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Sex differences in psychiatric comorbidity and clinical presentation in youths with conduct disorder

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Background: Conduct disorder (CD) rarely occurs alone but is typically accompanied by comorbid psychiatric disorders, which complicates the clinical presentation and treatment of affected youths. The aim of this study was to investigate sex differences in comorbidity pattern in CD and to systematically explore the 'gender paradox' and 'delayed-onset pathway' hypotheses of female CD. **Methods:** As part of the FemNAT-CD multisite study, semistructured clinical interviews and rating scales were used to perform a comprehensive phenotypic characterization of 454 girls and 295 boys with CD (9–18 years), compared to 864 sex- and age-matched typically developing controls. **Results:** Girls with CD exhibited higher rates of current major depression, anxiety disorders, post-traumatic stress disorder and borderline personality disorder, whereas boys with CD had higher rates of current attention-deficit/hyperactivity disorder. In line with the 'gender paradox' hypothesis, relative to boys, girls with CD showed significantly more lifetime psychiatric comorbidities (incl. Alcohol Use Disorder), which were accompanied by more severe CD symptoms. Female and male youths with CD also differed significantly in their CD symptom profiles and distribution of age-of-onset subtypes of CD (i.e. fewer girls with childhood-onset CD). In line with the 'delayed-onset pathway' hypothesis, girls with adolescent-onset CD showed similar levels of dimensional psychopathology like boys with childhood-onset CD, while boys with adolescent-onset CD had the lowest levels of internalizing psychopathology. **Conclusions:** Within the largest study of CD in girls performed to date, we found compelling evidence for sex differences in comorbidity patterns and clinical presentation of CD. Our findings further support aspects of the 'gender paradox' and 'delayed-onset pathway' hypotheses by showing that girls with CD had higher rates of comorbid lifetime mental disorders and functional impairments, and they usually developed CD during adolescence. These novel data on sex-specific clinical profiles of CD will be critical in informing intervention and prevention programmes.
Keywords: Conduct disorder; sex differences; psychiatric comorbidity; callous-unemotional traits.

Introduction

Conduct disorder (CD) is a neuropsychiatric disorder that is characterized by aggressive and antisocial behaviour in youths (American Psychiatric Association, 2013). Compared to other mental disorders, CD causes greater levels of impairment among affected individuals in almost all life domains (Erskine et al., 2014). While the prevalence of CD is about 3 times higher in boys than girls, it is nevertheless one of the most common disorders in female youths and a

Konrad and Kohls equally contributed to this work.

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major cause of referral to mental health services (Merikangas et al., 2010). However, we still know relatively little about the clinical presentation of girls with CD, including comorbidity pattern, symptom profiles or other phenotypic characteristics (Moffitt et al., 2008). This leaves important clinical and etiological questions unanswered. For instance, it is unclear whether sex-specific diagnostic protocols or treatments should be preferred over nonspecific ones, or whether there exist sex-specific risk and protective factors as well as developmental pathways to CD.

The majority of individuals with CD suffer from additional psychiatric conditions, including oppositional defiant disorder (ODD), attention-deficit/hyperactivity disorder (ADHD), substance use disorders (SUD) and internalizing disorders, such as depression, anxiety disorders and post-traumatic stress disorder (PTSD) (Bernhard, Martinelli, Ackermann, Saure, & Freitag, 2018; Copeland, Shanahan, Erkanli, Costello, & Angold, 2013). Compared to community-based samples, co-occurrence rates are generally higher in clinically referred populations (Greene et al., 2002), and this comorbidity is accompanied by greater impairment and poorer outcomes (Erskine et al., 2016). To date, few studies have investigated sex differences in comorbidity rates in youths with CD, and results are mixed. The limited data to date suggest comparably high rates of comorbid ADHD in both sexes, but a higher prevalence of depression and PTSD in girls than boys with CD, with inconsistent findings for SUD and anxiety disorders (reviewed in (Freitag et al., 2018)).

In addition to comorbidities, sex differences have been described for the presence of callous-unemotional (CU) traits, which have recently been incorporated in DSM-5 as the '*with Limited Prosocial Emotions*' (LPE) specifier of CD (American Psychiatric Association, 2013). Typically, CU traits are lower in girls compared to boys with CD (Colins, Van Damme, Fanti, & Andershed, 2017; Euler et al., 2015), but also within the general population (Essau, Sasagawa, & Frick, 2006; Fanti, Demetriou, & Kimonis, 2013). Moreover, girls with CD are more likely to display relational and reactive aggression as opposed to physical and proactive aggression, which are more frequently observed in boys with CD (Ackermann et al., 2019; Kroneman, Loeber, Hipwell, & Koot, 2009). When female CD presents with elevated CU traits, affected girls often show higher rates of relational and proactive aggression, bullying, rule-breaking and delinquency, but lower levels of internalizing problems, than girls with CD with low CU traits (Colins & Andershed, 2015).

Finally, it has also been suggested that age-of-onset and developmental pathways leading to CD might differ between boys and girls. For instance, childhood-onset CD (where CD symptoms emerge before age 10) is less common in girls than boys, whereas girls appear to catch up with boys in adolescence to show almost as high rates of adolescent-onset CD ((Moffitt, Caspi, Rutter, & Silva, 2001), although for contradictory findings, see Keenan, Wroblewski, Hipwell, Loeber, & Stouthamer-Loeber, 2010; Kratzer & Hodgins, 1999). In order to explain the female-specific clinical phenotype and developmental course of CD, two influential hypotheses have been proposed: first, the 'delayed-onset pathway' hypothesis suggests that many of the risk factors that contribute to the development of CD in girls, including neurocognitive deficits, a dysfunctional family environment and the presence of CU traits, may be present already in childhood, but do not lead to overt antisocial behaviour until affected girls reach adolescence (Silverthorn & Frick, 1999). Therefore, the delayed-onset pathway of CD in girls is assumed to resemble the childhood-onset pathway of CD in boys and that there exists no developmental pathway in female youths that is analogous to the adolescent-onset pathway in male youths (but see (Moffitt et al., 2001)). Second, the 'gender paradox' hypothesis posits that a disorder with a lower occurrence in a particular sex, such as seen in CD, may be associated with more severe symptoms, impairment and comorbidity in that sex (Eme, 1992). Preliminary evidence indeed suggests that girls with CD tend to have a greater aggregation of genetic and/or environmental risk factors (Berkout, Young, & Gross, 2011), and they may have more severe symptoms relative to boys with CD, despite a lower prevalence of conduct problems among girls in the general population (Tiet et al., 2001).

