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Continuity of aggressive antisocial behavior from childhood to adulthood: the question of phenotype definition

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Abstract

Aiming to clarify the adult phenotype of antisocial personality disorder (ASPD), the empirical literature on its childhood background among the disruptive behaviour disorders, such as attention deficit/hyperactivity disorder (AD/HD), oppositional defiant disorder (ODD), conduct disorder (CD), or hyperkinetic conduct disorder (HKCD), was reviewed according to the Robins and Guze criteria for nosological validity. At least half of hyperactive children develop ODD and about a third CD (i.e. AD/HD+CD or HKCD) before puberty. About half of children with this combined problem constellation develop severe criminality and/or antisocial personality disorder (ASPD) in adulthood. Family and adoption/twin studies indicate that AD/HD and CD share a high heritability, and that, in addition, there may be specific environmental effects for criminal behaviours. ”Zones of rarity” delineating the disorders from each other or from the normal variation, have not been identified. Neurophysiology, brain imaging, neurochemistry, neurocognition, or molecular genetics have not provided “external validity” for any of the diagnostic categories used today. Deficient mental functions, such as inattention, poor executive functions, poor verbal learning and impaired social interaction (empathy), seem to form unspecific susceptibility factors. As none of today’s proposed syndromes (e.g. AD/HD or psychopathy) seems to describe a natural category, a dimensional behavioural phenotype reflecting aggressive antisocial behaviours assessed by numbers of behaviours, the severity of their consequences and how early is their age at onset, which will be closely related to childhood hyperactivity, would bring conceptual clarity, and may form the basis for further probing into mental, cognitive, biological and treatment-related co-varying features.
1. Introduction

That problem behaviours in children may herald psychosocial problems in adult life is basically a universal insight and the mainstay of most educational efforts. The association has also been demonstrated in a number of longitudinal studies and forms the nucleus in phenotype definitions of adult impulsive behaviours, physical aggression, violation of societal norms, and deficient emotional reactions, that is antisocial personality disorder (ASPD, American Psychiatric Association (APA), 1994), dissocial personality disorder (ICD-10, World Health Organization, 1993) or psychopathy (Hare, 1980). Nevertheless, the nosological categories proposed to capture specific problem constellations both overlap and are heterogeneously defined.

Attention-Deficit Hyperactivity Disorder (AD/HD) is an umbrella term by definition consisting of three problem domains, inattention, hyperactivity and impulsivity, listed in two separate sets of criteria that may be met individually or together. Two persons who both have this diagnosis may theoretically not share a single criterion. The International Classification of Diseases, tenth edition (ICD-10, WHO, 1993) has based its corresponding definition solely on hyperactivity (Hyperkinetic Disorder), noting attention deficits as a common complication but not as part of the syndrome. If hyperkinesia is combined with outright antisocial behaviours, the diagnosis of hyperkinetic conduct disorder (HKCD) may be made. In the DSM-IV, Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) are instead treated as two separate disorders.
Other diagnostic categories that have been implicated in the context of aggressive behaviours are the autism spectrum disorders (ASD), describing deficits in social interaction or “empathy”, verbal and/or non-verbal communication and flexibility, and “paediatric mania” or bipolar disorder with irritable, elated mood swings. A brief overview of the current diagnostic definitions that may be related to antisocial behaviours provided by the DSM-IV and the ICD-10 is given in Table 1.

/Table 1 about here/

Assessing the validity of diagnostic concepts in psychiatric nosology is a continuous process, where, in the absence of knowledge about specific aetiological factors, definitions have to be regarded as preliminary and subject to revision. A seminal paper by Robins and Guze (1970) argued that a valid classification should be based on systematic empirical studies rather than on “a priori principles”, according to five specific criteria (Table 2). We have reviewed the literature by these criteria in order to

1. assess the validity of current categorical diagnoses and
2. propose more specific clinical descriptions of the development of aggressive antisocial behaviours.

/Table 2 about here/

2. Method
The studies assembled for this review were identified using systematic PubMed searches in October-November 2007 by the search terms detailed in Table 3. Hand-searches according to the reference lists of the most important textbooks on the field (Stoff, Breiling & Maser, 1997; Patrick, 2006; Quay & Hogan, 1999; Lahey, Moffitt, & Caspi, 2003) were also performed to identify studies published in non-indexed sources. Selected references of outstanding importance for the research questions were added for a revision of the manuscript in March 2009.

/Table 3 about here/

Clinical and population-based prospective studies of the longitudinal development of childhood hyperactivity were selected if they included: 1. a group size of at least a hundred subjects; 2. a longitudinal design with duration of at least four years starting in childhood and assessments performed in adult age; 3. assessments of behavioural disorders equivalent to contemporary diagnostic criteria; 4. descriptions of prevalence of criminality. An exception from the third criterion was made for the outstandingly important Dunedin study, which was initially based on behavioural descriptions that were not equivalent to psychiatric diagnoses. Papers were considered in detail, summarized in Table 4 and used for a meta-analysis of the adult outcome for cases identified with hyperactivity in relation to controls in terms of 1. diagnostic stability, 2. ASPD, 3. criminality, and 4. death by violence or accidents by Fischer’s exact tests. These longitudinal studies also address both the overlap between disorders/problem types (Robins & Guze criterion 3) and homo- vs. heterotype development (criterion 4). We subsequently assessed criterion 1, the specificity of clinical description (in relation
to non-disordered states and to other types of disorders); criterion 5, patterns of familial
aggregation and associations within and across diagnostic categories by family-
adoption and twin studies; and finally, criterion 2, “external” validators with the
extension proposed by Andreasen (1995), as detailed in Table 2.

