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Conduct disorder - a comprehensive exploration of comorbidity patterns, genetic and environmental risk factors

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ABSTRACT

Conduct disorder (CD), a common mental disorder in children and adolescents, is characterized by antisocial behavior. Despite similarities with antisocial personality disorder (ASPD) and possible diagnostic continuity, CD has been shown to precede a range of adult-onset mental disorders. Additionally, little is known about the putative shared genetic liability between CD and adult-onset mental disorders and the underlying gene-environment interplay. Here, we interrogated comorbidity between CD and other mental disorders from the Norwegian Mother, Father and Child Cohort Study (n = 114 500) and investigated how polygenic risk scores (PRS) for mental health traits were associated with CD/CD traits in childhood and adolescence. Gene-environment interplay patterns for CD was explored with data on bullying and parental education. We found CD to be comorbid with several child and adult-onset mental disorders. This phenotypic overlap corresponded with associations between PRS for mental disorders and CD. Additionally, our findings support an additive gene-environment model. Previously conceptualized as a precursor of ASPD, we found that CD was associated with polygenic risk for several child- and adult-onset mental disorders. High comorbidity of CD with other psychiatric disorders reflected on the genetic level should inform research studies, diagnostic assessments and clinical follow-up of this heterogenous group.

1. Introduction

Conduct disorder (CD) is a mental disorder emerging in childhood and early adolescence characterized by behavioral symptoms related to covert and overt antisocial behavior including the violation of rights of others and severe physical aggression (Fairchild et al., 2019). CD, with a prevalence ranging between 0.6% to 3.8%, and for questionnaire-based symptoms reaching up to 14% (Barican et al., 2022; Copeland et al., 2011), is considered the leading cause of disability among mental disorders for children aged 0–14 (GBD 2019 Mental Disorder Collaborators, 2022). Children diagnosed with CD have a 3-fold increased risk for a premature death (Scott et al., 2017). CD is also associated with a range of adverse outcomes later in life, including substance use, criminality, poor physical health as well as lower educational attainment and erratic

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patterns of employment (Fergusson et al., 2005; Kim-Cohen et al., 2003).

The core characteristics of CD are epitomized by persistent antisocial behavior. It has therefore been argued that there is a specific diagnostic continuity from childhood to adulthood starting with CD and its predecessor, oppositional defiant disorder (ODD) to antisocial personality disorder (ASPD) (Moffitt, 1993; Moffitt et al., 2008). Alternatively, CD may be phenotypically and genotypically associated to a range of mental disorders. There is little evidence to clarify this from large population-based studies. Early evidence from smaller longitudinal population-based samples on association patterns of child to adult mental disorders indicates that a substantial proportion of adults with a mental disorder diagnosis had a history of CD/ODD in childhood with links both to homotypic (CD predicts ASPD) and heterotypic continuity (CD predicts different disorders) (Kim-Cohen et al., 2003; Rutter et al., 2006; Shevlin et al., 2017). This is not unexpected, given that CD is frequently comorbid with a broad spectrum of externalizing disorders including ODD, substance use disorders and ADHD (Krueger et al., 2005), as well as with internalizing disorders including depression and anxiety (Copeland et al., 2013). Particularly, children with CD have 10 times higher risk of comorbid ADHD (Angold et al., 1999), whereas up to 40% of children and adolescents diagnosed with ADHD have been shown to demonstrate disruptive behavior symptoms, including CD/ODD (Larson et al., 2011; Smalley et al., 2007).

Antisocial traits including disruptive and aggressive behavior, like the majority of complex human traits, have substantial genetic underpinnings (Waltes et al., 2016). Heritability estimates for conduct problems based on twin studies are 40–70% (Jaffee et al., 2005; Slutske et al., 1997). CD is thought to be polygenic, i.e., involving additive effects of multiple genetic variants and pleiotropic, i.e., characterized by large genetic overlap across different neuropsychiatric disorders, thus resembling the complex genetic architecture of the majority of mental disorders (Grotzinger et al., 2022). The clinical heterogeneity of CD is reflected in intricate comorbidity patterns with contribution of proximal and distal environmental factors (i.e., familial psychosocial influences, peer relationships). Specifically, low parental education has been associated with emotional and behavioral problems in children compared with children whose parents have higher education (Horoz et al., 2022). Further, children exposed to domestic violence as well as school-based adverse exposure such as bullying have been shown to have externalizing behavior problems later on in life (Fowler et al., 2009; Musci et al., 2019). These factors have been suggested to interplay with genetic susceptibility across development (Hyde et al., 2016).

Molecular genetic methods such as large-scale genome-wide association studies (GWAS) have been used to identify genetic variants conferring risk for antisocial behavior including symptoms of disruptive behavior in CD (Tielbeek et al., 2017). To date, a couple of GWAS meta-analyses have revealed novel associations for broad antisocial behavior (Tielbeek et al., 2022) as well as for CD in the context of ADHD (Demontis et al., 2021). Interestingly, one of these studies found significant genetic correlations between antisocial behavior and neuropsychiatric traits such as ADHD and depressive symptoms using Linkage disequilibrium score regression (Tielbeek et al., 2022). In general, the specificity of findings in relation to CD traits appears to be low, as many identified genes have been associated with a range of different neuropsychiatric and neurodevelopmental disorders, emphasizing the role of polygenicity and genetic pleiotropy (Andreassen et al., 2023). Indeed, one can assume that the genetic liability confers risk of behavioral and emotional dysregulation (related to e.g., aggression and disinhibition) rather than the specific diagnosis of CD (van Goozen et al., 2022). Further, calculation of polygenic risk scores (PRS) is an efficient and easy interpretable molecular genetic approach which facilitates identification of such polygenic influences across traits and diagnoses (Choi et al., 2020). For example, higher PRS for schizophrenia has been associated with increased symptoms of CD and oppositionality in 8 years old children (Hannigan et al., 2021). However, we lack a comprehensive overview of the extent of the putative genetic overlap between CD and childhood and adult-onset mental disorders. Moreover, genome-wide studies of gene – environment interplay in CD have been limited due to insufficient sample sizes with available data both on genetics and environmental exposures.

