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# Facts of aggression

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# CHAPTER 7

## GENERAL DISCUSSION

## AIMS

This thesis aimed to provide insight in the etiology, predictors, and outcomes of aggression and antisocial behavior. The first part of this thesis focused on more conventional prediction of outcomes and continuation of aggression and antisocial behavior on the basis of the following constructs: parental psychopathology (**Chapter 2**), anxiety and depression (**Chapter 3**), and Oppositional Defiant Disorder symptoms (**Chapter 4**). Next, the second part of this thesis focused on novel biological markers of aggression, consisting of a review on the genetics of aggression (**Chapter 5**) and an empirical study on the metabolomics of aggression (**Chapter 6**).

## SUMMARY

Both childhood disruptive behavior (DB) and the presence of parental mental disorders are independently associated with risk of long-term negative outcomes. To further extend this knowledge, the goal of Chapter 2 was to investigate whether 9-year-old children with DB and parents with a mental disorder had worse outcomes in adolescence compared to children with DB and parents without a mental disorder. In line with earlier research, child DB was related to all outcomes in adolescence. Paternal MD was related to criminality, aggression, truancy, poor school performance, and a cumulative risk index of poor functioning, and maternal MD to peer problems, rule breaking, and truancy. A subsample of children with DB was created to study whether the presence of parental mental disorders added additional risk of worse outcomes in children with DB. This appeared to be the case; paternal MD predicted adolescent criminality, consequences of antisocial behavior, truancy, poor school performance, and cumulative risk, whereas maternal MD predicted peer problems. Interestingly, paternal MD was a better predictor than maternal MD, regardless of child DB at age 9.

**Chapter three** covered the comorbidity between anxiety, depression, and DB. The first aim was to investigate whether anxiety and depression in childhood predicted DB in adolescence. The second aim was to what extent these relations were attributable to environmental and genetic confounding by means of a discordant co-twin design. Discordant co-twin designs allow to control very stringently for confounding because both monozygotic and dizygotic twins

typically share their rearing environment, while sharing 50 and 100% of their genetic material, respectively. Although significant in crude models, anxiety and depression in childhood did not predict DB in adolescence, after correcting for childhood DB. Cross-sectional co-twin analyses childhood indicated that the relation between anxiety and DB was fully explained by environmental and genetic confounding, while the relationship between depression and DB remained intact after correction. This suggests a more robust relationship between depression and DB, as compared to anxiety and DB. However, it should be noted that the relationship between depression is confined to childhood at most, and does not contribute to adolescent DB.

**Chapter four** focused on the Oppositional Defiant Disorder (ODD) behaviors of irritability and oppositionality. It has been shown before that irritability and oppositionality are correlated to different types of problems. To expand on this research, we wanted to investigate whether clinic-referred children and adolescents could be classified into mutually exclusive classes on the basis of their irritability or oppositionality symptoms, and whether the resulting classes would have clinical utility. Parent- and teacher-reported ODD symptoms at referral were used to classify 5- to 18-year-old youths into groups by means of cluster-based modeling. Three classes emerged with high, moderate, and low levels of both irritability and oppositionality. At referral, the High ODD class experienced the highest levels of mental health problems and DSM classifications. Importantly, all ODD classes defined at intake were predictive of diagnostic and treatment outcomes months later. Notably, the High ODD class had higher rates of clinician-based classifications of ODD and Conduct Disorder, and the lowest levels of pre- and posttreatment global functioning. Additionally, the Low ODD class exhibited higher rates of Generalized Anxiety Disorder and fear disorders. In sum, irritability and oppositionality co-occur in clinic-referred youths to such an extent that classification based on one of these behaviours does not add to clinical inference. Instead, overall ODD symptom severity at referral should be used as a guidance for treatment.

**Chapter five** consisted of a literature review on the genomics of aggression, focussing on a review of reviews of the genetics of human aggression, as well as a review on the literature on Genome-wide Association Studies (GWASs). The reviewed literature indicates that aggression in humans is heritable to a considerable extent, with behaviour genetics studies finding heritability estimates of aggression in children and adults of around 50%. Seventeen GWASs on

aggression and antisocial behaviour were recovered, reporting 817 genetic variants showing suggestive significance ($p \leq 1.0E-05$), including 10 genome-wide significant associations ($p \leq 5.0E-08$). Nominal associations ($5.0E-08 \leq p \leq 1E-05$) were found in gene-based tests for genes involved in immune, endocrine, and nervous systems. However, these associations were not replicated across GWASs. In sum, this review suggests considerable heritability of aggression and antisocial behaviour, but also clearly emphasizes that the actual biological basis of these heritability estimates remains to be uncovered.

**Chapter six** presents the first urinary metabolomics study on childhood aggression, using both community-residing twins as well as clinic-referred children. The analytical design consisted of three phases: a discovery phase in twins scoring low or high on aggression; a replication phase in twin pairs discordant for aggression; and a validation phase in clinical cases and matched twin controls. In the discovery phase, six biomarkers were significantly associated with childhood aggression, of which the association of O-phosphoserine, and gamma-L-glutamyl-L-alanine remained significant after multiple testing. Although non-significant, the directions of effect were congruent between the discovery and replication analyses for six biomarkers and two neurotransmitter ratios and the concentrations of six amines differed between low and high aggressive twins. In the validation analyses, the top biomarkers and neurotransmitter ratios, with congruent directions of effect, showed no significant associations with childhood aggression. Higher levels of O-phosphoserine could indicate a dysregulation of the serotonergic and dopaminergic system, specifically a lack of conversion from L-tryptophan to serotonin as well as from L-tyrosine to dopamine. Gamma-L-glutamyl-L-alanine could potentially indicate a role for oxidative stress in childhood aggression.

## MAIN FINDINGS

1. Aggression and antisocial behavior were the best predictors for later aggression and aggression-related outcomes (**Chapters 2, 3, and 4**). The presence of psychopathology in fathers, not mothers, of children with disruptive behavior conferred an additional risk for long-term negative outcomes in adolescence (**Chapter 2**).
2. Subtyping, like on the basis of paternal mental disorders, can in some instances provide valuable insights (**Chapter 2**). However, especially in

individuals with significant problems (e.g., clinic-referred youths), multiple types of problems tend to co-occur next to one another. In these cases, instead of focusing on different types of behaviors, a focus on overall problem severity is more likely to give a reliable indication of prognosis and the amount of care required (**Chapter 4**).

3. This thesis indicates that is important to consider sample characteristics (e.g., community, at-risk, clinical) and the aim of the predictions (e.g., identification of at-risk individuals, diagnostics, gaining a deeper understanding of the etiology/development of aggression; **Chapters, 2, 4, and 6**).
4. Behavioral genetics research, which divides twin's individual differences in genetic and environmental components, indicates substantial heritability of aggression and antisocial behavior (**Chapter 5**). This in turn implies considerable biological differences related to aggressive behavior. However, these biological differences are not reflected in current, more direct measures of biology, specifically: Genome-wide Associations Studies and Metabolomics (**Chapters 5 and 6**).

## GENERAL DISCUSSION



First, although aggression correlates with a multitude of problems, there is substantial variability to what extent aggression is driven by these problems. In line with the (unnuanced) maxim that past behavior predicts future behavior (e.g., Colins et al., 2015; Kennealy, Skeem, Walters, & Camp, 2010), this thesis confirmed that the overall severity of aggression and antisocial behavior is a powerful predictor of aggression and aggression-related outcomes in both clinical and community settings, specifically disruptive behavior (DB) in Chapters 2 and 3, and Oppositional Defiant symptoms in Chapter 4. Although this finding proves valuable for risk assessment, it only partially explains why some youths remain aggressive (i.e., because they displayed aggression previously) nor provides clues on treatment or prevention.

A risk factor which does seem to provide additional clues was found in Chapter 2; the presence of paternal (not maternal) mental disorders conferred additional risk for worse outcomes in adolescence in addition to DB. This finding is important because it provides some insight in the way aggression is influenced, in this case; suboptimal parenting practices and genetic risk, and because it shows the importance of fathers as compared to mothers. Interestingly, most of

the research has focused on mothers (e.g., Kim-Cohen et al., 2005) instead of fathers. It is already known that parental psychopathology impairs parenting practices in several ways, reducing positive engagement activities, warmth, responsiveness, and control, as well as interfering in more indirect activities like selecting childcare or arranging goods and services for their child (Barker, Iles, & Ramchandani, 2017). Furthermore parental involvement, which is affected considerably by parental psychopathology, was found to be an important moderator of treatment effectiveness of aggression (Hendriks, Bartels, Colins, & Finkenauer, 2018). So, the presence of parental mental disorders, particularly mental disorders in the father, could provide some clues on how to ameliorate some of its negative long-term outcomes.

Second, the given (e.g., Dodge & Coie, 1987; Klahr & Burt, 2014; Moffitt, 1993) that some constructs or subtypes are better predictors of functioning raises the question whether researchers should focus on subtyping aggression and antisocial behavior or focus on its heterogeneity. Studies on subtypes of aggression and antisocial behavior have provided us answers to some very interesting questions. An example from this thesis concerns Oppositional Defiant Disorder (ODD) behaviors, which can be divided into at least two dimensions: an irritable dimension, consisting of touchy and angry behavior, and an oppositional dimension, consisting of hurtful and headstrong behavior. Irritability is mainly associated with affective problems, especially depression and anxiety (Hipwell et al., 2011; Vidal-Ribas et al., 2016), whereas oppositionality is correlated with symptoms of Attention Deficit Hyperactivity Disorder (ADHD) and Conduct Disorder (CD), as well as violent and non-violent delinquency. So, in this case, and multiple others, subtypes of aggression and antisocial behavior do provide valuable information to some extent. However, a focus on subtyping brings along some limitations.

One considerable limitation is the co-occurrence of different types of problem behavior. The more severe the problems of a child or adolescent, the more various kinds of subtyping approaches or classifications seem to lose their distinctiveness. To illustrate, in our clinic-referred sample no ODD classes were found which were solely high in irritability or solely high in oppositionality (Chapter 3), while these "pure" classes were found in community samples with substantially lower levels of problem behavior (Althoff et al., 2014; Herzhoff & Tackett, 2016; Kuny et al., 2013; Wesselhoeft et al., 2019). This overlap or intercorrelation of aggression with a multitude of problems corresponds with clinical reality in which comorbidity is

rule, not exception, and in which patients frequently change in their diagnostical classifications over time. This heterogeneity but relative stability of problems is captured in more recently introduced research constructs like the general psychopathology factor (i.e., p factor). This p factor reflects an overall index of severity of psychopathology (Caspi et al., 2014), making it a transdiagnostic construct which transcends conventional psychiatric classifications. This suggests that instead of solely focusing on subtypes, a focus on overall problem severity could provide a more reliable indication of prognosis and the amount of care required.

Third, what constitutes a reliable predictor of functioning in one setting could have considerably less predictive qualities in another setting. We have already mentioned that we discovered that irritability and oppositionality can be used to classify individuals in a community setting (Althoff et al., 2014; Herzhoff & Tackett, 2016; Kuny et al., 2013; Wesselhoeft et al., 2019), but not in a clinic-referred setting (Chapter 3). We also found that the mere presence of parental mental disorders confers a considerable risk of poor outcomes in adolescence in community-residing twins. However other research indicated that prevalence of parental mental disorders is substantially higher in clinic-referred samples (e.g., 40% of mothers and 30% of fathers; Wesseldijk et al., 2018), which is likely to be even higher because of considerable non-response (30-40%). So, while parental mental disorders are a very potent predictor of future outcome in community settings, this differentiating potential could well be less valuable in a clinical setting comprising of severe and complex patients, most of whom experience severe family problems. Instead of asking whether there is a parental mental disorder present or not, this setting would more likely require a shift to what kind of parental mental disorder is present, and its severity.

Fourth, behavioral genetics research implies considerable heritability of aggressive and antisocial behavior (Chapter 4). However, direct measures of biology do not reflect this estimate, following from our review on Genome-wide Association studies of aggression and antisocial behavior (Chapter 4), as well as the metabolomics study in Chapter 5. Very few significant effects of biological measures are found which contribute to tiny percentages of explained variance. Furthermore, while psychopathology as well as aggression have a genetic basis, it could be difficult to discern actual biological correlates because the same behavior (e.g., aggression) could have different “push” and “pull factors” per individual. Interestingly, neighborhood characteristics seem to influence heritability estimates

of aggressive and antisocial behavior, with higher socioeconomic neighborhood status correlating with higher heritability estimates (Tuvblad et al., 2006; Burt et al., 2016, Hendriks et al., 2020). In other words, aggressive behavior can be exhibited across individuals, but in a "good" neighborhood genetics are likely to exert a bigger influence, while the environment exerts a bigger influence in "bad" neighborhoods. The heterogeneity of aggressive behavior potentially complicates matters even further. To illustrate, there are indications that physical aggression has higher heritability estimates as compared to more broader concepts of aggression and antisocial behavior (Waltes, et al., 2016).

The discovery of actual biological bases of problem behavior, like aggression, becomes even more challenging when considering theories like differential susceptibility in which a sizeable minority of the population are more sensitive to environmental input: for better *and* for worse (Belsky, Bakermans-Kranenburg, & IJzendoorn, 2007). This means that, amongst others, genetic variants that are associated with poor outcomes in suboptimal situations can be associated with good outcomes in optimal situations. If this theory holds, this would, unfortunately, mean the need for larger sample sizes to discover functional genetic variants; sample size increases of 50 percent are mentioned to achieve similar statistical power as in conventional research (Del Giudice, 2017). But, more importantly, this would also mean that genetical risk markers cannot be used to make accurate individual predictions about risk without considering environmental input. The same genes which are associated with negative outcomes in individuals which were exposed to suboptimal environments are in other instances associated with positive outcomes in individuals which were exposed to optimal environments.

Another prominent critique is on the way aggression is measured in behavioral genetics research; with most of the time a parent rating the behavior of both twins. Heritability decreases substantially when actual observations or tasks are used as compared to a single rater for both twins (Tuvblad & Baker, 2011). Interestingly, only two studies exist which used an experimental paradigm to induce aggressive behaviors twins. One study in 7- to 9-year-old twins showed considerable influence of unique environmental influences (74% CI: 0.63–0.90), moderate influences of genetics (A= 20%, CI: 0–37), and a small effect of the shared environment (C = 6%, CI: 0–34; Achterberg, van Duijvenvoorde, van der Meulen, Bakermans-Kranenburg, & Crone, 2018), while a study in adult twins even showed a 100% unique environmental influence on aggression in the case

of increasing provocation (Dinić et al., 2020). These studies provide preliminary evidence of the importance of multiple measurements as well as environmental factors in provoked aggressive behavior.

Another, more metaphysical critique is the medical lens through which human behavior is perceived in this field of research. There is always some sort of moral judgement when (problematic) human behavior is defined as well as a specific cultural context in which this judgment is passed, whether it be a teacher rating a student's aggression or a psychiatrist diagnosing an antisocial personality disorder in a delinquent. This is very different than other medical disciplines in which it is more clear that a certain aspect of human physiology is not functioning as intended. In some instances, a lab test gives a definitive and reliable diagnosis, while the observations of the doctor are of secondary value. This is in stark contrast with psychiatry in which observations are key and where cultural knowledge is necessary. To illustrate, the expression of psychosis as well as its perception as a disease varies across the world (Kendler, Zachar, & Craver, 2019). Feelings of extreme guilt are very prevalent in western countries and hypothesized to be a byproduct of Christianity (Bhavsar & Bhugra, 2008), while in pre-industrial societies the delusion that one transforms into all different kinds of animals is very prevalent, which could be attributed to animist beliefs and the local flora and fauna (Garlipp, Gödecke-Koch, Dietrich, & Haltenhof, 2004). Importantly, these variations in expression do not negate that a common underlying biological agent is not present, of course, some common elements can be found, like the given that delusions and hallucination are present in some form. Rather, they do point out that finding a biological cause for aggression is potentially more difficult because it is a more universal human behavior than psychosis, and is far more context-dependent.



### Strengths and limitations

The studies in this thesis possessed several notable strengths. First, the use of multiple information sources (i.e., self-report, parents, teachers, clinicians, registries). Second, the studies spanned multiple settings, specifically clinic-referred and community samples. Third, state-of-the-art technologies were used, like the metabolomics approach to study childhood aggression and the machine learning-assisted literature search. Fourth, several studies possessed follow-up measurements, some spanning almost a decade. Fifth, the recruitment procedure in the CATSS and ODD papers substantially reduced selection bias. In case of

the CATSS paper all twins that were born in Sweden were approached, while in the ODD paper data were used which were collected as an integral part of a clinical protocol.

There are also several limitations that should be noted. First, the definition of aggression and antisocial behavior varied considerably across studies, (e.g., ODD and CD symptoms, ODD symptoms, aggressive behavior, aggressive and antisocial behavior), which hinders our ability to make precise comparisons. Second, only cross-sectional data were used in case of the metabolomics paper and the review of GWASs. It could for example be the case that some genetic variants are developmentally sensitive. Hypothetically, a gene could exert influence on aggression in 3-year-olds, while this wouldn't be the case in 15-year-olds. Third, this thesis focused primarily on risk factors, while it is known that protective factors like above-average intelligence, low impulsivity, living in a non-deprived non-violent neighborhood, and good family functioning can considerably lower the risk of developing aggression and/or antisocial behavior (Losel & Farrington, 2012).

**Clinical implications**

This thesis clearly suggests the importance of considering the specific setting in which risk assessments or predictions are made. Considerable research has been conducted on aggression and antisocial behavior in multiple settings (e.g., community and clinical). This thesis showed for example that the presence of parental mental disorders in childhood, especially those in fathers, can be a potent risk factor for poor psychosocial functioning in adolescence for children with DB. Although valuable, clinicians should be aware that findings from relatively high-functioning community samples sometimes find their way into clinical practice, while these would not necessarily hold up in clinical reality. To illustrate, very much to my surprise, physical exercise is not causally related to decreases in anxiety and depression in community-residing individuals (De Moor, Boomsma, Stubbe, Willemsen, & de Geus, 2008). However, randomized controlled trials (RCTs) targeting depressive individuals clearly indicate physical exercise to be effective in treating depression, with effect sizes being comparable to psychotherapy and antidepressants (Kvam, Kleppe, Nordhus, & Hovland, 2016). This is a powerful example of the ability of mental health professionals to initiate behavioral change in patients. Although community findings suggest that these depressive and anxious individuals would not have initiated physical

exercise by themselves, the same individuals did engage in this very beneficial behavior when offered in a care context. Another important implication is that the severity of problems should be a leading principle of diagnostics and treatment in clinical populations, not specific behavioral subtypes. If there is a focus on specific problems, these should be ones which are amendable to treatment or related to constructs which are amendable to treatment, for example parental mental disorders (Chapter 2).

**Directions for future research**

First, focussing on multiple biological systems, instead of one single system at a time, could give us a better indication what is happening biologically on an individual level. It is known that biological systems simultaneously interact with one another, therefore, such an approach could yield more robust results because it allows to study the aggregation and interaction of multiple biological system. In line with this idea, genetic, epigenetic, and metabolomic data which were collected within the ACTION framework are currently being combined into a cross-omics approach.