/Table 4 about here/

3. Results

3.1. Criteria 3 & 4: delineation and homotype progression

Six studies on clinic-referred children and six population-based prospective,
longitudinal studies following hyperactive children into adulthood were identified
(Table 4). All these studies had included children according to behavioural criteria at
base-line. Detailed figures for the follow-up of cases and controls in relation to our
defined outcome parameters are given in the bottom row of the Table with p-values for
comparisons. Studies included in the meta-analyses are indicated in the Table. The
studies that were not included in the meta-analyses did not provide precise figures for
cases versus controls or did not include certain measures, such as personality disorders,
in their follow-ups. Hyperactive children were at significantly increased risk for ASPD,
including CD. There were also more violent deaths in this group, but due to small
numbers, the difference in risk (1.3 % vs 0.3 %) did not reach statistical significance.
Diagnostic stability was surprisingly low, and only a small minority (6 %) of formerly
hyperactive children still met full criteria for AD/HD at follow-up. In contrast, the
prevalences of several other mental disorders were higher than that of AD/HD.
Some conclusions may be drawn from the joint studies. ODD is very common in hyperactive children. Almost all children who develop CD have had ODD, while a subgroup of children with ODD develop CD. A central question is whether hyperactivity in itself, without early-onset CD, increases the risk for ASPD and criminality. To study this association would require studies that systematically identified all cases with pre-pubertal CD within their study groups. We did not find any such study. Often CD was not clearly assessed at inclusion, and children varying broadly in age were included. A seven-year old with hyperactivity but not CD will be at risk during the rest of his childhood to develop the combination. It is therefore not possible by today’s literature to pin a risk increase for ASPD and criminality in adulthood on hyperactivity without early-onset CD, even if such an association may exist in real life.

3.2. Clinical description

Diagnostic criteria describe behaviours in relation to specific situations (e.g. “home”, “school”) or to different challenges (e.g. ”remaining seated when expected”, “to comply with adults’ requests”) (Table 1). At first glance, there seems to be no direct content overlaps. Yet, as items across the categorical definitions are worded in relation to heterogeneous contexts, they may still refer to common, more “molar” or general deficits. For example, deficits in behavioural and emotional inhibition are central to AD/HD, ODD, and CD, and can also play a role in some autism spectrum disorder (ASD) criteria (such as problems in sustaining a mutual conversation with others) or symptoms of mania (disinhibited behaviours with negative consequences). Similarly,
criteria referring to social interaction problems are found across all diagnostic categories (e.g. the AD/HD criterion; “often interrupts or intrudes on others”, or the HCD criterion; “socially disinhibited”, just as the at least four ODD and seven CD criteria that refer to interpersonal interaction, and the first group of ASD symptom criteria (DSM-IV)).

3.3. Age at onset

Diagnostic criteria are worded in relation to developmental phases, and all definitions of ‘disorder’ or ‘deficit’ have to relate to an idea about ‘normal’ development. Hence, the pattern of overlap between problems depends on the age at which the cross-section is made. Assessment methods (e.g. questionnaires, symptom lists, standardized observational schemes, and neuropsychological tests) for the preschool period have become more available, which has started to bear fruit in birth cohort studies (Angold & Egger, 2007).

Problems manifested early in development, already in the first years of life and at least well before puberty, may be more pivotal to the phenotype definitions, as studies across diagnostic categories have shown higher heritability and persistence over time for early-onset problems (Moffitt, 1993; Kim-Cohen et al., 2005). The DSM-IV defines early-onset CD as onset before 10 years. Among children with AD/HD, studies have indicated that virtually all cases of CD develop before the age of 12 (Biederman et al., 1996a). Conversely, most cases of early-onset CD have been shown to arise in children with hyperactive, “undercontrolled temperaments” (Lahey & Loeber, 1997; Moffitt, 1990).
Adolescent onset CD differs by being more related to peer groups, less hereditary and less persistent (Moffitt & Henry, 1991).

3.4. Treatment response

Response to treatment merits a review on its own, but let us here merely consider that at least four different types of pharmacological treatments have been studied and used to treat aspects of aggressive antisocial behaviours in children, adolescents, and adults, and that these may target specific neurobiological systems and problem types, which would make them candidates for phenotype markers. Psychostimulants are effective for hyperactivity (Biederman & Faraone, 2005), neuroleptics for aggression (Turgay, 2005), mood stabilizers for negative emotions in mood swings (Smith, Cornelius, Warnock, Bell & Young, 2007), and, possibly, anti-depressants for impulsivity (Popper, 1997). Psychotherapeutic and educative efforts may target behaviour patterns, deficient cognitive abilities and/or hampered personality maturation.

3.5. Familial aggregation

A unanimous literature describes a high familial aggregation of hyperactivity and AD/HD (e.g. Faraone, 2004). Twin studies have yielded a mean estimate of 76 % for the share of variance attributable to genetic factors (Faraone et al., 2005), which is in line with findings from adoption studies (Sprich, Biederman, Crawford, Mundy & Faraone, 2000). A substantial genetic overlap has been shown between AD/HD and ODD/CD (Nadder, Rutter, Silberg, Maes, & Eaves, 2002), and a recent twin study was interpreted as rejecting the hypothesis that they are three “independent” conditions (Rhee, Willcutt, Hartman, Pennington & DeFries, 2008). Family studies, however,
indicate that AD/HD with CD, just as CD on its own, carries an increased prevalence of CD and ASPD in relatives, while relatives to probands with AD/HD in the absence of CD (regardless of whether it is combined with ODD or not) do not have increased risk for criminality (Faraone et al., 2000; Faraone, Biederman, Jetton, & Tsuang, 1997). It therefore seems probable that there is a basic susceptibility for hyperactivity, to which specific genetic and environmental susceptibility factors for the progression into CD or criminal behaviours may be added (Maes, Silberg, Neale, & Eaves, 2007). Furthermore, there is increasing evidence that aggressive and non-aggressive antisocial behaviours can be etiologically differentiated, with the former being highly heritable (accounting for 65% of the variance, Burt, 2009). Genetic factors indeed seems to mediate the progression from early onset, persistent aggression and delinquency to a self-rated psychopathic personality in adolescence, while shared environmental factors are involved in the association to more general antisocial behaviour (Forsman, Larsson, Andershed & Lichtenstein, 2007). Among the facets of psychopathic personality, unique genetic effects were identified for the lack of emotional reactions and the antisocial behaviour, while the interpersonal dominance seeking was associated with both genetic and shared environmental factors (Larsson, Andershed & Lichtenstein, 2006).