In the present study, we use data from the population-based Norwegian Mother, Father and Child Cohort Study (MoBa) (Magnus et al., 2016) to investigate comorbidity patterns, genetic and environmental risk factors for CD and disruptive behavior. Comorbidity patterns are investigated across a range of mental disorders based on International Classification of Diseases 10th revision (ICD-10) diagnoses from specialist health services. Genetic risk is assessed with PRS for broad antisocial behavior, child-onset as well as adult-onset mental disorders to estimate shared genetic lability to CD. Concurrently, we repeat the analyses with questionnaire data of disruptive behavioral problems in 5- and 8-years old children to investigate the genotypic association patterns for CD traits not reaching diagnostic threshold. Further, we examine interplay between common genetic and environmental risk factors for CD and disruptive behavioral traits with data on parental educational attainment as well as exposure to being bullied. Based on epidemiological results on externalizing disorders, we hypothesize to find high comorbidity between CD and ADHD that will be reflected in shared genetic liability for these two disorders. While the associations between CD and disruptive behavioral traits and PRS for major mental disorders are analyzed in an exploratory manner, we expect to find an additive effect of genetic and environmental risk factors such as low parental educational attainment and exposure to being bullied.

2. Methods

2.1. Study sample

MoBa is the largest population-based prospective pregnancy cohort study of mothers, fathers and children in the world conducted by the Norwegian Institute of Public Health (Magnus et al., 2016; Paltiel et al., 2014). Participants were drawn from hospitals and obstetric units in all parts of Norway between 1999 and 2008. The consent rate of pregnant women to participate in the study was 41%. There are currently 114 500 children, 95 200 mothers and 75 200 fathers in the cohort. The present analyses were based on version 12 of the quality-assured dataset released for research in 2019. The sample for the present study included all children in MoBa, i.e., $n = 114\ 500$ for phenotypic analyses, $n = 76\ 577$ for genetic analyses (including $n = 25\ 712$ for questionnaire data (two timepoints: age 5 and 8 years)). Participation flow chart can be found in Supplementary Fig. S1 in Supplementary materials. Data collection in MoBa was based on a license from the Norwegian Data Protection Agency and approval from the Regional Committee for Medical and Health Research Ethics (REK 2016/1226).

Details on processing of genetic data including quality control procedures comprising complex sampling are described in Supplementary Note 1 in Supplementary materials.

2.2. Phenotypic measures

2.2.1. Diagnostic outcomes

Information on CD diagnoses from the specialist health services were retrieved from the Norwegian Patient Registry (NPR) (ICD-10 code: F91, $n = 598$). All government owned and government financed clinics all over Norway are obliged to report to NPR. They cover a very large proportion of mental health care for young people in Norway. Nordic registries have been shown to have good validity for a range of psychiatric disorders, including both severe mental disorders (Nesvag et al., 2017) and personality disorders (Kouppis and Ekselius, 2020). For comorbidity analyses we used psychiatric diagnoses subsumed under the following categories: substance use disorders (F10–19), psychotic disorders (F20–29), mood disorders (F30–39), anxiety disorders (F40 and

F41), obsessive-compulsive disorder (F42), adjustment disorders (F43), eating disorders (F50), disorders of psychological development (F80), hyperkinetic disorders (F90), disorders of conduct and emotions (F92), emotional disorders with childhood-onset (F93), disorders of social functioning with childhood-onset (F94), tic disorders (F95).

2.2.2. Dimensional outcomes

Conduct problems in pre-school children (5-years old) were measured using maternal reports related to children's behavioral and emotional psychopathology (5 items) from the Child Behavior Checklist (CBCL) (Achenbach and Ruffle, 2000). CBCL is a widely used parent rating questionnaire, both in clinical and for research purposes. It has been shown to have satisfactory specificity (92%) and sensitivity (71%) (Achenbach and Ruffle, 2000). CBCL is operationalised on a Likert scale of 0 (not true), 1 (sometimes true) and 2 (often true). For school-age children (8-years old) we used maternal reports on oppositional defiant disorder (ODD, 8 items) and conduct disorder (CD, 8 items) from the Rating Scale for Disruptive Behavior Disorders (RS-DBD) (Silva et al., 2005). RS-DBD is a parent/teacher rating scale based on the DSM system and is operationalised on a scale from 0 (never present), 1 (sometimes present), 2 (often present) and 3 (very often present). The analyses were based on questionnaire data from 25 712 individuals with complete datasets.

2.2.3. Putative risk factors

Parents' educational attainment was measured as the highest level of attained education recorded for the parent with the highest education for every child, as part of the MoBa questionnaire from week 15 of gestation.

Maternal report on the child's exposure to bullying and physical abuse (collected at 8 years and measured on a Likert scale 1 (never) – to 5 (many times a week).

Details on questionnaire selection and data curation for phenotypic measures are described in Supplementary Note 2 in Supplementary information.

2.3. Polygenic risk scores

Calculation of PRS was performed with PRSice2 (Choi and O'Reilly, 2019) ($P_T = 5 \times 10^{-8}$, 10^{-6}, 10^{-5}, 10^{-4}, 10^{-3}, 0.01, 0.05, 0.1, 0.5, 1) from the most recent GWAS based on European samples including mental disorders: schizophrenia (SCZ) (Trubetskoy et al., 2022), bipolar disorder (BD) (Mullins et al., 2021), major depressive disorder (MDD) (Wray et al., 2018), attention deficit hyperactivity disorder (ADHD) (Demontis et al., 2021), autism spectrum disorder (ASD) (Grove et al., 2019) as well as broad antisocial behavior (ASB) (Tielbeek et al., 2022), and height (as somatic comparator) (Yengo et al., 2018). Subsequently, following the state-of-the-art approach described by Coombes et al., we extracted the first principal component PRS across all *p*-value thresholds for use in our models (Coombes et al., 2020).

2.4. Statistical analyses

2.4.1. Comorbidity patterns for conduct disorder

We calculated odds ratio for diagnostic comorbidity patterns between CD and the other mental disorders. The pattern of diagnostic comorbidities between CD diagnosis and a range of different mental disorders was visualized with an UpSet plot implemented in the upset R package (Lex et al., 2014).

2.4.2. Associations between PRS and conduct disorder and related traits

Separate univariate logistic regression models were used to test for the associations between each PRS (ADHD, ASD, SCZ, BD, MDD, ASB, height) and CD diagnosis, controlling for ancestry by 10 genome-wide principal components, as well as age and sex. Height was used as a somatic comparator.

