# Conduct disorder

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Abstract | Conduct disorder (CD) is a common and highly impairing psychiatric disorder that usually emerges in childhood or adolescence and is characterized by severe antisocial and aggressive behaviour. It frequently co-occurs with attention-deficit/hyperactivity disorder (ADHD) and often leads to antisocial personality disorder in adulthood. CD affects ~3% of school-aged children and is twice as prevalent in males than in females. This disorder can be subtyped according to age at onset (childhood-onset versus adolescent-onset) and the presence or absence of callous-unemotional traits (deficits in empathy and guilt). The aetiology of CD is complex, with contributions of both genetic and environmental risk factors and different forms of interplay among the two (gene–environment interaction and correlation). In addition, CD is associated with neurocognitive impairments; smaller grey matter volume in limbic regions such as the amygdala, insula and orbitofrontal cortex, and functional abnormalities in overlapping brain circuits responsible for emotion processing, emotion regulation and reinforcement-based decision-making have been reported. Lower hypothalamic–pituitary–adrenal axis and autonomic reactivity to stress has also been reported. Management of CD primarily involves parent-based or family-based psychosocial interventions, although stimulants and atypical antipsychotics are sometimes used, especially in individuals with comorbid ADHD.

Conduct disorder (CD) often emerges in childhood or adolescence and is characterized by behaviours that violate the rights of others, such as physical aggression towards people or animals, theft, property damage and rule violations[1]. The prevalence of CD is ~3% in school-aged children and it is a leading cause of referral to mental health services[1,2], but it is paradoxically one of the least widely recognized and studied psychiatric disorders (see Supplementary Fig. 1 for publication trends in CD relative to other common disorders).

CD is associated with an exceptionally high societal and economic burden, accounting for ~1% of all years lived with disability and surpassing autism spectrum disorders and attention-deficit/hyperactivity disorder (ADHD) in this measure of global health burden[3]. Moreover, up to 60% of adults who developed a mental disorder had CD or its frequent developmental precursor, oppositional defiant disorder (ODD), earlier in life[4]. CD is not an episodic disorder like depression, with clear onset and offset phases, but more closely resembles a personality disorder. Although ~50% of individuals show desistance or remission of symptoms[5], others have chronic symptoms and develop personality disorders and criminal behaviours in adulthood.

A major criticism of the diagnostic criteria for CD is that they are entirely based on behavioural symptoms and are, therefore, uninformative about the underlying cognitive or emotional processes that drive these symptoms[6]. CD is also a highly heterogeneous disorder: >32,000 different symptom profiles could potentially lead to a CD diagnosis[7] and different symptom clusters have different developmental trajectories and aetiologies (particularly aggressive versus non-aggressive symptoms[8,9]). The diagnostic criteria include subtypes based on the age of onset of symptoms (childhood-onset CD versus adolescent-onset CD) and the presence or absence of limited prosocial emotions (LPEs). The symptoms defining LPEs, which include deficits in empathy, have been labelled the affective dimension of psychopathy[10] or callous-unemotional (CU) traits[11] in research.

Whether CD should be considered as a dimensional or a categorical construct is debated. Despite support for the former approach from some research, concerns remain about the clinical utility of the dimensional approach; thus, in this Primer, we focus on CD as a category (in keeping with the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; DSM-5). In addition, research suggests that CD forms part of a broader externalizing spectrum along with antisocial personality disorder, ODD, substance use disorder and ADHD[12–14] and that the genetic liability confers risk of externalizing disorders, impulsivity and disinhibition in general, rather than CD specifically[15–17]. This aetiological overlap between externalizing disorders has major

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implications for CD research because it makes it challenging to disentangle causal factors and pathophysiological mechanisms that are specific for CD relative to other externalizing spectrum disorders. In parallel with these developments, either for scientific or pragmatic reasons, many studies have either grouped individuals with different externalizing disorders together (particularly CD and ODD but also CD and ADHD) and/or have investigated externalizing symptoms as a dimensional construct in high-risk or clinical samples. These limitations should be considered when interpreting research findings on CD but also represent opportunities for future research — not only disentangling CD from common comorbid disorders but also explicitly contrasting dimensional and categorical approaches to CD and, if the former is strongly supported, enhancing the clinical utility of the dimensional approach.

In this Primer, we provide an overview of diagnostic approaches, review evidence regarding the aetiology and pathophysiology of CD and consider effective interventions and prevention programmes. We also consider the prevalence of CD and its impact on physical and mental health, and on social, educational and occupational outcomes. Finally, we highlight key challenges and gaps in current knowledge.

## Epidemiology

### *Prevalence*

The worldwide prevalence of CD is estimated to be 2–2.5%, with a prevalence of 3–4% in boys and 1–2% in girls[18]. Although these estimates suggest that CD is relatively uncommon at any given time, retrospective studies of lifetime prevalence and prospective studies of cumulative prevalence have suggested that ~10% of individuals are affected at some point during childhood and adolescence[19]. Whether the prevalence of CD has changed over time is debated. Some studies have suggested an increase in the prevalence of CD over recent decades[20,21], whereas others have suggested minimal changes in prevalence over this period[22]. CD is approximately twice as common in males as in females[23,24], and this finding has been observed across geographical regions[7,22]. Representative studies carried out in the United States did not report differences in prevalence between ethnic groups, with any apparent differences accounted for by socio-economic status disparities between such groups[25,26]. The typical age at onset of CD is during middle childhood or early adolescence[7,27], and, despite major cultural differences in what is considered acceptable childhood behaviour, there is little evidence suggesting that the prevalence of CD differs between countries[18,22]. Nevertheless, similar to other psychiatric disorders, the prevalence of CD has been estimated in only 5% of countries globally, of which data are available from 35.6% of high-income countries but only 1.6% of low-income or middle-income countries, and no countries in sub-Saharan Africa or Latin America[28].

Studies estimating the prevalence of CD typically focus on children between 5 and 18 years of age, despite evidence that CD can be reliably diagnosed in children <5 years of age[29]. The reluctance to diagnose CD earlier in life might be related to concerns regarding diagnostic stigma, the lack of developmentally appropriate diagnostic criteria, the high rates of aggressive behaviour that are typically observed in early childhood and the hope that most children <5 years of age with CD will receive help by also meeting the diagnostic criteria for ODD[30,31]. Studies of CD in children <5 years of age have generally yielded similar or slightly higher prevalence figures (up to 5%) than the prevalence observed in older individuals, with less evidence of sex differences[32]. CD is rarely studied in adults, with available studies suggesting a prevalence of ~1.0% in this population[7]; however, this comparatively lower prevalence might reflect the fact that some CD diagnostic criteria are not relevant for adults (for example, truancy from school) and rely on self-reported antisocial behaviour.

Whether the prevalence of CD increases from childhood to adolescence is disputed[33]; however, stronger evidence supports the age-related changes in symptoms. Indeed, aggressive behaviours decline in frequency with increasing age, whereas non-aggressive symptoms, particularly status offences, increase across adolescence[33,34]. Thus, although the prevalence of CD may be relatively stable, the specific symptom configurations that qualify children for a diagnosis change over time.

Although several subtypes of CD have been described (see Diagnosis, screening and prevention, below), epidemiological studies rarely report the prevalence of individual subtypes, and such studies do not apply strict DSM or International Classification of Diseases (ICD) diagnostic criteria, as precise estimates of subtype prevalence require samples much larger than those that are typically available for psychiatric epidemiology. Furthermore, as the main subtyping approach relates to age at onset, prevalence estimates derived from one-off cross-sectional assessments would be unreliable[35,36]. As such, whether adolescent-onset or childhood-onset CD is more common is unclear, although girls are over-represented in the adolescent-onset CD subgroup[27,37]. Few studies have estimated the prevalence of CD with CU traits, although it seems that 60–70% of children with CD do not have these traits[38].

### *Comorbidities*

Similar to many other childhood disorders, co-occurrence of CD with other emotional and behavioural problems is very common[39]. Indeed, children with CD have a

Box 1 | **Continuity between CD, ODD and antisocial personality disorder**

An enduring question about conduct disorder (CD) has been the life-course continuity from oppositional defiant disorder (ODD) to CD and from CD to adult antisocial personality disorder[30]. Although ODD typically has its onset before CD[43,44], many children with ODD never meet full criteria for later CD; similarly, many children with CD are not diagnosed with ODD[43,224,298]. Although CD is a strong risk factor for antisocial personality disorder, >50% of children with CD do not develop this disorder[299]. Furthermore, studies of diagnostic continuity from childhood to adulthood have identified CD as a common precursor of a range of adult behavioural and emotional disorders[4], suggestive of 'heterotypic' as well as 'homotypic' continuity.

15-fold higher risk of meeting criteria for ODD[40] (BOX 1), which is characterized by temper outbursts, defiant behaviours and irritability. Until DSM-5 was developed, ODD was precluded as a co-occurring diagnosis in individuals with CD[41,42], and early studies suggested that ODD was a precursor for CD, although more recent evidence suggests that transitions between these disorders are less common than previously thought[43]. Children with CD also have a 10-fold higher risk of ADHD than those without CD[39], making it challenging to clarify which impairments and outcomes are attributable to each disorder. Children with CD and comorbid ADHD have an earlier age of onset, more severe symptoms and a more persistent course than children with CD without ADHD, and they might also have higher rates of reading and intellectual disabilities[44–46]. In adolescence, CD is frequently associated with substance misuse[47]. Indeed, precocious substance use has been considered as a possible diagnostic criterion for CD[30]. In addition to externalizing disorders, CD frequently co-occurs with major depressive disorder, particularly in girls[39], although the temporal ordering of this association is unclear[47]. CD is also associated with anxiety disorders[39], although this finding might be better explained by the frequent comorbidity of CD and depression, and of depression with anxiety, than a direct association between CD and anxiety[40].

## Mechanisms/pathophysiology

### *Environmental risk factors*

Twin studies have demonstrated that ~50% of the variance in CD is attributable to environmental influences, of which prenatal, perinatal, familial and neighbourhood risk factors are thought to have a role[48,49] (FIG. 1). Of the prenatal risk factors, maternal smoking[50], alcohol use[51], drug use[52] and stress during pregnancy[53,54] are the best documented. Emerging evidence suggests that the effects of maternal stress during pregnancy on the development of the prefrontal cortex of the offspring might mediate the association of stress with CD symptoms[54]. In addition, maternal anxiety during the last trimester of pregnancy is associated with childhood-onset conduct problems that persist from childhood into adolescence in their offspring[55]. The effects of maternal prenatal stress and anxiety on the development of conduct problems seem to be unrelated to genetic factors or postnatal depression[56,57]. Moderate alcohol consumption (1–6 units per week) during pregnancy increased the risk of childhood-onset conduct problems, but not childhood-limited or adolescent-onset conduct problems, in children who were genetically vulnerable to the detrimental effects of alcohol[58].

Perinatal risk factors for CD include obstetric complications[59,60], parental psychopathology[61], malnutrition[62] and exposure to heavy metals[58]. Birth complications combined with early-life maternal rejection were linked to an increased risk of early-onset serious violence[60,63]. Birth complications are thought to compromise brain development, leading to dysfunction later in life; in particular, hypoxia disrupts subcortical structures and white matter tracts[64] that are associated with CD and might link birth complications with risk of CD. Consistent with this view, low IQ seems to mediate the association between birth complications and CD[65]. Similarly, malnutrition can lead to neurocognitive impairments through neuronal loss, changes in neurotransmitter function and neurotoxicity, which might increase the risk of CD[66]. Consistent with this hypothesis, frequent hunger during childhood is associated with greater impulsivity, poorer self-control and increased violence in adulthood, particularly in males[67]. Earlier studies in high-risk or clinical samples of children also suggested an association between exposure to heavy metals (such as lead) and CD[68], but other findings from a population-representative cohort controlling for low socio-economic status did not support this association[69].

As outlined in the next section, CD is one of the few psychiatric disorders for which there is evidence for substantial family environmental (or shared environmental) influences, as well as non-shared environmental influences[70]. Of the childhood and adolescence risk factors identified, maladaptive parenting, including harsh, coercive (for example, corporal punishment, shouting, swearing and threatening) and inconsistent discipline, and parent–child conflict are well-established and robust risk factors for conduct problems and CD in general[49,71] but also for childhood-onset conduct problems or CD[72] and CD with CU traits[73] in particular. Parental maltreatment is an important risk factor for CD[74,75], especially in children at high genetic risk (such as those with first-degree relatives with antisocial behaviour[76]). The strength of the association between maltreatment and CD is similar for males and females[77]. This association is highly relevant given that effective prevention and intervention strategies for CD mainly focus on parenting and family factors (see Prevention, below).

