to co-existing NDDs, i.e., ADHD, ASD, DCD, LD, and TD. The study was based on 4492 Swedish twins from the Child and Adolescent Twin Study in Sweden (CATSS), where we used screening measures of anxiety/depression at ages 9 and 15, and screening measures of NDDs at age 9.

2. Methods

2.1. Participants

The study is based on the Child and Adolescent Twin Study in Sweden (CATSS). CATSS is an ongoing population-based longitudinal study on somatic and mental health problems in childhood and adolescence (for a detailed description, see Anckarsäter et al., 2011). In brief, since 2004, parents of all Swedish twins born from July 1992 and onwards are contacted in connection with their twins' 9th or 12th birthday (CATSS-9) and are invited to participate in a telephone interview which includes measures of NDD symptoms, symptoms of anxiety, and depressive symptoms (the relevant measures for anxiety and depression at age 9 were included in CATSS from the 1998 cohort and onwards). When the twins reach the age of 15 years, families are contacted again and asked to fill out a web-based questionnaire, targeting various mental health problems (CATSS-15). CATSS-15 includes twins born from the 1st of January 1994 and onwards. CATSS-9 has an overall response rate of

approximately 70%. In the present study, data was available for 12,644 individuals born between 1998 and 2003, out of which 11,437 had complete data on the NDD measure, 10,429 had complete data on the depression measure, and 9016 individuals had complete data on the anxiety measure. A total of 8949 individuals had complete data on all three measures at age 9 (i.e., no missing values on any of the three measures). Out of these 8949 individuals, 4492 had complete data at both ages 9 and age 15 years. All measures were parent-reported. Fifty-three percent were female.

2.2. Measures at age 9 years

2.2.1. The Autism-Tics, ADHD, and other Comorbidities inventory (A-TAC)

The A-TAC (Hansson et al., 2005; Larson et al., 2010) is a fully structured 96-item parent-report telephone interview designed for large-scale epidemiological purposes. The A-TAC is based on symptom criteria and common clinical features of psychiatric disorders in childhood and adolescence and includes NDDs and other common problem areas in child and adolescent psychiatry. Items are scored as 0 (no), 0.5 (yes, to some extent), and 1 (yes), and are divided into modules corresponding to diagnostic domains (e.g., concentration & attention, impulsiveness & activity, social interaction, language). Distributions, Cronbach's α and heritability estimates are reported elsewhere (Anckarsäter et al., 2011). Cross-sectional and longitudinal validation studies show good to excellent cross-sectional and predictive validity for, among others, ADHD, ASD, DCD, LD, and TD (Larson et al., 2010; Mårland et al., 2017), indicating excellent screening properties. In the present study, scores ≥ 6 for ADHD sensitivity/specificity 0.91/0.73, ≥ 4.5 for ASD 0.91/0.80, ≥ 0.5 for DCD 0.63/0.68, ≥ 1.0 for LD 0.92/0.60, and ≥ 1.5 for TD 0.875/0.86 (Larson et al., 2010) were chosen as screening cutoffs for the respective NDD.

2.2.2. Short Mood and Feelings Questionnaire (SMFQ)

The SMFQ (Angold et al., 1995) is a 13-item subscale from the longer 33-item Mood and Feelings Questionnaire, measuring core depressive symptoms in children and adolescents aged 6 to 17 years. The parent-report version of the SMFQ is included in CATSS-9 from the 1998 cohorts and onwards. Parents are asked about their child's feelings and actions over the timeframe of the previous 2 weeks. Items are scored as 0 (no), 1 (yes, to a certain degree) and 2 (yes). Total SMFQ scores can range between 0 and 26. Total scores of 12 or higher may indicate a depressive disorder (Angold et al., 1995). The SMFQ has been found to correlate moderately highly with other measures of depression (Angold et al., 1995) and shows good discriminate validity between individuals with clinical depression and healthy individuals in a community sample (Thapar and McGuffin, 1998). In the present study, the scale has shown good internal consistency (Cronbach's $\alpha = 0.83$). A score ≥ 12 was used as a screening cutoff for depression in childhood, as has been suggested by Angold et al. (1995) to indicate a depressive disorder.

