Universitat Autònoma de Barcelona

Callous-Unemotional Traits among Children: Developmental and Moderating Factors

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Callous-Unemotional Traits among Children:

Developmental and Moderating Factors

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Presentation

This thesis focuses on the developmental study of callous-unemotional (CU) traits in a community sample of children that were followed up between ages 3 to 13. The empirical work presented in this thesis is framed in a larger ongoing longitudinal project examining child psychopathology risk factors and mental health outcomes [Grant PGC2018-095239-B-I00 (MICIU/FEDER)].

This thesis examines relevant factors in the etiology of CU traits, such as the role of gene-by-environment interactions and the trajectories of CU traits and stressful life events. Moreover, this thesis sought to provide meaningful cut-off scores to assess CU traits. Each of these aims led to three studies published in peer-reviewed journals. Therefore, the present dissertation is structured as a thesis by a compendium of publications.

Abstract

Objectives: Callous-Unemotional (CU) traits are associated with different environmental and personal risk factors. This research explores a gene-by-environment interaction between MAOA polymorphisms and parenting practices and analyses the developmental pathways of children with CU traits and stressful life events. Finally, cut-off scores for the teacher-rated Inventory of Callous-Unemotional traits are also provided.

Methods: A community sample of children was followed between ages 3 and 13, and different factors related to CU traits, such as environmental and personal factors, genotype, and mental health, were assessed annually. The statistical analysis includes linear regressions, logistic models, and receiver operating characteristic (ROC) curves.

Results: Sex-specific differences were found in children with CU traits, with girls being more vulnerable toward MAOAxParenting interactions than boys. In combination with stressful life events, CU traits co-occur in low-income households in which the caregivers suffer from economic and mental health problems. To correctly identify children with CU traits based on teacher information of the Inventory of Callous-Unemotional Traits (ICU), cut-off scores of 26 for boys and 22 for girls could be used.

Conclusions. This study explores environmental, genetic, and personal factors that influence CU traits from early childhood on and from a longitudinal perspective. The risk factors described in this thesis could help detect a subgroup of children with CU traits more vulnerable to severe psychosocial problems during childhood and adolescence. Moreover, this thesis offers valid ICU cut-off scores that can be used in clinical settings to identify children at high risk for developing conduct problems or oppositional defiant disorder. Finally, early detection of CU traits might be beneficial to tailoring early prevention programs.

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Chapter One: Introduction and Aims

Callous-Unemotional (CU) traits are characterized by socio-emotional difficulties that include lack of remorse or guilt, lack of empathy, unconcern about performance at school or work, and shallow or deficient affect (Frick et al., 2014). CU traits in children and adolescents are often interpreted as the affective dimension of adult psychopathy (Salekin, 2016), sharing core features such as low interpersonal emotional sensitivity, poor emotion recognition, deficits in prosocial behavior, and fearlessness (Waller & Hyde, 2018b). A significant body of research has shown that this subgroup of children and adolescents with CU traits are at higher risk of engaging in antisocial and aggressive behavior, indicating more severe conduct problems, and being implicated in crimes and delinquency (Frick et al., 2014). Poorer treatment outcomes are also related to CU traits and more stable trajectories of antisocial behavior (Frick & Myers, 2018). Therefore, the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition, (DSM-5) (American Psychiatric Association, 2013) has introduced CU traits as a "Limited Prosocial Emotions" specifier for conduct disorder (CD), and the International Classification of Diseases, 11th revision, (ICD-11) (World Health Organization, 2018) has adopted this specifier for the diagnosis of conduct-dissocial disorder and oppositional defiant disorder (ODD).

Interestingly, CU traits are also associated with other disorders, such as attention deficit hyperactivity disorder (ADHD) or autism spectrum disorder (ASD) (Leno et al., 2021). Therefore, CU traits could be a valid transdiagnostic specifier for describing a subgroup of children with more severe problems, not only in the diagnosis of CD or ODD but also in combination with other disorders (Herpers et al., 2012). For example, adolescents with ASD and comorbid CU traits show higher conduct, peer problems, and lower prosocial behavior (Leno et al., 2021). Also, children with ADHD and comorbid CU traits show more proactive aggression and severe conduct problems (Blader et al., 2013). Similarly, children with ODD and

comorbid CU traits show more severe patterns of ODD behavior, aggressive behavior, and more significant impairment (Ezpeleta et al., 2015; Hawes et al., 2013).

Estimating the prevalence of CU traits is rather complicated and depends on different factors, such as age, sample type, instruments, and informants used to assess CU traits. For example, previous research has focused mostly on middle-childhood and adolescent samples from community, clinic-referred, or delinquency contexts, using two different instruments such as the Antisocial Process Screening Device (Frick & Hare, 2002) or the Inventory of Callous-Unemotional Traits (Frick, 2004). Moreover, most studies have not treated CU traits as a stand-alone concept but in combination with CD (Colins et al., 2018). For example, Herpers et al. (2012) reviewed epidemiologic studies on CU traits and only found five studies based on community samples that analyzed CU traits separately from CD. Among these studies, the prevalence of only CU traits accounted for 3-11% among children and adolescents.

Similarly, Colins et al. (2018) found that the prevalence of only CU traits in a community sample of children was around 10%. In a clinical sample, up to 50% of children with CD also met the CU trait criteria, while children with only CU traits made up to 30% (Kahn et al., 2012). All in all, a prevalence between 10-30% could already be considered relatively high, making it essential to study CU traits outside of CD. Therefore, developing specific cut-off scores for instruments such as the Inventory of Callous-Unemotional traits may help practitioners correctly identify those children with high CU traits

CU traits and their associated Characteristics

Describing the biological, socioemotional, and cognitive characteristics of children and adolescents with CU traits has become a significant stream of research that helps to identify this subset of children at higher risk of presenting pathways to antisocial and psychopathic behavior. Different systematic reviews (Frick et al., 2014; Herpers et al., 2014;

Northam & Dadds, 2020; Squillaci & Benoit, 2021; Waller et al., 2020) have analyzed the current literature on the different characteristics of children with CU traits, but it has to be noted that they do not always control for CD or other disorders. Therefore, it is difficult to ascertain whether the correlates found in the metanalytic reviews are specific to CU traits only or are present in CU traits in combination with CD and other disorders.

Examining biological markers for CU traits has been one of the main aims of previous research. CU traits have been consistently linked to compromised limbic functioning, particularly a disrupted functioning of the amygdala, and a blunted stress response system, including altered hormonal functioning and physiological activation (Blair & Zhang, 2020; Frick et al., 2014; Herpers et al., 2014).

Neuroimaging studies have explored the volume and activation of different brain regions to investigate the neural correlates of CU traits. The findings indicate that high CU traits are associated with lower brain volumes and decreased cortical structures in frontotemporal regions (Bolhuis et al., 2019). Also, reduced amygdala volume (Cardinale et al., 2019) and an amygdala hypoactivation in response to fearful stimuli (Lozier et al., 2014), as well as a weaker connection between the amygdala and the orbitofrontal cortex was found (Graziano et al., 2022). These findings suggest that children with CU traits have diminished neural responses to emotional triggers in limbic brain regions typically implicated in affective processing. While the amygdala is the brain region responsible for a first affective evaluation, the orbitofrontal cortex processes information for decision-making. Blunted amygdala and frontal cortex functioning might be related to less fearfulness and inadequate attributions of affection (Herpers et al., 2014), which can be characteristics of CU traits. The hypoactivity and hypoconnectivity of the amygdala with other brain regions might also affect moral judgment and empathic behavior and become a risk factor for rule-breaking and aggression (Cardinale et al., 2018).

This altered brain activity among children with CU traits also influences the hormonal system, particularly cortisol levels (Polier et al., 2013). Cortisol is the stress hormone released into the organism through activating the amygdala, especially in response to fear. If the amygdala's activation is limited in children with CU traits, they should show lower cortisol levels. Hormonal studies have examined this hypothesis, indicating that children with increased CU traits show lower cortisol reactivity towards stressful stimuli such as listening to arguments (Wright et al., 2019). Similarly, electrophysiological studies have observed that elevated CU traits are associated with lower physiological arousal, so children with CU traits show lower changes in heart rate in response to an emotional movie (Frick et al., 2014; Herpers et al., 2014). The decreased stress-response system in children with CU traits might explain core characteristics of CU traits such as blunted emotional reactivity, fearlessness, and limited prosocial behavior (Polier et al., 2013).

In line with the neural correlates that have been linked to CU traits, the socio-emotional characteristics of this subgroup of children can be described as impaired and shallow. They show deficits in responding to others' distress (Waller et al., 2020), have difficulties in recognizing others' emotional expressions (Demetriou & Fanti, 2021), and show less preference for face already from early childhood on (Bedford et al., 2015). Thus, they report having difficulties in responding emotionally to others (Ciucci et al., 2015).

This impaired emotional reactivity has led to describing children with CU traits as "unemotional," but this is currently under debate. While one stream of research found that children with CU traits generally show low emotional reactivity towards all kinds of emotional stimuli, other studies show that it is only observed in response to fearful or sad stimuli (Northam & Dadds, 2020). Moreover, emotional reactivity might change during childhood, and younger children seem to be more emotionally sensitive when compared to adolescents, especially when they get frustrated or experience joy (Northam & Dadds, 2020). This

controversy would explain why the "unemotional" subscale of the ICU shows the weakest internal consistency and the lowest correlations with CU factors (callousness and uncaring) or other external criteria, such as CD symptoms (Benesch et al., 2014). Therefore, it would be more accurate to describe children with CU traits as fearless, more capable of managing their fear (Thomson et al., 2020), and less reactive towards sad emotions than to describe them universally as unemotional.

Blunted emotional reactivity is also related to difficulties in empathy, a social core characteristic of CU traits (Frick & Kemp, 2021). Empathy features a cognitive component (theory of mind) and an affective component (empathic arousal), and in the case of children with CU traits, a recent meta-analysis found deficits in both dimensions but also reduced prosociality and guilt (Waller et al., 2020). Therefore, it is proposed that the cognitive and affective deficits in empathy hinder children with CU traits from participating in prosocial behavior (to respond to others' needs to help them altruistically) and experiencing prosocial emotions (to resonate with others' feelings) (Herpers et al., 2012).

The deficit of empathy in children with CU traits is also associated with a lack of guilt and concern for the consequences of their acts (Frick & Kemp, 2021). As children with CU traits have these difficulties in empathy and emotional processing toward fear and sadness, they may also fail to feel negative emotions (guilt, shame) as a consequence of their transgressive behavior (Waller et al., 2020). Indeed, children with CU traits may know right and wrong behavior, thus showing intact moral conscience, but may not feel the associated moral emotion of guilt, which results in moral disengagement (Paciello et al., 2020). Further, these authors suggest that disengagement is linked to antisocial behavior, including rule-breaking, aggression, and violence, which are behaviors also observed among children with CU traits (Longman et al., 2016).

In addition to neural and emotional correlates, cognitive characteristics associated with CU traits have been found. Punishment insensitivity and reward dominance are probably CU traits' most observed cognitive features (Hawes et al., 2014). The fearless temperament of children with CU traits could explain their punishment insensitivity, as the low emotional arousal towards threats might impair the learning process about the consequences of their behavior, even if those consequences are negative in the form of punishments (Waller & Hyde, 2018b). Consequently, they seem to be more resistant to teacher's interventions in which limits are set (Allen et al., 2018), are less connected to school and more unconcerned about their performance (Fanti et al., 2017), show poor academic performance (Levine et al., 2022), and poorer treatment outcomes (Hawes et al., 2014).

Interestingly, hypersensitivity towards reward has been found among children with CU traits, who show a higher neural activation when they receive rewards than those without CU traits (Hawes et al., 2020). Therefore, using rewards in therapeutic contexts might be a promising strategy. For example, family-based therapy focusing on positive parent-child relationships and a reward system for desired behavior decrease CU traits in preschoolers (Donohue et al., 2021). Also, rewarding parenting practices seem to moderate the heritability of CU trait development (Henry, Dionne, Viding, Vitaro, et al., 2018), so when children experienced warm and rewarding parenting strategies, CU trait heritability was lower than when children experienced less rewarding strategies.

Further, reward sensitivity is often linked to impulsive behavior, poor inhibitory control, and a deficit to delay gratifications (Leshem & King, 2021). Impulsive traits are one of the core characteristics of child psychopathy, together with grandiose-manipulative traits and CU traits (Salekin, 2016). Therefore, it is no surprise that CU traits in childhood and adolescence can co-occur with impulsivity (Blader et al., 2013) and, consequently, with risk behavior (Thornton et al., 2019). Even preschoolers with CU traits can already present deficits in

executive functioning and impulsivity, resulting in more aggressive behavior in later childhood (Waller, Hyde, et al., 2017). Fanti et al. (2018) explain that CU traits, in combination with impulsivity, predict more severe CD and antisocial behavior due to the inability of the affected children to control socially inappropriate behaviors.

In sum, the review of the characteristics of children with high CU traits suggests a complex interplay between impaired brain functioning, emotional dysregulation, and difficulties in executive functioning, empathy, prosocial behavior, moral reasoning, and guilt. A few attempts have been made to define a model of the etiology of CU traits that integrates the core correlates and explains the mechanisms through which CU traits develop. For example, the Sensitivity to Threat and Affiliative Reward (STAR) model posits that the emotional deficit in reacting toward threats (e.g., fearlessness, lack of guilt), together with the shallow interpersonal relationships, explains the development of CU traits (Waller & Wagner, 2019). Future research should address such integrative approaches to understand better the role and interplay of the different correlates of CU traits.

Changes in CU Traits along Development

Previous longitudinal research has identified four developmental trajectories of CU traits from childhood to adolescence: an early childhood onset high stable group; an adolescent onset increasing group; an early childhood onset decreasing group; and a low, stable group (Fanti et al., 2017; Fontaine et al., 2010; Klingzell et al., 2016). The prevalence of the high stable group is around 6%, while the increasing and decreasing groups account for approximately 10% each (Docherty et al., 2019). Even though the early childhood onset group is the least prevalent, it is the most severely affected one, accumulating different environmental and personal risk factors, such as experiencing harsh parenting practices and shallow peer relationships, showing low social skills, and less self-regulation in comparison to the other groups of children (Fanti et al., 2017). Early onset high stable CU traits are also associated

with fearlessness and psychopathic personality traits (Klingzell et al., 2016). Among adult outcomes, this high stable group shows a higher risk for violent behavior and aggression in adulthood, being two times more likely to be arrested than the other groups (Docherty et al., 2019).

While most studies found the most significant differences between the early childhood onset group and the other three groups, Docherty et al. (2019) observed that the adolescent-onset increasing group shows similar outcomes to the early onset high stable group in terms of psychopathic traits and antisocial behavior in adulthood. At the same time, the decreasing group shows more risk for delinquency than children in the low, stable group. They suggest that showing CU traits at any time during childhood development might lead to problematic outcomes, though the mechanisms might be different for each trajectory and should be addressed in future research.

As early onset CU traits are related to more severely affected trajectories, researchers have started to address the development of CU traits in early childhood. The first question to be solved was whether CU traits could be measured in preschoolers as early as age 2 or 3. Results show that CU traits can already be observed and assessed around age 3 (Ezpeleta et al., 2013; Kimonis et al., 2016). At this age, and even before around age 1, children can already express affective empathy, that is, to resonate with others' feelings and engage in prosocial behavior (Wakschlag et al., 2018). However, Zumbach (2021) found that preschoolers with high CU traits often show deficits in empathic behavior and general socioemotional skills. Children with CU traits may also be less interested in interpersonal relationships. For example, children around age two who engage in low social affiliations are also at high risk of showing CU traits around age 3 (Perlstein et al., 2022). Further, it seems that babies who are more interested in objects than in faces and eye contact might show higher CU traits around

ages 2-3 (Bedford et al., 2015) and that preschoolers with CU traits experience more severe conduct problems in the preschool period (Longman et al., 2016).

Early CU traits predict socioemotional difficulties during childhood (Frick & Kemp, 2021). For example, CU traits at age 3 predict problem behavior at age 4 (Hyde et al., 2013), general externalizing behavior and global impairment, and a higher probability of mental health disorders at age 5 (Ezpeleta et al., 2015), and rule-breaking and aggressive behavior at age 10 (Waller et al., 2016).

All in all, these studies on early CU traits highlight two ideas: First, the importance of assessing CU traits multiple times during childhood and adolescence, as this would help to identify the child's trajectory and to establish more personalized treatment programs. Second, high CU traits can be considered a severe risk factor during development, especially in early childhood. Studies focusing on the longitudinal development of CU traits are thus needed to understand further how CU traits change during childhood and adolescence.

Genetic and Environmental Etiology of CU Traits

As mentioned, the etiology of CU traits has been studied from genetic and environmental perspectives and interaction studies on genetics and environment. Therefore, we will dedicate the following pages to further describing the role of genes in the development of CU traits, and later we will focus on two main environmental variables of CU traits: parenting practices and life stressors.

The Role of Specific Genes

Research on the biological etiology of CU traits has concentrated on conducting different kinds of genetic studies: quantitative genetic studies based on twin and adoption studies which analyze the contribution of genetic and environmental factors in the variance of CU traits; and molecular genetic studies, which determine the genetic mechanism of a gene in the

development of CU traits (Moore et al., 2019). Systematic revisions on genetic studies have identified that the heritability of CU traits ranges from 40-80% (Moore et al., 2019; Viding & McCrory, 2012a), depending on the age of the studied sample. Generally, the younger the studied sample, the higher the genetic influence on CU traits, which suggests that genes drive CU traits that appear in early childhood. For example, one of the few studies on preschoolers with CU traits found a heritability of 72% at age 2 and 65% at age 3 (Flom & Saudino, 2017), while results in children and adolescence seem to reach estimates between 36-67% (Viding et al., 2013).

Recent findings on genetic influences on developmental trajectories of CU traits found that childhood-onset CU traits (around age 7) seemed to be under stronger genetic influence than CU traits that emerged in later adolescence and that this early genetic contribution also influences CU traits over time (Takahashi et al., 2020). For example, CU traits at age 7 seem to explain up to 14% of the variation of CU traits at age 16 (Takahashi et al., 2020). Moreover, new genetic contributions to CU traits might emerge during childhood. For example, Henry, Dionne, Viding, Petitclerc, et al. (2018) studied twins between 7 and 12 years and found that the genetic influences on CU traits at age 7 remained stable through age 12, but that around age 9 and 10, new genetic influences emerged.

In addition to age, the genetic heritability of CU traits might also be under the effect of sex (Moore et al., 2019). Some studies have found that CU traits in boys are under more substantial genetic influence than CU traits in girls (Fontaine et al., 2010), but findings are still preliminary. Therefore, further research on CU trait heritability should address potential sex differences.

Another stream of research concentrated on finding candidate genes for CU trait development. While genome-wide studies did not show significant results for a single candidate gene for CU traits (Viding et al., 2013), molecular genetic studies have identified genes such

as Brain-derived neurotrophic factor (BDNF) (Willoughby et al., 2013), Catechol O-methyl-transferase (COMT) (Fowler et al., 2009), serotonin transporter (Widom et al., 2020) and oxytocin receptor gene (OXTR) (Ezpeleta et al., 2019) associated with the development of CU traits. These genes feature polymorphisms that contribute differently to neural plasticity (in the case of BDNF), serotonergic neurotransmission (in the case of COMT and serotonin transporter), and oxytocin regulation (in the case of OXTR). In this sense, the methionine allele VAL66MET of the BDNF gene, the low activity polymorphism of the serotonin transporter 5-HTTLPR, the heterozygous genotypes of GA and AA of OXTR, and the COMT Val/Val genotype have been related to CU traits. All in all, these polymorphisms may be related to an alteration of the regulation of the serotonergic and oxytocin systems, which may result in correlates of CU traits such as fearlessness, insensitivity towards punishment, and low empathy (Moore et al., 2019).

Thus, molecular genetic studies on antisocial behavior and aggression (Gard et al., 2019; Salvatore & Dick, 2016; Veroude et al., 2016) have identified another gene that might also be connected to CU traits: Monoamine Oxidase A gene (*MAOA)*. This gene encodes for the Monoamine Oxidase A enzyme (*MAO-A*), which is also involved in the serotonin system. MAOA features a long and short version of the gene's promoter region. Depending on the number of tandem repeats (uVNTR), the transcriptional efficiency of the gene is changed, resulting in low and high activity alleles (*MAOA*-L and *MAOA*-H, respectively) (Sabol et al., 1998). Because the *MAOA* gene is located on the X chromosome (Xp11.23), females can be homozygous (*MAOA*-LL/*MAOA*-HH) or heterozygous (*MAOA*-HL), whereas males are hemizygous (*MAOA*-L or *MAOA-H)*. Children and adolescents with *MAOA*-L, especially males, seem to engage in more aggressive and externalizing behavior, delinquency, use of weapons, or shootings compared to their peers who carry *MAOA*-H (Byrd & Manuck, 2014; Veroude et al., 2016). These findings might be explained by the impact of *MAOA*-L on brain activity, as

it is associated with amygdala hyperactivation and prefrontal cortex hypoactivation, which are involved in emotional processing, impulse control, and aggressive behavior (Meyer-Lindenberg et al., 2006).

Interestingly, carrying *MAOA*-L might only be a genetic risk factor in combination with adverse environments. Gene x Environment (G x E) interaction theorizes that genetic expression might interact with environmental factors, conferring vulnerability or plasticity towards developing certain behaviors (Belsky & Pluess, 2009). Indeed, previous G x E research has observed that boys with *MAOA*-L who have experienced maltreatment, physical abuse, or neglect are more likely to show conduct disorder, aggressive and antisocial behavior than those children that carry *MAOA*-H (Byrd & Manuck, 2014; Foley et al., 2004; Haberstick et al., 2014; Kim-Cohen et al., 2006; Prom-Wormley et al., 2009).

The studies on *MAOA* would suggest the idea that *MAOA* could be a risk gene that confers vulnerability to hostile environments (Ficks & Waldman, 2014). Further, *MAOA* could be interpreted as an example of a robust gene-by-environment interaction that can be explained from the diathesis-stress model: an interaction between a predispositional vulnerability, the diathesis, and the stress caused by life experiences. From another perspective, the differential susceptibility model (Belsky & Pluess, 2009) highlights that such vulnerability genes could be reconceptualized as plasticity genes, as they confer sensitivity towards adverse environments but may also confer benefits towards positive environments. Applied to CU traits, a G x E interaction that fits the diathesis-stress model was found on *MAOA*-L and maltreatment among male adolescents with comorbid attention deficit hyperactivity disorder (ADHD) (Fowler et al., 2009). However, this preliminary finding has not yet been explicitly replicated in the context of CU traits, in early childhood and for both sexes. Therefore, the question arises whether *MAOA* could also be considered a risk or plasticity gene in developing early CU traits in both negative and positive environments among both sexes.

The Role of Parenting Practices

Research on CU traits has addressed the issue of G x E interaction to explain CU trait etiology, highlighting the moderating role of the environment. Parenting practices are a relevant environmental factor, especially in early childhood (Glenn, 2019; Tomlinson et al., 2021). The genetic contribution to CU traits seems to be buffered by increasing warm and rewarding parenting practices and limiting harsh parenting strategies (Henry, Dionne, Viding, Vitaro, et al., 2018). Such a G x E interaction has already been observed in early childhood. For example, in an adoption study of babies and toddlers, positive reinforcement of adoptive mothers at 18 months was related to lower CU traits after ten months in the case of the babies whose biological mothers showed antisocial behavior (Hyde et al., 2016). These findings suggest that positive parenting strategies, including rewards, reinforcements, warmth, involvement, and consistent discipline, could be considered substantial protection factors for developing or increasing CU traits (Graziano et al., 2017).

Previous studies have observed the protective role of positive parenting practices on CU traits starting in early childhood. For instance, a combination of early maternal sensitivity to distress (responding to their child's crying, for example) and positive regard (or warmth) when children were 29 months old predicted lower CU traits during the preschool period (Wright et al., 2018). In addition, children whose parents engaged in more effective parent-child relationships and used reinforcement in middle childhood exhibited fewer CU traits (Muratori et al., 2016). Positive parenting practices also seem to confer long-lasting protecting effects, so parental warmth reported in preschool predicted fewer CU traits among adolescents (Goulter et al., 2020). Thus, low positive parenting practices have been related to higher CU traits (Pauli et al., 2021), emerging as a potent environmental risk factor for CU traits (Waller et al., 2015).

Negative and harsh parenting practices, including low responsiveness and involvement, punishment, distress, and inconsistent discipline, have also been linked to CU traits (Hawes et al., 2011). For example, a study on boys between 7 and 15 years showed that those with early onset CU traits had experienced more harsh parenting and maltreatment than children with low CU traits (Byrd et al., 2016). A systematic review on the relationship between parenting, CU traits, and antisocial behavior also concluded that negative parenting behaviors should be considered a risk factor for increasing CU trajectories, especially in preschoolers (Waller et al., 2013).