3.6. "External" validators

3.6.1. Neurophysiology

Gray’s motivational theory (1987) suggests three interdependent brain systems, two linked to the balance between activation and inhibition (the behavioral activation system (BAS) and the behavioral inhibition system (BIS)), and the fight-flight-freezing system.
Disinhibition purportedly results from an imbalance in BAS and BIS functioning, favouring behavioural activation. BIS activity has been measured by electrodermal responding, i.e. changes in the conductivity of the skin, which is increased by the sweating resulting from activation of the sympathetic autonomous nervous system (Fowles, 1988). A few studies in AD/HD have demonstrated attenuated electrodermal responses to stress (Iaboni, Douglas & Ditto, 1997), while studies of antisocial subjects have more consistently shown reduced responses as compared to controls (Gatzke-Kopp, Raine, Loeber, Stouthamer-Loeber & Steinhauer, 2002). Inhibition has also been assessed through neuroendocrine markers in response to stressors. Lower activity in the hypothalamic-pituitary-adrenal (HPA) axis in relation to stress has been reported both from groups with AD/HD and ODD/CD (e.g. Randazzo, Dockray & Susman, 2007; van Goozen, Fairchild, Snoek & Harold, 2007). Beauchaine (2001) has suggested an additional emotion regulation deficit in aggressive CD, adding to the BIS and BAS model, and possibly expressed as an inadequate vagal modulation of cardiac output (Beauchaine, Gatzke-Kopp & Mead, 2007).

A large number of EEG studies have found subjects with AD/HD to be characterized by an overall “theta excess” and “alpha slowing” (Barry, Johnstone & Clarke, 2003), but similar changes have been described in a very vast range of mental or neurological disorders (Hughes & John, 1999). In criminality, Raine (1997) summarized that there “have probably been hundreds of studies assessing EEGs in criminals, delinquents, psychopaths, and violent offenders”, showing these kinds of unspecific patterns.
A reduced amplitude of the event-related P3 (third positive) component potential (ERP), i.e. the wave of brain electrical activity emerging approximately 300 milliseconds following a rare stimulus, has also been unspecifically implicated across a spectrum of disorders, such as alcohol dependence, illicit drug dependence, nicotine dependence, AD/HD, ODD, CD and ASPD (Iacono, Carlson, Malone & McGue, 2002).

### 3.6.2. Brain imaging

Brain imaging studies are structural, functional, or both. Structural imaging is quantified for research purposes by measuring volumes, while functional imaging is measured by general (such as the blood flow or glucose metabolism) or specific (ligands for receptors or transmitter precursors) indicators of activity in specific regions of interest (ROIs).

A quantitative review of structural studies on AD/HD (Valera, Faraone, Murray & Seidman, 2007) based on more than 500 index children and young adolescents, and as many controls, showed significant volume reductions in the cerebellum, the callosal body, and the right caudate nucleus, and also for the total and right cerebral volume. A similar picture emerged in an MRI study of 24 adults with AD/HD (Seidman et al., 2006). Cortical reductions have also been longitudinally associated with persistence of AD/HD symptoms and poorer outcome (Shaw et al., 2006). Decreased or aberrant global and regional metabolism, especially in the striatum, has been a fairly consistent finding in studies of regional brain activity in AD/HD, while findings of changed activity in the prefrontal cortex have been less consistent (as reviewed in Bush, Valera & Seidman 2005).
In spite of an extensive literature on the structural neural underpinnings of aggression in children (van Goozen, Fairchild, Snoek & Harold, 2007), few studies have actually investigated children and adolescents defined as fulfilling criteria for CD. In Bussing and co-workers (2002), a small community sample of children with AD/HD in the presence or absence of CD were assessed by MRI and compared to controls, but no significant differences were detected. One study of early-onset CD in combination with AD/HD, however, found significantly reduced right temporal lobe volumes and a tendency to reductions in the prefrontal areas, as compared to healthy controls (Kruesi, Casanova, Mannheim & Johnson-Bilder, 2004). Another study of early-onset CD reported significantly reduced grey matter volumes in the bilateral anterior insular cortex and the left amygdala, which also correlated with dimensional measures of aggression and even more strongly with attention problems (Sterzer, Stadler, Poustka & Kleinschmidt, 2007).

In adults with different forms of antisocial behavior, the prefrontal cortex has been in focus for imaging studies ever since Damasio’s re-rendering of the Phineas Gage case (Damasio, Grabowski, Frank, Galaburda & Damasio, 1994). However, Harlow’s original case report rather presents a case of progressive bacterial encephalitis with recurrent fits (including epileptic states) than a specific status post the injury so elegantly depicted in the computer simulated imagery from Damasio’s paper. Significant prefrontal cortical volume loss was indeed demonstrated in 21 community-recruited adults with ASPD (Raine, Lencz, Bihrl, LaCasse & Colletti, 2000), while Dolan and co-workers (2002) found no significant frontal or temporal structural differences between a group of patients with high psychopathy scores and controls.
Functional or structural changes in brain regions involved in the regulation of emotional behavior, such as the temporal lobes and the limbic system, have been recurrent in imaging studies of adults with antisocial behaviour disorders (Anckarsäter, 2006). In adolescents with CD and AD/HD, aberrant functional reactions in the anterior cingulate cortex and the amygdala when processing negative affective stimuli, have also been observed (Sterzer, Stadler, Krebs, Kleinschmidt, & Poustka, 2005; Stadler et al., 2007).

Specific methodological problems for imaging studies include heterogeneous assessment procedures and image evaluation techniques. Just for AD/HD, Valera and co-workers (2007) emphasized the tremendous variability in the placement of ROIs, with differences in size and definition across studies that make quantitative meta-analyses virtually impossible. Measures of activity are expressed as relative regional signals in comparison to other brain structures, such as the contralateral hemisphere, occipital cortex, or the cerebellum. This may have influenced results since, for example, the cerebellum is also involved across social and emotional reactions, and we therefore do not know whether reduced regional/cerebellar ratios are due to cerebellar hyperactivity rather than hypoactivity in the studied region (Anckarsäter, 2006). In common with other studies comparing possible external markers between cases with antisocial life histories and controls, confounding factors are virtually impossible to control for in imaging studies, as are the effects of publishing biases.

3.6.3. Neurocognition
Clinical as well as community studies have found lower scores on intelligence tests in individuals with AD/HD as compared to control groups, particularly in verbal intelligence (e.g. Mariani & Barkley, 1997; Petersen, Pine, Cohen, & Brook, 2001), and a community twin study found common genetic influences behind inattention and reading difficulties, but not hyperactivity (Willcut, Pennington, Olson & 2007). The difference typically equals between a half and one standard deviation in intelligence quotients on the group level. Children and adolescents with ODD/CD have similar reductions in comparison to normal controls (Pennington, 2002), even after controlling for socio-economic and ethnic confounders (Moffitt, 2006). It is notably difficult to compare results on intelligence tests across populations, but it may be concluded that specific deficits or uneven profiles form more relevant models than general learning disabilities in the background to hyperactivity or antisocial behaviours.