The PRSs identified as significantly contributing to risk of CD in the univariate models were included as exposures in a multivariate logistic regression model with CD diagnosis as outcome. The explained variance (Nagelkerke pseudo-R^2) was calculated based on the results for each PRS and for the multivariate model. Pseudo-R^2 attributed to each model was calculated as the increase of pseudo-R^2 between a logistic model only with covariates and a model with the PRS(s) variable and covariates. The same procedure on calculation of Nagelkerke's pseudo-R^2 from logistic regression models has recently been applied by our group in another study based on the MoBa cohort (Jaholkowski et al., 2023).

The same analytic procedure was applied for the associations between subscales of CBCL and RS-DBD and each PRS. All CBCL and RS-DBD items were treated as binary variables and put in the analyses in the following order: 0 – not present versus 1 and 2 – present for the CBCL subscale and 0 – not present versus 1, 2 and 3 - present for the RS-DBD subscale. Additionally, the scales for antisocial behavior (5 items), conduct disorder (8 items) and oppositional defiant disorder (8 items) symptoms were subsumed and included as predictors in the linear regression models to check for the associations with PRSs for mental disorders.

2.4.3. Associations between environmental risk factors and conduct disorder and disruptive behavior

We investigated putative associations between two previously reported environmental risk factors for CD (Piotrowska et al., 2015; Singham et al., 2017) – low parental education and exposure to being bullied – and a diagnosis of CD as well as disruptive behavior. These analyses were performed with separate models for each environmental factor as well as combined in a logistic regression model.

2.4.4. Gene-environmental interplay for conduct disorder and related traits

We checked for additive associations with environmental factors by adding parental educational attainment and exposure to bullying and physical violence to the regression models described above. Putative gene-environment interaction was tested by adding an interaction term in the regression models. In order to investigate gene-environment correlations, we also tested for the association between each PRS and parental education as well as exposure to being bullied.

2.4.5. Sensitivity analyses

As CD has been shown to be comorbid with ADHD, we additionally conducted a supplementary analysis controlling for ADHD diagnosis for all the analyses including CD diagnosis as dependent variable.

All *p*-values were corrected for multiple testing using either Bonferroni correction (genetic associations with CD diagnosis) or Benjamini-Hochberg FDR-correction (genetic associations with CBCL and RS-DBD measures for separate questionnaire items).

3. Results

3.1. Comorbidity patterns of conduct disorder

In total, there were 598 children registered with a CD diagnosis (436 boys (72.9%), mean age 14.6 years) in the specialist health service, 0.5% of the present sample (n = 114 500). This percentage is in the lower range for any child behavioral disorders (1.62%; CI, 0.82 – 3.18) and falls within the range for conduct disorder diagnosis (0.24%; CI, 0.07–0.81), as previously shown in Norway (Boe et al., 2021). Thus, the present sample is representative and reflects the prevalence of CD in the Norwegian population. There was a complex pattern of diagnostic comorbidities between CD diagnosis and a range of different mental disorders, as visualized with an upset plot (Fig. 1). 64.1% of children diagnosed with CD were registered with a mental comorbidity (OR 15.1, $p<0.001$), 14.5% of children with CD had comorbidity with ADHD diagnosis (OR 14.54, $p<0.001$), followed by comorbidity with developmental disorders, as well as comorbidity with both ADHD and

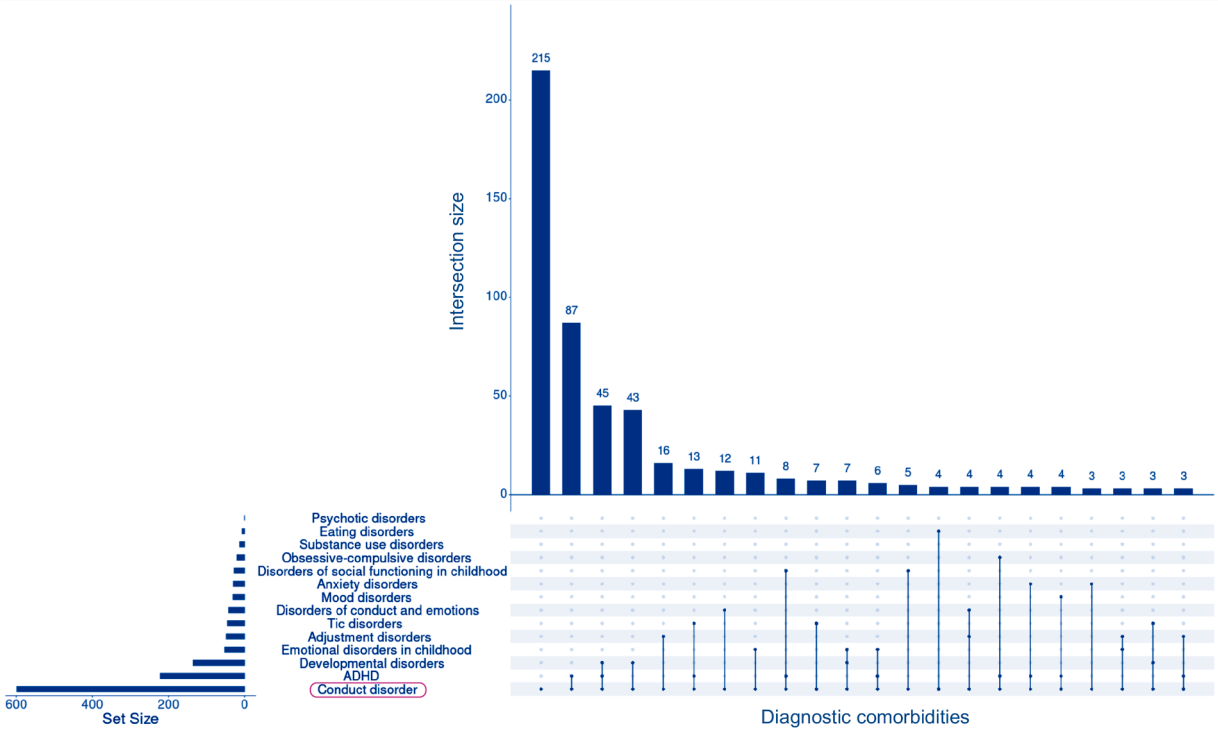

Fig. 1. Phenotypic comorbidity patterns between conduct disorder diagnosis and other ICD-10 based psychiatric diagnoses in MoBa. The linked dots from the reference diagnosis (conduct disorder marked in magenta) indicate the number of diagnostic comorbidities. The number of individuals with a given combination of comorbidities are specified above the bar plots. The size set to the left indicates the number of individuals with a given diagnostic category.

developmental disorders (see Supplementary Table 1 in Supplementary materials for a complete list). 35.9% (n = 215) of children diagnosed with CD had no mental comorbidities.