2.2.3. Screen for Child Anxiety Related Disorders (SCARED)

The SCARED (Birmaher et al., 1997) is a 41-item questionnaire intended to measure five child and adolescent anxiety symptom dimensions (i.e., panic disorder, generalized anxiety disorder, separation anxiety disorder, social phobia, and school anxiety/refusal) and is included in CATSS-9 from the 1998 cohorts and onwards (parent-report version). Items are scored as 0 (no), 1 (yes, to a certain degree) or 2 (yes), yielding a total score between 0 and 82. A total score equal or higher than 25 may indicate an anxiety disorder (Birmaher et al., 1999). The SCARED was found reliable in terms of internal consistency and test-retest reliability, shows significant correlations with other measures for childhood anxiety disorders, as well as good discriminant validity between anxiety and other mental disorders, and within anxiety disorders (Birmaher et al., 1997, 1999; Muris et al., 1998). In the present study, the scale has shown good internal consistency (Cronbach's $\alpha =$

0.88). We used a score ≥ 25 as a screening cutoff for anxiety in childhood, which has been suggested to indicate an anxiety disorder (Bir-maher et al., 1999).

2.3. Measures at age 15 years

2.3.1. Strengths and Difficulties Questionnaire (SDQ)

CATSS-15 contains the SDQ (Goodman, 1997) self- and parent-report version. The SDQ is a short 25-item behavioral screening questionnaire for children and adolescents between 3 and 16 years and was developed to assess externalizing and internalizing symptoms. The SDQ comprises five subscales (i.e., conduct problems, hyperactivity, emotional symptoms, peer problems, and prosocial behavior) with five items in each subscale. In the current study, the emotional symptoms subscale (parent-report) was used as an indicator of anxiety/depression in adolescence. The emotional symptoms subscale has 5 items with 3 response options: 0 (not true), 1 (somewhat true), and 2 (certainly true), yielding a total score between 0 and 10. The SDQ is widely used to screen for internalizing symptoms and correlates highly with other measures of internalizing symptoms in community samples of children and adolescents (Muris et al., 2003), indicating good criterion validity. Studies of the Swedish version of the SDQ symptom scales have confirmed the factor structure of the original English SDQ (Smedje et al., 1999) and results from a validation study of the Swedish SDQ indicate that the parental version discriminates well between community and clinical samples (Malmberg et al., 2003). In this study, the emotional symptoms subscale showed acceptable internal consistency (Cronbach's $\alpha = 0.71$). A total score above the 90th percentile (i.e., a score of ≥ 4) was used as a screening cutoff for anxiety/depression in adolescence, as has been suggested to indicate abnormal anxiety/depression in youth (Goodman, 2001).

2.4. Statistical analyses

For the main analysis, anxiety and depression cutoffs at age 9 were merged into a single variable (from this point on referred to as 'Anxiety/depression at age 9'). Included were individuals who were either above the SMFQ cutoff or the SCARED cutoff, or they could be above both cutoffs. This was done for two reasons: (1) to maximize the number of exposed cases, and (2) to create comparability with the SDQ emotional symptoms subscale which correlates with both anxiety and depression (Muris et al., 2003).