The central deficit behind the AD/HD symptom complex has been described as executive dysfunction, a broad construct referring to complex organizing of behaviour and various functions involved in the maintenance of behaviour on a goal set over time independently from external saliencies (Nigg, Willcutt, Doyle & Sonuga-Barke, 2005). Among these functions, executive motor disinhibition (especially notable in the Stop task) has been most consistently associated with AD/HD (Lijffijt, Kenemans, Verbaten, & van Engeland, 2005), as children with AD/HD have significantly longer reaction times to an inhibition signal than controls. Even if numerous studies have reported on abnormal results for tests of executive functions in AD/HD, negative reports have not been uncommon (Willcut, Doyle, Nigg, Faraone & Pennington, 2005). Other functions, such as reaction time to response signals, have been even more deviant in AD/HD, and
executive functions have been as deficient in other diagnostic categories, such as autism (Pennington & Ozonoff, 1996) and CD (Oosterlaan, Logan & Sergeant, 1998). By simply reading the diagnostic criteria, it is, however, obvious that several AD/HD criteria describe what has been defined as executive functions (and the tests are designed to measure), i.e. a lack of focus, direction and consideration of consequences. Coghill and co-workers (2005) suggested that inattention, but not hyperactivity/impulsivity, is associated with deficient executive functions and poor academic achievement, referring to clinical as well as community samples (e.g. Chhabildas, Pennington & Willcutt, 2001), and that hyperactivity/impulsivity is more closely related to dysfunctions of reward mechanisms (e.g. Sonuga-Barke, Dalen & Remington, 2003).

Castellanos and co-workers (2006) reviewed the model presented by Zelazo and Mullers (2003) on the functional differentiations within frontal cortices. They distinguished between more purely cognitive, “cool” aspects of executive functions associated with the dorsolateral frontal cortex, and "hot”, or affective, aspects, associated with the orbital and medial prefrontal cortex. In this model, ‘cool’ executive functions are elicited by relatively abstract, decontextualized problems, such as most of the tasks tested so far in AD/HD (e.g. working memory and tests requiring sustained attention and inhibitory activity). ‘Hot’ executive functions are required for problems that are characterized by high affective involvement or demand flexible or appropriate appraisals of the emotional significance of stimuli. For example, risky decision-making in the Iowa Gambling could be a ’hot’ executive function (Kerr & Zelazo, 2004). Deficits on this test have also been associated with hyperactivity/impulsivity (Toplak,
Jain & Tannock, 2005) and with symptoms of opposition and conduct problems (Ernst et al., 2003), but not with symptoms of inattention. Children with AD/HD have also exhibited marked difficulties in decoding affective facial expressions, with specific deficit in identifying anger and sadness (e.g. Pelc, Kornreich, Foisy & Dan, 2006).

The ‘hot’ executive functions thus resemble the functions ascribed to the limbic system, processing social stimuli by memories and emotions. Interestingly, clinical states associated with damage in the limbic system, in the non-dominant hemisphere or with reduced interhemispheric communication have shown common clinical features. Thus, problems with ‘hot’ executive functions, recognition of affects and visuospatial deficits may be found together (Raine et al., 2005). “Callous-unemotional” traits describe reduced emotional reactivity and are associated with antisocial behaviours (such as in the ASPD or psychopathy constructs) (Loney, Frick, Ellis & McCoy, 1998; Frick & Stuart, 2008). Reductions of these functions also recur in the non-verbal learning disability (NVLD) syndrome described by Rourke (1987), which also includes a risk for aggressive behaviours. The specificity of these problems in relation to the verbal executive functions has been disputed (Moffitt et al., 2008), and, conceptually, these definitions also overlap with core dysfunctions in the autism spectrum, such as deficits in social interaction and non-verbal communication. Inter-hemispheric transfer is targeted in research on brain processes relevant for autism (Nydén, Carlsson, Carlsson & Gillberg, 2004). Details of these parallels are, however, insufficiently known (Rogers, Viding, Blair, Frith & Happé, 2006), and clinical experience describe autistic social difficulties as qualitatively distinct.
In sum, two large aspects of neurocognition are often implicated as susceptibility factors for aggressive antisocial behaviour. One is related to problems with language, especially abstractions, deficient strategies, and the prefrontal cortex, the other to shallow affects, visuo-spatial problems, reduced emotional integration and non-verbal communication and the limbic circuitry, inter-hemispheric transfer and/or the non-dominant hemisphere. These broad domains recur across scientific models in relation to aggressive behaviours. Traditionally, verbal deficits have been proposed to be specific for CD (e.g. Caspi & Moffitt, 1995), but as spatial impairments have increasingly been brought in focus (e.g., Speltz, DeKlyen, Calderon, Greenberg & Fisher, 1999; Raine et al., 2005), it seems more reasonable to describe these two large domains of mental functional deficits, whose relations to each other remain insufficiently known.

3.6.4. Neurochemistry

Low serotonergic neurotransmission has been associated with emotionally driven, impulsive, destructive acts (e.g. Asberg, Traskman & Thoren, 1976; Brown et al., 1982; Virkkunen, Nuutila, Goodwin & Linnoila, 1987) but not with instrumental violence (Lidberg, Tuck, Asberg, Scalia-Tomba & Bertilsson, 1985; Gardner, Lucas & Cowdry, 1990). Kruesi and co-workers (1990) found that children with ODD/CD and/or AD/HD had lower concentrations of serotonin metabolites in the cerebrospinal fluid than children suffering from obsessive-compulsive disorder, and that these concentrations were inversely correlated with ratings of aggressive behaviours. At a two-year follow-up, the metabolite concentrations also predicted the severity of physical, aggressive behaviour and poor outcome (Kruesi et al., 1992). In contrast, Castellanos and co-workers (1994) found that the same metabolite concentrations were positively correlated...
with measures of aggression and impulsivity in a study of boys with AD/HD. Since this group was more hyperactive and less aggressive than the previous one, the authors speculated that serotonin measures may correlate with aggression only in groups of children with a core aggression problem.