As research has found that both negative and positive parenting practices can influence the development of CU traits (Dargis & Li, 2020; Waller, Shaw, et al., 2018), it is of no surprise that parent training has been the main focus of intervention to reduce CU traits (Hawes et al., 2014). For example, Fleming et al. (2022) adapted a standard parent-child intervention therapy (PCIT) to the demands of children with CU traits and worked with families whose children were between 3 to 7 years. Instead of only coaching parents in positive parenting practices (praise and expression of enjoyment, for example) and time-out procedures – which were the core components of the standard PCIT–, they included warm and affectioned behavior, rewards, and positive reinforcement in response to prosocial behavior of the child as crucial components of their adapted CU intervention program. The experimental results seem promising, as this adapted intervention program, compared to the standard one, reduced CU traits and showed better long-term results at a three-month follow-up, with children maintaining or even improving conduct problems and CU traits (Fleming et al., 2022; Kimonis et al., 2019). Therefore, a treatment recommendation would be to train parents in reward-driven approaches, which have been shown to reduce CU traits (Donohue et al., 2021).

Targeting early childhood practices is particularly important because it is a sensitive period for developing socioemotional skills (Waller & Hyde, 2018a). Parents play a central

role in modeling socioemotional behavior for their children, as the children learn how to react and interpret emotions and social cues through the parents' responses (Shaw et al., 2019). Such parent-driven effects on CU traits suggest that when parents engage in harsh and inconsistent parenting practices, children might adopt strategies such as harshness and punishments in their own emotional and behavioral repertoire and that they might interiorize that such behavior is socially acceptable. Lack of understanding of moral judgment, social behavior, and empathy might result from harsh or inconsistent parenting (Waller & Hyde, 2018a). For example, children who experienced parental harshness when they were 2 were more likely to show CU traits at age 4 (Waller et al., 2012); also, harsh parenting at age 4 increased the risk for showing higher CU traits in adolescence (Barker et al., 2011). Similarly, corporal punishment and poor monitoring predicted higher CU traits in children between 10 and 14 years (Childs et al., 2014). Also, low positive parenting predicted higher CU traits, but interestingly, this relationship was bidirectional, suggesting the existence of child-driven factors in parenting (Muratori et al., 2016).

Child-driven factors suggest that child CU traits might influence and change how parents engage with their children and which parenting strategies they adopt. For example, CU traits at age 2 predicted negative parenting practices when children were 3 years old (Flom et al., 2020); it seems that children with CU traits might elicit harsh or inconsistent parenting practices from their parents (Brown et al., 2017). Additionally, children with CU traits seem more aggressive in their interaction with parents, especially under negative parenting strategies (Kuay et al., 2021). Therefore, it is hypothesized that the behavioral and emotional correlates of CU traits such as fearlessness, emotional insensitivity, punishment insensitivity, and high reward sensitivity might influence parenting strategies (Waller, Shaw, et al., 2017). For example, children with CU traits and high negative affection seem to care less about negative parental practices than children with CU traits but with lower negative affection (Dargis & Li,

2020). The potential influence of positive or negative parenting strategies on children's development might be moderated by the unique correlates of CU traits, which simultaneously impact parenting practices.

For example, some parents might first engage in more coercive and harsh parenting in response to early childhood CU traits and correlated characteristics and might then experience the inefficacy of their parenting practices. Then, they might decide to change towards warmer and more rewarding parenting practices. A study has found that mothers of children with CU traits used involvement and reinforcement with their children (Wall et al., 2016). On the contrary, other parents might be more inconsistent and reported to change their strategies over time (Hawes et al., 2011); while other parents respond to their children's CU traits by less involvement, investing less time in monitoring and supervising their child (Muñoz et al., 2011). In this sense, parents of children with high CU traits report difficulties monitoring their child, being concerned over their child's safety, and experiencing less family connection, involvement, and functioning (Roberts, 2020). These difficulties may explain why parents doubt how to discipline and engage with their children with high CU traits.

At the same time, parenting practices are moderated by other environmental factors (Waller et al., 2015), such as SES and parental mental health. Low SES has been associated with poor parenting during childhood (Belsky et al., 2007), suggesting that families who experience low SES might also be exposed to personal difficulties, which affect parenting quality. Applied to CU traits, Mills-Koonce et al. (2016) observed that low SES and high household chaos in early childhood predicted lower parental sensitivity and higher harsh-intrusive parenting, which at the same time predicted higher CU traits. In a twin study, Waller, Hyde, Klump, et al. (2018) also found that families with low SES engaged in more harsh parenting, which was related to higher CU traits.

The parent's mental health status is also one of the more distal factors that can indirectly impact the development of CU traits through parenting practices. For example, Childs et al. (2014) found that depressive parents often use more corporal punishment, which, in turn, predicts higher CU traits in children between 10 and 14 years. When analyzing specifically how parental CU traits influence child CU traits through parenting practices, Dotterer et al. (2021) observed that when parents show CU traits, their adolescent children are also at higher risk of high CU traits and that these parents engage in more negative parenting practices and less parental warmth.

As was mentioned before, CU traits are highly heritable, so intergenerational studies have shown that maternal psychopathic traits have been associated with CU traits in childhood (Hyde et al., 2016; Zhong et al., 2020); whereas another study found that both maternal and paternal psychopathic traits predicted children's CU traits (Mendoza et al., 2018). Therefore, parental CU traits might present not only a genetic risk factor but also an environmental one through their impact on maladaptive or negative parenting practices (Waller & Hyde, 2018a). For example, parental CU traits could explain why some studies have found that children with CU traits are more likely to experience more abusive and intimidating parenting practices from early childhood on (Kohlhoff et al., 2020).

All in all, the role of parenting practices in the etiology of CU traits needs to be understood as a G x E and a person-by-context interaction, in which both child- and parent-driven factors interact with each other (Waller & Hyde, 2018a). Due to the complexity found in the interaction effect of parenting factors, studies are needed to examine specific associations between genetics and positive and negative parenting in the development of CU traits, especially in early childhood.

The Role of Stress

Another environmental risk factor that needs to be explored in the etiology of CU traits are stressful or adverse life events. For example, child maltreatment has been identified as a risk factor for CU traits in adolescents and youth, especially males (Joyner & Beaver, 2021; Oshri et al., 2019). However, while most of the research on stressors has focused on maltreatment and abuse, only a handful of studies have analyzed other stressful life events that might impact the development of CU traits (Kimonis, Centifanti, et al., 2014).

Stressful life events can include traumatic experiences (violence, death of a beloved one) and situations that derive from life transitions, such as changing schools or moving to a new neighborhood. Children and adolescents with CU traits seem to have experienced more stressful life events than children with lower CU traits (Domnanovich, 2010; Sharf et al., 2014) and report having a lower quality of life (Herpers et al., 2016). Interestingly, Kimonis, Centifanti, et al. (2014) found that negative life stressors predicted higher CU traits over time, but that also CU traits predicted controllable negative life stressors (such as peer problems or low academic achievement) along childhood. Children with CU traits who also show temperamental correlates such as fearlessness, lacking empathy, and risk-taking might actively pursue negative life events. At the same time, it may be that the environment (parents or peers, for example) reacts more negatively to the children's CU temperament, which leads to experiencing more negative life events.

A theoretical model that explains the influence of stressful life events on CU traits is the Adaptative Calibration Model (ACM). This theory posits that individuals adapt or "calibrate" themselves according to the type of supportive or stressful environments they must face and that there are individual differences in responding to stressors (Del Giudice et al., 2011). The authors suggest that severe and chronic stressful environments lead to a low-stress response, low empathy, higher aggression, risk-taking, and fearlessness, as the individual needs to

become unemotional towards such stressors as a way of surviving and coping with negative life events. These characteristics are well-known correlates of CU traits, so the ACM model suggests two pathways in the etiology of CU traits: an early-onset CU traits pathway based on genetic predisposition; and an "acquired" or "distressed" pathway in which the child develops CU traits as a response to severe stress, which might result in alterations in gene expression and hormonal functioning (McCrory et al., 2010). Carlson et al. (2015) explored the plausibility of the ACM model on youth with CU traits and observed that experiencing maltreatment in childhood was related to higher CU traits and risk behaviors, including fighting, alcohol consumption, and sexual risk behaviors. Also, Kerig et al. (2012) found that traumatic events were associated with higher CU traits and that the affected youth showed numbing of sadness and fear.

The ACM model and the role of stress or trauma are particularly interesting, considering primary and secondary CU traits. While primary CU traits refer to a temperamental or genetic predisposition that comprises difficulties in emotional processing, secondary CU traits are conceptualized as coping mechanisms in response to stress and trauma in the forms of parental neglect, maltreatment, or other adversities (Craig et al., 2020). Both variants might show similar CU characteristics and correlated externalizing behavior but differ significantly in internalizing behavior and emotional reactivity. Impaired emotional recognition and lower emotional reactivity seem to be core features of the primary variant (Dadds et al., 2018; Northam & Dadds, 2020), whereas anxiety, depression, post-traumatic stress disorder, and higher emotional reactivity seem to be common comorbidities in the secondary variant (Docherty et al., 2020; Kahn et al., 2013).

Most studies on variants of CU traits have been conducted in adolescent samples. For example, Cecil et al. (2018) observed that adolescents with the secondary variant (high CU traits and comorbid anxiety) suffered from more childhood maltreatment, psychological

distress (anger and post-traumatic stress disorder), and risk behavior including drug consumption, unsafe sex and suicidal intentions than adolescents with the primary variant (high CU traits without anxiety). Similarly, Docherty et al. (2020) studied a mixed sample of community and justice-involved adolescents. They found that the secondary variant of CU traits suffered from more mental health problems, more exposure to violence, and more aggressive behavior than the primary variant. In another community sample of adolescents, those of the secondary variant of CU traits engaged in more violent behaviors, had more hostile and abusive parents, were more affected by parenting, and showed higher impulsive behavior than those of the primary variant (Flexon, 2015).

Preliminary studies among younger children have produced mixed findings. For example, Dadds et al. (2018) explored primary and secondary variants of CU traits in 3- to 16-year-olds and observed that both variants had similar characteristics to those of the adolescent samples. In a younger sample of children between 3 and 7 years, primary and secondary variants were also observed, with the secondary variant showing higher psychopathology and being exposed to more environmental adversities than the primary variant (Ezpeleta et al., 2017). However, in another community sample of 7-year-old children, the primary and secondary variants showed different anxiety levels, but not on possible stressful life events such as harsh parenting (Humayun et al., 2014).

From a developmental perspective, it might be plausible that the primary variant of CU traits represents an early-childhood onset trajectory. In contrast, the secondary variant of CU traits could develop later in development, as it could take years of repeated exposure to stressful life events to develop CU traits (Craig et al., 2021). This secondary variant of CU traits would represent an increasing CU trait trajectory. However, it may also be the case that the impact of stressful life events on CU traits might differ across development (Kimonis et al., 2014a). More longitudinal studies are needed to analyze different environmental factors,

including stressors, from early childhood to adolescence to understand better the various pathways that could explain the two variants of CU traits.

Assessment of CU Traits

The interest in assessing CU traits from a clinical perspective has increased since the DSM-5 included a "Limited Prosocial Emotions" specifier for the diagnosis of CD, and the ICD-11 has introduced this specifier for the diagnosis of conduct-dissocial disorder and ODD (American Psychiatric Association, 2013; World Health Organization, 2018). CU traits in children and adolescents are often assessed with the Inventory of Callous-Unemotional Traits (ICU) (Frick, 2004). The ICU was designed to improve the limitations of the existing instruments to screen for CU traits, such as the Antisocial Process Screening Device (APSD) (a 20-item self-report scale), the Child Psychopathy Scale (a 41-item parent-report scale), or the Youth Psychopathic Traits Inventory (a 50-item self-report scale) (Kimonis, Fanti, et al., 2014). However, assessing CU traits with these instruments is complicated, as they only feature a few CU trait items. Also, the response options are limited, the items are worded in the same direction, the scales have not been validated or used in samples of younger children, and previous research indicates relatively poor internal reliability of these CU subscales (Cardinale & Marsh, 2020).

Considering these limitations, Frick (2004) developed the ICU intending to create a global instrument to assess CU traits from early childhood on. The ICU builds upon the CU subscale of the ASPD and includes 24 items (worded positively and negatively) dedicated to exploring only CU traits. In addition, a 4-point Likert-type scale from 0 (Not at all true) to 3 (Definitely true) was introduced to offer a broader range of responses. As the ICU covers early childhood to adulthood, five versions of the scale were developed: a youth self-report scale and teacher- and parent-report scales which feature a preschooler version and a youth version. Exploratory factor analyses of the ICU identified a three-factor model based on

callousness or reduced empathy, uncaring or lack of concern about performance and relationships, and an unemotionality or poor emotional reactivity scale (Essau et al., 2006). Generally, using the total ICU scale instead of the three subscales is more reliable in detecting CU traits and shows better predictive and concurrent validity (Kimonis et al., 2008; Ray et al., 2016; Ray & Frick, 2020). A meta-analysis of the ICU based on 115 studies also concludes that the total ICU scale of the self-report version has good internal consistency and works as a predictor of different severe outcomes such as externalizing behaviors, aggression, delinquency, and hyperactivity, as well as higher psychopathic traits and lower empathic behavior (Cardinale & Marsh, 2020). The ICU's parent- and teacher-report versions have been less studied, but preliminary results indicate similar findings as the ones of the self-report version, with good internal consistency and positive correlations with aggressive behavior and rule-breaking (Ueno et al., 2021).

Overall, the ICU has proved to be a valid instrument for identifying CU traits as a continuum, enabling practitioners to use the ICU scale to identify children and adolescents with higher or lower CU traits (Cardinale & Marsh, 2020; Ray & Frick, 2020). This dimensional approach might be sufficient for research purposes. However, in clinical settings, there is also a need to adopt a categorical approach in diagnosing CU traits (Kimonis, Fanti, et al., 2014), especially considering that children with CU traits can be compatible with the limited prosocial emotions specifier for CD or ODD. Previous research on whether CU traits are conceptualized as dimensional or as categorical indicates that CU traits should be considered as a continuum and that, if a classification in a dichotomous group (CU+ / CU-) is needed, the cut-off score should be established according to external validation criteria (Kliem et al., 2021). The debate is whether the ICU could function as a screening test for CU traits, with specific cut-off scores that enable practitioners to identify children as CU trait positives or CU negatives. It is to mention that the diagnostic process of identifying CU traits should not exclusively be

based on one test like the ICU, but rather include other qualitative instruments such as the Clinical Assessment of Prosocial Emotions (CAPE; Frick, 2013). Nevertheless, using the ICU as a screening test would have different benefits, such as helping practitioners identify those children at increased risk of CU traits in early childhood and providing more information for early diagnosis and treatment.

First attempts to define ICU cut-off scores have been made from different perspectives. One way of establishing cut-off scores is to rely on distributive norms of the ICU score in extensive population studies. Norms for the self-report ICU are available for European adolescents aged 11 to 17 (Kemp et al., 2019), and norms for the parent-, teacher-, and self-report versions are also available for German children and adolescents between the ages of 6 to 18 (Ueno et al., 2021). Norms for the parent-report ICU can also be found in the United States for children between 5 to 12 years (Bansal et al., 2022). These normative data can help to identify distribution-based cut-off scores by using a specific percentile, often equal to or above 80 or 90. For instance, the 95th percentile is used as a cut-off in Kemp's et al. (2019) European dataset, with direct ICU scores between 37 and 41 for boys and 32 and 35 for girls. Other authors have used the 80th percentile on parent-, teacher- and self-reported ICU scores, obtaining cut-off scores above 35 (Kumsta et al., 2012; Levy et al., 2015).

Another way to define cut-off scores is using external criteria to use empirically derived threshold scores from the ICU. From this perspective, the ICU would help identify CU traits and concurrent psychological and behavioral outcomes such as aggression, violent behavior, criminal activity, or conduct problems (Feilhauer et al., 2012; Kemp et al., 2021; Kimonis, Fanti, et al., 2014). For example, direct ICU scores for the parent-version that score over 24 identify high CU traits, conduct problems, and predict bullying behavior in children ages 6 to 12 (Kimonis, Fanti, et al., 2014). For the self-report version, a direct score of 26 identifies high CU traits and criminal activity (Feilhauer et al., 2012). For the teacher-report

version, a cut-off score of 33 predicts aggressive behavior, violence, and detained status in a mixed sample of community and justice-involved adolescents (Docherty et al., 2017). Similarly, direct ICU scores over 35 for the teacher-report version also distinguished children with high CU traits, conduct problems, and peer-reported meanness in a community sample of youth (Kemp, 2020).

These studies suggest that ICU cut-off scores should be sex-specific because the prevalence of CU traits is higher in boys than in girls and because girls with high CU traits may show more psychological impairment than affected boys (Euler et al., 2015). In addition, age is another factor that should be considered when establishing ICU cut-off scores because normative scores of the ICU might fluctuate on a cohort level (Carvalho et al., 2018; Essau et al., 2006). Finally, the type of informant is also essential, as ICU cut-off scores might vary, whether it is the parent, the teacher, or the child answering the ICU.

Moreover, further external validators for determining ICU cut-off scores are needed to provide evidence that the ICU scores can identify a subgroup of children who show CU traits and other associated outcomes, such as conduct problems and ODD. Thus, basing the cut-off scores on a whole trajectory of conduct problems or ODD could help to test if the ICU scores can detect clinically subgroups of children based on their trajectory.

Also, whereas research has focused on the ICU self-report version, research suggests that teachers seem to be valid informants (Figueiredo et al., 2022) that can reliably identify and distinguish CU traits from other externalizing behaviors, such as disruptive behavior, ADHD, or conduct problems (Willoughby et al., 2022). It is essential to further expand on these findings and test whether the ICU's teacher-report version can also discriminate subgroups of children, especially considering the need for early detection of preschoolers when the diagnosis depends on parents' and teachers' impressions of the child.

Aims and Outline of this Thesis

The studies presented in this thesis are part of an ongoing longitudinal research project examining childhood psychopathology and its developmental trajectories, risk, and protective factors. This thesis focuses on CU traits and aims to further understand the etiology of CU traits by examining a Spanish community-based sample of children that were followed up between ages 3 to 13. More specifically, the thesis sought to expand previous literature by:

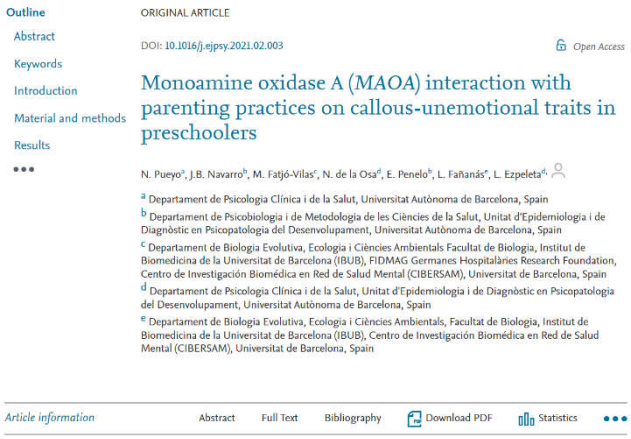
1) Analyzing how the MAOAVNTR polymorphisms interact with parenting practices in the development of preschool CU traits at ages 3 and 5, separately by sex.
2) Analyzing contextual and personal risk factors in early childhood (at the age of 3), as well as their mental health outcomes at the age of 10, depending on different CU traits and stressful life experience trajectories.
3) Contributing to meaningful cut-off scores for the teacher-rated ICU along childhood separately by age and sex.

These aims led to the following dissertation, which consists of three studies that have been previously published between 2021 and 2022.

Study 1 is dedicated to analyzing gene-by-environment (G x E) interactions between *MAOA* and positive parenting and punitive parenting practices on CU traits in boys and girls at the ages of 3 and 5. It was hypothesized that boys who carried the low-activity allele (*MAOA*-L) and girls who carried the high-activity allele (*MAOA*-HH) and who experienced punitive parenting styles would exhibit higher levels of CU traits. These children were also expected to show lower levels of CU traits when exposed to positive parenting practices. Another aim was to analyze these G × E interactions on CU traits at ages 3 and 5. Again, age-specific G x E interactions were expected.

The findings of the first study have been published in:

Pueyo, N., Navarro, JB., Fatjó-Vilas, M., De la Osa, N., Penelo, E., Fañanás, L., Ezpeleta, L. (2021). Monoamine oxidase A (*MAOA*) interaction with parenting practices on callous-unemotional traits in preschoolers. *European Journal of Psychiatry*, 35(4). DOI: 10.1016/j.ejpsy.2021.02.003.


Outline
Abstract
Keywords
Introduction
Material and methods
Results
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ORIGINAL ARTICLE

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Monoamine oxidase A (*MAOA*) interaction with parenting practices on callous-unemotional traits in preschoolers

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The European Journal of Psychiatry has an impact factor of 1.288 (2021) in the JCR and ranks Q4 in the field of Psychiatry.

Study 2 analyzes joint CU traits and stressful life event trajectories during childhood. The study aimed to expand on previous research on the construct of primary and secondary CU trait variants by examining the extent to which trajectories of both CU trait and stressful life event trajectories (SLE) are associated with different risk factors and mental health outcomes. More specifically, the study sought to extend previous studies by analyzing contextual risk factors (e.g., SES and family disadvantages), child characteristics (executive functioning) at age 3, and mental health outcomes at age 10, according to the developmental course of CU traits and SLE. Consistent with previous literature, it was expected that children with high CU traits and high levels of SLE would face more contextual risk factors, more executive functioning difficulties, and more mental health problems than children with increasing CU traits and low levels of SLE or children who showed neither CU traits nor SLE.

The findings of the second study have been published in:

Pueyo, N., Navarro, JB., De la Osa, N., Penelo, Ezpeleta, L. (2022). Describing callous unemotional traits and stressful life event trajectories: Differences on risk factors and mental health outcomes from the age of 3 to 10. *The Spanish Journal of Psychology*, 25, E17. doi:10.1017/SJP.2022.13

Describing Callous Unemotional Traits and Stressful Life Event Trajectories: Differences on Risk Factors and Mental Health Outcomes from the Age of 3 to 10

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Abstract

Callous Unemotional (CU) traits are associated with different environmental risk factors, such as negative stressful life events (SLE). The most common studied SLE associated with CU trait has been childhood maltreatment, but less is known about how other SLE impact the development of CU traits. Therefore, this work examines risk factors, personal factors (executive functioning), and mental health outcomes associated with the trajectories of Callous Unemotional (CU) traits and Stressful Life Events (SLE) in a community sample of children. A cohort of 377 preschoolers were followed up between ages 3 and 10. Several risk factors and outcomes for three trajectory groups (high CU/SLE; high CU/low SLE; and the reference group with low CU/SLE) were analyzed by using multiple post-hoc comparisons. We hypothesized that children with high CU/SLE would face more contextual risk factors, more executive functioning difficulties and more mental health problems than children with high CU/low SLE or the reference group. At the age of 3, children who showed high CU/SLE faced more early contextual adversity, including socioeconomic difficulties and maternal antisocial behavior than the other groups of children. At the age of 10, children with high CU/SLE presented more peer problems and higher psychopathology symptoms than the reference group, but no differences on mental health outcomes in comparison to the high CU/low SLE group. These results have potential implications for clinical practice and studies attempting to identify different CU subtypes in children.

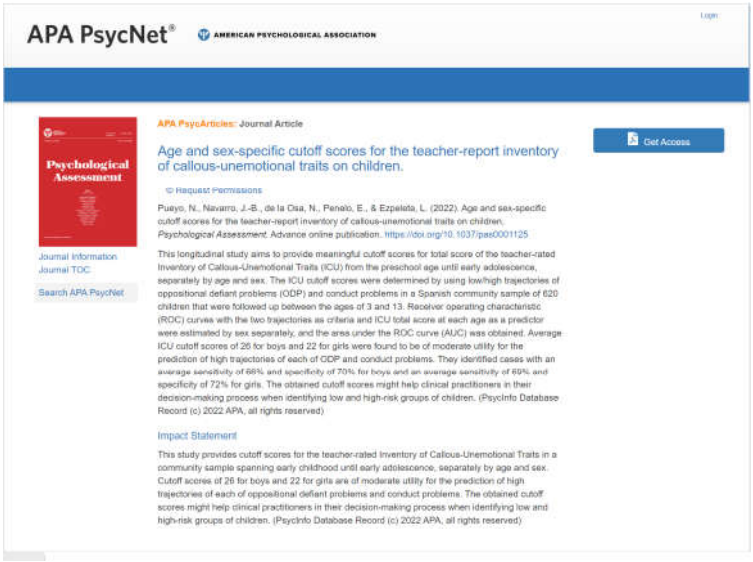
Keywords

The Spanish Journal of Psychology has an impact factor of 1.526 (2021) in the JCR and ranks Q3 in the field of Psychology/Multidisciplinary.

Study 3 is dedicated to establishing cut-off scores of CU traits. Specifically, the study aimed to define meaningful cut-off scores for the teacher-rated ICU total score from preschool to early adolescence, separately by age and sex. This work determines the ICU cut-off scores by using low/high trajectories of conduct problems and externalizing behaviors between ages 3 and 13. As previous studies have focused on self- and parent- reports and have not explored preschool samples ICU cut-off scores in adolescent samples, this report sought to extend previous research by providing ICU cut-off scores from early childhood based on a community sample of children. This study offers valid cut-off scores for children in the general population, making the questionnaire helpful not only in both clinical and educational settings.