Prevalence and odds ratios of NDDs in anxiety/depression were estimated in two steps. First, four groups were created based on the individual's cutoff (below or above) on the anxiety/depression measure at age 9 and 15. Second, numbers of ADHD, ASD, DCD, LD, and TD were compared among the four created groups (1) no anxiety/depression, i.e., at neither age 9 nor 15, (2) adolescent-onset anxiety/depression, i.e., anxiety/depression at age 15 but not at age 9, (3) childhood-onset anxiety/depression, i.e., anxiety/depression at age 9 but not at age 15, and (4) anxiety/depression at both ages 9 and 15. In addition, we created a collapsed variable indicating whether individuals scored above the screening cutoff for at least one of the NDDs ('any NDD'). Third, we used logistic regression models to regress the various NDDs on the anxiety/depression groups. Results are presented as odds ratios (OR), i.e., comparing the odds of the outcome in the exposed and unexposed group. The group 'no anxiety/depression' served as the reference group. In a second step, we adjusted for sex and birth year. For the collapsed variable 'any NDD', $p < 0.05$ was considered statistically significant. For the individual NDDs, i.e., ADHD, ASD, DCD, LD, and TD (yielding 5 tests), we applied Bonferroni correction to account for multiple comparisons and thus set the statistical significance threshold at $p < 0.01$.

2.5. Secondary analyses

For exploratory reasons, we calculated sex-specific prevalence estimates of ADHD, ASD, DCD, LD, TD, and any NDD, as well as prevalence estimates and OR estimates for the two age 9 measures individually, i.e., anxiety and depression, respectively. Furthermore, we calculated the mean scores for ADHD, ASD, DCD, LD, and TD in individuals below the respective cutoff.

All analyses were performed in R version 4.0.4. (R Core Team, 2021). Prevalence estimates were calculated with log-link, OR estimates with logit-link, using the gee-function from the R package 'drgee' (Zetterqvist and Sjölander, 2015). A cluster-robust sandwich estimator was applied to adjust the standard errors for the nested twin data.

3. Results

Descriptive statistics for sample variables are displayed in Table 1. Prevalence estimates of ADHD, ASD, DCD, LD, TD, and any NDD in absolute numbers and proportions for the four anxiety/depression groups are detailed in Table 2. The lowest prevalence was found for individuals without anxiety/depression. Individuals in the childhood-onset anxiety/depression group had substantially higher prevalence estimates of NDDs than the adolescent-onset group. That is, with the exception of LD, prevalence estimates were about twice (any NDD) to six times (ASD) higher in the childhood-onset group compared to the adolescent-onset group. The prevalence was highest in those with anxiety/depression at both ages 9 and 15. In this group, at least one NDD was present in 79.4% (95% confidence interval 66.7% – 94.6%) of the individuals. Prevalence estimates were furthermore high for ADHD (52.9%; 95% CI 38.1% – 73.6%), ASD (47.1%; 95% CI 32.5% – 68.2%), and LD (44.1%; 95% CI 30.4% – 64.0%).

ORs of ADHD, ASD, DCD, LD, TD, and any NDD can be found in Table 3. Individuals with childhood-onset anxiety/depression had substantially higher ORs of ADHD, ASD, DCD, LD, TD, or at least one of these NDDs, compared to individuals with adolescent-onset anxiety/depression. Highest ORs were found for individuals who scored above screening cutoffs for anxiety/depression at both ages 9 and 15. In this group, individuals had a 50.7 (95% CI 24.5 – 105.3) times higher odds of having ASD, a 15.5 (95% CI 7.7 – 31.4) times higher odds of having

Table 1

Descriptive statistics for study variables. Absolute number of individuals N (%) = 4492 (100).

		<i>n</i>	%
Sex	♂	2128	47.4
	♀	2364	52.6
Birth year	1998	483	10.8
	1999	864	19.2
	2000	802	17.9
	2001	783	17.4
	2002	759	16.9
	2003	801	17.8
Prevalence screening cutoffs	SMFQ	26	0.6
	SCARED	64	1.4
	SDQ	497	11.1
	ASD	108	2.4
	ADHD	364	8.1
	LD	550	12.2
	DCD	313	7.0
	TD	132	2.9
	Any NDD	1023	22.8

Note. SMFQ = Short Mood and Feelings Questionnaire, indicating childhood depression; SCARED = Screen for Child Anxiety Related Disorders, indicating childhood anxiety; SDQ = Strengths and Difficulties Questionnaire emotional symptoms subscale, indicating adolescent anxiety/depression; ASD = autism spectrum disorder; ADHD = attention-deficit/hyperactivity disorder; DCD = developmental coordination disorder; LD = learning disorder; TD = tic disorders; NDD = neurodevelopmental disorder.

