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CHAPTER 3

ASSOCIATIONS BETWEEN ANXIETY, DEPRESSION, AND DISRUPTIVE BEHAVIOR SPANNING CHILDHOOD AND ADOLESCENCE

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IN PREPARATION

ABSTRACT

Objective: To investigate whether childhood anxiety and depression are predictive of DB in adolescence, above and beyond childhood DB, and whether these prospective relations are subject to environmental and genetic confounding.

Methods: Parents of 9-year-old twins reported on depression, anxiety, and DB (N = 19,347). At follow-ups at ages 15 (n = 3,852) and 18 (n = 786) years, information about DB was collected via parent- and self-reports. The relationships between anxiety, depression, and DB at baseline, as well as DB at both follow-ups were quantified by negative binomial regressions. Next, to control for genetic and environmental confounding, co-twin control analyses were performed in monozygotic (McLaughlin et al.) and dizygotic (DZ) twin pairs discordant for anxiety (MZpairs = 91, DZpairs = 287) and depressive disorders (MZpairs = 104, DZpairs = 330), as well as affected twin cases and unrelated, unaffected twin controls ($n^{anxiety}$ = 908, $n^{depression}$ = 1018).

Results: Anxiety (Incidence Rate Ratio (IRR) = 1.07; 95% CI: 1.07, 1.08) and depression (IRR = 1.22; 95% CI: 1.21, 1.23) showed cross-sectional co-occurrence in childhood (*p*'s < .001). Longitudinally, childhood anxiety and depression predicted adolescent DB, but these associations became non-significant when controlling for childhood DB. Cross-sectional co-twin control analyses in childhood showed moderate relations between anxiety, depression, and DB in unrelated cases and controls ($d^{anxiety}$ = 0.59, $d^{depression}$ = 0.65), which were attenuated to small effect sizes in DZ and MZ twin pairs ($d^{anxiety}$ = 0.28, 0.26; $d^{depression}$ = 0.43, 0.30). Notably, in MZ twins, when controlling for comorbid depression, anxiety lost its association with DB, while depression retained its association with DB when controlling for comorbid anxiety.

Conclusion: In childhood, depression has a more robust association with DB than anxiety. However, neither childhood anxiety nor depression predict adolescent DB, suggesting fleeting and short-term relations at most.

Children with early-onset disruptive behavior (DB), like oppositional defiant and conduct disorder symptoms, often experience comorbid internalizing problems such as anxiety and depression (Bartels, Hendriks, Mauri, Krapohl, Whipp, Bolhuis, Conde, Luningham, Fung Ip, et al., 2018; Marshall, Arnold, Rolon-Arroyo, & Griffith, 2015). For example, children with conduct problems meet criteria for an anxiety disorder in 22-33% of community samples and 60%-75% of clinical samples (Granic, 2014). There are several explanations for this overlap between DB, anxiety, and depression. Some hypothesize depression to be a consequence of DB, because DB predisposes an individual to depression-invoking negative experiences, like peer rejection or academic failure (Patterson & Capaldi, 1990; Wolff & Ollendick, 2006). Conversely, the "acting out" hypothesis suggests that depression can also be expressed as DB, with depressive symptoms like irritability or hopelessness increasing the chances of engaging in DB (Kasen et al., 2001). The relation between anxiety and DB is more complicated, with anxiety being attributed with both increased and decreased DB (Cunningham & Ollendick, 2010; Granic, 2014; Klingzell et al., 2016; Raine, 2013). Anxiety is hypothesized to inhibit DB through increased sensitivity to social punishments and rewards (Cunningham & Ollendick, 2010), while a lack of anxiety or fear is associated with increased involvement in DB (Klingzell et al., 2016; Raine, 2013). High levels of anxiety are also believed to escalate into DB in case of defensive reactive aggression, and more indirectly through ego depletion (Granic, 2014). Although differentiation of internalizing problems in anxiety and depression could potentially provide valuable insights into its co-morbidity with DB, literature on the long-term influence of anxiety and depression on the development of DB from childhood into late adolescence is sparse and inconclusive.

These diverse roles of anxiety and depression on DB in youths are mostly based on longitudinal research focussing on either childhood (Fanti et al., 2018), or adolescence (Fanti, Colins, & Andershed, 2019; Fontaine et al., 2019), while not much is known about how anxiety and depression relate to the development of DB from childhood into late adolescence. Specifically, some studies report predictive value of anxiety and depression on later DB in the community (Jolliffe et al., 2019 Loeber, Ahonen & Palacios, 2019; Reinke & Ostrander, 2008). There are also indications of considerable cross-sectional comorbidity, but a lack of (Leadbeater, Thompson, & Gruppuso, 2012), or reverse longitudinal relationships (Burke, Loeber, Lahey, & Rathouz, 2005). Even so, other research suggests a cascade of

increasing DB and increasing anxiety and depression (Thompson, Leadbeater, & Ames, 2015). Although there are a number of studies focusing on anxiety and depression as outcomes of DB, these do not include anxiety and depression as predictors at baseline (for an overview: Reising, Ttofi, Farrington, & Piquero, 2019). All in all, the available literature on DB, anxiety, and depression covering both childhood and adolescence is both sparse and conflicting.