Taken together, while there is accumulating evidence that points to sex differences in the clinical phenotype among youths with CD, results are, however, rather mixed, and previous studies have been limited by including only small proportions of girls with CD, as well as relying on data from highly selected samples, such as those seeking treatment or those from specific geographic regions (e.g. Dunedin, NZ; Pittsburgh, USA). Thus, there is a need to better understand the extent to which the clinical presentation of CD differs between girls and boys, and whether female-specific theories are required to explain the origins of antisocial behaviours in girls. For instance, the presence of sex differences in co-occurring psychiatric conditions associated with CD may suggest that CD represents a different syndrome in the two sexes, possibly with a different developmental course. If true, this would have important treatment implications such that treatment delivery may need to be tailored to the sex of the patient (Pepler, Madsen, Webster, & Levene, 2005).

Thus, the current study aimed at examining sex differences in comorbidity patterns and clinical presentation in the largest and most comprehensively assessed sample of youths with CD recruited to date. We hypothesized that, relative to boys, girls with CD would show the following: (a) more current

internalizing disorders and psychopathology; (b) lower levels of CU traits and different presentations of aggressive behaviour (e.g. less physical aggression); (c) higher overall rates of lifetime comorbidities related to more severe CD symptoms and impairment, in line with the 'gender paradox' hypothesis; and finally (d) higher rates of the adolescent-onset (vs. childhood-onset) CD subtype that resembles the childhood-onset male subtype with respect to dimensional psychopathology, presence of CU traits and types of aggression (e.g. proactive aggression), in line with the 'delayed-onset pathway' hypothesis.

Methods

Participants

This study included 749 youths with CD (60.6% girls) and 864 typically developing controls (TDCs; 64.8% girls), 9–18 years of age ($M = 14.2 \pm 2.4$ years), from the FemNAT-CD consortium (Freitag et al., 2018). We oversampled girls as a key aim of the consortium was to address the lack of data on female CD. Both community-based and clinically referred individuals were recruited through community outreach and from mental health clinics, welfare institutions and youth offending services. Youths with CD met diagnostic criteria for current CD according to DSM-IV-TR criteria. TDCs were free of any current psychiatric disorder (except specific learning disorders) and had no history of CD, ODD and ADHD. Exclusion criteria for both groups were IQ < 70 (based on estimates from two subtests of age-appropriate Wechsler scales; (Wechsler, 1999, 2003, 2008)), autism spectrum disorders, schizophrenia, bipolar disorder or mania, neurological disorders and genetic syndromes. Local ethics committees approved the study protocol. Written informed consent was obtained for all participants.

Clinical measures

Psychiatric diagnoses. We used the Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime version (K-SADS-PL), administered separately to participants and their caregivers by trained staff members, to assess current and lifetime psychiatric diagnoses according to DSM-IV-TR criteria (Kaufman et al., 1997). Where available, medical records were consulted. Note that ODD and ADHD were diagnosed using DSM-5 criteria (i.e. age-of-symptom onset for ADHD <12 years; co-occurring diagnoses of ODD and CD were allowed). Inter-rater reliabilities (IRR; $N = 75$) of CD, ODD, ADHD, major depressive disorder (MDD) and generalized anxiety disorder (GAD) diagnoses were high (Cohen's κs ≥ 0.84, agreement rates $\geq 92\%$). In order to reduce the number of comorbidities for further analyses, all anxiety, elimination, eating and depressive disorders were collapsed into an overarching category, respectively. Using the K-SADS-PL, we determined the following: (a) disorder severity of CD as mild, moderate or severe; (b) severity for the four CD symptom domains (i.e. symptom counts for aggression to people/animals, destruction of property, deceitfulness/theft and rule violation); and (c) CD age-of-onset subtype (i.e. childhood-onset CD: presence of at least one characteristic CD symptom prior to age 10; adolescent-onset CD: absence of any CD symptoms prior to age 10). Two modules from the K-SADS-PL DSM-5 working draft (provided by J. Kaufman) were used to assess disruptive mood dysregulation disorder (DMDD) and autism spectrum disorder. Additionally, borderline personality disorder (BPD) was assessed using the semi-structured Diagnostic Interview for DSM-IV Personality Disorders (Zanarini, Frankenburg, Sickel, & Yong, 1996).

CU traits. The Youth Psychopathic traits Inventory (YPI; Andershed et al. 2002) is a 50-item self-report measure of psychopathic traits with responses to be given on a 4-point Likert scale. In this paper, the overall CU trait score (summary score of 15 items; e.g. '*When other people have problems, it is often their own fault, therefore, one should not help them'.)* was used to assess CU traits among other psychopathic-like traits. The CU trait subscale showed good internal consistency in the present sample (Cronbach's $\alpha = .81$). Psychopathic-like traits were further evaluated by the grandiose-manipulative (20 items; Cronbach's $\alpha = .91$) and the impulsive-irresponsible (15 items; Cronbach's $\alpha = .85$) subscales of the YPI.