Table 2

Prevalence of autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), developmental coordination disorder (DCD), learning disorder (LD), tic disorders (TD), and any neurodevelopmental disorder in absolute numbers and relative numbers with 95% confidence intervals in the whole sample and individuals with anxiety/depression (AnxDep).

	Number of individuals/Total number of individuals % (95% CI)				
	Whole sample	No AnxDep	AnxDep at age 15 but not at age 9	AnxDep at age 9 but not at 15	AnxDep at both ages 9 and 15
ASD	108/4492 2.4 (2.0 – 2.9)	68/3950 1.7 (1.3 – 2.2)	15/463 3.2 (1.9 – 5.5)	9/45 20.0 (10.5 – 38.1)	16/34 47.1 (32.5 – 68.2)
ADHD	364/4492 8.1 (7.3 – 9.0)	267/3950 6.8 (6.0 – 7.6)	62/463 13.4 (10.6 – 17.0)	17/45 37.8 (25.4 – 56.2)	18/34 52.9 (38.1 – 73.6)
LD	550/4492 12.2 (11.3 – 13.3)	439/3950 11.1 (10.1 – 12.2)	86/463 18.6 (15.3 – 22.6)	10/45 22.2 (12.9 – 38.3)	15/34 44.1 (30.4 – 64.0)
DCD	313/4492 7.0 (6.2 – 7.8)	249/3950 6.3 (5.6 – 7.2)	43/463 9.3 (7.0 – 12.3)	7/45 15.6 (7.8 – 31.2)	14/34 41.2 (26.9 – 63.0)
TD	132/4492 2.9 (2.5 – 3.5)	103/3950 2.6 (2.1 – 3.2)	15/463 3.2 (2.0 – 5.3)	5/45 11.1 (4.9 – 25.2)	9/34 26.5 (14.9 – 47.0)
Any	1023/4492 22.8 (21.5 – 24.2)	823/3950 20.8 (19.5 – 22.3)	150/463 32.4 (28.3 – 37.1)	23/45 51.1 (38.3 – 68.2)	27/34 79.4 (66.7 – 94.6)

Table 3

Associations between anxiety/depression (AnxDep) and autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), developmental coordination disorder (DCD), learning disorder (LD), tic disorders (TD), and any neurodevelopmental disorder (NDD). Figures are odds ratios (ORs; 95% confidence intervals).

NDD	OR (95% CI)			
	No AnxDep [†]	AnxDep at age 15 but not at age 9	AnxDep at age 9 but not at age 15	AnxDep at both ages 9 and 15
ASD	1.0	1.9 (1.1 – 3.5)	14.3 (6.2 – 32.7)	50.7 (24.5 – 105.3)
ADHD	1.0	2.1 (1.6 – 2.9)	8.4 (4.4 – 15.9)	15.5 (7.7 – 31.4)
LD	1.0	1.8 (1.4 – 2.4)	2.3 (1.1 – 4.6)	6.3 (3.2 – 12.3)
DCD	1.0	1.5 (1.1 – 2.1)	2.7 (1.2 – 6.2)	10.4 (5.1 – 21.4)
TD	1.0	1.3 (0.7 – 2.2)	4.7 (1.8 – 11.9)	13.4 (6.1 – 29.9)
Any	1.0	1.8 (1.5 – 2.3)	4.0 (2.2 – 7.2)	14.7 (6.3 – 34.0)

[†] Reference category.

Note. Bold estimates indicate significance at the 0.01 level, except for 'Any NDD', where alpha was set to 0.05.

ADHD, and a 14.7 (95% CI 6.3 – 34.0) times higher odds of having at least one NDD compared to individuals without anxiety/depression. The adjusted analyses followed the same pattern and can be found in Table S1, which is available online.