Another suggestion for future research would be an increased focused within twin research on experimental studies as well as randomized controlled trials. Twin research allows for very stringent controls for genetic and environmental confounding. Unfortunately, most of the literature, including chapter 4 of this thesis, has focused on observational studies. An increased focus on experiments and randomized controlled trials would allow for increased causal inference regarding characteristics that precipitate antisocial behavior and effectiveness of potential treatments, while maintaining the very stringent environmental and genetic controls which are characteristic of twin research. It should be noted that these approaches would require extensive recruitment efforts when studying high aggression and antisocial behavior. Twins are already relatively rare (15.9 twin births per 1000 births; Glasner, Van Beijsterveldt, Willemsen, & Boomsma, 2013), moreover including sufficient numbers of relevant individuals is greatly exacerbated by the fact that youths (and their families) who are high in aggression and antisocial behavior are less likely to participate in research in the first place, and are far more likely to drop out than their non-aggressive counterparts.

The increasing focus on aggression and antisociality as behaviors which are displayed in all individuals certainly has its merits to some extent, and can explain why in extreme situations (e.g., war) a lot of people can engage in very

serious aggressive acts. However, under normal circumstances only a very small percentage of the population causes the majority of problems, to illustrate; 1% of Sweden's population is responsible for 63% of all violent crime convictions (Falk et al., 2014). In this regard antisocial careers and academic careers aren't that different in their distribution of output (Laherrere & Sornette, 1998); a minority of individuals is responsible for a majority of the work done (i.e., highly cited researchers and childhood-onset chronic offenders). On the other hand, a majority gets a minority of the work done (i.e., PhD students/postdocs who quit science and children/adolescents who display developmentally normative antisocial behavior). Consequently, to achieve the highest gains in terms of societal costs and suffering, researchers should focus on the developmental trajectories of this elite of antisocial "high-achievers", not the average individual.

# SUPPLEMENTARY MATERIALS

# SUPPLEMENT TO CHAPTER 2

Children with early-onset disruptive behavior: parental mental disorders predict poor psychosocial functioning in adolescence

**Chapter 2, Supplement 1. ICD codes of parental mental disorders**
ICD-10
F10 Mental and behavioural disorders due to use of alcohol, except x.5
F11 Mental and behavioural disorders due to use of opioids, except x.5
F12 Mental and behavioural disorders due to use of cannabinoids, except, x.5
F13 Mental and behavioural disorders due to use of sedatives or hypnotics, except x.5
F14 Mental and behavioural disorders due to use of cocaine, except x.5
F15 Mental and behavioural disorders due to use of other stimulants, including caffeine, except x.5
F16 Mental and behavioural disorders due to use of hallucinogens, except x.5
F17 Mental and behavioural disorders due to use of tobacco, except x.5
F18 Mental and behavioural disorders due to use of volatile solvents, except x.5
F19 Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances, except x.5
F20 Schizophrenia
F21 Schizotypal disorder
F22 Persistent delusional disorders
F23 Acute and transient psychotic disorders
F24 Induced delusional disorder
F25 Schizoaffective disorders
F28 Other nonorganic psychotic disorders
F29 Unspecified nonorganic psychosis
F30 Manic episode
F31 Bipolar affective disorder
F32 Depressive episode
F33 Recurrent depressive disorder
F34 Persistent mood [affective] disorders
F38 Other mood [affective] disorders
F39 Unspecified mood [affective] disorder

F40 Phobic anxiety disorders
F41 Other anxiety disorders
F42 Obsessive-compulsive disorder
F43 Reaction to severe stress, and adjustment disorders
F44 Dissociative [conversion] disorders
F45 Somatoform disorders
F48 Other neurotic disorders
F50.0 Anorexia nervosa
F50.1 Atypical anorexia nervosa
F50.2 Bulimia nervosa
F50.3 Atypical bulimia nervosa
F50.9 Eating disorder, unspecified
F51 Nonorganic sleep disorders
F60 Specific personality disorders
F60.0 Paranoid personality disorder
F60.1 Schizoid personality disorder
F60.2 Dissocial personality disorder
F60.3 Emotionally unstable personality disorder
F60.4 Histrionic personality disorder
F60.5 Anankastic personality disorder
F60.6 Anxious [avoidant] personality disorder
F60.7 Dependent personality disorder
F60.8 Other specific personality disorders
F60.9 Personality disorder, unspecified
F61 Mixed and other personality disorders
F63 Habit and impulse disorders
F64 Gender identity disorders
F70 Mild mental retardation
F71 Moderate mental retardation
F72 Severe mental retardation
F73 Profound mental retardation
F78 Other mental retardation
F79 Unspecified mental retardation
F80 Specific developmental disorders of speech and language
F81 Specific developmental disorders of scholastic skills
F82 Specific developmental disorder of motor function
F83 Mixed specific developmental disorders

F84 Pervasive developmental disorders
F84.0 Childhood autism
F84.1 Atypical autism
F84.3 Other childhood disintegrative disorder
F84.4 Overactive disorder associated with mental retardation and stereotyped movements
F84.5 Asperger's syndrome
F84.8 Other pervasive developmental disorders
F84.9 Pervasive developmental disorder, unspecified
F88 Other disorders of psychological development
F89 Unspecified disorder of psychological development
F90 Hyperkinetic disorders
F91 Conduct disorders
F91.0 Conduct disorder confined to the family context
F91.1 Unsocialised conduct disorder
F91.2 Socialised conduct disorder
F91.3 Oppositional defiant disorder
F91.8 Other conduct disorders
F91.9 Conduct disorder, unspecified
F92 Mixed disorders of conduct and emotions
F92.0 Depressive conduct disorder
F92.8 Other mixed disorders of conduct and emotions
F92.9 Mixed disorder of conduct and emotions, unspecified
F93 Emotional disorders with onset specific to childhood
F94 Disorders of social functioning with onset specific to childhood and adolescence
F95 Tic disorders
F98 Other behavioural and emotional disorders with onset usually occurring in childhood and adolescence

ICD-9
295.0 Simple type
295.1 Disorganised type
295.2 Catatonic type
295.3 Paranoid type
295.4 Acute schizophrenic episode
295.5 Latent schizophrenia

295.6 Residual schizophrenia
295.7 Schizo-affective type
295.8 Other specified types of schizophrenia
295.9 Unspecified schizophrenia

296.0 Manic disorder, single episode
296.1 Manic disorder, recurrent episode
296.2 Major depressive disorder, single episode
296.3 Major depressive disorder, recurrent episode
296.4 Bipolar affective disorder, manic
296.5 Bipolar affective disorder, depressed
296.6 Bipolar affective disorder, mixed
296.7 Bipolar affective disorder, unspecified
296.8 Manic-depressive psychosis, other and unspecified
296.9 Other and unspecified affective psychoses
297 Paranoid states
298 Other nonorganic psychoses
299.0 Infantile autism
299.1 Disintegrative psychosis
299.8 Other specified early childhood psychoses
299.9 Unspecified
300.0 Anxiety states
300.1 Hysteria
300.2 Phobic disorders
300.3 Obsessive-compulsive disorders
300.4 Neurotic depression
300.5 Neurasthenia
300.6 Depersonalisation syndrome
300.7 Hypochondriasis
300.8 Other neurotic disorders
300.9 Unspecified neurotic disorder
301 Personality disorders
301.0 Paranoid personality disorder
301.1 Affective personality disorder
301.2 Schizoid personality disorder
301.3 Explosive personality disorder
301.4 Compulsive personality disorder

301.5 Histrionic personality disorder
301.6 Dependent personality disorder
301.7 Antisocial personality disorder
301.8 Other personality disorders
301.81 Narcissistic personality
301.82 Avoidant personality
301.83 Borderline personality
301.84 Passive-aggressive personality
301.89 Other
301.9 Unspecified personality disorder
303 Alcohol dependence syndrome
304 Drug dependence
305.0 Alcohol abuse
305.9 Other, mixed, or unspecified drug abuse
307.1 Anorexia nervosa
307.2 Tics
307.3 Stereotyped repetitive movements
307.4 Specific disorders of sleep of nonorganic origin
307.50 Eating disorder, unspecified
307.51 Bulimia
307.52 Pica
307.53 Psychogenic rumination
307.54 Psychogenic vomiting
307.59 Other
311 Depressive disorder, not elsewhere classified
312 Disturbance of conduct not elsewhere classified
312.0 Undersocialised conduct disorder, aggressive type
312.00 Unspecified
312.01 Mild
312.02 Moderate
312.03 Severe
312.1 Undersocialised conduct disorder, unaggressive type
312.10 Unspecified
312.11 Mild
312.12 Moderate
312.13 Severe
312.2 Socialised conduct disorder

312.20 Unspecified
312.21 Mild
312.22 Moderate
312.23 Severe
312.3 Disorders of impulse control, not elsewhere classified
312.4 Mixed disturbance of conduct and emotions
312.8 Other specified disturbances of conduct, not elsewhere classified
312.81 Conduct disorder, childhood onset type
312.82 Conduct disorder, adolescent onset type
312.89 Other conduct disorder
312.9 Unspecified disturbance of conduct
313.8 Other or mixed emotional disturbances of childhood or adolescence
313.81 Oppositional disorder
313.82 Identity disorder
313.83 Academic underachievement disorder
313.89 Other
313.9 Unspecified emotional disturbance of childhood
314.0 Attention deficit disorder
314.00 Without mention of hyperactivity
314.01 With hyperactivity
314.1 Hyperkinesis with developmental delay
314.2 Hyperkinetic conduct disorder
314.8 Other specified manifestations of hyperkinetic syndrome
314.9 Unspecified hyperkinetic syndrome
317 Mild mental retardation
318 Other specified mental retardation
318.0 Moderate mental retardation
318.1 Severe mental retardation
318.2 Profound mental retardation
319 Unspecified mental retardation
ICD-8
291 Alcoholic psychosis
295.0 Simple type
295.1 Hebephrenic type
295.2 Catatonic type
295.3 Paranoid type
295.4 Acute schizophrenia episode

295.5 Latent schizophrenia
295.6 Residual schizophrenia
295.7 Schizo-affective type
295.8 Other
295.9 Unspecified type
296.0 Involutional melancholia
296.1 Manic-depression psychosis, manic type
296.2 Manic depressive psychosis, depressed type
296.3 Manic-depressive psychosis, circular type
296.8 Other
296.9 Unspecified
297 Paranoid states
298 Other psychoses
300 Neuroses
300.0 Anxiety neurosis
300.1 Hysterical neurosis
300.2 Phobic neurosis
300.3 Obsessive compulsive neurosis
300.4 Depressive neurosis
300.5 Neurasthenia
300.6 Depersonalisation syndrome
300.7 Hypochondriacal neurosis
300.8 Other
300.9 Unspecified neurosis
301 Personality disorders
301.0 Paranoid
301.1 Affective
301.2 Schizoid
301.3 Explosive
301.4 Anankastic
301.5 Hysterical
301.6 Asthenic
301.7 Antisocial
301.8 Other
301.9 Unspecified
303 Alcoholism
304 Drug dependence

308 Behaviour disorders of childhood
310 Borderline mental retardation
311 Mild mental retardation
312 Moderate mental retardation
313 Severe mental retardation
314 Profound mental retardation
315 Unspecified mental retardation

## Chapter 2, Supplement 2. Additional information on measures

### Outcome measures at age 15

***Self-reported aggression***

Aggressive behavior was assessed using the 23-item Reactive and Proactive Aggression Questionnaire (RPQ) (Raine et al., 2006). The RPQ includes 11 items that focus on reactive aggression (e.g., "Reacted angrily when provoked by others", "Gotten angry when frustrated"), and 12 items that focus on proactive aggression (e.g., "Had fights with others to show who was on top", "Taken things from other students"). The items are coded as 0 ("never"), 1 ("sometimes"), or 2 ("often").

***Self-reported crime***

The Self-reported Delinquency Scale (SRD; Ring, 1999) was used to assess the frequency of 13 non-violent criminal acts (e.g., vandalism, car theft, burglary, drug dealing) and nine violent criminal acts (e.g., hurting persons, hurting animals, sexual offenses). Each item is coded on a 6-point Likert scale, ranging from 0 ("never") to 5 ("more than 10 times").

***Self-reported alcohol misuse***

Alcohol misuse was assessed using the Self-reported Alcohol and Drug Use (Englund, 2016). First, a dichotomous variable "Frequent Alcohol Consumption" (no/yes) was created based upon the question: "Have you been drinking beer, wine or liquor last month?". A second question was asked concerning frequency of intoxication "How often do you feel drunk when you drink alcohol?", which was rated on a 6-point Likert scale ranging from 0 ("I don't drink") to 5 ("every time"). Based upon this second question, a dichotomous variable "Frequent Alcohol Intoxication" was created and differentiated between those who were not or rarely intoxicated (score 0-3) and those who were (very) often intoxicated (score 4-5). Finally, "Alcohol Misuse" was defined as being above the cut-off for

Frequent Alcohol Consumption and/or Frequent Alcohol Intoxication (of note, using this approach about 30% of the sample were identified as misusing alcohol).

***Self-reported truancy***

Following prior work (Norén Selinus et al., 2015), truancy of the child was assessed using one SRD item ("Did you ever skip school"), with scores ranging from 0 ("never") to 4 ("more than 10 times").

***Parent-reported conduct problems***

Conduct problems of the child were assessed using the Conduct Problems subscale of the Strengths and Difficulties Questionnaire (SDQ).(Goodman, 1997) SDQ items (Lansford et al.) scored on this and the other SDQ scales mentioned below range from 0 ("not true"), 1 ("somewhat true") and 2 ("certainly true").

***Parent-reported emotional problems***

Emotional problems of the child were assessed using the 5-item (e.g., "Often unhappy, down-hearted or tearful") Emotional Problems subscale of the SDQ parent version.

***Parent-reported peer problems***

Peer problems of the child were assessed through the 5-item (Lansford et al.)") Peer Problems subscale of the SDQ parent version.

***Parent-reported prosocial behavior***

Prosocial behavior of the child was assessed through the 5-item (Lansford et al.) Prosocial Behavior subscale of the SDQ parent version. Of note, a higher prosocial behavior score is indicative of less problems.

**Outcome measures at age 18**

***Self-reported aggression***

Aggression was assessed using the 11-item Aggression subscale of the Life History of Aggression Questionnaire.(Coccaro et al., 1997) Youth were asked how many times in their lives they had committed certain aggressive acts (Lansford et al.). Answers were given on a 6-point Likert scale ranging from 0 ("no event") to 5 ("more times than I can count").

***Self-reported crime and truancy***

Self-reported crime and truancy were assessed using the same Self-reported Delinquency Scale as at age 15 years (see outcome measures at age 15).

***Self-reported alcohol misuse***

Alcohol misuse was assessed using the Alcohol Use Disorders Identification Test (AUDIT). (Saunders et al., 1993) The AUDIT covers alcohol consumption,

drinking behavior (dependence), and alcohol-related problems. The first eight items have five response categories, and are coded from 0 to 4. Items nine and 10 have three response categories and are coded as: 0, 2 or 4. An example of a question concerning alcohol-related problems is: "How often during the last year did you have a feeling of guilt or remorse after drinking", with answers ranging from 0 ("never") to 4 ("daily or almost daily"). The cutoff for alcohol misuse for women is set at a value of 6 or higher, for men at 8 or higher.(Saunders et al., 1993)

***Self-reported consequences of antisocial behavior***

The 4-item Consequences of Antisocial Behavior subscale of the Life History of Aggression Questionnaire measures social consequences due to antisocial behavior of the reporter (Lansford et al.).

***Parent-reported aggression***

Aggression was assessed by means of the 16-item Aggressive Behavior subscale of the Adult Behavior Checklist (ABCL)(Achenbach & Rescorla, 2003) parent version. Parents rated aggression of their child over the last 6 months (Lansford et al.) on a 3-point Likert scale ranging from 0 ("not true") to 2 ("very true or often true").

***Parent-reported rule-breaking behavior***

Rule-breaking behavior was assessed by the 13-item ABCL Rule-breaking Behavior subscale (Lansford et al.).

***Parent-reported emotional problems***

Emotional problems were assessed by the 14-item ABCL Anxious/Depressed subscale (Lansford et al.).

***Registered school performance***

School performance of the child was assessed using the sum of the final grades of 16 subjects (e.g., math, English) in primary school. The grades were obtained through the National School Register. Swedish school grades range from 0 (equivalent to an F) to 20 (equivalent to an A). The total score on all 16 subjects ranged from 0 (equivalent to an F on all subjects) to 320 (equivalent to an A on all subjects).

## Chapter 2, Supplement 3. Internalizing and externalizing mental disorders

It could be the case that the "what-question" (ie, Is there an internalizing or externalizing MD present in the parents?) might be more important than the "who-question" (ie, Does the mother or the father have a MD?), especially since a higher prevalence of externalizing disorders in fathers than in mothers might explain why paternal disorder was most often related to the reported antisocial

outcomes in the subsample of children with DB at age 18. We differentiated between parental external disorders (ie, at least one parent had an externalizing MD) and internalizing disorders (ie, at least one parent had an internalizing MD) and included these two predictors in a model, together with the control variables (for details see Table S6). Results showed that when predicting outcomes at age 18, parental internalizing disorder (6.7% in the sample of children with DB at age 18) was positively related to consequences of antisocial behaviour (OR = 1.80; 95% CI = 1.06; 3.05) and truancy (OR = 2.02; 95% CI = 1.14; 3.57), whereas parental externalizing disorder (3.0%) was positively related to violent criminality (OR = 2.94; 95% CI = 1.28; 6.77), aggression (OR = 2.58; 95% CI = 1.24; 5.35), alcohol misuse (OR = 2.34; 95% CI = 1.03; 5.32), and the cumulative risk index (OR = 1.38; 95% CI = 1.15; 1.67).

However, these analyses do not rule out the possibility that prospective links between externalizing and internalizing disorders and outcomes differ across mothers and fathers. To explore this possibility, we also tested a model with four predictors (paternal externalizing disorder, 1.8%; paternal internalizing disorder, 2.4%; maternal externalizing disorder, 1.7%; and maternal internalizing disorder, 4.4%;) together with the control variables. Results showed (i) that paternal externalizing disorder was related to violent criminality (OR = 4.10; 95% CI = 1.19; 14.14) and the cumulative risk index (OR = 1.39; 95% CI = 1.14; 1.71); (ii) paternal internalizing disorder to truancy (OR = 3.13; 95% CI = 1.41; 6.94) and poor school performance (OR = 2.42; 95% CI = 1.05; 5.73), and (iii) that maternal externalizing disorder was positively related to emotional problems (OR = 3.90; 95% CI = 1.11; 13.69), for details see Table S7. In short, the outcomes of these analyses suggest that the "what-" and "who-question" are equally important.