Dimensional assessment of psychopathology. Caregivers completed the Child Behavior Checklist (CBCL/4-18) about their child's behaviour over the past six months (Achenbach, 1991). Raw scores were converted to gender- and age-standardized *T*-scores based on country-specific normative data for each of the following behavioural problem scales: (a) eight syndrome scales (i.e. anxious/depressed, withdrawn, somatic complaints, social problems, thought problems, attention problems, rule-breaking behaviour and aggressive behaviour), (b) two 'broadband' scales assessing internalizing problems (sum of anxious/depressed, withdrawn and somatic complaints scores) and externalizing problems (sum of rule-breaking and aggressive behaviour) and (c) a total problems score (the sum of all problem scores).

Reactive and proactive aggression. Participants reported on their own aggressive behaviours using the Reactive-Proactive aggression Questionnaire (RPQ), which includes 11 items related to 'reactive aggression' and 12 items related to 'proactive aggression' (Raine et al., 2006). Cronbach's alphas for these subscales were 0.75 and 0.88, respectively.

Statistical analyses

We compared frequencies (in %) of current and lifetime comorbid disorders, of CD severity and impairments in different settings (e.g. school) between boys and girls with CD by multivariate logistic regression models with sex, age and their interaction as predictors since boys with CD were significantly younger than girls with CD, and the prevalence of psychiatric disorders tends to be higher in older subjects (Merikangas et al., 2010). Adjusted ORs are reported. Dimensional measures of psychopathology (CBCL) were analysed using multivariate ANCOVA models with age as covariate. A comorbidity index counting the total number of psychiatric disorders and a total CD symptom score (K-SADS-PL) were constructed and then analysed by ANCOVA models with age as covariate to test for between-sex differences in CD, followed by analyses of associations separately for boys and girls. Finally, interaction effects between CD-onset subtype and sex were analysed for psychopathic-like traits, aggression type and dimensional psychopathology. Evidence for the 'delayed-onset pathway' hypothesis comparing boys with childhood-onset CD and girls with adolescent-onset CD was further quantified using Bayesian analyses to make inferences on the difference (or the lack thereof) of the two group means, as recommended by Masson (Masson, 2011). To do so, we estimated Bayes factors that constitute a natural ratio to compare the marginal likelihoods between a null and an alternative hypothesis (Bayes factors ≤ 3: no evidence for H0; Bayes factors ≥ 10: positive evidence for H0). Study site effects with regard to recruitment strategies were further controlled as described online in Appendix S1 in the Supporting Information. Statistical analyses were conducted with SPSS v25 (IBM Corp., Armonk, NY).

Results

Comorbidities

As shown in Table 1, current comorbid ODD was present in the majority of the CD patients (77%), with comparable frequencies in boys and girls. In contrast, the prevalence of comorbid DMDD was comparably low in both sexes (2%). Regarding sex differences, girls with CD had higher rates of current MDD, anxiety disorders and PTSD than boys with CD. For anxiety disorders, there was also a sex-by-age interaction effect, driven by older girls with CD showing more anxiety disorders. Additionally, more girls with CD than boys met criteria for BPD. Boys with CD, however, exhibited significantly higher rates of current ADHD compared with girls.

Lifetime, but not current, prevalence of alcohol use disorder (AUD) was higher in girls than boys with CD. There was also a significant sex-by-age interaction effect for AUD, which was likely driven by a tendency for an earlier age of onset in girls vs. boys with CD (12.5 vs. 14.1 years, $p = .11$). Lifetime diagnoses of depression and PTSD were more prevalent in girls compared to boys with CD, while comorbid lifetime ADHD and Tic disorder were more frequently observed in male vs. female cases.

Regarding multiple comorbidities, there were no sex differences in average number of current comorbid disorders (girls: 2.9 ± 1.4, boys: 2.8 ± 1.3, $F(1,746)<1$, $p = .39$, $\eta_p^2 = .001$). However, after correcting for age, girls with CD had more lifetime comorbidities than boys with CD (3.5 ± 1.6 vs. 3.2 ± 1.5, $F(1,746) = 4.1$, $p < .05$, $\eta_p^2 = .005$; Figure 1).

Effects of main recruitment strategy per study site are documented in the Supporting Information. Youths with CD from sites with predominately clinically based recruitment strategies had a significantly higher number of current and lifetime comorbidities compared to youths from sites with less than 50% clinically referred youths with CD (ps < .001); these effects, however, did not differ between the two sexes.

Dimensional psychopathology

Figure 2 shows the dimensional measures of caregiver-reported psychopathology (CBCL), separately