One reason for these inconsistencies in literature could be that the co-occurrence between anxiety, depression, and DB is not necessarily causal, with confounding by environmental and genetic factors explaining some of the inconsistent relationships. For instance, although increased neighbourhood disadvantage is correlated with increased DB, only specific acts of DB (i.e., nonviolent criminal acts) are actually influenced by neighbourhood disadvantage (Burt, Klump, Gorman-Smith, & Neiderhiser, 2016). Additionally, putative causal relations between anxiety, depression, and DB could also be confounded by genetic pleiotropy, since different phenotypes (e.g., anxiety, depression, and DB) are influenced by the same genes (Ligthart & Boomsma, 2012). Put differently, differences between groups of genetically unrelated individuals who also differ in environments could be substantially inflated. This raises the question whether intercorrelations among anxiety, depression, and DB are actually indicative of causal relationships or epiphenomenal.

Fortunately, the co-twin control method enables researchers to account for a greater extent for environmental and genetic confounding compared to more conventional case-control designs, enabling researchers to give a more robust statement on the potential causality of associations (Lichtenstein et al., 2002 Svartengren, Svedberg & Pedersen, 2002). This is because both monozygotic and dizygotic twin pairs share the same prenatal and rearing environment. In addition, dizygotic twins share 50% of their genetic makeup, while monozygotic twins are genetically (nearly) identical. Because of these genetic and environmental similarities, monozygotic and dizygotic twin pairs who are discordant on one trait allow for a stringent within-pair comparison of another trait that is hypothesized to be causally associated with the discordance. In other words, in a discordant twin pair the unaffected co-twin can function as a well-matched control for the affected twin. If there is a causal relation, we expect twins affected by anxiety or depression to exhibit higher levels of DB than their non-affected counterpart. Therefore, selection of twin pairs that are discordant on depression or anxiety (e.g., one twin has an anxiety disorder, the other co-twin has not; one twin has a

depressive disorder, the other co-twin has not) has great value to study putative causal relationships between, anxiety, depression, and DB. To our knowledge no twin study to date has focussed on the association between anxiety, depression, and DB covering childhood and adolescence, whilst using a co-twin design.

This study will investigate (1) if childhood anxiety and/or depression are cross-sectionally associated with DB (2) and predictive of DB in middle and late adolescence. If significant associations are found, (3) co-twin control analyses will be used to investigate whether the co-occurrence of DB, anxiety, and depression is likely to be causally related or due to genetic or environmental confounding. We expect anxiety and depression to be significantly related to DB, although depression to a larger extent. Furthermore, we expect co-twin analyses consisting of twin pairs that are discordant on anxiety and twin pairs that are discordant on depressive disorders to gauge putative causal relationships with DB.

METHODS

Participants

The Child and Adolescent Twin Study in Sweden (CATSS) is a nationwide longitudinal study that targets all twins born in Sweden since July 1992. Parents of twins were administered the Autism-Tics, AD/HD and other Comorbidities inventory (A-TAC; Anckarsäter et al., 2011), the Screen for Child Anxiety Related Disorder (SCARED; Birmaher et al., 1997), and the Short Mood and Feelings Questionnaire (SMFQ; Angold, Costello, Messer, & Pickles, 1995) by telephone in connection with the twins' ninth birthday. The families were contacted again in connection with the twins' 15th birthday and at age 18. The follow-up at 15 years includes twins born in 1994 and onward, whereas the follow-up at 18 years includes twins born in 1992 and onward. At both follow-up assessments, at least one parent and both twins were invited to participate.

At baseline (age 9), parents completed the A-TAC, SCARED, and SMFQ as described below (see Measures). At baseline, for 19,347 twins data were available. Of these twins 4,540 participated at the first follow-up and 1,286 at the second follow-up. Because the SMFQ and the SCARED were later included in the CATSS study, considerably less data was available at follow-ups as compared to baseline. For the present longitudinal analysis, participants were selected for whom measures of interest were available at age 9 (baseline) and age 15 (first follow-up), resulting in a sample of 3,852 children, and for whom outcome

measures of interest were available at age 9 (baseline) and age 18 (second follow-up), resulting in a sample of 786 children.