**Chapter 2, Table S1** Overview of Disruptive Behavior Items

| Oppositional Defiant Disorder items |
|---|
| Gate items |
| Has there ever been a time when s/he would be angry to the extent that s/he cannot be reached? |
| Does s/he often argue with adults? |
| Does s/he often tease others by deliberately doing things that are perceived as provocative? |
| Is s/he easily offended, or disturbed by others? |
| Is s/he easily teased? |

**Chapter 2, Table S1** Continued.

| Additional items |
|---|
| Has there ever been a time when s/he would be angry to the extent that s/he is out of control without there being any particular triggering event? |
| Has there ever been a time when s/he would be angry to the extent that s/he is out of control in connection with changes? |
| Does s/he often lose temper? |
| Does s/he refuse following other people's directives? |
| Is s/he often vindictive or cruel? |
| Does s/he often treat significant others badly or without respect? |
| Does s/he often blame others for own mistakes or bad actions? |
| Conduct Disorder items |
| Gate items |
| Has s/he ever deliberately been physically cruel to anybody? |
| Does s/he often start fights? |
| Does s/he often lie or cheat? |
| Does s/he steal things at home or outside home? |
| Has s/he ever engaged in shoplifting? |
| Additional items |
| Does s/he often threaten, harass or humiliate others? |
| Is s/he cruel to insects? |
| Has s/he ever started a fire? |
| Has s/he ever sexually abused other children? |
| Has s/he ever been detained by the police? |
| Has s/he ever used a deadly weapon? |
| Has s/he ever robbed anyone or else unlawfully acquired other people's property by means of directs threats? |
| Has s/he ever purposely attempted to destroy other people's property? |
| Has s/he ever broken into someone else's home, premises or car? |
| Is s/he often out late at night without consent (beginning before 13 years of age)? |
| Has s/he ever ran away from home and stayed away over night at least two times (or one time if it was for an extended period of time)? |
| Is s/he often absconding (beginning before 13 years of age)? |

Note: The additional items were administered if the parents endorsed one or more of the gate items with "yes to some extent" or "yes".

**Chapter 2, Table S2** Frequencies and Percentages of Membership of Disorder Category Membership for Mothers at Waves 15 and 18 Years

| | Wave 15 Years (n = 195) | | Wave 18 Years (n = 84) | |
|---|---|---|---|---|
| Disorder category | Frequency | Percentage | Frequency | Percentage |
| Anxiety, obsessive compulsive, dissociative, and somatoform disorders | 74 | 37.9 | 38 | 45.2 |
| Depressive disorders | 72 | 36.9 | 23 | 27.4 |
| Substance abuse and dependence | 27 | 13.8 | 17 | 20.2 |
| Psychotic disorders | 24 | 12.3 | 8 | 9.5 |
| Personality disorders | 10 | 5.1 | 7 | 8.3 |
| Reactions to severe stress and PTSD | 38 | 19.5 | 15 | 17.9 |
| Other[a] | 18 | 9.2 | 7 | 8.3 |

Note: Frequencies and Percentages refer to having at least one disorder in the respective disorder category. This implies, for example, that a mother who has a borderline personality disorder was counted as having a Personality Disorder, whether or not she met criteria for other personality disorders. The sample sizes refer to the number of mothers in each group and therefore deviates from the number of children exposed to maternal MD in Tables 1 and 2 of the main text. PTSD = post-traumatic stress disorder.

[a] Disorder categories with very low prevalences (≤ 5 or lower) were included in the "Other" disorder category to guarantee the confidentially of the parents and child.

**Chapter 2, Table S3** Frequencies and Percentages of Disorder Category Membership for Fathers at Waves 15 and 18 Years

| | Wave 15 Years (n = 170) | | Wave 18 Years (n = 77) | |
|---|---|---|---|---|
| Disorder category | Frequency | Percentage | Frequency | Percentage |
| Anxiety, obsessive compulsive, dissociative, and somatoform disorders | 45 | 26.5 | 15 | 19.5 |
| Depressive disorders | 33 | 19.4 | 22 | 28.6 |
| Substance abuse and dependence | 62 | 36.5 | 26 | 33.8 |
| Psychotic disorders | 26 | 15.3 | 13 | 16.9 |
| Personality disorders | 6 | 3.5 | 6 | 7.8 |
| Reactions to severe stress and PTSD | 31 | 18.2 | 15 | 19.5 |
| Other[a] | 13 | 7.6 | 7 | 9.1 |

Note: Frequencies and Percentages refer to having at least one disorder in the respective disorder category. This implies, for example, that a father who has a major depressive disorder was counted as having a Depressive Disorder, whether or not he met criteria for other depressive disorders, such as Dysthymic Disorder. The sample sizes refer to the number of fathers in each group and therefore deviates from the number of children exposed to paternal MD in Tables 1 and 2 in the main text. PTSD = post-traumatic stress disorder.

[a] Disorder categories with very low prevalences (≤ 5 or lower) were included in the "Other" disorder category to guarantee the confidentially of the parent and child.

**Chapter 2, Table S4** Dichotomous Cutoff Values for Follow-up at Age 15 Years and Age 18 Years

| Child age at assessment | Variable | Theoretical range | Cut point |
|---|---|---|---|
| 15 years | | | |
| | Nonviolent crime (SR) | 0-5 | ≥1 |
| | Violent crime (SR) | 0-5 | ≥1 |
| | Proactive aggression (SR) | 0-24 | ≥2 |
| | Reactive aggression (SR) | 0-22 | ≥7 |
| | Truancy (SR) | 0-4 | ≥1 |
| | Frequency of alcohol consumption beer (SR) | 0-1 | ≥1 |
| | Frequency of alcohol consumption other (SR) | 0-1 | ≥1 |
| | Frequency of alcohol intoxication (SR) | 0-5 | ≥3 |
| | Conduct problems (PR) | 0-10 | ≥3 |
| | Emotional problems (PR) | 0-10 | ≥5 |
| | Peer problems (PR) | 0-10 | ≥3 |
| | Prosocial behavior (PR) | 0-10 | ≥6 |
| 18 Years | | | |
| | Nonviolent crime (SR) | 0-5 | ≥1 |
| | Violent crime (SR) | 0-5 | ≥1 |
| | Aggression (SR) | 0-55 | ≥10 |
| | Consequences of aggression (SR) | 0-20 | ≥1 |
| | Truancy (SR) | 0-4 | ≥3 |
| | Alcohol misuse (SR) | 0-40 | boys: ≥8, girls: ≥6 |
| | Rule-breaking behavior (PR) | 0-26 | ≥14 |
| | Aggression (PR) | 0-32 | ≥10 |
| | Emotional problems (PR) | 0-28 | ≥17 |
| | School performance (Reg.) | 0-320 | ≥210 |

Note: PR = parent-reported; Reg. = registry; SR = self-reported.

**Chapter 2, Table S5** Odds Ratios and 95% Confidence Intervals of the Fixed Part of the Crude and Adjusted Main Effects Models at Follow-up 15 Years in a Subsample of Children With Disruptive Behavior

| | | Criminality | | Aggression | | Problems | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Violent (SR) | Nonviolent (SR) | Proactive (SR) | Reactive (SR) | Conduct (PR) | Emotional (PR) | Peer (PR) | Alcohol (SR) | Truancy (SR) | Low prosocial (PR) | Cumulative risk[a] |
| Predictor | Model | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) |
| Paternal MD | 3 | 1.35 | 1.18 | 0.91 | 1.02 | 1.29 | 1.23 | 1.34 | 1.12 | 1.16 | 0.89 | 1.09 |
| | | [0.88, 2.08] | [0.78, 1.77] | [0.55, 1.49] | [0.66, 1.56] | [0.86, 1.92] | [0.79, 1.93] | [0.92, 1.95] | [0.71, 1.76] | [0.78, 1.72] | [0.55, 1.43] | [0.94, 1.27] |
| | 4 | 1.36 | 1.17 | 0.91 | 1.02 | 1.28 | 1.26 | 1.29 | 1.13 | 1.13 | 0.88 | 1.09 |
| | | [0.88, 2.10] | [0.78, 1.76] | [0.55, 1.50] | [0.67, 1.57] | [0.86, 1.92] | [0.81, 1.97] | [0.89, 1.88] | [0.71, 1.78] | [0.76, 1.68] | [0.54, 1.42] | [0.93, 1.27] |
| Maternal MD | 3 | 0.91 | 1.07 | 0.95 | 0.92 | 1.05 | 0.77 | **1.64**** | 0.93 | 1.36 | 1.16 | 1.04 |
| | | [0.57, 1.45] | [0.71, 1.60] | [0.58, 1.56] | [0.61, 1.39] | [0.71, 1.54] | [0.49, 1.21] | [1.13, 2.38] | [0.60, 1.42] | [0.93, 2.00] | [0.75, 1.80] | [0.90, 1.20] |
| | 4 | 0.89 | 1.05 | 0.96 | 0.92 | 1.03 | 0.76 | **1.62*** | 0.92 | 1.35 | 1.17 | 1.03 |
| | | [0.55, 1.42] | [0.70, 1.58] | [0.58, 1.57] | [0.61, 1.39] | [0.70, 1.51] | [0.48, 1.20] | [1.12, 2.34] | [0.60, 1.42] | [0.92, 1.99] | [0.76, 1.82] | [0.89, 1.20] |

Note: n = 2215. Model 1 = crude model including the control variables: gender child, parental education level, maternal age at birth, and paternal age at birth; Model 2 = adjusted model including paternal MD, maternal MD, and the same control variables as model 1. MD = mental disorder; *OR* = odd ratio; PR = parent-reported; SR = self-reported. Boldface values indicate statistical significance.

[a] Cumulative risk was predicted through negative binomial regressions.

*$p$ <.05; **$p$ <.01.

**Chapter 2, Table S6** Odds Ratios and 95% Confidence Intervals of the Fixed Part of the Crude and Adjusted Main Effects Models at Follow-up 18 Years in a Subsample of Children with Disruptive Behavior With Parental Internalizing and Parental Externalizing Disorders as Predictors

| | | Criminality | | Aggression | | Problems | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Violent (SR) | Nonviolent (SR) | Aggression (SR) | Aggression (PR) | Conseq. of antisocial behavior (SR) | Rule-break. (PR) | Emotional (PR) | Alcohol (SR) | Truancy (SR) | Poor school performance (Reg.) | Cumulative risk[a] |
| Predictor | Model | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) |
| Internalizing MD | 1 | 1.54 [0.90, 2.62] | 1.44 [0.81, 2.56] | 1.14 [0.66, 1.95] | 1.04 [0.67, 1.63] | **1.90*** [1.12, 3.22] | 1.34 [0.76, 2.34] | 1.03 [0.61, 1.74] | 1.30 [0.73, 2.32] | **2.09*** [1.19, 3.69] | 1.69 [0.91, 3.13] | **1.21*** [1.03, 1.43] |
| | 2 | 1.38 [0.82, 2.32] | 1.36 [0.77, 2.42] | 1.01 [0.59, 1.75] | 1.00 [0.63, 1.60] | **1.80*** [1.06, 3.05] | 1.30 [0.75, 2.24] | 0.94 [0.55, 1.59] | 1.18 [0.65, 2.14] | **2.02*** [1.14, 3.57] | 1.59 [0.84, 2.99] | 1.16 [0.99, 1.36] |
| Externalizing MD | 1 | **3.16**** [1.35, 7.38] | 1.87 [0.77, 4.52] | **2.59*** [1.25, 5.35] | 1.42 [0.69, 2.91] | 1.87 [0.81, 4.35] | 1.39 [0.63, 3.07] | **2.24*** [1.01, 4.98] | **2.44*** [1.09, 5.43] | 1.68 [0.70, 4.01] | 1.95 [0.81, 4.68] | **1.44**** [1.18, 1.75] |
| | 2 | **2.94*** [1.28, 6.77] | 1.74 [0.73, 4.18] | **2.58*** [1.24, 5.35] | 1.42 [0.67, 2.98] | 1.62 [0.71, 3.70] | 1.30 [0.60, 2.78] | 2.27 [1.00, 5.18] | **2.34*** [1.03, 5.32] | 1.42 [0.59, 3.41] | 1.73 [0.70, 4.28] | **1.38**** [1.15, 1.67] |

Note: n = 1190. Model 1 = crude model including the control variables: gender child, parental education level, maternal age at birth, and paternal age at birth; Model 2 = adjusted model including internalizing MD, externalizing MD, and the same control variables as model 1. Internalizing MDs refers to having one or more disorders in one or more of the following disorders: anxiety, depressive, bipolar, OCD, eating, and post-traumatic stress, Externalizing MDs refers to having one or more disorders in one or more of the of the following disorders: substance abuse, behavior, and antisocial personality. Conseq. = consequences; MD = mental disorder; OR = odd ratio; PR = parent-reported; Reg. = registry; Rule-break. = rule-breaking; SR = self-reported. Boldface values indicate statistical significance.

[a] Cumulative risk was predicted through negative binomial regressions.

*$p$ <.05; **$p$ <.01.

**Chapter 2, Table S7** Odds Ratios and 95% Confidence Intervals of the Fixed Part of the Crude and Adjusted Main Effects Models at Follow-up 18 Years in a Subsample of Children with Disruptive Behavior With Paternal and Maternal Internalizing and Paternal and Maternal Externalizing Disorders as Predictors

| | | Criminality | | Aggression | | Problems | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Violent (SR) | Nonviolent (SR) | Aggression (SR) | Aggression (PR) | Conseq. of antisocial behavior (SR) | Rule-break. (PR) | Emotional (PR) | Alcohol (SR) | Truancy (SR) | Poor school performance (Reg.) | Cumulative risk[a] |
| Predictor | Model | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) |
| Internalizing MD Father | 1 | 1.15 [0.51, 2.61] | 1.65 [0.68, 4.00] | 1.40 [0.64, 3.04] | 1.05 [0.50, 2.21] | 1.61 [0.76, 3.43] | 1.02 [0.39, 2.71] | 0.62 [0.25, 1.53] | 1.03 [0.42, 2.53] | **3.14**** [1.42, 6.95] | **2.46*** [1.05, 5.79] | 1.20 [0.93, 1.55] |
| | 2 | 1.08 [0.48, 2.44] | 1.55 [0.62, 3.85] | 1.34 [0.61, 2.94] | 0.99 [0.47, 2.10] | 1.57 [0.73, 3.40] | 1.01 [0.38, 2.70] | 0.64 [0.26, 1.58] | 0.98 [0.39, 2.45] | **3.13**** [1.41, 6.94] | **2.42*** [1.02, 5.73] | 1.18 [0.92, 1.52] |
| Internalizing MD Mother | 1 | 1.71 [0.87, 3.35] | 1.24 [0.60, 2.56] | 0.96 [0.46, 1.98] | 1.10 [0.64, 1.87] | 1.96 [0.99, 3.88] | 1.48 [0.77, 2.86] | 1.40 [0.76, 2.59] | 1.40 [0.67, 2.93] | 1.65 [0.78, 3.49] | 1.24 [0.54, 2.83] | 1.20 [0.98, 1.48] |
| | 2 | 1.49 [0.77, 2.89] | 1.12 [0.54, 2.33] | 0.83 [0.39, 1.76] | 1.12 [0.62, 2.00] | 1.80 [0.90, 3.62] | 1.37 [0.73, 2.58] | 1.20 [0.63, 2.29] | 1.21 [0.56, 2.63] | 1.64 [0.77, 3.46] | 1.14 [0.48, 2.73] | 1.14 [0.93, 1.40] |
| Externalizing MD Father | 1 | **4.87*** [1.42, 16.64] | **3.68*** [1.08, 12.52] | **2.57*** [1.11, 5.94] | 1.96 [0.76, 5.05] | 2.20 [0.81, 5.93] | 1.51 [0.49, 4.67] | 1.16 [0.44, 3.06] | **3.00*** [1.12, 8.07] | 1.44 [0.50, 4.19] | 2.00 [0.68, 5.87] | **1.50**** [1.26, 1.78] |
| | 2 | **4.10*** [1.19, 14.14] | 3.35 [0.94, 11.96] | 2.37 [0.95, 5.89] | 2.17 [0.82, 5.73] | 1.80 [0.62, 5.24] | 1.31 [0.48, 3.59] | 0.85 [0.26, 2.77] | 2.61 [0.98, 6.97] | 1.20 [0.38, 3.79] | 1.71 [0.54, 5.45] | **1.39**** [1.14, 1.71] |
| Externalizing MD Mother | 1 | 2.41 [0.80, 7.28] | 1.54 [0.45, 5.26] | 1.75 [0.62, 4.98] | 0.73 [0.32, 1.67] | 1.89 [0.59, 6.06] | 1.73 [0.59, 5.09] | **4.01*** [1.23, 13.04] | 2.38 [0.72, 7.82] | 1.21 [0.33, 4.52] | 1.57 [0.48, 5.21] | 1.35 [0.99, 1.86] |
| | 2 | 1.62 [0.54, 4.83] | 1.18 [0.36, 3.88] | 1.54 [0.47, 5.04] | 0.57 [0.21, 1.57] | 1.34 [0.42, 4.23] | 1.44 [0.55, 3.75] | **3.90*** [1.11, 13.69] | 1.82 [0.53, 6.26] | 1.01 [0.26, 3.94] | 1.34 [0.35, 5.12] | 1.19 [0.86, 1.65] |

Note: n = 1190. Model 1 = crude model including the control variables: gender child, parental education level, maternal age at birth, and paternal age at birth; Model 2 = adjusted model including maternal/paternal internalizing MD, maternal/paternal externalizing MD, and the same control variables as model 1. Internalizing MDs refers to having one or more disorders in one or more of the following disorders: anxiety, depressive, bipolar, OCD, eating, and post-traumatic stress, Externalizing MDs refers to having one or more disorders in one or more of the following disorders: substance abuse, behavior, and antisocial personality. CI = confidence interval; Conseq. = consequences; MD = mental disorder; *OR* = odd ratio; PR = parent-reported; Reg. = registry; Rule-break. = rule-breaking; SR = self-reported. Boldface values indicate statistical significance.

[a] Cumulative risk was predicted through negative binomial regressions.

*$p$ <.05; **$p$ <.01.

# SUPPLEMENT TO CHAPTER 3

Associations between anxiety, depression, and disruptive behavior spanning childhood and adolescence

## Chapter 3, Supplement 1. Additional information on measures

**Chapter 3, Table S1** Overview of Disruptive Behavior Items

| |
|---|
| Oppositional Defiant Disorder items |
| Gate items |
| Has there ever been a time when s/he would be angry to the extent that s/he cannot be reached? |
| Does s/he often argue with adults? |
| Does s/he often tease others by deliberately doing things that are perceived as provocative? |
| Is s/he easily offended, or disturbed by others? |
| Is s/he easily teased? |
| Additional items |
| Has there ever been a time when s/he would be angry to the extent that s/he is out of control without there being any particular triggering event? |
| Has there ever been a time when s/he would be angry to the extent that s/he is out of control in connection with changes? |
| Does s/he often lose temper? |
| Does s/he refuse following other people's directives? |
| Is s/he often vindictive or cruel? |
| Does s/he often treat significant others badly or without respect? |
| Does s/he often blame others for own mistakes or bad actions? |
| Conduct Disorder items |
| Gate items |
| Has s/he ever deliberately been physically cruel to anybody? |
| Does s/he often start fights? |
| Does s/he often lie or cheat? |
| Does s/he steal things at home or outside home? |
| Has s/he ever engaged in shoplifting? |
| Additional items |
| Does s/he often threaten, harass or humiliate others? |
| Is s/he cruel to insects? |
| Is s/he cruel to other animals? |
| Has s/he ever started a fire? |

**Chapter 3, Table S1** Continued.

| |
|---|
| Has s/he ever sexually abused other children? |
| Has s/he ever been detained by the police? |
| Has s/he ever used a deadly weapon? |
| Has s/he ever robbed anyone or else unlawfully acquired other people's property by means of directs threats? |
| Has s/he ever purposely attempted to destroy other people's property? |
| Has s/he ever broken into someone else's home, premises or car? |
| Is s/he often out late at night without consent (beginning before 13 years of age)? |
| Has s/he ever ran away from home and stayed away over night at least two times (or one time if it was for an extended period of time)? |
| Is s/he often absconding (beginning before 13 years of age)? |

*Note*. The additional items were administered if the parents endorsed one or more of the gate items with "yes to some extent" or "yes".