Table 1 Current and lifetime comorbidity rates in girls versus boys with CD

Comorbidities	CD_{female} *n* (%)	CD_{male} *n* (%)	Sex effect		Age effect		Sex*Age	
			OR	*p*	OR	*p*	OR	*p*
Current								
ADHD	138 (30.4%)	132 (44.7%)	1.514	**.012**	0.780	**<.001**	0.948	.479
ODD	357 (78.6%)	225 (76.3%)	0.758	.151	0.794	**.001**	0.946	.556
AUD	34 (7.5%)	17 (5.8%)	0.445	.139	1.462	**.002**	1.530	.077
SUD	84 (18.5%)	52 (17.6%)	0.848	.532	1.420	**<.001**	1.340	.028
Depression	85 (18.7%)	33 (11.2%)	0.532	**.006**	1.033	.610	0.910	.333
Adjustment	13 (2.9%)	5 (1.7%)	0.662	.463	1.219	.239	0.815	.413
DMDD	9 (2.0%)	6 (2.0%)	0.828	.754	0.985	.932	0.833	.445
Anxiety	62 (13.7%)	34 (11.5%)	0.576	**.043**	0.982	.799	0.754	**.007**
OCD	8 (1.8%)	5 (1.7%)	0.953	.935	0.867	.394	1.146	.582
PTSD	49 (10.8%)	12 (4.1%)	0.336	**.002**	0.960	.597	1.324	.079
Tics	1 (0.2%)	7 (2.4%)	54.638	.187	3.396	.282	0.214	.179
Elimination disorders	14 (3.1%)	18 (6.1%)	1.753	.200	0.696	**.002**	1.111	.503
Eating disorders	4 (0.9%)	0 (0.0%)	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*
BPD	81 (22.7%)	13 (5.4%)	0.197	**<.001**	1.229	**.004**	1.204	.281
Lifetime								
ADHD	145 (31.9%)	144 (48.8%)	1.734	**.001**	0.805	**<.001**	0.971	.694
ODD	382 (84.1%)	235 (79.7%)	0.690	.074	0.853	**.030**	0.858	.135
AUD	53 (11.7%)	21 (7.1%)	0.344	**.026**	1.458	**<.001**	1.537	**.044**
SUD	129 (28.4%)	62 (21.0%)	0.655	.074	1.534	**<.001**	1.249	.070
Depression	151 (33.3%)	46 (15.6%)	0.386	**<.001**	1.107	.057	0.905	.238
Adjustment	20 (4.4%)	6 (2.0%)	0.446	.111	1.117	.388	0.820	.341
DMDD	11 (2.4%)	6 (2.0%)	0.669	.490	0.908	.514	0.904	.649
Anxiety	79 (17.4%)	58 (19.7%)	0.959	.842	0.977	.713	0.827	**.030**
OCD	9 (2.0%)	5 (1.7%)	0.847	.771	0.862	.344	1.154	.553
PTSD	79 (17.4%)	17 (5.8%)	0.286	**<.001**	1.080	.246	1.213	.165
Tics	3 (0.7%)	13 (4.4%)	5.633	**.021**	0.723	.194	1.057	.841
Elimination disorders	48 (10.6%)	47 (15.9%)	1.405	.149	0.822	**.007**	1.037	.707
Eating disorders	11 (2.4%)	0 (0.0%)	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*

CD, conduct disorder (454 girls, and 295 boys with CD); ADHD, attention-deficit/hyperactivity disorder; ODD, oppositional defiant disorder; AUD, alcohol use disorder; SUD, substance use disorder; DMDD, disruptive mood dysregulation disorder; OCD, obsessive–compulsive disorder; PTSD, post-traumatic stress disorder; TICs, TIC disorder; elimination disorder = enuresis/encopresis; BPD, borderline personality disorder (data from 357 girls and 241 boys with CD); OR, odds ratio based on logistic regression analysis with sex, age and their interactions as predictors. Bold values indicate significant results.

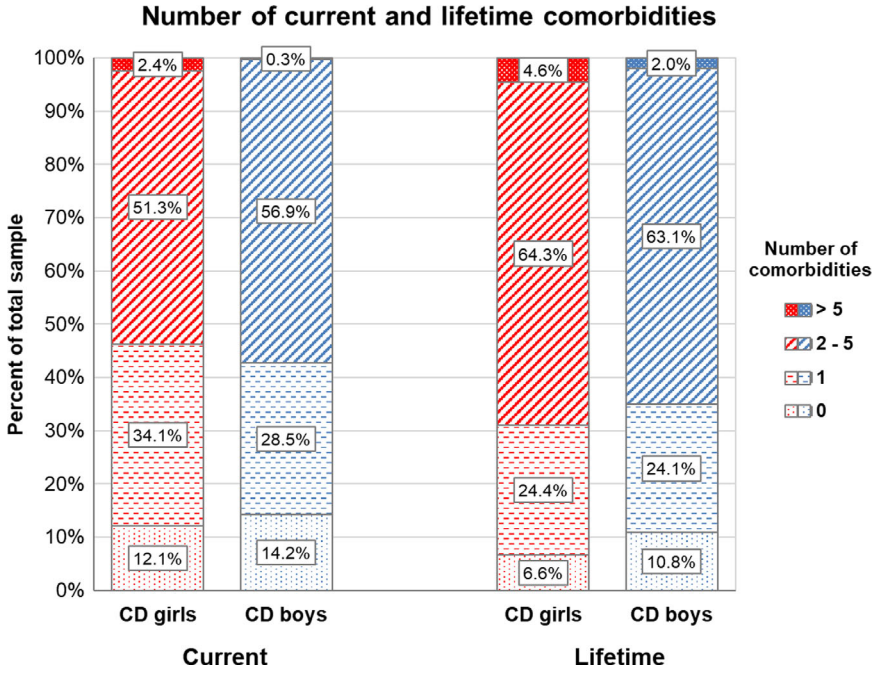

Figure 1 Frequencies of current and lifetime psychiatric comorbidities, plotted separately for boys and girls with CD

for group and sex. Significant main effects of group emerged for all CBCL scores, with CD participants scoring higher than TDCs (*p*s < .001, η_p^2s: 0.12–0.66, indicating large effect sizes). Furthermore, group × sex interaction effects were present for externalizing ($p = .03$, $\eta_p^2 = 0.004$) and internalizing symptoms ($p = .003$, $\eta_p^2 = 0.007$), as well as for all subscales (*p*s < .01; η_p^2s: 0.01–0.024), except for somatic complaints, social problems and aggressive behaviours. The interaction effects were driven by comparably low/average problem behaviours in TDC boys and girls, but particularly elevated scores in girls vs. boys with CD across these subscales.

Sex differences in CD symptoms and impairment

While there were no significant sex differences in total CD symptoms (CD_f vs. CD_m: 5.4 ± 2.3 vs. 5.6 ± 2.3, $p = .072$) or in deceitfulness/theft (1.4 ± 0.8 vs. 1.4 ± 0.9, $p = .61$), girls relative to boys with CD showed significantly fewer physical aggression symptoms (1.8 ± 1.2 vs. 2.3 ± 1.2, $p < .001$) and less destruction of property (0.5 ± 0.6 vs. 0.7 ± 0.6, $p < .001$), but more serious rule violations (1.6 ± 1.1 vs. 1.0 ± 1.0, $p < .001$). The most prevalent symptoms in girls with CD were lying (30%) and truancy (26%), followed by initiating physical fights (23%), while in boys these were initiating physical fights (38%), lying (36%) and nonaggressive stealing (28%).