Lower cerebrospinal fluid concentrations of serotonin metabolites have also been reported in several studies of aggressive antisocial adults and youths with CD (Berman, Kavoussi & Coccaro, 1997). The ratio between the dopamine and serotonin metabolites in the CSF, which reflects the serotonergic regulation of dopaminergic activity, was positively associated with aggression, AD/HD and CD in two separate studies of adult offenders (Soderstrom, Blennow, Sjodin & Forsman, 2003). The dopamine systems play a central role in the regulation of attentional processes, psychomotor activity and reward-seeking behavior (e.g. Krause, Dresel, Krause, Kung & Tatsch, 2000; Spencer, Biedermann, Wilens & Farone, 2002). Stimulants, such as methylphenidate, probably reduce AD/HD symptoms by increasing the release of dopamine and norepinephrine (Biederman, 2005).

In addition to neurotransmitters, hormones have been studied as covariates to antisocial behaviours. Activated thyroid hormones (in relation to precursors) have been associated with AD/HD symptoms in clinical (Stein & Weiss, 2003) as well as community study groups (Alvarez-Pedrerol et al., 2007), and have been predictive of criminal recidivism in studies among both young lawbreakers (Levander, Mattsson, Schalling & Dalteg, 1987) and adult criminals (Stahlenheim, 2004). As depression has been associated with the inverse pattern, this may, however, not express a direct link but a lack of depressive
reactivity among the more cold-hearted and thereby recidivism-prone subjects (Soderstrom & Forsman, 2004).

Testosterone increases aggressive behaviours (Archer, 1991) and the mere prevalence of violence and criminality in young men as compared to elder men and women, and the increased aggression noticed in females in the premenstrual phase (Dougherty, Bjork, Huang & Moeller, 1997), makes testosterone a prime suspect in the quest for biological background factors to aggression. Testosterone has been related to delinquency, alcoholism, and drug use among adults, as well as to conduct problems in childhood (e.g. Dabbs, Carr, Frady & Riad, 1995). Effect sizes for these relations are typically small, but tend to be larger for males from lower socioeconomic backgrounds. Some studies also have failed to find any relationship between aggression and testosterone (e.g. van Bokhoven et al., 2006).

3.6.5. Molecular genetics

In a comprehensive review of the search for molecular genetic markers for AD/HD, Bobb and co-workers (2005) concluded that of all publications on associations between AD/HD and specific gene variants, 36 % were positive, 17 % showed trends, and 47 % were negative. This was uncorrelated with sample size, but studies using dimensional measures, or case-control models, tended to report more positive findings than categorical or family based studies. It was also a clear trend that positive, dimensional, and case-control studies were published earlier than more recent negative replications using family-based models. Again, the publication bias is described as a major obstacle
to understand and interpret the results, while underpowered samples and selected populations add to the weakness of possible interpretations.

Linkage studies of AD/HD have identified specific chromosome regions, that have also been implicated in aggressive behaviours (e.g. Kendler et al., 2006), leading to the possible conclusion that "AD/HD co-segregates with disruptive behaviours as a unique, phenotypically variable trait as evidenced by highly significant pair-wise linkages" (Jain et al., 2007). Findings for various definitions of CD or aggression have been inconsistent, but these studies have generally been based on study cohorts originally assembled to study other problem definitions, such as substance abuse (e.g. Stallings et al., 2005).

In association studies, the most thoroughly investigated genes are those implicated in serotonergic and dopaminergic neurotransmission. Repeat polymorphisms, some of which have been shown to be functional, have been studied in relation to aggressive behaviours in the genes for the dopamine receptor 4, the dopamine transporter, the serotonin transporter, and the monoamine oxidase type A. The latter is especially interesting for disorders with a skewed sex ratio as it is located on the X chromosome. The gene for the serotonin receptor 2A contains several single nucleotide polymorphisms that have been studied in relation to psychiatry. Other genes that have been studied in relation to behavioural disorder include those coding for other enzymes and receptors involved in monoaminergic neurotransmission, sexual hormone metabolism, and a vast array of proteins involved in brain development.
So far, no study has indicated any polymorphism or gene locus that may effect the variance in the phenotypical definitions described above by more than a minute effect (typically with odds ratios well below 2 or effect sizes maximally at a couple of percents, Kendler, 2005).

During recent years, intense interest has been focused on interactions between specific genotypes and environmental factors as a possible key to disentangle the inconsistent findings from univariate association studies. The first paper to identify such effects was published in 2002 by Caspi and co-workers, who could show that maltreated boys with the high-activity polymorphism in the MAO-A gene were less likely to develop antisocial behaviours than maltreated boys with the low-activity polymorphism, while the polymorphism did not have any effect on the variation of antisocial behaviours in the population at large. This finding has been replicated in several independent studies (e.g. Foley et al., 2004; Kim-Cohen et al., 2006), while others have been negative (e.g. Widom & Brzustowicz, 2006; Young et al., 2006). A range of similar interactions have been proposed, e.g. that “maternal insensitivity” may lead to aggressive behaviours, specifically in the presence of the DRD4 seven repeat polymorphism (Bakermans-Kranenburg & van Ijzendoorn, 2006). The enthusiasm evoked by this line of reports of complex models has faltered as replications have proved as inconsistent as for univariate associations. Simulated analyses by categorical phenotypes and logistic regressions also repeatedly yield models with significant main effect of the environment, no significant main effect of the genotype, and significant GxE interactions, regardless of whether meaningful or nonsense data are used (Eaves, 2006).
In the last few years, new approaches to psychiatric molecular genetics have been called for, focusing on molecular rearrangements and other modifications thought to influence the translation of the genes and thereby the functional activity of its enzymatic end product. Besides some studies of parental imprinting (Kent et al., 2008), convincing associations with behavioural features have not yet been presented for such “epigenetic” models.