For the co-twin control analyses three samples were formed. The first sample consisted of unrelated individuals, which were twins with parent-reported depressive disorder and/or an anxiety disorder and an identical number of unaffected, unrelated twin controls with neither depression nor anxiety (anxiety: 454 cases vs. 454 controls; depression: 509 cases vs. 509 controls). The second sample consisted of dizygotic twin pairs discordant for depression or anxiety (i.e., one twin has depression/anxiety – the other twin has neither depression or anxiety (anxiety = 287 pairs; depression = 330 pairs). Third, a sample of monozygotic twin pairs discordant for depression or anxiety was selected (anxiety = 91 pairs; depression = 104 pairs).

Baseline measures at age 9 years

Parent-reported disruptive behavior

Parent-reported disruptive behavior (DB) of the twin was assessed using the A-TAC (Anckarsäter et al., 2011), which consists of 96 questions covering symptoms of common child and adolescent psychiatric disorders, including oppositional defiant disorder (ODD) and conduct disorder (CD). The A-TAC ODD and CD subscales consist of five gate questions, each asking a parent about lifetime presence of ODD and CD symptoms in his/her child, respectively. The answering options are coded as 0 ("No"), 0.5 ("Yes, to some extent"), or 1 ("Yes"). All A-TAC questions are included in Supplement 1, available online.

Parent-reported anxiety

Anxiety of the twin was assessed using the parent-version of the SCARED, which consists of 38 items, and is aimed at screening for signs of anxiety disorders in children (Birmaher et al., 1997). The questionnaire covers the following disorders and problems: panic, social anxiety, separation, and generalized anxiety disorders, as well as school avoidance and somatic problems. Answers are given on a 3 point scale, and are coded as: 0 ("Not True or Hardly Ever True"), 1 ("Somewhat True or Sometimes True"), or 2 ("Very True or Often True"). Scores of 25 or higher are indicative of an anxiety disorder. Continuous scores were used in the initial cross-sectional and longitudinal analyses. In the twin control analyses, a clinical cutoff indicating the presence of an anxiety disorder was used to define case or control status (i.e., 1 = anxiety disorder present; 0 = anxiety disorder absent).

Parent-reported depression

Depression of the twin was assessed using the parent-version of the SMFQ, which consists of 13 items, and measures depression in childhood and adolescence (Angold et al., 1995). Answers are given on a 3 point scale, and are coded as: 0 ("No"), 1 ("Yes, to a certain agree"), or 2 ("Yes"). Scores of 8 or higher are indicative of a depressive disorder. Continuous scores were used in the initial cross-sectional and longitudinal analyses. In the twin control analyses, a clinical cutoff indicating the presence of a depressive disorder (i.e., 1 = depressive disorder present; 0 = depressive disorder absent), was used to define case and status.

Parental education

The educational level of each parent was obtained during the telephone interview at baseline. First, education level was coded into three different categories: 1 (completed primary school or less [9 years of formal education]); 2 (completed a high school education [10-12 years]); and 3 (university studies or equivalent [>13 years]). Next, educational level of both parents were summed, resulting in a score ranging from 2 to 6. If information about the education of one parent was missing, the educational level of the other parent with available data was imputed.

Disruptive behavior at age 15 years

Information on various forms of DB were collected at age 15 years, relying on self- and parent-reports. Reactive (or impulsive) and proactive (or planned) aggression were assessed through a youth self-report questionnaire (Raine et al., 2006). Criminality was assessed with a self-report tool that assessed the frequency of violent and nonviolent criminal acts (Ring, 1999). Conduct problems of the twin were assessed using the Conduct Problems subscale of the Strengths and Difficulties Questionnaire (SDQ) parent version and self-report version. Bullying perpetration was measured by the Revised Olweus Bully/Victim Questionnaire (OBVQ; Olweus, 1996). Details of these measures (including example items) are provided in Supplement 1, available online.

Similar to prior research (Roetman et al., 2019), a cumulative index was computed by summing the times that a twin was above the cut-off used to define involvement in DB on several variables measuring different aspects of DB (see Analyses). The score for this index ranged from "0" (indicating that the twin exhibited no disruptive behaviors measured at follow-up) to "7" (indicating that the twin engaged in all DB behaviors at the follow-up at 15 years for prevalences, see Table 1).

Disruptive behavior at age 18 years

Information was collected on various forms of DB at age 18 years, relying on self- and parent-reports. Aggression was assessed using self-report (Coccaro et al., 1997) and parent-report questionnaires (Achenbach & Rescorla, 2003). Nonviolent and violent criminality were assessed with the same self-report tool that was used at age 15. Rule-breaking behavior was assessed by the parent-reported Adult Behavior Checklist (ABCL; Achenbach & Rescorla, 2003). Consequences of antisocial behavior were assessed through a self-report questionnaire that taps social consequences (e.g., reprimands) caused by involvement in antisocial behaviour (Coccaro et al., 1997). Details of these measures are given in Supplement 1, available online.