## Disruptive behavior at age 15 years

### *Self-reported aggression*

Aggressive behavior was assessed using the 23-item Reactive and Proactive Aggression Questionnaire (RPQ).(Raine et al., 2006) The RPQ includes 11 items that focus on reactive aggression (e.g., "Reacted angrily when provoked by others", "Gotten angry when frustrated"), and 12 items that focus on proactive aggression (e.g., "Had fights with others to show who was on top", "Taken things from other students"). The items are coded as 0 ("never"), 1 ("sometimes"), or 2 ("often").

### *Self-reported crime*

The Self-reported Delinquency Scale (SRD)(Ring, 1999) was used to assess the frequency of 13 non-violent criminal acts (e.g., vandalism, car theft, burglary, drug dealing) and nine violent criminal acts (e.g., hurting persons, hurting animals, sexual offenses). Each item is coded on a 6-point Likert scale, ranging from 0 ("never") to 5 ("more than 10 times").

### *Parent- and self-reported conduct problems*

Conduct problems of the twin were assessed using the Conduct Problems subscale of the Strengths and Difficulties Questionnaire (SDQ).(Goodman, 1997) SDQ items (e.g., "Often has temper tantrums or hot tempers") scored on this and the other SDQ scales mentioned below range from 0 ("not true"), 1 ("somewhat true") and 2 ("certainly true").

***Bullying perpetration***

The Bullying Perpetration subscale of the Revised Olweus Bully/Victim Questionnaire (OBVQ; Olweus, 1996) was used to measure self-reported bullying behavior (Solberg and Olweus, 2003). The scale consists of nine questions covering various types of bullying behaviors (e.g., "I called another student(s) mean names and made fun of or teased him or her in a hurtful way."). Answers ranged from 1 ("It has not happened in the last couple of months") to 5 ("Several times a week"). In line with prior work (Solberg and Olweus, 2003), being a bully perpetrator was defined as answering one or more of these questions with a 3 or higher ("2 or 3 times a month").

**Disruptive behavior at age 18 years**

***Self-reported aggression***

Aggression was assessed using the 11-item Aggression subscale of the Life History of Aggression Questionnaire.(Coccaro et al., 1997) Youth were asked how many times in their lives they had committed certain aggressive acts (e.g., "Gotten into verbal fights or arguments with other people"). Answers were given on a 6-point Likert scale ranging from 0 ("no event") to 5 ("more times than I can count").

***Self-reported crime***

Self-reported crime was assessed using the same Self-reported Delinquency Scale as at age 15 years (see outcome measures at age 15).

***Self-reported consequences of antisocial behavior***

The 4-item Consequences of Antisocial Behavior subscale of the Life History of Aggression Questionnaire measures social consequences due to antisocial behavior of the reporter (e.g., "Had discipline problems in schools that resulted in a reprimand by the school principal or in suspensions or expulsion").

***Parent-reported aggression***

Aggression was assessed by means of the 16-item Aggressive Behavior subscale of the Adult Behavior Checklist (ABCL)(Achenbach & Rescorla, 2003) parent version. Parents rated aggression of their twin over the last 6 months (e.g., "Physically attacks people" and "Argues a lot") on a 3-point Likert scale ranging from 0 ("not true") to 2 ("very true or often true").

***Parent-reported rule-breaking behavior***

Rule-breaking behavior was assessed by the 13-item ABCL Rule-breaking Behavior subscale (e.g., "Breaks rules at work or elsewhere" or "Lying or cheating").

## Chapter 3, Supplement 2. Analyses with dichotomous measures of anxiety and depression

At baseline 9, crude models indicated that anxiety (IRR = 3.63; 95% CI: 3.39), and depressive disorders (IRR = 4.18; 95% CI: 3.93, 4.45), as well as 3.89), were significantly related to DB ($p$'s < .001). When included simultaneously in an adjusted model, both anxiety (IRR = 2.35; 95% CI: 2.16, 2.56), and depressive disorders (IRR = 3.19; 95% CI: 2.96, 3.44) retained their associations with DB ($p$'s < .001).

Longitudinally, crude models indicated that DB at 9 years was predictive ($p$'s < .001) of DB at 15 (IRR = 1.11; 95% CI: 1.09, 1.13) and 18 years (IRR = 1.17; 95% CI: 1.03, 1.06). Similar crude models indicated no significant predictive effects on DB for anxiety disorders at 15 and 18 years. For depressive disorders significant predictive effects were found on DB at 15 (IRR = 1.33; 95% CI: 1.09, 1.63; $p$ = .006) and 18 years (IRR = 1.75; 95% CI: 1.29, 2.38; $p$ < .001).

When DB, anxiety, and depressive disorders at 9 years were included simultaneously in one model, DB retained its predictive associations ($p$'s < .001) with DB on 15 years (IRR = 1.09; 95% CI: 1.08, 1.10), and 18 years (IRR = 1.09; 95% CI: 1.06, 1.12). Both anxiety and depressive disorders lost their association with DB at 15 years and age 18 years. Interaction models did not indicate significant interactions between DB and anxiety and depressive disorders at 15 years, and for anxiety disorders at 18 years. At 18 years, a significant interaction emerged between depressive disorders and DB (IRR = 0.88; 95% CI: 0.81, 0.96), however it should be noted that this interaction was underpowered (i.e., only seven 18-year-olds had a depression at baseline 9 years vs. 779 without a depression).

# SUPPLEMENT TO CHAPTER 4

## Classes of oppositional defiant disorder behavior in clinic-referred children and adolescents: concurrent features and outcomes

**Chapter 4, Table S1** Oppositional Defiant Behavior Items of the Development and Well-Being Assessment (DAWBA)

| Dimensions | Parent-version | Teacher-version |
|---|---|---|
| Irritable | Had temper outbursts? | Temper tantrums or hot tempers |
| | Been touchy or easily annoyed? | Easily annoyed by others |
| | Been angry and resentful? | Angry and resentful |
| Oppositional | Seemed to do things to annoy other people on purpose? | Deliberately does things to annoy others |
| | Blamed others for his/her own mistakes or bad behaviour? | Blames others for his/her own mistakes |
| | Argued with grown-ups? | Argues a lot with adults |
| | Taken no notice of rules, or refused to do as s/he is told? | Disobedient at school |
| | Been spiteful? | Spiteful |
| | Tried to get back at someone | Tried to get back at someone |

**Chapter 4, Table S2** Steps in the Symptom-based ODD behavior Latent Class Analysis in Children Aged 5 through 11 (n = 1499)

| Analysis | LL | BIC | BIC (sample adjusted) | AIC | Entropy | Bootstrap p-value |
|---|---|---|---|---|---|---|
| 1-class | -8973.139 | 18026.717 | 17991.773 | 17968.279 | | |
| 2-class | -6446.922 | 13040.095 | 12976.560 | 12933.844 | 0.847 | |
| 2-class (corrected for bivariate residuals) | Model did not converge | | | | | |
| 2-class (corrected for bivariate residuals) no sex | | | | | | |
| 3-class | -6190.631 | 12607.951 | 12509.473 | 12443.262 | 0.822 | |
| 3-class (corrected for bivariate residuals) | -6101.663 | 12481.203 | 12360.488 | 12279.326 | 0.786 | |
| 3-class (corrected for bivariate residuals) no sex | -6105.268 | 12473.788 | 12359.426 | 12282.536 | 0.789 | <.001 |
| 4-class | -6148.064 | 12603.255 | 12469.833 | 12380.128 | 0.788 | |
| 4-class (corrected for bivariate residuals) | -6096.880 | 12537.450 | 12388.144 | 12287.760 | 0.760 | |
| 4-class (corrected for bivariate residuals) no sex | -6101.081 | 12523.915 | 12384.140 | 12290.163 | 0.752 | <.001 |
| 5-class | -6112.966 | 12613.498 | 12445.132 | 12331.933 | 0.752 | |

*Note.* AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; LL = Log-likelihood

**Chapter 4, Table S3** Steps in the Symptom-based ODD behavior Latent Class Analysis in Children Aged 12 through 18 (n = 686)

| Analysis | LL | BIC | BIC (sample adjusted) | AIC | Entropy | Bootstrap p-value |
|---|---|---|---|---|---|---|
| 1-class | -4200.938 | 8473.717 | 8438.790 | 8423.877 | | |
| 2-class | -2914.504 | 5959.626 | 5896.123 | 5869.008 | 0.865 | |
| 2-class (corrected for bivariate residuals) | -2736.718 | 5675.893 | 5577.464 | 5535.436 | 0.868 | |
| 2-class (corrected for bivariate residuals) no sex | -2736.730 | 5669.387 | 5574.133 | 5533.461 | 0.866 | <.001 |
| 3-class | -2788.057 | 5778.571 | 5680.141 | 5638.114 | 0.838 | |
| 3-class (corrected for bivariate residuals) | -2720.288 | 5688.749 | 5568.093 | 5516.576 | 0.798 | |
| 3-class (corrected for bivariate residuals) no sex | -2720.447 | 5676.005 | 5561.700 | 5512.893 | 0.794 | <.001 |
| 4-class | -2756.396 | 5787.089 | 5653.733 | 5596.792 | 0.797 | |
| 4-class (corrected for bivariate residuals) | | | | | | |
| 4-class (corrected for bivariate residuals) no sex | | | | | | |
| 5-class | -2730.075 | 5806.287 | 5638.004 | 5566.150 | 0.821 | |

*Note.* AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; LL = Log-likelihood

**Chapter 4, Table S4** Steps in the Symptom-based ODD Behavior Latent Class Analysis

| Analysis | LL | BIC | BIC (sample adjusted) | AIC | Entropy | Bootstrap p-value |
|---|---|---|---|---|---|---|
| 1-class | -18918.397 | 37936.757 | 37895.454 | 37862.795 | | |
| 2-class | -9412.654 | 18986.786 | 18920.066 | 18867.309 | 0.850 | |
| 2-class (corrected for bivariate residuals) | | | | | | |
| 2-class (corrected for bivariate residuals) age-only | | | | | | |
| 2-class (corrected for bivariate residuals) sex-only | | | | | | |
| 2-class (corrected for bivariate residuals) no covariates | | | | | | |
| 3-class | -9044.693 | 18343.135 | 18238.289 | 18155.386 | 0.816 | |

**Chapter 4, Table S4** Continued.

| Analysis | LL | BIC | BIC (sample adjusted) | AIC | Entropy | Bootstrap p-value |
|---|---|---|---|---|---|---|
| 3-class (corrected for bivariate residuals) | | | | | | |
| 3-class (corrected for bivariate residuals) age-only | | | | | | |
| 3-class (corrected for bivariate residuals) sex-only | | | | | | |
| 3-class (corrected for bivariate residuals) no covariates | | | | | | |
| 4-class | -8965.953 | 18277.927 | 18134.956 | 18021.906 | 0.861 | |
| 4-class (corrected for bivariate residuals) | | | | | | |
| 4-class (corrected for bivariate residuals) age-only | | | | | | |
| 4-class (corrected for bivariate residuals) sex-only | | | | | | |
| 4-class (corrected for bivariate residuals) no covariates | | | | | | |
| 5-class | -8909.591 | 18257.476 | 18076.379 | 17933.181 | 0.792 | |
| 5-class (corrected for bivariate residuals) | -8832.732 | 18172.963 | 17963.272 | 17797.464 | 0.745 | |
| 5-class (corrected for bivariate residuals) age-only | -8837.797 | 18152.336 | 17955.353 | 17799.595 | 0.743 | 0.2174 |
| 5-class (corrected for bivariate residuals) sex-only | -8863.570 | 18203.881 | 18006.898 | 17851.140 | 0.750 | |
| 5-class (corrected for bivariate residuals) no covariates | -8878.032 | 18202.048 | 18017.774 | 17872.065 | 0.708 | |
| 6-class | -8879.034 | 18288.634 | 18069.411 | 17896.067 | 0.775 | |

*Note.* AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; LL = Log-likelihood.

**Chapter 4, Table S5** Steps in the DSM-based ODD Latent Class Analysis

| Analysis | LL | BIC | BIC (sample adjusted) | AIC | Entropy | Bootstrap p-value |
|---|---|---|---|---|---|---|
| 1-class | -19997.511 | 40094.984 | 40053.681 | 40021.022 | | |
| 2-class | -8823.071 | 17807.618 | 17740.898 | 17688.142 | 0.917 | |
| 2-class (corrected for bivariate residuals) | Model did not converge | | | | | |
| 2-class (corrected for bivariate residuals) age-only | | | | | | |
| 2-class (corrected for bivariate residuals) sex-only | | | | | | |
| 2-class (corrected for bivariate residuals) no covariates | | | | | | |
| 3-class | -8159.108 | 16571.965 | 16467.119 | 16384.216 | 0.899 | |
| 3-class (corrected for bivariate residuals) | -7988.821 | 16339.042 | 16189.717 | 16071.642 | 0.832 | |
| 3-class (corrected for bivariate residuals) age-only | -7995.788 | 16337.598 | 16194.627 | 16081.577 | 0.821 | |
| 3-class (corrected for bivariate residuals) sex-only | -7989.519 | 16325.059 | 16182.088 | 16069.037 | 0.820 | |
| 3-class (corrected for bivariate residuals) no covariates | -7996.763 | 16324.168 | 16187.551 | 16079.525 | 0.821 | <.001 |
| 4-class | -8067.291 | 16480.604 | 16337.633 | 16224.582 | 0.851 | |
| 4-class (corrected for bivariate residuals) | -7998.807 | 16389.771 | 16227.737 | 16099.614 | 0.835 | |
| 4-class (corrected for bivariate residuals) age-only | -8005.390 | 16379.870 | 16227.368 | 16106.781 | 0.834 | |
| 4-class (corrected for bivariate residuals) sex-only | -7999.153 | 16367.396 | 16214.893 | 16094.306 | 0.833 | |
| 4-class (corrected for bivariate residuals) no covariates | -8006.650 | 16359.322 | 16216.351 | 16103.300 | 0.832 | <.001 |
| 5-class | -8015.251 | 16468.797 | 16287.700 | 16144.503 | 0.829 | |
| 5-class (corrected for bivariate residuals) | -7978.415 | 16433.571 | 16236.589 | 16080.830 | 0.816 | |
| 5-class (corrected for bivariate residuals) age-only | -7985.638 | 16417.259 | 16232.985 | 16087.275 | 0.805 | |
| 5-class (corrected for bivariate residuals) sex-only | -7982.488 | 16410.959 | 16226.685 | 16080.976 | 0.815 | |
| 5-class (corrected for bivariate residuals) no covariates | -7991.713 | 16398.652 | 16227.086 | 16091.426 | 0.808 | <.001 |
| 6-class | -7980.686 | 16491.939 | 16272.716 | 16099.372 | 0.827 | |

*Note.* AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; LL = Log-likelihood.

**Chapter 4, Table S6** Means and Standard Deviations of the DSM-based ODD Classes on Highest Prevailing Parent- and Teacher-reported SDQ Scores

| | ODD classes | | |
|---|---|---|---|
| | High ODD | Moderate ODD | Low ODD |
| | (n = 565) | (n = 693) | (n = 906) |
| SDQ Total Problems (SD) | 23.29 (5.28) | 20.51 (4.83) | 18.28 (4.71) |
| SDQ Emotional Problems (SD) | 6.05 (2.57) | 5.69 (2.55) | 5.75 (2.50) |
| SDQ Conduct Problems (SD) | 5.75 (1.90) | 4.21 (1.70) | 3.28 (1.66) |
| SDQ Hyperactivity (SD) | 7.77 (2.14) | 7.39 (2.25) | 6.51 (2.53) |
| SDQ Peer Problems (SD) | 4.55 (2.20) | 4.05 (2.28) | 3.55 (2.16) |
| SDQ Prosocial (SD) | 6.27 (1.99) | 7.00 (1.97) | 7.57 (1.83) |

*Note.* N = 2164. SDQ = strengths and difficulties questionnaire.

**Chapter 4, Table S7** Prevalence of DAWBA Classifications of the DSM-based Oppositional Defiant Disorder Classes

| | ODD classes | | |
|---|---|---|---|
| | High ODD | Moderate ODD | Low ODD |
| | (n = 565) | (n = 693) | (n = 906) |
| ODD [n(% of class)] | 493 (87.3%) | 388 (56.0%) | 78 (8.6%) |
| CD [n(% of class)] | 154 (27.3%) | 43 (6.2%) | 22 (2.4%) |
| ADHD [n(% of class)] | 318 (56.3%) | 314 (45.3%) | 216 (23.8%) |
| Depressive disorders [n(% of class)] | 102 (18.1%) | 93 (13.4%) | 138 (15.2%) |
| Generalized anxiety [n(% of class)] | 114 (20.2%) | 107 (15.4%) | 134 (14.8%) |
| Fear disorders [n(% of class)] | 131 (23.2%) | 136 (19.6%) | 184 (20.3%) |
| Autism spectrum disorders [n(% of class)] | 39 (6.9%) | 36 (5.2%) | 24 (2.6%) |

*Note.* N = 2164. ADHD = attention deficit hyperactivity disorder; CD = conduct disorder; ODD = oppositional defiant disorder.

**Chapter 4, Table S8** Prevalence of Clinical Classifications of the DSM-based Oppositional Defiant Disorder Classes

| | ODD class | | |
|---|---|---|---|
| | High ODD | Moderate ODD | Low ODD |
| | (n = 540) | (n = 653) | (n = 848) |
| ODD [n(% of class)] | 78 (14.4%) | 57 (8.7%) | 42 (5.0%) |
| CD [n(% of class)] | 41 (7.6%) | 15 (2.3%) | 13 (1.5%) |
| ADHD [n(% of class)] | 206 (38.1%) | 249 (38.1%) | 300 (35.4%) |
| Depressive disorders [n(% of class)] | 34 (6.3%) | 38 (5.8%) | 65 (7.7%) |
| Generalized anxiety [n(% of class)] | 13 (2.4%) | 23 (3.5%) | 56 (6.6%) |
| Fear disorders [n(% of class)] | 7 (1.3%) | 15 (2.3%) | 39 (4.6%) |
| Autism spectrum disorder [n(% of class)] | 131 (24.3%) | 169 (25.9%) | 186 (21.9%) |

*Note.* N = 2041. ADHD = attention deficit hyperactivity disorder; CD = conduct disorder; ODD = oppositional defiant disorder.