3.2. PRS associations for conduct disorder and disruptive behavioral traits

PRSs for a range of child- and adult-onset mental disorders were associated with both CD diagnosis and disruptive behavioral symptoms.

A diagnosis of CD (ICD-10-based) was significantly associated with PRS for ADHD (β = 0.25; 95% CI, 0.15 - 0.35; $p = 5.66 \times 10^{-7}$), MDD (β = 0.18; 95% CI, 0.08 - 0.28; p = 0.0002) and ASD (β = 0.13; 95% CI, 0.03 - 0.23; p = 0.006), Bonferroni corrected. We found no other significant associations between CD diagnosis and PRSs for other mental disorders, ASB or height (Fig. 2). Demographic information on the subsample used in the PRS associations for CD can be found in Supplementary materials (Supplementary Table 2).

Disruptive behavioral traits relating to antisocial behavior (AB),

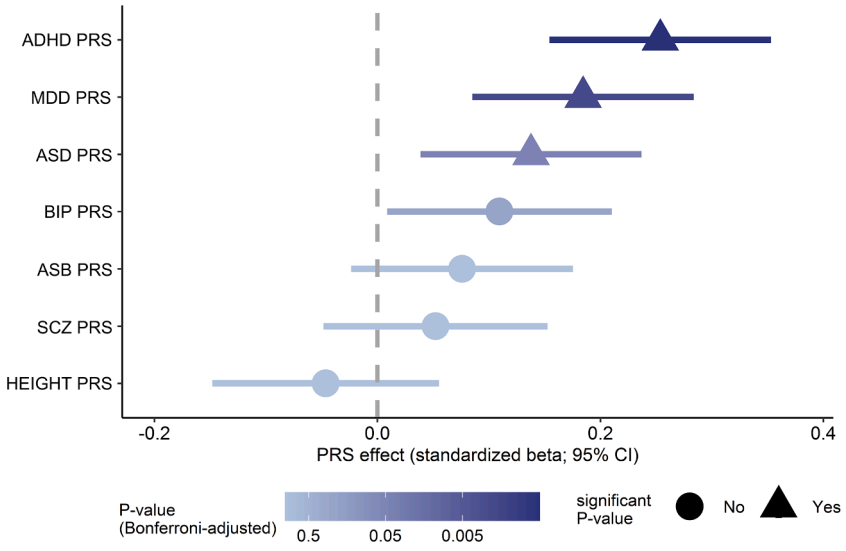

Fig. 2. Associations between conduct disorder diagnosis (ICD-10 based) from Norwegian Patient Registry and polygenic risk scores for a range of mental disorders. MDD major depressive disorder; ADHD attention deficit hyperactivity disorder; BIP bipolar disorder; ASD autism spectrum disorder; SCZ schizophrenia; ASB antisocial behaviour; PRS polygenic risk score. Error bars represent the 95% CI of the estimate value. The vertical line represents an effect estimate equal to zero. The logistic regression models included age, sex and the 10 first PCs as covariates. All p-values corrected with Bonferroni for multiple testing.

oppositional defiant disorder (ODD) and CD based on MoBa-questionnaires showed an overlapping pattern of genetic associations including PRSs for both child (ADHD, ASD) and adult-onset mental disorders (MDD, BIP, SCZ) (Fig. 3), with the most significant associations with PRS for ADHD (AB: $\beta = 0.1$; 95% CI, 0.08 – 0.12; $p = 2.0 \times 10^{-16}$; CD: $\beta = 0.1$; 95% CI, 0.08 – 0.11; $p = 2.0 \times 10^{-16}$; ODD: $\beta = 0.21$; 95% CI, 0.17 – 0.25; $p = 2.0 \times 10^{-16}$). See Supplementary Table 3 in Supplementary materials for summary statistics for all genetic associations.

The results for separate question items related to AB, ODD and CD can be found in the supplementary materials (Supplementary Fig. S2 in Supplementary materials).

A logistic regression model for CD diagnosis including PRSs for several mental disorders combined revealed significant associations for ADHD PRS ($\beta = 0.21$; 95% CI, 0.10 to 0.31; $p = 7.75 \times 10^{-5}$) and MDD PRS ($\beta = 0.13$; 95% CI, 0.03 to 0.24; $p = 0.0116$). We found no other associations between CD diagnosis and PRSs for other mental disorders, AB or height in the combined model (Fig. 4a). For the CD diagnosis, the combined PRS explained more variance (Nagelkerke $R^2 = 0.0077$) than individual PRSs for ADHD (Nagelkerke $R^2 = 0.0054$), MDD (Nagelkerke $R^2 = 0.0029$) or ASD (Nagelkerke $R^2 = 0.0016$) (Fig. 4b).

3.3. Associations between environmental risk factors and conduct disorder

We found significant associations between parental education and exposure to being bullied and CD when performing separate tests, but when including both environmental exposures to a multiple regression model, only exposure to bullying remained significant ($\beta = 1.98$; 95% CI, 1.38 to 2.57; $p = 5.89 \times 10^{-11}$) (Fig. 5).