Also for this follow-up a cumulative index was computed by summing the times that a twin was above the cut-off. This index ranged from "0" (no disruptive behaviors measured at follow-up at 18 years) to "6" (the twin engaged in all DB behaviors at the follow-up at 18 years; for prevalences, see Table 1)

Analyses

The various continuous variables tapping DB at ages 15 and 18 years were substantially skewed, even after data normalization transformations. Therefore, consistent with a large body of research, dichotomized variables were used for the DB measures at both follow-ups (Bechtold et al., 2016; Kerr et al., 1997). Specifically, all DB measures, except self-reported crime and bullying perpetration, were dichotomized into high (i.e., the 30% highest scores, 1, which is indicative of low functioning) versus low (i.e., 70% lowest scores, 0). These cut-offs were implemented because Swedish norms were unavailable for the majority of the DB measures. In line with prior research on the prediction of criminal outcomes (Camp et al., 2013; Colins et al., 2015), we used dichotomized variables (no offenses versus one or more offenses) to define violent and nonviolent criminality, while for bullying perpetration reliable cut-offs were available. Consequently, all these dichotomized DB variables were summed to form disruptive behavior scores at ages 15 and 18 years, respectively (see Disruptive Behavior Scores at Ages 15 and 18 Years). Furthermore, to ease interpretability and to uniformly conduct negative binomial regressions, presence of DB at age 9 years was treated as a count variable, with scores of 0.5 ("Yes, to some extent") and 1 ("Yes") being coded to 1 (i.e., this disruptive behaviour is present), while a score of 0 indicated the absence of a DB.

Table 1 Descriptive Statistics for Children with Complete data at Baseline, and Age 15 Years, and Baseline and 18 Years

		Total sample at 9 years (N = 19,706)		Total sample at 15 years (N = 3,852)		Total sample at 18 years (N = 786)	
Variable function and child age at assessment	Variable	Mean (*SD*)	Range	Mean (*SD*)	Range	Mean (*SD*)	Range
Variables at 9 years	Disruptive behavior (PR)	1.40 (2.30)	0-14	1.04 (1.90)	0-13	1.08 (1.98)	0-13
	Anxiety (PR)	5.96 (7.03)	0-74	4.72 (5.68)	0-50	4.72 (5.49)	0-47
	Anxiety disorder classification (PR) [n(%)]	523 (2.7%)	0-1	51 (1.3%)	0-1	10 (1.3%)	0-1
	Depression (PR)	0.99 (2.42)	0-25	0.79 (1.93)	0-24	0.66 (1.81)	0-24
	Depressive disorder classification (PR) [n(%)]	577 (2.9%)	0-1	62 (1.6%)	0-1	7 (0.9%)	0-1
	Parental education level (PR)	4.72 (0.97)	2-6	5.39 (0.89)	2-6	5.35 (0.92)	2-6
	Child's gender male (PR) [n(%)]	9901 (50.2%)	0-1	1749(45.7%)	0-1	360 (45.8%)	0-1
Disruptive behavior at follow-up	Cumulative disruptive behavior index [n(%)]				0-7		0-6
	0 behaviors			1598 (41.5%)		181 (23.0%)	
	1 behavior			873 (22.7%)		168 (21.4%)	
	2 behaviors			550 (14.3%)		171 (21.8%)	
	3 behaviors			368 (9.5%)		116 (14.7%)	
	4 ≤ behaviors			463 (12.0%)		150 (19.1%)	

Note. PR = parent-reported; SR = self-reported.

Cross-Sectional and longitudinal associations between anxiety, depression and DB

Generalized linear mixed models (GLMMs) for negative binomial regression were used to investigate cross-sectional and longitudinal relations between anxiety, depression and DB at ages 15 and 18 years. GLMMs combine both linear mixed models and generalized linear models, and enable the introduction of random effects. The introduction of a random effect (i.e., twins nested within families) is needed to correct for dependency between twins and dependency of observations (i.e., one parent reporting on the behavior of two twins). In this study, a robust estimator (Huber/White/sandwich estimation) was used to estimate the covariance. This estimator corrects for the dependence of observations and other departures from normality, such as under- and overdispersion. Wald χ^2 tests were used to test the fixed effects. For the fixed effects corresponding incidence rate ratios (IRRs) and 95% confidence intervals (CIs) were computed and reported.