Distributions of CD severity did not differ significantly between the sexes, although boys tended to show more severe CD (CD_{male} vs. CD_{female}: 24.7% vs. 22.9%, $OR = 1.44$, $p = .058$). Impairments caused by current CD symptoms did not differ between boys and girls with CD regarding peers and family (*p*s > .095). However, girls with CD reported greater impairment at school than boys despite similar IQs (91.5% vs. 80.9%, OR = 0.39, $p < .001$). There was also a medium positive correlation between number of lifetime comorbidities and total number of CD symptoms in girls ($r = .27$, $p < .001$), but not in boys with CD ($r = .09$, $p = .14$). The correlation was significantly stronger in girls than in boys (Fisher's $Z = 2.35$, $p < .01$; Figure 3).

Testing the 'delayed-onset pathway' hypothesis: Effects of CD age of onset in boys versus girls

The majority of girls with CD (68.1%) had adolescent-onset CD, whereas childhood-onset CD was more common in boys (57.2%; OR = 0.39, $p < .001$). Average age of onset of CD was 11.6 years in girls versus 9.6 years in boys ($t = 5.3$, $p < .001$). We subsequently analysed the CD-onset type by sex interaction effects in order to test whether age of onset of CD was differentially related to psychopathic-like traits (YPI), aggression type (RPQ) and dimensional psychopathology (CBCL) in girls versus boys. In order to control for sex differences in these measures in the normal population, YPI and RPQ scores were *z*-transformed based on sex-specific data from the present TDC sample, and additionally sex-specific T-values were used from the CBCL manual. As the two childhood-onset subtypes were younger than the adolescent-onset subtypes, which is partly due to the nature of these subtypes, we report all findings with and without controlling for age effects.

RPQ aggression scores did not differ between CD-onset subtypes (Table 2). However, significant sex by

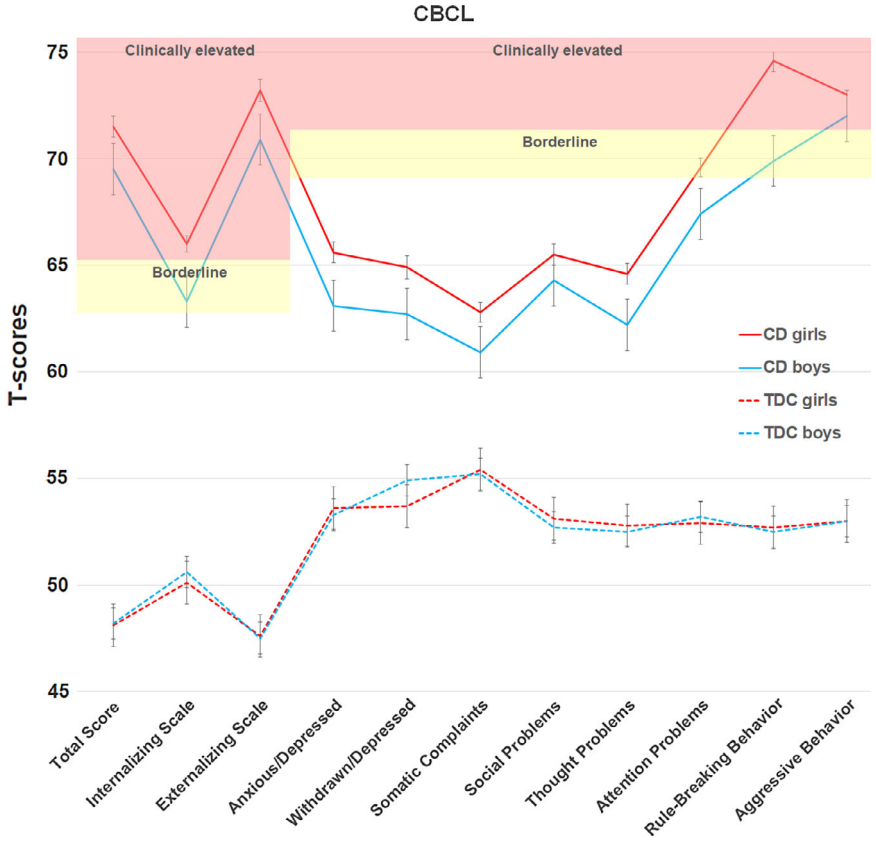

Figure 2 Female- vs. male-specific profiles on dimensional measures of psychopathology in CD and typically developing controls (TDC) as assessed with the CBCL