3.4. Gene-environmental interplay for conduct disorder and disruptive behavioral symptoms

When including exposure to being bullied in the regression model only the association between PRS for ADHD and CD diagnosis remained significant, whereas after adding parental education, both PRSs for ADHD and MDD remained significant (Fig. 6). Contribution of exposure to being bullied for the association between CD and ADHD PRS was: $\beta = 1.97$; 95% CI, 1.38 to 2.57; $p = 6.70 \times 10^{-11}$. The respective results for parental education were ADHD ($\beta = -0.59$; 95% CI, −0.80 to −0.38; $p = 2.74 \times 10^{-8}$), MDD ($\beta = -0.61$; 95% CI, −0.81 to −0.40; $p = 8.34 \times 10^{-9}$). We observed the same pattern for the disruptive behavioral traits and PRSs for several mental disorders (Supplementary Fig. S3 in Supplementary materials shows results for questionnaire data on AB, CD, ODD and PRSs for mental disorders and parental education; and Supplementary Fig. S4 in Supplementary materials for CD and ODD and exposure to bullying). Thus, the current results are in accordance with an additive model between genetic liability and these environmental factors for risk of CD and related traits.

We found indications of gene-environment correlation between exposure to bullying and genetic lability for a range of mental disorders. Exposure to being bullying was associated with PRSs for both child and adult-onset mental disorders including ADHD PRS ($\beta = 0.11$; 95% CI, 0.08 to 0.14; $p = 2 \times 10^{-16}$), MDD PRS ($\beta = 0.10$; 95% CI, 0.08 to 0.13; $p = 9.05 \times 10^{-16}$), ASB PRS ($\beta = 0.07$; 95% CI, 0.04 to 0.09; $p = 6.50 \times 10^{-8}$), ASD PRS ($\beta = 0.05$; 95% CI, 0.03 to 0.08; $p = 5.78 \times 10^{-6}$), and BIP PRS ($\beta = 0.04$; 95% CI, 0.02 to 0.07; $p = 0.0003$) (Fig. 7).

There was no statistical interaction between parental education / exposure to bullying and PRSs for mental disorders / antisocial behavior for CD diagnosis and related symptoms (AB, CD and ODD traits).

3.5. Sensitivity analysis with ADHD diagnosis

When controlled for a diagnosis of ADHD only the association between the ADHD PRS and CD diagnosis remained significant among the PRSs for mental disorders (Supplementary Fig. S5 in Supplementary materials).

4. Discussion

In this large population-based cohort study of children, we explored comorbidity patterns, genetic and environmental risk factors for CD and CD related traits. The main results were a widespread pattern of associations between CD and child- and adult-onset mental disorders, as well as associations between genetic risk scores for child- and adult-onset

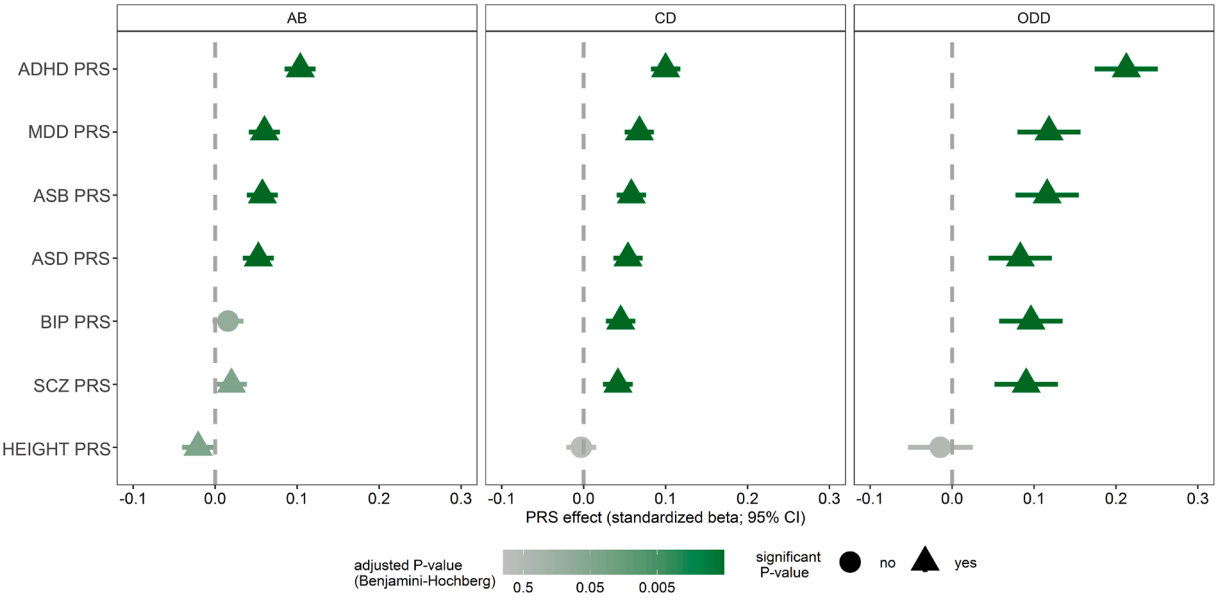

Fig. 3. Associations between antisocial behaviour (AB), conduct disorder traits (CD), oppositional defiant disorder traits (ODD) (based on MoBa questionnaires) and polygenic risk scores for a range of mental disorders. MDD major depressive disorder; ADHD attention deficit hyperactivity disorder; BIP bipolar disorder; ASD autism spectrum disorder; SCZ schizophrenia; ASB antisocial behaviour; PRS polygenic risk score. Error bars represent the 95% CI of the estimate value. The vertical line represents an effect estimate equal to zero. The logistic regression models included sex and the 10 first PCs as covariates. All *p*-values corrected with FDR for multiple testing.