The findings of the third study have been published in:

Pueyo, N., Navarro, J.B., de la Osa, N., Penelo, E., & Ezpeleta, L. (2022). Age and sex-specific cut-off scores for the teacher-report inventory of callous unemotional traits on children. *Psychological Assessment, 34*(7), 611-619. https://doi.org/10.1037/pas0001125



Psychological Assessment has an impact factor of 6.083 (2021) in the JCR and ranks Q1 in the field of Psychology/Clinical.

In this thesis, first, a description of the methodology that was used in the three studies is presented. Next, the complete publications are displayed in the Results section. Finally, this thesis's preliminary results are discussed with clinical implications for intervention and a review of strengths, limitations, and directions for future research. The reader may opt to read the method section that presents the methodology of the three papers or the specific methodology in each paper.

Chapter Two: Methodology

Participants

The sample of the three studies stems from a longitudinal study on risk factors of psychopathology in children starting at age 3 (Ezpeleta et al., 2014). The sampling design included two phases. In the first phase, 1341 families of 2283 (58.7%) children who were randomly selected from the census of early childhood schools in Barcelona (Spain) agreed to participate (33.6% high socioeconomic status (SES), 43.1% middle, and 23.3% low; 50.9% boys). In the second phase, a parent-rating of ODD symptoms (8 items) based on three items of the conduct problems scale of the Strengths and Difficulties Questionnaire (SDQ) (temper tantrums, disobedient and spiteful) plus four additional items from the Diagnostic and Statistical Manual of Mental Disorders (4th Edition; DSM-IV) (American Psychiatric Association, 2000) to conform ODD symptomatology (annoys, blames, touchy, angry) was used to screen children with possible psychological problems.

Two groups were finally considered: the screening positive group (+) included all children with scores above the 90th percentile on the screening measure or with a positive response for any of the eight DSM-IV ODD symptoms (n = 417; 49.0% boys) and the screening negative group (-) incorporated a random group of children who did not reach the positive criteria (n = 205; 51.2% boys). Both groups (n = 622) participated in the longitudinal study. No statistically significant sex differences (p = .82), SES (p = .08), or type of school (p = .85) between participants and drop-outs were found.

Table 1 summarizes the participants and materials used in the three studies.

Table 1

Summary. of participants and materials used in each of the three studies

	Study 1	Study 2	Study 3
Participants	368	377	620
Age	3 –5	3 –10	3 –13
Sex (male, %)[1]	51.9	54.1	50.1
SES[2]			
High	36.4	39.9	34.7
Middle[3]	44.3	45.1	51.9
Low[4]	19.3	15.1	13.5
		Materials	
ICU	CU traits as dependent variable	CU traits as trajectory variables	CU traits as dependent variable
Genotype	MAOA as independent variable		
APQ	Positive and negative parenting practices as independent variable		
SDQ	Mental health of children reported by parents as adjusting variable	Mental health of children reported by parents and teachers as dependent variable	Mental health of children reported by parents and teachers as trajectory variables
SLE Checklist		SLE as trajectory variables	
ASR		Maternal mental health problems as dependent variable	
BRIEF-P		Inhibition/Emotional Control as dependent variable	
DICA-PPYC			Mental health outcomes as a gold standard

ICU: Inventory of Callous Unemotional Traits; APQ: Alabama Parenting Questionnaire; SDQ: Strengths and Difficulties Questionnaire; SLE: Stressful Life Events Checklist; ASR: Adult Self-Report; BRIEF-P: The Behavior Rating Inventory of Executive Function-Preschool; DICA-PPYC: Diagnostic Interview for Children and Adolescents for Parents of Preschool and Young Children.

Participants of study 1: Only Caucasian children were included to control possible ethnic or racial variations in *MAOA* allele frequencies. *MAOA* genotype was available for 368 children (59.2%). Table 1 of study 1 presents the demographic information for age 3.

Participants of study 2: This study builds upon three trajectories of CU traits, and the number of SLE found in Ezpeleta et al. (2019). The analyzed sample consisted of 377 children who were followed from age 3 to 9. The three trajectories defined the three groups of

[1] Mean ages 3 and 10.
[2] Mean ages 3 and 10.
[3] Includes: Middle-high/middle for Study 2 and 3.
[4] Includes: Middle-low/low for Study 2 and 3.

participants used for the present study: Trajectory 1 (226; 59.9%) is the reference group and describes a group of children with a low and stable profile for both CU scores and the number of SLE (CU-/SLE-); Trajectory 2 (127; 33.7%) includes children with increasing high CU scores and a low and stable number of SLE (CU+/SLE-); and Trajectory 3 (24; 6.4%) refers to children with both stable high CU scores and a stable high number of SLE (CU+/SLE+) (see Figure 2 of study 2). The available data at age 10 (n = 320) was used to study the mental health outcomes (see Table 1 of study 2 for a description).

Participants of study 3: 620 children were assessed yearly from the ages of 3 to 13 (11 assessment points). Table 1 of study 3 describes the available sample at ages 3 and 13.

Measures

A summary of the instruments used in the three studies is shown in Table 1.

Common instruments in the three studies

Callous-unemotional traits. The *Inventory of Callous-Unemotional Traits* (ICU; Frick, 2004) includes 24 items using a 4-point Likert-type scale from 0 (*not at all true)* to 3 (*definitely true*). The ICU total score is the sum of the ratings of all the items, reversed when necessary, and higher scores indicate higher levels of CU traits. Teachers annually answered the ICU.

Study 1: The total ICU was answered by teachers when the children were 3 and 5 years old.

Study 2: Teachers responded the ICU annually when children were between 3 and 10 years old. The total ICU score was used for obtaining the developmental trajectories.

Study 3: The total ICU for each year answered by teachers when the children were between ages 3 and 13 was analyzed to obtain the cut-off scores.

Cronbach's alpha for the total score through follow-ups in the sample ranged from .88 to .93.

Children's Mental health: The *Strengths and Difficulties Questionnaire* (SDQ) (Goodman, 1997) is a brief screening questionnaire for the mental health of children based on five scales of five items each (0: *not true* to 2: *certainly true*). Parents and teachers annually answered the SDQ.

Study 1: The SDQ completed by teachers when children were 3 years old was analyzed. The conduct problems subscale (Ordinal alpha = .85) was introduced as an adjusting term in linear regression models.

Study 2: The SDQ completed by parents and teachers when children were 3 and 10 years old was analyzed. The total difficulties score (20 items, range 0-40) and the scale scores of emotional problems (5 items, range 0-10), conduct problems (5 items, range 0-10), hyperactivity (5 items, range 0-10) and peer problems (5 items, range 0-10) were used. Ordinal alpha values in the present sample ranged from .79 to .93 for parents and from .79 to .92 for teacher ratings.

Study 3: The SDQ completed by teachers when children were between 3 and 13 years old was analyzed. For oppositional defiant problems (ODP), three items of the conduct problems scale of the SDQ were used (temper tantrums, disobedient and spiteful), together with four additional items that were included based on the DSM-IV ODD symptomatology criteria at ages 3 and 4: annoys, blames, touchy, angry. At ages 5-7, another item was included, argumentative, which is not included in the SDQ5-16. For conduct problems, the specific SDQ scale was used. Ordinal alpha values ranged from .91 to .96 for ODP scores and from .83 to .91 for conduct problem scores.

Additional Measures used in Study 1

Genotype. Genomic DNA was extracted from children's buccal mucosa on a cotton swab using the Real Extraction DNA Kit (Durviz S.L.U., Valencia, Spain). A detailed description of the genotyping process can be found in the Materials section of Study 1. The

genotyping success rate was 92.5% ($N = 368$), leaving 33 individuals with an undetermined uVNTR polymorphism. In line with previous studies, the *MAOA* genotypes were grouped according to their functionality (Caspi et al., 2002; Fergusson et al., 2012). The low-activity *MAOA* genotype includes individuals with the 3-repeat allele, whereas the high-activity *MAOA* genotype includes participants with 3.5, 4, or 5 repeats.

Parenting Practices. The *Alabama Parenting Questionnaire Preschool Revision* (APQ-Pr) (Frick, 1991) and the Spanish adaptation (de la Osa et al., 2014) consists of 24 items on a 5-point Likert scale which measures three dimensions of parenting: positive parenting, inconsistent parenting, and punitive parenting. The positive parenting (12 items) and punitive parenting (5 items) scores that were analyzed in this study were answered by parents when the children were 3 years old (5.8% father, 48.5% mother, 44.7% both). The internal consistency in our sample showed an acceptable value for positive parenting (Cronbach's alpha = .75) but a low value for punitive parenting (alpha = .42).

Additional Materials used in Study 2

Stressful Life Events (SLE): SLE were registered through the *Life Events Checklist* (Johnson & McCutcheon, 1980), which includes 25 SLE that the mother or caregiver reported. These events include moving to a new house or school, a new brother/sister, parents' fights, separation/divorce, a new father/mother, the death of a family member, and child abuse, among others. In each follow-up, a life event was registered as present if the child was exposed to it at least once during the previous year (the year between assessments). The total number of SLE (range 0-25) at each age (3-10 years) was combined with the ICU total score to obtain the developmental trajectories.

Demographics: Socio-demographic variables were assessed through dichotomic questions about economic problems in early infancy, the achieved level of parents' studies, and the

main caregiver's employment. Moreover, SES was assessed according to the Hollingshead Four-Factor Index of Social Status (Hollingshead, 1975).

Parental Mental Health: *Adult Self-Report* (ASR; Achenbach & Rescorla, 2003) assesses dimensional psychopathology in adults between the ages of 18 and 59. The data on mothers' mental health status when children were 3 years old were analyzed for this study. The scale scores for anxious/depressed (18 items, range 0-36), aggressive behavior (15 items, range 0-30), rule-breaking (14 items, range 0-28), and the total score (120 items, range 0-240) were considered. Ordinal alpha values in the sample were .92, .89, .68 and .91, respectively.

Executive Functions: The *Behavior Rating Inventory of Executive Function preschool version* (BRIEF-P; Gioia et al., 2003) assesses behaviors reflecting the executive functions in daily life in preschool children. Teachers completed the inventory when children were 3 years old. The instrument consists of 63 items on a 3-point ordered scale from 1 (*never*) to 3 (*often*). Two dimensions of executive functioning, inhibitory control (the ability to suppress thoughts or actions that are irrelevant to the task) (16 items, range 16-48) and emotional control (9 items, range 9-27), were used.

Additional materials used in study 3

The *Diagnostic Interview for Children and Adolescents for Parents of Preschool and Young Children* (DICA-PPYC; Ezpeleta et al., 2011) is a semi-structured diagnostic interview for assessing common psychological disorders according to the DSM-5 criteria. ODD and Conduct disorder (CD) diagnoses were used to describe the presence of psychopathological diagnoses in the sample at ages 3 and 13. Ordinal alpha values were .96 and .94, respectively.

Procedure

The project was approved by the Ethics Committee on Animal and Human Experimentation of the Autonomous University of Barcelona which follows the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The recruitment of the

families took place at the schools whose Heads and parents were provided with a description of the study's aims and procedures. Participating families gave written consent before their inclusion in the study and were invited to answer the screening questionnaire SDQ3-4. The questionnaire was completed at home and returned to the schools. Families who met screening criteria were contacted by telephone and interviewed at the school by previously trained psychologists or supervised psychology students. The interview consisted of a semi-structured diagnostic interview and other psychological assessment instruments. All interviewers were blind to the screening group, and all interviews were audio recorded. Then parents answered the questionnaires on demographic variables, child characteristics, and mental health, and, at the schools, the teachers were asked to answer the questionnaires on child characteristics.

For the annual follow-up, parents and teachers were assessed each year at the school by a team of interviewers. All participants gave their informed consent before their inclusion in the study. In addition, the Spanish law on protecting personal data (3/2018, from the 5th of December) was followed.

Data Analysis

Statistical analysis was done using Stata and MPlus. As the sampling design was two-stage, all the analyses were weighted by the inverse probability of selection in the second sampling phase.

Statistical analysis of Study 1

The G × E analyses were conducted using separate multiple linear regressions for each sex, with the dependent variable being ICU scores at 3 and 5 years old (4 regression models in total). The independent variables were *MAOA* alleles, APQ-Pr Positive and APQ-Pr Punitive measured at age 3, and the first-order interaction terms between *MAOA* genotypes and the two environmental characteristics. When a significant interaction was found, simple effects of each environmental variable were calculated separately for each genotype, while differences

between genotypes were calculated for the mean of the two quantitative environmental variables. The SDQ conduct problems scale and socioeconomic status (SES) at baseline (age 3) were included in all models as adjusting terms. The two measures of parenting style were retained in the model, although their interactions had been deleted. Additionally, the ICU score at age 3 was included as a covariable in models predicting the ICU score at age 5.

Statistical analysis of Study 2

Different demographic and psychological measurements obtained at the age of 3 and 10 were compared between trajectories using multiple posthoc comparisons. Linear regression models for continuous, logistic models for binary, and multinomial logistic models for polytomous measures were estimated. In the analysis of outcomes at the age of 10, the available scores at the age of 3 were included as covariates. The risk of type I error was corrected by Šidák's (1967) approach. Cohens' *d* effect size was calculated for each contrast. According to Cohen (1992) absolute values of *d* were interpreted as follows: null effect for values < 0.20, small effect for values 0.20-0.50, medium effect for values 0.50-0.80 and large effect for values > 0.80.

Statistical analysis of Study 3

Growth Mixture Models (GMM) with one process at each time were estimated for obtaining trajectories using direct scores of ODP and SDQ conduct problems. The Robust Maximum Likelihood (MLR) estimation method was used. Models with two growth patterns (trajectories) were selected for each of the two processes. The classification accuracy in two trajectories was assessed through adequate average posterior probabilities, entropy values equal to or greater than .70, and a minimum of 20 participants in each trajectory.

Receiver operating characteristic (ROC) curves with the two trajectories as a gold standard and the ICU total score at each age as a predictor were estimated separately by sex, and the area under the ROC curve (AUC) was obtained. A value of AUC < .70 is considered

non-predictive; AUC from .70 to .80 is considered acceptable; AUC from .80 to .90 is considered excellent and AUC > .90 is considered outstanding (Hosmer et al., 2013). The optimal ICU total score cut-off was selected as the score that maximizes sensitivity (Se) and specificity (Sp) by minimizing the square of the distance between the point (0, 1) on the upper left-hand corner of ROC space and any point on ROC curve, with equals costs for false positive and false negative misclassifications (Hajian-Tilaki, 2013).

Chapter Three: Results

Study 1

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ORIGINAL ARTICLE

Monoamine oxidase A (*MAOA*) interaction with parenting practices on callous-unemotional traits in preschoolers

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Abstract
Background and Objectives: From a gene-by-environment perspective, parenting in interaction with the polymorphism in the Monoamine oxidase A (MAOA) gene (*MAOA*-uVNTR) might also be associated with increased callous-unemotional traits (CU) in preschoolers. *MAOA*-uVNTR results in differential enzyme activity, so that high-activity alleles (*MAOA*-H) are linked to reduced dopamine, serotonin, and norepinephrine availability in comparison to low-activity allele (*MAOA*-L). As *MAOA*-uVNTR has been previously described to moderate the relationship between childhood parental maltreatment and aggressive and antisocial behavior, it may also play a role in CU traits etiology.

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Methods: Data was collected through questionnaires answered by parents and teachers. *MAOA*-uVNTR was genotyped in 368 Caucasian children from a community sample (51.9% male). Multiple linear regression analyses were conducted to analyze the interaction effect of *MAOA* genotypes and both positive parenting and punitive parenting practices on CU traits at two different periods (3 and 5 years old) and separately by sex.
Results: No significant interactions were found for boys. Among girls, a significant interaction effect was found for *MAOA*-LL carriers, who showed higher CU traits at age 5 when exposed to higher punitive or positive parenting at age 3.
Conclusions: Our study provides the first evidence for significant *MAOA* × early parenting effects on CU traits in preschoolers, specifically among female *MAOA*-LL carriers. This suggests that the *MAOA*-LL genotype for girls is associated with higher sensitivity to both positive and punitive parenting in girls, so that *MAOA*-LL emerges as a genotype that confers higher vulnerability to parental influences.

Introduction

Callous Unemotional (CU) traits are seen as precursors of adult psychopathy and have been added to the DSM-5 as a specifier to diagnose conduct disorder under the term 'limited prosocial emotions' (LPE) in order to identify a subgroup of children and adolescents who show a distinct prosocial and emotional functioning such as lack of empathy, lack of guilt and deficits in emotional expression.[1]

CU traits are highly heritable, and a meta-analysis estimated that genetic factors account for 42% and 68% of the variation of CU traits.[2] Takahashi et al.[3] found that the genetic effect on CU traits varies depending on the developmental path of CU traits, so that childhood-onset CU traits (around age 7) seem to be under a higher genetic influence than CU traits that develop later across adolescence. Moreover, they indicate that the course of CU traits seems to be dynamic, with environmental influences accounting for 23.5% of the variance of initial CU traits, but for 56.4% in the stability of these traits. Among the environmental factors that influence the development of childhood CU traits, parenting practices have been the focus of most studies.[4] Harsh, inconsistent parenting and corporal punishment have also been identified as risk factors for increases in CU traits in pre-schoolers.[5] At the same time, positive parenting can be considered a protective factor and strategies such as positive reinforcement, parental sensitivity and warmth have shown to predict lower CU levels among children.[6]

Certainly, not all children are equally vulnerable to certain parenting practices in the development of CU traits. Some research suggests that sensitivity to parenting practices might be explained through individual genetic variability.[7] In this sense, Gene by Environment (G × E) interaction studies have focused on the diathesis-stress model and have found that certain genotypes confer vulnerability to adverse environments. From another perspective, the differential susceptibility model[8] suggests individuals might be more susceptible to adverse parenting styles, but at the same time, might also benefit more from positive parenting practices. Both models show that genetic influences shape an individual's sensitivity towards social environments, such as parenting. While one study found a salient G × E interaction in CU trait development on BDNF and harsh parenting,[9] the question arises whether other candidate genes for CU traits might also moderate the effect of parenting practices on CU traits development.

To provide more insight into the complex relationship between genes, parenting practices and CU trait development, the current study focuses on Monoamine Oxidase A gene (*MAOA)*. Moore et al.[10] identified, among other candidate genes for CU traits, *MAOA*. This gene encodes for the Monoamine Oxidase A enzyme (MAO-A) that catalyzes the degradation of brain neurotransmitters such as serotonin, dopamine, and norepinephrine.[11] Deficits in the serotonin system have been associated with CU traits,[12] but the specific role of *MAOA* in the etiology of CU traits has remained unexamined.

The *MAOA* gene has a variable number of tandem repeats (uVNTR) polymorphism in its promoter sequence. The different allelic variants of this polymorphism are associated with changes in the transcriptional efficiency of the gene, which results in low and high enzymatic activity alleles (*MAOA*-L and *MAOA*-H, respectively).[13] As the *MAOA* gene is located on the X chromosome (Xp11.23), males inherit a single allele and are therefore hemizygous for either *MAOA*-L or *MAOA-H*, whereas females can be homozygous (*MAOA*-LL/*MAOA*-HH) or heterozygous (*MAOA*-HL). The lower MAO-A activity results in different neurochemical, neural and behavioral alterations[14] and has been identified as the ''risk allele'' for antisocial behavior[15] and aggressive behavior,[16] especially among males. *MAOA*-L has also been associated with CU traits in male adolescents with comorbid attention deficit/hyperactivity disorder.[17] Thus, neuroimaging studies have shown that the *MAOA*-L allele has an impact on altering neural circuits such as the amygdala or the prefrontal cortex, which are implicated in aggressive behavior and emotional processing.[18]

Research also indicates the existence of a robust sex-dependent G × E interaction on *MAOA*-L and childhood maltreatment, showing that males who carry the *MAOA*-

L allele and are exposed to abuse or maltreatment also develop more antisocial behavior[19] and conduct disorder.[20] Studies on females are less frequent and present less robust findings, but suggest that *MAOA*-HH confers vulnerability towards adversity, resulting in the ''risk allele'' for antisocial behavior.[15]

Based on previous G × E studies, we hypothesized the presence of sex dependent G × E interactions on CU trait development on preschoolers, so that boys who carried the *MAOA*-L allele and girls who carried the *MAOA*-HH allele and who experienced punitive parenting styles would exhibit higher levels of CU traits. At the same time, these children would show lower levels of CU traits when exposed to positive parenting practices. Moreover, we examined these G × E interactions on CU traits at two different periods (ages 3 and 5), which represent initial and ending points of preschool age. Preschool age is a developmental period in which empathy, emotional expression and conscience emerge, making it an important time in the pathway to early CU traits.[21] During these years, children are very sensitive to parenting practices and research has shown that positive parenting practices protect children from socioemotional difficulties, while harsh practices increase the risk of developing externalizing problems and CU traits.[22] Because genetic influences seem to be more important at earlier ages than later in development,[23] we hypothesized that G × E interactions would be different across age.[3]

Material and methods

Participants

In the context of a longitudinal study of psychological risk factors during development, a random sample of 2,283 children from the census of preschoolers in grade P3 (3-year-olds) in Barcelona (Catalonia, Spain) were screened for behavioral problems.[24] This began with an initial screening using the parent-administered Strengths and Difficulties Questionnaire (SDQ)[25] enriched with four additional oppositional defiant disorder items to complete the DSM-IV description. A total of 1,341 families (58.7%) agreed to participate. In a second stage of the sampling, all the children who screened positively for behavioral problems and an additional 30% of the children with negative screening scores continued and were assessed annually. Of those included, 622 families (89.4 %) agreed to participate further. No statistically significant differences in sex ($p = .82$) or type of school ($p = .85$) between participants and drop-outs were found. For the present study, which corresponds to a prospective design with independent variables assessed at age 3 and dependent variables assessed at ages 3 and 5, only Caucasian children were included, to control possible ethnic or racial variations in *MAOA* allele frequencies.[13] *MAOA* genotype was available for 368 children (59.2%). Table 1 presents the demographic information at age 3.

Table 1 Characteristics of the Sample (N = 368).

Sex; *n (%)*	Male	191 (51.9)
Socioeconomic status; *n (%)*	High	134 (36.4)
	Middle	163 (44.3)
	Low	71 (19.3)
One-parent family; *n (%)*		17 (4.6)
Age of the parents; *mean (SD)*	Mother	36.7 (4.1)
	Father	39.2 (5.4)

Materials

Individual variables

CU traits outcome. The Inventory of Callous-Unemotional Traits (ICU)[26] was answered by teachers when the children were 3 and 5 years old. The ICU is a 24-item and 4-point Likert scale questionnaire that assesses CU traits, and the total score was used. In our sample, Cronbach's alpha for the total score at both 3 years old and 5 years old was .90.

Genotype. Genomic DNA was extracted from children's buccal mucosa on a cotton swab using the Real Extraction DNA Kit (Durviz S.L.U., Valencia, Spain). The Polymerase Chain Reaction (PCR) was carried out using 1 μl of DNA and 14 μl of mix. The cycling parameters of the PCR were as follows: an initialization step at 94 °C for 2 min, followed by 30 cycles of denaturation at 94 °C, annealing at 66 °C for 1 min, extension at 72 °C for 1 min and a final elongation at 72 °C for 15 min. The primers used were *MAOA*-Forward: 5′-ACA GCC TGA CCG TGG AGA AG-3′ (marked with fluorochrome HEX) and *MAOA*-Reverse: 5′-GAA CGG ACG CTC CAT TCG GA-3′. 1 μl of the resulting amplified DNA was mixed with 10 μl of HI-DI formamide and 0.4 μl of ROX and kept at 95 °C for 5 min before being put in the freezer for 1 min. The uVNTR polymorphism of the *MAOA* gene was genotyped using GeneMapper® Software v4.1. The genotyping success rate was 92.5% ($N = 368$), leaving 33 individuals with an undetermined uVNTR polymorphism. Ten per cent of the individuals were randomly selected for re-genotyping to confirm the validity and accuracy of the method. This re-testing showed 100% reproducibility. Regarding the Hardy-Weinberg equilibrium, the genotype of the MAOA activity for women in the sample (n = 177) was in equilibrium ($\chi^2 = 0.097$, $p = .95$). There was no need to test the equilibrium for males since their genotype distribution is the same as their allelic distribution (they only have one copy of the *MAOA* gene).

In line with previous studies, the *MAOA* genotypes were grouped according to their functionality.[19,27] The low-activity *MAOA* genotype includes individuals with the 3-repeat allele, whereas the high-activity *MAOA* genotype includes participants with 3.5, 4 or 5 repeats.

Environmental variables

The environmental variables were measured when the children were 3 years old.