## Chapter 4, Supplement 1. Detailed measures

### Clustering Variables

ODD symptoms were measured by the Dutch parent and teacher versions of the DAWBA, a widely-used computerized diagnostic interview which generates DSM-IV classifications. The parent version of the DAWBA has a gate-item which inquires if the child had exhibited any ODD-related symptoms in the last six months (i.e., "Not doing what they are told, being irritable or annoying, having temper outbursts, and so on"). The response on this gate item ranges from 0 (on average less difficult or problematic than other children), to 1 (about average) to 2 (on average more difficult or more problematic). If the parent endorses this gate-item with a 2, the ODD part of the DAWBA is activated, which inquires after the occurrence of the eight DSM-IV ODD symptoms in the last six months. The ODD part of the DAWBA is also activated when the parent indicates a score of 3 or higher on the SDQ conduct problems scale, which consists of five questions, and which is an integral part of the DAWBA. The teacher version of the DAWBA always directly asks teachers about all eight DSM-IV ODD symptoms. Of note, the Dutch version of the DAWBA separates the original DSM criterion of "vindictive and spiteful" into two different questions (see Table S1), resulting in a total of nine ODD symptoms. Assessment of impairment and persistence is considered a crucial diagnostic criterion for identifying individuals whose psychiatric disorders are of clinical significance.

Therefore, the DAWBA also asks parents and teachers whether ODD symptoms have resulted in impairment in various developmental contexts (e.g., "Has his/her awkward behavior interfered with making and keeping friends") and whether these symptoms have been present for more than 6 months. The impairment questions are rated from 0 ("Not at all") to 3 ("A great deal") and the persistence question is rated by 0 ("No") or 1 ("Yes").

Whereas prior research on ODD classes merely considered if ODD symptoms were present or absent (from here onwards referred to as the *symptom approach*), the present study also considered symptom persistence (6 months ≤) and impairment (from here onwards referred to as the *DSM app*roach). Specifically, according to this first approach an ODD symptom was coded as 1 ("behavior present") when endorsed as 1 ("A little more than others") or higher (2: "A lot more others"), while a score of 0 ("Not more often than others") was dichotomized as 0 ("behavior absent") (0 = 0; 1, 2 = 1). For the DSM approach, more stringent criterion for ODD presence were used; a symptom was coded as 1 ("behavior present") when endorsed as 2 ("A lot more than others"), while lower scores were coded as 0 ("behavior absent") (0, 1 = 0; 2 = 1). In addition, the reported ODD symptom was required to be present for six months or longer, and to cause impairment according to parent- and/or teacher-ratings. In both the symptom and DSM-approach parent- and teacher-ratings were combined by using highest prevailing scores (i.e., if at least one informant indicated an ODD behavior to be present, the behavior was indicated as present). Finally, the nine DAWBA ODD symptoms will be used as clustering variables in the person-oriented analyses (i.e., latent class analysis) to assign youths to mutually exclusive classes.



## External variables for cluster comparisons: concurrent features at referral

### *Dimensionally assessed mental health and other problems*

The SDQ is a brief screening questionnaire that was completed as part of the DAWBA. The SDQ consists of 25 items which are scored on a 3-point Likert scale 0 ("not true"), 1 ("somewhat true") and 2 ("certainly true"), and is subdivided in 5 subscales: Conduct Problems, Emotional Problems, Hyperactivity, Peer Problems, and Prosocial Behavior. The Total Problems scale consists of all SDQ items, minus the Prosocial Behavior scale. Because items of the Conduct Problems scale were used as gate items for the ODD symptoms, this scale was

not used in class comparisons. Highest prevailing scores of parent-, teacher-, and, if applicable -youth self-report were used in the subsequent analyses.

***Categorically assessed mental health problems***

The DAWBA reports of parents, teachers, and youths who were at least 11 years of age, were used to generate *computer-generated DSM classifications* at referral. These classifications are based on predictions on the probability of the presence of various mental disorders. For each disorder, five categories are given, ranging from 0 (0.1 % of children in this category have the disorder in question) to 5 (70% of children in this category have the disorder in question). The categories were dichotomized into a "disorder absent" category ranging from values 0 to 3 (15% of children in this category have the disorder in question) and a "disorder present" category spanning values 4 (50% of children in this category have the disorder in question) and 5 (Goodman et al., 2011). To ease the interpretation of the results, and in line with previous recommendations (Stringaris & Goodman, 2009a), several DAWBA computer-generated DSM classifications were combined into disorder categories, from here onwards referred to as *DAWBA computer-generated DSM disorder categories*. Specifically, the category "depressive disorders" refers to the presence of major depressive disorder, dysthymic disorder, and/or depressive disorder not otherwise specified, whereas the category "fear disorders" refers to the presence of separation anxiety disorder, panic disorder, agoraphobia specific, and/or social phobia.

## External variables for cluster comparisons: longitudinal features

***Categorically assessed mental health problems***

Psychiatric disorders, as defined by the DSM-IV, were determined at the end of a diagnostic process consisting of multidisciplinary psychiatric and psychological (semi-structured) evaluation conform clinical diagnostic guidelines by psychiatrists and psychologists. These evaluations took place on average 3.81 months (SD = 3.34) after completion of the DAWBA at referral. Any clinical classification, not just primary classifications, were included in the analyses. This was done to optimally use the classifications provided by the multidisciplinary team and because the DAWBA also provides multiple classifications per individual. From here onward, we refer to these disorders and disorder categories as *Multidisciplinary Team-based Classifications of DSM Disorders and Disorder Categories*.

***Global functioning***

DSM-based Global Assessment Functioning (GAF) scores give an indication of social, occupational, and psychological functioning of an individual, with a

score of "100" indicating extremely high functioning, while "1" indicates severe impairment (e.g., persistent danger of severely hurting self or others, suicidal acts). General functioning of the youth at the beginning and end of treatment was measured through clinician-rated GAF scores.

## Chapter 4, Supplement 2. Latent class analysis model selection

The following steps were taken to select the best fitting latent class solution. First, models were selected on the basis of the Bayesian Information Criterion (BIC), which is considered to be the most reliable index of model fit in LCA after non-parametric bootstrapping.(Nylund, Asparouhov, & Muthén, 2007) Although other indices of model fit were also studied, including: entropy, loglikelihood, Akaike information criterion (AIC). In the second step, to control for local independence, the Pearson chi-squared test of model fit was used to determine if main effects between items should be included in the model. When the Pearson chi-squared test of model fit indicated significance ($p < .05$), the item-pair with the highest bivariate residuals was included as a direct effect (e.g., the item-pair vindictive and spiteful), and the model rerun. This process was repeated until the Pearson chi-squared index indicated non-significance.(Asparouhov & Muthén, 2015) The third step focussed on the influence of the covariates age and gender on the model, which was investigated by deleting the covariates in a stepwise manner. If exclusion of a covariate(s) resulted in a better model fit, the better fitting model was included in consequent analyses. The fourth step consisted of estimating model fit through non-parametric bootstrapping. The number of random starts perturbations varied per solution and was in each example increased until the best loglikelihood was replicated during the bootstrap runs. If a p-value was greater than .05 (indicating model fit) the model was chosen. When the p-value was lower than .05, the next most appropriate model was fitted, starting with step two.

### Symptom-based latent class analysis: stability of age covariate

Because the symptom-based Latent Class Solution required age as a covariate, the robustness of age was investigated. This was done by running separate LCA's on two age groups: 11 years or younger (n = 1499), and 12 years or older (n = 686). Unfortunately, the five factor solution did not hold up with three classes found in the younger group and two-class solutions in the older group. Specifically, separate LCAs extracted three classes in children aged 11 or younger (n = 1499), and two classes in adolescents aged 12 or older (n = 686; see Tables S2-S3).

# SUPPLEMENT TO CHAPTER 5

Genomics of human aggression: current state of genome-wide studies and an automated systematic review tool

**Chapter 5, Supplement S1** Definitions of Aggression in Reviews

| Concept | Definitions | References |
|---|---|---|
| Reactive/hostile/ affective/impulsive aggression | Angry or frustrated responses to a real or perceived threat (Tuvbald,Baker, 2011)<br>Aggressive response to a perceived threat or provocation (Waltes et al., 2015) | Tuvblad&Baker, 2011<br>Craig et al, 2009;<br>Waltes et al, 2015 |
| Proactive/ instrumental/pre-mediated aggression | Planning, the motive of the act extends beyond harming the victim (Tuvbald,Baker, 2011)<br>Planned antisocial behaviour that anticipates a reward or dominance over others (Waltes et al., 2015) | |
| Direct/physical aggression | Intentionally causing pain or harm to the victim | Tuvblad&Baker, 2011 |
| Indirect/relational aggression | Relational social manipulation such as gossip and peer exclusion | |
| Chronic physical aggression | Tendency to use physical aggression more frequently than the large majority of a birth cohort over many years | Tremblay et al, 2018;<br>Provencal et al., 2015 |
| Externalizing behaviour | Behavior that directs problematic energy outward and is expressed as aggression, defiance, bullying, vandalism, theft, and other socially unacceptable actions | Anholt&Mackay, 2012<br>Dick et al, 2016 |
| Aggression and anger-related traits associated with suicidal behaviour | Anger can be conceptualized as a core construct of related traits or variables inwardly and/or outwardly expressed such as aggression, rage, and hostility (Spielberger et al, 1985 cite: Baud, 2005)<br>Aggression and anger-related traits are considered risk factors for suicidal behaviour | Baud, 2005 |
| Aggression related phenotype | A dimensional trait including externalizing behaviour, anger, delinquency, criminality, violence or a diagnostic category (conduct disorder, oppositional defiant disorder, callous unemotional, and antisocial personality) | Fernandez-Castillo, Cormand, 2016 |

| Concept | Definitions | References |
|---|---|---|
| Frustrative non-reward aggression | Behaviours that correspond to the withdrawal or prevention of reward | RDoC nomenclature Veroude et al, 2015 |
| Defensive aggression | Behaviors caused by the perception of an immediate threat, which have the goal of eliminating the threat | |
| Offensive (or proactive) aggression | Instrumental behaviors aimed at achieving a positive goal, often in the face of competition or in the context of social hierarchies | |
| Aggression as behavior category in conduct disorder (CD) | CD is a developmental disorder characterized by a consistent pattern of externalizing behavior, developing during childhood or adolescence, where an individual displays aggression toward people or animals, destroys property, exhibits deceit by lying or stealing, and/or seriously violates societal rules or norms (DSM-V)<br>Conduct disorder is a psychiatric disorder of childhood and adolescence characterized by aggression toward people and animals, destruction of property, deceitfulness or theft, and serious violation of rules (Salvatore & Dick, 2018) | DSM-V<br>Salvatore et al, 2018 |
| Antisocial behaviour | Refers to actions that violate social norms in ways that reflect the violation of others' rights | Moffit, 2005; Gard et al, 2018 |
| Aggression as violence | *No definition is given* | Vassos et al, 2014 |

## Chapter 5, Supplement S2. Search terms used to extract papers from databases

Search terms are reported for each subject and database respectively.

### *Pubmed*

Searchterms for reviews on genetics of aggression:
((“Aggression/genetics”[Mesh] OR ((“genetics”[tiab] OR “Genetic Techniques”[mesh] OR “Genetic Phenomena”[mesh] OR “Genes”[mesh] OR “genes”[tiab] OR “gene”[tiab] OR “heredity”[tiab] OR “hereditary”[tiab] OR “Epigenomics”[mesh] OR epigenetic*[tiab] OR “Polymorphism, Genetic”[mesh] OR polymorphism*[tiab] OR “Genotype”[mesh] OR genotype*[tiab] OR “Genome”[mesh] OR genome*[tiab] OR “systems genetics approach”[tiab] OR “systems genetics”[tiab] OR “Genome-Wide Association Study”[Mesh] OR “genome wide association”[tw] OR “genomic wide association”[tw] OR “GWA Study”[tw] OR “GWA Studies”[tw] OR “GWAS”[tw] OR “GWASs”[tw] OR “epigenome wide association”[tw] OR ((“genome wide”[tw] OR “genomic wide”[tw]) AND “association”[tiab]) OR “genetic association”[tw] OR “Genetic Association Studies”[Mesh] OR “candidate genes”[tw] OR “candidate gene”[tw] OR “candidates genes”[tw] OR “SNP”[tw] OR “SNPS”[tw] OR “Polymorphism, Single Nucleotide”[Mesh] OR “single nucleotide polymorphisms”[tw] OR “single nucleotide polymorphism”[tw] OR “Polymorphism, Genetic”[Mesh] OR “Genetic Polymorphisms”[tw] OR “Genetic Polymorphism”[tw] OR “Genomic Structural Variation”[tw] OR “DNA Copy Number Variations”[tw] OR “Pharmacogenomic Variants”[tw] OR “Restriction Fragment Length Polymorphism “[tw] OR “Single-Stranded Conformational Polymorphism “[tw] OR “Genomic Structural Variations”[tw] OR “DNA Copy Number Variation”[tw] OR “Pharmacogenomic Variant”[tw] OR “Restriction Fragment Length Polymorphisms”[tw] OR “Single-Stranded Conformational Polymorphisms”[tw]) AND (“Aggression”[mesh:noexp] OR “aggression”[tiab] OR aggression*[tiab] OR “aggressive behavior”[tiab] OR “aggressive behaviour”[tiab] OR “aggressive behaviors”[tiab] OR “aggressive behaviours”[tiab] OR aggressive behavi*[tiab] OR “Anger”[mesh] OR “anger”[tiab] OR “Rage”[mesh] OR “angry”[tiab] OR “Hostility”[mesh] OR “hostility”[tiab] OR “hostile”[tiab] OR “Violence”[mesh:noexp] OR “violence”[tiab] OR “violent”[tiab] OR (violen*[tiab] AND (crime*[tiab] OR crimin*[tiab])) OR (aggress*[tiab] AND (crime*[tiab] OR crimin*[tiab])) OR

aggressive trait*[tiab] OR "hyperaggression"[tiab] OR hyperaggress*[tiab] OR "oppositional defiant disorder"[tiab] OR "oppositional defiant"[tiab] OR oppositional defiant*[tiab] OR "conduct disorder"[tiab] OR "conduct disorders"[tiab] OR conduct disorder*[tiab] OR "Antisocial Personality Disorder"[mesh] OR "antisocial personality disorder"[tiab] OR "antisocial personality disorders"[tiab] OR "anti-social personality disorder"[tiab] OR "anti-social personality disorders"[tiab] OR (aggressi*[tiab] AND ("proactive"[tiab] OR "reactive"[tiab] OR "impulsive"[tiab] OR "physical"[tiab])))) NOT ("Animals"[mesh] NOT "Humans"[mesh]) NOT ("Neoplasms"[mesh] OR "cancer"[tw] OR "tumour"[tw] OR "tumours"[tw] OR "tumor"[tw] OR "tumors"[tw] OR "aggressive treatment"[tiab] OR ("Mental Disorders"[mesh] NOT ("Attention Deficit and Disruptive Behavior Disorders"[Mesh] OR "Conduct Disorder"[Mesh] OR "Antisocial Personality Disorder"[Mesh])) OR "Nervous System Diseases"[mesh] OR "Congenital, Hereditary, and Neonatal Diseases and Abnormalities"[Mesh]) AND ("Review"[ptyp] OR "review"[tw] OR review*[tw] OR overview*[tw] OR "systematic"[sb]))

Searchterms for genome-wide studies:
(("Genome-Wide Association Study"[Mesh] OR "genome wide association"[tw] OR "genomic wide association"[tw] OR "GWA Study"[tw] OR "GWA Studies"[tw] OR "GWAS"[tw] OR "GWASs"[tw] OR "epigenome wide association"[tw] OR (("genome wide"[tw] OR "genomic wide"[tw]) AND "association"[tiab]) OR "genetic association"[tw] OR "Genetic Association Studies"[Mesh]) AND ("Aggression"[Mesh:noexp] OR "aggression"[tw] OR aggression*[tw] OR "aggressive behavior"[tw] OR "aggressive behaviour"[tw] OR "aggressive behaviors"[tw] OR "aggressive behaviours"[tw] OR aggressive behavi*[tw] OR "Anger"[mesh] OR "anger"[tw] OR "rage"[mesh] OR "angry"[tw] OR "Hostility"[mesh] OR "hostility"[tw] OR "hostile"[tw] OR "Violence"[Mesh:noexp] OR "violence"[tw] OR "violent"[tw] OR (violen*[tw] AND (crime*[tw] OR crimin*[tw])) OR (aggress*[tw] AND (crime*[tw] OR crimin*[tw])) OR aggressive trait*[tw] OR "hyperaggression"[tw] OR hyperaggress*[tw] OR "oppositional defiant disorder"[tw] OR "oppositional defiant"[tw] OR oppositional defiant*[tw] OR "conduct disorder"[tw] OR "conduct disorders"[tw] OR conduct disorder*[tw] OR "Antisocial Personality Disorder"[Mesh] OR "antisocial personality disorder"[tw] OR "antisocial personality disorders"[tw] OR "anti-social personality disorder"[tw] OR "anti-

social personality disorders"[tw] OR (aggressi*[tw] AND ("proactive"[tw] OR "reactive"[tw] OR "impulsive"[tw] OR "physical"[tw]))) NOT ("Animals"[mesh] NOT "Humans"[mesh]))

***Embase***

Searchterms for reviews on genetics of aggression:
(("genetics".ti,ab OR exp *"genetics"/ OR exp *"Genetic Procedure"/ OR exp *"Heredity"/ OR exp *"molecular genetic phenomena and functions"/ OR exp *"Gene"/ OR "genes".ti,ab OR "gene".ti,ab OR "heredity".ti,ab OR "hereditary".ti,ab OR *"Epigenetics"/ OR epigenetic*.ti,ab OR exp *"Genetic Polymorphism"/ OR polymorphism*.ti,ab OR exp *"Genotype"/ OR genotype*.ti,ab OR exp "Genome"/ OR genome*.ti,ab OR "systems genetics approach".ti,ab OR "systems genetics".ti,ab OR *"Genome-Wide Association Study"/ OR "genome wide association".mp OR "genomic wide association". mp OR "GWA Study".mp OR "GWA Studies".mp OR "GWAS".mp OR "GWASs".mp OR "epigenome wide association".mp OR (("genome wide".mp OR "genomic wide".mp) AND "association".ti,ab) OR "genetic association".mp OR *"Genetic Association Study"/ OR "candidate genes".mp OR "candidate gene".mp OR "candidates genes".mp OR "SNP".mp OR "SNPS".mp OR *"Single Nucleotide Polymorphism"/ OR "single nucleotide polymorphisms". mp OR "single nucleotide polymorphism".mp OR exp *"DNA Polymorphism"/ OR "Genetic Polymorphisms".mp OR "Genetic Polymorphism".mp OR "Genomic Structural Variation".mp OR "DNA Copy Number Variations". mp OR "Pharmacogenomic Variants".mp OR "Restriction Fragment Length Polymorphism ".mp OR "Single-Stranded Conformational Polymorphism ".mp OR "Genomic Structural Variations".mp OR "DNA Copy Number Variation". mp OR "Pharmacogenomic Variant".mp OR "Restriction Fragment Length Polymorphisms".mp OR "Single-Stranded Conformational Polymorphisms". mp) AND (exp *"Aggression"/ OR "aggression".ti,ab OR aggression*.ti,ab OR "aggressive behavior".ti,ab OR "aggressive behaviour".ti,ab OR "aggressive behaviors".ti,ab OR "aggressive behaviours".ti,ab OR aggressive behavi*.ti,ab OR exp *"Anger"/ OR "anger".ti,ab OR exp *"Rage"/ OR "angry".ti,ab OR exp "Hostility"/ OR "hostility".ti,ab OR "hostile".ti,ab OR *"Violence"/ OR "violence".ti,ab OR "violent".ti,ab OR (violen*.ti,ab AND (crime*.ti,ab OR crimin*.ti,ab)) OR (aggress*.ti,ab AND (crime*.ti,ab OR crimin*.ti,ab)) OR

aggressive trait*.ti,ab OR “hyperaggression”.ti,ab OR hyperaggress*.ti,ab OR *”oppositional defiant disorder”/ OR “oppositional defiant disorder”.ti,ab OR “oppositional defiant”.ti,ab OR oppositional defiant*.ti,ab OR *”conduct disorder”/ OR “conduct disorder”.ti,ab OR “conduct disorders”.ti,ab OR conduct disorder*.ti,ab OR *”Antisocial Personality Disorder”/ OR “antisocial personality disorder”.ti,ab OR “antisocial personality disorders”.ti,ab OR “anti-social personality disorder”.ti,ab OR “anti-social personality disorders”.ti,ab OR (aggressi*.ti,ab AND (“proactive”.ti,ab OR “reactive”.ti,ab OR “impulsive”.ti,ab OR “physical”.ti,ab))) AND exp “Humans”/ NOT (exp “Neoplasm”/ OR “cancer”.mp OR “tumour”.mp OR “tumours”.mp OR “tumor”.mp OR “tumors”.mp OR “aggressive treatment”.ti,ab OR (exp “Mental Disease”/ NOT (“Attention Deficit Disorder”/ OR “Conduct Disorder”/ OR “Antisocial Personality Disorder”/)) OR exp “Neurologic Disease”/ OR exp “Congenital Disorder”/) AND (exp “Review”/ OR “review”.mp OR review*.mp OR overview*.mp OR exp “systematic review”/)) NOT (conference review or conference abstract).pt