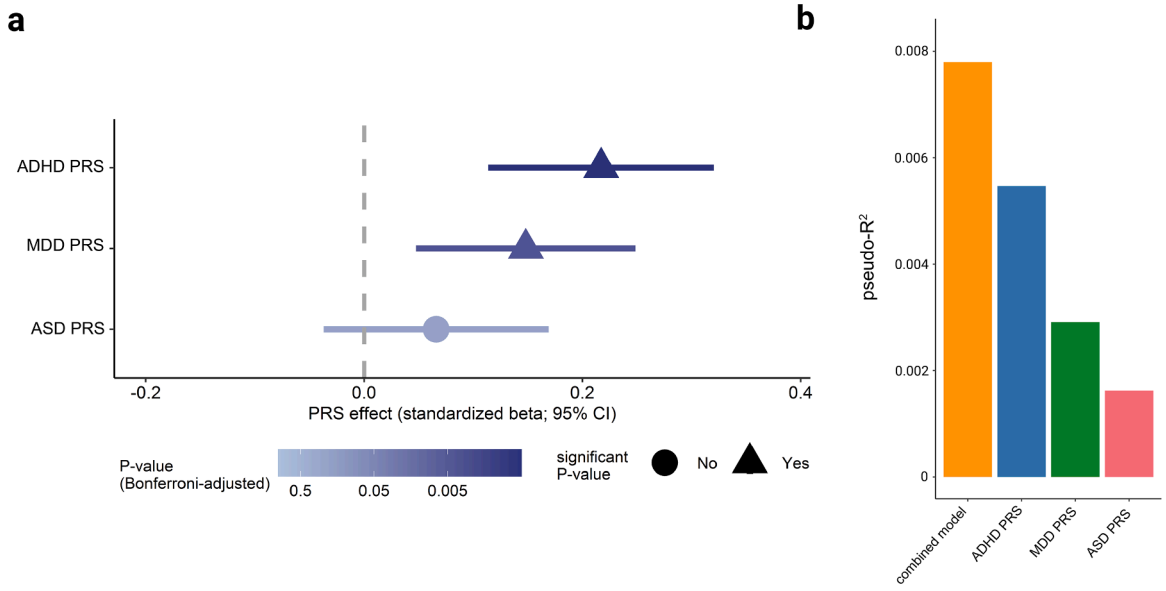

Fig. 4. **(a)** Multivariate logistic regression model for the associations between conduct disorder diagnosis and polygenic risk scores for a range of mental disorders. ADHD attention deficit hyperactivity disorder; MDD major depressive disorder; ASD autism spectrum disorder; PRS polygenic risk score. Error bars represent the 95% CI of the estimate value. The vertical line represents an effect estimate equal to zero. The logistic regression models included age, sex and the 10 first PCs as covariates. **(b)** Nagelkerke's pseudo-R^2 from logistic regression models for the associations between the CD diagnosis and PRSs for mental disorders.

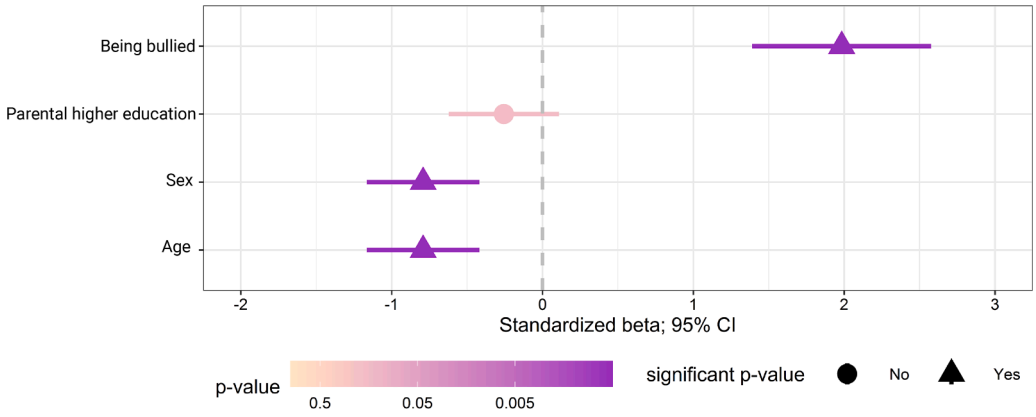

Fig. 5. Associations between exposure to bullying, parental education and conduct disorder diagnosis. The vertical line represents an effect estimate equal to zero. The logistic regression models included age and sex. All *p*-values corrected with Bonferroni for multiple testing.

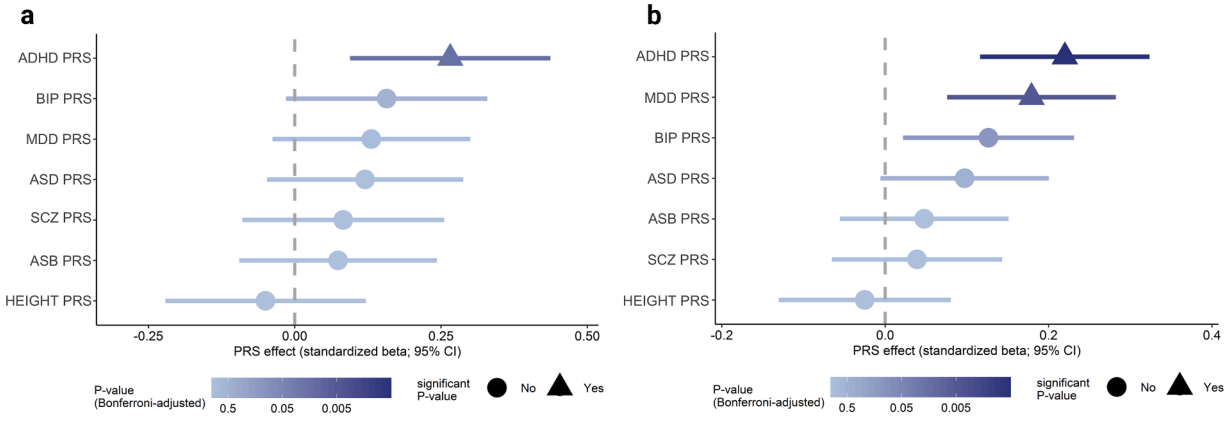

Fig. 6. Associations between conduct disorder diagnosis and polygenic risk scores for a range of mental disorders. The model was controlled for **(a)** exposure to bullying, **(b)** parental education. MDD major depressive disorder; ADHD attention deficit hyperactivity disorder; BIP bipolar disorder; ASD autism spectrum disorder; SCZ schizophrenia; ASB antisocial behaviour; PRS polygenic risk score. Error bars represent the 95% CI of the estimate value. The vertical line represents an effect estimate equal to zero. The logistic regression models included age, sex and the 10 first PCs as covariates. All *p*-values corrected with Bonferroni for multiple testing.