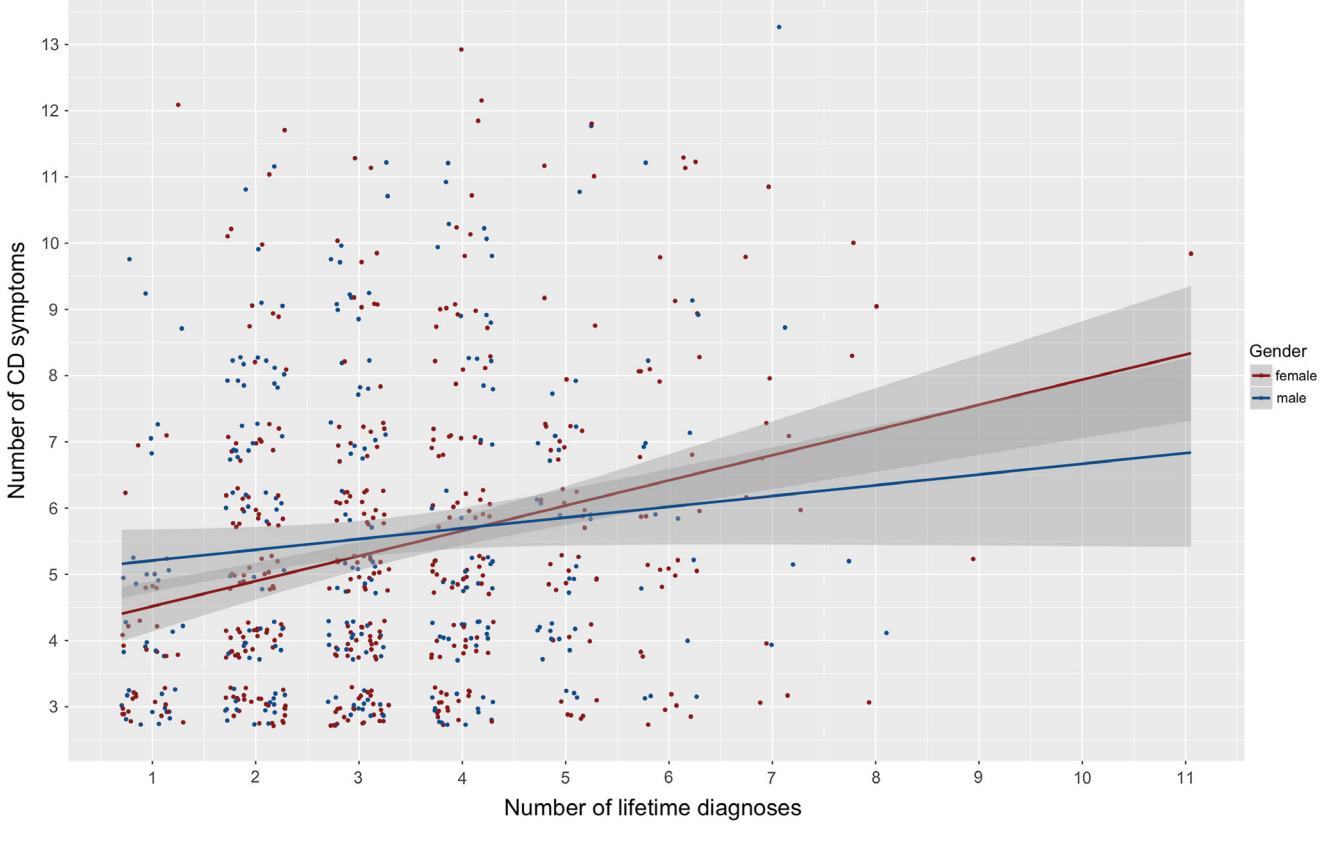

Figure 3 Scatterplot depicting the strength of association between number of lifetime psychiatric diagnoses and CD symptoms, with separate regression lines and 95% confidence intervals for boys and girls with CD

CD-onset interaction effects emerged for CU and grandiose-manipulative traits in the YPI, showing stronger deviations from sex-specific norms in girls with adolescent-onset CD compared to boys with childhood-onset CD (grandiose-manipulative traits: η_p^2 = .012; CU traits: η_p^2 = .014); these findings also hold when controlling for age (both YPI scores: η_p^2 = .011). Additionally, CD-onset subtype was significantly associated with differences in dimensional psychopathology, with lower CBCL total and externalizing scores in youths with adolescent-onset CD versus youths with childhood-onset CD, irrespective of sex. Interestingly, internalizing psychopathology was the lowest in boys with adolescent-onset CD compared with the other subtypes (η_p^2 = .008, corrected for age: η_p^2 = .007) which did not differ among each other.

Finally, in case of the absence of sex by CD-onset interaction effects, Bayes analyses were applied to further quantify the evidence for the 'delayed-onset pathway' hypothesis, such that there are *no* phenotypic subtype differences in the specific contrast comparing adolescent-onset girls and childhood-onset boys with CD (H0). There was indeed substantial evidence for the null hypothesis with respect to dimensional psychopathology in the CBCL (Bayes factor for externalizing symptoms = 10.1, and for total score = 10.5), but neither for the reactive (Bayes Factor = 0.05) and proactive aggression type (Bayes Factor = 0.02) nor for the YPI impulsive-irresponsible traits (Bayes Factor = 0.0). Note, that the Bayes results were not corrected for age.

Discussion

Within the largest study of CD in girls performed to date, we demonstrated that female and male youths with CD differed significantly in current and lifetime comorbid psychiatric disorders. Importantly, girls with CD had a higher number of lifetime comorbidities which was associated with greater CD symptoms, in line with the 'gender paradox' hypothesis. Similarly, girls with CD also scored higher on dimensional measures of internalizing symptoms, attention problems and rule-breaking behaviour. Sex differences also emerged regarding CD-specific symptoms; that is, girls exhibited fewer symptoms of physical aggression or destruction of property, but more serious rule violation symptoms than boys with CD. However, they more frequently reported an adolescent-onset of CD than boys, and there was evidence for a lack of specific subtype differences between adolescent-onset girls compared to childhood-onset boys with respect to dimensional psychopathology, which both is in line with the 'delayed-onset pathway' hypothesis.