Parenting Practices. The Alabama Parenting Questionnaire Preschool Revision (APQ-Pr)[28,29] consists of 24-items on a 5-point Likert scale which measures three dimensions of parenting: positive parenting, inconsistent parenting and punitive parenting. Positive parenting (12 items) and punitive parenting (5 items) scores were answered by parents when the children were 3 years old (5.8% father, 48.5% mother, 44.7% both), were taken into consideration. The positive parenting subscale measures how frequently the parent interacts in games and shared time and how often they use positive reinforcement to foster appropriate behavior. The punitive parenting subscale measures how often the

Table 2 Zero-order correlations between ICU scores at ages 3 and 5, parental styles, SES and SDQ-conduct problems at age 3, separately by sex.

	1.	2.	3.	4.	5.	6.
1. ICU at age 3		.35*	.12	.18*	.07	.54*
2. ICU at age 5	.34*		.07	.03	.08	.13
3. APQ-Pr Punitive parenting	.09	.04		−.14	−.05	.13
4. APQ-Pr Positive parenting	−.15*	.06	−.21*		−.13	.13
5. Socioeconomic status	.04	−.03	.08	.04		.01
6. SDQ-conduct problems	.57*	.13	.21*	−.17*	.03	

Above diagonal correlations for boys. Below diagonal correlations for girls. *p < .05.

parent spanks, slaps or yells at their children to punish inappropriate behavior.[30] The internal consistency in our sample showed an acceptable value for positive parenting (Cronbach's alpha = .75) but a low value for punitive parenting (alpha = .42). As both scales had few items (6 for positive parenting and 3 for corporal punishment) and most of them showed skewed distributions, inter-item mean correlation was also calculated, resulting in acceptable values of $r = .31$ for positive parenting and $r = .25$ for punitive parenting.

The Strengths and Difficulties Questionnaire (*SDQ*)[25] is a 25-item screening questionnaire for child behavior and emotional problems. Teachers answered the questionnaire when the children were 3 years old and the conduct problems subscale (Ordinal alpha = .85) was introduced as an adjusting term in linear regression models.

Procedure

The study was approved by the ethics review committee of the author's institution. Schools were informed and the participating parents had to provide written consent. The families who met the inclusion criteria and were willing to participate were contacted by telephone and interviewed at the school. The questionnaires were administered at the end of the course to guarantee that teachers knew the children they were evaluating well.

Statistical analysis

The data was analyzed using STATA 16.0 for Windows. The Type I error was fixed at .05. To compare means of APQ-Pr between genotypes, Student's t-tests were calculated for boys, while analysis of variance with post-hoc comparisons and Bonferroni correction for multiple comparisons was estimated for girls.

The G × E analyses were conducted using separate multiple linear regressions for each sex with the dependent variable being ICU scores at 3 and 5 years old (4 regression models in total). The terms entered in each model as independent variables were *MAOA* alleles, APQ-Pr Positive and APQ-Pr Punitive measured at age 3, and the first-order interactions terms between *MAOA* genotypes and the two environmental characteristics. Non-significant interactions were removed from the model and in that case main effects coefficients were reported. Conversely, in the presence of significant interaction, simple effects of each environmental variable were calculated separately for each genotype, while differences between genotypes were calculated for the mean of the two quantitative environmental variables. The SDQ conduct problems scale and socioeconomic status (SES) were included in all models as adjusting terms at baseline (age 3). The two measures of parenting style were retained in the model although its interactions had been deleted. Additionally, the ICU score at age 3 was included as a covariable in models predicting ICU score at age 5.

Normality of the dependent variable (ICU total score) was verified separately for boys and girls at age 3 and 5 using two graphical inspection techniques, boxplot and standardized normal probability plot. Inspection of the boxplot also confirmed normality of residuals for each regression model estimated.

Results

Table 2 shows the zero-order Pearson correlations between CU traits at ages 3 and 5, parenting, SES and conduct problems, separately for boys and girls. The highest positive associations were between CU traits and conduct problems at age 3, and between the two CU traits measures. There were some relevant differences among sexes. The relationship between CU traits at age 3 and positive parenting was direct for boys, but inverse for girls. Also, the association between punitive parenting and conduct problems was stronger for girls than for boys.

Allelic and genotypic frequencies and distribution of environmental factors

The H allele was present in 69.1% ($n = 132$) of the boys and the L in 30.9% ($n = 59$). The HH genotype was present in 48.6% ($n = 86$) of the girls, HL in 42.9% ($n = 76$) and LL in 8.5% ($n = 15$). Table 3 shows that there were no statistically significant differences in the two environmental scores considered in relation to the genotypes for either boys or girls.

G × E interactions on CU traits

Table 4 shows the results of the linear regressions modelling CU traits at ages 3 and 5 from *MAOA*, APQ-Pr Positive and APQ-Pr Punitive (measured when the children were 3 years old) and its interaction separately for boys and girls. No statistically significant effect was found on CU traits at age 3.

Table 3 Distribution of environmental factors at age 3 by sex and genotype.

	Boys (*n*=191)			Girls (*n* = 177)					
	H (*n* = 132)	L (*n* = 59)	*p* (H vs L)	HH (*n* = 86)	HL (*n* = 76)	LL (*n* = 15)	*p* (HH vs HL)	*p* (HH vs LL)	*p* (HL vs LL)
APQ-Pr Parenting practices									
Punitive; *mean (SD)*	3.73 (1.94)	3.63 (1.87)	.740	3.89 (1.96)	3.46 (1.64)	3.07 (1.53)	.384	.305	1
Positive; *mean (SD)*	41.06 (3.91)	40.46 (4.11)	.338	41.69 (3.80)	40.17 (3.80)	39.87 (6.08)	.054	.323	1

Table 4 MAOAx Parenting (at age 3) results on ICU scores for boys and girls at ages 3 and 5.

	Boys				*Girls*		
Response: ICU at age 3	*B*	*p*	95% *CI (B)*		*B*	*p*	95% *CI (B)*
APQ-Pr Punitive × *MAOA*		.816				.576	
APQ-Pr Positive × *MAOA*		.250				.092	
APQ-Pr Punitive parenting	0.35	.349	−0.39; 1.10		0.02	.948	−0.67; 0.72
APQ-Pr Positive parenting	0.26	.123	−0.07; 0.60		−0.07	.576	−0.33; 0.19
MAOA: L/LL vs. H/HH	−1.31	.373	−4.21; 1.59		3.16	.059	−0.12; 6.45
HL vs. HH	-	-	-		−0.01	.996	−2.61; 2.60
Response: ICU at age 5	***B***	***p***	95% ***CI (B)***		***B***	***p***	95% ***CI (B)***
APQ-Pr Punitive × *MAOA*		.906				**<.001**	
APQ-Pr Positive × *MAOA*		.126				**.002**	
APQ-Pr Punitive parenting	0.14	.697	−0.56; 0.84	for HH	0.65	.283	−0.54; 1.84
				for HL	−0.49	.453	−1.77; 0.79
				for LL	**4.17**	**<.001**	**2.26; 6.08**
APQ-Pr Positive parenting	−0.03	.872	−0.44; 0.37	for HH	0.02	.954	−0.55; 0.58
				for HL	0.06	.846	−0.51; 0.63
				for LL	**1.20**	**<.001**	**0.71; 1.68**
MAOA: L/LL vs. H/HH	−0.07	.969	−3.35; 3.21		8.05	<.001	3.82; 12.28
HL vs. HH	-	-	-		0.67	.652	−2.27; 3.61

Boys are hemizygous H or L; All regression coefficients are adjusted by SDQ conduct problems scale and SES, additionally models at age 5 are adjusted by ICU score at age 3; the B column shows main effect in absence of significant interaction, and simple effects when interaction is significant.
Bold values signifies the values are significant.

The prediction of CU traits at age 5 shows non-significant parenting effects (measured at age 3) for boys, but significant differences for girls. In the analysis of CU for girls at age 5, there was evidence of an interaction between punitive parenting (APQ-Pr Punitive) and *MAOA* gene ($p < .001$). Higher levels of punitive parenting at age 3 were associated with higher levels of CU traits only in the LL genotype subgroup ($p < .001$) (Fig. 1A). An interaction with positive parenting (APQ-Pr Positive) at age 3 was also detected when predicting CU at age 5 in the group of girls ($p = .002$) (Fig. 1B). Increased scores in APQ-Pr Positive parenting (age 3) lead to significantly higher CU scores at age 5 only for the LL genotype ($p < .001$). The effect of increasing punitive parenting at age 3 on CU traits at age 5 for LL genotype ($B = 4.17$) was larger than the effect of increasing positive parenting ($B = 1.20$).

Discussion

We analyzed the G × E interaction hypothesis that *MAOA* polymorphism moderates the impact of parenting practices at age 3 on the risk of CU traits in male and female preschoolers at two different stages (ages 3 and 5). Contrary to our hypothesis, we found that the effect of early parenting practices on CU traits is not moderated by *MAOA* alleles for boys, but it is for girls at age 5. In line with our hypothesis on age specific G × E interaction in later stages, we found a salient G × E interaction only among girls at age 5. This is in line with previous research that found that age and sex function as moderating factors of CU traits on parenting practices.[6] In our study, we moreover include genetic vulnerability in the etiology model, suggesting that girls who carry the *MAOA*-LL genotype show higher CU traits at age 5

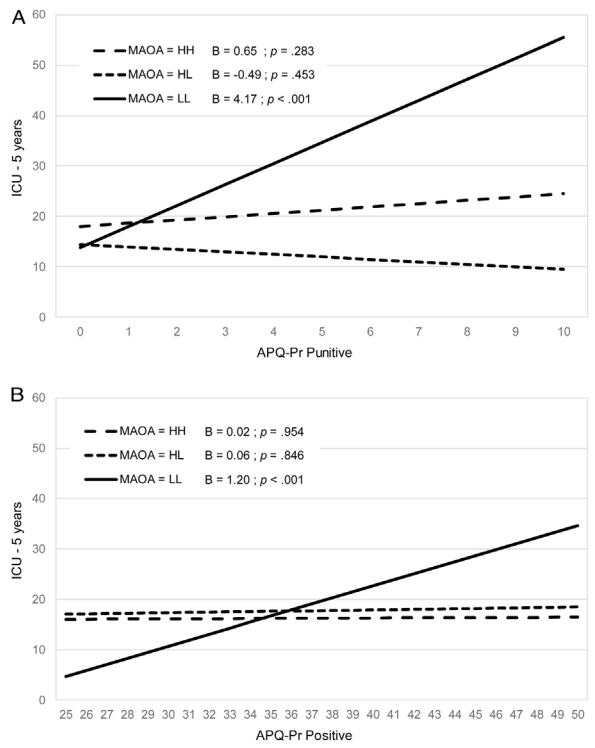

Figure 1 Regression lines for effect of APQ-Pr Punitive (A) and APQ-Pr Positive (B) at age 3 on ICU-5 years for girls depending on MAOA.
A. APQ-Pr Punitive.
B. APQ-Pr Positive.

when exposed to punitive and positive parenting at age 3. This suggests that the *MAOA*-LL genotype for girls is associated with higher sensitivity to both positive and punitive parenting in girls, so that *MAOA*-LL and not the hypothesized *MAOA*-HH allele, emerges as a genotype that confers higher vulnerability to environmental influences. Interestingly, the effect of punitive parenting on CU trait development among female *MAOA*-LL carriers was three times higher than the effect of positive parenting.

All in all, we might fail to replicate the expected G × E interactions because the studies on which we have built our hypothesis were conducted mostly in children who experienced severe early childhood experiences.[20] As the cited *MAOA* x Early adversity interactions might be of a specific nature, it is possible that *MAOA* acts as a moderating factor only when children experience extreme forms of maltreatment or trauma,[31] but not when they face less punitive environments such as parenting practices. Moreover, most *MAOA* x Early adversity interaction studies focused on antisocial behavior as an outcome, and only Fowler et al.[17] specifically addressed CU traits in their MAOA x Early adversity interaction study. Therefore, our novel and counterintuitive findings could be explained by the fact that antisocial behavior and CU traits are different constructs that may have distinct underlying G × E interactions.[32]

The sex specific G × E interaction in our study could be explained by sex differences in heritability of CU traits. Boys seem to be under greater genetic influences than girls, whereas for girls the influence of environmental factors is higher.[33] At the same time, the individual differences on vulnerability towards certain environments might be moderated by gender.[34] Thus, we studied *MAOA*, which is an X-linked gene and operates differently in males and females.[35] Females can be heterozygous and might undergo an X-inactivation of one of the alleles and show allelic expression of only one of the two alleles.[36] Therefore, understanding the effects of *MAOA* is complicated as it is unclear if one allele is inactivated or not, which leads to sex differences in *MAOA* product.[36] Moreover, G × E interactions might be under the differential effect on gender through the impact of different hormones in males and females, such as testosterone.[32] Finally, the *MAOA* promoter region also revealed to be affected by an epigenetic mechanism that involves a chemical modification to the DNA which is called DNA methylation.[37] This mechanism can modify gene expression and is considered a risk for mental disorders.[38] As studies on specific *MAOA* promoter methylation have identified higher methylation in females, especially among those with the low activity genotype,[39,40] we cannot exclude the possibility that DNA methylation influenced our findings.

Although findings are inconsistent, most studies support *MAOA*-HH as the risk allele for females on antisocial behavior.[15] Nonetheless, we report a *MAOA*-LL genotype-specific role on the increase in CU traits in 5-years old girls in interaction with early parenting practices. Our results would be in line with the alternative stream of studies that have identified *MAOA*-LL as the risk allele for antisocial behavior among females.[41,42] As this is the first study to include females in a *MAOA* x Environment interaction study on CU traits, our findings should be interpreted with caution and should be replicated to clarify which alleles might confer vulnerability towards environment in the development of CU traits among girls.

In our study, the *MAOA*-LL x Punitive parenting interaction on girls increased CU traits at age 5, which would be consistent with previous research that associates harsh parenting with CU traits.[2] When parents engage in physical and verbal abuse, communicate poorly and distance themselves from their children, this directly influences the child's ability to understand and interpret emotions and social situations.[22] Thus, when children experience harsh parenting or low parental warmth, they might react with negativity or aggression towards their parents. In turn, children with CU traits also seem to elicit more punitive parenting practices from their parents, resulting in a bidirectional influence between harsh parenting practices and child CU traits.[43] At the same time, not all children are equally sensitive towards parenting practices, so that identifying a subgroup of children (in our case, girls at age 5 who carry *MAOA*-LL alleles) can help explain the biological vulnerability towards environmental factors and its effect on CU traits.[10] Thus, our study has showed that girls who experience punitive parenting and carry the *MAOA*-LL allele increment almost three times more their CU traits than those who are exposed to positive parenting. This suggests that early harsh parenting behaviors have a deeper impact on girl's CU traits than positive parentings. In line with developmental child psychopathology theories, early harsh parenting has severe long-term effects on the biological and psychophysiological reactivity of children and impacts their stress response systems.[44] Children that have experienced punitive or coercive parenting practices might show higher levels of arousal and anxiety,

as well as altered reward-processing and fear-processing systems.[44,45] As such, punitive parenting also predicts CU traits from early childhood on, but positive parenting, in contrast, seems to have a more deteriorating effect on CU traits.[22] Interestingly, the *MAOA*-LL x Positive parenting interaction predicts higher CU traits among girls at age 5. Even though positive parenting is generally considered to prevent and reduce the risk of CU trait development among preschoolers and children,[45] studies have also shown that among preschoolers, positive parenting strategies can predict CU traits.[6] It might be that parents of children with CU traits engage in more positive parenting practices such as parental warmth or giving rewards to respond to their challenging children's CU behavior.

Moreover, girls might be under a greater parental influence, as they are generally more closely monitored by their parents.[46] Daughters are also treated with more reasoning and dialogue, whereas sons experience more authoritarian parenting practices[47] and parents might be more prone to respond at daughter's behavior with positive parenting strategies. Thus, early CU trait behavior of girls might elicit both punitive and positive parenting practices at age 3, which, at the same time, are moderated by *MAOA*-LL on CU traits at age 5.

Also, parents that have to take care of children with CU traits show higher parental inconsistencies and change their parental strategies over time.[6] Applied to our study, this would suggest that parents might initially have started with more positive reinforcement and parental warmth at age 3 to counter their daughter's emerging CU behavior,[43] but, at the same time, they also adopted more punitive practices. This would explain why girls at age 5 carrying *MAOA*-LL alleles showed higher CU traits when exposed to both positive and negative parenting at age 3. In that sense, our findings could then be an indicator of the dynamic nature of parenting practices and its reciprocal effect on CU traits, moderated by genetic vulnerabilities.

Finally, the lack of interaction at age 3 across sex might be explained by the fact that early childhood onset CU traits are under a higher genetic influence than later developed CU traits.[3] This builds on current research that analyzes genetic effect changes over time and according to different CU developing paths, in which early emerging CU traits show higher heritability. This is in line with our findings, because CU traits at age 3 (early onset CU traits) showed no G × E interaction, while CU traits at age 5 among girls (later-on CU traits) can be predicted by a G × E interaction. In our sample, it seems that it is later in development (at age 5) when the interplay of gender, genetic vulnerability and environment on CU traits becomes salient.

This study has several key strengths. It includes a prospective G × E design, with repeated assessment of CU traits. As early childhood is a period when children are very sensitive to emotion regulation, our study permitted testing whether early life environments (parenting practices) at different times were associated with the development of CU traits. Moreover, while most of the G × E research on CU has focused on high-risk children who have experienced maltreatment, our study used data from a community sample of preschoolers to study how *MAOA* interacts in less aversive environments on CU trait development. Another strength of this study is the use of the SDQ conduct problems scale as a control covariate in our regression models. CU traits are often comorbid with antisocial behavior or CD, so further isolation of the possible effect of CD provides more accurate *MAOA* x E interaction models of CU traits. Also, the socioeconomic status of the families was used as a control covariate. Finally, this study included positive and negative environmental factors in the G × E interaction models because most of the *MAOA* x E interaction studies on CU traits to date have studied genetic effects on exposure to strongly aversive environmental factors such as negative life events or harsh parenting styles.[17,48] Hence, studying positive and less aversive contexts helps to clarify how these G × E interactions work in both environments.

Nevertheless, the present study also has some notable limitations that should be considered. First, while our results are in line with previous studies focused on the *MAOA* gene,[20,49] we are aware of the methodological and statistical concerns that gene by environment (G × E) interaction studies have raised, such as small effect sizes and limited statistical power.[50] In this regard, although our total sample size (n = 368) is larger than other studies on G × E interaction on CU traits,[9] it might not have enough power to estimate small effects. Second, we cannot rule out the possibility that G-E correlations (rGE) might explain our findings,[20] so that our G × E interaction on girls might be mediated by passive rGE (parents transmit to their daughters a genetic susceptibility towards CU traits) or evocative rGE (girls with a certain genotype may show CU traits that traits elicit punitive parenting). Future research should test for the presence of rGE in the MAOAx Parenting interactions on CU traits. Third, our G × E design has focused only on one specific environmental factor (parenting), while there are other environmental factors that might be influencing CU traits.[4] Therefore, Gard et al. suggest[51] that further studies should address more complex relationships between multiple environment (G × E × E) or multiple genes (G × G × E). Thus, the authors highlight novel and more sophisticated molecular genetic approaches such as neurogenetics which provide promising results to find polygenic risk scores, instead of focusing on a single candidate gene as the present study does. Also Imaging G × E interaction studies are of interest in gaining a deeper understanding of how neural alterations mediate the effects of G × E interactions to psychopathology.[51] Fourth, there is a small number of girls in the LL genotype due to the usual genotypic distribution. Fifth, parenting practices were measured using self-reports which may be under the effect of distortions such as social desirability or individual interpretation of the items. Sixth, the study focuses on a short period of time (ages 3 and 5), so it is unclear which G × E interactions could be present in later childhood development, as the effect of environmental factors may vary according to the timing of the experiences.[32]

All in all, the results indicate that the influence of the *MAOA* x Parenting on CU traits is sex- and age-specific. If replicated, our study suggests that early parenting experiences at age 3 might have long-term effects, resulting in a sex-specific G × E interaction for girls in later phases of development. Understanding how genes might interact with parenting practices in early childhood is crucial in preventing early CU symptoms from developing into more severe forms of conduct disorder or antisocial behavior,[45] as parenting strategies are among the most salient risk fac-

tors. Thus, treatment models of CU traits often focuses on cognitive-behavior strategies and parent-child interventions, with treatment outcomes that are generally poor or limited.[2] Underlying G × E mechanisms might contribute to explain why some children show a worse treating response than others, so that children carrying certain risk alleles might be more sensitive than others towards parenting strategies.[7] These G × E mechanisms of CU traits development might need to be considered in the process of designing effective treatment interventions. For example, interventions on parent-child interactions in clinical settings should take into consideration possible sex-differences and specifically address parent-girl relationships when CU behaviors appear already in early childhood.

As G × E interactions might have cascading influences on development and stability of CU traits in older children,[3] longitudinal approaches need further exploration in order to analyze the underlying mechanisms that could shape different developing pathways to CU traits. Thus, our approach might help to identify a group of children who are more vulnerable to their environment in a certain developmental period, providing insight on individual differences in the development of CU traits.

Ethical considerations

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Conflict of interest

The authors have no conflict of interest to declare.

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Study 2

Post-print retrieved from https://ddd.uab.cat/record/258377?ln=ca: Pueyo, N., Navarro, J.B., de la Osa, N., Penelo, E., & Ezpeleta, L. (2022). Describing callous unemotional traits and stressful life event trajectories: Differences on risk factors and mental health outcomes from the age of 3 to 10. *The Spanish Journal of Psychology*, 25, E17. doi:10.1017/SJP.2022.13.

Describing Callous Unemotional Traits and Stressful Life Event Trajectories: Differences on Risk Factors and Mental Health Outcomes from the Age of 3 to 10

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CONFLICT OF INTEREST

The authors have no conflicts to declare.

Describing Callous Unemotional Traits and Stressful Life Event Trajectories:

Differences on Risk Factors and Mental Health Outcomes from the Age of 3 to 10

Abstract

Callous Unemotional (CU) traits are associated with different environmental risk factors, such as negative stressful life events (SLE). The most common studied SLE associated with CU trait has been childhood maltreatment, but less is known about how other SLE impact the development of CU traits. Therefore, this work examines risk factors, personal factors (executive functioning), and mental health outcomes associated with the trajectories of Callous Unemotional (CU) traits and Stressful Life Events (SLE) in a community sample of children. A cohort of 377 preschoolers were followed up between ages 3 and 10. Several risk factors and outcomes for three trajectory groups (high CU/SLE; high CU/low SLE; and the reference group with low CU/SLE) were analyzed by using multiple post-hoc comparisons. We hypothesized that children with high CU/SLE would face more contextual risk factors, more executive functioning difficulties and more mental health problems than children with high CU/low SLE or the reference group. At the age of 3, children who showed high CU/SLE faced more early contextual adversity, including socioeconomic difficulties and maternal antisocial behavior than the other groups of children. At the age of 10, children with high CU/SLE presented more peer problems and higher psychopathology symptoms than the reference group, but no differences on mental health outcomes in comparison to the high CU/low SLE group. These results have potential implications for clinical practice and studies attempting to identify different CU subtypes in children.

Key Words

Callous unemotional traits, childhood, mental health, outcomes, risk factors

Describing Callous Unemotional Traits and Stressful Life Event Trajectories: Differences on Risk Factors and Mental Health Outcomes from the Age of 3 to 10

Callous-unemotional (CU) traits are characterized by lack of empathy, lack of guilt, shallow emotional expression, and lack of concern about performance and describe a subgroup of children who are at more risk for conduct problems and antisocial behavior along development (Frick et al., 2014). Considering the severity and associated risk factors of CU traits, the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition, (DSM-5) (American Psychology Association, 2013) has included CU traits as a "Limited Prosocial Emotions" specifier for conduct disorder (CD) (Frick & Myers, 2018), and the International Classification of Diseases 11th revision (ICD-11) (World Health Organization, 2018) has adopted this specifier for the diagnosis of oppositional defiant disorder (ODD) and CD (Evans et al., 2017).

CU traits are often interpreted as the affective dimension of adult psychopathy (Salekin, 2018), sharing core features such as low interpersonal emotional sensitivity, poor emotion recognition, deficits in prosociality and fearlessness (Waller & Hyde, 2017). Research has also found that high CU traits in childhood increase the risk for developing psychopathy in adulthood (Hawes et al., 2017). Thus, CU traits are strongly associated with antisocial behavior such as aggression and rule-breaking (Frick et al., 2014; Muñoz & Frick, 2012), which have been linked with the behavioral dimension of adult psychopathy. More specifically, CU traits are associated with violence, delinquency, and criminality (Kahn et al., 2013; Robertson et al., 2020), aggressive behavior such as bullying (Cantone et al., 2021) and substance abuse (Donohue et al., 2021). Children with CU traits also show a more stable pattern of CD and antisocial behavior (Frick et al., 2014), which may explain the poor treatment outcomes that characterizes this subgroup of children (Hawes et al., 2014).