Three different models were run to test cross-sectional and longitudinal associations between anxiety, depression, and DB. The first model was a crude effects model consisting of one predictor at baseline (i.e., depression, or anxiety in both cross-sectional and longitudinal analyses, DB at baseline was added as an additional predictor in the longitudinal analyses to predict DB at follow-ups 15 and 18 years), together with two theoretically relevant control variables: parental education level and sex of the child. In the second model, depression and anxiety at baseline were included simultaneously in an adjusted model, together with the same covariates. In the longitudinal models DB at baseline was included as an additional predictor to predict DB at the follow-ups. The third model included two interaction terms, one including DB and anxiety, and a second including DB and depression.

Co-twin control analyses

The co-twin control design was used to further investigate significant relationships between anxiety, depression, and DB. Regular case-control studies of unrelated individuals can result in overestimation of effects between exposure and outcome, because these designs are less able to control for confounding due to unmeasured environment (e.g., low SES is driving the association between internalizing problems and DB) and genetic background of individuals (e.g., the development of internalizing problems is a simple co-occurrence to DB). Co-twin designs enable researchers to control for both confounders to some extent because twins, especially children, share a substantial part of their (rearing) environment and have substantial (i.e., dizygotic twins share 50% of their genetic makeup)

or complete genetic overlap (monozygotic share nearly 100% of their genetic makeup; Lichtenstein et al., 2002).

In line with prior work (Dinkler et al., 2017; Stubbe, de Moor, Boomsma, & de Geus, 2007), this co-twin control design was put into practice by comparing twins on the basis of depressive and anxiety cases separately, with case status defined by the clinical cut-offs of the MFQ (i.e., depression) and the SCARED (i.e., anxiety), respectively. First, comparisons between an even number of unrelated twin cases and unaffected twin controls were performed, simulating a conventional case-control design. A significant association in this comparison can indicate a causal relationship, but fails to control for unmeasured environment and genetic background. This is because cases and controls are genetically unrelated and do not share (rearing) environments. Second, comparisons were made within dizygotic twin pairs discordant for the presence of anxiety and depression, (i.e., one twin has an anxiety disorder/depression, the other twin has neither an anxiety disorder or depression). This comparison allows to control for shared environment, because twin pairs grow up in the same environment, and controls for genetic confounding to some extent (i.e., dizygotic twins share 50% of their genetic makeup). A significant association in this stage of the analyses indicates that effects in case-control studies are due to unmeasured environmental factors. Third, comparisons were made within monozygotic twin pairs discordant for anxiety and depression, respectively. The identical genetic makeup of monozygotic twins allows to control for genetic confounding. Importantly, a significant association between DB and anxiety and/or depression gives stronger support for a causal effect.

Because of the use of count data, the first comparison was made using the Mann-Whitney test (i.e., two independent samples of cases and controls), while the second and third comparisons were made by means of the Wilcoxon signed-rank test (i.e., dependent samples of dizygotic and monozygotic twin cases and co-twin controls). We used $p < .05$ as an indicator of statistical significance. Two-tailed tests were used in all analyses.

Attrition

At age 15 years, there were 1583 out of 5435 children who were not included in the analyses because of some degree of missing data. Children with (versus without) missing data were more often boys (45.4% versus 47.4%, $p < .05$) and had parents with lower educational levels ($p < .001$). No differences were found in

baseline levels of anxiety, depression, and DB. At age 18 years, 1034 out of 1820 children were excluded because of missing data. Significant differences emerged between children with and without missing data in terms of parental education ($p < .001$), while no differences in sex, anxiety, depression, and DB were found.

RESULTS

Anxiety, depression, and DB

At baseline 9, crude negative binomial regression models indicated that anxiety (IRR = 1.07; 95% CI: 1.07, 1.08) as well as depression (IRR = 1.22; 95% CI: 1.21, 1.23), were significantly related to DB (p's < .001). When included simultaneously in an adjusted model, both anxiety (IRR = 1.05; 95% CI: 1.04, 1.05) and depression (IRR = 1.15; 95% CI: 1.14, 1.16) retained their associations with DB (p's < .001).

Longitudinally, crude negative binomial regression models indicated that DB at 9 years was predictive (p's < .001) of DB at 15 (IRR = 1.11; 95% CI: 1.09, 1.13) and 18 years (IRR = 1.17; 95% CI: 1.11, 1.24). Similar crude models indicated significant predictive effects for depression on DB at 15 (IRR = 1.04; 95% CI: 1.03, 1.06; $p < .001$) and 18 years (IRR = 1.05; 95% CI: 1.02, 1.09; $p = .002$). For anxiety, a significant effect on DB was found at 15 years (IRR = 1.01; 95% CI: 1.00, 1.02; $p = .001$), though not at 18 years.