4. Summary and proposition.

The literature on longitudinal development of hyperactivity is quite consistent on some basic figures: the majority of children identified as hyperactive, at least during some period, develop a pattern of social interaction characterized by opposition, which, in at least a third, progresses into pre-adult antisocial behaviour. In about a fifth of the original group, this will persist into an ASPD in adulthood. This behaviour progression corresponds to the HKCD and ASPD or dissocial PD in the ICD-10 or in the DSM-system to HD in AD/HD, ODD, CD and ASPD. In AD/HD with CD, ODD at some stage is so common that it is not predictive for later CD development (Biederman et al., 1996a; Biederman, Mick, Faraone & Burback, 2001). Childhood-onset CD, when the full picture is developed at least before puberty, is a very different condition from adolescent CD in terms of prognosis, patterns of comorbidity, and background factors. While adolescent CD has been shown to be mainly a social phenomenon (Moffitt, 1993), the early-onset form is almost always developed from hyperactivity. A dimensional behavioural phenotype of life-time aggressive antisocial behaviours, in which early-onset is a marker of severity, seems far more consistent with the empirical literature as reviewed in this paper than a categorical model of diagnoses. The
Longitudinal studies give at hand that a young age at onset of aggressive antisocial behaviours will reflect the presence of childhood hyperactivity, and thereby identify it as a promising candidate for assessments of the severity of the antisocial behaviour, even if we are far from understanding the mathematics of this association. In addition to the age at onset, the severity may be measured by the behaviour expressions (for example the number of aggressive behaviour incidents sorted by the types of behaviours), and by the psychosocial adverse effects. To merely count the number of diagnostic items that are met, as in most assessment schemes in use today, seems a poor choice for scientific quantification.

Since no demarcation or “zone of rarity” between subjects with antisocial behaviours and the normal variation has been demonstrated, all categorizations rely on arbitrarily defined “cut-offs”. All these behaviours are probably waxing and waning in their expression. Conduct problems have been shown to fluctuate above and below the current diagnostic cut-off level (Biederman, Mick, Faraone & Burback, 2001), and there seems to be good reason to consider also sub-threshold problems. Situational factors rather than the underlying susceptibility may determine the actual symptom expression at a precise moment, which calls for a developmental perspective in phenotype assessments, especially in studies trying to establish underlying mechanisms to problems.

This persistent pattern of early-onset antisocial aggressive behaviours is the back-bone of all phenotype definitions related to interpersonal violence and criminality, i.e. hyperactivity, CD, ASPD, dissocial PD and psychopathy. Open research questions are
whether inattention should be noted as a co-existing problem to hyperactivity (as in the ICD-10) or as a facet in a common syndrome (as in the DSM-IV), whether hyperactivity in itself, without CD, predicts adulthood ASPD (Lilienfeld & Waldman, 1990), and whether ASPD or psychopathy in adulthood should include one, two or three “facets” of mental problems in addition to the antisocial aggressive behaviours (such as childhood-onset disinhibited behaviours, lack of emotional reactions and dominance-seeking interpersonal attitudes (Cooke, Michie & Skeem, 2007; Vitacco, 2007). A childhood-onset, developmental, dimensional phenotype definition of aggressive antisocial behaviours, in relation to which all other forms of mental and/or psychosocial co-varying problems may be independently studied, resolves all these problems.

As for the first of these research questions, inattention is a vague definition that has not really been studied in relation to adult outcomes. In the heterogeneous AD/HD construct, inattention may, just as hyperactivity, be regarded as a result of impulsivity, or the behaviour manifestations could be regarded as results of inattention. As a result of these definitional ambiguities, we do not know if psychostimulants treat inattention, hyperactivity or some more underlying phenomenon. Both inattention and impulsivity merit clear definitions, through clinical signs and psychometric tests, and to be studied in their own rights.

To the next question, whether childhood hyperactivity carries a risk for adult ASPD or criminality in the absence of early CD, we have not found any new evidence to contradict Lilienfeld and Waldmans conclusion from 1990 that the risk for adult negative outcomes is mediated by early onset antisocial behaviours. Most research
projects presented to this date may not answer this issue, as they have included a wide age range from start or have not systematically assessed both CD and hyperactivity before the proposed cut-offs at ages 10, 12 or at puberty. Again, a dimensional description from of antisocial aggressive behaviours, where early-onset hyperactivity and aggressive behaviours are markers of severity, fits the data presented.

Third, there is the issue of various definitions of personality disorder, including “psychopathy”. Epidemiological data were collected for the DSM-IV (Widiger et al., 1996), but assessed the overlap with different mental problem types to a limited extent. The nosology of the proposed “psychopathy” construct has been addressed by psychometric analyses of samples gathered from the penal system, which are inadequate to answer whether these problem types belong in a common syndrome. The “facet” proposed to capture the specific interpersonal manipulative dominance-seeking of “psychopathy” rather reflects what is usually called “wickedness” in social relationships, and it merits further research to validate its style as a mental disorder.

A vast array of studies on “external validators” have demonstrated statistical group differences between subjects with behaviour disorders and controls, and sometimes even a statistical covariation between a laboratory measure and clinical ratings of severity. Overall, no specific “marker” has been identified for any of the diagnostic categories proposed and used today, and the two most salient features in this literature are the consistency of differences between cases and controls, for which the publication bias plays an unknown role, and the lack of specificity in relation to diagnostic definitions.
Being clear about what is spoken of is essential for research into mental phenomena. As long as we do not have access to data that permits factor or cluster analyses across the whole spectrum of mental problems, it seems useless to pursue controversies about how to join problems defined on heterogeneous levels such as behaviours, emotions or cognitive abilities into syndromes. Instead, a clearly defined behavioural phenotype of aggressive antisocial behaviours with an early-onset, which will most often be linked to hyperactivity, as a marker of severity may both fit the current literature and form the starting point for the study of all possible susceptibility factors.
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childhood abuse and neglect, MAOA genotype, and risk for violent and
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comorbidity: a twin study of reading disability and attention-deficit/

monoamine metabolite levels in male arsonists. Arch Gen Psychiatry, 44(3),
241-247.