The majority of boys and girls with CD showed at least one lifetime comorbidity, but only ~7% of girls and ~11% of boys had 'pure' CD; this closely resembles the results of the Dunedin study (Moffitt et al., 2001). Overall, girls with CD had

Table 2 CD age-of-onset subtype by sex effects

	CD_{female} Childhood-Onset (1; *n* = 138) *M* (*SD*)	CD_{female} Adolescent-Onset (2; *n* = 295) *M* (*SD*)	CD_{male} Childhood-Onset (3; *n* = 166) *M* (*SD*)	CD_{male} Adolescent-Onset (4; *n* = 124) *M* (*SD*)	Sex effect *F*	Onset effect *F*	Sex* Onset *F*	Post hoc comparisons
Age (years)	13.8 (2.4)	15.4 (1.5)	13.0 (2.4)	15.5 (1.6)	3.4	**172.1*** **	**9.2** **	(2 = 4) > 1 > 3
YPI self-report[a]								
Grandiose-manipulative	1.1 (1.4)	0.8 (1.3)	0.2 (1.2)	0.4 (1.3)	**31.1*** **	.59	**7.9** **	2 > 3; 1 > (3 = 4)
Callous-unemotional	1.3 (1.4)	1.0 (1.4)	0.6 (1.2)	0.9 (1.3)	**8.8** **	1.03	**7.5** **	2 > 3; 1 > (3 = 4)
Impulsive-irresponsible	1.6 (1.3)	1.6 (1.3)	0.8 (1.4)	1.2 (1.3)	**30.5*** **	.95	1.02	Girls > Boys
RPQ[a]								
Reactive aggression	1.8 (1.3)	1.9 (1.3)	1.5 (1.5)	1.7 (1.4)	**5.6***	0.2	.01	Girls > Boys
Proactive aggression	3.2 (3.8)	3.2 (3.6)	2.0 (2.7)	2.5 (2.7)	**11.6*** **	1.1	.52	Girls > Boys
CBCL (*T*-scores):								
Total score	73.1 (8.4)	70.9 (8.8)	71.3 (8.1)	67.1 (9.6)	**11.9** **	**7.4 ** **	1.4	Girls > Boys; Childhood-onset > Adolescent-onset
Internalizing symptoms	66.7 (9.6)	66.0 (10.6)	65.1 (9.6)	60.9 (10.2)	**12.9***	1.2	**4.2***	4 < (1 = 2 = 3)
Externalizing symptoms	74.8 (6.8)	72.4 (8.7)	72.0 (7.7)	69.4 (8.9)	**14.1*** **	**8.3** **	.03	Girls > Boys; Childhood-onset > Adolescent-onset

CD, conduct disorder; YPI, Youth Psychopathic traits Inventory; RPQ, Reactive-Proactive aggression Questionnaire; CBCL, Child Behavior Checklist.

[a]Sex-specific *z*-scores based on TDC sample data.

*$p \leq .05$; **$p \leq .01$; ***$p \leq .001$; *F* statistics is reported with age as covariate. Bold values indicate significant results.

significantly more comorbid lifetime psychiatric disorders than boys. However, while ODD was the most frequent comorbid disorder in both sexes, affecting ~75% of all youths with CD, girls and boys did not differ in current or lifetime ODD rates. This finding contradicts the notion that ODD may be a less frequent precursor in the developmental pathway to CD in girls than boys (Silverthorn & Frick, 1999). In contrast to ODD, the prevalence of DMDD was low (2%, as assessed using the K-SADS-PL), although it also did not differ between the sexes. This fits with an earlier study showing that ODD can occur without DMDD symptoms and that CD+ODD comorbidity does not increase the risk of having DMDD (Mayes, Waxmonsky, Calhoun, & Bixler, 2016).

Relative to boys, girls with CD showed more current internalizing disorders (depression, anxiety and PTSD), and higher rates of BPD, but lower rates of current ADHD. This greater female-specific risk for comorbid depression and PTSD fits with previous observations (Bernhard et al., 2018; Zoccolillo, 1993), but it is at odds with work showing similar rates of comorbid anxiety disorders in girls and boys with CD (Marmorstein, 2007). Of interest, comorbid anxiety disorders have been variously discussed as either a protective or harmful factor in the context of CD, such that anxiety might attenuate the severity and persistence of CD in youths (Mason et al., 2004) or, conversely, it has been suggested to lead to greater impairment (Maser & Cloninger, 1990). Considering that the higher rate of comorbid disorders in girls with CD was associated with more severe CD symptoms in the present study, it is likely that comorbid anxiety disorder may lead to greater impairment, at least in female CD. However, it also conceivable that greater impairment, for instance at school, that is caused by CD symptoms can contribute to higher distress and more symptoms of anxiety.

The high rate of comorbid BPD in girls with CD, affecting almost 1/4 of girls but only 5% of boys with CD, is also noteworthy as it supports several other studies of adult offenders and incarcerated individuals reporting a high prevalence of BPD particularly in female inmates (Drapalski, Youman, Stuewig, & Tangney, 2009). BPD in adolescent girls with CD may identify a subgroup in which core symptoms of BPD, such as affective instability, hypersensitivity to interpersonal threats or shame proneness, lead to conduct problems, including reactive aggression (Mancke, Herpertz, & Bertsch, 2015), constituting important clinical targets for intervention and prevention programmes.

Girls with CD also showed higher rates of lifetime AUDs and tended to have higher rates of lifetime SUDs. This appeared to be driven by an earlier age of onset of these disorders in girls versus boys with CD. Our findings are consistent with previous studies of female prisoners who often show a high degree of comorbid psychopathology, including AUD and SUD (Lewis, 2006).

Notably, we found evidence for site-specific effects such that youths with CD from sites with predominately clinically based recruitment strategies showed higher rates of current and lifetime comorbidities than youths from sites with predominantly community-based recruitment. These effects, however, did not differ between the two sexes, indicating that the recruitment strategy affected the presence of comorbid disorders but not differentially so in boys and girls with CD. As our FemNAT-CD sample represents a large European cohort based on both clinical recruitment and nonclinical recruitment, but notably with an overall estimated 75% of youths with CD from clinical services, the observed high rates of comorbid disorders are comparable to other studies focusing, for instance, on hospitalized patients with CD (e.g. (Patel, Amaravadi, Bhullar, Lekireddy, & Win, 2018)). The comorbidity rates presented here, however, differ from purely epidemiological community-based studies, such as the British Child Mental Health Survey (Maughan, Rowe, Messer, Goodman, & Meltzer, 2004) or the Great Smoky Mountains Study (Rowe, Costello, Costello, Angold, Copeland, & Maughan, 2010) which both reported overall lower rates of co-occurring mental disorders in youths with CD.