When DB, depression, and anxiety at 9 years were included simultaneously in one negative binomial regression model, DB retained its predictive associations (p's < .001) with DB on 15 years (IRR = 1.11; 95% CI: 1.09, 1.13), and 18 years (IRR = 1.09; 95% CI: 1.06, 1.12). Both depression and anxiety lost their associations with DB on age 15 and 18 years. Interaction models did not indicate significant interactions between DB and depression and anxiety at 15 years, and 18 years. Similar analyses were also conducted with dichotomous anxiety and depression measures, which were based on the presence or absence of an anxiety or depressive disorder. These analyses yielded identical results (see Supplement 2, available online).

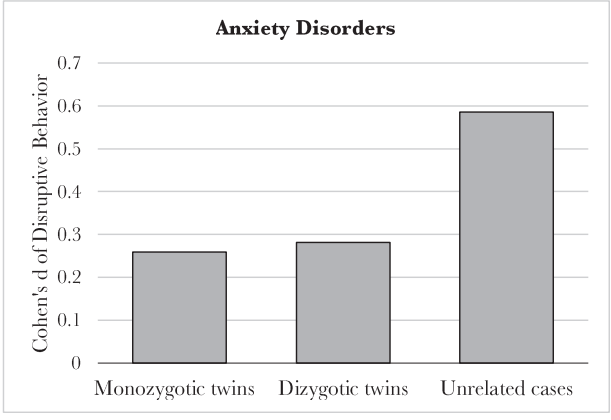
Co-twin control analyses

Although anxiety and depression did show very clear cross-sectional relations with DB at 9 years, longitudinal relations when controlling for baseline DB were non-existent. Therefore co-twin analyses were not performed on the longitudinal

data. To gain a deeper understanding of the causal relations between DB and depression and anxiety, and in line with prior work (Dinkler et al., 2017; Stubbe et al., 2007), we conducted co-twin control analyses at baseline in childhood.

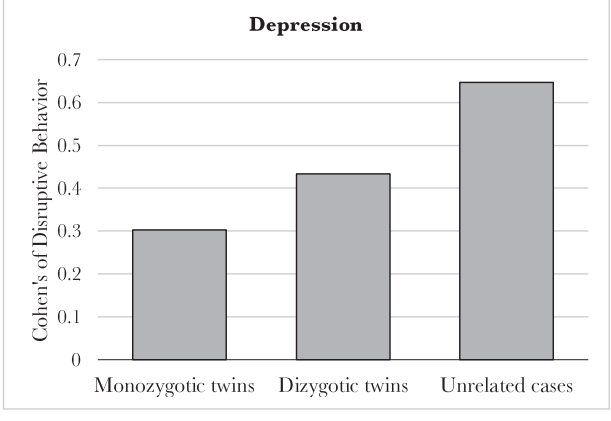
For both anxiety and depression, monozygotic twins, dizygotic twins, and unrelated cases differed significantly from their unaffected co-twin or unaffected, unrelated controls in terms of DB (p's < .001; Figures 1 and 2). Effect sizes were attenuated from medium to small in monozygotic and dizygotic twin pairs, as compared to the analyses in unrelated cases. Furthermore, effect sizes of monozygotic twins and dizygotic twins did not differ considerably. See Tables 2 and 3 for descriptives of the anxiety and depression co-twin samples, respectively.

Figure 1



MZ twins = 182; DZ twins = 574; Unrelated Cases and Controls = 908.

Figure 2



MZ twins = 208; DZ twins = 660; Unrelated Cases and Controls = 1018.

Table 2 Descriptive Statistics for the Anxiety Co-twin Control Analyses at Baseline

	Monozygotic twins		Dizygotic twins		Unrelated cases	
	Anxiety cases (n = 91)	Anxiety controls (n = 91)	Anxiety cases (n = 287)	Anxiety controls (n = 287)	Anxiety cases (n = 454)	Anxiety controls (n = 454)
Variable	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Disruptive behavior (PR)	3.79 (3.39)	2.62 (3.25)	4.80 (3.78)	2.75 (3.13)	4.65 (3.68)	0.88 (1.53)
Anxiety (PR)	31.76 (6.86)	13.01 (7.12)	33.34 (8.54)	9.52 (6.57)	33.14 (8.39)	5.07 (5.57)
Anxiety disorder classification (PR) [n(%)]	91 (100%)	0 (0%)	287 (100%)	0 (0%)	454 (100%)	0 (0%)
Depression (PR)	5.84 (5.11)	1.90 (2.86)	6.71 (6.11)	2.12 (3.38)	6.73 (5.97)	0.00 (0.00)
Depressive disorder classification (PR) [n(%)]	29 (31.9%)	4 (4.4%)	106 (36.9%)	19 (6.6%)	171 (37.7%)	0 (0%)
Parental education level (PR)	4.44 (1.14)	-	4.52 (0.90)	-	4.48 (1.00)	4.79 (0.97)
Child's gender male (PR) [n(%)]	32 (25.2%)	-	141 (59.1%)	149 (51.9%)	214 (47.1%)	229 (50.4%)