While the construct of psychopathy is only applied to adults, CU traits can already be observed from early childhood on (Kimonis et al., 2016) and there is evidence that CU traits in early childhood co-occur with psychopathic traits and can therefore be considered the precursors to adult psychopathy (Klingzel et al., 2016). Moreover, early onset CU traits have been linked with fearlessness, aggressive behavior, and rule-breaking (Waller & Hyde, 2017) and are considered a risk factor for severe conduct problems (Donohue et al., 2021) and low socio-emotional competencies (Zumbach et al., 2021). Early childhood CU traits also predict externalizing behavior (Song et al., 2016) and severe and persistent antisocial behavior over time (Willoughby et al., 2014).

Genetic and environmental influences on the etiology of CU have been vastly studied. Genetic studies have shown that the heritability of CU traits accounts for between 36% and 67% of the variation of CU traits (Moore et al., 2019). Interestingly, sex-differences in CU trait heritability have also been observed and indicate that boys might be under greater genetic influence on CU traits than girls. Thus, CU traits are more prevalent in boys than in girls (Ueno et al., 2021) and sex differences have been found in the severity, the stability, and the associated difficulties of CU traits (Euler et al., 2015). For example, boys score higher on CU traits and show more externalizing problems such as antisocial behavior and impulsivity, whereas girls high on CU traits exhibit better affective empathy and more internalizing problems such as anxiety and depression (Cardinale & Marsh, 2020).

Studies on environmental influences have identified negative stressful life events (SLE) as risk factors in the development of CU traits (Kimonis et al., 2014). The most common studied SLE associated with CU trait development have been maltreatment or neglect (Dackis et al., 2015), experiencing high levels of chaos at home (Fontaine et al., 2011; Mills-Koonce et al., 2016), or harsh parenting (Waller & Hyde, 2018). Even a bidirectional effect of these SLE and CU traits has been described by Kimonis et al. (2014), suggesting that children with CU

traits might evoke SLE from their environment by their characteristics or their predisposition to risky behavior. These SLE often have a deep psychological impact in the life of individuals because they change their life circumstances and their coping and adaptation strategies, which might lead to psychological distress (Johnson, 1982). Especially during early childhood, SLE have been found to have an impact on childhood development, contributing to mental health outcomes such as conduct problems, posttraumatic stress disorder and attention-deficit/hyperactivity disorder (ADHD) and anxiety (Humphreys & Zeanah, 2015).

Related to SLE, the socioeconomic status (SES) of the family is a stressful risk factor for children's development and evidence shows that children who live in low SES contexts show more psychopathology (Peveril et al., 2021). Similarly, Piotrowska et al. (2015) reported in a meta-analysis that lower SES was associated with CU traits and antisocial behavior. The relationship between SES and externalizing behavior in children can be described through the family stress model, which suggests that low SES families might experience greater household chaos and lower family income, so that these parents face more personal difficulties than parents in middle or high SES contexts. Thus, parents in low SES contexts are at higher risk of developing mental disorders (Reiss et al., 2019), which can impact their parenting style. For example, when mothers suffer from depression or anxiety, they seem to have more difficulties with parenting and might face their children's CU traits with less discipline and less involvement (Hawes et al., 2011). Also, when mothers show antisocial behavior or psychotic traits they might engage in more impulsive reactions towards their children or act with more irresponsibility, so these maternal externalizing problems predict child mental health problems such as CD, ODD or depressive symptoms (Fanti & Lordos, 2021). Studies have observed a positive relationship between child CU traits and maternal psychopathological traits (Barker et al., 2011), maternal antisocial behavior (Hyde et al., 2016) and maternal psychopathic traits (Zhong et al., 2020).

The role of SLE and associated contextual risk factors in the etiology of CU traits seems to be crucial considering Karpman's (1946) theoretical model on primary and secondary variants of psychopathy, which show similar psychopathic traits, but differ in emotional reactivity and etiology. The primary variant is described as the traditional or idiopathic subtype with low levels of anxiety, whereas the secondary variant is considered the distressed subtype with high levels of anxiety and exposure to traumatic or stressful events (Craig et al., 2021).

Building upon this theory, studies have started to investigate primary and secondary variants on CU traits but have focused mostly on justice-involved male youth samples (Craig et al., 2021). This stream of research was able to identify a subgroup of adolescents with high CU traits and high levels of anxiety, who had also experienced severe traumatic events or SLE. While this high CU/high anxiety group is described as a secondary variant of CU traits, the primary variant has been identified as a group of adolescents with high CU traits, no exposure to SLE and low anxiety. Although both variants involve similar phenotypic CU traits, they differ in specific outcomes derived from them. For example, in a community sample of socially deprived youths (age 18), the secondary variants of CU traits experienced more psychological distress and ADHD and engaged in more behavioral risks such as substance use, suicidal ideation and unsafe sex (Cecil et al., 2018) than the primary variant. Similarly, in a sample of adolescents (age 11-18), that were recruited from a mental health care center, the secondary variant showed more impulsivity, externalizing behaviors, and aggression than the primary variant (Kahn et al., 2013). Meehan et al. (2017) also identified that among the secondary variant, youth faced more prenatal and postnatal levels of family adversity and maternal psychopathology, more psychopathology such as ADHD, CD or ODD, and more emotional and academic difficulties than the primary variant.

The few studies conducted on young children highlight similar results than those on adolescents, and suggest that the secondary variant, in comparison to the primary variant,

occurs with more psychosocial difficulties (Ezpeleta et al., 2017) and mental health problems such as depression or CD (Goulter et al., 2017; Huang et al., 2020), more peer problems and antisocial behavior (Humayun et al., 2014), more deficits in self-regulation and cognitive functioning (Fanti & Kimonis, 2017) and more exposure to trauma or SLE (Cecil et al., 2014). On the other hand, the primary variant, in comparison to the secondary variant, occurs with low anxiety, low levels of SLE and more emotional deficits in responding to others (Dadds et al., 2018).

The previous results seem to suggest that the secondary, distressed, variant of CU traits is associated with impaired executive functioning, which includes difficulties in behavior inhibition and emotion control. Neurobiological studies have shown that chronic stress alters brain structures and functions of the prefrontal cortex, which is the brain region responsible for executive functioning (Girotti et al., 2019). Therefore, exposition to severe SLE could harm neural development, resulting in self-regulation problems and a deficient impulse control. In combination with CU traits, these executive functioning deficits can lead to more peer problems and aggressive behavior (Waller et al., 2017). A systematic understanding of how executive functioning contributes to secondary variants of CU traits is still lacking and needs to be further addressed.

Besides research on primary and secondary variants of CU traits, longitudinal intrapersonal studies on CU traits have found variations of CU traits along development, with groups of children presenting low, unstable (increasing and decreasing) or stable high CU traits. Evidence suggests that children (7-12 years) in the stable high CU trait group often experience more SLE and show more severe mental health outcomes, such as conduct problems and hyperactivity when compared to children in the other groups (Fontaine et al., 2010). Similarly, Byrd et al. (2016) conducted a longitudinal study on a community sample of boys between 7 to 15 years old and found the stable high CU trait group to be associated with more

psychosocial adversity and maltreatment, as well as with child characteristics such as fearlessness and difficulties in anger-management, and with externalizing problems such as conduct problems and ADHD. Stable high CU traits are also associated with low SES (Fontaine et al., 2018), which is a strong predictor for SLE (Kimonis et al., 2014). Most of these studies have predominantly focused on middle childhood (5-11 years) or youth (12-18 years), but less is known about CU trait development, contextual risk factors, personal factors (executive functioning) and mental health outcomes in early childhood, comprising the preschool period (3-5 years) (Fanti & Kimonis, 2017).

All in all, SLE might influence the development of CU traits along childhood, but the extant literature has not yet examined how joint CU traits and SLE trajectories might be associated with different contextual risk factors such as gender, economic problems, low educational backgrounds of parents, as well as maternal psychopathology. Therefore, the objective of this study was to analyze contextual risk factors (i.e., economic problems, family disadvantages and maternal mental illness) and personal factors (executive functioning) in early childhood (at the age of 3), as well as their mental health outcomes at the age of 10, depending on different CU traits and SLE trajectories. Because the period between 3 and 10 years is a sensitive window to the development of social and emotional behavior, the impact of joint CU trait and SLE might have negative consequences for child's psychosocial adjustment (Humphreys & Zeanah, 2015). Based on the existing literature (Craig et al., 2021), we hypothesized that children with high CU traits and high levels of SLE would face more contextual risk factors, more executive functioning difficulties and more mental health problems than children with increasing CU traits and low levels of SLE or children who showed neither CU traits nor SLE.

Identifying the contextual and individual characteristics of children with CU traits in early childhood might be important in the light of the poor treatment outcomes that have been

found among those children with higher CU traits (Hawes et al., 2014). Therefore, focusing on their distinct SLE trajectories could be crucial to detecting at-risk groups of children and tailoring more personalized interventions that may change negative developmental CU trait courses. Also, gaining knowledge on the trajectories toward mental health problems is important for realizing how the early risk factors and later outcomes associated with CU traits could be prevented.

Method

Participants

The sample comes from a longitudinal study of behavioral problems starting at the age of 3 (Reference deleted to avoid author identification). A double-phase sampling design, as summarized in Figure 1, was employed. The first phase started with a random sample of 2,283 children selected from the census of early childhood schools in Barcelona. From these, 1,341 families (58.7%) agreed to participate (50.9% boys; 33.6% high SES, 43.1% middle-high/middle SES and 23.3% middle-low/low SES). In the second phase of the sampling, a parent-rating of ODD symptoms (8 items) based on the four items of the conduct problems scale of the Strengths and Difficulties Questionnaire (SDQ) plus four additional ODD items to complete the Diagnostic and Statistical Manual of Mental Disorders (4th Edition; DSM-IV) description was used to screen children with possible psychological problems. Exclusion criteria were showing autism spectrum disorder or intellectual disability, planning to live abroad the next year and limited understanding of the Spanish language. Two groups were considered: the screen-positive group included all the children with scores above the cut-off point (90^{th} percentile) of the SDQ or with a positive response for any of the eight ODD symptoms (n = 417; 49.0% boys); and the second group, considered screen-negative, was a random selection of 28% of the children who did not reach the positive criteria (n = 205; 51.2% boys). The number of children in the screening-positive group was higher than those from the

screening-negative group to increase the number of participants with potential psychological problems, as it was assumed that the occurrence of psychological problems in a community sample is lower than in clinical samples.

The follow-up study, consisting of a yearly evaluation from the age of 3 to 10 years old (8 assessment points), started with a sample of 622 children. The mean and standard deviation (*SD*) of the age at the different follow-ups that provided data for the risk factors and outcomes was: 3.77 (0.34) at baseline (age 3) and 9.65 (0.35) at the last follow-up (age 10).

In a previous study of Ezpeleta et al. (2019), Latent Class Growth Analysis (LCGA) for two parallel processes (CU traits and the number of SLE experienced each year) was used on follow-up data from age 3 to 9. The analyzed sample consisted of the 377 children who completed at least 4 of 7 follow-up assessments (see Table 1 for a description). To select the optimal solution, models with one to five latent classes of growth patterns (trajectories) were compared using statistical criteria (AIC, BIC, adjusted BIC, average posterior probabilities, entropy values and a minimum of 20 participants in each trajectory) and clinical interpretability. The 3-trajectory solution showed the highest entropy (.859), high posterior probabilities of class membership (.951, .925 and .884 for diagonal values), a sample size above 20 for each trajectory and was clinically interpretable. These three trajectories defined the three groups of participants used for the present study: Trajectory 1 (226; 59.9%) is the reference group and describes a group of children with a low and stable profile for both CU scores and the number of SLE (CU-/SLE-); Trajectory 2 (127; 33.7%) includes children with increasing high CU scores and a low and stable number of SLE (CU+/SLE-); and Trajectory 3 (24; 6.4%) refers to children with both stable high CU scores and a stable high number of SLE (CU+/SLE+) (Figure 2). The available data at age 10 (n = 320) was used to study the mental health outcomes (see Table 1 for a description).

Measures

Developmental Trajectories

The Inventory of Callous-Unemotional Traits (ICU; Frick, 2004) includes 24 items which can be grouped into three subscales (Uncaring, Callousness and Unemotional) to identify children with CU traits. Psychometric research on the ICU has presented evidence for high internal consistency, convergent and criterion validity of the total ICU score (range 0-72) across different samples, especially for the parent- and teacher-report versions (Cardinale & Marsh, 2020). While most of the research on the ICU has focused on self- and parent-report, preliminary studies on the teacher-report version of the ICU have found that teachers seem to be more reliable as informants for CU traits than the child or adolescents themselves (Docherty et al., 2017; Ueno et al., 2021). Teachers may be more aware of certain CU traits such as indifference about performance or socioemotional problems that may become more salient in school settings than in a more familiar context (Ueno et al., 2021). The teachers of our study responded using a 4-point Likert-type scale from 0 (*not at all true)* to 3 (*definitely true*). The specific validation for the ICU that was used in this study can be found in [Reference deleted to avoid author identification]. The total score was used for obtaining the developmental trajectories. Cronbach's alpha for the total score through follow-ups in the present sample ranged from .88 to .93.

SLE were registered through the *Life Events Checklist* (Johnson & McCutcheon, 1980) that includes 25 SLE which were reported by the mother or caregiver. These events include moving to a new house or school, a new brother/sister, parents' fights, separation/divorce, a new father/mother, death of a family member, child abuse, among others. In each follow-up, a life event was registered as present if the child was exposed to it at least once during the previous year (the year between assessments). The total number of SLE (range 0-25) at each age was combined with the ICU total score to obtain the developmental trajectories.

Risk factors at the age of 3

Demographic and contextual variables were assessed through dichotomic questions about economic problems in early infancy, achieved level of studies of the parents and employment of the main caregiver. Moreover, SES was assessed according to the Hollingshead Four-Factor Index of Social Status (Hollingshead, 1975). This index includes weighted scaled scores of the occupation and educational attainment of the mother and father, which were categorized in 3 groups: low/middle-low, middle/middle-high and high SES.

Parental Mental Health: *Adult Self-Report* (ASR; Achenbach & Rescorla, 2003) assesses dimensional psychopathology in adults between ages 18 and 59. It contains 126 items with 3 response options from 0 (*not true*) to 2 (*very true/often true*). The internal consistency of the original ASR version shows alpha values of .82 to .95 and can be considered good (Guerrero et al., 2020). Mothers reported on their mental health status when children were 3 years old. The current study considered the scale scores for anxious/depressed (18 items, range 0-36), aggressive behavior (15 items, range 0-30), rule-breaking (14 items, range 0-28) and the total score (120 items, range 0-240). Ordinal alpha values in the present sample were .92, .89, .68 and .91, respectively.

Personal factors at the age of 3

Executive Functions: The *Behavior Rating Inventory of Executive Function preschool version* (BRIEF-P; Gioia et al., 2003) assesses behaviors reflecting the executive functions in daily life in preschool children. The questionnaire has shown good internal consistency reliability with Cronbach's alpha coefficients ranging between .86 and .95 when applied to normative samples of 2 to 5-year-old children (Gioia et al., 2003). Teachers completed the inventory when children were 3 years old. The instrument consists of 63 items on a 3-point ordered scale from 1 (*never*) to 3 (*often*). Two dimensions of executive functioning, inhibitory control (the ability to suppress thoughts or actions that are irrelevant to the task) (16 items, range 16-

48) and emotional control (9 items, range 9-27), were used. Higher scores show higher difficulties in executive functioning. Ordinal alpha values in the present sample were .96 and .94 respectively. The specific validation for the BRIEF-P that was used in this study can be found in [Reference deleted to avoid author identification].

Mental Health outcomes at the age of 10

The *Strengths and Difficulties Questionnaire* (SDQ) (Goodman, 1997) is a brief screening questionnaire for the mental health of children which comprises five scales of five items each (0: *not true* to 2: *certainly true*). A meta-analysis of the psychometric properties of the SDQ has found strong internal consistency for both the parent- and the teacher-report version (Stone, et al. 2010). Only a few studies have evaluated the psychometric properties of the SDQ applied in young children (age 3 and 4), but the preliminary results show that the parent-report version of the SDQ is a valid instrument with an internal consistency for its subscales between .66 and .83 (Croft et al. 2015). The specific validation for the SDQ at the age of 3 that was used in this study can be found in [Reference deleted to avoid author identification]. The SDQ was completed by parents and teachers when children were 3 and 10 years old. The total difficulties score (20 items, range 0-40) and the scale scores of emotional problems (5 items, range 0-10), conduct problems (5 items, range 0-10), hyperactivity (5 items, range 0-10) and peer problems (5 items, range 0-10) were used. Ordinal alpha values in the present sample ranged from .79 to .93 for parents and from .79 to .92 for teacher ratings.

Procedure

The project was approved by the Ethics Committee on Animal and Human Experimentation of the author's institution that follows the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The recruitment of the families took place at the schools whose Heads and parents were provided with a description of the study's aims and procedures. Participating families gave written consent before their inclusion in the study and

were invited to answer the screening questionnaire SDQ3-4. The questionnaire was completed at home and returned to the schools. Families who met screening criteria were contacted by telephone and were interviewed at the school by previously trained psychologists or psychology students who were supervised. The interview consisted of a semi-structured diagnostic interview and other psychological assessment instruments. All interviewers were blind to the screening group and all interviews were recorded. Then parents answered the questionnaires on demographic variables, child characteristics and mental health and, at the schools, the teachers were asked to answer the questionnaires on child characteristics.

For the annual follow-up, parents and teachers were assessed each year at the school by the team of interviewers. To obtain the information from the parents, both father and mother were called. Most of the time only mothers attended the appointment, in other occasions it was only fathers and in other occasions both attended. There were no statistically significant differences in the score of the questionnaires between mothers, fathers or both as informants. All participants gave their informed consent before their inclusion in the study. The Spanish law on protection of personal data (3/2018, from 5th of December) was followed.

Data Analysis

The statistical analysis was carried out using Stata 16. Given the multistage sampling procedure used, the analyses were weighted by the inverse probability of selection in the second phase of sampling, to reestablish the proportionality between the sample and the population. Different demographic and psychological measurements obtained at the age of 3 and 10 were compared between trajectories using multiple post-hoc comparisons. Linear regression models for continuous, logistic models for binary and multinomial logistic models for polytomous measures were estimated. In the analysis of outcomes at the age of 10, the SDQ scores at the age of 3 were included as covariates. The risk of type I error was corrected by Šidák's (1967) approach. Cohens' *d* effect size was calculated for each contrast. According to Cohen

(1992) absolute values of *d* were interpreted as follows: null effect for values < 0.20, small effect for values 0.20-0.50, medium effect for values 0.50-0.80 and large effect for values > 0.80.

Results

Comparison of the Trajectories in Early Childhood (Risk Factors and Personal Factors) at the Age of 3

Table 2 provides the comparison between trajectories of demographic characteristics, contextual risk factors, maternal psychopathology and personal factors (executive functioning) at baseline (age 3). CU+/SLE- children (trajectory 2), in comparison with CU-/SLE- children (trajectory 1- reference group), were mostly males, had a higher percentage of mothers with lower educational level and showed more inhibition problems at the age of 3. The effect size for these comparisons was medium ($d \geq 0.67$). Children with CU+/SLE+ (trajectory 3) compared with the reference group, were more likely to grow up in families with low/middle-low SES, with caregivers that were less often employed and had early economic problems when the children were between 0-3 years old. In addition, their mothers had lower educational level and scored higher in rule-breaking behavior. The effect size for these comparisons was large ($d \geq 0.88$). The CU+/SLE+ group (trajectory 3) in comparison with the CU+/SLE group (trajectory 2) pertained more frequently to low/middle-low SES, had early economic problems, had more unemployed caregivers and their mothers engaged in more rule-breaking behavior. The effect size for these comparisons was medium ($d \geq 0.73$).

Comparison of the Trajectories on Mental Health Outcomes at the Age of 10

Table 3 presents the descriptive data obtained on mental health scores for each trajectory and their comparisons. Children in the CU+/SLE- group (trajectory 2), in comparison to CU-/SLE- children (trajectory 1- reference group), scored higher on all the teacher-reported mental health problems, but no differences were found when the informants were parents. The

effect sizes for emotional and peer problems were small ($d \leq 0.45$), whereas for hyperactivity the effect size reached medium value ($d = 0.77$). Conduct and total problems had large effect sizes ($d \geq 0.85$). Children in the CU+/SLE+ group (trajectory 3), compared with CU-/SLE- children (trajectory 1- reference group), scored higher on parent-reported problems with peers and overall problems, showing large effect sizes for both outcomes ($d \geq 0.93$). No differences were found for teacher-reported mental problems. No differences were observed in the mental health outcomes between CU+/SLE- (trajectory 2) and CU+/SLE+ (trajectory 3) children.

Discussion

The current study analyses contextual risk factors, maternal psychopathology, personal factors (executive functioning) and mental health outcomes of co-occurring CU traits and SLE trajectories along childhood, between the ages of 3 and 10 years. The aim was to examine if children with high CU traits, who were also sustainably exposed to high levels of stressors (CU+/SLE+), would face more contextual risk factors (including socioeconomic problems and maternal psychopathology), lower executive functioning and more mental health problems in comparison to children with increasing high CU traits and low stress (CU+/SLE-) or children with low CU traits and low stress (CU-/SLE-; reference group).

The results only support our hypothesis partially. CU+/SLE+ children were more likely to face early contextual adversity in forms of low SES, unemployment, early economic problems, and maternal psychopathology than the children from the other two trajectories. The CU+/SLE+ trajectory was the smallest group in our sample (only 24 participants), but also the one which experienced the highest early risk environments. The highest scores on mental health problems were also found in this CU+/SLE+ trajectory, but the comparison between the other two trajectories (reference group and CU+/SLE-) did not reach statistical significance. Contrary to our hypothesis, we found neither poorer executive functioning among CU+/SLE+ children at the age of 3, nor differences on mental health outcomes reported by teachers and parents at the age of 10 in comparison to CU+/SLE- children. This suggests that

children with CU traits and different levels of SLE show similar executive functioning and mental health outcomes, but different contextual risk factors. Worse outcomes in peer relations and higher psychopathology symptoms reported by parents were only observed when comparing CU+/SLE+ children to the reference group.

When analyzing the different contextual risk factors of CU+/SLE+ children in comparison to the other two trajectories, our results are in line with previous research, which has revealed that children with high CU traits also suffered from more contextual risk factors such as parental mental health problems, that are related to socioeconomic difficulties (Piotrowska et al., 2015). Low SES and its associated risk factors (unemployment and lower educational backgrounds) might increase the parental vulnerability to develop mental health problems (Vukojević et al., 2017), resulting in more deficient parent-child relationships and problematic parenting styles (Schneider & Schenk-Fontaine, 2021). Similar results were observed in our study, as the CU+/SLE+ trajectory was socioeconomically more disadvantaged (lower SES, higher early economic problems and unemployment) and lived with mothers who engage in higher rule breaking behavior when comparing these variables to the other two trajectories. These results are not surprising, because parents who show antisocial behavior might also engage in more authoritarian parenting styles (Zhong et al., 2020). Thus, harsh parenting styles are a predictor of children's CU traits (Waller et al., 2017) and parental psychopathology has been associated with higher CU traits (Cecil et al., 2015). Possible psychopathological conditions of the mothers should be considered as an additional risk factor when analyzing developing pathways of CU traits among children.

Another factor that should be further examined is the role of sex differences in CU trait development. In our study, we observed more boys in the CU+/SLE- and CU+/SLE+ trajectories than in the reference group. This finding is consistent with previous research indicating that CU traits in boys are higher and more prevalent than in girls (Pihet et al., 2015). Thus,

boys have found to be more vulnerable towards biological factors (Moore et al., 2019) and seem to be more prevalent in the primary variant of CU traits (Docherty et al., 2016), while girls are more vulnerable towards environmental factors and are more likely to be found among the secondary variant of CU traits. However, our results did not show any sex-differences between the CU+/SLE- and the CU+/SLE+ trajectories. Future research that examines the developmental pathways on CU traits for boys and girls separately is needed.

Furthermore, the children in the CU+/SLE- seem to show distinct personal factors that might predisposition them towards CU behavior, such as inhibitory control deficits. The role of early inhibition problems is especially important, as CU traits together with low executive function work as comorbid risk markers for poor psychosocial adjustment, more peer rejection and more aggressive behavior than children with CU traits, but intact executive functioning (Waller et al., 2017). Previous research has observed that increasing CU traits are associated with ADHD, suggesting that early childhood CU traits in combination with executive function deficits could describe a distinct developmental pattern (Byrd et al., 2016; Squillaci & Benoit, 2021). Our study would support this finding, as the CU+/SLE- trajectory has a higher presence of psychopathology in comparison to the reference group regarding all domains (emotional, behavioral, hyperactivity, social) reported by teachers at the age of 10. Surprisingly, parents did not describe any mental health issues for this group of children. A possible reason for this is that parents and teachers experience and interact with children in different settings. Therefore, teachers could be more sensitive towards impulsive, drive and externalizing behavior, which is more salient in normative and social environments such as schools (Papageorgiou et al., 2008). Teachers might then perceive children with increasing high CU traits as more problematic than their parents would, as their disruptive behavior could have a negative impact on the classroom activities and the relationship with other classmates (Allen et al., 2018).