Other environmental risk factors include deviant peers, low socio-economic status, poverty and community violence. Data from birth cohort, epidemiological and genetically informative studies suggest that the association between deviant peers and CD reflects both social selection and social causation[49,78]. In addition, recent evidence indicates that some involvement with deviant peers during adolescence is normative[79] and effective parenting can buffer these effects[80]. A small, but significant association between low socio-economic status and conduct problems, which was independent of sex, has been reported in one meta-analysis, with a stronger association between low socio-economic status and CU traits[81]. Low socio-economic status was associated with a 3.5-fold increased risk of life-course-persistent CD compared with adolescence-limited CD in a

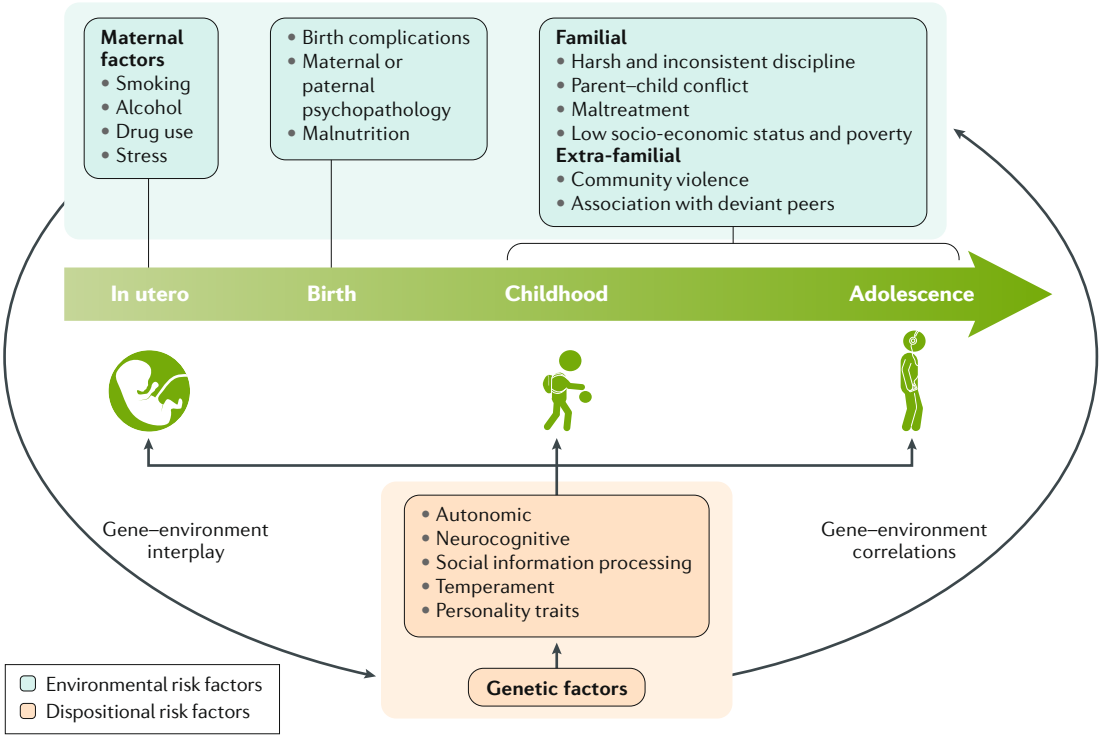


Fig. 1 | **Environmental and dispositional risk factors for CD.** Environmental and dispositional risk factors for conduct disorder (CD) and conduct problems operate at different stages in the lifespan. The importance of these risk factors varies depending on the developmental stage. For example, harsh and inconsistent discipline is more likely to be important in influencing risk during childhood whereas associating with deviant peers is more likely to be important during adolescence[80]. Along similar lines, temperamental factors in infancy may increase the risk of later CD whereas personality traits in childhood or adolescence may confer an increased risk of CD. Genetic factors exert their effects across all developmental stages. Furthermore, some risk factors might be more important for certain subtypes of CD; for example, genetic factors are thought to have a more important role in the development of antisocial behaviour in youths with CD and callous-unemotional (CU) traits, with minimal effects of shared environmental influences, whereas genetic and shared environmental influences are equally important in youths with CD without CU traits[93]. Some of these effects of environmental risk factors may be mediated through epigenetic alterations to produce the phenotype of CD, which is characterized by alterations on a molecular level, on a brain network level and on a behavioural level.

recent epidemiological study[72]. In addition, an association between community violence and CD has been demonstrated[82], with stressful life events, peer and parent–child conflict and maternal stress identified as key mediating factors and sex and race as moderating variables[83].

Although many environmental risk factors have been identified for CD, these factors are not specific for CD[49,84], and elucidating whether these are true causal risk factors or mere associations and identifying the mechanisms through which they operate is challenging owing to confounding variables, reverse causation, social selection or drift and misidentification.

### *Heritability*

Several studies have investigated the role of genetics in CD (see REF.[85] for a review). Reported heritability estimates were between 5% and 74%[86] in twin studies comprising 1,400–17,000 individuals using DSM-IIIR-based and DSM-IV-based symptom assessments, with the most comprehensive studies reporting estimates of 40–50%[76]. Importantly, a multivariate twin study identified two separate genetic factors that contribute to CD, one of which relates to rule breaking and the other to overt aggression[70], suggesting that CD is not a unified construct in terms of its genetic architecture. Heritability estimates for conduct problems are higher in males than in females[14,87], but the implicated genetic factors seem to largely overlap[88]. The genetic contribution to CD increases from childhood to adolescence[86,89]; however, the genetic contribution is not stable over time, suggesting that partly different genes contribute to CD at different stages of the lifespan[86,90].

No heritability estimates are available for the DSM-defined CD subtypes regarding age at onset or severity. Although several cohort studies have assessed conduct problems repeatedly across childhood and adolescence, these studies concentrated on longitudinal changes over time rather than comparing childhood-onset and adolescent-onset CD subtypes. However, twin studies have demonstrated partly distinct genetic influences on severity-related conduct problems, with a higher heritability reported for aggressive behaviours than for non-aggressive behaviours[88,91]. The heritability of CD with CU traits has been estimated at 45–67%, which is higher than for CD alone[92,93]. One study used an approach based on genotypes of single-nucleotide polymorphisms (SNPs) to estimate heritability and demonstrated

a negligible heritability due to SNPs in a sample of almost 3,000 individuals, which had a heritability of 64% for CU traits from twin studies[94]. This finding was likely due to the limited sample size.

Going forward, it will be important to take into account that CD is likely not a unified construct in terms of its genetic architecture. Thus, dimensional approaches might be better suited than categorical approaches to investigate the heritability of CD and its underlying mechanisms. Given the limited specificity of genetic liability to different psychiatric disorders[95], and the extensive comorbidity observed in individuals with CD, which is often not sufficiently accounted for in genetic studies, disentangling genetic contributions and identifying genetic factors that are specific for CD will be challenging. Dimensions, and perhaps also latent constructs derived on the basis of broadly assessed externalizing behaviours[17], might prove more suitable than categories for this purpose.

### *Molecular genetics*

Heritability studies suggest that the genetic architecture of CD in most individuals involves additive effects of many genetic variants, each with small effect sizes. Indeed, CD, like most mental disorders, is thought to have a complex, multifactorial aetiology that is characterized by polygenic inheritance and genetic heterogeneity across individuals, supplemented by the effects of environmental factors that may interplay with genetic factors at any point during development (FIGS 1,2).

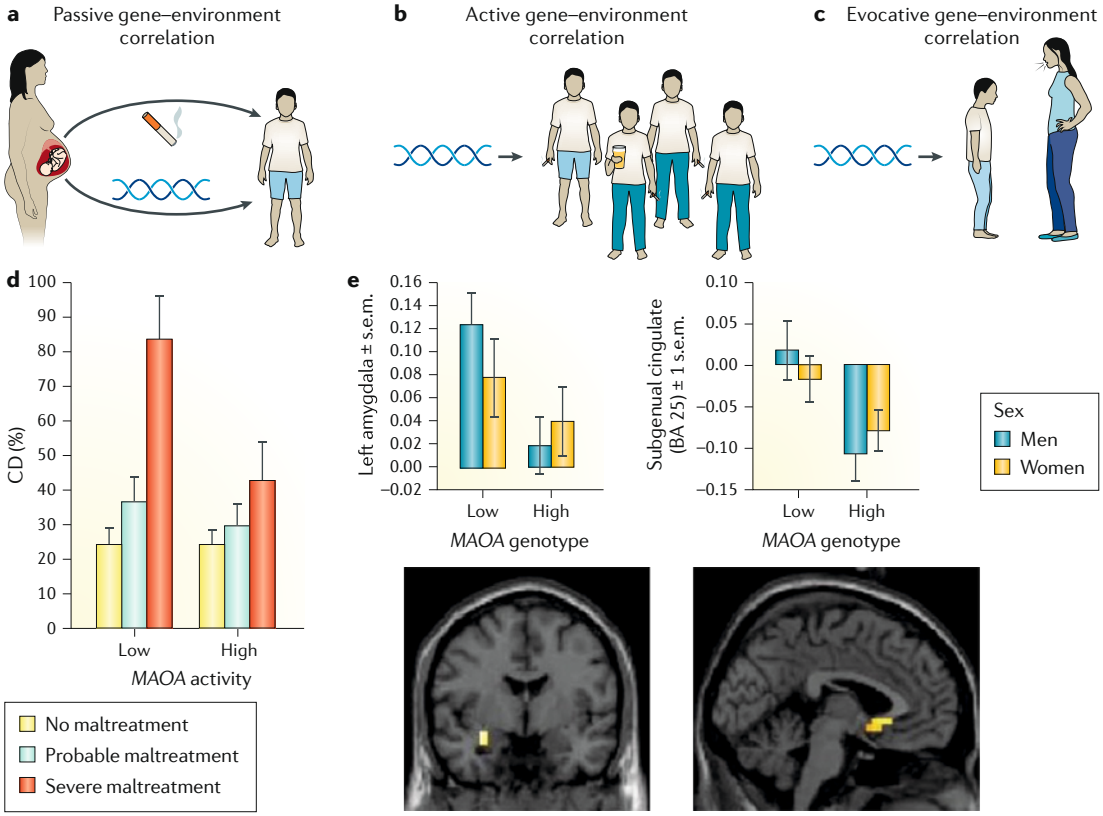


Fig. 2 | **Genetic influences on CD. a** | Passive gene–environment correlation occurs when children inherit genetic variants that also contribute to the environment that the parents create[316]. Examples of this form of correlation include genes that increase the risk of psychopathology and increase the probability that the parent will maltreat their child. Parents may transmit to their child a genetic liability for conduct disorder (CD) and provide an abusive rearing environment reflecting the parents' genetic liability. **b** | Active gene–environment correlation occurs when the child's genes predispose them to seek out certain environments; for example, they choose to associate with antisocial peers and/or seek out highly stimulating but dangerous environments. Owing to the effect of the child's genes on their friendship choices or 'niche-picking', their risk of developing CD is increased. **c** | Evocative gene–environment correlations occur when the child's genes predispose them to behave in a way that evokes certain environmental influences. Owing to the negative treatment that the child's behaviour evokes from parents and other authority figures (such as coercive or harsh punishment), their risk of developing CD is increased. **d** | Gene–environment interaction (G×E) studies investigate whether genes moderate the effects of positive or negative environmental influences. One of the most consistent findings in the CD literature is that *MAOA* (encoding the monoamine oxidase A enzyme) moderates the effect of childhood maltreatment on risk of CD[317]; males carrying the low-activity variant of *MAOA* are more susceptible to the deleterious effects of maltreatment[128]. **e** | One explanation for this increased susceptibility is that low-activity *MAOA* carriers are more reactive to emotional stimuli and less capable of regulating their emotions, as evidenced by increased amygdala and reduced subgenual anterior cingulate responses to emotional stimuli[318]. This may increase the risk of reactive aggression and is particularly problematic if the individual grows up in a hostile environment or is physically abused. BA, Brodmann's Area. Panel **d** adapted with permission from REF.[128], AAAS. Panel **e** adapted with permission from REF.[318], Proceedings of the National Academy of Sciences of the United States of America.

Early studies used candidate-gene-based approaches and often had very small sample sizes, making them frequently underpowered, non-representative and challenging to replicate[96]. Candidate genes were mainly related to serotonergic and dopaminergic neurotransmission (such as genes encoding the sodium-dependent serotonin transporter (*SLC6A4*), the catechol-*O*-methyltransferase enzyme (*COMT*), the monoamine oxidase A enzyme (*MAOA*) and the sodium-dependent dopamine transporter (*SLC6A3*))[85]. Genes encoding the oxytocin receptor (*OXTR*) and the vasopressin V1a receptor (*AVPR1A*)[97] have also been associated with CD-related behavioural constructs such as aggression, antisocial behaviour, behavioural disinhibition and/or delinquency, suggesting that multiple overlapping phenotypes are influenced by the same genes (pleiotropy). *RBFOX1* (encoding an important regulator of neurodevelopmental processes) has recently been implicated in CD-related behaviours across diverse studies[98].