Our dimensional parent-reported CBCL data indicate that girls display more severe psychopathology than boys with CD, with respect to both internalizing and externalizing behaviours. These data complement the categorical findings of greater lifetime comorbidities and school-based impairments among girls with CD, although the overall severity of CD symptoms was similar in both sexes. Importantly, the significant positive association between CD severity and number of comorbidities, which was only present in girls but not in boys, supports the 'gender paradox' hypothesis, suggesting that psychiatric comorbidities might particularly contribute to the female-specific burden of disease (or vice versa). It should be stressed, though, that we only tested the clinical component of the 'gender paradox' hypothesis in the present study, but did not explore etiological aspects of it, including biological (e.g. genetic load) and environmental risk factors. Clearly, this needs to be addressed in future studies to provide a more complete picture of the 'gender paradox' hypothesis with regard to CD.

As expected, childhood-onset CD was less frequently observed in girls than boys, supporting the assumption that a prominent trajectory exists in girls that typically onsets in adolescence (Moffitt et al., 2001; Silverthorn & Frick, 1999). However, when taking normative sex differences into account, age of onset of CD was differentially associated with callous-unemotional and grandiose-manipulative traits as well as internalizing psychopathology in girls versus boys with CD. Interestingly, girls with adolescent-onset CD showed higher but not lower levels of psychopathic-like traits than boys with childhood-onset CD, and boys with adolescent-onset

CD had the lowest scores of dimensional internalizing psychopathology. However, as we could not confirm any differences in CU traits or aggression type in boys with CD dependent on their age-of-onset subtype, as suggested by previous studies ((Rowe, Maughan, et al., 2010), but see (Jambroes et al., 2016)), the clinical relevance of subtyping youths with CD based on disorder onset needs further comparative evaluation across both sexes.

Although this is the largest and most comprehensive study of its kind to date, our results have to be considered in light of several limitations. First, it should be noted that there are major sex differences in the incidence of mental disorders in the general population. For example, while boys are more likely than girls to fulfil diagnostic criteria for ADHD in nonclinical, epidemiological as well as in clinically referred samples (Ramtekkar, Reiersen, Todorov, & Todd, 2010), major depression, anxiety disorders and PTSD are more frequently observed in girls (Merikangas et al., 2010). As we explicitly excluded TDCs with current and lifetime externalizing diagnoses as well as any other current psychiatric disorder (except specific learning disorders), our sample includes a 'super-normal' TDC group which is suboptimal for investigating case–control comparisons in comorbidity rates. Ideally, one would want to be as inclusive as possible in recruiting controls, thus allowing participants with, for instance, an internalizing disorder to take part. This would ensure that the CD and TDC groups would only differ in terms of CD. Hence, the current study design prevents us from drawing firm conclusions in terms of whether sex ratios for comorbidities in CD differ systematically from the general population. Second, the mixed approach of clinical and nonclinical recruitment renders comparisons with earlier studies difficult, while increasing the representativeness of the sample. Please note, though, that our study was not designed to specifically answer epidemiological questions but rather to reveal reliable information on between-sex differences in the clinical phenotype of CD. Third, age of onset of CD was assessed using retrospective reports which may provide less reliable data about the exact emergence of behavioural problems in childhood. Thus, our findings, particularly with regard to the 'delayed-onset pathway' hypothesis, need to be replicated in prospective longitudinal studies with repeated assessments across development. Fourth, although relational aggression is an important research focus on phenotypic sex differences in aggression (Marsee et al., 2014), we did not include this variable in the current study. The reason for that is that relational aggression was the topic of a recent publication by the FemNAT-CD consortium specifically dedicated to this topic (see (Ackermann et al., 2019)), and we wanted to avoid duplicating findings. In our previous report, as expected, we found that girls with CD showed significantly higher levels of relational aggression compared to boys with CD. Since both study samples largely overlap, we can assume that this also holds for the CD group investigated here. Bearing the different caveats in mind, our findings are consistent with the idea that there may be sex-specific clinical presentations and developmental pathways leading to CD. Consequently, service delivery to patients with this highly impairing disorder needs to account for potential sex differences in treatment targets and comorbidity patterns.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Appendix S1

Figure S1. This STROBE diagram shows the flow of participants from screening to enrollment in the current study

Table S1. Number of Participants per Group and Sex by Country

Table S2. Psychotropic Medication and Service Use of Girls and Boys with CD

Supplementary Results. Phenotypic differences between youths with CD recruited from sites with predominately clinically referred recruitment strategies (> 50%) versus sites with predominately community-based recruitment strategies

Table S3. Current and lifetime comorbidity rates in girls versus boys with CD (including site effect of recruitment)

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Key points

- Although CD is less common in girls than boys, female CD is associated with a higher rate of lifetime comorbidities which is in turn associated with more severe CD symptoms.
- Relative to boys, girls with CD showed higher rates of comorbid current depression, anxiety disorders and PTSD, lifetime alcohol use disorder and BPD, but lower rates of current ADHD.
- Girls with CD were more likely to have the adolescent-onset form of CD and had fewer symptoms of physical aggression and destruction of property, but showed more serious rule violations, than boys with CD.
- In line with the 'delayed-onset pathway' hypothesis, girls with adolescent-onset CD showed similar levels of dimensional psychopathology, including externalizing symptoms, like boys with childhood-onset CD, while boys with adolescent-onset CD had the lowest levels of internalizing psychopathology.

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