Searchterm for genome-wide studies
((“Genome-Wide Association Study”/ OR “genome wide association”.ti,ab OR “genomic wide association”.ti,ab OR “GWA Study”.ti,ab OR “GWA Studies”.ti,ab OR “GWAS”.ti,ab OR “GWASs”.ti,ab OR “epigenome wide association”.ti,ab OR ((“genome wide”.ti,ab OR “genomic wide”.ti,ab) AND “association”.ti,ab) OR “genetic association”.ti,ab OR “Genetic Association Study”/) AND (exp “Aggression”/ OR “aggression”.ti,ab OR aggression*.ti,ab OR “aggressive behavior”.ti,ab OR “aggressive behaviour”.ti,ab OR “aggressive behaviors”.ti,ab OR “aggressive behaviours”.ti,ab OR aggressive behavi*.ti,ab OR exp “Anger”/ OR “anger”.ti,ab OR exp “Rage”/ OR “angry”.ti,ab OR exp “Hostility”/ OR “hostility”.ti,ab OR “hostile”.ti,ab OR “Violence”/ OR “violence”.ti,ab OR “violent”.ti,ab OR (violen*.ti,ab AND (crime*.ti,ab OR crimin*.ti,ab)) OR (aggress*.ti,ab AND (crime*.ti,ab OR crimin*.ti,ab)) OR aggressive trait*.ti,ab OR “hyperaggression”.ti,ab OR hyperaggress*.ti,ab OR “oppositional defiant disorder”/ OR “oppositional defiant disorder”.ti,ab OR “oppositional defiant”.ti,ab OR oppositional defiant*.ti,ab OR “conduct disorder”/ OR “conduct disorder”.ti,ab OR “conduct disorders”.ti,ab OR conduct disorder*.ti,ab OR “Antisocial Personality Disorder”/ OR “antisocial personality disorder”.ti,ab OR “antisocial personality disorders”.ti,ab OR “anti-social personality disorder”.

ti,ab OR “anti-social personality disorders”.ti,ab OR (aggressi*.ti,ab AND (“proactive”.ti,ab OR “reactive”.ti,ab OR “impulsive”.ti,ab OR “physical”.ti,ab))) AND exp “Humans”/ NOT (conference review or conference abstract).pt)

***Web of Science***

Searchterms for reviews on genetics of aggression:
(ti=(“genetics” OR “genetics” OR “Genetic Procedure” OR “Heredity” OR “molecular genetic phenomena and functions” OR “Gene” OR “genes” OR “gene” OR “heredity” OR “hereditary” OR “Epigenetics” OR epigenetic* OR “Genetic Polymorphism” OR polymorphism* OR “Genotype” OR genotype* OR “Genome” OR genome* OR “systems genetics approach” OR “systems genetics” OR “Genome-Wide Association Study” OR “genome wide association” OR “genomic wide association” OR “GWA Study” OR “GWA Studies” OR “GWAS” OR “GWASs” OR “epigenome wide association” OR ((“genome wide” OR “genomic wide”) AND “association”) OR “genetic association” OR “Genetic Association Study” OR “candidate genes” OR “candidate gene” OR “candidates genes” OR “SNP” OR “SNPS” OR “Single Nucleotide Polymorphism” OR “single nucleotide polymorphisms” OR “single nucleotide polymorphism” OR “DNA Polymorphism” OR “Genetic Polymorphisms” OR “Genetic Polymorphism” OR “Genomic Structural Variation” OR “DNA Copy Number Variations” OR “Pharmacogenomic Variants” OR “Restriction Fragment Length Polymorphism “ OR “Single-Stranded Conformational Polymorphism “ OR “Genomic Structural Variations” OR “DNA Copy Number Variation” OR “Pharmacogenomic Variant” OR “Restriction Fragment Length Polymorphisms” OR “Single-Stranded Conformational Polymorphisms”) AND ts=(“Aggression” OR “aggression” OR aggression* OR “aggressive behavior” OR “aggressive behaviour” OR “aggressive behaviors” OR “aggressive behaviours” OR “aggressive behavi*” OR “Anger” OR “anger” OR “Rage” OR “angry” OR “Hostility” OR “hostility” OR “hostile” OR “Violence” OR “violence” OR “violent” OR (violen* AND (crime* OR crimin*)) OR (aggress* AND (crime* OR crimin*)) OR “aggressive trait*” OR “hyperaggression” OR hyperaggress* OR “oppositional defiant disorder” OR “oppositional defiant disorder” OR “oppositional defiant” OR “oppositional defiant*” OR “conduct disorder” OR “conduct disorder” OR “conduct disorders” OR “conduct disorder*” OR “Antisocial Personality Disorder” OR “antisocial

personality disorder" OR "antisocial personality disorders" OR "anti-social personality disorder" OR "anti-social personality disorders" OR (aggressi* AND ("proactive" OR "reactive" OR "impulsive" OR "physical"))) NOT ts=("Neoplasm" OR "cancer" OR "tumour" OR "tumours" OR "tumor" OR "tumors" OR "aggressive treatment" OR ("Mental Disease" NOT ("Attention Deficit Disorder" OR "Conduct Disorder" OR "Antisocial Personality Disorder")) OR Neurolog* OR Congenital* OR neonat* OR newborn*) AND ts=("Review" OR "review" OR review* OR overview* OR "systematic review") NOT ti=("veterinary" OR "rabbit" OR "rabbits" OR "animal" OR "animals" OR "mouse" OR "mice" OR "rodent" OR "rodents" OR "rat" OR "rats" OR "pig" OR "pigs" OR "porcine" OR "horse" OR "horses" OR "equine" OR "cow" OR "cows" OR "bovine" OR "goat" OR "goats" OR "sheep" OR "ovine" OR "canine" OR "dog" OR "dogs" OR "feline" OR "cat" OR "cats")) OR (ts=("genetics" OR "genetics" OR "Genetic Procedure" OR "Heredity" OR "molecular genetic phenomena and functions" OR "Gene" OR "genes" OR "gene" OR "heredity" OR "hereditary" OR "Epigenetics" OR epigenetic* OR "Genetic Polymorphism" OR polymorphism* OR "Genotype" OR genotype* OR "Genome" OR genome* OR "systems genetics approach" OR "systems genetics" OR "Genome-Wide Association Study" OR "genome wide association" OR "genomic wide association" OR "GWA Study" OR "GWA Studies" OR "GWAS" OR "GWASs" OR "epigenome wide association" OR (("genome wide" OR "genomic wide") AND "association") OR "genetic association" OR "Genetic Association Study" OR "candidate genes" OR "candidate gene" OR "candidates genes" OR "SNP" OR "SNPS" OR "Single Nucleotide Polymorphism" OR "single nucleotide polymorphisms" OR "single nucleotide polymorphism" OR "DNA Polymorphism" OR "Genetic Polymorphisms" OR "Genetic Polymorphism" OR "Genomic Structural Variation" OR "DNA Copy Number Variations" OR "Pharmacogenomic Variants" OR "Restriction Fragment Length Polymorphism " OR "Single-Stranded Conformational Polymorphism " OR "Genomic Structural Variations" OR "DNA Copy Number Variation" OR "Pharmacogenomic Variant" OR "Restriction Fragment Length Polymorphisms" OR "Single-Stranded Conformational Polymorphisms") AND ti=("Aggression" OR "aggression" OR aggression* OR "aggressive behavior" OR "aggressive behaviour" OR "aggressive behaviors" OR "aggressive behaviours" OR "aggressive behavi*" OR "Anger" OR "anger" OR "Rage" OR "angry" OR "Hostility" OR "hostility" OR "hostile" OR "Violence" OR "violence" OR

"violent" OR (violen* AND (crime* OR crimin*)) OR (aggress* AND (crime* OR crimin*)) OR "aggressive trait*" OR "hyperaggression" OR hyperaggress* OR "oppositional defiant disorder" OR "oppositional defiant disorder" OR "oppositional defiant" OR "oppositional defiant*" OR "conduct disorder" OR "conduct disorder" OR "conduct disorders" OR "conduct disorder*" OR "Antisocial Personality Disorder" OR "antisocial personality disorder" OR "antisocial personality disorders" OR "anti-social personality disorder" OR "anti-social personality disorders" OR (aggressi* AND ("proactive" OR "reactive" OR "impulsive" OR "physical"))) NOT ts=("Neoplasm" OR "cancer" OR "tumour" OR "tumours" OR "tumor" OR "tumors" OR "aggressive treatment" OR ("Mental Disease" NOT ("Attention Deficit Disorder" OR "Conduct Disorder" OR "Antisocial Personality Disorder")) OR Neurolog* OR Congenital* OR neonat* OR newborn*) AND ts=("Review" OR "review" OR review* OR overview* OR "systematic review") NOT ti=("veterinary" OR "rabbit" OR "rabbits" OR "animal" OR "animals" OR "mouse" OR "mice" OR "rodent" OR "rodents" OR "rat" OR "rats" OR "pig" OR "pigs" OR "porcine" OR "horse" OR "horses" OR "equine" OR "cow" OR "cows" OR "bovine" OR "goat" OR "goats" OR "sheep" OR "ovine" OR "canine" OR "dog" OR "dogs" OR "feline" OR "cat" OR "cats"))

NOT (conference review or conference abstract).pt

Searchterms for genome-wide studies:
(ts=("Genome-Wide Association Study" OR "genome wide association".mp OR "genomic wide association".mp OR "GWA Study".mp OR "GWA Studies".mp OR "GWAS".mp OR "GWASs".mp OR "epigenome wide association".mp OR (("genome wide".mp OR "genomic wide".mp) AND "association") OR "genetic association".mp OR "Genetic Association Study") AND ts=("Aggression" OR "aggression" OR aggression OR "aggressive behavior" OR "aggressive behaviour" OR "aggressive behaviors" OR "aggressive behaviours" OR aggressive behavi OR "Anger" OR "anger" OR "Rage" OR "angry" OR "Hostility" OR "hostility" OR "hostile" OR "Violence" OR "violence" OR "violent" OR ("violen*" AND ("crime*" OR "crimin*")) OR ("aggress*" AND ("crime*" OR "crimin*")) OR "aggressive trait*" OR "hyperaggression" OR "hyperaggress*" OR "oppositional defiant disorder" OR "oppositional defiant disorder*" OR "oppositional defiant*" OR "conduct disorder*" OR "Antisocial

Personalit*" OR "anti-social personalit*" OR (aggressi* AND ("proactive" OR "reactive" OR "impulsive" OR "physical"))) NOT ti=("veterinary" OR "rabbit" OR "rabbits" OR "animal" OR "animals" OR "mouse" OR "mice" OR "rodent" OR "rodents" OR "rat" OR "rats" OR "pig" OR "pigs" OR "porcine" OR "horse" OR "horses" OR "equine" OR "cow" OR "cows" OR "bovine" OR "goat" OR "goats" OR "sheep" OR "ovine" OR "canine" OR "dog" OR "dogs" OR "feline" OR "cat" OR "cats"))

***Cochrane***

Searchterms for reviews on genetics of aggression:
(("genetics" OR "genetics" OR "Genetic Procedure" OR "Heredity" OR "molecular genetic phenomena and functions" OR "Gene" OR "genes" OR "gene" OR "heredity" OR "hereditary" OR "Epigenetics" OR epigenetic* OR "Genetic Polymorphism" OR polymorphism* OR "Genotype" OR genotype* OR "Genome" OR genome* OR "systems genetics approach" OR "systems genetics" OR "Genome-Wide Association Study" OR "genome wide association" OR "genomic wide association" OR "GWA Study" OR "GWA Studies" OR "GWAS" OR "GWASs" OR "epigenome wide association" OR (("genome wide" OR "genomic wide") AND "association") OR "genetic association" OR "Genetic Association Study" OR "candidate genes" OR "candidate gene" OR "candidates genes" OR "SNP" OR "SNPS" OR "Single Nucleotide Polymorphism" OR "single nucleotide polymorphisms" OR "single nucleotide polymorphism" OR "DNA Polymorphism" OR "Genetic Polymorphisms" OR "Genetic Polymorphism" OR "Genomic Structural Variation" OR "DNA Copy Number Variations" OR "Pharmacogenomic Variants" OR "Restriction Fragment Length Polymorphism " OR "Single-Stranded Conformational Polymorphism " OR "Genomic Structural Variations" OR "DNA Copy Number Variation" OR "Pharmacogenomic Variant" OR "Restriction Fragment Length Polymorphisms" OR "Single-Stranded Conformational Polymorphisms") AND ("Aggression" OR "aggression" OR aggression* OR "aggressive behavior" OR "aggressive behaviour" OR "aggressive behaviors" OR "aggressive behaviours" OR "aggressive behavi*" OR "Anger" OR "anger" OR "Rage" OR "angry" OR "Hostility" OR "hostility" OR "hostile" OR "Violence" OR "violence" OR "violent" OR (violen* AND (crime* OR crimin*)) OR (aggress* AND (crime* OR crimin*)) OR "aggressive trait*" OR "hyperaggression" OR hyperaggress*

OR “oppositional defiant disorder” OR “oppositional defiant disorder” OR “oppositional defiant” OR “oppositional defiant*” OR “conduct disorder” OR “conduct disorder” OR “conduct disorders” OR “conduct disorder*” OR “Antisocial Personality Disorder” OR “antisocial personality disorder” OR “antisocial personality disorders” OR “anti-social personality disorder” OR “anti-social personality disorders” OR (aggressi* AND (“proactive” OR “reactive” OR “impulsive” OR “physical”))) NOT (“Neoplasm” OR “cancer” OR “tumour” OR “tumours” OR “tumor” OR “tumors” OR “aggressive treatment” OR (“Mental Disease” NOT (“Attention Deficit Disorder” OR “Conduct Disorder” OR “Antisocial Personality Disorder”)) OR Neurolog* OR Congenital* OR neonat* OR newborn*))

Searchterms for genome-wide studies:
((“Genome-Wide Association Study” OR “genome wide association”.mp OR “genomic wide association”.mp OR “GWA Study”.mp OR “GWA Studies”.mp OR “GWAS”.mp OR “GWASs”.mp OR “epigenome wide association”.mp OR ((“genome wide”.mp OR “genomic wide”.mp) AND “association”) OR “genetic association”.mp OR “Genetic Association Study”) AND (“Aggression” OR “aggression” OR aggression OR “aggressive behavior” OR “aggressive behaviour” OR “aggressive behaviors” OR “aggressive behaviours” OR aggressive behavi OR “Anger” OR “anger” OR “Rage” OR “angry” OR “Hostility” OR “hostility” OR “hostile” OR “Violence” OR “violence” OR “violent” OR (“violen*” AND (“crime*” OR “crimin*”)) OR (“aggress*” AND (“crime*” OR “crimin*”)) OR “aggressive trait*” OR “hyperaggression” OR “hyperaggress*” OR “oppositional defiant disorder” OR “oppositional defiant disorder*” OR “oppositional defiant*” OR “conduct disorder*” OR “Antisocial Personalit*” OR “anti-social personalit*” OR (aggressi* AND (“proactive” OR “reactive” OR “impulsive” OR “physical”))):ti,ab,kw

***PsycINFO***

Searchterms for reviews on genetics of aggression:
TI((“genetics” OR “genetics” OR “Genetic Procedure” OR “Heredity” OR “molecular genetic phenomena and functions” OR “Gene” OR “genes” OR “gene” OR “heredity” OR “hereditary” OR “Epigenetics” OR epigenetic* OR “Genetic Polymorphism” OR polymorphism* OR “Genotype” OR genotype*

OR “Genome” OR genome* OR “systems genetics approach” OR “systems genetics” OR “Genome-Wide Association Study” OR “genome wide association” OR “genomic wide association” OR “GWA Study” OR “GWA Studies” OR “GWAS” OR “GWASs” OR “epigenome wide association” OR (((“genome wide” OR “genomic wide”) AND “association”) OR “genetic association” OR “Genetic Association Study” OR “candidate genes” OR “candidate gene” OR “candidates genes” OR “SNP” OR “SNPS” OR “Single Nucleotide Polymorphism” OR “single nucleotide polymorphisms” OR “single nucleotide polymorphism” OR “DNA Polymorphism” OR “Genetic Polymorphisms” OR “Genetic Polymorphism” OR “Genomic Structural Variation” OR “DNA Copy Number Variations” OR “Pharmacogenomic Variants” OR “Restriction Fragment Length Polymorphism “ OR “Single-Stranded Conformational Polymorphism “ OR “Genomic Structural Variations” OR “DNA Copy Number Variation” OR “Pharmacogenomic Variant” OR “Restriction Fragment Length Polymorphisms” OR “Single-Stranded Conformational Polymorphisms”) AND (“Aggression” OR “aggression” OR aggression* OR “aggressive behavior” OR “aggressive behaviour” OR “aggressive behaviors” OR “aggressive behaviours” OR “aggressive behavi*” OR “Anger” OR “anger” OR “Rage” OR “angry” OR “Hostility” OR “hostility” OR “hostile” OR “Violence” OR “violence” OR “violent” OR (violen* AND (crime* OR crimin*)) OR (aggress* AND (crime* OR crimin*)) OR “aggressive trait*” OR “hyperaggression” OR hyperaggress* OR “oppositional defiant disorder” OR “oppositional defiant disorder” OR “oppositional defiant” OR “oppositional defiant*” OR “conduct disorder” OR “conduct disorder” OR “conduct disorders” OR “conduct disorder*” OR “Antisocial Personality Disorder” OR “antisocial personality disorder” OR “antisocial personality disorders” OR “anti-social personality disorder” OR “anti-social personality disorders” OR (aggressi* AND (“proactive” OR “reactive” OR “impulsive” OR “physical”))) NOT (“Neoplasm” OR “cancer” OR “tumour” OR “tumours” OR “tumor” OR “tumors” OR “aggressive treatment” OR (“Mental Disease” NOT (“Attention Deficit Disorder” OR “Conduct Disorder” OR “Antisocial Personality Disorder”)) OR Neurolog* OR Congenital* OR neonat* OR newborn*) AND (“Review” OR “review” OR review* OR overview* OR “systematic review”)) **OR** MJ((“genetics” OR “genetics” OR “Genetic Procedure” OR “Heredity” OR “molecular genetic phenomena and functions” OR “Gene” OR “genes” OR “gene” OR “heredity” OR “hereditary” OR “Epigenetics” OR epigenetic* OR “Genetic