More recent genome-wide association studies (GWAS) attempted to identify genetic variants involved in CD and conduct problems using unbiased, data-driven approaches. The first GWAS of CD was performed in a family-based study of children with ADHD and did not yield any genome-wide significant findings, which might be expected owing to the small number of participants ($n = 938$)[99]. The second GWAS included 3,963 individuals and demonstrated significant associations between *C1QTNF7* (linked to glucose metabolism and insulin signalling) and conduct problems[100], although replication of this finding is pending. Other GWAS have been performed for related constructs in children and adolescents, such as behavioural disinhibition[101,102], psychopathic traits[103], Child Behavior Checklist (CBCL) dysregulation[104], ODD[105] and aggression[106]. In adults, antisocial personality disorder[107], extreme violence[108], hostility[109], proneness to anger[110] and antisocial behaviour[111] have been studied. Collectively, these studies had small sample sizes and most did not yield genome-wide significant findings, with those that did still requiring independent replication. Combining data from individual GWAS in meta-analyses has provided further information regarding the genetic architecture of CD-related behaviour. Indeed, one such meta-analysis demonstrated an association between *AVPR1A* and aggressive behaviour in a large, population-based child sample[112]. A second large meta-analysis found no genome-wide significant findings for antisocial behaviour in the total sample but reported sex-discordant loci, providing evidence for non-complete overlap in the biological mechanisms underlying antisocial behaviour in males and females[113] (see also REF.[114]).

Overall, the specificity of GWAS findings for conduct problems and CD traits seems to be low, and many implicated genes are also associated with other psychiatric disorders, particularly neurodevelopmental disorders[115,116]. Exploiting such evidence for pleiotropy among genetic contributions to different types of antisocial behaviour and integrating data from candidate gene studies and GWAS with human and animal studies of severe genetic mutations have allowed the identification of involved biological pathways, which has consolidated the evidence for the involvement of serotonergic, dopaminergic and neuroendocrine pathways in the pathophysiology of CD[114,117]. In addition, novel mechanisms that are involved in CD-related (aggressive) behaviours have been revealed, including alterations in G protein-coupled receptor signalling pathways, axon guidance, reelin signalling in neurons and ERK/MAPK signalling[118,119]. A novel focus in genome-wide studies that has not yet been evaluated in CD is the study of rare genetic variants of potentially larger effect size through copy-number variant analysis and exome or whole-genome sequencing. As rare variants have been implicated in CD-related phenotypes (for example, ADHD[120–122]), systematic investigation could be informative.

### *Gene–environment interplay*

How and whether an individual's genes influence exposure to certain environmental factors (evocative, active or passive gene–environment correlations (rGE)), and/or whether children with different genetic risk factors react differently to specific environmental factors (gene–environment interaction (G×E); FIG. 2) have been studied in CD. The environmental factors assessed in G×E studies to date mainly constitute familial psychosocial factors (most notably childhood maltreatment or neglect and maternal warmth), peer relationships, neighbourhood factors and stress[123]. In one study, CD symptom levels influenced peer deviance, supporting a role for rGE in CD[124]. In addition, permissive environments (less parental control or supervision or higher peer deviance) increase the genetic contribution to CD-related behaviours, whereas more supportive environments reduce the genetic contribution, consistent with G×E models[85,125]. Similarly, a large study of adopted individuals demonstrated that the effect of an unfavourable environment (having an adoptive parent who is a criminal) on subsequent development of CD-related behaviour (criminality) was larger in genetically vulnerable individuals (those with a biological parent who was a criminal) than in adoptees without a genetic predisposition[126]. In a more recent study, whereas biological mothers' antisocial behaviour predicted early CU traits in offspring, adoptive mothers' positive parenting was shown to buffer this effect[127].

Candidate-based designs have been largely used to date for molecular studies of G×E and have been hampered by the same sample size and limited reproducibility issues as other genetic studies in CD[123]. Seminal early work on interactions between *MAOA* genotype and childhood maltreatment in the development of antisocial behaviour[128] constitutes one of the few findings that have held up more consistently in meta-analyses[129] (FIG. 2). The requirement for large sample sizes, probably in the 10,000–50,000 range, with information on both genetics and environment has thus far constrained genome-wide studies of G×E[130].

How G×E operates at the molecular level is yet to be clarified. An attractive model is that environmental experiences can lead to epigenetic modifications of DNA and chromatin, which are key regulators of gene transcription[131,132]. In particular, DNA modification through methylation could mediate G×E effects, as it is the most

stable form of epigenetic modification. Epigenetic studies of psychiatric disorders in humans have been limited by the fact that epigenetic modifications are highly tissue-specific[132], and, in general, DNA methylation in the brain correlates poorly with DNA methylation in accessible tissues such as blood[133]. Nevertheless, several studies have demonstrated DNA methylation patterns in blood that correlate with brain-based measures (such as cortical thickness) and cognitive and behavioural measures (such as aggression)[134–136]. A study in primates demonstrated overlapping epigenetic changes linked to maternal deprivation in blood T cells and the frontal cortex[137]. In addition, several candidate-gene-based studies[138,139] and a first small epigenome-wide study implicate DNA methylation in conduct problems[140].

## Brain mechanisms

### *Neurocognitive processes*

Compared with typically developing individuals, youths with CD show deficits in facial[141] and vocal[142] emotion recognition (but not general face recognition), affective empathy[143], decision-making and reinforcement learning[144] when tested using neurocognitive tasks. In addition, biases in decision-making have been reported in several studies, such that youths with CD are more influenced by potential rewards and less influenced by punishment than controls[145,146], with recent work suggesting that reward processing abnormalities might be specific to males with CD[147].

Recognition of distress cues (fearful and sad expressions) and affective empathy seem to be disproportionately impaired in those with CD with CU traits[148,149] (although see REF.[143], which found affective empathy deficits in CD with and without CU traits). This profile of impairment differs from the cognitive empathy deficit seen in individuals with autism spectrum disorders[149]. By contrast, emotion recognition, emotional learning and decision-making seem to be equally impaired in females and males with CD, and in those with childhood-onset and adolescent-onset forms of CD[141,145]. 'Cool' executive functions such as planning, task-switching or working memory have received less attention, but evidence suggests that CD is associated with independent deficits in some of these processes even after accounting for comorbid ADHD[150,151], which is itself linked to executive dysfunction. Nevertheless, it should be noted that most research in this area has been cross-sectional; thus, it is unclear whether these neurocognitive deficits cause CD symptoms and drive development of the clinical phenotype and whether certain impairments map onto specific clusters of CD symptoms (for example, physical aggression).

### *Functional MRI studies*

***Emotion processing.*** Most functional MRI (fMRI) studies of CD have focused on emotion processing, using tasks that involve the participants viewing emotional images, facial expressions of emotion or empathy-eliciting stimuli (such as hands in painful situations). Lower activation of the dorsal and rostral anterior cingulate cortex (ACC), medial prefrontal cortex and ventral striatum was observed in youths with CD compared with typically developing controls in one meta-analysis that included 24 studies[152] (FIG. 3). In addition, amygdala and striatal under-activation was observed in youths with CD or ODD during emotion processing or reinforcement-related tasks in another meta-analysis[153].

Youths with CD and CU traits showed additional reductions in ventromedial prefrontal cortex, thalamus and ventral striatal activation, but higher dorsolateral prefrontal cortex and caudate activation during emotion processing, than typically developing youths[152]. Moreover, negative associations between CU traits and neural responses have been reported in subcortical and cortical regions, such as the amygdala, anterior insula and ACC[154] (but see REF.[155], in which no associations with CU traits were detected). These regions are involved in processing distress or pain cues in others, potentially accounting for the positive association between CU traits and proactive (instrumental) aggression (as empathic responses that normally inhibit aggressive behaviour are disrupted). By contrast, studies that have directly compared youths with CD and CU traits and those without CU traits have shown heightened responses to distress cues in the amygdala in those without CU traits, which could be related to increased risk of reactive aggression[154,156].

Only a few studies have compared childhood-onset and adolescent-onset subtypes of CD; however, the available evidence indicates that both subgroups show lower amygdala, insula, orbitofrontal cortex and ventromedial prefrontal cortex responses during emotion processing[155]. In addition, atypical medial prefrontal cortex and anterior insula responses to emotional faces were observed in girls with adolescent-onset CD[157]. Functional connectivity has been investigated in a small number of task-based studies, with atypical amygdala–orbitofrontal cortex connectivity reported in youths with CD and CU traits[158,159], whereas a recent study showed atypical amygdala–ACC connectivity in individuals with CD without CU traits during facial emotion processing[160]. These data suggest that the prefrontal regulation of subcortical regions (such as the amygdala) is impaired in some individuals with CD, which might lead to emotion regulation problems. These changes could, in turn, increase the risk of threat-based reactive aggression.

***Reinforcement-based decision-making.*** Poor decision-making in CD, irrespective of the level of CU traits, is thought to be underpinned by deficits in three computational processes underlying reinforcement-based decision-making and their associated neural substrates[161]. The first is reward processing; individuals with CD have decreased striatal and ventromedial prefrontal cortex responses to rewarding stimuli[162] (for example, monetary gains). The second is punishment processing, which mostly manifests as abnormally increased striatal and ventromedial responses to punishing stimuli[162,163]. The third process is avoidance learning, whereby youths with CD have behavioural deficits and reduced anterior insula, dorsomedial prefrontal cortex and caudate responses to stimuli that should be avoided[162]. Dysfunctions in these three processes are hypothesized to increase the risk of frustration-based reactive aggression and antisocial behaviour more generally[161].

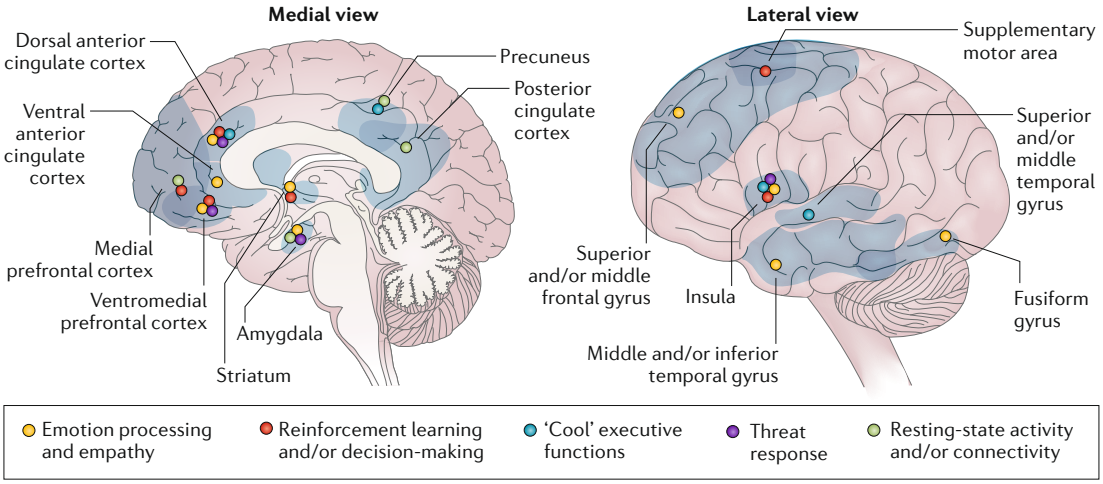


Fig. 3 | **Brain regions which are under-responsive or less active in CD.** Functional MRI (fMRI) studies of emotion processing, particularly emotional face and pain processing, have revealed lower activity in a brain network comprising the amygdala, anterior insula, anterior cingulate cortex, striatum, superior frontal gyrus, fusiform gyrus and superior temporal gyrus in children and adolescents with conduct disorder (CD)[152,153]. These regions have been implicated, respectively, in emotion recognition, empathy and interoception (awareness of one's physiological state), emotion regulation, reward processing, response inhibition, face processing and perception of biological motion in typically developing individuals. Children and adolescents with CD have deficits in many of these processes when tested using neurocognitive tasks[161], as well as structural abnormalities in overlapping brain regions, suggesting that lower neural reactivity and neurocognitive deficits may have a structural basis. Reduced responses have also been reported in brain circuits involved in 'hot' (motivationally relevant) executive functions, such as decision-making and reinforcement learning (that is, the ventral striatum, ventromedial prefrontal cortex, dorsal anterior cingulate cortex, insula and supplementary motor area). These regions are implicated in reward and loss processing, cognitive aspects of executive control and control of internally generated movements. Although more mixed than for regions involved in emotion processing, structural deficits in overlapping regions, particularly the striatum and orbitofrontal cortex, and impaired performance on neurocognitive tasks assessing decision-making and reinforcement learning have been reported in adolescents with CD[161,173]. 'Cool' executive function tasks (assessing purely cognitive processes, such as planning or working memory) have been employed less frequently, but these have revealed lower precuneus, superior temporal, dorsal anterior cingulate cortex and insula responses in CD[153]. Finally, emerging evidence suggests that CD is associated with reduced resting-state activity, particularly in the amygdala, and lower functional connectivity within the 'default mode network' (especially the medial prefrontal–posterior cingulate cortex core subsystem) responsible for self-referential thought and imagining the future consequences of one's actions[169].