3.1. Secondary analyses

Sex-specific numbers for ADHD, ASD, DCD, LD, TD, and any NDD were low but showed that, except for LD and any NDD, males in all four anxiety/depression groups had a higher prevalence of NDDs than females (see Table S2). Prevalence and OR patterns for age 9 anxiety and depression separately can be found in Tables S3-S6, and were similar to those in the main analysis, albeit individuals above screening cutoffs for depression at age 9 had overall slightly higher NDD prevalence estimates compared to those above screening cutoffs for anxiety at age 9. Mean scores for ADHD, ASD, DCD, LD, and TD in individuals below the respective cutoff were generally twice to four times higher in individuals with anxiety/depression at both ages 9 and 15 than those of the whole sample (see Table S7 for mean scores for ADHD, ASD, DCD, LD, and TD, and Table S8 for sex-specific mean scores).

4. Discussion

In this study, we examined a variety of NDDs, i.e., ADHD, ASD, DCD, LD, and TD in individuals with childhood-onset vs adolescent-onset anxiety and depression in a longitudinal, population-based study of 4492 Swedish twins. Our results showed that NDDs are extremely common in individuals screening positive for anxious/depressive symptoms in both childhood and adolescence.

We found different prevalence patterns in childhood-onset versus adolescent-onset anxiety/depression, i.e., all NDDs were found to be more common in childhood-onset anxiety/depression, which extends findings by Masi et al. (2004) who detected a higher rate of externalizing disorders (including ADHD) in children compared to adolescents with anxiety disorders. We also showed that all NDDs, both above and below the diagnostic threshold, tended to be overrepresented in individuals with childhood-onset anxiety/depression. Our findings validate those by Rice et al. (2019) who compared depressive symptom trajectories in adolescence and showed that an early-adolescence onset group displayed elevated levels of childhood ADHD and other NDD symptoms. There are several possible explanations for these findings. Childhood anxiety and depression might share more common genetics with NDDs than has been stated previously. The Brainstorm Consortium reported positive genetic correlations between anxiety disorders and ADHD and ASD (Anttila et al., 2018). For major depression, significant positive genetic correlations were recently reported for ADHD and ASD by the Cross-Disorder Group of the Psychiatric Genomics Consortium (2019). Beside overlapping genetics, NDDs and anxiety/depression have also been shown to be correlated with several environmental risk factors. Preterm birth has been associated with depression, ADHD, and ASD (Franz et al., 2018; Lampi et al., 2012; Nosarti et al., 2012). In a recent study, Pettersson et al. (2019) studied birth weight and several subsequent psychiatric disorders in a sample of over 500,000 individuals and found that lower birth weight was associated with an increased risk of developing anxiety, depression, ADHD, and ASD. However, the estimates were largely derived from adult samples. It is therefore possible that associations between anxiety/depression and NDDs are underestimated, i.e., stronger associations might be found if childhood-onset anxiety/depression would be considered. Finally, children with NDDs might be more prone to develop symptoms of anxiety and depression, as around age 9, children start to see themselves for the first time with the eyes of another (Lagerheim, 1988), potentially causing a negative self-view on their own otherness compared to neurotypical children (Gillberg, 1987). Supporting evidence shows that for example, youth with ASD had significantly lower self-ratings on self-esteem questionnaires than neurotypical individuals, and self-esteem was strongly associated with depression (McCauley et al., 2019). It is also possible that experienced distress may mediate associations between NDDs and anxiety/depression, which has been suggested for the relationship between ASD and anxiety and depression, respectively (e.g., Baron et al., 2006; van Steensel et al., 2011).