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Searchterms for genome-wide studies:
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***Academic Search Premier***

Searchterms for reviews on genetics of aggression:
TI(("genetics" OR "genetics" OR "Genetic Procedure" OR "Heredity" OR "molecular genetic phenomena and functions" OR "Gene" OR "genes" OR "gene" OR "heredity" OR "hereditary" OR "Epigenetics" OR epigenetic* OR "Genetic Polymorphism" OR polymorphism* OR "Genotype" OR genotype* OR "Genome" OR genome* OR "systems genetics approach" OR "systems genetics" OR "Genome-Wide Association Study" OR "genome wide association" OR "genomic wide association" OR "GWA Study" OR "GWA Studies" OR "GWAS" OR "GWASs" OR "epigenome wide association" OR (("genome wide" OR "genomic wide") AND "association") OR "genetic association" OR "Genetic Association Study" OR "candidate genes" OR "candidate gene" OR "candidates genes" OR "SNP" OR "SNPS" OR "Single Nucleotide Polymorphism" OR "single nucleotide polymorphisms" OR "single nucleotide polymorphism" OR "DNA Polymorphism" OR "Genetic Polymorphisms" OR "Genetic Polymorphism" OR "Genomic Structural Variation" OR "DNA Copy Number Variations" OR "Pharmacogenomic Variants" OR "Restriction Fragment Length Polymorphism " OR "Single-Stranded Conformational Polymorphism " OR "Genomic Structural Variations" OR "DNA Copy Number Variation" OR "Pharmacogenomic Variant" OR "Restriction Fragment Length Polymorphisms" OR "Single-Stranded Conformational Polymorphisms") AND ("Aggression" OR "aggression" OR aggression* OR "aggressive behavior" OR "aggressive behaviour" OR "aggressive behaviors" OR "aggressive behaviours" OR "aggressive behavi*" OR "Anger" OR "anger" OR "Rage" OR "angry" OR "Hostility" OR "hostility" OR "hostile" OR "Violence" OR "violence" OR

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OR crimin*)) OR “aggressive trait*” OR “hyperaggression” OR hyperaggress* OR “oppositional defiant disorder” OR “oppositional defiant disorder” OR “oppositional defiant” OR “oppositional defiant*” OR “conduct disorder” OR “conduct disorder” OR “conduct disorders” OR “conduct disorder*” OR “Antisocial Personality Disorder” OR “antisocial personality disorder” OR “antisocial personality disorders” OR “anti-social personality disorder” OR “anti-social personality disorders” OR (aggressi* AND (“proactive” OR “reactive” OR “impulsive” OR “physical”))) NOT (“Neoplasm” OR “cancer” OR “tumour” OR “tumours” OR “tumor” OR “tumors” OR “aggressive treatment” OR (“Mental Disease” NOT (“Attention Deficit Disorder” OR “Conduct Disorder” OR “Antisocial Personality Disorder”)) OR Neurolog* OR Congenital* OR neonat* OR newborn*))

AND TX(“Review” OR “review” OR review* OR overview* OR “systematic review”)

NOT ti(“veterinary” OR “rabbit” OR “rabbits” OR “animal” OR “animals” OR “mouse” OR “mice” OR “rodent” OR “rodents” OR “rat” OR “rats” OR “pig” OR “pigs” OR “porcine” OR “horse” OR “horses” OR “equine” OR “cow” OR “cows” OR “bovine” OR “goat” OR “goats” OR “sheep” OR “ovine” OR “canine” OR “dog” OR “dogs” OR “feline” OR “cat” OR “cats”)

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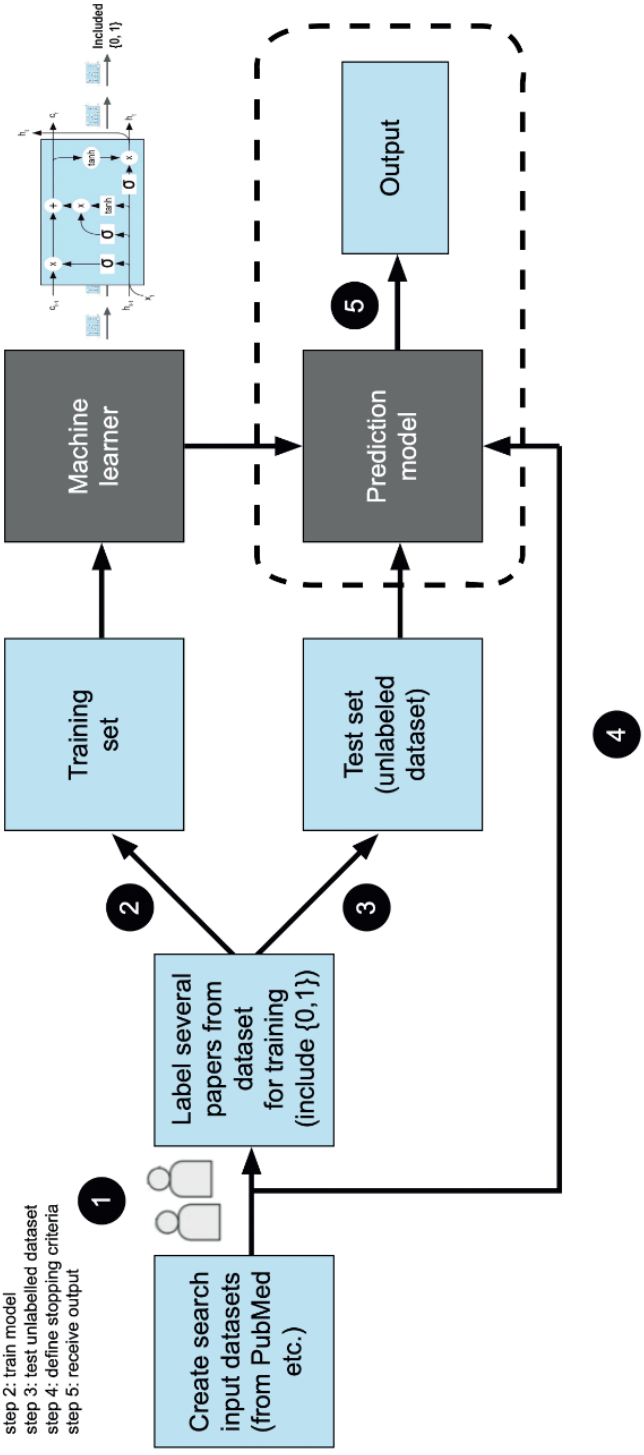
## Chapter 5, Supplement S3. Additional materials on automated screening

Automated screening of titles and abstracts was performed with use of Automated Systematic Review Software (ASR) developed by researchers from Utrecht University, the Netherlands (PI A.G.J. van de Schoot) for screening abstracts and titles. The software is hosted at https://github.com (*Automated systematic reviews by using Deep Learning and Active Learning*, 2019). ASR is based on supervised machine learning approach with classification approach (the papers are classified in categories—i.e., 1=included or 0=not-included). The oracle modus is used to perform a systematic review with interaction by the reviewer.

During the training phase, the model is created, and in the prediction phase, the model is used to predict the future results of a literature search (see Figure S3.1).

**Chapter 5, Figure S3.1** Process scheme of training and testing sets using ASR

step 0: create search input datasets (from PubMed etc.)
step 1: label several papers from dataset for training (include {0,1})
step 2: train model
step 3: test unlabelled dataset
step 4: define stopping criteria
step 5: receive output



We had two objectives in applying ASR:

1) To analyze screening parameters of ASR (time of screening, inclusion and exclusion rates, false positive rates (FPR), false negative rates (FNR), true positive rates (TPR), true negative rates (TNR), and receiver operating characteristics (ROC)) and compare it with parameters of manual screening (time of screening, inclusion and exclusion rates as workload characteristics);
2) To contribute to the current systematic review by predicting inclusion/exclusion in a large data set of records based on generated ASR models. To make automated screening of ASR on large dataset of records to make a new contribution to the current systematic review.

The following steps were done in our systematic review:

0. several literature searches were done in PubMed to create a training dataset with key words "human aggression GWAS", "human aggression genetic association studies", "human aggression epigenetics" (2,955 records)
1. the training dataset was labelled by reviewers to create training sets (0=not-included, 1=included) and comprised 152 positives and 2803 negatives labels
2. ASR models were trained with training sets from the labelled training dataset (500 records)
3. models with different parameters were used for screening
4. the ROC analyses were performed to define FNR and thresholds of positive and negative results

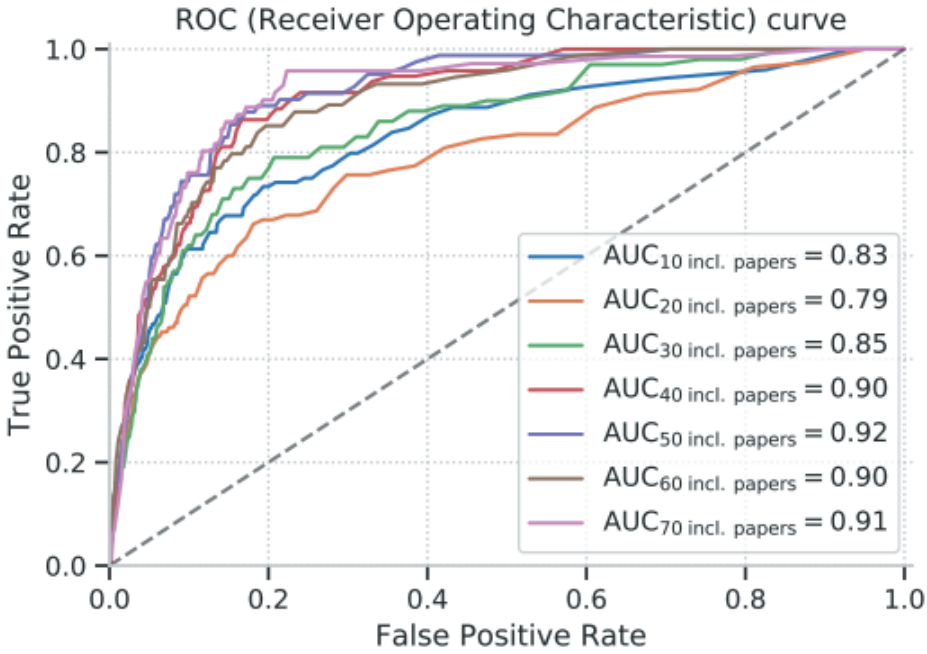
Receiver operating characteristics (ROC) analyses were performed on the models including different number of records labelled as "included": $N_{\text{label=1}}$ = [10, 20, 30, 40, 50, 60, 70] from the randomly selected training set of size $N_{\text{training dataset}}$ = 500 from the prelabeled list of $N$ = 2,955 records. All models perform considerably better than random, since $\text{AUC} \in [0.79, 0.92$ (see Figure S3.2). We selected the model where we used $N_{\text{label=1}}$ = 50, since it resulted in the minimal FPR=0.39 at FNR ≤ 0.03 with optimal threshold of prediction.

**Chapter 5, Table S3.1** ROC parameters used for model selection.

| $N_{label=1}$ | Minimal false positive rate at FNR≤ 0.03 | Maximum threshold of prediction at FNR≤ 0.03 |
|---|---|---|
| 10 | 0.934363 | 0.01 |
| 20 | 0.878205 | 0.03 |
| 30 | 0.604671 | 0.09 |
| 40 | 0.571186 | 0.03 |
| 50* | 0.386431 | 0.12 |
| 60 | 0.583788 | 0.05 |
| 70 | 0.455537 | 0.06 |

*The model using $N_{label=1}$ = 50 exhibits the lowest minimal FPR at FNR ≤ 0.03

**Chapter 5, Figure S3.2** ROC curves for the trained models




AUC=area under the curve

Once the optimal model was defined, screenings were repeated on different datasets:

a. 1,713 records of potential reviews on genetics of human aggression (see Supplement S2);
b. 356 records of potential GWASs on genetics of human aggression (see Supplement S2);
c. 2,069 records that join together (1) and (2) datasets;
d. a new dataset of 14,400 records done with a wide search "humanANDaggressionANDgenes" in the same databases as previous datasets.

Screenings (1)-(3) were used to compare the parameters of automated screening with manual screening (see Table S3.2).
By screening dataset (3) with $N = 2{,}069$ ASR predicted relevant records and recovered 50 of the 51 expert-labelled true positives, yielding TPR = 0.980. The ASR model mislabeled 1 record as not-relevant from expert labeled true positive, yielding FNR = 0.020. The performance of the model applied to the above search is high. FPR was 0.600, meaning that a reduction in reading time of ~40% is expected.

It is worth noting that model generation and using it for predicting takes ~ 1 hour on a regular computer.

**Chapter 5, Table S3.2** Comparison of titles and abstracts screening performed manually and automated

| Step | Dataset | Screening type | Input Sample | Inclusion* | Inclusion rate | Exclusion | Exclusion rate |
|---|---|---|---|---|---|---|---|
| Training set | Training dataset | ASR | 2,955 | 152 | 5,1% | 2,803 | 94,9% |
| Titles and abstracts screening | Reviews | Manual | 1,713 | 26 | 1,5% | 1,687 | 98,5% |
| | | ASR | 1,713 | 1,018 | 59,4% | 695 | 40,6% |
| | GWASs | Manual | 356 | 25 | 7,0% | 331 | 93,0% |
| | | ASR | 356 | 243 | 68,3% | 113 | 31,7% |
| | "Human aggression genes" | ASR | 14,400 | 7,297 | 50,7% | 7,103 | 49,3% |

Note * The inclusion numbers done on the base of titles and abstracts screening (not the final number of articles included in the review)
ASR=Automated Systematic Review

### *False-negative result*

Sonuga- Barke EJ, Lasky-Su J, Neale BM, Oades R, Chen W, Franke B, et al. Does parental expressed emotion moderate genetic effects in ADHD? An exploration using a genome wide association scan. Am J Med Genet B Neuropsychiatr Genet. 2008;147B(8):1359-68.

### *Papers selected by researchers from automated selection in addition to traditional selection*

### *Reviews*

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**Chapter 5, Supplement S4** Phenotypes in Genome-wide Association Studies on Aggression

| Factor | Trait (subscale) | Measurement instrument | Study |
|---|---|---|---|
| Externalizing | Hostility (anger) | Irritability Scale of the Buss-Durkee Hostility Inventory (BDHI) | Merjonen 2011 |
| | Anger temperament and anger reaction | Spielberger State-Trait Anger Scale (SSTAS) | Mick 2014; Salvatore 2015 |
| | Physical aggression | Question in self-report "Did you ever get into physical fights while using marijuana?" | Montalvo-Ortiz 2018 |
| | Destructiveness, aggression | Parental Account of Childhood Symptoms (PACS) | Sonuga-Barke 2008; Anney 2008 |
| | Aggressive behaviour | Child Behavioural Checklist (CBCL) | Mick 2011; Pappa 2016; Tielbeek 2017 |
| | Hyperactive-impulsive | Conners Parent Rating Scale (CPRSR) | Anney 2008; Aebi 2016; Brevik 2016 |
| | Oppositionality and defiance | Conners Parent Rating Scale (CPRSR) | |
| | Conduct problems | CD based on Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) | Dick 2011; Tielbeek 2012 |
| | Conduct problems | Strengths and Difficulties Questionnaire (SDQ) | Viding 2010; Pappa 2016 |
| | Aggression and CD | composite of measures | McGue 2013 |
| | Antisocial behaviour | Strengths and Difficulties Questionnaire (SDQ) | Viding 2010; Pappa 2016 |
| | Antisocial behaviour | ASPD based on Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) | Tielbeek 2012; Salvatore 2015 |
| | Violent behaviour | Crime characteristics | Tiihonen, 2014; Rautiainen 2016 |

## Chapter 5, Supplement S5. Reported genetic variants in chromosomes in genome-wide association studies

$N_{studies}$=17, $N_{variants}$ =817

See Excel, Supplement S5, available online.

**Chapter 5, Supplement S6** Overview of Reported Genetic Variants in Chromosomes in Genome-wide Association Studies on Aggression

| Chromosome | N variants at suggestive significance ($p < 1E^{-05}$) | Number of SNPs at genome-wide significance ($p < 5.0E^{-08}$) | Genes with nearby or inside location of SNPS at genome-wide significance ($p < 5.0E^{-08}$) |
|---|---|---|---|
| 1 | 53 | 1 | |
| 2 | 81 | 2 | *HTR2B; PSMD1* |
| 3 | 40 | | |
| 4 | 35 | 2 | *C1QTNF7* |
| 5 | 52 | | |
| 6 | 54 | 1 | *LINC00915* |
| 7 | 79 | | |
| 8 | 25 | | |
| 9 | 49 | | |
| 10 | 56 | | |
| 11 | 62 | 2 | |
| 12 | 34 | | |
| 13 | 8 | 1 | |
| 14 | 15 | | |
| 15 | 9 | | |
| 16 | 27 | | |
| 17 | 19 | | |
| 18 | 21 | | |
| 19 | 6 | | |
| 20 | 44 | | |
| 21 | 26 | | |
| 22 | 8 | | |
| X | 4 | 1 | |
| | 817 | 10 | 4 |

*Note*. $N_{studies}$=17

# SUPPLEMENT TO CHAPTER 6

## Chapter 6, Supplement 1. Brief description of buccal sample collection for (epi)genetics in ACTION in the Netherlands Twin Register

Buccal cells for DNA isolation and genotyping were collected during two days and were also collected from parents and additional siblings. All parents provided written informed consents for their own and their children's participation. Genotyping was done on the Axiom (N = 861; Ehli et al., 2017) or the GSA array (N = 2,151; Beck et al., 2019). Genotyping data were analyzed to establish zygosity (Odintsova et al., 2019), of which parents received the results.

For epigenetics 108 extra twins with buccal-cell samples and longitudinal aggression data were included from the NTR database. Thus in total 1,475 twins (737 complete pairs), either with first-morning urine ($N$ = 1,362) and/or buccal-cell swabs ($N$ = 1,468), were included in the ACTION project (Table S1). In the twins, epigenetic markers were measured on the Illumina EPIC 850K array (Van Dongen et al., 2018).