***Acute threat response.*** A number of studies have examined neural responses to threat stimuli in CD. Most studies have found reduced amygdala and ventromedial prefrontal cortex and ACC responses to visual threat cues (for example, a snarling dog) in youths with CD compared with controls[164,165] (but see REF.[166], which found increased amygdala responses in the CD group). Although no studies have examined the influence of age at onset or sex, there is evidence that CU traits are negatively related to ventromedial prefrontal cortex responses to visual threat cues[165] and amygdala responses during fear conditioning[167] and social provocation paradigms[156]. Conversely, increased responses in these regions are thought to increase the risk of threat-based reactive aggression[161].

***Resting-state fMRI.*** Relative to task-based studies, there have been fewer resting-state fMRI studies, but these studies have also revealed reduced intrinsic amygdala and insula activity in CD[168] as well as reduced functional connectivity in the core subsystem of the default mode network (linking the anterior medial prefrontal cortex with the posterior cingulate cortex)[169,170] or the anterior part of the default mode network, which overlaps with the core subsystem[171]. The core subsystem is implicated in self-referential cognition, which could explain why individuals with CD have impairments in decision-making (that is, they find it harder to imagine the consequences of their actions or compare different options) and empathy, as this requires making self–other distinctions[143]. In another study, adolescents with CD and CU traits had abnormally increased connectivity between the basolateral amygdala and the ACC and medial prefrontal cortex and reduced centromedial amygdala–orbitofrontal cortex connectivity compared with those without CU traits and typically developing youths[172]. These findings suggest that intrinsic brain activity and connectivity are altered in youths with CD relative to typically developing adolescents, particularly in the default mode network and circuits involving the amygdala.

### *Structural MRI studies*

Atypical neural responses and functional connectivity in youths with CD are likely underpinned by differences in brain structure or structural connectivity. Indeed, two recent meta-analyses of voxel-based morphometry structural MRI studies of youths with CD, ODD or conduct problems[153,173] and one of youths with aggressive behaviour[174] have shown consistent reductions in grey matter volume across cortical (such as ventrolateral,

medial prefrontal, middle temporal, superior temporal and anterior insular cortices) and subcortical (amygdala, caudate and putamen) regions. Individuals with childhood-onset conduct problems showed reductions in left amygdala and anterior insula grey matter volume compared with typically developing youths[173] (FIG. 4). There is evidence that sex moderates the relationship between CD and grey matter volume changes[175] and that levels of CU traits influence cortical and subcortical grey matter volume in youths with conduct problems[173,176], but these preliminary findings require replication in larger samples[173]. Furthermore, findings for grey matter volume can be difficult to interpret with respect to biological properties of brain tissue as it is a composite measure of thickness, surface area and folding[177]. Surface-based morphometry (SBM) methods enable researchers to investigate these measures separately, and SBM studies in healthy individuals have revealed that these cortical properties have distinct aetiologies and developmental trajectories[177].

To date, evidence from SBM studies suggests that the most consistent structural abnormalities in CD are reduced cortical thickness in the ventromedial prefrontal cortex, orbitofrontal cortex, superior temporal cortex, fusiform gyrus, precentral gyrus and precuneus (FIG. 4). These regions are implicated in moral and affective decision-making, face processing, motor functions and self-referential processing, respectively. Although surface area findings have been inconsistent, reduced gyrification in the ventromedial prefrontal cortex, orbitofrontal cortex and ACC has been reported in three studies[178–180]. One study showed that although childhood-onset and adolescent-onset CD participants did not differ in cortical thickness and surface area, individuals with childhood-onset CD had increased folding in several temporal and frontal regions, with CU traits correlating positively with insula folding[181]. Interestingly, two studies have shown a negative association between CU traits and cortical thickness in the right superior temporal cortex[179,180] and the lingual gyrus and fusiform gyrus[180,181], regions that are involved in decision-making and face processing. Although most studies have investigated male-only samples, a recent large-scale study showed that both female and male adolescents with CD have lower cortical thickness and higher folding in the ventromedial and orbitofrontal cortices[182], whereas sex-specific effects of CD were observed for cortical folding and surface area in other regions.

Although abnormal functional connectivity in CD has been reported in task-based and resting-state fMRI studies, diffusion tensor imaging findings on white matter structural connectivity have been inconsistent in both the nature and loci of reported effects[183]. Indeed, both lower (often interpreted as greater integrity) and higher white matter diffusivity have been reported in association, commissural and projection pathways in youths with CD[183]. Interestingly, there is consistent evidence that antisocial personality disorder in adults is associated with white matter alterations in the same tracts that are altered in youths with CD, but with a consistent pattern of higher diffusivity, interpreted as reduced integrity, in adults[183]. Methodological factors and demographic and clinical characteristics of the samples have probably contributed to these inconsistent findings[183]. In addition, many studies have failed to account for heterogeneity within CD in relation to CU traits, which might be problematic given that two recent studies showed that CU traits influenced the pattern of white matter connectivity differences in youths with CD[184,185]. Finally, to date, most studies have focused on males[186] or females[187] with CD alone, with studies including mixed-sex samples[188] probably underpowered to test for sex differences.

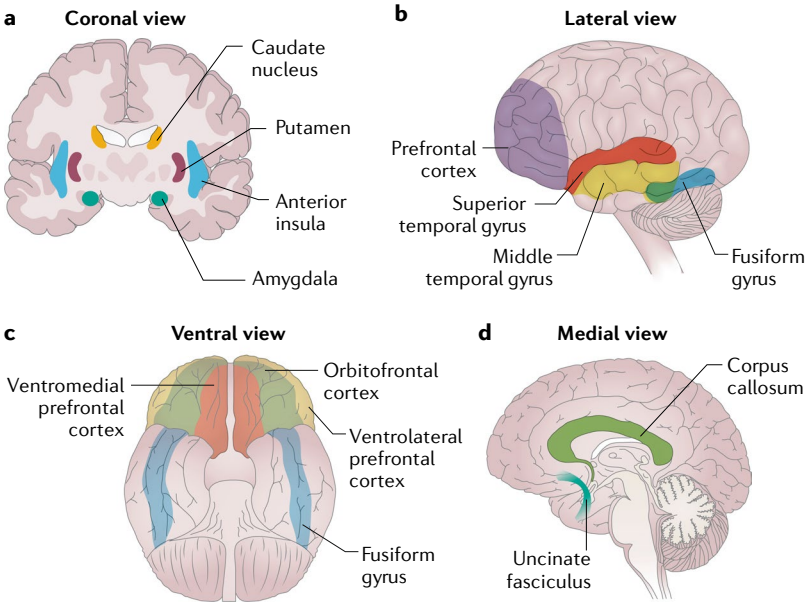


Fig. 4 | **Structural brain abnormalities in CD.** This figure shows the subcortical and cortical regions and white matter tracts that have been consistently implicated in voxel-based morphometry, surface-based morphometry and diffusion tensor imaging studies of conduct disorder (CD)[173,179,183]. These brain regions and tracts are implicated in a number of neurocognitive processes that are impaired in CD. It is important to note that many of these regions are structurally and functionally connected and probably operate as circuits. **a** | A coronal section through the brain showing the amygdala, anterior insula, caudate and putamen where grey matter volume reductions have been observed in CD. The amygdala is a subcortical region involved in fear conditioning, decision-making, salience detection, affective empathy and mediating threat responses. The anterior insula is a cortical region involved in empathy and interoception (awareness of body states). The caudate and putamen are subcortical nuclei that together form the dorsal striatum, involved in stimulus–response habit formation and cognitive control. **b** | Lateral view of the brain showing the prefrontal and temporal cortices. Reductions in grey matter volume have been reported in these regions in CD. The medial prefrontal cortex has an important role in social cognition and the prefrontal cortex is broadly implicated in decision-making and reinforcement learning. In the temporal cortex, the middle temporal gyrus is critical for autobiographical memory, whereas the superior temporal gyrus is involved in verbal processing and perception of biological motion. **c** | A view from below the brain showing the ventromedial, orbitofrontal and ventrolateral prefrontal cortices and the fusiform gyrus. Lower grey matter volume in the prefrontal cortices and fusiform gyrus and reduced cortical thickness in overlapping regions are reported in CD. The ventromedial prefrontal cortex is implicated in emotion regulation and reinforcement learning and there are strong anatomical and functional connections between this region and the amygdala. The orbitofrontal cortex is implicated in decision-making, the ventrolateral prefrontal cortex has a central role in response inhibition and the fusiform gyrus is involved in face recognition. **d** | A midline section showing two white matter tracts implicated in CD: the corpus callosum and uncinate fasciculus. The corpus callosum is the largest white matter tract and commissural pathway in the brain and is critically involved in interhemispheric communication. The uncinate fasciculus connects the ventromedial and orbitofrontal cortex with the anterior temporal lobe, which includes the amygdala. It conveys socio-emotional and memory-related information.

Overall, neuroimaging evidence suggests that CD is associated with atypical brain structure, function and connectivity, and this is not only true for forms of CD that emerge in childhood — similar abnormalities are reported in adolescent-onset CD. There is also increasing evidence that CD with CU traits is linked to reduced (whereas CD without CU traits is associated with heightened) neural responses to emotional stimuli, and CU traits might influence some of the structural and white matter connectivity differences observed in youths with CD. Given the widespread nature of the brain-based differences observed to date, it seems that CD, similar to other psychiatric disorders[189] affects multiple brain circuits rather than isolated regions. Nevertheless, it should be noted that most of these neuroimaging studies had small sample sizes, increasing the risk of false positives and false negatives[190], and none adopted longitudinal designs to investigate brain development in CD. Furthermore, most of the studies reviewed above did not systematically examine the influence of comorbid conditions such as ADHD[191] (but see REFS[192–195], which have investigated the influence of ADHD comorbidity) or ODD (probably as before DSM-5, ODD could not be diagnosed when CD was present, meaning that studies on CD did not investigate the effect of ODD on their results). Thus, it is possible that some of above findings might have been influenced by comorbid conditions. Finally, although proximal (for example, childhood maltreatment[196]) and distal (low socio-economic status[197]) risk factors for CD are known to influence brain development, how they relate to the structural and functional brain abnormalities identified in CD remains to be established.

### *Neuroendocrinology and psychophysiology*

Several early studies reported low basal cortisol levels in individuals with CD[198,199]; however, more recent, methodologically stronger studies have provided limited evidence for basal cortisol abnormalities. In fact, some studies reported higher cortisol levels in the afternoon or evening[200], giving rise to a flatter cortisol profile, which is indicative of impaired negative feedback mechanisms rather than lower secretion across the day. Smaller cortisol awakening responses have also been reported in adolescents with disruptive behaviour disorders[201] or those with CD with CU traits specifically[202], although this is not a consistent finding (for example, see REF.[200] for a study that found no differences between groups). Although the findings on basal and day or morning profiles of cortisol secretion are mixed, there is consistent evidence that children and adolescents with CD or ODD show cortisol hyporeactivity to stress[200,203]. In addition, comorbid CD or ODD predicts cortisol hyporeactivity in children with ADHD[204,205], although ADHD is not itself associated with cortisol hyporeactivity[205]. Only a few studies have assessed the effects of CU traits on cortisol reactivity; some reported that CU traits predict hyporeactivity[206] whereas other studies found no association between CU traits and cortisol reactivity[204]. Notably, most studies have been cross-sectional, therefore longitudinal research is needed to investigate whether cortisol hyporeactivity predicts the emergence of CD or CU traits in high-risk populations and whether hypothalamic–pituitary–adrenal axis (HPA) function normalizes in those who remit[207]. As HPA axis function is influenced by exposure to environmental adversity at different developmental stages[208], and common environmental risk factors (for example, maltreatment) are implicated in CD and HPA axis dysfunction, an important open question is whether HPA axis dysfunction leads to CD or vice versa.

Psychophysiological studies have provided consistent evidence for an association between low resting heart rate, as well as blunted heart rate responses to stress, and CD (and related phenotypes, such as aggression or delinquency[209]). The largest study in this area ($n$ = 710,264) demonstrated significant associations between low resting heart rate in adolescence and violent crime convictions in adulthood in males[210]. However, a recent large European study found no differences in the resting heart rate of individuals with CD compared with controls, even when considering males alone[211]. Lower resting skin conductance levels and reduced skin conductance responses to emotional stimuli[212], particularly during fear conditioning[213], have also been reported in CD. An important prospective longitudinal study with a 20-year follow-up period demonstrated an association between impaired fear conditioning in childhood (at age 3 years) and later adult crime (at age 23 years)[214], whereas another study showed that fear conditioning was inversely related to rates of criminal offending among a sample of adolescent offenders[215]. Together, these studies indicate that CD is associated with neuroendocrine and psychophysiological abnormalities, particularly under stressful or emotionally charged conditions, and such abnormalities may be predictive of future antisocial behaviour.