When addressing the question of whether children with CU+/SLE+ feature different mental health outcomes than children in the other trajectories, our comparisons between children with CU+/SLE+ and the reference group did not reach significance on teachers' reports on mental health, although effect size values are medium-high (3 of 5 above 0.90). This is likely due to the small sample size of the CU+/SLE+ trajectory and the resultant lack of power for these comparisons. When parents reported mental health problems, this CU+/SLE+ trajectory showed higher peer-problems and overall problems in comparison to the reference group. As parents of children in this distressed trajectory seem to be under higher psychosocial vulnerability, they also might perceive their child as being more problematic due to their dysfunctional parent-child relationship.

Contrary to our hypothesis, no significant differences on mental health outcomes were found when comparing children in the CU+/SLE+ and CU+/SLE- trajectories. These results need to be interpreted in the light of primary and secondary variants of CU traits, as it could be expected that the CU+/SLE+ trajectory would face higher emotional problems, considering it the secondary variant of CU traits. However, among our sample there were no differences between both trajectories on the mental health outcomes, including emotional problems. This supports the idea that there is great inconsistency in the findings on whether the behavioral and psychological outcomes among primary and secondary variants are unique or not (Craig et al., 2021). If replicated, our results would further suggest that children who show CU+/SLE+, but also those with CU+/SLE-, might not differ phenotypically on socioemotional and psychological outcomes. Instead, the underlying mechanism of their developmental pathways may be distinct, due to their different level of exposure to SLE and other contextual risk factors. We would then propose that CU+/SLE- children could be described as the primary variant of CU trait, hypothesizing that they are under a greater influence of non-environmental factors, whereas CU+/SLE+ children could be identified as the secondary variant of

CU traits, describing a subtype of children who experience early contextual risk factors. Among these children, CU traits might emerge as an adaptive mechanism towards those stressful environments, impacting negatively on their social behavior and emotional processing development (Kahn et al., 2013).

Strengths and Limitations

The current study has several strengths, including a prospective longitudinal design of 8 years, a community-sample of children and multiple informants. However, some limitations should be taken into consideration. First, working with a community sample implies low presence of psychological dysfunction or mental health problems. Moreover, among the three trajectories, the group of children with CU+/SLE+ had a small sample size, which might affect the statistical power of our study. Second, our study design allowed us to associate risk factors and outcomes to the different trajectories, but they cannot be interpreted as causal risk factors and outcomes. Third, some scale scores show low alpha values (e.g., ASR rule-breaking), as the items are characterized by a low variance, because most participants' response option was negative (e.g., *not true*).

Clinical implications

The present study helps to gain a better understanding on how CU traits develop along childhood according to different levels of SLE exposure, and our conclusions could be generalizable to community children with an occidental lifestyle. The joint CU-SLE approach helps to evaluate and to identify contextual adversities and developmental characteristics in children with CU traits, which have been associated with poor treatment responses in reducing CU traits (Hawes et al., 2014). Therefore, boys experiencing low SES and related contextual risk factors (e.g., early economic problems, unemployment of the caregiver, maternal antisocial behavior) might be under greater risk of facing a CU+/SLE+ trajectory. This subgroup of children could be identified as more vulnerable, implying that CU trait evaluations in clinical

contexts should also explore other factors such as gender, SLE, SES or psychosocial adversity.

Moreover, children in the CU+/SLE+ trajectory need treatment models which focus not only on children's social and emotional regulation skills or parent training (Hawes et al., 2014) but also on the reduction of stressors in the developmental contexts of these children (family, school, social environment). Such broader multidisciplinary treatment approaches could also target maternal psychopathology and more specifically maternal antisocial behavior, which can harm the parent-child relationships (Maliken & Katz, 2013). Improvement in treatment results might be achieved by including interventions on children's socioemotional skills and parents training, but also on stress coping strategies targeted at the parents to improve how they deal with general psychosocial disadvantages and specific SLE (Devenish et al., 2017). Intervention studies that assess how children's exposure to SLE and co-occurring CU traits might moderate the effects of treatment programs are needed to establish the components that show higher treatment effects.

In conclusion, the joint analysis of CU traits and SLE on developmental differences along childhood allows understanding and characterizing the etiological pathways of CU traits. Our results suggest that CU traits need to be studied in a more global context, focusing not only on early childhood SLE and psychosocial adversity, but also on later mental health outcomes.

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Table 1.

Description of Sociodemographic and Clinical Variables at Ages 3 and 10 years-old

	Age 3	Age 10
n	377	320
Sex (% boys)	54.8	53.4
Socioeconomic status (%)		
High	38.9	40.8
Middle-high/Middle	45.5	44.7
Middle-low/Low	15.7	14.5
ASR Total (mother reported) – *M*	27.3	--
(*SD*)	(16.9)	--
BRIEF-P Inhibition – *M* (*SD*)	22.7	--
BRIEF-P Emotional Control – *M*	(6.7)	
(*SD*)	12.2	
	(3.6)	
SDQ Total (parents reported) – *M*	8.9 (4.5)	5.3 (5.0)
(*SD*)	7.4 (5.6)	6.7 (6.0)
SDQ Total (teachers reported) – *M*		
(*SD*)		

ASR: Adult Self-Report; BRIEF-P: The Behavior Rating Inventory of Executive Function-Preschool; SDQ: Strengths and Difficulties Questionnaire

Table 2

Differences on Trajectories Depending on Sociodemographic and Contextual Factors, Maternal Mental Illness and Executive Function

	Trajectory 1 CU-/SLE- *n* = 226 %	Trajectory 2 CU+/SLE- *n* =127 %	Trajectory 3 CU+/SLE+ *n* = 24 %	Global *p* χ^2 (*p*)	Trajectory 2 *vs.* 1 *OR* (χ^2; *p*)	Trajectory 3 *vs.* 1 *OR* (χ^2; *p*)	Trajectory 3 *vs.* 2 *OR* (χ^2; *p*)
Demographics							
Sex (% Boys)	44.2	70.9	70.0	18.97 (< .001)	**3.07 (16.8; < .001)**	2.95 (4.6; .093)	0.96 (0.0; .100)
Socioeconomic status[1]							
High	41.0	39.8	12.6				
Middle/Middle-High	48.4	41.4	39.9	22.53 (< .001)	0.88 (0.2; .959)	2.69 (2.7; .269)	3.05 (3.2; .204)
Low/Middle-Low	10.6	18.8	47.5		1.83 (2.6; .291)	**14.6 (20.0; < .001)**	**7.98 (11.2; .003)**
Contextual variables (% Yes)							
Economic problems 0-3 years-old	2.1	0.5	20.0	17.95 (< .001)	0.22 (1.8; .438)	**11.6 (12.0; .002)**	**52.5 (12.2; .002)**
Mother's education: basic studies	26.8	42.7	69.9	18.65 (< .001)	**2.04 (7.1; .023)**	**6.35 (15.2; < .001)**	3.11 (5.3; .062)
Father's education: basic studies	38.5	39.7	66.7	5.23 (.073)			
All caregivers are working	84.4	83.9	58.9	7.68 (.022)	0.97 (0.0; .999)	**0.27 (7.3; .021)**	**0.27 (6.2; .039)**
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	*F (p)*	*d (F; p)*	*d (F; p)*	*d (F; p)*
ASR (mother-reported at the age of 3)							
Anxious/depressed	6.13 (4.33)	6.12 (3.87)	8.02 (5.45)	11.63 (<.001)	0.00 (0.0; .991)	0.38 (0.0; .864)	0.40 (0.1; .812)
Aggressive behavior	3.71 (3.20)	4.28 (3.22)	5.44 (5.04)	3.77 (.001)	0.18 (0.4; .545)	0.41 (0.4; .533)	0.27 (0.1; .810)
Rule breaking	0.88 (1.07)	1.12 (1.15)	2.42 (2.23)	4.54 (.004)	0.22 (1.3; .247)	**0.88 (6.5; .011)**	**0.73 (4.0; .046)**
Total	26.26 (16.34)	27.62 (15.60)	38.71 (24.02)	10.12 (<.001)	0.09 (0.0; .977)	0.61 (1.3; .264)	0.55 (0.9; .336)
BRIEF-P (at the age of 3)							
Inhibition	21.03 (5.66)	25.45 (7.43)	24.24 (7.31)	14.08 (< .001)	**0.67 (26.2; < .001)**	0.49 (4.4; .105)	0.16 (0.5; .847)
Emotional Control	11.73 (3.23)	12.72 (5.99)	13.33 (4.65)	3.34 (.037)	0.21 (4.5; .101)	0.40 (3.0; .229)	0.11 (0.4; .896)

Trajectory 1: Children showing low CU traits and experiencing low stressful life events; Trajectory 2: Children showing increasing high CU traits and experiencing low stressful life events; Trajectory 3: Children showing high CU traits and experiencing high stressful life events; Trajectories comparison *p*-values are corrected for multiple comparison using Sidak's approach; In bold significant comparison; *d*: Cohen's *d* effect size; [1]Comparison of OR between trajectories related to High SES as reference category; ASR: Adult Self-Report; BRIEF-P: The Behavior Rating Inventory of Executive Function-Preschool.

Table 3

Comparison of The Trajectories on Mental Health Outcomes at the Age of 10

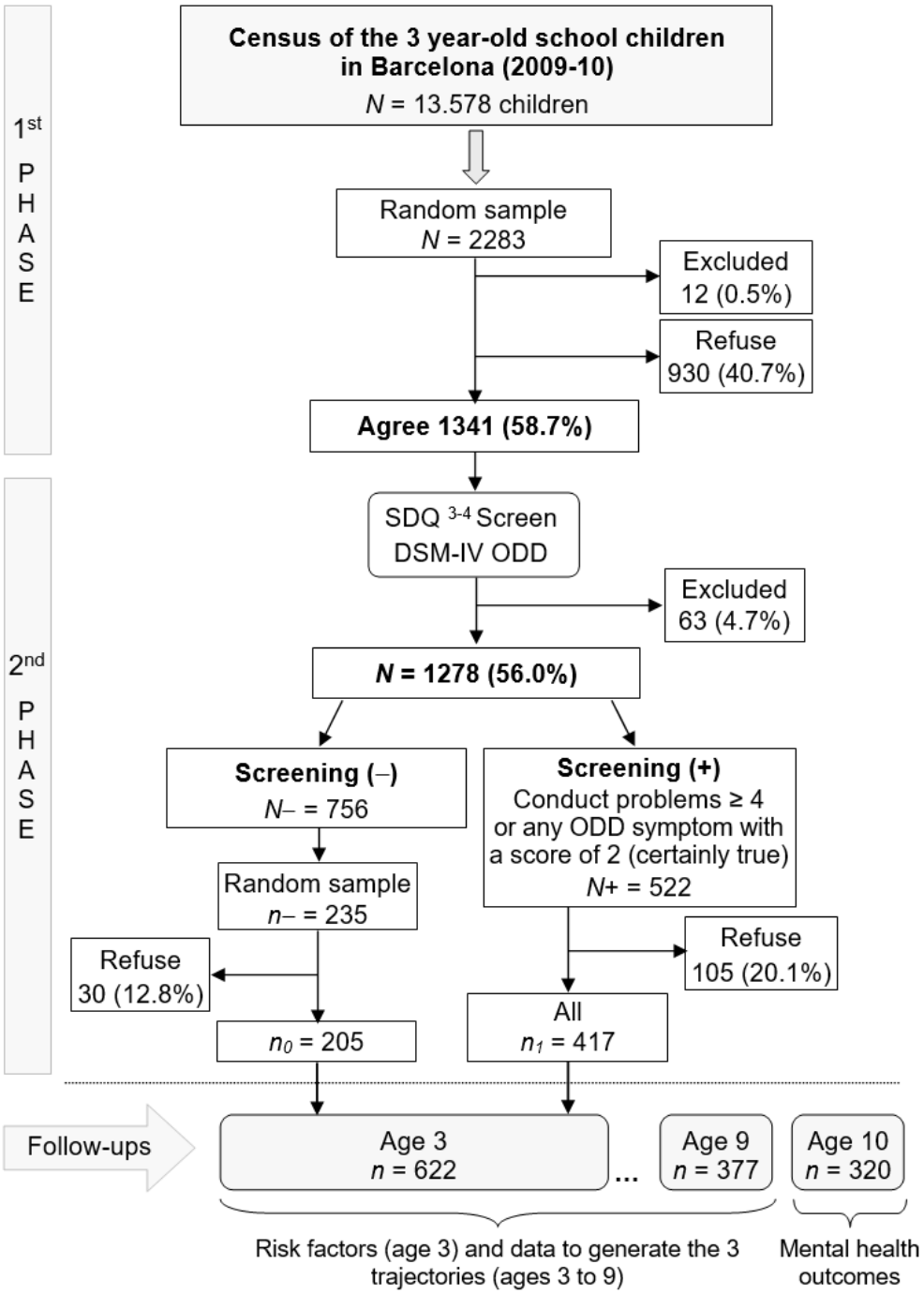
	Trajectory 1 CU-/SLE- *n* = 196	Trajectory 2 CU+/SLE- *n* =110	Trajectory 3 CU+/SLE+ *n* = 14		Trajectory 2 *vs.* 1	Trajectory 3 *vs.* 1	Trajectory 3 *vs.* 2
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	*F (p)*	*d (F; p)*	*d (F; p)*	*d (F; p)*
SDQ-Parents (at the age of 10) [1]							
Emotional	0.95 (1.52)	1.11 (1.45)	2.00 (2.19)	7.55 (<.001)	0.11 (2.0; .401)	0.56 (2.7; .274)	0.48 (1.3; .577)
Conduct	0.77 (1.12)	1.32 (1.56)	1.63 (1.59)	7.78 (<.001)	0.41 (5.2; .069)	0.63 (2.7; .275)	0.20 (0.2; .951)
Hyperactivity	2.24 (2.30)	3.20 (2.66)	4.11 (2.69)	22.52 (<.001)	0.39 (4.0; .131)	0.75 (2.9; .250)	0.34 (0.4; .879)
Peer	0.54 (1.08)	0.72 (1.45)	2.00 (1.79)	7.39 (<.001)	0.14 (0.3; .917)	**0.99 (7.3; .022)**	0.79 (5.5; .058)
Total	4.49 (4.35)	6.35 (5.45)	9.74 (6.73)	23.65 (<.001)	0.38 (4.2; .116)	**0.93 (6.2; .039)**	0.55 (2.0; .397)
SDQ-Teachers (at the age of 10) [1]							
Emotional	1.16 (1.57)	1.87 (2.31)	1.87 (2.03)	3.66 (.013)	**0.36 (6.3; .036)**	0.39 (1.6; .495)	0.00 (0.0; .999)
Conduct	0.62 (1.15)	2.05 (1.95)	2.05 (1.87)	22.14 (< .001)	**0.89 (22.5; < .001)**	0.92 (4.2; .122)	0.00 (0.0; 1.000)
Hyperactivity	2.05 (2.30)	4.16 (3.10)	4.66 (3.02)	28.26 (< .001)	**0.77 (15.0; < .001)**	0.97 (5.3; .064)	0.16 (0.4; .888)
Peer	0.90 (1.42)	1.64 (1.84)	1.48 (1.49)	6.99 (< .0001)	**0.45 (6.6; .031)**	0.40 (0.9; .718)	0.10 (0.2; .973)
Total	4.73 (4.37)	9.72 (7.11)	10.06 (6.21)	26.98 (< .001)	**0.85 (18.5; < .001)**	0.99 (5.6; .055)	0.05 (0.0; .999)

Trajectory 1: Children showing low CU traits and experiencing low stressful life events; Trajectory 2: Children showing increasing high CU traits and experiencing low stressful life events; Trajectory 3: Children showing high CU traits and experiencing high stressful life events; Trajectories comparison *p*-values are corrected for multiple comparisons using Sidak's approach. In bold significant comparison; *d*: Cohen's *d* effect size; [1]: Adjusted by the same measure at baseline; SDQ: Strengths and Difficulties Questionnaire.

FIGURE LEGENDS

Figure 1

Two-Phase Sampling Design and Study Follow-ups



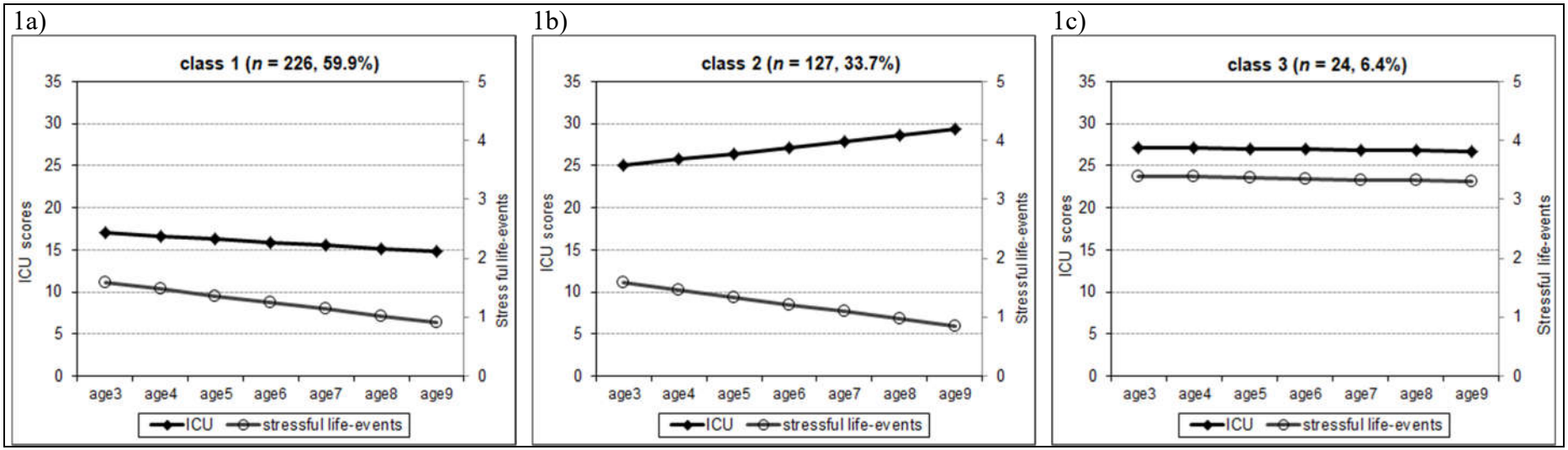


*Figure 2. Trajectories of callous-unemotional scores and number of stressful life events by classes (N weighted) combining both measures. [*From Ezpeleta, L., Penelo, E., de la Osa, N., Navarro, J. B., Fañanás, L., & Fatjó-Vilas, M. (2019). Association of OXTR rs53576 with developmental trajectories of callous-unemotional traits and life events from 3 to 9 year-old community children. *Journal of Abnormal Child Psychology*, 47, 1651-1662. https://doi.org/10.1007/s10802-019-00548-z. Printed with permission*]*

Study 3

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Age and Sex-specific Cut-off Scores for the Teacher-report Inventory of Callous Unemotional Traits on Children

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The project was approved by the Ethics Committee on Animal and Human Experimentation of the Universitat Autònoma de Barcelona. Families gave written consent for the assessment.

This study follows the Journal Article Reporting Standards for quantitative and longitudinal studies and the eight guidelines of the Transparency and Openness Promotion. Therefore, we inform that the data, materials, and analysis syntax of this study cannot be made publicly available due to ethical restrictions protecting the confidentiality of the families involved. Also, the study and the analysis plan were not preregistered.

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Abstract

This longitudinal study aims to provide meaningful cut-off scores for total score of the teacher-rated Inventory of Callous Unemotional Traits (ICU) from the preschool age until early adolescence, separately by age and sex. The ICU cut-off scores were determined by using low/high trajectories of oppositional defiant problems and conduct problems in a Spanish community sample of 620 children that were followed up between the ages of 3 and 13. Receiver operating characteristic (ROC) curves with the two trajectories as criteria and ICU total score at each age as a predictor were estimated by sex separately, and the area under the ROC curve (AUC) was obtained. Average ICU cut-off scores of 26 for boys and 22 for girls were found to be of moderate utility for the prediction of high trajectories of each of oppositional defiant problems and conduct problems. They identified cases with an average sensitivity of 66% and specificity of 70% for boys; and an average sensitivity of 69% and specificity of 72% for girls. The obtained cut-off scores might help clinical practitioners in their decision-making process when identifying low and high-risk groups of children.

Keywords: callous-unemotional traits, community samples, cut-off scores, early childhood, longitudinal.

Public Significance Statements

This study provides cut-off scores for the teacher-rated Inventory of Callous-Unemotional Traits in a community sample spanning early childhood until early adolescence, separately by age and sex. Cut-off scores of 26 for boys and 22 for girls are of moderate utility for the prediction of high trajectories of oppositional defiant problems, and conduct problems. These cut-off scores might help clinical practitioners when identifying low and high-risk groups of children.

Age and sex-specific Cut-off Scores for the Teacher-report Inventory of Callous Unemotional Traits on Children

Callous-unemotional traits (CU traits) (e.g., lack of guilt and empathy, shallow emotion display and irresponsibility) in children and adolescents are considered a risk factor for adult psychopathy (Frick et al., 2014). Even from the preschool age, CU traits can be identified and used in clinical settings to describe a subgroup of preschoolers who show psychosocial impairment, including conduct problems, difficulties in emotional recognition, and aggressive behavior (Frick & Myers, 2018; Kimonis et al., 2016). Among older children and adolescents, high CU traits are related to externalizing behavior and can predict greater antisocial behavior, criminality, violence, and impulsive behavior in adulthood (Frick et al., 2014).

To identify this subset of children and adolescents with CU traits, the Inventory of Callous-Unemotional Traits (ICU) (Frick, 2004) is among the most used instruments. The ICU was designed to improve certain limitations of the Antisocial Process Screening Device (APSD) (Frick & Hare, 2002) by providing a wider range of items to capture CU traits. Psychometric research on the ICU has widely focused on the self-reported version and has presented evidence for a 3-factor structure so that the 24 items of the ICU can be grouped into three subscales (Uncaring, Callousness, and Unemotional) (Essau et al., 2006). However, using the self-report ICU total score instead of the three subscale scores is more reliable to detect CU traits and shows better predictive and concurrent validity (Kimonis et al., 2008; Ray et al., 2016). A meta-analysis has shown high internal consistency and convergent validity, as well as validity evidence based on relations to external variables of the ICU total score across different samples (Cardinale & Marsh, 2020). This study also reveals that the total ICU scores of parent- or teacher-reports are able to predict externalizing behavior, low empathy, aggression, delinquency, hyperactivity, and higher psychopathic traits.

Although the ICU is widely used to assess CU traits, researchers have only recently begun to explore ICU cut-off scores. One explanation for this lack of thresholds might be that

the ICU was not conceptualized as a categorical diagnostic tool (Kimonis & Goulter, 2017). It was rather designed to establish a dimensional description of CU traits (Herpers et al., 2017). By establishing an empirical cut-off score, the ICU could be used as a screening instrument for identifying children and adolescents who show high CU traits and, therefore, might be at higher risk of antisocial behavior (Pihet et al., 2015).

With the introduction of the "Limited Prosocial Emotions" specifier in the diagnosis of conduct disorder in the Diagnostic and Statistical Manual of Mental Disorders (5th Edition; DSM-5) (American Psychiatric Association, 2013), there is an unmet need for using a categorical perspective of CU traits and its corresponding clinical ICU cut-off scores. Different approaches to define these cut-off scores have been used. Providing normative data for the different informant versions of the ICU is one of them. There are European self-report ICU norms for adolescents aged 11 to 17 (Kemp et al., 2019) and for the parent-, teacher-, and self-report versions for children and adolescents between the ages of 6 to 18 (Ueno et al., 2021). There are also parent-report ICU norms in the United States for children aged 5 to 12 (Bansal et al., 2020).

Such normative data help to define distribution-based cut-off scores that can be used to distinguish children and adolescents with low and high CU traits. To establish them, percentiles equal to or above 80 or 90 have been used in different datasets. For instance, in Kemp et al.'s (2019) European sample of self-report versions of the ICU, the 95th percentile is used as a cut-off, obtaining direct scores between 37 and 41 for boys and 32 and 35 for girls. Kumsta et al. (2012) used the 80th percentile of the parent - and self-reported ICU scores (direct scores of 46 and 30, respectively) in an adoption study on adolescents to identify high CU trait groups. This 80th percentile was also used among a clinical sample of male adolescents using the teacher-report version (direct scores equal to or above 40) (Levy et al., 2015). Among community adolescents aged 11 to 13, the 94th percentile (direct scores above 39) for

the self-report ICU has been applied as a cut-off to identify high CU traits (Viding et al., 2009).

These studies have mostly explored the parent and self-reported versions of the ICU, with resulting cut-off scores for the ICU total score that vary from 36 to 46 for the parent version and from 30 to 39 for the self-report version. It is of concern that these studies apply the 80^{th} or 90^{th} percentile arbitrarily on the three informant versions of the ICU, without taking into consideration the informant of the ICU, type of sample (community, clinical, at-risk samples), the sex of the children or their age. Likewise, the resulting low/high CU trait groups could be very heterogeneous and include a large number of false positives or false negatives, depending on the criterion variables that might has been used (Kimonis et al., 2014; Szabó et al., 2017).