Table 1. Currently used diagnostic definitions for childhood-onset behavioural disorders

<table>
<thead>
<tr>
<th>Diagnostic categories</th>
<th>Diagnostic code</th>
<th>Age at onset</th>
<th>Problem dimensions</th>
<th>Definitional level (cf. temperament as patterns of reactions to stimuli/percepts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD/HD</td>
<td>314.01</td>
<td>0- years</td>
<td>Hyperkinesia</td>
<td>Behaviours in face of situations demanding motor activity control</td>
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<td></td>
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<td></td>
<td></td>
<td>F90.9</td>
</tr>
<tr>
<td>ASD</td>
<td>299.00</td>
<td>0- years</td>
<td>Social interaction / Communication</td>
<td>Behaviour, cognition and emotion in relation to others</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F84.0</td>
</tr>
<tr>
<td>AD/HD</td>
<td>314.01</td>
<td>4- years</td>
<td>Impulsivity</td>
<td>Behaviours in conversations and queues</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F90.9</td>
</tr>
<tr>
<td>ODD</td>
<td>313.81</td>
<td>4- years</td>
<td>Opposition</td>
<td>Emotional expressions and behaviours in face of other people</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F91.3</td>
</tr>
<tr>
<td>AD/HD</td>
<td>314.00</td>
<td>~6- years</td>
<td>Inattention</td>
<td>Behaviours in face of situations demanding attention and executive functions (school work)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F90.0C</td>
</tr>
<tr>
<td>Mania</td>
<td>296.0x</td>
<td>?</td>
<td>Agitation, irritability, elation, grandiosity</td>
<td>Dysregulated behaviours related to unstable mood</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F30.1</td>
</tr>
<tr>
<td>CD</td>
<td>312.81</td>
<td>~ 4.5-5- y</td>
<td>“Criminality”</td>
<td>Behaviours in contradiction with norms and regulations</td>
</tr>
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<td></td>
<td></td>
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<td>F91.0-2</td>
</tr>
</tbody>
</table>
Table 2. Criteria for diagnostic validity


1. Clinical description (including unique symptoms that do not occur in other disorders, sex, age, precipitating factors, response to various forms of treatment).

2. Laboratory studies identifying biological or other so called “markers” for the disorder. In addition, Andreasen proposed “external” validators from molecular genetics, molecular biology, neurochemistry, neuroanatomy, neurophysiology and cognitive neuroscience.

3. Delimitation from other disorders.

4. Follow-up studies showing a homotype progression, i.e. that the disorder remains stable over time.

5. Family studies showing higher familial aggregation as compared with control groups.
Table 3. Search terms for literature searches in PubMed, in October-November 2007

<table>
<thead>
<tr>
<th>Term</th>
<th>Term</th>
<th>Term</th>
<th>Term</th>
<th>Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>“ADHD”</td>
<td>“ADD”</td>
<td>“hyperactivity”</td>
<td>“hyperkinetic”</td>
<td>“attention-deficit disorder”</td>
</tr>
<tr>
<td>“oppositional defiant disorder”</td>
<td>“conduct disorder”</td>
<td>“disruptive behavior”</td>
<td>“antisocial behaviour”</td>
<td>“antisocial behaviour”</td>
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<td></td>
<td></td>
<td></td>
<td>“behaviour”</td>
<td>“behaviour”</td>
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<td></td>
<td></td>
<td></td>
<td>“children”</td>
<td>“adolescents”</td>
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<tr>
<td>“delinquency”</td>
<td>“criminality + children”</td>
<td>“criminality + adolescents”</td>
<td>“aggression + children”</td>
<td>“aggression + adolescents”</td>
</tr>
<tr>
<td>“neuropsychology”</td>
<td>“neurocognitive”</td>
<td>“cognitive”</td>
<td>“executive function”</td>
<td>“inhibition”</td>
</tr>
<tr>
<td>“motivation”</td>
<td>“reward”</td>
<td>“state regulation”</td>
<td>“diagnostic imaging”</td>
<td>“diagnostic techniques”</td>
</tr>
<tr>
<td>“MRI”</td>
<td>“fMRI”</td>
<td>“PET”</td>
<td>“EEG”</td>
<td>“HPA”</td>
</tr>
<tr>
<td>“hormones”</td>
<td>“endocrine”</td>
<td>“neurotransmitter”</td>
<td>“gene”</td>
<td>“genetic”</td>
</tr>
</tbody>
</table>