## Diagnosis, screening and prevention

### *Clinical diagnosis*

CD is included in the most recent editions of both of the major psychiatric classification systems, the DSM and the ICD. DSM-5 (REF.[42]) (BOX 2) and the 11th edition of the ICD (ICD-11 (REF.[216])) have the same general descriptions of the defining features of CD as involving repetitive and persistent patterns of behaviour in which others' rights or major age-appropriate norms are violated, as indicated by aggression to people or animals, destruction of property, deceitfulness or theft or serious rule violations. As these definitions result in very heterogeneous groups of individuals, both the DSM-5 and ICD-11 include multiple subtypes. For example, the childhood-onset subtype (one or more symptoms before 10 years of age) and the adolescent-onset subtype (all symptoms emerge after 10 years of age) were based on research that showed that the earlier the onset of CD symptoms, the more severe and chronic the behaviours and the stronger the neurodevelopmental influences (for example, impulsivity, CU traits and low intelligence) on the behaviours[217,218]. Thus, the childhood-onset versus adolescent-onset subtypes seem to have both clinical (predicting impairment and outcome) and aetiological (predicting unique causal processes) uses, although the most appropriate age to place this cut-off is debated[30,217]. The DSM-5 also includes a specifier for mild, moderate and severe manifestations

of CD based on the number of symptoms present and the degree of harm they cause others.

In addition, both the DSM-5 and ICD-11 include the LPE specifier[42,216], which is applied to children who meet criteria for CD with additional symptoms (BOX 2). The only difference in the definition of LPE between the two classification systems is that the ICD-11 includes an additional symptom that is related to indifference to punishment. This specifier can be applied only to individuals with CD using the DSM-5 classification; however, this specifier can be applied to children who meet criteria for ODD as well as CD in ICD-11. Youths with serious conduct problems and CU traits seem to have more stable behaviour problems, more severe aggression and poorer responses to treatment than those without CU traits[219]. In addition, youths with CD and CU traits have partly distinct genetic and environmental risk factors from their counterparts with CD only, suggesting distinct causal processes and developmental pathways in the former subgroup[219]. Finally, in contrast to the long-held notion that CU traits and anxiety are incompatible with each other, it has been argued that subdividing individuals with CD and CU traits into those with low or high levels of anxiety (so-called 'primary' and 'secondary' CU traits) could be informative[220].

Box 2 | **DSM-5 criteria for CD**

A. A repetitive and persistent pattern of behaviour in which the basic rights of others or major age-appropriate societal norms or rules are violated, as manifested by the presence of at least 3 of the following 15 criteria in the past 12 months from any of the categories below, with at least 1 criterion present in the past 6 months.

**Aggression to people and animals**

- Often bullies, threatens or intimidates others
- Often initiates physical fights
- Has used a weapon that can cause serious physical harm to others (for example, a bat, brick, broken bottle, knife or gun)
- Has been physically cruel to people
- Has been physically cruel to animals
- Has stolen while confronting a victim (for example, mugging, purse snatching, extortion or armed robbery)
- Has forced someone into sexual activity

**Destruction of property**

- Has deliberately engaged in fire setting with the intention of causing serious damage
- Has deliberately destroyed others' property (other than by fire setting)

**Deceitfulness or theft**

- Has broken into someone else's house, building or car
- Often lies to obtain goods or favours or to avoid obligations (that is, 'cons' others)
- Has stolen items of nontrivial value without confronting a victim (for example, shoplifting, but without breaking and entering, or forgery)

**Serious violations of rules**

- Often stays out at night despite parental prohibitions, beginning before 13 years of age
- Has run away from home overnight at least twice while living in the parental or parental surrogate home, or once without returning for a lengthy period
- Is often truant from school, beginning before 13 years of age

B. The disturbance in behaviour causes clinically significant impairment in social, academic or occupational functioning.
C. If the individual is 18 years of age or older, criteria are not met for antisocial personality disorder.

**Age at onset subtype**

- Childhood-onset type: at least one criterion characteristic of CD is present before 10 years of age
- Adolescent-onset type: absence of any criteria characteristic of CD before 10 years of age
- Unspecified onset: when the age at onset of CD is unknown or insufficient information is available to determine this

**With limited prosocial emotions specifier**

This specifier is applied to children who meet diagnostic criteria for CD and who also show two or more of the following symptoms over an extended period (that is, ≥12 months) and across multiple relationships and settings.

- Lack of remorse or guilt
- Callous — lack of empathy
- A lack of concern about educational or occupational performance
- Shallow emotions

CD, conduct disorder; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. From REF.[42].

### *Key approaches to diagnosis*

The diagnostic assessment of children and adolescents with potential CD should include several factors (TABLE 1). First, individuals should be assessed for a wide range of conduct problems, particularly the level of aggression and the harm this behaviour causes other individuals, as these factors are critical to determine the required treatment intensity and the restrictiveness of the setting in which to provide this treatment, whilst maintaining others' safety. Second, individuals should be assessed for a wide range of co-occurring problems, including other mental health disorders, legal problems, social issues and educational difficulties. If feasible, a medical examination should be performed to assess for signs of maltreatment, malnutrition and untreated infections. Third, assessing for the most common risk factors that could be targeted in treatment is important[218], including harsh and inconsistent parenting, sensation-seeking, problems regulating emotions and, importantly, attentional problems, impulsivity and hyperactivity associated with ADHD. Fourth, assessing the age at which the child's behaviour problems first emerged and whether the child has elevated CU traits across multiple relationships and settings is important and can help to develop a comprehensive, yet individualized, approach to treatment[221].

### *Screening*

Screening for CD is important to identify children at risk of severe behaviour problems early in development when treatment is most effective[221]. The most common method for screening for problems that can lead to CD is for parents and/or teachers to complete rating scales including a range of common behaviour problems and then determine whether the child's behaviour problems are non-normative for a child of their age (TABLE 1). Thus, optimal screening identifies problem behaviours when they already cause impairment, but critically this occurs before the child meets the full criteria for CD (such as some features of aggression or meeting the criteria for ODD) and early in development when behaviours are more malleable (for example, the preschool years). For example, the FAST Track intervention assessed kindergarten students for classroom conduct

problems using 14 items from the teacher-delivered Teacher Observation of Childhood Adaptation-Revised (TOCA-R)[222], following which children scoring in the top 40% were screened for home conduct problems by parents using 24 items on the Child Behavior Checklist[223]. Children who met the screening criteria were included in a targeted prevention programme. Of note, this screening study started at school, given that young children who show problems at school typically also show problems at home, whereas the opposite is not true, and young children who show problems outside the home are at the highest risk of later adjustment problems[224]. Thus, in younger children, including teacher ratings in the screening process is important. In older children and adolescents, the importance of assessing self-reported conduct problems increases, as the child's antisocial behaviours increasingly occur away from parents or teachers[225].

Of note, the FAST Track screening used 'local norms' to determine non-normative levels of conduct problems, which was feasible in this study owing to the large sample available. However, some scales that have norms derived from large population-based samples can also be used to screen for conduct problems. For example, the Strengths and Difficulties Questionnaire (SDQ) includes a five-item conduct problems scale that has normative data available across multiple countries and language translations[226] and is an effective screening tool for CD[227]. The Eyberg Child Behavior Inventory (ECBI) and Sutter-Eyberg Student Behavior Inventory-Revised (SESBI-R) provide a more comprehensive screening of the child's conduct problems at home and school, respectively[228]. These scales require the parent or teacher to rate 36 problem behaviours (taking ~10 minutes), and normative cut-offs are available for children and adolescents aged between 2 years and 16 years. Of note, in addition to rating the frequency of problem behaviours, as is common for most screening scales, the parent or teacher also rates whether the behaviours cause problems at home or school.

Table 1 | **Assessment of CD and assessment instruments**

| Approach | Methods | Reasoning |
|---|---|---|
| • Assess a wide range of conduct problems<br>• Assess the amount of harm a child's behaviour is causing to other individuals<br>• Assess the level of impairment that the child's behaviour is causing in multiple situations and settings (such as home, school, work and interpersonal relationships) | • Norm-referenced behaviour rating scales from multiple informants who interact with the child in different settings (such as ASEBA, BASC-3, ECBI, SDQ and SESBI-R)[a]<br>• Unstructured clinical interviews with the child and other adults who see the child in different settings[a]<br>• Behavioural observations of the child interacting with adults and peers (such as BASC-3 SOS or DPICS)[b]<br>• Structured or semi-structured diagnostic interviews with the child and other adults who see the child in different settings (such as DISC or K-SADS)[b] | Children with CD can vary greatly in the types and severity of their antisocial behaviours |
| • Screen broadly for a wide range of common problems that often occur with CD, including psychiatric disorders (for example, ADHD, anxiety, depression, substance use disorders and self-harm), legal problems, educational difficulties (such as academic underachievement or dropping out of school) and social problems (such as poor peer relationships[280,286])<br>• Follow up positive screens with more in-depth assessments | • Norm-referenced behaviour rating scales that cover a broad range of potential problems in adjustment (such as ASEBA, BASC-3 or SDQ)[a]<br>• Unstructured clinical interviews with the child and other adults who know the child well[a]<br>• Structured or semi-structured diagnostic interviews with the child and other adults who know the child well (such as DISC or K-SADS)[b]<br>• Review of school records[b]<br>• Standardized measure of academic achievement (such as WJ–IV-TA)[b] | Children with CD often have multiple comorbid disorders and/or problems in adjustment |
| • Screen for a wide range of individual risk factors, such as low intelligence, sensation-seeking, inattention or impulsivity, rebelliousness and emotion regulation problems<br>• Screen for a wide range of contextual risk factors that could contribute to the child's behaviour problems, such as harsh and inconsistent parenting, parental psychopathology, family conflict, friendships with delinquent peers and exposure to violence both inside and outside the home | • Norm-referenced behaviour rating scales that cover key domains of personality and temperament (such as ASEBA, BASC-3 or SDQ)[a]<br>• Rating scales assessing parenting and family conflict (such as APQ or BASC-3)[a]<br>• Unstructured clinical interviews with child and other adults who interact with the child[a]<br>• Observations of parent–child interactions (such as DPICS)[b]<br>• Standardized tests of intelligence (such as WISC-V or WASI)[b] | CD often results from multiple risk factors within both the child and his or her context |
| • Obtain history of when the child's behaviour problems first emerged (such as before or after age 10 years)<br>• Assess for the presence of callous-unemotional traits | • Unstructured clinical interview with child and parents to provide history of behavioural problems[a]<br>• Behaviour rating scales assessing callous-unemotional traits from child, parents and other informants (such as CPTI or ICU)[a]<br>• Structured or semi-structured diagnostic interviews with child and parents that assess age at onset of behaviour problems (such as DICA, DISC or K-SADS)[b]<br>• Review of school records[b] | There can be multiple causal pathways to CD, each involving somewhat distinct risk factors that could necessitate an individualized approach to treatment |

ADHD, attention-deficit/hyperactivity disorder; APQ, Alabama Parenting Questionnaire; ASEBA, Achenbach System of Empirically Based Assessment; BASC-3, Behavioral Assessment System for Children, Third Edition; BASC-3 SOS, BASC-3 Student Observation System; CD, conduct disorder; CPTI, Child Problematic Traits Inventory; DICA, Diagnostic Interview for Children and Adolescents; DISC, Diagnostic Interview Schedule for Children; DPICS, Dyadic Parent-Child Interaction Coding System; ECBI, Eyberg Child Behavior Inventory; ICU, Inventory of Callous-Unemotional traits; K-SADS, Kiddie-Schedule for Affective Disorders and Schizophrenia; SESBI-R, Sutter-Eyberg Student Behavior Inventory-Revised; SDQ, Strengths and Difficulties Questionnaire; WASI, Wechsler Abbreviated Scale of Intelligence; WISC-V, Wechsler Intelligence Scale for Children-5th Edition; WJ–IV-TA, Woodcock Johnson 4th Edition Tests of Achievement. [a]Essential. [b]Helpful.

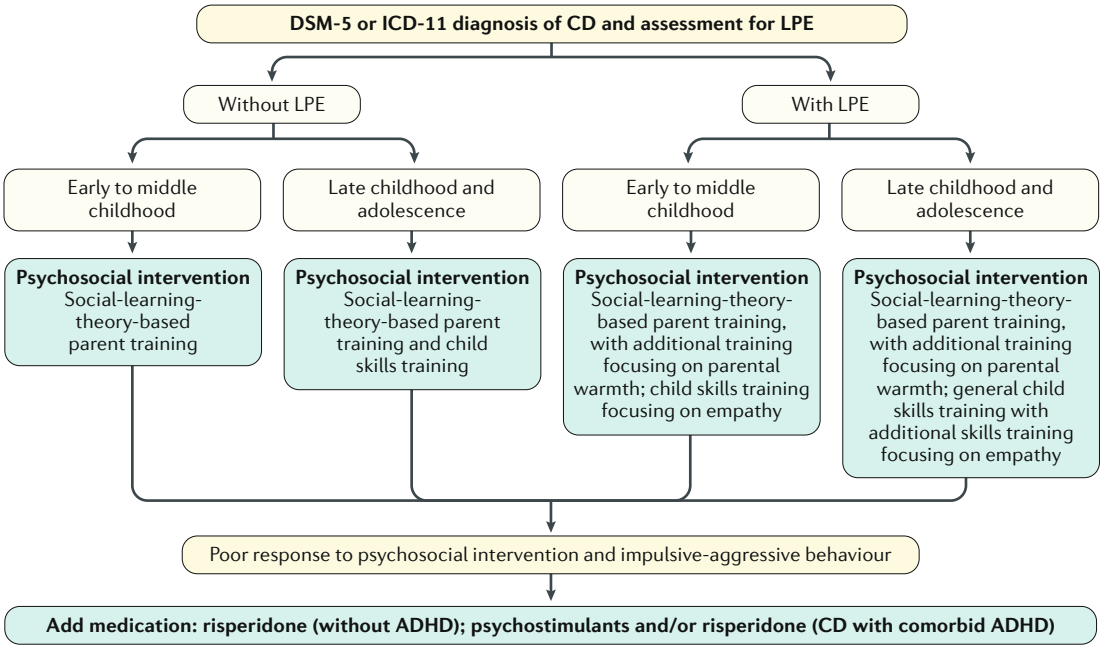


Fig. 5 | **Management of CD without comorbid disorders in different developmental periods.** The clinical management of conduct disorder (CD) includes psychosocial family-based interventions with parents or primary caregivers for patients at all ages, but additional interventions vary according to the age of the patient, the presence or absence of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) limited prosocial emotions (LPEs) specifier for CD (also known as callous-unemotional traits), the severity of impulsive-aggressive behaviour and the presence or absence of comorbid psychiatric disorders. ADHD, attention-deficit/hyperactivity disorder; ICD-11, International Classification of Diseases, 11th edition.