Therefore, in recent years, there has been growing interest in determining ICU cut-off scores following associations with psychological and behavioral outcomes (Kemp et al., 2021). From this perspective, ICU cut-off scores are established by using an external criterion measure which allows identifying not only high CU trait groups but also concurrent psychosocial difficulties such as aggression, violent behavior, criminal activity, conduct problems, or bullying (Feilhauer et al., 2012; Kemp et al., 2021; Kimonis et al., 2014). For example, Kimonis et al. (2014) identified that direct ICU scores of 24 and 27 for mother-reports and father-reports, respectively, could detect co-occurring high CU traits and high conduct problems and predict bullying behavior among children aged 6 to 12 years.

Focusing on the ICU self-report, Feilhauer et al. (2012) found that a direct score of 26 could identify high CU traits and discriminate adolescent offenders from the control group. To date, only two studies have explored empirical teacher-reported ICU cut-off scores. Docherty et al. (2017) explored the three versions of the ICU (parent, teacher and self-report) and found that a cut-off direct score of 33 for the teacher-report version of the ICU could

predict aggression, violence, and detained status in a mixed sample of community and justice-involved adolescents. Similar cut-off scores were found by Kemp et al. (2019) for a community sample of youth, with sex-specific empirical thresholds for the teacher-report ICU where direct scores between 35-50 in adolescent boys and 35-38 in adolescent girls identified high CU traits, conduct problems, and peer-reported meanness.

These previous studies on ICU cut-off scores indicate that the age and sex of the children, type of informant, and even the settings of the study should be taken into consideration when establishing the cut-off scores (Carvalho et al., 2018; Kimonis, Fanti & Singh, 2014). Therefore, cut-off scores should be sex-specific to provide a valid diagnostic approach and guarantee a more efficient intervention strategy (Kemp et al., 2021) for two reasons; because the prevalence of CU traits is higher in boys than in girls (Ueno et al., 2021) and girls with elevated CU traits show more severe psychosocial difficulties than affected boys (Euler et al., 2015).

Moreover, age-specific cut-off scores are also needed because CU traits may undergo changes between childhood and adolescence (Essau et al., 2006). Even though CU traits remain rather stable over time on an individual level, there might be fluctuations of normative scores of CU traits at different ages on a cohort level. One stream of research has revealed that children show higher self-reported ICU scores than adolescents (Carvalho et al., 2018; Ueno et al., 2021), whereas, in another study, adolescents scored higher than their younger peers (Essau, 2006). As the effect of age needs to be further explored, establishing thresholds for different age groups might be crucial to reliably detect high CU traits over childhood and adolescence.

Gaining insight into the teacher-reported ICU cut-off scores for preschoolers (starting at age 3) from community samples is of special interest for different reasons. First, exploring the less-studied teacher-report ICU scores will offer further evidence on its validity, putting

greater emphasis on teachers as informants for CU traits. Preliminary studies have found that teachers seem to be more reliable as informants for CU traits than the child or adolescent itself (Docherty et al., 2017; Ueno et al., 2021). They have also observed that the teacher-report ICU scores show better classification accuracy than other informant-reported version scores (Kemp et al., 2021). Certain CU traits, for example, indifference about performance or difficulties in prosocial behavior, may be identified easier in school settings than in the context of the family, implying that teachers may be more aware of these aspects than parents or the youth themselves (Ueno et al., 2021). Second, ICU cut-off scores for preschool samples have not yet been established, but early childhood is recognized as being a crucial developmental period for socio-affective maturity (Carter et al., 2004). Early callous-unemotional behavior can predict severe psychosocial impairment, aggression, and rule-breaking behavior in late childhood (Waller et al., 2016). Therefore, providing validated and empirical cut-off scores to detect high CU traits from early years could improve the diagnostic process and enable clinical practitioners to identify a high-risk group of children with difficulties in prosocial emotions. Third, focusing on a community sample can help provide valid cut-off scores for the general population, making the questionnaire scores useful not only in a clinical context but also in educational settings.

Finally, this longitudinal study aims to provide meaningful cut-off scores for the teacher-rated ICU total score from the preschool age until early adolescence (ages 3-13), separately by age and sex. As the literature indicates that early childhood CU traits are associated with severe conduct problems (Longman et al., 2016) and oppositional defiant disorder (ODD) (Willoughby et al., 2011), ICU cut-off scores will be determined by using developmental trajectories empirically obtained for each of the previous aforementioned two measures as external categorial criteria.

Method

Participants

The sample comes from a longitudinal study on risk factors of psychopathology in children starting at age 3. The sampling design included two phases which are summarized in Figure 1. In the first phase, 1341 families of 2283 (58.7%) children, randomly selected from the census of early childhood schools in Barcelona (Spain), agreed to participate (33.6% high socioeconomic status (SES), 43.1% middle, and 23.3% low; 50.9% boys). In the second phase, a parent-rating of ODD symptoms (8 items) based on the conduct problems scale of the Strengths and Difficulties Questionnaire (SDQ) plus additional items from the Diagnostic and Statistical Manual of Mental Disorders (4th Edition; DSM-IV) based ODD was used to screen children with possible psychological problems. Two groups were finally considered: the screening positive group (+) included all children with scores above the 90th percentile on the screening measure or with a positive response for any of the eight DSM-IV ODD symptoms (n = 417; 49.0% boys) and the screening negative group (-) incorporated a random group of children who did not reach the positive criteria (n = 205; 51.2% boys). Both groups (n = 622) participated in the longitudinal study.

The sample used in the present study included 620 children (because there was no ICU data for two children) who were assessed yearly from the age of 3 to 13 years (11 assessment points). Table 1 shows a description of the available sample at the age of 3 and 13 years. SES was assessed according to the Hollingshead Four-Factor Index of Social Status (Hollingshead, 1975). This index includes weighted scaled scores of the occupation and educational attainment of the mother and father, which were categorized in 5 groups. The lowest sample size was found at age 13 when 318 children participated. There were no differences in sex (p = .630) due to attrition, although the available sample at age 13 had a higher SES (p < .001).

Measures

The Inventory of Callous-Unemotional Traits (ICU; Frick, 2004) includes 24 items that teachers responded to annually using a 4-point Likert-type scale from 0 (*not at all true)* to 3 (*definitely true*). The ICU total score is the sum of the ratings of all the items, reversed when necessary, and higher scores indicate greater CU traits. The total score demonstrated good internal consistency (Cronbach's α in the present sample ranged from .88 to .93 over time).

The *Strengths and Difficulties Questionnaire* (SDQ) (Goodman, 1997) is a brief screening questionnaire for the mental health of children based on five scales of five items each (0: *not true* to 2: *certainly true*). Teachers completed the questionnaire annually when children were between 3 and 13 years old. Different scale scores of the adapted Spanish version were used. For oppositional defiant problems (ODP), three items of the conduct problems scale of the SDQ were used (temper tantrums, disobedient and spiteful), together with five additional items that were included based on the DSM-IV ODD symptomatology criteria (annoys, blames, touchy, angry, argumentative). For conduct problems, the specific SDQ scale was used. Ordinal alpha values ranged from .91 to .96 for ODP scores and from .83 to .91 for conduct problem scores.

The *Diagnostic Interview for Children and Adolescents for Parents of Preschool and Young Children* (DICA-PPYC; Ezpeleta et al., 2011) is a semi-structured diagnostic interview for assessing a set of common psychological disorders according to the DSM-5 criteria. ODD and Conduct disorder (CD) diagnoses were used to describe the level of psychopathology in the sample at ages 3 and 13.

Procedure

This project was approved by the Ethics Committee on Animal and Human Experimentation of the author's institution and follows the ethical standards of the 1964 Declaration

of Helsinki and its later amendments. Families were recruited from schools and those who met screening criteria and gave their consent to participate in the study were assessed annually by teachers.

Data Analysis

The statistical analysis was conducted with MPlus 8.5 and Stata 16. As the sampling design was two-stage, all the analyses were weighted by the inverse probability of selection in the second phase of sampling. To estimate groups of individual trajectories for direct scores of ODP and SDQ conduct problems, Growth Mixture Models (GMM) with one process at each time were estimated. The Robust Maximum Likelihood (MLR) estimation method was used. The growth models included intercept (I), linear (S), and quadratic trend (Q) fitted over the 11 available annual assessments from ages 3 to 13. Time was rescaled to 0-10, so the first-year assessment (at age 3) represented the intercept (i.e., the basal direct score). Models with two growth patterns (trajectories) were obtained for each of the two processes. The accuracy of the classification in two trajectories was assessed through adequate average posterior probabilities, entropy values equal to or greater than .70, and a minimum of 20 participants in each trajectory.

Receiver operating characteristic (ROC) curves with the two trajectories as criteria and the ICU total score at each age as a predictor were estimated separately by sex, and the area under the ROC curve (AUC) was obtained. Following Hosmer et al., (2013) a value of AUC < .70 is considered non-predictive; AUC from .70 to .80 is considered acceptable; AUC from .80 to .90 is considered excellent and AUC > .90 is considered outstanding. The optimal ICU total score cut-off was selected as the score that maximizes sensitivity (Se) and specificity (Sp) by minimizing the square of the distance between the point (0, 1) on the upper left-hand corner of ROC space and any point on ROC curve, with equals costs for false positive and false negative misclassifications (Hajian-Tilaki, 2013).

Transparency and Openness

This study follows the Journal Article Reporting Standards for quantitative and longitudinal studies and the eight guidelines of the Transparency and Openness Promotion. Therefore, we inform that the data, materials, and analysis syntax of this study cannot be made publicly available due to ethical restrictions protecting the confidentiality of the families involved. Also, the study and the analysis plan were not preregistered.

Results

Descriptive Data

Table 2 shows the mean scores for the ICU total score at each follow-up along childhood from 3 to 13 years separately by sex. The mean ICU scores showed fluctuations over age and across sex. Focusing on age, the highest mean ICU scores were found at ages 10 to 13 among boys and at ages 3 and 4 among girls. Focusing on sex, boys' mean scores ranged between 21.5 (age 11) and 24.3 (age 13), whereas girls' mean scores were significantly lower than the boys' scores, ranging between 17.5 (age 11) and 19.3 (age 3).

When applying the 80th percentile to establish normative cut-off scores for identifying high CU traits (Kumsta et al., 2012), ICU cut-off scores showed age and sex-specific variations, with scores ranging between 29 and 36 for boys and between 23 and 27 for girls (Table 2).

Growth Mixture Models

For each analyzed score (ODP and SDQ-conduct), the 2-trajectory solution (low and high) from GMM was selected to act as criterion for estimating ROC curves with the ICU total score as predictor. Average posterior probabilities were in the range .90-.97, entropy values were in the range .80-.86, and the minimum *N* was 77 for the high ODP trajectory, all of them indicating an adequate goodness of fit. Figure 2 shows the 2-trajectory solutions for the

two measures. A reference line with the percentile 75 value has been added to each figure to help delimitate low versus high scores.

Average Sensitivity, Specificity and Predictive Value of ICU Scores for ODP and Conduct Problems

The ICU total score was able to distinguish boys on low *vs.* high ODP trajectories (with average values of AUC = 73.7%; Se = 67.8%; Sp = 69.3%) and conduct problem trajectories (with average values of AUC = 73.7%; Se = 67.7%; SP = 69.5%). The optimal average cutoff scores fell around a raw score of 26 for both measures (Tables 3-4).

For girls, the ICU total score was also able to discriminate low *vs.* high ODP trajectories (with average values of AUC = 74.4%; Se = 69.5%; Sp = 72.6%) and conduct problem trajectories (with average values of AUC = 74.2%; Se = 69.6%; Sp= 72.1%). The optimal average cutoff score fell around a raw score of 22 for both measures (Tables 3-4).

Age and Sex-Specific Sensitivity, Specificity and Predictive Value of ICU Scores for ODP and Conduct Problems

For ODP trajectories (Table 3), the ICU total score showed acceptable-excellent predictability, especially between the ages of 6 to 9 where the AUCs reached their highest value, ranging between 75.2% and 81.8% for boys; and between 80.7% and 84.7% for girls. The ICU raw total cut-off score at which there was optimal discrimination between belonging to a low or high ODP trajectory ranged between 24 and 29 for boys; and between 21 and 27 for girls (excluding the cut-off of 17 at age 13). The best discrimination was found at age 6, when a cut-off score of 28 could identify boys on a high ODP trajectory with an AUC = 81.8%, providing the best trade-off between Se (72.1%) and Sp (75.4%). For girls, the best discrimination was achieved at age 8, when a cut-off score of 23 could discriminate belonging to a high ODP trajectory with an AUC = 85.3%, with Se = 78.9% and Se = 77.0%.

For trajectories related to conduct problems (Table 4), the ICU total score showed acceptable predictability from the ages of 6 to 13 for boys (AUCs between 72.2% and 79.9%); and excellent predictability between the ages of 6 and 10 for girls (AUCs between 81.3% and 84.3%). The ICU total score cut-off at which there was optimal discrimination between belonging or not belonging to the high conduct problem trajectory ranged between 22 and 27 for boys (excluding the cut-off of 33 at age 13); and between 20 and 25 for girls (also excluding the cut-off of 18 at age 13). The best discrimination was found at age 8, when a cut-off score of 27 could identify the boys belonging to a high conduct problem trajectory with an AUC = 79.9%, providing the best trade-off between Se (75.9%) and Sp (75.6%). For girls, the best discrimination was identified at age 7, when a cut-off score of 24 could discriminate females on a high conduct problem trajectory with an AUC = 84.3%, with Se = 76.9% and Sp = 80.4%.

Overall, the empirical approach through ROC analysis revealed that average ICU cut-off scores of 26 for boys and 22 for girls can be of moderate utility for the prediction of high trajectories of each of ODP and conduct problems, identifying cases with an average Se of 66% and Sp of 70% for boys; and an average Se of 69% and Sp of 72% for girls.

Discussion

The aim of this study was to provide cut-off scores from preschool age to late childhood for the teacher-reported ICU version, separately by age and sex. Our results indicate that the discriminative capacity of the ICU total scores between low and high trajectories of each of ODP and conduct problem measures is more accurate in mid-childhood (6-9 years) than in the developmental extremes of early childhood (3-5 years) or early adolescence (10-13 years). Even if the ICU score has shown to be a valid tool to assess CU traits in preschoolers (Kimonis et al., 2016), this is the first study that has explored early childhood ICU cut-off scores. Further research in this early developmental stage is needed to understand how these

cut-off scores, the Se, and the Sp of the ICU may vary. More data are available among community and delinquency-involved adolescent samples, suggesting that the teacher-report ICU cut-off score is allocated around 33 (Docherty et al., 2017; Kemp et al., 2021), which is between 7 and 9 points higher than our obtained scores. Also, normative data shows that for the teacher-report ICU version, adolescents between 11 and 14 years score higher on the ICU than children aged 6 to 10 years (Ueno et al., 2021). These results may suggest that when children reach puberty, certain adolescent behaviors (such as rule-breaking, shallow emotional display, etc.) may be compatible with CU traits. Thus, more CU behaviors are observed during adolescence, resulting in higher ICU cut-off scores for youth than for children. Consequently, AUC, Se, and Sp of ICU scores may change in adolescent samples, as our results indicate.

The type of informant of the ICU might also be a factor to consider in understanding the classification accuracy across ages. Our study focused on the teacher-reported ICU version, which is one of the less-studied ICU informant versions. Even though the role of teacher-student relationships in children with CU traits is only scarcely studied, teachers experience children in a school context where punishment insensitivity, impaired reward processing, low intrinsic motivation, and low socioemotional abilities can specifically be observed (Allen et al., 2018). Therefore, teachers, in comparison to parents, might have a more objective view when rating the ICU items as they are in touch with a great variety of children and adolescents. For example, in Ueno et al.'s (2021) study on ICU norms, teachers reported higher mean ICU scores across age and sex than parents. The same tendency was observed in ICU cut-off scores (Kemp et al., 2021), where the empirical teacher-reported ICU cut-off score (35) was 12 points higher than the parent-reported score (23). This study also found higher classification accuracy in the teacher-report version of the ICU score for conduct problems and peer-reported meanness in comparison to the parent- and self-report ICU versions. These findings,

together with our preliminary results, indicate that teachers are valid informants for CU traits in childhood and adolescence and that the teacher-report ICU version should be more widely used in clinical and research settings. This would help to gain further evidence on possible differences between parent and teacher-reported ICU versions and the different resulting ICU cut-off scores.

Our study also found sex-specific effects on ICU cut-off scores across age. The fact that lower cut-off scores were found among girls is in line with previous research (Kemp et al., 2021; Ueno et al., 2021). As girls generally score lower on CU traits than boys (Pihet et al., 2015), the current stream of research on CU traits has vastly focused on boys. Knowledge of how girls express CU traits is still limited, but preliminary findings show that girls with high CU traits engage in more internalizing behavior (depression and anxiety) (Euler et al., 2015) and show more chronic and severe ODD/conduct disorder trajectories (Kroneman et al., 2011) than boys. Interestingly, girls with CU traits might not robustly show a lack of guilt or empathy (Pardini et al., 2012), which might be explained by the biological and environmental differences between sexes, such as sex-specific brain structure differences in areas involving empathy or gender differences in the socialization process, where girls are more encouraged than boys to be empathic, caring, and sensitive towards others (Hipwell et al., 2007). In line with this hypothesis, Essau et al. (2006) found that the "uncaring" scale score of the ICU was not a predictor of problematic behavior in girls, but it was for boys. Applied to our results, it is of no surprise that the ICU scores showed lower classification accuracy in discriminating each of ODP and conduct problem trajectories when comparing girls to boys. Thus, it would be of interest to analyze ICU cut-off scores as predictors for internalizing behaviors, separately by sex, to better understand sex differences in CU traits together with other socioemotional difficulties such as anxiety or depression.

Finally, in our study, the proposed data-driven ICU cut-off scores to define high-risk groups of boys and girls are less stringent than when applying normative cut-off scores as, for example, the 80th percentile. Using such normative cut-off scores might result in identifying a heterogeneous group of children that share similar high CU traits but might differ in other characteristics. Therefore, this approach might be more useful in clinical samples to identify specifically high CU traits among children who might already have been identified as belonging to a high-risk group. Nevertheless, according to our results, when such percentiles are used as an ICU cut-off score, we are possibly excluding a group of children that are also susceptible to high risk, even though their ICU scores do not reach a "clinical significance." For this reason, using the data-driven approach is especially important for early detection and prevention purposes when working with community samples. Because our data-driven approach shows lower ICU cut-off scores than using, for example, the 80th percentile cut-off, more children with high-risk trajectories could be identified. This larger group of children might show greater heterogeneity with probably more comorbidities and other demographic risk factors. That would be in line with previous research suggesting that the developmental pathways to CU traits are diverse (Frick et al., 2013). Therefore, the empirical ICU cut-off scores might be less stringent than the normative thresholds and might also help to detect a group of children who are at high risk and might need preventive and therapeutic intervention programs.

Constraints on Generality

The participants of our study were children from a community sample in Spain. We expect our results to generalize to other community sample children with similar socioeconomic and cultural backgrounds. A direct replication would follow a community sample of children from early childhood to early adolescence using the adapted versions of the used

instruments. We have no reason to believe that the results depend on other characteristics of the participants, materials, or contexts.

This study has notable strengths, such as a large sample size, community environment, empirical trajectories used as outcomes, and longitudinal approach of 11 years during which multiple teachers reported the children's development that was used to obtain ICU cut-off scores. Also, the study focused on the less-studied teacher-report ICU version, and both sexes were analyzed separately to provide more accurate ICU cut-off scores. The ROC analysis that was applied to establish empirical ICU cut-off scores is also a strength as only a few studies have used this approach (Docherty et al., 2017; Kemp et al., 2021; Kimonis et al., 2014), making it a promising field of research. In addition, normative data based on the 80th percentile was also presented. Finally, the external criterion was based not only on an individual score on certain tests but also on the whole childhood trajectory of two different, but somewhat overlapping, constructs of ODP and conduct problems.

Despite these strengths, the results of this study need to be considered in light of some limitations. First, the study only focused on the teacher-report ICU version. As multi-informant approaches provide a more consistent CU trait assessment and are considered best-practice (Kimonis & Goulter, 2017), including other-report versions in future studies would be of interest. Second, the results might be valid for Spanish children only, and replication studies in other countries are needed to confirm the provided ICU cut-off scores. Finally, the predictive validity was analyzed through ODP and conduct problem trajectories. Both trajectories share three items of the SDQ, therefore, this overlap might explain the similar results on AUCs, sensitivity, and specificity. Including criterion variables such as clinical diagnoses of conduct disorder, ODD, or hyperactivity could therefore provide specific clinical ICU cut-off scores. As our study focused on a community sample, the prevalence of such diagnoses was

too low to include them as criterion variables. Further studies on more clinical samples might explore this empirical approach in establishing cut-off scores.

Clinical Implications

Our research could be a useful aid in CU trait assessments as researchers and clinical practitioners could apply the provided ICU cut-off scores to identify a subgroup of children with high CU traits and high risk of sustained ODP and conduct problem trajectories, especially if the provided cut-off scores have been tested and replicated in other studies. Our data-driven approach to establish ICU cut-off scores has resulted in less stringent thresholds that might identify a larger group of high-risk children than applying an arbitrary percentile. This is important because clinicians should take into consideration that children who do not necessarily show clinically high CU traits (e.g., over the 80th percentile) could benefit from early detection and prevention of other associated difficulties such as ODP or conduct problems. In this sense, working with such a categorial CU trait approach together with the dimensional model would be useful to personalize the treatment approach through a deeper understanding of specific problematic domains. Moreover, our results suggest that early childhood CU trait scores can already detect a subgroup of children in high-risk trajectories with moderate accuracy and average Se and Sp between 66% and 72%. These values of Se and Sp are important to prevent false negatives or false positives during the diagnostic process. In this sense, the developmental window of 6 to 10 years seems to be the most accurate for correctly identifying CU traits and ODP or conduct problems, implying clinical practitioners should pay more explicit attention when children show CU traits in this phase. Finally, CU trait assessments should be based on multi-informant reports, counting on teachers as valid informants for identifying CU trait behaviors.

In conclusion, this is the first study that provides empirical cut-off scores for the teacher-report ICU in a longitudinal sample of 3- to 13-year-old children. The provided ICU

scores demonstrated the capacity to identify children with high CU traits and ODP or conduct problem trajectories with average cut-off scores of 26 for boys and 22 for girls. These thresholds might help clinical practitioners in their decision-making process when identifying low and high-risk groups of children. However, it should be noted that a final diagnosis should never rely on a single test score but rather explore different sources of information. Future research should continue to evaluate empirical ICU cut-off scores according to the different informant-versions, age, sex, context, and other external criteria.

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Table 1

Descriptives of the Sample at Ages 3 and 13 Years

	Age 3	Age 13
N	600	318
Sex (% boys)	50.4	49.8
SES (%)		
High	35.4	33.9
Middel-high/Middel	46.2	57.6
Middel-low/Low	18.4	8.5
Ethnia (%)		
Caucasian	91.1	95.2
Latino	4.7	1.5
Other	4.2	3.3
DSM-5 ODD diagnose (%)		
Boys	4.9	7.9
Girls	9.0	11.6
DSM-5 CP diagnose (%)		
Boys	1.2	0.0
Girls	0.6	0.0
ODP score – *M* (*SD*)		
Boys	3.3 (3.1)	3.1 (3.6)
Girls	3.2 (3.2)	1.9 (2.8)
SDQ-Conduct score – *M* (*SD*)		
Boys	2.0 (2.1)	1.5 (2.0)
Girls	1.7 (2.0)	0.9 (1.5)

Note. SES: Socioeconomic status. DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. ODD: Oppositional defiant disorder. CP: Conduct problems disorder. ODP: Oppositional defiant problems. SDQ: Strengths and Difficulties Questionnaire-Conduct problems.

Table 2

Descriptives of ICU Total Score at Each Follow-up Separately by Sex

	Boys			Girls			Mean comparison
Age	*N*	*M (SD)*	*P80*	*N*	*M (SD)*	*P80*	*p*
3	313	23.0 (10.3)	32	307	19.3 (9.4)	26	< . 001
4	308	22.6 (10.7)	29	301	19.0 (9.4)	27	< . 001
5	281	21.8 (9.4)	30	283	17.7 (9.3)	25	< . 001
6	234	23.2 (10.3)	31	230	17.7 (8.9)	24	< . 001
7	232	22.4 (9.7)	31	237	17.5 (9.3)	26	< . 001
8	218	22.7 (11.9)	32	211	17.6 (10.3)	25	< . 001
9	226	22.0 (10.0)	30	219	18.5 (10.7)	27	< . 001
10	216	23.6 (11.4)	33	213	17.2 (8.4)	23	< . 001
11	224	21.5 (11.2)	30	232	17.5 (9.8)	25	< . 001
12	177	22.9 (10.9)	31	188	18.6 (9.9)	27	< . 001
13	158	24.3 (13.1)	36	160	18.3 (10.1)	27	< . 001

Note. ICU: Inventory of Callous Unemotional Traits. *P80*: Cut-off scores for the 80th Percentile.