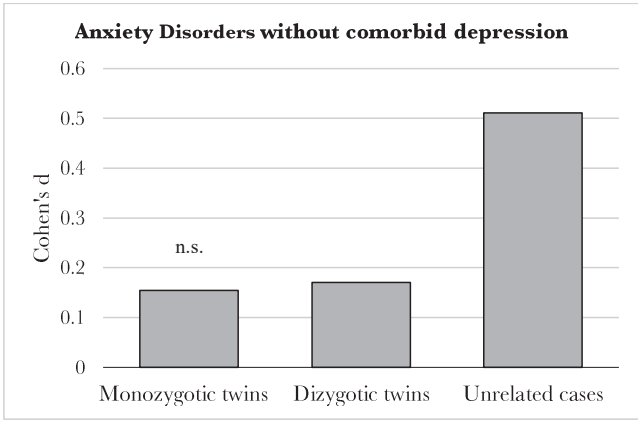
Note. PR = parent-reported; SR = self-reported.

Table 3 Descriptive Statistics for the Depression Co-twin Control Analyses at Baseline

	Monozygotic twins		Dizygotic twins		Unrelated cases	
	Depression cases (n = 104)	Depression controls (n = 104)	Depression cases (n = 330)	Depression controls (n = 330)	Depression cases (n = 509)	Depression controls (n = 509)
Variable	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Disruptive behavior (PR)	4.70 (3.63)	3.07 (3.03)	5.51 (3.80)	2.51 (2.87)	5.38 (3.81)	0.88 (1.52)
Anxiety (PR)	19.55 (14.17)	11.40 (9.94)	19.88 (13.95)	9.41 (8.65)	20.02 (13.79)	3.76 (4.54)
Anxiety disorder classification (PR) [n(%)]	104 (100%)	0 (0%)	330 (100%)	0 (0%)	509 (100%)	0 (0%)
Depression (PR)	10.57 (3.18)	2.30 (2.36)	11.77 (4.02)	1.88 (2.12)	11.62 (3.96)	0.00 (0.00)
Depressive disorder classification (PR) [n(%)]	104 (100%)	0 (0%)	330 (100%)	0 (0%)	509 (100%)	0 (0%)
Parental education level (PR)	4.54 (1.09)	-	4.54 (0.94)	-	4.53 (0.98)	4.79 (0.99)
Child's gender male (PR) [n(%)]	45 (43.3%)	-	192 (58.2%)	161 (48.8%)	284 (55.8%)	258 (50.7%)

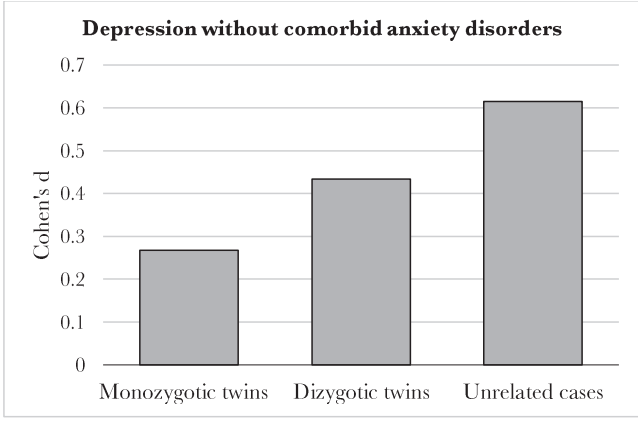
Note. PR = parent-reported; SR = self-reported.

Figure 3



MZ twins = 122; DZ twins = 348; Unrelated Cases and Controls = 674. n.s. = not significant.

Figure 4



MZ twins = 138; DZ twins = 428; Unrelated Cases and Controls = 566.

Because comorbidity between anxiety and depression is common (Cummings, Caporino, & Kendall, 2014), the same co-twin control analyses were conducted in cases with anxiety disorders without comorbid depression, and in cases with depression without comorbid anxiety disorders. These analyses resulted in attenuation of the relationships in unrelated cases and controls and the discordant dizygotic twin pairs, all (p's $\leq .001$; Figures 3 and 4). But more importantly, in monozygotic discordant twin pairs the relation between anxiety disorders and DB became non-significant, while the relation between DB and depression

remained significant (d = 0.27, p = .002). This indicates that the association between anxiety and DB is explained by comorbid depression, with the relationship between anxiety and DB being completely explained by confounding when controlling for this comorbidity. In the end, these results suggest that the relationship between DB and depression is less sensitive to environmental and genetic confounding than anxiety.