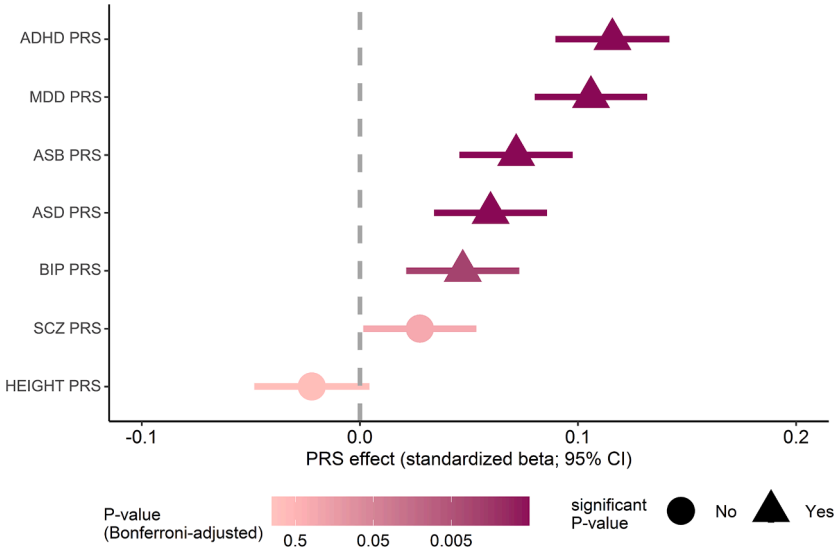

Fig. 7. Gene-environment associations between exposure to being bullied and polygenic risk scores for a range of mental disorders. MDD major depressive disorder; ADHD attention deficit hyperactivity disorder; BIP bipolar disorder; ASD autism spectrum disorder; SCZ schizophrenia; ASB antisocial behaviour; PRS polygenic risk score. Error bars represent the 95% CI of the estimate value. The vertical line represents an effect estimate equal to zero. The logistic regression models included age, sex and the 10 first PCs as covariates.

mental disorders and CD diagnosis/CD traits. Additionally, we found indications of gene-environment interplay between genetic risk of mental disorders, low parental educational attainment and exposure to being bullied. Our results are supportive of a heterotypic pattern of CD and related traits underpinned by overlapping genetic liability, and, while they are consistent with previous findings from smaller epidemiological and genetic studies, they contribute with several novel insights.

More specifically, on the clinical level, we found an intricate pattern of diagnostic comorbidities between CD diagnosis and several neuropsychiatric disorders, where ADHD was most prevalent. This is in line with recent findings, placing CD within the externalizing spectrum (Carragher et al., 2015; Krueger et al., 2005; Willner et al., 2016), as it frequently co-occurs with other emotional and behavioral disorders, in particular ADHD (Angold et al., 1999). This comorbidity pattern was largely reflected on the genetic level as we found significant associations between CD and genetic liability for ADHD as well as ASD, a disorder which is also characterized by difficulties in regulating emotion and behavior (Mazefsky et al., 2013). Additionally, a diagnosis of CD was associated with PRS for major depression. While conduct problems and depression are manifested by different symptoms, CD frequently co-occurs with internalizing disorders, particularly depression and anxiety (Copeland et al., 2013). Thus, these findings support that the comorbidity is partially driven by a shared genetic architecture. When controlled for a diagnosis of ADHD, only the association between ADHD PRS and CD diagnosis remained significant, indicating a true underlying shared genetic liability for CD and ADHD. Indeed, findings from a recent GWAS meta-analysis of disruptive behavioral disorders in relation to ADHD indicate an increased load of common genetic risk variants associated with aggressive behavior shared by both CD/ODD and ADHD (Demontis et al., 2021).

Further, our analyses on CD traits revealed a widespread pattern of genetic associations with the majority of investigated mental disorders characterized by different ages of onset, severity as well as clinical presentation. These results fit into a broader picture emerging from large-scale genomic studies which have revealed substantial genetic correlations among mental disorders (Brainstorm et al., 2018; Cross-Disorder Group of the Psychiatric Genomics, 2019; Smoller et al., 2019). Particularly, common genetic risk has been shown to correlate significantly among ADHD, bipolar disorder, schizophrenia and depressive disorder (Brainstorm et al., 2018). A recent GWAS meta-analysis across 8 major neuropsychiatric disorders found that 109 out of the total of 146 loci were linked to at least 2 disorders (Cross-Disorder Group of the Psychiatric Genomics, 2019). Taken together, this implicates that the genetic influences on psychopathological traits are highly pleiotropic and indicative for their largely interconnected nature transgressing the borders of diagnostic classification (Hindley et al., 2022). In accordance with this stance, our results on disruptive behavioral traits not reaching diagnostic threshold extend this line of evidence by revealing a broad genetic liability for different mental disorders in the general population. One possible explanation of such a broad genetic liability in our study can be underlying shared polygenic risk which is causally involved in the development of traits linked to abnormalities in emotion processing, a well-known common denominator of mental disorders (Sharma and McClellan, 2021). Interestingly, we found associations between both PRSs for externalizing (i.e., ADHD) and internalizing (i.e., major depression) disorders and disruptive behavioral traits. This is in line with previous work which found moderate genetic overlap between internalizing and externalizing high-order dimensions of psychopathology (Kendler et al., 2011).

Our findings could also be linked to the recently proposed hypothesis of the general genetic component of mental disorders succinctly conceptualized as a genetic *p factor* (Selzam et al., 2018). Still, the potential clinical relevance of such a broad representation of psychopathology is a matter of a debate (Fried et al., 2021). A nation-wide registry study from Sweden of nearly 3.5 million full and half-siblings demonstrated a shared general genetic factor of eight major mental disorders as well as convictions of violent crimes (Pettersson et al., 2016). Common genetic determinants of severe mental disorders and violent outcomes were also revealed by a study which utilized an overlapping sample of Swedish twins and siblings (Sariaslan et al., 2016). In our sample, we also found associations between PRS for broad antisocial behavior (ASB) and disruptive behavioral traits, thus confirming previously reported correlations between the genetic risk of antisociality and disruptive behavioral outcomes based on smaller samples. Importantly, we calculated PRS for broad antisocial behavior from the most recent and largest GWAS meta-analysis (n = 85 359) which identified the first significant associations for ASB (Tielbeek et al., 2022), making our study one of the first to replicate their findings in an independent large sample. Yet, contrary to Tielbeek et al. (Tielbeek et al., 2022) who found PRS for ASB to be more strongly correlated with

severe manifestations of antisocial outcomes, in our study these associations were present for conduct disorder traits not reaching diagnostic threshold and not for the CD diagnosis.