### *Prevention*

To date, established causal models of CD have informed programmes intended for primary or universal prevention that are aimed at the general population, selective prevention programmes that are aimed at children exposed to individual or contextual risk factors and indicated prevention programmes that are aimed at children with subclinical levels of conduct problems. Selective and indicated prevention programmes rely on similar principles to existing psychosocial interventions for CD (see Management, below).

Universal and selective prevention programmes for aggression had effect sizes ranging from zero to small in recent systematic reviews and meta-analyses, whereas effect sizes for indicated prevention programmes were mostly small to medium[229]. One meta-analysis found a small but significant effect (Cohen's $d = 0.24$) of selective and indicated prevention programmes on delinquency, corresponding to an ~13% reduction in delinquent behaviour compared with care as usual or no intervention[230]. As the most chronic and severe trajectories of antisocial behaviour often begin early in childhood, effective treatments for disruptive behaviours in the preschool and early primary school years are key for the prevention of CD. Parenting interventions based on social learning principles have been recommended as a first-line intervention for these disorders in early childhood[231] and have large effects in this period[232]. The various risk and protective factors that are targeted in effective prevention programmes reflect developmental theory regarding the proximal influences on antisocial behaviour at different ages[233,234].

## Management

Effective management of CD aims to reduce the core symptoms, improve emotion regulation in individuals with reactive aggression and emotion dysregulation, to enhance moral development and social skills and to reduce symptoms of comorbid psychiatric and developmental disorders. It also aims to improve educational outcomes and employability and to minimize criminal behaviours[235].

Effective management and treatment rely heavily on the involvement of mental health professionals and services. Lasting behavioural change is most likely to occur through behavioural interventions that primarily target parents or primary caregivers and/or the child or adolescent's home context and peer group and that draw on developmental models to inform the selection of treatment targets according to the child's age. Evidence-based interventions for CD are outlined in FIG. 5, and those for CD with comorbid psychiatric or developmental disorders are outlined in FIG. 6.

### *Behavioural interventions*

The most cost-effective treatments for CD focus on the quality of parenting in early to middle childhood[236], and, on the basis of the large effects produced by relatively brief (such as 10-week) treatments in early childhood (such as <8 years of age), intervention in this period can be considered optimal[232] (BOX 3). Given that outcomes of childhood-onset CD are more detrimental than those of adolescent-onset CD[236], early intervention parenting programmes should be offered to all parents of children

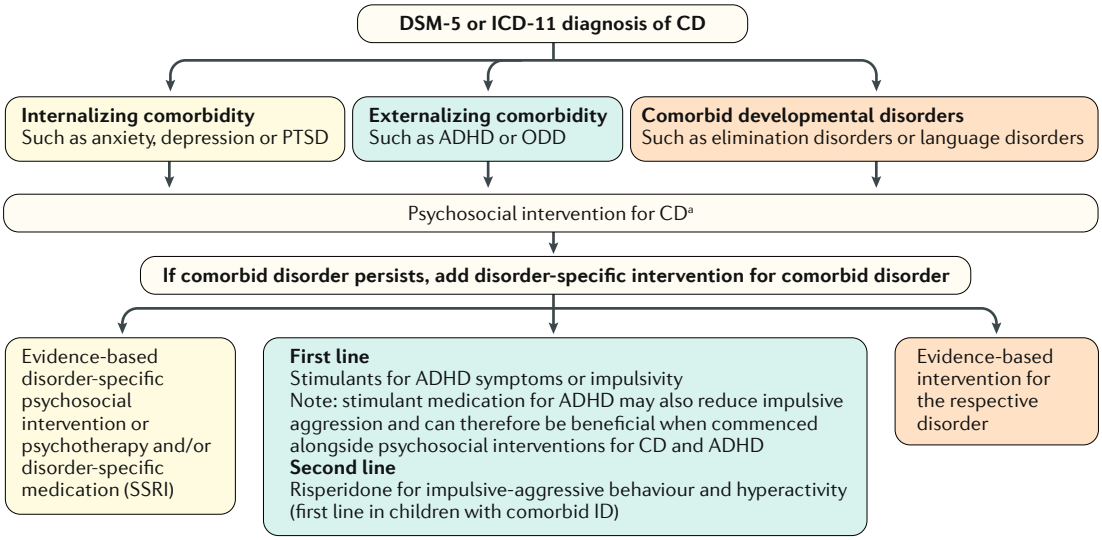


Fig. 6 | **Management of CD in those with comorbid disorders.** Children and adolescents with conduct disorder (CD) have high rates of comorbid psychiatric disorders, which also need to be treated using evidence-based methods. Psychosocial family-based interventions are at the core of all interventions, but additional targeted evidence-based interventions for comorbid developmental, internalizing or externalizing disorders should also be provided. ADHD, attention-deficit/hyperactivity disorder; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ICD-11, International Classification of Diseases, 11th edition; ID, intellectual disability; ODD, oppositional defiant disorder; PTSD, post-traumatic stress disorder; SSRI, selective serotonin reuptake inhibitor. [a]See FIG. 5.

with CD. The programmes could be provided by local health and social services, paediatricians and kindergarten and school teachers and could alert parents to the availability of these interventions[237].

***Psychosocial interventions in early to middle childhood.*** Evidence-based guidelines for the treatment of conduct problems in early and middle childhood (3–11 years of age) and meta-analyses recommend behavioural parent training (also known as parent management training) based on social learning theory as a first-line approach[238,239] (FIG. 5). This intervention seems to be most beneficial early in childhood, when large effects have been reported[232]. Manualized parenting training programmes, which have been found to be efficacious in at least two randomized controlled trials in different countries, include the Parent Management Training Oregon Model[240], the Triple P–Positive Parenting Program[241] and the Incredible Years programme[242,243]. Importantly, the effectiveness trials of such interventions in real-world settings have shown comparable outcomes to those conducted under highly controlled conditions[239].

These interventions share a number of core components, including a central focus on increasing parental warmth and positive reinforcement of desirable child behaviour followed by a discipline-focused component in which parents are trained to provide effective instructions to their children and apply consistent, non-aggressive consequences to set limits on negative child behaviours. Skills training for parents typically emphasizes active methods such as in-session modelling (demonstration) of these components by therapists, role-play and homework[244]. The most substantial differences between programmes are seen in the supplementary components, such as strategies for parents to teach children problem-solving skills and to target other stressors within the family.

Children derive increasing benefit from direct participation in cognitive-behavioural skills training with increasing age, wherein social problem-solving, together with social-cognitive processes and deficits related to self-regulation, are targeted. Delivery of cognitive-behavioural skills training should be concurrent with parent training[245]. A key example is Problem-Solving Skills Training[1], which comprises 25 weekly group-training sessions with children 7–13 years of age, allowing for the practice of skills with peers. For children with CD and CU traits, the effects of such treatment might be enhanced by the addition of emotion processing training with children and parents[246]. Treatment effects for youth-focused cognitive-behavioural interventions have had substantially smaller effect sizes (very small) than parent training interventions (small to medium) in early to late childhood[238,247]. Nevertheless, especially for children with severe CD, a multimodal approach including both child-focused and parent-focused components is recommended[238].

***Psychosocial interventions in late childhood and adolescence.*** In late childhood and adolescence, multicomponent treatments that integrate family strategies, behavioural strategies and cognitive-behavioural therapy are most effective[244]. The parenting components of these interventions are based on social learning theory but differ from the interventions used for younger children (for example, age-appropriate consequences for limit-setting might include loss of privileges for adolescents rather than time out for younger children). The most established treatments are Multisystemic

Therapy (MST) and Treatment Foster Care Oregon (TFCO), which were both developed, and are mainly implemented, in the United States. In Europe, interventions would mainly involve psychoeducation for parents, or in serious cases, removal of the child from the family and placement in youth welfare institutions or juvenile detention facilities.

MST[248] targets antisocial behaviours and is delivered in the day-to-day environment (such as home or school) by a treatment team consisting of a therapist, case manager and behaviour management specialist, typically over 3–5 months. Goals focus on improving family functioning and parenting skills; increasing the adolescent's association with prosocial peers; and improving their social, emotion regulation and problem-solving skills, school performance and community support. This intervention is particularly intensive, with closely supervised therapists who have low caseloads to allow for multiple weekly contacts and on-call support 24 hours a day, 7 days a week. In two meta-analyses, small intervention effects on delinquency were mainly shown for youths <15 years of age with severe antisocial behaviour, and psychopathology and substance use were reduced in all age groups compared with treatment as usual (individual counselling or family therapy)[249,250]. Positive outcomes seem to rely on the use of intensive procedures to monitor the quality of treatment delivery by practitioners. In research outside the United States, support for MST has been somewhat mixed. Indeed, one large, community-based, multisite trial in the United Kingdom demonstrated no long-term benefit or superior cost-effectiveness for MST compared with standard services[251]. Given that standard services for youths in the juvenile justice system vary widely between countries, MST could offer fewer benefits when delivered in countries with stronger social welfare systems.

TFCO[252] is a community-based programme in which youths are placed for 6–9 months with trained foster caregivers (one per foster home), who implement a daily token-based reinforcement system and establish clear and consistent limits. During this time, youths have weekly contact with individual therapists who provide support and advocacy in addition to group-based skills training that is focused on social problem-solving skills, anger expression and educational or vocational planning. Biological parents concurrently receive intensive behavioural parent training that is designed to assist in the reintegration of the youth in their home and community following treatment completion. Two randomized controlled trials in delinquent youths have shown large reductions in early pregnancy in girls, a reduction in violence in boys and small reductions of delinquency and criminal referrals in both sexes compared with community-based residential group care[253]. However, the positive effects of TFCO seem to be limited to youths with particularly severe CD[250].

Other adolescent interventions are classified as probably efficacious treatments[254]. These interventions include Functional Family Therapy[255], a family-based intervention that was designed to increase family problem-solving skills, emotional cohesion and related parenting skills and is generally delivered over a 3-month period. Other interventions are group-format cognitive-behavioural-therapy-based skills training programmes for adolescents within detention facilities (such as Equipping Youth to Help One Another[254,256]) and the community (such as Solution-Focused Group Therapy programme[254,257]). As noted for younger children, adding emotion-processing skills training to family-based treatment components could further enhance outcomes when adolescents with CD have CU traits[246].

### *Special education and detention facilities*

Many children and adolescents with CD are placed in special education, foster care, youth welfare institutions or the juvenile justice or detention system[258]. No population-based data are available that compare the rate of children placed in these institutions across different countries. In general, well-controlled outcome studies regarding the use of these facilities are scarce.

One large study in the United States has found clear evidence that special education provided to children with conduct problems in secondary (but not primary) school increases the risk of high school non-completion and the severity of CD[259]. No sufficiently large controlled studies have been carried out to assess the long-term outcome of foster care or youth welfare placements for children with CD. It is likely that outcomes vary according to the intervention method implemented by the foster parents or in the youth welfare institutions. High rates of psychiatric disorders, substance abuse and suicide have been reported after detention in the United States in the general population[260,261], and incarceration can

Box 3 | **Mediators, predictors and moderators of intervention outcomes**

The effects of family-based interventions on child outcomes are mediated by changes in the parenting mechanisms emphasized in social learning models of conduct disorder (CD). Whether these effects are predominantly accounted for by increases in positive parenting or decreases in negative parenting is less clear[300,301]. There is some evidence that mechanisms of change might be best captured by composite measures of parenting that combine positive and negative characteristics, quality of discipline (such as consistent, inconsistent or lax) and monitoring or supervision (such as awareness of their child's activity and location) rather than any single domain. However, when examined individually, monitoring or supervision has been found to be least important[302]. Critically, even in interventions targeting adolescents that include extensive youth-focused skills training, changes in parenting practices appear to play a key part in determining youth outcomes[303].