DISCUSSION

This study aimed to investigate cross-sectional relations between childhood anxiety, depression and disruptive behavior (DB), and whether childhood anxiety and depression were predictive of DB in adolescence. Furthermore, significant relationships were subjected to a co-twin control analysis to gauge the extent of environmental and genetic confounding.

In accordance to our hypotheses as well as previous research (Bartels, Hendriks, Mauri, Krapohl, Whipp, Bolhuis, Conde, Luningham, Ip, et al., 2018; Granic, 2014; Marshall et al., 2015), cross-sectional relationships were found between anxiety, depression, and DB; with depression showing a stronger relation to DB than anxiety. This likely reflects the observation that, regardless of the direction of effect, depression is uniformly associated with increased levels of DB (Kasen et al., 2001; Patterson & Capaldi, 1990; Wolff & Ollendick, 2006), while anxiety is attributed with both increased and decreased DB (Cunningham & Ollendick, 2010; Granic, 2014; Klingzell et al., 2016; Raine, 2013). In contrast to our expectations, longitudinal effects of childhood anxiety and depression on adolescent DB were not found; although both were predictive of adolescent DB in crude models, these lost significance when controlling for childhood DB at baseline. This finding potentially indicates that DB is the driving factor behind its comorbidity with anxiety and depression and not the other way around. It is already widely known that childhood DB is related to a wide variety of poor outcomes in adolescence, ranging from poor school performance to substance abuse (e.g., Colins, Fanti, & Andershed, 2020; Roetman et al., 2019), and also shows higher stability than anxiety and depression (de la Vega, Piña, Peralta, Kelly, & Giner, 2018; Hannigan, Walaker, Waszczuk, McAdams, & Eley, 2017; Nivard et al., 2015).

A co-twin control design was used to assess whether the cross-sectional associations between anxiety, depression, and DB in childhood were attributable

to environmental and genetic confounding. Although, cross-sectional comorbidity between anxiety, depression, and DB is widely reported in the literature (Bartels, Hendriks, Mauri, Krapohl, Whipp, Bolhuis, Conde, Luningham, Ip, et al., 2018; Granic, 2014; Marshall et al., 2015), these analyses indicated that associations between anxiety and DB could be completely attributed to confounding, while the associations between depression and DB, albeit small (d = 0.27), withstood this stringent test. In combination with the non-significant longitudinal associations spanning into adulthood, this means that based on the current data it is highly likely that anxiety is not causally related to DB, and depression very probably as well. In case of depression, another less likely possibility could be that DB influences depression or vice versa, but that these effects are transient and do not influence DB in the long-term (Thompson et al., 2015). Unfortunately, this hypothesis could not be tested because follow-up measurements took place many years after baseline (6 and 9 years) and spanned very different developmental timeframes (i.e., middle childhood and late adolescence).

This study has considerable strengths; we used a large community sample of twins spanning childhood and late adolescence, containing both twin- and parent-reported measures. As always, this study had several limitations. The baseline measurement in childhood and the follow-up measurements in adolescence were relatively far apart, which could be problematic if interrelations between anxiety, depression, and DB are transient or cascading. Attrition between baseline and follow-ups were substantial. However, the fact that measures for anxiety and depression were introduced later during this study also substantially contributed to the differences in sample size. Measures of DB varied across baseline and follow-ups. However, it should also be noted that DB at 9 years can be expressed very differently than DB in adolescence (e.g., Tremblay, 2014; Vitaro et al., 2006). Although we had a substantial number of twin pairs which were discordant for anxiety and depressive disorders, these clinical classifications were based on parent-report, not by mental health professionals. Furthermore, although childhood DB in this study consisted of oppositional defiant and conduct disorder symptoms, in the overwhelming majority of cases requirements were not met for diagnoses of oppositional defiant disorder or conduct disorder. Future research should be conducted to investigate whether these findings hold up in children who have severe DB or with formal disruptive behavior disorder diagnoses.

In sum, although anxiety and depression show considerable comorbidity with DB and cause significant distress, these associations are likely secondary

to DB and not causally related. This study suggests that treatment of DB should be the main focus of clinicians in case of comorbidity with internalizing problems, because of DB's severity and associations with a multitude of other worse outcomes. This study also emphasizes the need for extensive control for confounding, be it through inclusion of additional measures or behaviour genetic designs (e.g., twin, adoption).