## Chapter 6, Supplement 2. Medication use and other covariates

In the sensitivity analyses we assessed the potential impact of preexisting chronic conditions, medication use, or vitamin use on differences in biomarker levels and neurotransmitter ratios between the MZ twins scoring high and low on aggression.

Medication use has been assessed in the twin cohort through parent report at the time of urine collection, in the clinical cohort medication use was extracted from the patient files. ATC codes (https://www.whocc.no/atc_ddd_index/) were assigned to the medications used at the time of urine collection in both cohorts. Based on the ATC codes medications could be classified. At time of urine collection children included in the current study used medications classified as: alimentary tract and metabolism (A), cardiovascular system (C), dermatological (D), genito-urinary system and sex hormone (G), systemic hormonal preparations (H), anti-infectives for systemic use (J), nervous system (N) and respiratory system (R) medications.

Children were most frequently using nervous system or respiratory system medications, which is consistent with reported incidences of asthma or allergies. The respiratory medications included nasal preparations (R01), drugs for

obstructive airway diseases (R03) and antihistamines for system use (R06). The nervous system medications included analgesics (N02, e.g., paracetamol use), antiepileptics (N03), psycholeptics (N05), psychoanaleptics (N06) and other nervous system drugs (N07; here chiefly antivertigo medications). Medications belonging to the N05 and N06 classes (e.g., aripiprazole [N05AX12] or methylphenidate [N06BA04]) are also considered psychotropic medications and are prescribed for the treatment of psychiatric disorders, including for example attention-deficit/hyperactivity disorder. In **Table 1** we included an overview of the number of children on psychotropic medications in both cohorts.

## Chapter 6, Supplement 3. Aggressive Behavior item-based biomarker discovery

### Assessment of aggressive behavior

At or near the time of biological sample collection parents completed the CBCL. The CBCL Aggressive Behavior subscale consists of 18 items assessing multiple aspects of aggressive behavior (see Table S4). Parents were asked to indicate the applicability of each item to their child's behavior over the past 6 months. Answer categories ranged from "not true" (coded as "0"), to "somewhat or sometimes true" (coded as "1"), and "very true or often true" (codes as "2"). All items were dichotomized to reflect case/control status, with items scored as "not true" defining control status. The answer categories "somewhat or sometimes true" and "very true or often true" both reflected case status. Endorsement of the original answer categories as well as the dichotomized answer categories have been supplied in Table S4. In the NTR, items from mother-rated CBCL Aggressive Behavior subscale were analyzed, in the Curium-LUMC cohort the majority (90%) of ratings was also by the mother.

### Statistical analyses

In the item-based discovery, replication and validation phases the same subjects as in the original discovery, replication and validation phases were classified as cases or controls based on each of the 18 CBCL Aggressive Behavior items (see section 3.1). GEE analyses, including sex and age as covariates, assessed the relationship of the biomarkers and neurotransmitter ratios with item case-control status. Analyses were corrected for relatedness using an 'exchangeable' correlation structure. The FDR of 5% at a threshold of $p \leq 0.05$ for 1602 tests

(biomarkers) or 126 tests (ratios) are provided. Note, that because of the large number of tests interpretation of the discovery phase in terms of significance is complex. The top 25% most associated biomarkers or ratios per item were tested in the replication phase. In the replication phase the FDR of 5% for 414 tests (biomarkers) and 54 tests (ratios) at $p \leq 0.05$ was used. Finally, in the validation phase the biomarkers or ratios with congruent directions of effect in the discovery and validation phase and which were significantly associated with item case-control status in the validation phase were assessed. For those items without significantly associated biomarkers or ratios, the top 5 biomarkers or top ratio were assessed in the replication phase. The significance threshold was set at $p \leq 0.05$ with a 5% FDR for 88 tests (biomarkers) and 18 tests (ratios) to control multiple testing.

## Results

### *Participant descriptives*

Both the original and dichotomized responses for each of the 18 items have been included in Table S4. Case and control status on an item-to-item basis vary considerably across children (Table S4). It must be noted that for some items, particularly the more extreme items such as "Threatens other people", item endorsement is low across all groups (Table S4). As a consequence, meaningful interpretation of associated metabolites, other biomarkers and neurotransmitters is not always feasible.

## Association of urinary metabolites and other biomarkers with Aggressive Behavior items

### *Discovery*

The discovery analyses showed significant metabolites or other biomarkers for each of the 18 Aggressive Behavior items, overall 3.8% of the tests were significant, however, after correcting for multiple testing none of the item-specific metabolites or other biomarkers remained significant (Table S13). Comparing the top 25% metabolites and other biomarkers for overall aggression, we observe that of the 23 metabolites or other biomarkers in the top 25% between 2 and 12 overlap per item (Table S14). Of the overlapping metabolites or other biomarkers

approximately 78% have congruent directions of effect among the overall aggression and item-specific analyses (Table S14).

***Replication***

The top 25% most associated metabolites and other biomarkers per item were assessed for replication in a sample of twin pairs discordant for aggression. In the replication analyses 29 metabolites or other biomarkers were significantly associated with aggression items, here only 12 of the 18 aggression items had significantly associated metabolites or other biomarkers (Table S15). In total 8.5% of the total number of conducted tests were significant. Five of the significantly associated metabolites or other biomarkers were also included in the top 25% for overall aggression. In the replication analyses isocitrate was associated with 'Disobedient at home' ($\beta = 0.26$; $SE = 0.10$; $p = 0.008$), for overall aggression this metabolite was not significant and showed an opposite direction of effect in the replication analysis. 'Disobedient at home' was also significantly associated with norepinephrine levels ($\beta = 0.22$; $SE = 0.10$; $p = 0.03$), in the overall aggression replication analysis this metabolite was also significantly associated, before multiple testing correction; however the association was in the opposite direction (mean difference = -0.19; $p = 0.02$). The associations of ethanolamine with 'Disobedient at school', isocitrate with 'Threatens' and succinic acid with 'Temper' were in the same direction of effect as observed for overall aggression (Table S7 and S15). Only ethanolamine was significantly associated with both 'Disobedient at school' ($\beta = -0.31$; $SE = 0.14$; $p = 0.03$) and with overall aggression (mean difference = -0.20; $p = 0.03$). After correction for multiple testing 10 of the 15 (66.7%) metabolites or other biomarkers associated with 'Threatens' were still significant (Table S15). However only 3 children were cases for 'threaten other people' (Table S4). For the other 11 items none of the metabolites or other biomarkers remained significant after correction for multiple testing (Table S15). Overall, we observed congruent directions of effect in the discovery and validation analyses for 3-19 out of 23 (13.0-82.6%) top 25% amines, organic acids and biomarkers per item (Table S14).

***Validation***

For the validation analyses we selected the top 5 most associated metabolites or other biomarkers from the replication analyses with congruent directions of effects in the discovery analyses. For the 'Fights' item only 3 metabolites or other biomarkers showed congruent direction of effect between the discovery and the replication, therefore, only these 3 were included. In the validation analyses

neopterin is significantly associated with 'Argues' (β = -0.25; *SE* = 0.10; *p* = 0.01) and L-proline with 'Mean' (β = -0.28; *SE* = 0.12; *p* = 0.02). None of the other biomarker-item combinations were significant and after correction for multiple testing, the associations of neopterin with 'Argues' and L-proline with 'Mean' were no longer significant (Table S16). Overall, congruent directions of effect between the replication and validation were observed for 0-4 out of the top 5 (0%-80%) amines, organic acids and biomarkers per item (Table S14).

## Association of urinary neurotransmitter pathways with aggressive behavior items

### *Discovery*

To elucidate the role of serotonergic, dopaminergic and GABAergic neurotransmitter pathways we performed discovery analyses with gee analyses for each of the 18 items of the CBCL Aggressive Behavior subscale. The discovery analyses showed that the catabolic dopamine neurotransmitter ratio 3MT to HVA was significantly associated with the 'Stubborn' (β = -2.50; *SE* = 1.16; *p* = 0.03) and 'Sulks' (β = -3.17; *SE* = 1.59; *p* = 0.05) items. The catabolic GABA neurotransmitter ratio GABA to succinic acid was significantly associated with the 'Physically attacks people' (β = -2.49; *SE* = 0.90; *p* = 0.01), 'Suspicious' (β = -1.82; *SE* = 0.83; *p* = 0.03) and 'Teases' (β = -2.34; *SE* = 0.88; *p* = 0.01) items. The anabolic GABA neurotransmitter L-glutamic acid to GABA was significantly associated with 'Disobedient at School' (β = -3.34; *SE* = 1.62; *p* = 0.04). After correction for multiple testing none of the neurotransmitter ratio-item associations was significant and none of the neurotransmitter ratios involved in the anabolism or catabolism of serotonin, dopamine or GABA significantly associated with the other 12 aggressive behavior items (Table S17). None of the most associated neurotransmitter ratios per item were included in the top 25% most associated neurotransmitter items for overall aggression. Of the 7 neurotransmitter ratios congruent directions of effect between the overall aggression discovery results and the item specific results were observed for 6 ratios across 17 items, with no congruent directions of effect observed for the ratio of 5HTP to serotonin and for the 'Sudden changes in mood or feelings' item (Table S18).

### *Replication*

Replication of the top 25% most associated neurotransmitter ratios from the item-specific discovery analyses were performed in the sample of twins discordant for

overall aggression. The anabolic dopamine ratio L-phenylalanine to L-tyrosine was significantly associated with the 'Fights' ($\beta$ = -0.85; *SE* = 0.42; $p$ = 0.04) and 'Threatens' ($\beta$ = -1.19; *SE* = 0.39; $p$ = 0.002) items, though these associations did not survive multiple testing (Table S19). The direction of effect of L-phenylalanine to L-tyrosine for the 'Fights' and 'Threatens' items were congruent with the direction of effect as observed in the discovery analyses (Table S18). None of the other neurotransmitter ratio aggression item combinations reached significance in the replication analyses (Table S19) and the congruence of effect directions ranged from none ('Mean') to all (3; 'Threatens'), with an average of 1.5 (Table S18).

***Validation***

The top neurotransmitter ratio for each item was assessed in a sample of clinical cases and twin controls. Before correction for multiple testing the anabolic dopamine neurotransmitter ratio L-phenylalanine to L-tyrosine was significantly associated with the 'Disobedient at school' ($\beta$ = 4.64; *SE* =1.96; $p$ = 0.02) and 'Loud' ($\beta$ = 4.18; *SE* = 2.00; $p$ = 0.04) items (Table S20). For 'Disobedient at school' the direction of effect has flipped as compared to the replication analysis, for 'Loud' the direction of effect was congruent across the replication and validation phases (Table S18). Neurotransmitter ratios were not significantly associated with any of the other 16 aggression items and after correction for multiple testing the ratio of L-phenylalanine to L-tyrosine was not significantly associated with 'Disobedient at school' or 'Loud' (Table S20). In addition to the congruent direction of effect for 'Loud' we also observed congruent directions of effect of 'MoodSwings', 'Suspicious' and 'Teases' (Table S18).



## Chapter 6, Supplementary Text 4. Description of aggression measures

In Table S5 we present the mean scores of the twins included in this project for aggression as obtained by different raters and instruments at different ages. The following questionnaires have been included in this overview:

The Aggressive Behavior scale of the ASEBA Child Behavior Checklist (CBCL) for preschool children (1.5-5 years; Achenbach et al., 2017) as rated by mothers and fathers of the twins at age 3.

The Aggressive Behavior scale of the Devereux Child Behavior (DCB) rating scale (Molenaar, Middeldorp, van Beijsterveldt, & Boomsma, 2015; Van Beijsterveldt, Verhulst, Molenaar, & Boomsma, 2004) as rated by mothers and fathers of the twins at age 5.

The Aggressive Behavior scale of the ASEBA CBCL for school-aged children (6-18 years; Achenbach et al., 2017) as rated by mothers and fathers of the twins at ages 7 and 10.

The Aggressive Behavior scale of the ASEBA Teacher Rating Form (TRF; Achenbach et al., 2017) as rated by teachers of the twins at ages 7, 10 and 12.

The Conduct Problems scale of the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997, 2001) as rated by mothers and fathers of the twins at age 10.

The Conduct Disorder (CD) and Oppositional Defiant Disorder (ODD) scales from the Autism - Tics, ADHD and other Comorbidities inventory (A-TAC; Hansson et al., 2005; Kerekes et al., 2014) as rated by mothers and fathers of the twins at age 10.

The Aggressive Behavior scale of the ASEBA Brief Problem Monitor (BPM; Chorpita et al., 2010) as rated by mothers and father of the twins at age 12.

**Chapter 6, Table S1** Descriptives for all twin pairs with urine (N = 1,362) and/or DNA (N = 1,468).

| | Concordant Low | Discordant Low (n = 196) | Discordant High (n =196) | Concordant High |
|---|---|---|---|---|
| N (N complete twin pairs) | 676 (337) | 392 (196) | | 406 (203) |
| Mean (SD) age sample collection | 9.4 (1.9) | 10.1 (1.7) | | 9.5 (1.8) |
| Range age sample collection | 5.6 - 12.6 | 6.1 - 12.7 | | 5.8 - 12.9 |
| N (%) females | 354 (52.4%) | 88 (44.9.6%) | 82 (41.8%) | 177 (43.6%) |
| N (%) MZ twins | 540 (79.9%) | 160 (81.6%) | 160 (81.6%) | 370 (91.1%) |
| Mean CBCL (SD) aggression score | 2.7 (3.8) | 4.5 (4.4) | 6.3 (5.8) | 7.5 (6.0) |

**Chapter 6, Table S2** Primary DSM-IV classification of the clinical cases (*N* = 183)

| DSM classification | N (% of total sample) |
|---|---|
| ADHD combined type | 45 (24.6%) |
| Pervasive developmental disorder not otherwise specified | 40 (21.9%) |
| Autistic disorder | 33 (18.0%) |
| ADHD inattentive type | 13 (7.1%) |
| Learning disorder not otherwise specified | 12 (6.6%) |
| Adjustment disorder | 9 (4.9%) |
| Generalized anxiety disorder | 3 (1.6%) |
| Obsessive compulsive disorder | 2 (1.1%) |
| Undifferentiated somatoform Disorder | 2 (1.1%) |
| Separation anxiety disorder | 2 (1.1%) |
| Posttraumatic stress disorder | 2 (1.1%) |
| Reactive attachment disorder | 2 (1.1%) |
| Other | 14 (7.7%) |
| Total classifications | 179 |

*Note*. Not all clinical cases have received classifications because data were collected before the diagnostic process was ended. Classifications with a prevalence smaller than two have been grouped under "Other". ADHD = Attention Deficit Hyperactivity Disorder; DSM = Diagnostic and Statistical Manual of Mental Disorders.

## Supplementary Tables 3 through 8 are available online

**Chapter 6, Table S9** Sensitivity analyses for the 5 amines, organic acids and other biomarkers included in the validation phase. Sensitivity analyses were performed with paired t-tests in MZ twins discordant for aggression, after removal of the MZ twin (and co-twin) with a preexisting chronic condition or was on medication or vitamin supplements during urine collection. All p-values have been adjusted for multiple testing using the FDR of 5% for 15 tests.

| | | | Low aggression | | High aggression | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Analysis | Platform | Metabolite | mean | sd | mean | sd | Mean difference | df | t | p-value | FDR p-value |
| No chronic condition | Amines | Gamma. Glutamylglutamine | -0.09 | 0.91 | -0.21 | 0.90 | -0.14 | 132 | -1.94 | 0.05 | 0.65 |
| No chronic condition | Organic acids | Glyceric.acid | -0.02 | 0.85 | 0.13 | 0.96 | 0.12 | 132 | 1.33 | 0.19 | 0.65 |
| No chronic condition | Amines | L.Arginine | 0.16 | 1.00 | 0.10 | 1.06 | -0.08 | 132 | -0.78 | 0.44 | 0.75 |
| No chronic condition | Organic acids | Succinic.acid | 0.13 | 0.92 | 0.11 | 0.96 | -0.03 | 132 | -0.46 | 0.65 | 0.75 |
| No chronic condition | Other | creatinine | 0.15 | 0.95 | 0.21 | 0.95 | 0.02 | 132 | 0.28 | 0.78 | 0.78 |
| No medication | Amines | Gamma. Glutamylglutamine | -0.09 | 0.91 | -0.21 | 0.90 | -0.11 | 116 | -1.42 | 0.16 | 0.65 |
| No medication | Organic acids | Glyceric.acid | -0.02 | 0.85 | 0.13 | 0.96 | 0.12 | 116 | 1.24 | 0.22 | 0.65 |
| No medication | Amines | L.Arginine | 0.16 | 1.00 | 0.10 | 1.06 | -0.07 | 116 | -0.56 | 0.57 | 0.75 |
| No medication | Organic acids | Succinic.acid | 0.13 | 0.92 | 0.11 | 0.96 | -0.04 | 116 | -0.53 | 0.60 | 0.75 |
| No medication | Other | creatinine | 0.15 | 0.95 | 0.21 | 0.95 | 0.03 | 116 | 0.33 | 0.74 | 0.78 |
| No vitamines | Amines | Glyceric.acid | -0.02 | 0.85 | 0.13 | 0.96 | 0.15 | 115 | 1.56 | 0.12 | 0.65 |
| No vitamines | Organic acids | Gamma. Glutamylglutamine | -0.09 | 0.91 | -0.21 | 0.90 | -0.08 | 115 | -1.03 | 0.30 | 0.75 |
| No vitamines | Amines | creatinine | 0.15 | 0.95 | 0.21 | 0.95 | 0.06 | 115 | 0.70 | 0.48 | 0.75 |
| No vitamines | Organic acids | L.Arginine | 0.16 | 1.00 | 0.10 | 1.06 | -0.08 | 115 | -0.65 | 0.52 | 0.75 |
| No vitamines | Other | Succinic.acid | 0.13 | 0.92 | 0.11 | 0.96 | 0.04 | 115 | 0.53 | 0.60 | 0.75 |

## Supplementary Table 10 is available online

**Chapter 6, Table S11** Replication of the top 25% most strongly associated neurotransmitter ratios. Replication analyses were performed with paired t-tests for 189 twin pairs discordant (high-low)on aggression status. Analyzes were performed on the residuals as obtained with linear regression after regressing out sex and age at urine collection. The p-values have been adjusted for multiple testing using the FDR of 5% for 3 tests. * 3MT = 3-methoxytyramine; 5HTP = 5-hydroxy-L-tryptophan; HVA = homovanillic acid

| Neurotransmitter pathways | Ratio* | Low aggression mean | Low aggression sd | High aggression mean | High aggression sd | Mean difference | df | t | p-value | FDR p-value |
|---|---|---|---|---|---|---|---|---|---|---|
| Dopamine | 3MT:HVA | -0.38 | 24.80 | 2.72 | 26.53 | 3.00 | 188 | 1.28 | 0.20 | 0.61 |
| Dopamine | L-phenylalanine: L-tyrosine | 1.33 | 6.20 | 1.01 | 4.30 | -0.32 | 188 | -0.58 | 0.56 | 0.84 |
| Serotonine | 5HTP:serotonin | 1.52 | 15.83 | 1.94 | 29.14 | 0.36 | 188 | 0.15 | 0.88 | 0.88 |

## Supplementary Tables 12 through 20 are available online