The highest NDD prevalence and odds ratio estimates were found for individuals above screening cutoffs for anxiety/depression in both childhood and adolescence. In this group, roughly 80% of the individuals had at least one NDD, irrelevant of sex. In clinical practice, screening for NDDs should therefore always be done if a young person repeatedly presents with symptoms of anxiety and/or depression, and, if indicated, further assessment should be performed. Those presenting with anxiety/depression in adolescence had modest odds for at least one NDD (OR: 1.8) compared to individuals without anxiety/depression. Given the increasing prevalence of, and tendency to over-diagnosis of ADHD (Kazda et al., 2021) and ASD (Rødgaard et al., 2019), a rigorous anamnestic screener for NDDs, rather than full NDD clinical assessment in all cases, would probably be sufficient in adolescents and alleviate the mental health system. From an intervention perspective, age of onset of anxiety/depression symptomatology should be considered, as treatment approaches may need to differ for children and adolescents. For example, the Centers for Disease Control and Prevention recommend parent training in behavior management as a first treatment step for very young (aged < 6 years) children with ADHD, while for older children and adolescents, it is recommended to combine medication treatment with other types of behavior therapy and training, such as behavioral interventions in the classroom and organizational skills training (Centers for Disease Control and Prevention, 2020). For anxiety disorders, concerns have been raised regarding available randomized controlled trials which include broad ranges of age groups, giving little attention to age-specific phenotypes or effects (Creswell et al., 2020). Our study forwards this notion by showing that in the very youngest of children, particular attention to NDDs is of great importance when planning treatment.

The current study has several strengths, including the large sample size, validated assessment instruments covering a variety of NDDs, and the utilization of a longitudinal population-based sample with groups of children and adolescents at ages 9 and 15.

However, the findings also need to be interpreted in the light of limitations. All measures were based on parent-reports. It is impossible to evaluate if parents responded more often if their child had a more complex psychopathology and parents were looking for help, or, vice versa, that they might not have participated because of more severe symptomatology in their child. Also, non-responding parents might have a higher degree of psychopathology themselves, as evident from other studies (Cheung et al., 2017; Kessler et al., 1995). Therefore, findings should be interpreted with caution regarding generalizability. With parent-reported measures in general, there is a possibility that parents might not be fully aware of their child's psychopathological symptomatology, as specifically anxiety, depression, and some NDDs are often "internalized" (Comer and Kendall, 2004), and symptoms/problems might show outside of parental "coverage" (e.g., with friends or in school). Anxiety and depression cutoffs at age 9 were merged into a single variable which was done for power issues and to mirror the instrument used at age 15, which correlates with both anxiety and depression. While combining anxiety and depression into one variable may constitute an important limitation of the study, we tried to approach this question by calculating prevalence estimates and OR:s for age 9 anxiety and depression cutoffs separately (see Tables S3 – S6). The results showed that associations between NDDs and anxiety and depression, respectively, were similar to the associations found in the main analyses. Finally, we neither investigated whether children received treatment for their psychopathological symptoms, nor did we have access to data on parental psychopathology, familial history of psychiatric disorders, socioeconomic status, or body mass index, which, theoretically, could have confounded associations in this study.

CRedit authorship contribution statement

Sabrina Doering: Conceptualization, Methodology, Formal analysis, Writing – original draft. **Linda Halldner:** Writing – review &

editing. **Henrik Larsson:** Writing – review & editing. **Christopher Gillberg:** Writing – review & editing. **Ralf Kuja-Halkola:** Conceptualization, Methodology, Software, Writing – review & editing. **Paul Lichtenstein:** Writing – review & editing. **Sebastian Lundström:** Conceptualization, Methodology, Writing – original draft, Supervision.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Availability of data and materials

The datasets are available on reasonable request from the corresponding author at sabrina.doering@gu.se.

Ethics approval and consent to participate

The parents were informed about the study in connection with their twins' 9th and 15th birthday. Participating in interviews, after being informed about the study, is regarded as verbal informed consent (age 9) and, at age 15 the parents agreed to participate via a web-questionnaire and digitally consented after being informed about the study. Both the CATSS-9 and 15 have ethical approval from the Swedish Ethical Review Authority (DNR: 2010/597–31/1; 2016/2135–31; 2009/739–31–5) in which the procedures above were described and approved. All methods were carried out in accordance with relevant guidelines and regulations.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.psychres.2022.114556](https://doi.org/10.1016/j.psychres.2022.114556).

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