Table 3

AUC, Cut-off, Sensitivity and Specificity of ICU Total Score to Discriminate Trajectories of ODP Separately by Sex

	Boys					Girls				
Age	*N* High trajectory	*AUC (%)*	Cut-off	*Se (%)*	*Sp (%)*	*N* High trajectory	*AUC (%)*	*Cut-off*	*Se (%)*	*Sp (%)*
3	50	67.7 (62.2;72.9)	27	60.0	67.2	27	65.0 (59.4;70.3)	21	60.0	61.6
4	50	74.8 (69.5;79.5)	27	63.6	76.4	27	73.7 (68.3;78.5)	21	76.7	64.2
5	46	69.6 (63.9;74.9)	24	71.2	64.9	24	75.7 (70.3;80.6)	25	61.5	82.6
6	38	81.8 (76.2;86.5)	28	72.1	75.4	18	81.5 (75.9;86.3)	23	75.0	76.7
7	37	75.2 (69.1;80.7)	24	76.2	61.5	18	80.7 (75.1;85.5)	24	75.0	78.6
8	39	79.7 (73.7;84.9)	29	73.8	77.3	18	85.3 (79.9;89.8)	23	78.9	77.0
9	37	78.8 (72.9;84.0)	26	72.5	69.8	16	84.7 (79.3;89.2)	27	75.0	83.1
10	35	73.8 (67.3;79.6)	27	72.2	66.3	17	79.8 (73.9;84.9)	22	77.8	76.5
11	33	72.6 (66.2;78.4)	27	65.7	73.7	23	73.9 (67.8;79.4)	22	66.7	79.1
12	31	72.1 (64.8;78.7)	25	64.5	64.1	19	58.5 (51.2;65.5)	22	47.4	69.9
13	27	64.6 (56.5;72.1)	29	53.8	66.2	16	59.1 (51.1;66.8)	17	70.6	49.7
M		73.7	26.6	67.8	69.3		74.4	22.5	69.5	72.6

Note. AUC: Area under the ROC curve. ICU: Inventory of Callous Unemotional Traits. ODP: Oppositional Defiant Problems. *Se*: Sensitivity. *Sp*: Specificity.

Table 4

AUC, Cut-off, Sensitivity and Specificity of ICU Total Score to Discriminate Trajectories of SDQ-Conduct Separately by Sex

	Boys					Girls				
Age	*N* High trajectory	*AUC (%)*	Cut-off	*Se (%)*	*Sp (%)*	*N* High trajectory	*AUC (%)*	Cut-off	*Se (%)*	*Sp (%)*
3	67	68.7 (63.2;73.8)	27	60.3	69.3	31	59.7 (54.0;65.2)	21	55.3	61.6
4	66	74.8 (69.5;79.6)	26	63.4	74.8	31	68.8 (63.3;74.0)	21	65.8	63.9
5	61	67.8 (62.0;73.2)	24	65.7	65.7	29	68.1 (62.4;73.5)	25	52.9	82.8
6	48	77.7 (71.8;82.9)	27	66.1	74.2	21	83.8 (78.4;88.3)	23	80.0	78.5
7	53	72.2 (65.9;77.9)	24	68.4	62.2	22	84.3 (79.1;88.7)	24	76.9	80.4
8	49	79.9 (73.9;85.0)	27	75.9	75.6	20	83.6 (77.9;88.3)	22	78.3	76.0
9	51	74.0 (67.7;79.6)	25	65.5	67.1	19	84.0 (78.5;88.5)	23	81.8	73.1
10	46	75.3 (68.9;81.0)	27	70.8	68.7	20	81.3 (75.5;86.2)	22	78.3	77.9
11	45	73.5 (67.2;79.2)	25	69.4	69.8	25	78.8 (73.0;83.8)	20	75.0	74.4
12	37	75.2 (68.0;81.4)	22	84.6	57.5	21	64.6 (57.4;71.3)	22	54.5	71.2
13	30	72.4 (64.7;79.2)	33	54.8	80.0	16	59.0 (51.0;66.7)	18	66.7	53.5
M		73.7	26.1	67.7	69.5		74.2	21.9	69.6	72.1

Note. *AUC*: Area under the ROC curve. ICU: Inventory of Callous Unemotional Traits. SDQ: Strengths and Difficulties Questionnaire. *Se*: Sensitivity. *Sp*: Specificity.

Figure 1

Study Sampling Design and Follow-ups

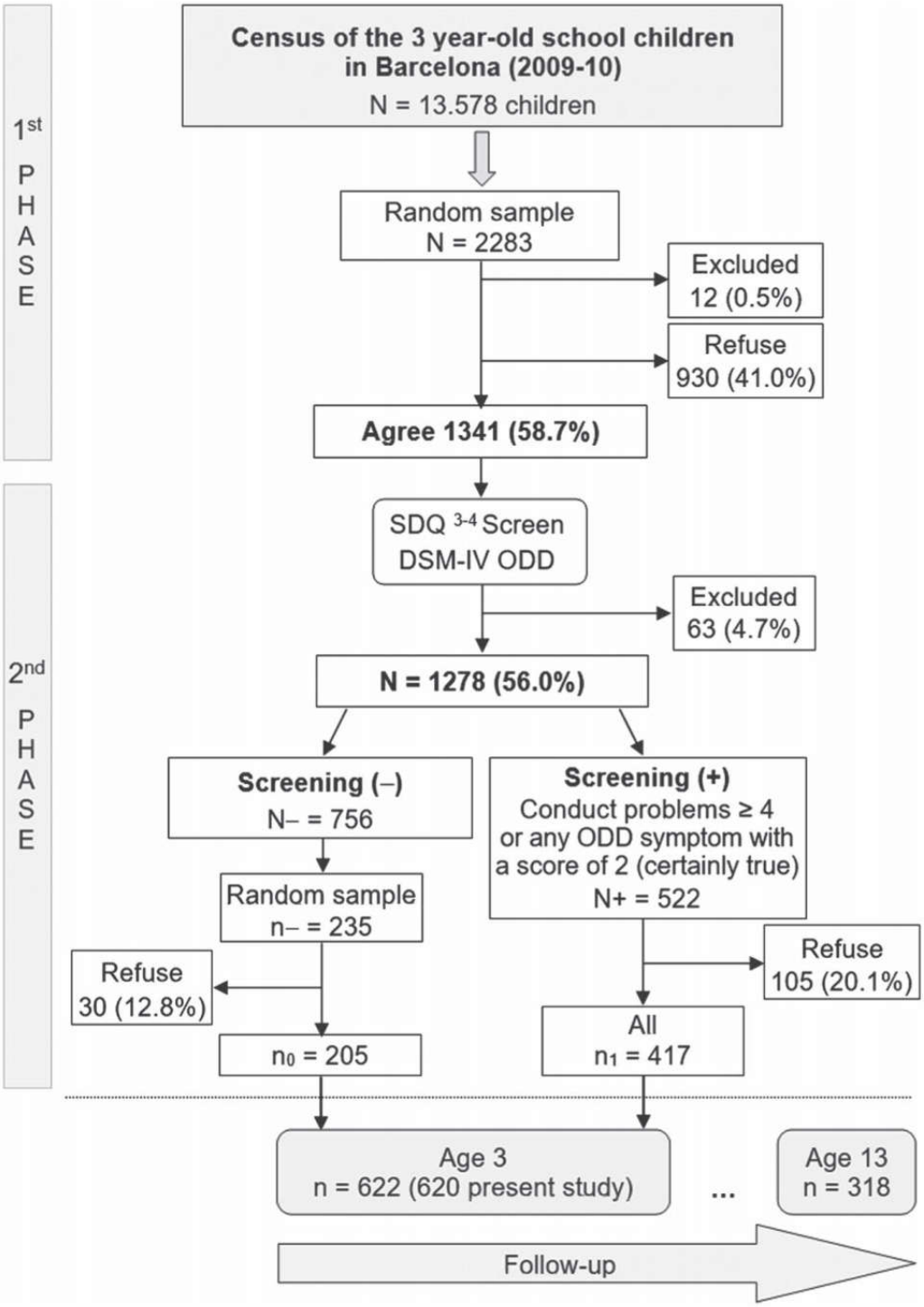
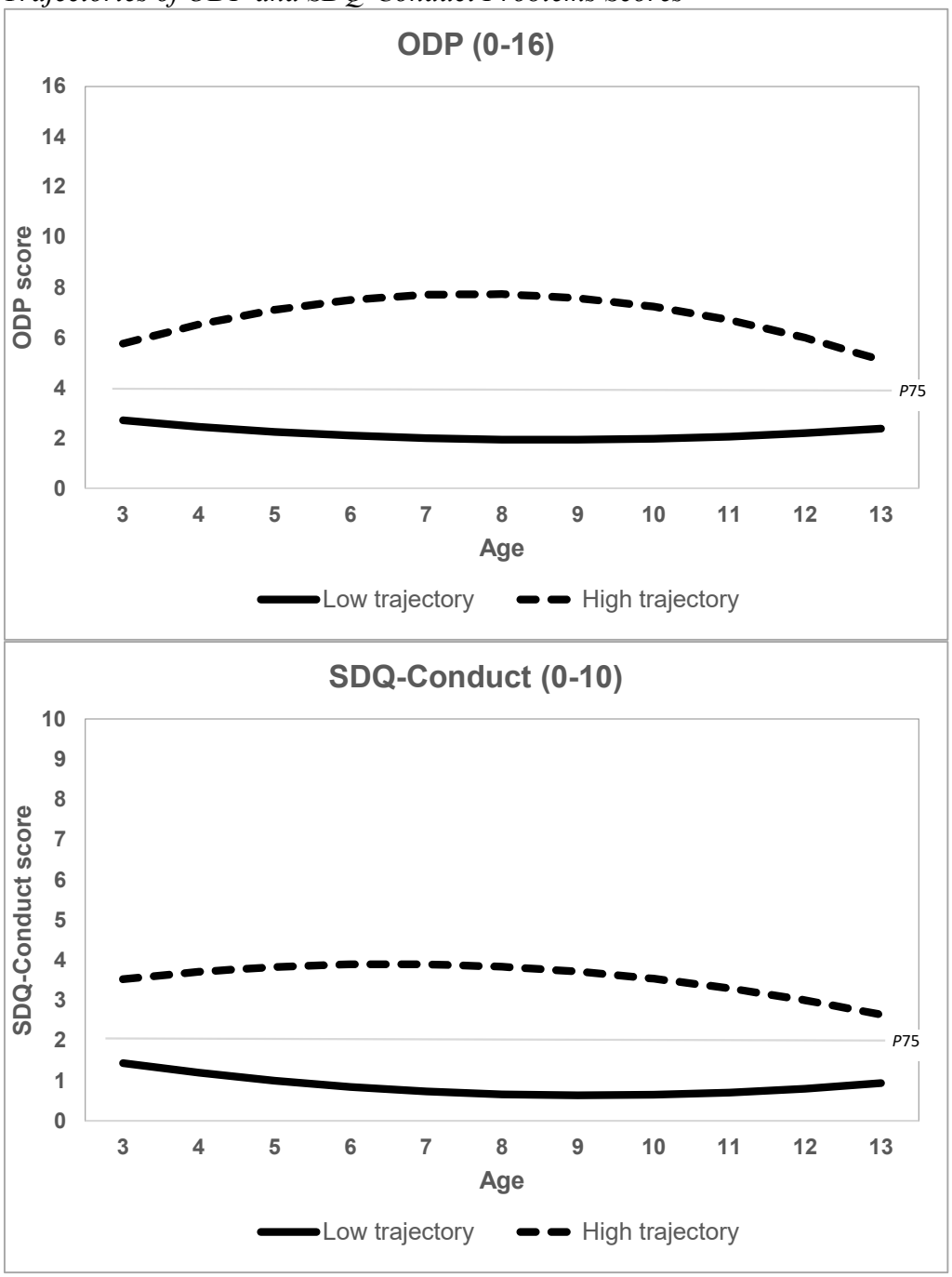


Figure 2

Trajectories of ODP and SDQ-Conduct Problems Scores



Note. Each panel shows the 2 trajectories separately for each measure.
ODP: Oppositional defiant problems. SDQ: Strengths and Difficulties Questionnaire. *P*75: 75th Percentile

Chapter Four: Discussion

Integration of Findings

This bundled thesis consists of two studies that explore different developmental and moderating factors in the development of CU traits and one that proposes empirical cut-off scores for the ICU.

The aim of study 1 was to analyze a G x E interaction on MAOAVNTR polymorphisms and parenting practices in 3- and 5-year-old boys and girls. The results suggest age- and sex-specific differences in this G x E interaction, as a significant interaction was only found for girls at age 5 but not for boys at age 3 or 5. Moreover, the genotype confers overall sensitivity or vulnerability towards positive and punitive parenting practices for girls was MAOA-LL.

The aim of study 2 was to describe contextual and personal risk factors in early childhood and later mental health outcomes of trajectories that combine CU traits and stressful life experiences. It seems that, combined with stressful life events, CU traits co-occur in low-income households in which the caregivers experience economic and mental health problems, which act as early contextual risk factors. In addition, mental health outcomes for this trajectory seem to be associated with peer and general mental health problems. Interestingly, the trajectory of high CU traits but low stressful life events shows similar mental health outcomes as the high CU traits and high stressful life events trajectory.

The aim of study 3 was to propose empirically derived cut-off scores for the teacher-rated ICU along childhood for boys and girls. The results indicate that to identify children with CU traits based on teacher information correctly, cut-off scores of 26 for boys and 22 for girls could be used.

These three studies, when considered together, suggest some crucial findings about the etiology of CU traits from early childhood on. First, differences in CU traits according to age and sex were observed. Study 1 highlighted the impact of early parenting practices on CU traits only at age 5 (and not age 3) and only for girls carrying the MAOA-L allele; study 2 found that boys were significantly overrepresented in the CU trait groups, and study 3 showed how the ICU cut-off scores and 80th percentiles differed according to age and sex, with more consistent findings around age 6 to 9, and higher scores for boys than for girls.

Previous research has observed age-specific genetic effects on CU traits (Takahashi et al., 2020), suggesting that children with early-onset CU traits may show temperamental characteristics that are under genetic influence; while, at the same time, other genetic factors become more salient in the expression of different abilities that mature along childhood and with interaction with the environment. The results of study 1 would support this hypothesis, as early parenting (both positive and negative) at age 3 was related to CU traits two years later. Therefore, sensitivity towards parenting might not only be moderated by sex but also by age. It seems that both genes and environment interact at different periods in the development of CU traits, and further research on candidate genes is needed to understand better this complex interplay of genetic predisposition or plasticity and other factors of the environment.

In addition, we speculate that early childhood and adolescence, the two extremes of childhood development, are moments when behaviors correlated to CU traits such as tantrums, rule-breaking, and shallow empathy could be part of normal development. In early childhood, children are still learning to manage their emotions and engage in empathic behavior, whereas, in adolescence, youth are differentiating themselves from their parents and can engage momentarily in more aggressive behavior, risk-taking, and

less empathic behavior. Therefore, middle childhood might emerge as a more stable developmental period to assess CU traits with more validity. Nevertheless, this does not contradict the need to detect CU traits as early as possible, as early-onset CU traits are associated with more severe psychosocial problems and, therefore, need to be urgently addressed in prevention and treatment programs (Viding & McCrory, 2012b).

The sex differences found in the three studies are consistent with recent research. For example, the G x E interaction of study 1 was only observed in girls, which would support the idea that CU traits seem to be more heritable in boys than in girls; and that girls seem to be more vulnerable to environmental influences (Fontaine et al., 2010; Weeland et al., 2015). Specifically, girls might be more sensitive towards parenting practices than boys, which would explain why parental warmth at age 4 predicted a decrease of CU traits almost 10 years later only in girls (Barker et al., 2011). Additionally, only certain girls would be more sensitive towards parenting practices, which suggests that sex differences in CU traits should be considered when personalizing treatment programs, understanding that positive parenting might not have the same impact on boys as on girls and that individual genetic predispositions towards parental sensitivity might explain treatment resistance (Pluess & Belsky, 2011). Thus, the ICU cut-off scores of study 3 showed that girls obtained lower scores than boys, which is well-documented in previous research (Docherty et al., 2017; Pechorro et al., 2019; Ueno et al., 2021). Study 2 also found that being a boy could be considered a risk factor for CU traits, which is consistent with the fact that CU traits are more prevalent in boys than in girls (Pihet et al., 2015). Given these differences, it is surprising that only a few CU trait studies have included females in their samples, leaving questions about how girls express their callousness relatively unanswered (Euler et al., 2015).

Second, CU traits are associated with environmental risk factors such as parenting practices (Study 1), economic status (Study 2), and maternal psychopathology (Study 2). These three factors are indirectly related, as maternal mental health and economic status can negatively affect parenting quality. In turn, negative or low positive parenting is a risk factor for developing CU traits (Waller et al., 2015).

Third, CU traits and stressful life events should be explored jointly, as they can describe a unique trajectory resembling the secondary variant of CU traits (Study 2). Previous research has defined the secondary variant of CU traits as the "distressed" group with histories of trauma, maltreatment, and anxiety. Thus, our findings that this group of children showed more parent-reported peer and general problems than the CU/SLE- group help to characterize primary and secondary variants of CU traits.

Fourth, empirical cut-off scores for the ICU can reliably predict trajectories of ODD and OPD (Study 3). This finding is essential, considering that children with CU traits seem more resistant to treatment than children without CU traits (Hawes et al., 2014). Therefore, treatment intervention with children that show ODD/CU or OPD/CU should focus on core features of CU traits, such as low empathy and emotional reactivity, to provide more effective and long-lasting treatment results (Kimonis et al., 2019).

All in all, the main findings of this thesis are in line with previous research on CU traits. However, the novel findings on G x E interaction and joint trajectories of CU traits and SLE, and also the proposed empirical ICU cut-off scores along childhood, can facilitate the understanding of the etiology of CU traits. In addition, they should help identify children with CU traits at higher risk and predict possible trajectories to personalize prevention, intervention, and treatment processes.

Clinical Implications

Our work has several implications for the diagnosis and treatment of CU traits. First, as the development of CU traits can start in early childhood and show a stable trajectory along childhood and adolescence, early detection of CU traits is needed to prevent children and families from more severe psychosocial difficulties and define early intervention programs (Pardini & Frick, 2013).

A thorough assessment of CU traits is often only found in research contexts, not clinical practice. Therefore, it would be important to understand CU traits -with or without comorbid CD – as a transdiagnostic risk factor that should be explored, especially when children show externalizing behavior (Viding & McCrory, 2012). Thus, the process of assessment should explore more distal risk factors such as parenting practices, parental mental health, SES, and stressful life experiences, as these factors can explain different pathways to CU traits, different levels of CU trait severity, and different forms of externalizing behavior along childhood (Squillaci & Benoit, 2021). While exploring such indicators of social adversity, clinical psychologists should consider that the environmental influence can be moderated by genetic predisposition so that not all children will be equally sensitive to their environment. In addition, integrating the notion of G x E interaction in the developmental model of CU traits might help better understand how CU traits develop and, thus, tailor more efficient prevention and treatment strategies.

At the same time, such environmental factors should also be considered when personalizing treatment programs. These programs often focus on parent-child interaction, which can indirectly influence parents' mental health or socioeconomic status. For example, offering specific psychoeducation on CU traits in parent-child interactions and psychotherapeutically approaching parents' mental health problems could be a novel approach in the treatment of CU traits, understanding that CU traits are not only a problem

of the child but of the whole family. Focusing on the role of the mother, primarily when she engages in antisocial behavior, could also be a promising intervention approach to reduce CU traits through more positive reinforcing parenting strategies (Waller et al., 2015).

In addition to the role of the parents, children who experience social disadvantages (low SES, parental mental health problems) are more prone to experience more stressful life events. Therefore, these children and their families would benefit from intervention programs that target CU traits and broader psychoeducational intervention on stress management and coping strategies, for example. However, it would be a novel approach to include such psychoeducational interventions, as most evidence-based intervention programs for preschoolers and children with CU traits, such as PCIT-CU (Kimonis et al., 2019) and PCIT-ED (Donohue et al., 2021), use positive and warm parenting strategy training. In addition, specific empathy pieces of training as core components do not specifically target other contextual difficulties that the child or the family might face (Bjørnebekk & Thøgersen, 2022). Therefore, our results would support the idea of personalizing the intervention programs specifically to the contextual needs of the child and their family, especially when they experience low SES and mental health difficulties.

In this thesis, we proposed valid categorical cut-off scores for the ICU. These thresholds could be used in clinical and research contexts when there is the need to establish if a child exhibits or does not exhibit CU traits. For example, the benefit of such a categorical approach might be necessary for the diagnosis of conduct disorder by helping to determine if the Limited Prosocial Emotions specifier should be applied or not (Kimonis, Fanti, et al., 2014). Furthermore, the proposed cut-off scores may help identify children at higher risk for developing conduct problems and ODD.

Strengths and Limitations

Strengths

This thesis has notable strengths. First, it includes large sample size and is based on a community sample of children. Second, the longitudinal approach of up to 11 follow-ups enabled us to establish empirical trajectories and explore their associated risk factors and outcomes from early childhood on. Third, this thesis focuses on the less-studied teacher-report ICU version, providing evidence that teachers are valid informants to assess CU traits in children. Fourth, results are presented separately by sex and age, as previous research has shown that these two factors impact the development of CU traits differently. Finally, novel approaches in the study of CU traits were applied, such as the G x E exploration in study 1 or the ROC analysis to establish the cut-off scores of study 3.

Limitations

A few limitations should be considered when interpreting the results of the current thesis. First, as this thesis was conducted in a community sample, the prevalence of mental health problems with clinical significance was low. Further studies, including clinical population, might be needed. Second, the study only focused on teachers as informants for CU traits, but it would be interesting to include other informants, such as parents and the children themselves. This multi-informant approach is considered best practice in clinical settings (Kimonis & Goulter, 2017). Third, the results (and specifically the provided ICU cut-off scores) might be valid for Spanish children only, and replication studies in other countries are needed to confirm the results found in our studies. Fourth, the statistical power might be affected by the small sample size of the studied subgroups of children.

Future Directions

Although this thesis tried to answer some questions regarding CU traits from preschool years, others remain unanswered and should be considered in further investigations.

The sex differences in this thesis highlight the importance of conducting studies on female samples, or at least on mixed samples, to understand better how CU traits are expressed differently in girls and boys. Thus, the age differences that we observed suggest the need to continue exploring CU traits with longitudinal studies that help to define trajectories, risk and protection factors, and outcomes along childhood. Especially studies that start in early childhood are needed to understand better how the early onset CU trait trajectory differs from the later onset CU trait trajectory. At the same time, such an early onset CU trait trajectory should be under more genetic influence, so G x E interaction studies with a longitudinal approach are needed to find support for this hypothesis. Future research could provide a better understanding of the longitudinal trajectories of CU trait development.

This thesis supports the idea that children with CU traits are a heterogenous group with different correlated child characteristics that can moderate or mediate risk trajectories. Further studies exploring such characteristics and CU traits would help design prevention programs and target individuals at higher risk (Masi et al., 2018).

Moreover, the studies on primary and secondary variants of CU traits have often conceptualized primary CU traits as CU traits without anxiety or without the experience of adversity and secondary variants as CU traits in combination with anxiety or adversity. However, studies investigating joint trajectories of CU traits, adversity, and anxiety are limited, so future research should explore these trajectories' risk factors and

outcomes, helping to strengthen the theory on primary and secondary variants in CU traits. Furthermore, studies need to analyze primary and secondary variants in CU traits from early childhood to answer the question of when secondary variants of CU traits can be observed and at which periods the genetic or environmental influence becomes more critical. At the same time, future studies on treatment response should explore genetic and environmental factors and primary and secondary variants of CU traits to understand differences and similarities in treatment adherence and impact.

Regarding the exploration of ICU cut-off scores, future research could use clinical diagnoses as criterion variables, such as conduct disorder, ODD, or hyperactivity. In addition, we have shown that the ICU cut-off scores vary according to age, and other authors suggest that the validity of measuring CU traits would be higher in later adolescence when CU traits become more stable (Pardini et al., 2012); future research should address at which time point ICU cut-off scores offer better validity.

Finally, our studies are based on a community sample of children, and more research on such non-clinical, non-delinquent samples is needed to understand the impact of CU traits on child development.

Conclusions

- CU traits are age- and sex-specific and can be considered a risk-marker from early childhood on.
- A MAOAxParenting interaction has been observed on CU traits among girls, not boys. This interaction was found at age 5 but not at age 3.
- The MAOA-LL genotype for girls is more sensitive to positive and punitive parenting and confers more vulnerability towards parental influences.

- High CU/SLE describes a trajectory characterized by early contextual adversity, socioeconomic difficulties and maternal antisocial behavior in early childhood, and peer problems and higher mental health problems. High CU/ low SLE show similar mental health outcomes.
- Age- and sex-specific ICU cut-off scores should be considered when assessing CU traits.
- Average total ICU cut-off scores of 26 for boys and 22 for girls predict high trajectories of oppositional defiant problems and conduct problems, with average sensitivity and specificity around 66-72%.

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