Summarizing our results on the disruptive behavioral traits from a developmental perspective, we found a widespread pattern of genetic associations for child-, adult-onset mental disorders as well as ASB which were present in pre-school children (5 years old). This pattern was even more widespread (i.e., including PRS for schizophrenia and bipolar disorder) for middle childhood (8 years old). These findings indicate a developmentally stable broad genetic influence on childhood psychopathology related to the CD phenotype and implicate an increased general genetic vulnerability conferring risk for a plethora of traits and behaviors implicated in impulsivity, impaired self-regulation or dysfunctional emotional processing present early in life course.

This broad risk for CD traits conferred by genetic factors is further modified by the social environment. Indeed, current research on antisocial behavior and related traits converges on the stance that environmental and psychosocial risk factors interplay with the genetic underpinnings across development (Kretschmer et al., 2022; Shewark et al., 2021; Waltes et al., 2016). This is supported by the current associations between low parental education as well as exposure to being bullied and a diagnosis of CD. When incorporated in the genetic association analyses for CD and CD traits, both these environmental factors influenced the models, thus they may imply an additive effect with genetic liability. These findings are in line with previous research on gene-environment interplay in broad antisocial behavior, including studies of CD using behavioral genetics approaches interrogating family and peer factors in twins and adoptees (Hyde et al., 2016; Kendler et al., 2008). However, this is the first study to demonstrate these effects on a large population-based sample with genetic informative data using polygenic risk scores on several mental disorders as well as broad antisocial behavior. Additionally, we found a gene-environment correlation between exposure to being bullied and genetic vulnerability for all investigated mental disorders and antisocial behavior. These results corroborate and extend findings from a UK-based population cohort study which identified exposure to bullying in childhood and adolescence to be associated with genetic risk for mental health vulnerabilities (depression and ADHD) as well as risk taking (Schoeler et al., 2019). While our findings further support the hypothesis of an important role of underlying genetic susceptibility for the association between exposure to being bullied and broad psychiatric vulnerability (Singham et al., 2017), they can reflect involvement of different pathways leading to adverse outcomes. For example, genetic susceptibility for a given mental disorder (e.g., ADHD, depression, antisocial behavior, autism spectrum disorder or bipolar disorder) can heighten the risk of the respective symptoms and thus indirectly increase vulnerability for adverse outcomes such as bullying. Keeping in mind that exposure to bullying is heritable (Ball et al., 2008) and that our environment is partly shaped by our genes, one possible mechanism is an active gene-environment correlation, i.e., children's genes predispose them to search for particular environments (van Goozen et al., 2022). Here, genetic predisposition to e.g., antisocial behavior can lead the child seeking out delinquent groups and deviant peers ("niche-picking"). This process is even more clearly demonstrated as an evocative gene-environment correlation (Veldkamp et al., 2019) where the child's genetically influenced traits (e.g., antisocial behavior) evoke a certain response from the environment (e.g., bullying). Furthermore, our findings on the association between genetic risk for antisocial behavior and exposure to being bullied corroborate the genetic underpinnings of the cycle of violence hypothesis, i.e., being exposed to early violence make individuals more prone to be violent later in life (Wright and Fagan, 2013).

There are some limitations in our study. First, the MoBa sample, bearing resemblance to other prospective cohort studies is influenced by selection effects, including selective attrition of individuals with poorer somatic and mental health over time. This can potentially explain why the prevalence of CD diagnosis was at a lower range (i.e., 0.5%) compared with the previously reported worldwide prevalence at approximately 2.5% (Polanczyk et al., 2015). Second, the MoBa children have not reached adulthood yet, thus we do not know how the genetic risk patterns will correspond with actual prevalence of mental disorder diagnoses in this cohort. Third, as both the effect sizes for PRSs of mental disorders on CD traits as well as variance explained by the PRSs (Nagelkerke's pseudo-R^2) are relatively small, these findings have limited utility in a clinical setting, as they are not applicable on an individual level. Further, "exposure to being bullied" variables were based on maternal reports and measured only at age 8 years; thus, we cannot exclude the possibility of bias as we did not have data on self-reported measures or any other collateral measure of similar variables related to peer environment.

To conclude, our findings implicate a widespread comorbidity pattern for CD encompassing major mental disorders with corresponding associations at genetic level. This genetic vulnerability interplays with environmental factors, particularly exposure to being bullied. An in-depth understanding of these comorbidity and gene-environment interplay patterns in relation to disruptive behavioral problems in children is of importance for prevention as well as early treatment with potential implications for youth justice and educational systems in a long-term perspective.

Data statement

Data from the Norwegian Mother, Father and Child Cohort Study and the Medical Birth Registry of Norway used in this study are managed by the national health register holders in Norway (Norwegian Institute of public health) and can be made available to researchers, provided approval from the Regional Committees for Medical and Health Research Ethics (REC), compliance with the EU General Data Protection Regulation (GDPR) and approval from the data owners. The consent given by the participants does not open for storage of data on an individual level in repositories or journals. Researchers who want access to data sets for replication should apply through helsedata.no. Access to data sets requires approval from The Regional Committee for Medical and Health Research Ethics in Norway and an agreement with MoBa.

CRediT authorship contribution statement

Natalia Tesli: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Piotr Jaholkowski:** Conceptualization, Data curation, Formal analysis. **Unn K Haukvik:** Writing – review & editing. **Andreas Jangmo:** Data curation, Formal analysis. **Marit Haram:** Writing – review & editing. **Jaroslav Rokicki:** Writing – review & editing. **Christine Friestad:** Writing – review & editing. **Jorim J Tielbeek:** Methodology, Writing – review & editing. **Øyvind Næss:** Writing – review & editing. **Torbjørn Skardhamar:** Writing – review & editing. **Kristin Gustavson:** Writing – review & editing. **Helga Ask:** Writing – review & editing. **Seena Fazel:** Methodology, Writing – review & editing. **Martin Tesli:** Conceptualization, Data curation, Supervision. **Ole A Andreassen:** Funding acquisition, Project administration, Supervision.

Declaration of Competing Interest

O.A.Andreassen is a consultant to HealthLytix and received speaker's honorarium from Lundbeck, Sunovion and Janssen. No other disclosures were reported.

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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.2023.115628.

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