There is little evidence that demographic factors such as sex, ethnicity or socioeconomic status affect the outcomes of interventions for conduct problems. Moreover, the effectiveness of evidence-based parenting programmes does not seem to diminish when they are disseminated in countries with different cultures and service provisions from those in which the interventions were originally developed[304]. Study cohorts that comprise higher proportions of ethnic minorities and girls show particularly strong benefits from family-based interventions, thereby emphasizing the generalizability of such interventions[305].

Outcomes of psychosocial treatments for CD can be predicted and moderated by characteristics of parents (such as maternal depression) and children (such as comorbid internalizing symptoms), although findings have been mixed[300,306]. Evidence regarding child callous-unemotional (CU) traits has been somewhat more consistent. Although many youths with CD and CU traits seem to respond to treatment, most studies have found that CU traits predict relatively poor treatment outcomes, independent of conduct problem severity before treatment[219,307]. The clinical outcomes of youths with CU traits can be enhanced by including parent–child components that target emotion processing deficits in family-based interventions[246].

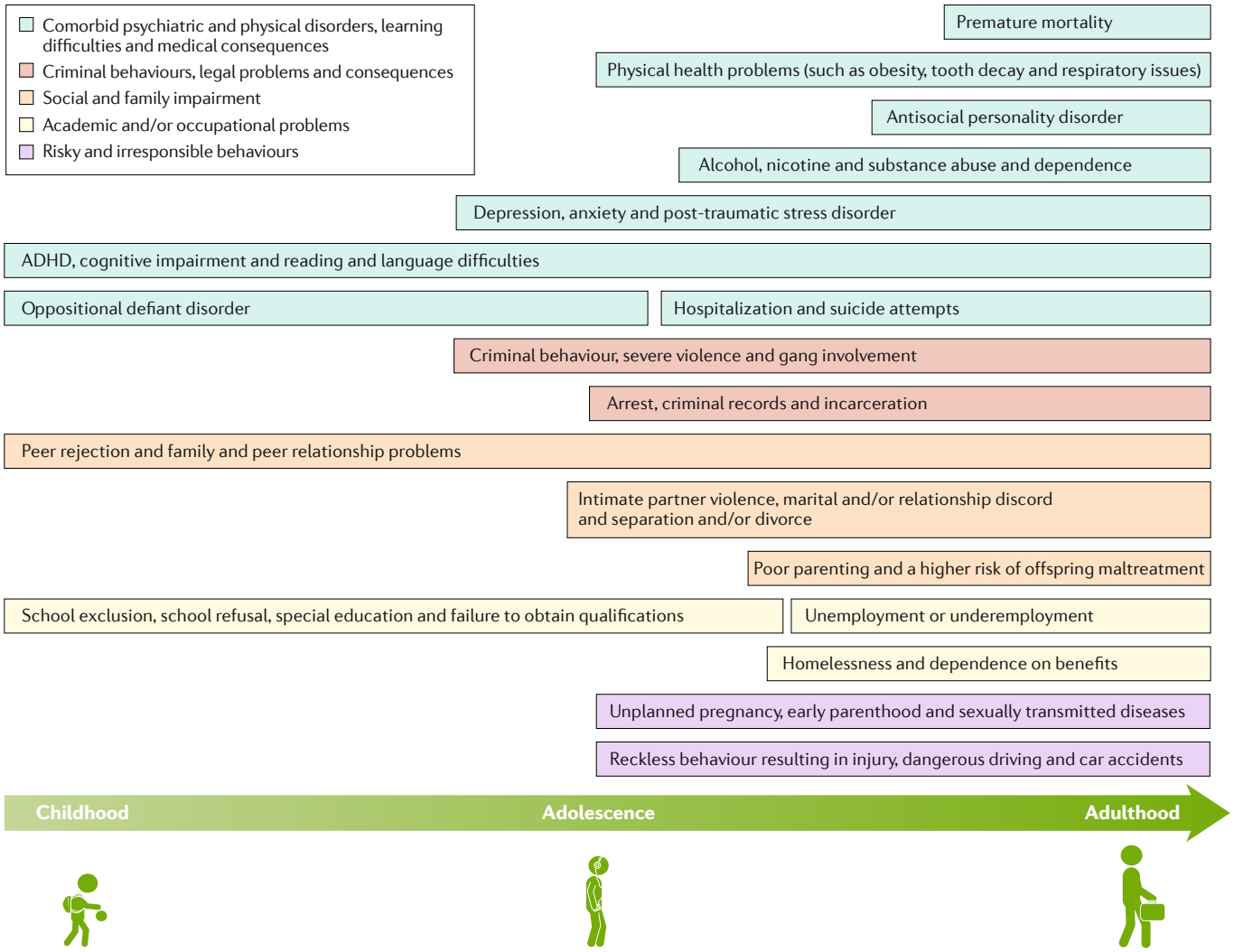


Fig. 7 | **Quality of life and CD.** Conduct disorder (CD) is associated with functional impairments across the lifespan. The earliest impairments occur in educational and social domains, with children with CD frequently being excluded from school or taught in specialist educational settings and being rejected by their peers owing to aggressive or disruptive behaviour. CD is also associated with a high physical and mental health burden, with attention-deficit/hyperactivity disorder, oppositional defiant disorder and developmental language disorders common comorbidities in childhood and adolescence and depression, anxiety and alcohol and substance use disorders frequently emerging in adolescence[235]. Antisocial personality disorder or borderline personality disorder can occur in the transition to adulthood, along with serious criminal behaviour and gang involvement. Many individuals with CD become involved in the criminal justice system, and a significant minority are incarcerated[279]. Individuals with CD are more likely than their peers to be dependent on benefits, to become homeless and to be hospitalized or attempt suicide[280]. In addition, these individuals have children earlier, with more unplanned pregnancies, have more children than their peers and are more likely to display parenting problems, contributing to the intergenerational transmission of CD[235,279]. CD also has a major detrimental effect on the well-being of the affected individual's family members (not shown), with parents receiving legal sanctions or being socially excluded owing to their child's behaviours. In addition, parents and siblings of individuals with CD are often assaulted or verbally abused in their own homes.

lead to additional psychiatric disorders, such as major depressive disorder or post-traumatic stress disorder. In addition, one study reported increased criminal behaviour after youth incarceration[262]. The US-based Society of Adolescent Health and Medicine has, therefore, summarized several compelling arguments in favour of reducing youth incarceration[263]. Together, many widely used interventions for adolescents with CD lack evidence on efficacy and cost-effectiveness and may have iatrogenic effects.

### *Psychopharmacological interventions*

CD should primarily be treated using the psychosocial interventions discussed above. Nevertheless, pharmacological therapy is indicated in some instances, such as in children and adolescents with CD and comorbid ADHD. Individuals with CD and high levels of reactive aggression and severe emotion dysregulation can be given antipsychotics if psychosocial interventions have not led to a meaningful reduction in reactive aggression. Stimulants and neuroleptics are the most frequently

Box 4 | **The Research Domain Criteria**

The US National Institute of Mental Health's Research Domain Criteria (RDoC) initiative is an attempt to move away from symptom-based approaches to defining disorders and, instead, to classify the underlying neurocognitive mechanisms leading to disorders by focusing on neurobiology and observable behaviour. Disorders can arise owing to abnormalities in any of six domains: negative valence, positive valence, cognition, social processes, arousal or regulatory systems and sensory systems. Abnormalities in these processes are defined using a matrix that includes genes, molecules, cells, circuits, physiology, behaviour, self-report and paradigms[308].

The RDoC approach is still under development but has the potential to advance conduct disorder (CD) research and particularly to guide aetiological research. For example, the distinct causal processes leading to CD in children with versus without callous-unemotional (CU) traits can be explained using the RDoC domains, with the subgroup with CU traits having impairment in social and affiliative systems, whereas the subgroup without CU traits appear to display problems in regulatory systems (particularly those involved in regulating negative emotions and responses to aversive situations (such as anxiety and frustration))[161].

However, the RDoC approach has been criticized for ignoring the role of the environment and gene–environment interactions in the aetiology of mental disorders, as well as key developmental influences[16,309]. The construct validity of the domains has not yet been demonstrated, and the behaviours investigated within RDoC are argued to be too far removed from most patients' problems[309]. Most importantly, the RDoC approach currently lacks clinical utility, although the alternative perspective on psychopathology it provides could lead to the development of new, transdiagnostic or tailored interventions in the future.

studied and effective medications in CD or conduct problems in children with ADHD[264–266]. In addition, atomoxetine, clonidine, carbamazepine, sodium valproate and lithium have been studied in low-quality randomized controlled trials in children with ADHD and CD or aggressive behaviour but are not recommended for use in individuals with CD owing to small effect sizes and frequent adverse effects.

***Stimulants.*** Meta-analyses have shown medium to large effect sizes of psychostimulants (such as methylphenidate and amphetamines) on conduct problems in children and adolescents with CD, predominantly in those with comorbid ADHD[264,267]. Indeed, stimulant treatment should be commenced before or at the same time as psychosocial interventions for CD in those with comorbid ADHD. In one study, adding risperidone therapy to parent training and methylphenidate in 6–12-year-old children with ODD or CD with comorbid ADHD and severe aggression reduced aggressive behaviour but not CD symptoms[268]. In addition, at the 12-month follow-up point, most patients no longer adhered to the treatment protocol, and the treatment groups did not differ in CD symptoms or aggressive behaviour[269]. This study highlights the challenges involved in ensuring long-term compliance with pharmacological treatments for CD.

***Antipsychotics.*** Risperidone was shown to have large short-term effects on irritability and reactive aggression in 5–18-year-olds with ODD or CD in one meta-analysis[266]. Although the long-term efficacy and safety were established in children with ODD or CD and low IQ[270,271], long-term use of atypical antipsychotics leads to weight gain and metabolic syndrome[266]; therefore, the lowest effective dose should be administered for the shortest time possible.

### *Comorbid psychopathology*

The most frequent comorbid psychiatric and developmental disorders in individuals with CD are ADHD, ODD, developmental language disorder, dyslexia, anxiety disorders, depression, post-traumatic stress disorder and substance use disorders[272,273]. With the exception of ADHD, which is treated using stimulants (see Stimulants, above), the treatment of individuals with CD and comorbid psychopathology involves psychosocial treatments that target CD followed by specific interventions for the comorbid disorder if symptoms do not improve (FIG. 6). Psychotherapy studies in individuals with CD and anxiety or depression have shown that modular treatments that combine evidence-based interventions for CD (such as parent training) and depressive and anxiety disorders (such as individual cognitive-behavioural therapy) resulted in short-term and long-term improvements of symptoms of all disorders in children between 7 and 13 years of age[274,275]. No systematic studies of developmental language disorder or post-traumatic stress disorder treatment in CD have been performed. As effective intervention for developmental language disorder requires parental involvement and compliance, it can be implemented effectively only after family-based interventions for CD have been successfully completed.

### *Ineffective or harmful interventions*

Harmful interventions are those that exacerbate or prolong symptoms or induce negative adverse effects. Harsh, military-style 'boot camp' programmes, and programmes that attempt to deter delinquent individuals by taking them to visit prisons[276], are often ineffective or harmful. However, some evidence suggests that programmes involving contact with deviant peers might lead to positive outcomes when youths are well supervised and supported and are actively engaged in skills training[277]. Generally, many interventions and programmes in current use have not been evaluated by high-quality studies.

## Quality of life

Overall, the 2010 Global Burden of Disease study found that CD is one of the leading causes of disability in many world regions[3]. Little research has investigated the effect of CD on quality of life (QOL) as a tightly defined construct. Most QOL measures are inappropriate for use in children with CD owing to a focus on general health ratings, days in which health was poor or the individual was restricted in their everyday activities. Most research on QOL in childhood psychiatry has focused on clinically referred populations and is, therefore, likely to systematically exclude youths with CD as they rarely receive clinical treatment. Thus, we focus here on the effect of CD on important domains of functioning in childhood and adulthood.

Children with CD are more likely than their peers to experience a broad range of negative outcomes (FIG. 7). Prospective studies monitoring children with CD into late adolescence and young adulthood have shown that they are at increased risk of criminal behaviour, substance use, lower educational attainment, emotional

distress, suicidality, teen pregnancy, cardiovascular risk and high-risk sexual behaviour[4,278,279].

Large-scale longitudinal studies monitoring children with CD into adulthood have indicated that negative outcomes observed in young adulthood are still observed in middle adulthood, even after many of the symptoms of CD attenuate, and that the deleterious adult effects are as broad ranging as those observed earlier in the lifespan. These effects are not entirely explained by the presence of antisocial personality disorder or other psychiatric disorders. In addition, childhood-onset CD is associated with new risk related to economic insecurity, physical health and early mortality in adulthood, and those with childhood-onset CD that persists into adolescence have the most severe impairments in adulthood compared with those with time-limited CD in either childhood or adolescence[235,279–283] (although see REF.[284] for a meta-analysis that showed similarly poor outcomes in childhood-onset and adolescent-onset forms of CD). Not surprisingly, CD is associated with high levels of adult service utilization and societal and personal costs across criminal justice, health and social welfare sectors[285].