In addition, the reference list of each paper was reviewed for additional studies. Papers for the analyses were chosen according to relevance for the validity criteria, mainly among publications dating from 2000 or after, following cited publications into earlier decades.
<table>
<thead>
<tr>
<th>Main reference</th>
<th>Cases</th>
<th>Controls</th>
<th>Follow-up</th>
<th>AD/HD</th>
<th>Conduct disorder identified at follow-up about 10% “antisocial disturbed” among cases</th>
<th>Antisocial personality disorder and criminality</th>
<th>Violent deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Montreal</strong> Hechtman &amp; Weiss, 1986</td>
<td>104 (95 boys and 9 girls) hyperactive children (aged 6-12), 24 had psychopharm treatment</td>
<td>45 matched ‘hypernormal’ school-mate controls</td>
<td>61/104 (59%) followed up at age 21-33, by clinical assessments and court records</td>
<td>22/61 (36%) vs. 1/41 (2%) had “at least one moderately or severely disabling symptom”</td>
<td>ASPD 14/60 (23%) vs. 1/41 (2%)a</td>
<td>2 MC accidents + 1 suicide vs. 0°</td>
<td></td>
</tr>
<tr>
<td><strong>New York</strong> Group 1 Mannuzza, Klein, Bessler, Malloy &amp; LaPadula, 1993</td>
<td>103 (Group 1) and 104 (Group 2) hyperactive boys (aged 6-12), all had “medication and/or behavior therapy”</td>
<td>100+78 matched ‘hypernormal’ non-psychiatric male outpatient controls</td>
<td>91/103 (88%) and 85/104 (82%) followed up at mean ages 26 and, 24, by structured assessments and, for the first group, by official files.</td>
<td>7/91 (8%) vs. 1/95 (1%) (group 1)a 27/100 (27%) vs. 8/100 (8%) (group 1)q ASPD 16/91 (18%) vs. 2/95 (2%)a incarcerations 5/91 (5%) vs. 0/95 (0%) (group 1)</td>
<td>ASPD 10/85 (12%) vs. 2/73 (3%)b criminality not reported (group 2)</td>
<td>1 accident, 1 stab wound, 1 possible suicide vs. 0 (group 1)a</td>
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<tr>
<td><strong>New York</strong> Group 2 Mannuzza, Klein, Bessler, Malloy &amp; LaPadula, 1998</td>
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<td></td>
<td>3/85 (4%) vs. 0/73 (0%) (group 2)q 30/94 (32%) vs. 6/78 (8%) (group 2)b</td>
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<tr>
<td><strong>Boston</strong> Biederman et al., 1996b</td>
<td>140 referred or recruited boys with ADHD (aged 6-17), 89% had stimulants</td>
<td>120 unmatched control boys from out-patient services or recruited by advertisements</td>
<td>112/140 (80%) were followed-up at age 16-27 by new assessments</td>
<td>ADHD: 63/112 (58%) had “full or subthreshold ADHD” vs. 6/105 (6%)</td>
<td>ASPD 12/94 (13%) vs. 2/96 (2%)a criminality not reported</td>
<td>none mentioned</td>
<td></td>
</tr>
<tr>
<td><strong>Los Angeles</strong> Satterfield, Hoppe &amp; Schell, 1982</td>
<td>110 hyperactive boys (aged 6-12), “most” or “all” had stimulants</td>
<td>75 matched, paid, public school controls, 13 non-ADHD brothers of cases</td>
<td>81% were followed up until age 25 through official records</td>
<td>not assessed</td>
<td>ASPD not assessed felony arrests 21% vs. 1%.</td>
<td>none mentioned</td>
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</tr>
<tr>
<td><strong>Wisconsin</strong> Barkley, Fischer, Smallish &amp; Fletcher, 2004</td>
<td>158 hyperactive children (144 boys, 14 girls, aged 4-12), 22% had stimulants</td>
<td>81 matched non-hyperactive controls recruited among the subjects’ friends</td>
<td>147/158 (93%) were followed up at age 19-25 through structured interviews and official records.</td>
<td>8/147 (5%) vs. 0/73 (0%)q 53/123 (43%) vs. 1/66 (1.5%) had developed CD at 8 year follow-upa</td>
<td>ASPD 31/147 (21%) vs. 3/73 (4%)a arrested ≥ 2 times 58/147 (39%) vs. 9/73 (12%)</td>
<td>1 suicide vs. 1 car crash and 1 non-violent death (sudden heart arrest)q</td>
<td></td>
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<tr>
<td><strong>Developmental Trends Study</strong> Loeber, Green, Lahey, Frick &amp; McBumett, 2000</td>
<td>177 outpatient boys (aged 7-12), 111/177 (63%) AD/HD, 71/177 (40%) ODD, 68/177 (38%) CD, no group defined as controls</td>
<td></td>
<td>on average 92% followed-up until age 19</td>
<td>not assessed</td>
<td>ASPD 60/158 (38%) 38% of AD/HD-probands in wave 1 met ASPD criteria as adults. 54% of CD-</td>
<td>none mentioned</td>
<td></td>
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<tr>
<td>Location</td>
<td>Study Details</td>
<td>Follow-up and Outcomes</td>
<td>Medication Notes</td>
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<tr>
<td>Gothenburg</td>
<td>61 population based cases (47 boys, 14 girls, aged 7) 90% ADD, 10% DCD, no stimulants 51 population-based controls (27 boys, 24 girls) matched for SES and age 55/61 (90%) followed up with structured assessments and official files at age 22</td>
<td>Severe hyperactivity impulsivity 8/55 (15%) vs. 1/46 (2%) severe inattention 24/55 (44%) vs. 3/46 (7%), combination of both 5/55 (9%) vs. 0/46 (0%)</td>
<td>Discontinued prior to assessment</td>
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<tr>
<td>Pittsburg</td>
<td>Population-based sample, 1517 boys, aged 7-13, enriched for disruptive behaviors, no info on medication no group defined as controls &gt;83% followed-up until age 19-25 years with interviews</td>
<td>Prevalence of AD/HD decreased from 15% to 8% from youngest to oldest sample in the youngest and oldest sample groups AD/HD was not a risk factor for persistent serious delinquency.</td>
<td>No mentioned</td>
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<tr>
<td>Cambridge</td>
<td>Population-based sample from “working class area”, 411 boys, aged 8-9, 34/411 (8.3%) had only HIA, 59/411 (14.4%) had HIA and “conduct problems”, no info on medication no group defined as controls 93% followed up by interviews until age 48</td>
<td>not assessed</td>
<td>no deathsa ASPD 10/55 (18%) VS. 1/46 (2%)a Criminal offences 8/55 (15%) vs. 0/46 (0%)</td>
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<tr>
<td>Dunedin</td>
<td>1037 children, from birth cohort (52% boys, 48% girls), aged 3-, 53/925 (5.7%) had ADD at age 11 (45 boys and 8 girls), 85% of these were also hyperactive, no info on medication no group defined as controls 93% average participation, followed-up until age 32</td>
<td>not reported</td>
<td>226/1012 (22%) 41/226 (18%) in this group had ADHD ASPD 40/973 (4.1%) at age 26 22 deaths at age 32 no info on causes</td>
<td>No figures provided Hyperactivity/impulsivity and early CPs, but not inattention, predicted arrest deceased not specified</td>
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<tr>
<td>San Francisco</td>
<td>Population based sample of 332 hyperactive children (78% boys, 22%) 160 populations based, gender matched controls 81% were followed up at age 23-30 through self reports and official arrest</td>
<td>not assessed</td>
<td>Hyperactivity/impulsivity and early CPs, but not inattention, predicted arrest deceased not specified</td>
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</table>

a Not assessed.
<table>
<thead>
<tr>
<th>Study</th>
<th>Population Description</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
</table>
| Great Smoky Mountain, Costello et al., 1996| Population-based sample of 1420 children, aged 9-13, enriched for disruptive behaviors, Of children aged 9-10 ADHD 21/936 (2.2%) ODD 20/936 (2.1%) CD 25/936 (2.7%), no info on medication. | No group defined as controls, 83% average participation, followed-up until age 16-21 | 4.1% lifetime prevalence of AD/HD at age 16, 9.0% lifetime prevalence of CD at age 16, ASPD not assessed, CD in combination with anxiety or depression, but not ADHD, predicted arrests for severe/violent offences |}

<table>
<thead>
<tr>
<th>Metaanalyses of cases vs. controls</th>
<th>Results</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>23/378 vs. 1/287</td>
<td>p&lt;.001</td>
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<tr>
<td>136/429 vs. 18/349</td>
<td>p&lt;.001</td>
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<tr>
<td>93/532 vs. 11/424</td>
<td>p&lt;.001</td>
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<tr>
<td>7/530 vs. 1/353</td>
<td>p&lt;.014</td>
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</table>

*Used in metaanalysis

*Fisher's exact test