As CD is associated with individual risk factors (such as low IQ and attention problems) and family factors (such as low socio-economic status and parental maltreatment), it is possible that the negative outcomes experienced by individuals with CD are due to these factors. However, prospective studies have suggested that many, if not most, of the adolescent and adult effects of childhood-onset CD persist after accounting for these risk factors, with the strongest persisting associations with criminality and mental health[279,281,282,285,286]. Conversely, the associations of early conduct problems with educational or employment outcomes are weakened after accounting for low IQ and attention problems[279].

Conduct problems in childhood are, therefore, one of the strongest signals we have of future impairment. The substantial future costs to children, their families and society justify substantial, and ideally early, investments in preventing and responding to symptoms when they first emerge.

## Outlook

### *Raising awareness*

Relative to other psychiatric disorders, CD is underrecognized and frequently goes undiagnosed and untreated in many children and adolescents who seek help or are in contact with mental health services[2]. This is wholly avoidable as CD can be identified reliably through parent or teacher reports of mostly observable behaviours. Consequently, we believe that researchers and clinicians have a responsibility to raise awareness of CD among their colleagues and the general public and to communicate that effective evidence-based treatments and prevention programmes are available. In addition, a greater degree of mental health input into the youth justice, prison, educational and legal systems is required, as are better links between the different services that work with youths with CD.

Research on CD is dramatically underfunded in many countries including the United States[287] and the United Kingdom[288]. Despite conduct problems being the most common reason for referral to child and adolescent mental health services in these countries[1,289] and the robust evidence supporting the association between CD and poor outcomes[286], CD is not discussed in funding reports such as The Anatomy of NIMH Funding or UK Mental Health Research Funding. The reasons for this omission are not clear. Possible explanations include the common misconception that individuals with CD do not have a mental health disorder but, instead, are merely 'behaving badly' or the fact that "the severity and pervasiveness of the consequences of conduct problems could lead to a diffusion of responsibility and an absence of strong advocates"[287]. In this context, and because the disorder places such a large burden on patients, their families and society, CD should be treated as a major public health issue. Accordingly, interventions for CD should be properly resourced, and research funding should be allocated to CD on an equal basis to other psychiatric disorders, such as ADHD and autism spectrum disorder (Supplementary Fig. 1).

### *Mechanisms/pathophysiology*

Many outstanding questions and challenges lie ahead regarding the aetiology and pathophysiology of CD, and addressing these should help refine diagnosis and treatment approaches. The Research Domain Criteria (RDoC) initiative of the US National Institute of Mental Health offers an alternative approach to understanding the mechanisms underlying CD (BOX 4). A better

Box 5 | **CD as a neurodevelopmental disorder**

According to Raine[310], a neurodevelopmental disorder is a condition that originates in infancy or childhood (but potentially in prenatal life); is characterized by abnormalities in brain development that could affect brain structure or function throughout the lifespan; is associated with neurocognitive deficits; has an aetiology that is, at least partly, genetic; has a relatively stable course across the lifespan; and results in poorer adult outcomes across multiple domains.

Some individuals with conduct disorder (CD) fulfil all of these criteria, although some do not have problems in childhood, whereas others have difficulties in childhood but subsequently 'grow out' of CD. Thus, the case for childhood-onset persistent CD (also known as 'life-course persistent CD') being a neurodevelopmental disorder is particularly strong. Furthermore, the fact that CD with callous-unemotional (CU) traits is more pervasive and persistent than CD without CU traits[311] has led several authors to argue that the former is more likely to be a neurodevelopmental disorder than the latter[312]. The evidence supporting the conceptualization of CD as a neurodevelopmental disorder includes its moderate heritability (which is higher in CD with CU traits[93]), the overlap between genetic liability for CD and other disorders that are considered 'neurodevelopmental', its association with abnormalities in brain structure and function, its robust links with neuropsychological deficits (particularly in emotion processing) and its poor adult prognosis (even in those who 'grow out' of CD). The most directly relevant evidence comes from studies reporting higher rates of markers of abnormal brain development (enlarged cavum septum pellucidum) in both adolescents with CD[313] and adults with antisocial personality disorder[314]. On the point about childhood origins, some disorders that are considered 'neurodevelopmental', such as schizophrenia, frequently do not emerge until late adolescence or adulthood, whereas others, such as attention-deficit/hyperactivity disorder, frequently remit in the transition to adulthood[315]. However, some authors have argued that longitudinal neuroimaging data showing that brain development is disrupted are needed to conclude that CD is a neurodevelopmental disorder[310]. Conceptualizing CD as a mental health disorder with neurodevelopmental origins also has major implications for the youth justice, prison, educational and legal systems — it may encourage a less punitive and more treatment-focused approach.

Table 2 | **Emerging technologies, approaches and initiatives in CD research**

| Area | Approach | Comments |
|---|---|---|
| Technological advances | Genome-wide association studies, exome sequencing and whole-genome sequencing | Identify rare genetic mutations of potentially larger effect (copy-number variations), genome-wide significant common genetic variants and development of a polygenic risk score for CD |
| | Epigenetics or epigenomics | Characterize the effects of established environmental risk factors on gene expression (especially DNA methylation) and links to CD subtypes or phenotypes |
| | Animal models | Provide model systems to screen for drugs that might reduce CD symptoms and understand the mechanisms underlying the effects of environmental risk factors (for example, maltreatment or chronic stress) that are challenging to study in a valid and ethical way in humans |
| Innovation in clinical practice and diagnosis | Enhance diagnostic methods for assessing CD subtypes in clinical settings | To improve personalized clinical practice and develop, test and standardize innovative methods for assessing key indicators of subtypes of CD, such as age at onset and limited prosocial emotions, which can be used in a wide range of clinical settings |
| | Online parent training programmes and psychoeducation about CD | To improve access to evidence-based treatments and disseminate knowledge of effective parenting strategies, especially for hard-to-reach families, development of online platforms would be beneficial |
| | Using knowledge of CD subtypes and mechanisms to inform and personalize clinical practice | Neuropsychological, neuroimaging and genetic studies could inform the identification of subtypes that might require different treatments and potentially move away from a symptom-based approach to more directly target underlying mechanisms; intervention studies could also stratify according to the identified subtypes |
| | Monitoring symptom change and improving treatment delivery using new technologies | Mobile technologies could allow clinicians to track improvements in symptoms as treatment progresses and coach parents to improve their parenting practices in vivo (that is, in real-life situations) |
| | Development of therapeutic games and interventions delivered using virtual reality | Computerized and virtual-reality-based therapy could target specific problems (for example, tolerance of provocation or helping patients take the perspective of victims to enhance empathy) and increase acceptability of treatment |
| Longitudinal research designs | Longitudinal multimodal neuroimaging studies | Understanding relationships between aberrant brain development and development of CD symptoms should be a key objective, as well as understanding how different brain abnormalities (structure versus function) relate to each other over time |
| | Birth cohort studies starting in the prenatal period | Studies of this kind that investigate and quantify the magnitude of effects of different environmental, genetic and dispositional risk factors over time (including those occurring in prenatal life) are needed to identify the most important modifiable risk factors and inform theories of CD development |
| | Family-based studies that investigate multiple generations using genetically sensitive designs | Knowledge of how CD is transmitted intergenerationally is urgently needed — this has major practical implications for prevention and treatment |
| International collaboration | ENIGMA Antisocial Behaviour working group | As many neuroimaging and genetic studies of CD have been small and underpowered, combining data across multiple laboratories, studies and age groups has the potential to identify the most robust neurobiological changes and genetic markers for CD and quantify the size of the effects; it will also allow us to take a lifespan perspective on CD |
| | European Commission-funded consortia on CD and aggression | These cross-European consortia have adopted multilevel designs investigating CD and aggression from multiple perspectives, including genetics and neuroimaging, and phenotypes related to CD such as callous-unemotional traits (MATRICS) or subtypes of aggression (ACTION) and sex differences in CD (FemNAT-CD) |

ACTION, Aggression in children: unraveling gene-environment interplay to inform treatment and intervention strategies; CD, conduct disorder; ENIGMA, Enhancing Neuro-Imaging and Genetic research through Meta-Analysis; FemNAT-CD, Neurobiology and Treatment of Adolescent Female Conduct Disorder; MATRICS, Multidisciplinary Approaches to Translational Research in Conduct Syndromes.

understanding of pathophysiology could inform targeted prevention efforts for specific subgroups. Indeed, future research using systematic and statistically advanced subtyping and dimensional approaches should focus on identifying more narrowly defined clinical subgroups with more specific environmental and neurobiological vulnerabilities. At present, no well-powered GWAS or epigenetic or G×E studies specifically focusing on different subtypes of CD have been carried out. The impact of comorbidity also needs to be studied more systematically by stratifying patients according to the presence or absence of comorbidity in future neurocognitive and neuroimaging studies. Despite robust evidence for sex differences in the prevalence of CD, comparatively little is known about sex differences in the aetiology and pathophysiology of CD[290]. In addition, whereas much of the evidence reviewed here supports the classification of CD as a neurodevelopmental disorder, further evidence from longitudinal studies is needed (BOX 5).

As noted by the Grand Challenges in Global Mental Health Initiative[291], there is a pressing need for prospective longitudinal studies that start in the prenatal period that combine multiple levels of analysis (such as assessing environmental, genetic, neuroimaging and behavioural factors; TABLE 2). These studies are needed to identify and quantify how different risk factors operate to cause CD and clarify how they are related to different subtypes and developmental trajectories of CD. Such studies could contribute to the development and refinement of models of CD, as even the most established

neurocognitive models[292] have not been tested in prospective longitudinal studies. These studies could also help us understand how risk of CD is transmitted across generations, beyond the genetic contribution to such risk. These prospective longitudinal and family-based studies will be costly and time-intensive and will require interdisciplinary collaboration.

Despite robust evidence for an association between CD and physical health problems (such as obesity) in adulthood, little is known about the mechanisms that mediate these associations. Given the small sample sizes of existing imaging and genetic studies of CD, much would be gained from sharing existing data sets in international collaborations such as Enhancing NeuroImaging and Genetic research through Meta-Analysis (ENIGMA)[293] or the Psychiatric Genomics Consortium. These initiatives could lead to the discovery of biomarkers and identification of new treatment targets.

### *Prevention*

Given the enormous personal and societal costs associated with CD and its negative effects across the lifespan, increasing funding for the prevention of CD is a key priority. Studies have identified several modifiable environmental and individual risk factors for CD that could be targeted early in life by preventive work. However, more research is needed to determine the most influential risk factors and to tailor these prevention efforts to the characteristics of subgroups of youths with CD and their families. A key challenge will be to convince policy-makers and health-care commissioners to adopt a long-term perspective as the financial resources and commitment needed might not lead to reduced public spending until decades later[287].

### *Treatment*

In the absence of biomarkers for CD and its subtypes, current treatments largely target symptoms[294]. Similar to other areas of psychiatry and medicine, we expect to see a greater emphasis on personalized treatments for CD in the future — interventions will increasingly be tailored to the individual's specific difficulties, incorporating knowledge of causal pathways[219] (TABLE 2). As a starting point, intervention trials could stratify patients on the basis of neurobiological or neuropsychological characteristics to examine whether treatments are more effective in specific subgroups. Another important area for future therapeutic innovation is the development and evaluation of interventions for children and adolescents that live outside the family (those in foster care or looked-after children living in children's homes or youth welfare institutions), as CD is three to four times more common in these groups than in the general population[295]. Given the cost-effectiveness and flexibility of delivery of online parent training interventions, the use of these interventions is likely to increase over the next decade. However, we urge caution here, as initial evaluations of such programmes have revealed very low engagement and retention rates[296], and online interventions potentially exclude disadvantaged families with limited reading ability, familiarity with computers or Internet access. For these reasons, online interventions should be offered as an adjunct to, rather than a replacement for, standard individual or group-based interventions. Finally, there is promising evidence that dietary interventions such as omega-3 supplementation could reduce aggression and antisocial behaviour[297].

As William Wordsworth put it, "The child is father of the man"; many children with CD go on to develop antisocial personality disorder in adulthood and place a disproportionate burden on our health-care, legal, educational and social welfare systems. Consequently, tackling the root causes of CD early in life and providing effective treatments for individuals who develop CD are likely to lead to major benefits for the patients, their families and society. We are optimistic that methodological advances combined with large-scale international and interdisciplinary collaboration will lead to step changes in our understanding of the aetiology of CD. These developments will, in turn, allow us to optimize the diagnosis, treatment and prevention of CD.

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### Competing interests
C.F. has served as a consultant on autism spectrum disorders for Desitin and Roche. She receives royalties for books on autism spectrum disorders, attention-deficit/hyperactivity disorder and depression. B.F. has received educational speaking fees from Medice. All other authors declare no competing interests.

### Publisher's note


### Supplementary information
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**Eyberg Child Behavior Inventory:** https://www.parinc.com/products/pkey/97
**Inventory of Callous-Unemotional traits:** https://sites01.lsu.edu/faculty/pfricklab/icu/
**Kiddie-Schedule for Affective Disorders and Schizophrenia:** http://pediatricbipolar.pitt.edu/resources/instruments
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